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► **To cite this version:**

V. Siroux. Early exposure to endocrine disruptors and respiratory health. *Revue Française d'Allergologie*, 2020, 60, pp.178 - 179. <10.1016/j.reval.2020.02.028>. <hal-03490968>

**HAL Id: hal-03490968**

**<https://hal.science/hal-03490968v1>**

Submitted on 22 Aug 2022

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## **Exposition précoce aux perturbateurs endocriniens et santé respiratoire**

### **Early exposure to endocrine disruptors and respiratory health**

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Key words: phenols, phthalates, lung, allergy, children

Mots clés : Phénols, phtalates, respiratoire, allergie, enfants

## **Manuscript**

With changes in our lifestyles and the development of synthetic chemistry, exposures to chemicals are nowadays ubiquitous. Phenols and phthalates compounds are among the most produced chemicals in the world, at a level of about 5 to 10 million tons / year for phenols. Phenols, such as parabens, triclosan, benzophenone-3, are used in sunscreens, cosmetics, pharmaceuticals, and paper products because of their bactericidal and fungicidal properties. Some dichlorophenols are intermediates in the production of room deodorizers and herbicides. Phthalates are predominantly used as plasticizers to confer flexibility and are present in many plastic products, such as polyvinyl chloride floor covering, toys, and food packaging. Some phthalates are used in fragrances, cosmetics, and medications. Exposure to these chemicals or their precursors is widespread. In the recent European Helix project, phthalate metabolites and phenols were detected in the urine of 97% or greater in pregnant women and children, in accordance with previous observations in the National health and Nutrition Examination Survey (NHANES) in US.(1)

The ubiquitous presence of phthalates and the potential consequences of human exposure have raised concerns, particularly in young children, because they are more likely to be exposed to phthalate than adults due to their hand-to-mouth behaviors, and because early-life exposure is expected to be a particular vulnerability window to these compounds. Animal studies have suggested an effect of some phenols on brain organization and behavior, respiratory health, cancer (breast, prostate), metabolic disorders and weight growth or obesity. In vivo and in vitro research has shown that many of these compounds are endocrine disruptors, which is officially recognized by the EU chemical agency for BPA and some phthalates. Early development requires specific and accurate timing of hormone action to promote proper growth of tissues and organs, and EDs compounds can interfere with the endogenous activities of these hormones. Moreover, experimental studies have suggested additional biological mechanisms, by which in utero exposure to phenols and phthalates could adversely affect respiratory health in childhood. Phthalates are suspected to modulate the immune system resulting in pro-allergic effects. For instance, Di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DnBP) and Diisononyl phthalate (DINP) may modify the balance between the T-Helper type 1 (Th1) and T-helper type 2 (Th2), favoring a Th2-dependant production. These compounds are also assumed to modulate the

inflammatory response and to induce oxidative stress. Regarding the phenols, bisphenol A might modulate the immune system by increasing induced th2-polarization and increasing IgE serum level and the production of pro-allergic mediators such as cytokine IL4. Moreover, prenatal exposure to bisphenol A was associated with bronchial eosinophilic inflammation and airway hyper-responsiveness in mice, suggesting a potential negative effect in lung function in humans through a pro-inflammatory action.

A growing number of prospective epidemiological studies investigated the effects of early-life exposure to these compounds on children's immune development, respiratory health and allergy. These epidemiological studies highlighted some statistically significant associations, but results are still inconsistent regarding the compounds reported. For example, some epidemiological studies investigating the associations between prenatal exposure to bisphenol A on respiratory outcomes suggested deleterious associations,(2–4) while other studies did not (5). Similarly, most prospective birth cohort studies addressing the impact of prenatal phthalate exposures in respiratory and allergic outcomes have reported association, predominantly with high molecular weight phthalates (2,6) though there are exceptions (3). In a recent study based on the CHAMACOS mother-child cohort, some high molecular weight phthalates were associated with an atopic cytokine profile and poorer lung function but none of the biomarker tested were associated with increased risk in atopic diseases.(7) In the Helix European cohort study, using an exposome approach, i.e investigating a broad range of prenatal and postnatal environmental exposures (considering 17 exposures families for the outdoor, indoor chemical and lifestyle domains), Agier et al. showed that a lower FEV1 was associated with postnatal exposure to ethyl-paraben and phthalate metabolites.(8) Several studies reported potential sexually-dimorphic effects of some phenols and phthalates on respiratory health. For example, a recent cross-sectional analysis in the National Health and Nutrition Examination Survey (2005-2014) showed that methyl paraben and propyl paraben were associated with an increased risk of reporting emergency department visit among boys with asthma.(9)

Further larger prospective studies are needed to strengthen the current suggestions for a role of early life exposures to phenols and phthalates in respiratory health and allergy. These further studies need to overcome some weaknesses of most of previous studies related first to the exposure assessment and secondly to the restricted way of addressing the exposure-health association. In most previous studies the exposure assessment was based on a small

number ( $\leq 3$ , most often one) of maternal urine samples collected during pregnancy. Because of the low persistence of these chemicals (half-life below one day in humans) and of the temporal variability in exposure, urinary concentrations are highly variable. Therefore, a small number of urine samples imperfectly reflects the average exposure throughout the whole foetal life, which leads to bias in association studies. Thus, further studies need to rely on a large number of urine sample to assess exposures. A further limitation of most of the previous studies relies on the fact that they investigated the effect of each compound alone and did not address the possible “cocktail effect”. In daily life, populations are simultaneously exposed to a wide range of these compounds. Epidemiological studies considering each compound exposure separately are unable to totally understand co-exposures and account for the potential effect of combined exposure to several phenols and phthalates. Thus, further epidemiological studies need to consider jointly the effect of various phenols and phthalate compounds on health outcomes.

### **Remerciements**

The French National Research Program for Environmental and Occupational Health of Anses (PENDORE\_2018/1/264).

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