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Review

Health effects of ozone focusing on childhood asthma: What is now known – a review from an epidemiological point of view

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HIGHLIGHTS

- Short-term exposures to ozone have been proven to affect childhood asthma.
- Epidemiological studies confirmed that ozone exposure influence asthma development.
- Causality between ozone and childhood asthma is still to prove.

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ABSTRACT

Protecting the health of children and the environment is an essential objective for the health policies of any modern society, being also crucial for a sustainable development, according to the World Health Organization. Evaluating the risk of developing childhood asthma is one of the four priority issues identified by the European Commission, according to the European Union Environment and Health Action Plan.

Accordingly, this review aimed to update information concerning the effects of exposure to ozone on childhood asthma, thus helping in the development of strategies for further research. Studies have been demonstrating strong associations between the exposure to ozone and asthma. However, the complexity of exposure patterns, the changes in the vulnerability of children at various stages of development, and the practical limitations of research, lead to a still incomplete understanding of the ozone impact on the health of children. Difficulties on the interpretation of epidemiological studies to evaluate chronic effects are mainly due to an absence of studies designed specifically to address this question and to inherent limitations in characterizing exposure. The more rigorous studies provided new evidences for chronic effects of ozone on small airway function and possibly on asthma, but substantial uncertainties remain.

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1. Introduction

Ground-level ozone (O₃) is one of the most harmful air pollutants in Europe today (EEA, 2011a). To protect human health from

the respective effects, air quality legislation for Europe sets: (i) a target value of 120 µg m⁻³ (daily maximum of 8-h averages) that should not be exceeded more than 25 d per year; (ii) an information threshold of 180 µg m⁻³ (1-h average); and (iii) an alert threshold of 240 µg m⁻³ (1-h average) (Directive 2008/50/EC). According to the European Environment Agency (EEA), in the summer of 2010 and for the first time in 4 years, the information

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threshold was exceeded in northern Europe. The alert threshold was exceeded 44 times in nine European Union (EU) Member States being more incident in northern Italy and northern Portugal (EEA, 2011b).

O₃, as a strong oxidant, impairs biological tissues namely of the lungs, causing increased medication use, illness and death (OECD, 2008). It is even suggested that there is no safe level for O₃ exposure, posing a health risk even at concentrations below the legislated (OECD, 2008). Considering the general population, persons with respiratory diseases, elderly and children are the higher risk groups. Children are highly vulnerable to environmental hazards, being considered a risk group for several reasons including their relative higher amount of air inhalation (the air intake per weight unit of a resting infant is twice that of an adult), their not fully developed immune system and lungs and also their higher amount of time spent outdoors. As a result, children will have substantially higher exposures to air pollutants than adults (Schwartz, 2004; WHO, 2004).

Several studies have demonstrated a strong association between the exposure to O₃ and asthma, even more significant for asthmatic children (McDonnell et al., 1997; Salvi, 2007).

This review aimed to update information concerning the effects of exposure to O₃ on childhood asthma, thus helping in the development of strategies for further research.

2. General aspects of O₃ and how it affects human health

O₃ is a colourless gas, strong oxidizing agent and a normal constituent of the atmosphere, with peak concentrations in the middle stratosphere. As consequence of anthropogenic activities, O₃ represents two major and distinct environmental concerns: in the stratosphere, because of its concentration decrease and near surface, because of its concentrations increase (Godish, 2004). It differs from the other tropospheric pollutants because of its secondary origin. Major sources of ground-level O₃ concentrations are stratospheric intrusions, particularly during spring months, and photochemical processes. The latter involve a complex series of reactions with nitrogen dioxide and volatile organic compounds catalysed by sunlight radiation (Alvim-Ferraz et al., 2006). Major sink processes of O₃ are photochemical processes, transport by wind and deposition (Colls, 2002; Godish, 2004; USEPA, 2006).

