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Infants' indoor and outdoor residential exposure to benzene and respiratory health in a Spanish cohort☆

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ABSTRACT

Benzene exposure represents a potential risk for children's health. Apart from being a known carcinogen for humans (group 1 according to IARC), there is scientific evidence suggesting a relationship between benzene exposure and respiratory problems in children. But results are still inconclusive and inconsistent. This study aims to assess the determinants of exposure to indoor and outdoor residential benzene levels and its relationship with respiratory health in infants. Participants were 1-year-old infants (N = 352) from the INMA cohort from Valencia (Spain). Residential benzene exposure levels were measured inside and outside dwellings by means of passive samplers in a 15-day campaign. Persistent cough, low respiratory tract infections and wheezing during the first year of life, and covariates (dwelling traits, lifestyle factors and sociodemographic data) were obtained from parental questionnaires. Multiple Tobit regression and logistic regression models were performed to assess factors associated to residential exposure levels and health associations, respectively. Indoor levels were higher than outdoor ones (1.46 and 0.77 $\mu g/m^3$, respectively; $p < 0.01$). A considerable percentage of dwellings, 42% and 21% indoors and outdoors respectively, surpassed the WHO guideline of 1.7 $\mu g/m^3$ derived from a lifetime risk of leukemia above 1/100 000. Monitoring season, maternal country of birth and parental tobacco consumption were associated with residential benzene exposure (indoor and outdoors). Additionally, indoor levels were associated with mother's age and type of heating, and outdoor levels were linked with zone of residence and distance from industrial areas. After adjustment for confounding factors, no significant associations were found between residential benzene exposure levels and respiratory health in infants. Hence, our study did not support the hypothesis for the benzene exposure effect on respiratory health in children. Even so, it highlights a public health concern related to the personal exposure levels, since a considerable number of children surpassed the abovementioned WHO guideline for benzene exposure.

1. Introduction

A recent WHO report about "preventing disease through healthy environment" claimed that 12.6 million deaths in 2012, representing almost a quarter of the global deaths worldwide, were attributable to unhealthy environments (WHO, 2016). Of these, 1.7 million involved children under 5 years of age, the main causes being respiratory tract infections and diarrheic diseases. Regarding household and ambient air pollution, 4.3 and 3.7 million deaths can be attributable to these factors, respectively (Lim et al., 2012).

Due to their behavioral patterns, children are considerably more exposed to air pollution than adults. Inhalation rate is higher than in adults and infants' height places them much closer to the exhaust pipes of cars (Landrigan et al., 2004; Moya et al., 2004). Moreover, children's respiratory system is characterized by its high vulnerability since development of the lungs is not fully completed until around the third year of life (Schittny and Burri, 2007). During

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the developmental period, certain toxic exposures such as tobacco smoke and air pollutants could have an influence on the normal development of the lungs. This, in turn, could determine respiratory illnesses later in childhood and adulthood (Duijts, 2012; Shi et al., 2007).

Benzene, a volatile organic compound (VOC) derived from petroleum, is a common solvent. The main source of benzene is tobacco smoke, but its levels indoors are also increased after using gas stoves, and cleaning or painting products (Kotzias et al., 2005; Topp et al., 2004; WHO, 2010). Outdoor sources are traffic exhaust fumes, and emissions from industrial facilities and/or gas stations. Levels of this pollutant in indoor air are usually higher than outdoors, since it is more commonly derived from household sources and activities.

Apart from being known carcinogens, according to the International Agency for Research on Cancer (IARC, 2012), some VOCs such as formaldehyde or benzene have been suggested to play a role in the development of respiratory diseases (Ferrero et al., 2014; Fuentes-Leonarte et al., 2009; IARC, 2012; WHO, 2010). They could irritate the airways or alter the multipathway inflammation mechanisms in epithelial lung cells after inhalation at normal concentrations indoors (ranging within $\mu g/m^3$) (Mascelloni et al., 2015; Pariselli et al., 2009; Wang et al., 2014). However, the strongest and most consistent evidence on respiratory effects in epidemiological studies in children are for formaldehyde, while for benzene exposure evidence is still scarce and inconclusive (Bolden et al., 2015; Heinrich, 2011; Mendell, 2007; Roda et al., 2013).

