

The Association between Asthma and Allergic Symptoms in Children and Phthalates in House Dust: A Nested Case–Control Study

Carl-Gustaf Bornehag,^{1,2,3} Jan Sundell,² Charles J. Weschler,^{2,4} Torben Sigsgaard,⁵ Björn Lundgren,¹ Mikael Hasselgren,³ and Linda Hägerhed-Engman¹

¹Swedish National Testing and Research Institute, Borås, Sweden; ²Technical University of Denmark, Lyngby, Denmark; ³Public Health Science, Karlstad University, Karlstad, Sweden; ⁴University of Medicine and Dentistry New Jersey–Robert Wood Johnson Medical School and Rutgers University, Piscataway, New Jersey, USA; ⁵Aarhus University, Aarhus, Denmark

Global phthalate ester production has increased from very low levels at the end of World War II to approximately 3.5 million metric tons/year. The aim of the present study was to investigate potential associations between persistent allergic symptoms in children, which have increased markedly in developed countries over the past three decades, and the concentration of phthalates in dust collected from their homes. This investigation is a case–control study nested within a cohort of 10,852 children. From the cohort, we selected 198 cases with persistent allergic symptoms and 202 controls without allergic symptoms. A clinical and a technical team investigated each child and her or his environment. We found higher median concentrations of butyl benzyl phthalate (BBzP) in dust among cases than among controls (0.15 vs. 0.12 mg/g dust). Analyzing the case group by symptoms showed that BBzP was associated with rhinitis ($p = 0.001$) and eczema ($p = 0.001$), whereas di(2-ethylhexyl) phthalate (DEHP) was associated with asthma ($p = 0.022$). Furthermore, dose–response relationships for these associations are supported by trend analyses. This study shows that phthalates, within the range of what is normally found in indoor environments, are associated with allergic symptoms in children. We believe that the different associations of symptoms for the three major phthalates—BBzP, DEHP, and di-n-butyl phthalate—can be explained by a combination of chemical physical properties and toxicologic potential. Given the phthalate exposures of children worldwide, the results from this study of Swedish children have global implications. **Key words:** allergy, asthma, BBzP, children, DEHP, homes, phthalates. *Environ Health Perspect* 112:1393–1397 (2004). doi:10.1289/ehp.7187 available via <http://dx.doi.org/> [Online 15 July 2004]

Airborne phthalate esters are present at detectable levels across the surface of Earth. They were first identified in outdoor urban air (Cautreels and Van Cauwenbergh 1976a, 1976b) and subsequently have been recognized as global pollutants (Atlas and Giam 1981; Giam et al. 1978) and major constituents of indoor air (Weschler 1980, 1984). Their presence in outdoor and indoor environments reflects their large emission rates coupled with moderate atmospheric lifetimes. The total global consumption of phthalate esters is estimated to exceed 3.5 million metric tons/year, with di(2-ethylhexyl) phthalate (DEHP) constituting roughly 50% of the market share (Cadogan and Howick 1996). Consumption of di-n-butyl phthalate (DnBP) and n-butyl benzyl (BBzP) phthalate is smaller but still quite large (> 100,000 metric tons/year each) (Cadogan and Howick 1996). Although DEHP plasticizes numerous products, roughly 95% of the current production is used in polyvinyl chloride (PVC) (National Toxicology Program 2003), where it typically constitutes 30% of PVC by weight (Cadogan and Howick 1996; Kavlock et al. 2002b). DnBP is used in latex adhesives, in nail polish and other cosmetic products, as a plasticizer in cellulose plastics, as a solvent for certain dyes, and, to a lesser extent than DEHP, as a plasticizer in PVC (Kavlock et al. 2002c). BBzP is a plasticizer for

vinyl tile, carpet tiles, and artificial leather and is also used in certain adhesives (Kavlock et al. 2002a).

Research groups have assessed the exposures of various populations to phthalate esters by using their metabolites in human urine as biomarkers [Barr et al. 2003; Blount et al. 2000; Centers for Disease Control and Prevention (CDC) 2003; Koch et al. 2003]. The biomarker results translate to daily exposures for DnBP, BBzP, and DEHP of 1.5, 0.88, and 0.71 µg/kg/day in the United States (Kohn et al. 2000); 0.95, 0.71, and 0.84 µg/kg/day in the United States (derived from data from Barr et al. 2003, their Table 1, using the procedure outlined by Kohn et al. 2000); and 5.22, 0.60, and 13.8 µg/kg/day in Germany (Koch et al. 2003). These findings confirm the relatively large daily exposure to phthalates in industrialized countries. Although the dominant route of exposure to DnBP, BBzP, and DEHP is thought to be via ingestion (Fromme et al. 2004; Kavlock et al. 2002a, 2002b, 2002c), few if any population-based data are available to support this statement. Indeed, a recent study has demonstrated associations between phthalate concentrations in inhaled air and urinary monoester metabolites (Adibi et al. 2003).

The incidence of asthma and allergy has increased throughout the developed world over the past 30 years (Beasley et al. 2003).

The short interval over which it has occurred implies that the increase is caused by changes in environmental exposures rather than genetic changes (Etzel 2003; Strachan 2000). Changes in indoor environments warrant special attention because indoor air constitutes a dominant exposure route. Increased exposures to allergens and/or adjuvants (enhancing factors) may each be partially responsible for the increase. Multidisciplinary reviews of the scientific literature on associations between indoor exposures and asthma and allergies (Ahlbom et al. 1998; Andersson et al. 1997; Bornehag et al. 2001; Schneider et al. 2003; Wargocki et al. 2002) indicate that the underlying causal factors responsible for these increases remain unknown.

The use of plasticized products and, consequently, exposures to phthalate esters have increased dramatically since the end of World War II. Phthalate esters have been suggested to act as either allergens or adjuvants (Jaakkola et al. 1999; Oie et al. 1997). Several recent studies have examined the ability of different phthalate esters to function as adjuvants in BALB/c mice injected with a known antigen. DEHP displayed an adjuvant effect with immunoglobulin G1 at a concentration of 2,000 mg/mL after both one and two boosters (Larsen et al. 2001b). In contrast, DnBP only showed an adjuvant effect with immunoglobulin G1 after the second booster (Larsen et al. 2002), and BBzP showed no adjuvant effect (Larsen et al. 2003). Consistent with these results, the monoesters of DEHP showed an adjuvant effect whereas the monoesters of DnBP and BBzP did not (Larsen et al. 2001a).

The present study is a nested case–control study on 198 symptomatic children and 202 healthy controls, including detailed clinical examinations by physicians in parallel

Address correspondence to C.G. Bornehag, Public Health Sciences, Karlstad University, 651 88 Karlstad, Sweden. Telephone: +46-54-700-25-40. Fax: +46-54-700-25-23. E-mail: carl-gustaf.bornehag@kau.se

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