Ground-level O₃ concentrations have a seasonal pattern, having its higher values in summer. The daily profile also presents a pattern following the daily solar cycle and also the variations of anthropogenic activities. Fig. 1 shows the typical annual profile of O₃ for urban, and industrial sites, and also rural sites at low (below 500 m) and higher altitudes (rural-high) in Europe from 1999 to 2009. Several studies have concluded that O₃ concentrations are clearly higher at rural areas than at urban ones (Syri et al., 2001; Bayer-Oglesby et al., 2004; Dueñas et al., 2004; Jalaludin et al., 2004; Priftis et al., 2007; Sousa et al., 2008; EEA, 2011a). This tendency is also observed in Fig. 1, with background sites having higher concentrations mainly due to lower nitrogen oxides' concentrations, long range transport and natural emissions from vegetation. The rural sites at higher altitudes (rural-high) presented the highest concentrations which can be also due to vertical transport (CCDRN, 2008; EEA, 2011a; Sousa et al., 2011a). The differences in the O₃ levels between the years can be explained by meteorological variations.

As referred above, O₃ is a very powerful oxidizing agent and so it can react with a wide range of cellular components and biological materials. There is consistent experimental and observational evidence that O₃ has adverse effects on human health, plausibly promoting both acute and chronic effects (Curtis et al., 2006; OECD, 2008). A very large number of studies on the acute effects of O₃ exposure in humans have been performed, employing differ-

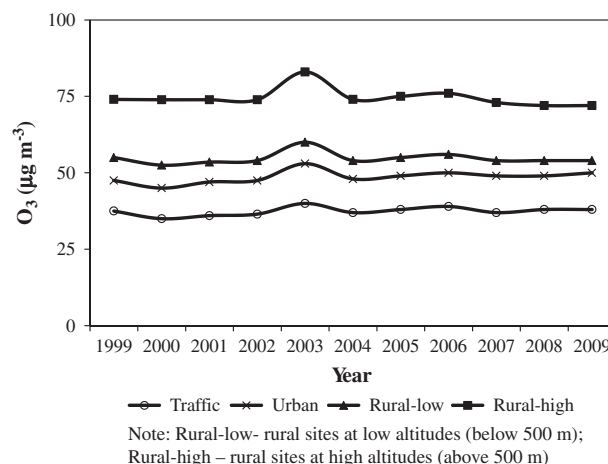


Fig. 1. Annual profile of O₃ for traffic, industrial and rural sites in Europe from 1999 to 2009 (adapted from EEA, 2011a).

ent experimental approaches, such as single or continuous exposures, controlled exposures at rest or during exercise, exposures at ambient levels and evaluation of effects on subjects with pre-existing pulmonary diseases such as asthma or chronic bronchitis (WHO, 2008).

The effects on asthma have been also studied in relation with long-term exposures to O₃ (WHO, 2006). Asthma is a complex respiratory disease whose symptoms include dyspnoea, wheezing, chest tightness and recurrent cough (Alvim-Ferraz et al., 2005). This is one of the respiratory diseases that has been directly associated with air pollution, featuring an accumulation of inflammatory cells and mucus in the airways, with bronchoconstriction and a generalized airflow limitation (Donaldson et al., 2000; Trassande and Thurston, 2005). Asthma is a classical multifactorial disease whose aetiology is complex, involving both genetic and environmental triggers. The prevalence has risen steeply over the last 30 years at a rate that cannot be explained simply on genetic grounds. Clearly there are important environmental factors which have influenced this sharp rise (Lenney, 2009). The main factors to consider in asthma aetiology are the genetic influences, diet and obesity, viral infections, allergen exposure, tobacco smoke and other pollutants as nitrogen dioxide, sulphur dioxide, O₃, diesel exhaust and particulate matter (Corrigan, 2012; Lenney, 2009). The genetic relationships to asthma in children depend on the many and complex interactions between in utero, neonatal and external environmental factors, all of which vary depending on the specific asthma phenotype and even in a single patient these vary over time (Lenney, 2009). Genome screens have linked inheritance of various chromosomal regions with an increased risk of asthma (Corrigan, 2012), but no gene for asthma has still been identified. The relation between diet and asthma prevalence has been extensively investigated over recent years. Fast food diet and obesity increases have led to speculation about lack of nutrients and obesity playing a role in asthma causation, but there is no conclusive evidence. Breastfeeding reduces the risk of eczema in atopic 'at risk' children, but the evidence relating to asthma is also inconclusive (Corrigan, 2012). Diet has been considered as a trigger influencing prevalence and/or severity by some authors, but needs careful assessment depending on the asthma phenotype (Lenney, 2009). Respiratory viruses are the most common cause of asthma exacerbations in children with asthma; viruses are responsible for 85% of all childhood exacerbations. A bacterial infection as a cause for childhood asthma development is a topic of growing interest (Lenney, 2009; Corrigan, 2012). Early life sensitization to allergens, particularly indoor allergens such as house dust mite, is a major risk

factor for the development of asthma in children, but only in the genetically predisposed, raising doubts as to whether allergic sensitization is actually causative of asthma or reflects parallel susceptibility pathways arising from common genetic origins (Corrigan, 2012).

