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The effects of ozone on human health

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Abstract Ozone is a highly reactive, oxidative gas associated with adverse health outcome, including mortality and morbidity. Data from monitoring sites worldwide show levels of ozone often exceeding EU legislation threshold and the more restrictive WHO guidelines for the protection of human health. Well-established evidence has been produced for short-term effects, especially on respiratory and cardiovascular systems, associated to ozone exposure. Less conclusive is the evidence for long-term effects, reporting suggestive associations with respiratory mortality, new-onset asthma in children and increased respiratory symptom effects in asthmatics. The growing epidemiological evidence and the increasing availability of routinely collected data on air pollutant concentrations and health statistics allow to produce robust estimates in health impact assessment routine. Most recent estimates indicate that in 2013 in EU-28, 16,000 premature deaths, equivalent to 192,000 years of life lost, are attributable to ozone exposure. Italy shows very high health impact estimates among EU countries, reporting 3380 premature deaths and 61 years of life lost (per 100,000 inhabitants) attributable to ozone exposure.

Keywords Air pollution · Oxidative stress · Respiratory diseases · Health impact assessment · Mortality · Morbidity · Susceptible groups

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Introduction

Outdoor air pollution is a mixture of particles and gases and has been extensively associated with a series of acute and chronic health effects. A relevant component of this harmful mixture of pollutants is ozone.

In the recently published Global Burden of Disease (GBD) Study, Forouzanfar and GBD Risk Factors Collaborators (2016) reported 4.1 million disability-adjusted life years (DALYs) attributable to ozone exposure in 2015. DALYs are common metrics used in epidemiology to quantify the disease burden and are calculated as the number of years lost due to ill health, disability or early death. The GBD Study 2015 is the most extensive and updated research on the evidence for attributable deaths, DALYs and trends in exposure for many individual and environmental factors from 1990 to 2015.

Ozone is naturally present in the stratosphere, and it plays a vital role for life system against the ultraviolet radiation from the sun. In the troposphere, it is classified as a secondary pollutant because it is not directly emitted, but it is formed through chemical reactions from precursors. Ozone has two main primary precursors, volatile organic compounds (VOCs), including alkanes, alkenes, aromatic hydrocarbons, carbonyl compounds, alcohols, organic peroxides and halogenated organic compounds, and nitrogen oxides (NOx), and reactions among them occur in the presence of sunlight. Other important elements involved in ozone formation are carbon monoxide and methane (EPA 2012, 2015; WHO 2006).

The chemical reactions start with the oxidation of VOC or CO and the formation of organic (RO2) or peroxy (HO_2) radicals, which react with NO to give NO_2. This is, in turn, photolysed to give a ground-state oxygen atom, O(3P), and through reaction with molecular oxygen, a molecule of ozone is formed. The primary source of OH radicals in the

atmosphere is the reaction of electronically excited O atoms with water vapour. Ozone levels are synthesized in a complex and non-linear relation with the concentrations of its precursors, and the processes involved are influenced by various factors, such as the concentrations of precursors, the atmospheric mixing, the intensity and spectral distribution of sunlight and the processing on cloud and aerosol particles (EPA 2012; WHO 2008). Two main regimes have been extensively described: low and high NOX regimes. When NOX concentrations are low, as it occurs in continental, rural and suburban areas, the formation of ozone typically increases with increasing NOX levels, and it is substantially independent from VOC levels. In high-NOx regimes, also called VOC-sensitive regimes, observed in urban areas, close to busy streets, or in industrial areas, ozone concentrations decrease with increasing NOx and increase with increasing VOCs. In this regime, NO_2 reacts and eliminates OH radicals which would otherwise oxidize VOCs to produce peroxy radicals. In these conditions, the ozone formation processes are thus influenced by the availability of free radicals. The production of free radicals is also dependent on the availability of solar radiation and/or on the concentrations of VOCs (EPA 2012; WHO 2008).

All these processes also lead to the formation of other photochemical products, such as peroxyacetyl nitrate, nitric acid and sulfuric acid, and to other compounds, such as formaldehyde and other carbonyl compounds.