As part of the multicenter prospective INMA project (for its acronym in Spanish: Infancia y Medio Ambiente) (Guxens et al., 2012), a previous study assessed the relationship between ambient exposure to benzene and NO_2 in residential dwellings in two developmental periods of children (prenatal and during 1st year of life), and respiratory health in children aged 1 in four INMA cohorts (Aguilera et al., 2013). Exposure levels in both periods were estimated by means of land use regression (LUR) models and predicted for residential addresses. LUR models were based on measurements in more than 50 representative locations spread over each study area during the mothers' pregnancy (years 2004–2007). Regarding respiratory health associations, benzene exposure in the prenatal period was not related to respiratory infections or symptoms. In the INMA cohort of Valencia, one study has empirically measured and described residential exposure levels to VOCs (specifically to benzene, toluene, ethyl benzene and xylene, known as BTEX compounds) in indoor and outdoor air in half of the dwellings with an infant population during their first years of life (Esplugues et al., 2010). Here, we examined levels of residential exposure to benzene measured indoors and outdoors at the first year of life, as well as its relationship with respiratory health in infancy.

Thus, the purposes of this study were to assess (i) the environmental, lifestyle and individual factors associated to benzene exposure levels measured directly inside and outside the dwellings at age 1, and (ii) their relationship with respiratory symptoms and problems suffered by infants during their first year of life.

2. Methods

2.1. Study population

The study population consisted of children participating in the INMA Project in Valencia (Spain). Their mothers were recruited during pregnancy between November 2003 and June 2005 at the first prenatal health examination at the reference hospital (Hospital “La Fe” in Valencia) (Guxens et al., 2012; Ramón et al., 2005). At birth, 787 newborns were included in the INMA-Valencia cohort. Of these, 708 participated at follow up at one year of age (2006–2007). Participants in the present study were a subsample of 352 children with available measurements of any of the pollutants monitored at age 1 (VOC or NO2) (Supplementary Fig. 1). Written informed consent was obtained from parents and the study was approved by the ethics committee of the reference hospital. The study area of the INMA-Valencia cohort covers around 1372 km^2 including 34 municipalities with a wide range of sociodemographic and environmental traits. The area is made up of a typically urban zone (city of Valencia), a metropolitan area containing the neighboring towns around the city of Valencia, a semi-urban area dedicated to industrial and agricultural activity, and a typically rural zone.

2.2. Benzene exposure assessment

Residential benzene exposure levels were measured inside and outside the dwellings during the children's first year of life (years 2006–2007). They were monitored in a 15-day campaign by means of passive samplers located in the living room of each dwelling and outside the home in a window or on a balcony. The method for benzene level measurement has been described elsewhere (Esplugues et al., 2010a). Briefly, passive samplers were stainless steel tubes 8.9 cm in length and with an internal diameter of 0.5 cm containing a solid sorbent for chemical fixing (Tenax TA 60/80; Analytical Columns, New Addington, Croydon, England). Chemical analyses consisted in thermal desorption of the samples coupled to gas chromatography with flame ionization detection (TD/GC/FID). The detection limit (DL) was 1.04 $\mu g/m^3$. Benzene levels for residences below the DL (36% indoors and 42% outdoors) were considered as DL/2.

2.3. Respiratory outcomes

At the first-year follow up, health information was obtained by means of a questionnaire administered to parents by trained personnel. Questions on respiratory symptoms and diagnosis during the previous 12 months were based on a structured questionnaire from the AMICS study (Sunyer et al., 2001; Polk et al., 2004). Respiratory outcomes in the present study were (i) persistent cough (lasting more than 3 weeks), (ii) low respiratory tract infections (LRTI) including doctor's diagnosis of bronchitis, bronchiolitis or pneumonia, and (iii) wheezing, considered as dichotomous variables. Specific questions (in Spanish) and further information can be found in Supplementary Fig. 2.

2.4. Covariates

Information related to environmental exposure or respiratory health was also obtained by a questionnaire administered to parents in different visits. Information gathered during the first trimester of pregnancy were maternal age, educational level, maternal country of birth, familial history of allergies and zone of residence; during the third trimester they were maternal tobacco consumption during pregnancy and social class based on parental occupation; and at the first-year follow up, they were parental tobacco consumption, frequency of traffic in the nearest street, distance to an industrial area, number of rooms and rooms equipped with air conditioning, number of people living at home, daily ventilation rate, household size, attendance at day-care centers, type of cooking and heating, household pesticide use, habitual use of painting and cleaning products such as bleach, ammonia, hydrochloric acid, degreasers, solvent stain-removers, sprays for air fresheners and perfumed products.

In addition, NO_2 exposure levels during pregnancy and at age 1 were tested as confounder variables. Details of the methodology for the estimation of residential ambient exposure levels to NO_2 during