Exposure of children to tobacco smoke in utero or early childhood increases their risk of developing wheeze. Epidemiological and experimental evidence suggests that diesel exhaust particulates and O₃ promote sensitization to allergens. Many pollutants exacerbate asthma but there is little evidence that they predispose to its development (Corrigan, 2012).

Asthma is increasing all over Europe and a large portion of this increase is in childhood, being now the most common respiratory disease in western European children (EEA, 2005; Anthracopoulos et al., 2007). On average 7% of EU-25 children aged 4–10 have problems with asthma although there is a significant variation between EU countries (EEA, 2005). Undoubtedly, persons with asthma, especially asthmatic children, are sensitive to air quality and several studies have demonstrated a strong association between exposure to air pollution and worsening of asthma (Ware et al., 1993; Leikauf et al., 1995; Jedrychowski and Flak, 1998; Ramadour et al., 2000; Friedman et al., 2001; Parnia et al., 2002; D'Amato, 2005; Ho et al., 2007; Salvi, 2007; Sousa et al., 2009a, 2011a; Akinbami et al., 2010).

3. Legal biddings

Concerning the negative health effects of O₃ on human health, a number of organizations have been assessing and defining guidelines and limits for pollutant concentrations on ambient air. The WHO Regional Office for Europe, in Copenhagen, has been undertaking a highly successful effort at providing very concise assessments of a number of air pollutants considered to pose health and/or environmental threats for European countries. It is however important to emphasize that the air quality guidelines, above referred as being generated under WHO responsibility are not air quality standards; rather, the guidelines represent appropriate concentrations for certain averaging times (1-h, 24-h, 1-year) recommended by international experts and to be considered by national or international authorities for promulgation of air quality standards (Grant et al., 1999).

Since the early 1970s, the EU has been working to improve air quality by controlling emissions of harmful substances into the atmosphere, improving fuel quality, and integrating environmental protection requirements into the transport and energy sectors. After 40 years the system of environmental controls is now understood. Concerning health impacts, the EU assessment concluded that there is a reduction in life expectancy due to O₃ associated with 21 000 cases of premature mortality in 2020 (WHO, 2008). The severe consequences on life quality are even worst for children and elderly, as well as for citizens suffering of asthma and cardiovascular diseases because of their particular vulnerability. In monetary terms, for 2020 the damage to human health alone was estimated between 189 and 609 M€ per year (COM (2005) 447 fi-

nal). In Europe, emissions of many air pollutants have fallen substantially since 1990, primarily resulting in improved air quality over the region. However, since 1997, measured concentrations of O₃ in the air have not shown any significant improvement despite the decrease in precursor emissions. A significant proportion of the urban population of Europe still live in cities where EU air quality limits set for the protection of human health are exceeded, namely concerning O₃ (EEA, 2011a). Consequently, the need to reduce exposure to air pollution remains an important issue. In the case of O₃ the co-operation between Member States is required to address the causes of O₃ pollution, because it is a secondary pollutant, and thus, as above referred the reactions by which it is formed take place over few days and are influenced by emissions of primary pollutants over scales of many hundreds of kilometres (Alvim-Ferraz et al., 2006).

Table 1 shows the O₃ air quality standards for the protection of human health defined by the European Union and the United States Environmental Protection Agency (USEPA), and also the guidelines provided by WHO. As it can be seen the USEPA standards are the most permissive ones, even though the 8-h standard was updated in 2010. WHO considered that all the information from epidemiological studies together with evidence from both chamber and field studies (indicating that there is considerable individual variation in response to O₃), provided a good case for reducing the previous 8-h guideline of 120–100 µg m⁻³ already in 2005 (WHO, 2008). Additionally, WHO considers that it would be extremely important to achieve this target, because significant reductions could be observed in risks for acute and chronic health effects from air pollution. Furthermore, progress towards the guideline values should be the final objective of air quality management and health risk reduction in all areas (WHO, 2008).