Ozone precursors are emitted by natural and anthropogenic sources. Natural sources comprise biogenic emissions from vegetation, microbes and animals and abiotic emissions from biomass burning and lightning. Ozone precursors have a wide range of stationary and mobile anthropogenic sources, such as motor vehicle exhausts, industrial emissions and chemical solvents.

This critical review is made of two main sections. The first one provides an overview of the principal proposed mechanisms of action when inhaled ozone enters the respiratory tracts and a synthesis of the updated evidence of acute and chronic effects which has been associated to ozone exposure. The second section focuses on health impact assessment (HIA). In this framework, basing on the available knowledge on European air quality data, population exposed, background mortality and morbidity data and consistent evidence on the health effects reviewed in the first section, the most updated health impact estimates, in terms of mortality and morbidity, attributable to ozone exposure, are presented. A focus on the Italian situation is shown, too.

Toxicity of ozone

Ozone is a high reactive, oxidative gas with a low solubility in water. Because of its chemical characteristics, exposure to ozone occurs almost exclusively by inhalation. Some studies have reported effects in the tear duct epithelial cells of individuals exposed to ambient ozone levels (Rojas et al. 2000) and in the skin of laboratory animals exposed to high levels of ozone (Valacchi et al. 2004). However, findings from experimental studies suggest that absorption of ozone does not occur in innermost compartments of dermis, and it is likely that effects on skin are restricted to the upper layers of the dermis.

After inhalation, ozone is mostly absorbed by the upper respiratory tract and conducted in intrathoracic airways (Bush et al. 1996; Sarangapani et al. 2003). Since oral inhalation allows lower ozone removal rates than nasal inhalation, vigorous physical activity leads to higher penetration into the lung. Other factors that influence ozone absorption are age and gender: higher levels of absorption are observed in children and women, because of variations in airway size (Bush et al. 1996). Bell et al. (2014) recently reviewed the role of main susceptibility and vulnerability factors which may influence ozone-related health effects, such as gender, age, socioeconomic status and occupation. According to the authors, age is the most robust susceptibility factor, with elderly reporting major health risks related to ozone exposure. Limited or suggestive evidence was found for gender and occupation, with higher risks among women and people with unemployment or lower occupational status. No significant results were observed in studies focusing on ethnic minorities, persons with low education and availability of air conditioning.

Because of its low solubility in water, ozone is not effectively removed by the upper respiratory tract. Consequently, the major part of inhaled ozone reaches the lower respiratory tract and dissolves in the thin layer of epithelial lining fluid (ELF). The ELF comprises a complex mixture of proteins, lipids and antioxidants which play the fundamental protection against pathogens and foreign substances. Consequently to the reactions of ozone with these ELF components, various products with different reactivity (i.e. secondary oxidation products) are formed. The quantity of ozone reaching the tissues is influenced by the thickness of the ELF and of the mucus layer: a thicker ELF generally leads to lower doses of ozone to the tissues. Additionally, the formation of secondary oxidation products is strictly dependent on the quantity of antioxidants and other substances in the ELF. These processes reduce the reactions of ozone with underlying tissues and the penetration into the respiratory tract.

The oxidative stress induced by the secondary oxidation products may cause cellular injury and altered cell signalling in the respiratory tract. These secondary products are also responsible of the inflammatory cascade following exposure to ozone. Various studies have indicated chemokines and cytokines, eicosanoids, vascular endothelial adhesion molecules and tachykinins in mediating this response. Some other key pathways have been described as mode of action of ozone in the respiratory tract, which include the activation of neural reflexes, the initiation of inflammation, the alterations of

epithelial barrier function, the sensitization of bronchial smooth muscle, the modification of innate and adaptive immunity and airway remodelling.

Subjects with pre-existing pulmonary disease, such as chronic bronchitis, asthma or emphysema, show increased risks for ozone-related health effects because of the differences in the quantity of absorbed ozone. Thus, toxicity of ozone depends on a wide range of factors, and there is a great variability of individual responses to any given ground-level ozone concentration.

Acute health effects

There is a very large volume of literature focusing on the acute effects of ozone exposure. It has been extensively reviewed by WHO in recent years (WHO 2004, 2006, 2013a, b). As with other air pollutants' exposure, severity of health effects and number of people affected may be represented through a pyramid.