Another enhanced matter in the European Directive on ambient air quality and cleaner air for Europe (Directive 2008/50/EC) is the necessity of developing modelling techniques. The development of mathematical tools able to predict O₃ concentrations has been drawing the attention of many scientists all over the world during the last 20 years (Schmidt et al., 2001; Ballester et al., 2002; Schlinck et al., 2003, 2006; Borrego et al., 2006; Mallet and Sportisse, 2006; Sousa et al., 2006, 2007, 2009b; Monteiro et al., 2007). Due to the harmful effects of this gas, the prediction of O₃ concentrations becomes a fundamental tool, concerning the anticipated implementation of strategies to improve public health, namely on providing early warnings to the population, and concerning the reduction of the number of measuring sites.

4. Health impacts

Studies concerning O₃ effects on the respiratory system have shown that: (i) short-term exposure impairs pulmonary function; (ii) transient obstructive pulmonary alterations may occur for 6.6 h of exposures to levels of 160 µg m⁻³ (controlled exposures), which is a concentration many times surpassed all over the world; (iii) asthmatics and those with allergic rhinitis are more susceptible to transient alterations in respiratory function due to acute

Table 1

Ozone air quality standards for human health protection according to European and United States of America legislation, and World Health Organization (WHO) guidelines.

Period	Directive 2008/50/EC (µg m ⁻³)	USEPA (NAAQS ^a)	WHO (air quality guidelines ^b)
1 h – Alert threshold	240	–	–
1 h – Information threshold	180	240 µg m ^{-3c}	–
8 h – Human health protection	120	150 µg m ⁻³	100 µg m ⁻³

^a Based on the 2010 and 2008 standards.

^b Based on the 2005 air quality guidelines of WHO.

^c EPA revoked the 1-h ozone standard in all areas, although some areas have continuing obligations under that standard (“anti-backsliding”); the standard is attained when the expected number of days per calendar year with maximum hourly average concentrations above 0.12 ppm is ≤ 1.

exposure; (iv) changes in pulmonary function and reduction of airway antioxidant defences are immediate consequences of exposure; (v) airway responsiveness is enhanced in both healthy individuals and asthmatics (WHO, 2006). Also, studies performed under field conditions, such as summer camps, have detected transient functional effects at lower levels than those observed in controlled exposures. This discrepancy may be due to concomitant exposure to other pollutants and/or difficulties in precisely determining individual exposure. Additionally, field studies are conducted for a higher number of days, thus increasing the power of detecting a significant effect (USEPA, 2006; WHO, 2006). The effect of O₃ on respiratory morbidity has also great evidence, being school absenteeism, hospital admissions or emergency department visits for asthma, respiratory tract infections and exacerbation of chronic airway diseases the most common health outcomes studied (Li et al., 2011; Samoli et al., 2011). A 20% increase in school absenteeism was reported in a study in Mexico City, being associated with ambient O₃ concentrations higher than 260 µg m⁻³ for two consecutive days, being the effect amplified by low temperature (Cortez-Lugo et al., 1998). Also, in northern Nevada, absenteeism was studied in elementary schools and it was estimated an increase of 13% per 100 µg m⁻³ of O₃ increase (WHO, 2006). There are large multi-city studies relating hospital admissions for respiratory diseases and Chronic Obstructive Pulmonary Disease (COPD) to ambient O₃ levels. The associations were observed after controlling for temporal trends in admission rates, day-of-week and seasonal effects, gaseous and particulate air pollution, and climatic factors. Effects of O₃ on respiratory admissions seem stronger during warmer weather (Atkinson et al., 2001; Halonen et al., 2008; Mascarenhas et al., 2008; WHO, 2008; Arbex et al., 2009). A study in the Connecticut area reported that an 100 µg m⁻³ increase in 1 h O₃ was associated with increased likelihood of wheeze (by 35%) and chest tightness (by 47%) (Gent et al., 2003). Also in seven American communities a cohort of 846 asthmatic children living in city centres aged 4–9 years was evaluated, and an increase of 30 µg m⁻³ in O₃ was associated with a higher risk of morning symptoms (Odds Ratio – OR: 1.16; 95% confidence interval – CI: 1.02–1.30) and with a 0.59% decline in morning peak expiratory flow rates (PEFRs) (95% CI: 0.13–1.05). The range of relative risks (RR) of mortality due to respiratory diseases was between 0.23% and 6.6%, for an increase of 20 µg m⁻³ in O₃ concentrations, depending on the age group, season of the year and model specifications (Mortimer et al., 2002). Determining the specific cause for mortality is more difficult due to reduced statistical power to examine the associations and the lack of clarifying information of death causes (USEPA, 2006).

The effect of short-term exposure to ambient O₃ on cardiovascular function and the initiation and progression of cardiovascular disease in laboratory animals and human populations is an emerging field. Few studies have been conducted in this field, however showing associations of acute effects to O₃ exposure (Wong et al., 2002; Brook et al., 2004; Herotin et al., 2007). The vast majority of the studies obtained positive and significant associations between variations in ambient O₃ levels and increased morbidity. The effects were manifested among children, elderly people, asthmatics and those with COPD. Kalantzi et al. (2011) aiming to access the relationship between the frequency of hospitalizations due to respiratory and cardiovascular diseases and air pollution, found that elevations in ambient O₃ levels were consistently associated with increased hospitalizations both for respiratory or cardiovascular problems. A study performed in the Massachusetts area reported reduced heart rate variability (well-documented risk factor for cardiac disease) of 11.5% (95% CI: 0.4–21.3) with a 2.6 µg m⁻³ increment in the previous 4-h average of O₃, being the effect stronger in men with ischemic heart disease and hypertension (Park et al., 2004). Furthermore, another study performed

in the Boston area reported an increased risk of arrhythmia in patients who had implanted defibrillators, associated with short-term increases in ambient O₃ (Rich et al., 2005) with an OR of 2.1 (95% CI: 1.2–3.5) for a 44 µg m⁻³ increase in O₃ concentration during the hour before the arrhythmia. A more recent study (Weichen- thal et al., 2011) conducted a crossover study to examine the relationship between traffic pollution and acute changes in heart rate variability of cyclists, concluding that short-term exposures to O₃ may contribute to altered autonomic modulation of the heart immediately after cycling. These studies provided biological likelihood for the associations between morbidity and mortality due to cardiac problems and O₃ level. Nevertheless, according to WHO 10 out of 15 studies focusing on cardiovascular diseases showed no significant effects of O₃ (WHO, 2006) and there was no clear positive effect of O₃ on any of the particular outcomes evaluated in those studies (myocardial infarction, sudden death, stroke, congestive heart failure and peripheral arterial diseases). Still, in Asia, O₃ was associated with mortality due to stroke (WHO, 2006).

Evidence for O₃ chronic effects has also been increasing in the last decades (McDonnell et al., 1999; Binková et al., 2004). Preferably, a long-term assessment of O₃ effects in humans should include epidemiological studies investigating cumulative O₃ exposure in association with three types of health outcomes, namely, lung function reduction, development of atherosclerosis, death or reduction on life expectancy and increase of asthma (WHO, 2008). Measures of lung function have most often been used as an objective early marker of chronic pulmonary effects. Several studies have shown associations between O₃ exposure and small airway function and seasonal changes on lung function growth (WHO, 2006). The epidemiologic data, collectively, indicate that the current evidence is suggestive but inconclusive for respiratory health effects from long-term O₃ exposure (USEPA, 2006). The development of atherosclerosis was also studied, but the association with long-term O₃ exposure is not yet quite clear (WHO, 2006). Several studies have reported associations between long-term O₃ concentrations and death rates, being, nevertheless, inconsistent. Recent cohort studies have associated “warm-weather O₃” and cardiopulmonary mortality, with a RR of 1.08 (95% CI: 1.01–1.16) and a significantly “protective” association for lung cancer (HEI, 2000). A cohort from the American Cancer Association observed increased mortality from cardiopulmonary diseases but not lung cancer associated with long-term summertime exposure to O₃ (Pope et al., 2002). In the 15-year follow-up of the Adventist Health Study of Smog (AHSMOG), lung cancer was significantly associated with O₃ level among men; associations were positive for other causes of death but not statistically significant (McDonnell et al., 1999). Nevertheless, cohort studies include, at least in theory, both chronic and acute effects. Thus effects observed in cohort studies may not necessarily be solely due to chronic effects (WHO, 2008).

4.1. Impact on childhood asthma

Several studies have been conducted regarding the association of O₃ and respiratory problems in children, where asthma exacerbation is usually the focus of study. Gent et al. (2003) examined during 6 months (from April 1 through September 30, 2001), the simultaneous effect of O₃ and PM_{2.5} at levels below USEPA standards, on daily respiratory symptoms and rescue medication use. The study was performed considering 271 asthmatic children younger than 12 years old and living in Massachusetts. Levels for O₃ were 118 µg m⁻³ (maximum 1-h average) and 102 µg m⁻³ (8-h average) and for PM_{2.5} was 13 µg m⁻³ (24-h average). It was concluded that even for O₃ levels below US EPA standards (controlling for fine particle concentration), the children with severe asthma had a significantly increased risk of worsening the respiratory

symptoms. Triche et al. (2006) examined respiratory effects of O_3 in infants with asthmatic mothers. The study enrolled 780 women delivering babies between 1994 and 1996 at south-western Virginia. After excluding those influenced by environmental tobacco smoke, 691 infants were followed between 10 June and 31 August 1995 and/or 10 June and 31 August 1996. Measurements of O_3 (24-h average, peak 1-h and maximum 8-h running average), $PM_{2.5}$ and PM_{10} (both 24-h average) were performed. The 24-h average O_3 concentration was $70.4 \mu g m^{-3}$. Average concentration of both maximum daily 8-h running averages ($109 \mu g m^{-3}$) and daily 1-h peak ($121.6 \mu g m^{-3}$) for the period studied were below the US EPA standards. The average concentration of $PM_{2.5}$ ($23.2 \mu g m^{-3}$) was also below the US EPA standard. Models relating O_3 and respiratory symptoms were developed controlling temperature, humidity, $PM_{2.5}$ and coarse particles. It was concluded that even at low levels of O_3 exposure, infants had a significantly increased risk of worsening respiratory symptoms, particularly if their mothers have a history of physician-diagnosed asthma. Mar and Koenig (2009) also performed a study concerning the influence of O_3 and asthma hospitalizations in Seattle, Washington from 1998 to 2002. It were observed associations between both O_3 metrics and emergency department visits in children. For the maximum daily 1- and 8-h average O_3 concentrations, the RRs were 1.08 (95% CI, 1.00–1.18) and 1.11 (95% CI, 1.02–1.21), respectively, at 3 d lag. Lin et al. (2008) investigated the impact of chronic exposure to high O_3 levels on childhood asthma admissions in New York State, by following a birth cohort born in New York State during 1995–1999 to first asthma admission or until December 2000. Asthma admissions were significantly associated with increased O_3 levels for all chronic exposure indicators (OR 1.16–1.68), with a positive dose–response relationship. Stronger associations were found among younger children and low sociodemographic groups. On the contrary, Samoli et al. (2011) that investigated the short-term effects of O_3 on paediatric asthma emergency in Athens, Greece over the period 2001–2004, reported a statistically significant association of O_3 with the increase of asthma admissions among older children in the summer. On the contrary, Silverman and Ito (2010) investigated the relationship between severe asthma morbidity and O_3 in the warm season (April to August) in New York City. Results showed that age was a significant effect modifier for hospitalizations, and children age 6–18 years consistently had the highest risk. For each $44 \mu g m^{-3}$ increase in O_3 , there was a 19% (95% CI, 1–40%) increased risk for intensive care unit admissions and a 20% (95% CI, 11–29%) increased risk for general hospitalizations. In the Weichenthal et al. (2011) study, to examine the relationship between traffic pollution and respiratory function in urban cyclists O_3 was not associated with significant changes in the respiratory outcomes.

In general there is little evidence that O_3 is responsible for the increase in the number of children developing asthma symptoms (asthma prevalence) (EEA, 2005). Additionally, the comparison between studies is most times a difficult task, because the criteria for analysis are not conveniently established; previous studies considered different criteria, namely concerning the parameters selected for asthma identification, the presence of other pollutants, the age of the children, the exposure assessment and others like the confounding effects of environmental tobacco smoke, and the study power. McConnell et al. (2010) evaluated the relationship of new-onset asthma with traffic-related pollution near homes and schools. In this study, parent-reported physician diagnosis of new-onset asthma was identified during 3 years of follow-up of a cohort of 2497 kindergarten and first-grade children who were asthma- and wheezing-free at study entry into the Southern California Children's Health Study. Traffic-related pollution exposure was assessed based on a line source dispersion model of traffic volume, distance from home and school and local meteorology. This

Southern California did not find evidence for main effects of regional O_3 with asthma, consistent with results from previous analyses in older Children's Health Study cohorts, although the authors have previously shown that O_3 modified the effect of outdoor exercise in a genetically susceptible subgroup (McConnell et al., 2002; 2010). Moreover, Clark et al. (2010) investigated the effect of exposure to ambient air pollution in utero and during the first year of life on risk of subsequent asthma diagnosis in a population-based nested case-control study with children born in south-western British Columbia in 1999 and 2000 ($n = 37\ 401$) for incidence of asthma diagnosis up to 3–4 years of age using outpatient and hospitalization records. Exposure to ambient air pollution for the gestational period and first year of life using high-resolution pollution surfaces derived from regulatory monitoring data as well as land use regression models adjusted for temporal variation. For a $10 \mu g m^{-3}$ increase on O_3 concentrations a protective effect was observed (in utero OR: 0.83, 95% CI: 0.77–0.89; first-year exposure OR: 0.81, 95% CI: 0.74–0.87) (Clark et al., 2010). On the contrary, Akinbami et al. (2010) that aimed to assess the association between chronic O_3 exposure and childhood asthma among children aged 3–17 years old living metropolitan areas across the United States, concluded that children living in areas with higher O_3 concentrations were more likely to have asthma 1.56 (95% CI: 1.15–2.10). This study included children sampled in the 2001–2004 National Health Interview Survey ($N = 34\ 073$). O_3 levels (12-month average) were compiled by county for 2000–2004. The association between O_3 and childhood asthma outcomes described in local areas and/or for acute exposures is also seen in this cross-sectional study of chronic exposure in US metropolitan areas (Akinbami et al., 2010).

Also Ho et al. (2007) that investigated the relationship of air pollution and weather to adolescent asthma prevalence and attack rate, found association between asthma prevalence and O_3 . The association between O_3 and the prevalence of asthma symptom wheezing was assessed by Kim et al. (2011) in Korea, which conducted a prospective survey during a 2-year period on 1340 children selected from metropolitan cities and industrial areas. O_3 exposure was significantly associated with the 12-month prevalence of wheeze (OR per $10 \mu g m^{-3}$: 1.372; 95% CI: 1.016–1.852).

Also the differences in the prevalence of asthma in children living in rural and non-rural environments have been target of study; however, different conclusions have been achieved.

Priftis et al. (2007) compared, over a period of 8 years, the respiratory health of schoolchildren living at urban (478 children) and rural (342 children) areas, through the assessment of parent completed questionnaire (performed in three phases: 1995/1996; 1999/2000; and 2003/2004) and also by evaluating spirometry indices in the two first phases; concentrations of NO_2 , SO_2 , O_3 and PM_{10} were recorded, the annual average concentrations being: (i) for NO_2 , $31\text{--}42 \mu g m^{-3}$ (urban) and $4\text{--}15 \mu g m^{-3}$ (rural); (ii) for SO_2 , $10\text{--}19 \mu g m^{-3}$ (urban) and $3\text{--}10 \mu g m^{-3}$ (rural); (iii) for O_3 , $60\text{--}80 \mu g m^{-3}$ (urban) and $40\text{--}70 \mu g m^{-3}$ (rural); and (iv) for PM_{10} , $55 \mu g m^{-3}$ (urban, 2001) and $68 \mu g m^{-3}$ (urban, 2002); the rates of wheezing for children living in urban and rural areas were similar and remained so for the eight studied years; children living at rural areas had lower forced vital capacity (FVC) in the first phase and higher forced expiratory flow over the mid-range of expiration ($FEF_{25\text{--}75\%}$) in both phases; this study concluded that in Greece, urban living with long-term exposure to outdoor air pollutants did not result in an increased prevalence of asthma among schoolchildren. The International Study of Asthma and Allergies in Childhood (ISAAC) was created to maximize the value of epidemiological research into asthma and allergic diseases in children by establishing a standardized methodology and facilitating international collaboration (Asher et al., 1995). This study has been trying to estimate childhood asthma prevalence over 50 countries. Com-

parisons between rural and urban environments have been also performed. Results have already shown that asthma prevalence has been growing in countries like Scotland, Finland, Australia, Korea, Holland, Norway and Portugal (Barros et al., 1999; Chrischilles et al., 2004; Kim et al., 2011; SPAIC, 2011).

Few other studies have addressed the long-term effects of O₃ on lung function in children, and results have been inconsistent (Gauderman et al., 2004; Clark et al., 2010). Gauderman et al. (2004) recruited 1759 children with 10 years old in average, from 12 schools in southern Californian communities and measured air pollutant concentration and lung function annually for 8 years; the annual average concentrations of air pollutants in the different communities, from 1994 to 2000 were: (i) for O₃ 60–130 µg m⁻³; (ii) for NO₂ 8–75 µg m⁻³; (iii) for PM₁₀ 15–65 µg m⁻³; and (iv) for PM_{2.5} between 5 and 28 µg m⁻³; results of the study provided evidence that lung development, measured by the growth in FVC, forced expiratory volume in the 1st second (FEV₁) and maximal mid-expiratory flow (MMEF), is reduced in children with ages between 10 and 18 years old exposed to higher levels of air pollution.

These and other studies relating lung function and air pollution mixtures could not discern the independent effects of pollutants because of their common sources and the degree of correlation between them (Jedrychowski et al., 1999; Peters et al., 1999; Gauderman et al., 2004; Lewis et al., 2005). Sousa et al. (2011b) reported a study in which the influence of O₃ on childhood asthma was evaluated without the confounding effects of other pollutants. In the first phase (Sousa et al., 2008) O₃ concentrations at six rural areas were compared with those at an urban area influenced by traffic emissions; the influence of nitrogen oxides and volatile organic compounds on O₃ concentrations was also evaluated. All rural areas had very high O₃ concentrations and very low concentrations of other pollutants (Sousa et al., 2008). One of those areas was selected to evaluate the specific impact of O₃ on childhood asthma without the confounding effects of other pollutants. In a second phase asthma prevalence was evaluated through the assessment of questionnaires (Sousa et al., 2009a); the prevalence rate of asthma in children living at the selected area with high O₃ concentrations (exposed area) was compared with that of children living at one area with similar geography and meteorology, but low concentrations of O₃ and of other pollutants (unexposed area). Concerning children, similar lifestyle, diet, socio economic status and exposure to indoor pollutants were also found at both areas, meaning that the main difference between the exposed and the unexposed areas was related with O₃ concentrations; therefore, it was possible to evaluate the specific impact of O₃ on asthma prevalence. In the third phase (Sousa et al., 2011b) the prevalence of childhood asthma was evaluated through lung function tests, validating the previously estimated one assessed through questionnaires, and was compared to the prevalence reported at an unexposed area (with low O₃ concentrations), aiming to evaluate the influence of exposure to high O₃ levels. It was concluded that children living at the area mainly polluted by O₃ had a 3 times higher risk (RR 2.84; OR 3.02) of having asthma than those living at the area without O₃ influence. Nevertheless, no causative role could be withdrawn for this study, so research in this field is still a very emerging issue.

5. Concluding remarks

The health effects of O₃ have been interesting a great number of researchers all over the world. Short-term exposures to high ozone concentrations have been proven to affect asthmatic children. Concerning long-term effects, namely the development of childhood asthma, causality is still to prove, although, a great number of epidemiological studies have been confirming the influence of ozone

exposure in the development of asthma. Studies have been demonstrating strong associations between the exposure to ozone and asthma. The complexity of exposure patterns, the changes in the vulnerability of children at various stages of development, and the practical limitations of research, lead to a still incomplete understanding of the ozone impact on the health of children. Difficulties on the interpretation of epidemiological studies to evaluate chronic effects are mainly due to an absence of studies designed specifically to address this question and to inherent limitations in characterizing exposure. The more rigorous studies provided new evidences for chronic effects of ozone on small airway function and possibly on asthma, but substantial uncertainties remain.

Future research should include more epidemiological studies specifically designed to investigate ozone association with childhood asthma, considering criteria already established to help in the comparison. Also, a high study power would help in the understanding of the effects. The necessity to support causality could be fulfilled by performing clinical studies.

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