Less severe health conditions, at the bottom of the pyramid, affect the majority of people, whereas most serious endpoints, such as death or hospital admission, at the top of the pyramid, are experienced by fewer persons (Fig. 1).

Mortality

Major contribution to the evidence on the effects of short-term exposure to ozone relative to mortality has been provided by two large recent multicentre studies: the Air Pollution and Health: a European and North American Approach (APHENA) study (Katsouyanni et al. 2009) and the Public Health and Air Pollution in Asia (PAPA) study (HEI 2010, 2011; Wong and Health Review Committee 2010).

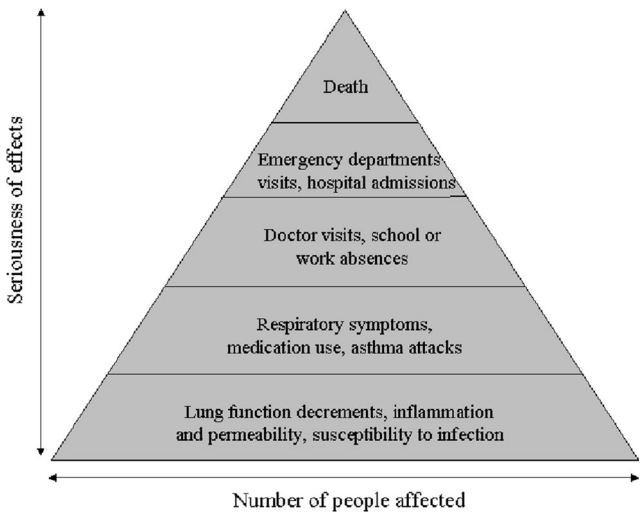


Fig. 1 Pyramid of health effects caused by ozone

The APHENA project is an extensive network of researchers participating to multicity European APHEA project, to the US National Morbidity, Mortality and Air Pollution Study (NMMAPS) study and to the multicity Canadian study. The APHENA study pooled data from 12 cities in Canada, 90 in the USA and 32 in Europe in order to evaluate the coherence of multiple time series studies and to produce a robust estimate of the relation between ozone increases and mortality.

The PAPA study also applied a standardized protocol in all locations, to collect data and perform statistical analyses, pooling results from six large Asian cities (Bangkok, Hong Kong Special Administrative Region, Shanghai, Wuhan, Chennai and Delhi).

Other recent European studies have been conducted in England and Wales (Pattenden et al. 2010), France (Lefranc et al. 2009), Italy (Stafoggia et al. 2010), Spain (Ballester et al. 2006) and Greece (Kassomenos et al. 2012).

Peng et al. (2013) published the statistical methods used for the re-analyses of APHENA data, using and comparing various methods, such as natural spline (ns), penalized regression spline (ps) and various degrees of freedom (dfs), in order to remove long-term trends and time-dependent confounders. Results of these re-analyses are shown in Fig. 2.

Overall, authors estimated an excess of mortality risk of 0.26% (95% CI 0.15–0.37%) related with a 10 μg/m^3 increase in 1-h daily maximum ozone. Among all models applied, the strongest effect estimate resulted from model using natural splines and 8 df per year. Results from European and US studies were similar, whereas those from Canada showed higher risk estimates. Authors hypothesized some explanations of this different pattern, including the influence of other co-varying pollutants, and the residual confounding in the Canadian data from unmeasured seasonal or meteorological factors. Authors also discussed about the role of the availability of more accurate exposure and outcome data in Canada, as compared with the European countries and the USA, but the authors themselves stated that this explanation seems unlikely, and they do not provide any data to pursue this conjecture. Authors concluded that the re-analyses of APHENA data confirmed ozone-related acute mortality risk previously reported and that the implementation of an extensive statistical protocol leads to a robustness of results to the method of data analysis.

Pulmonary system effects

Many experimental studies focused on the acute effects of ozone exposure relative to respiratory health. The relation exposure-respiratory outcome was investigated at various conditions, such as controlled exposures at rest or during exercise, exposures at ambient levels and in subjects with pre-existing pulmonary diseases, such as asthma or chronic bronchitis. Human studies have the main advantage to avoid the need of extrapolating results from experimental studies

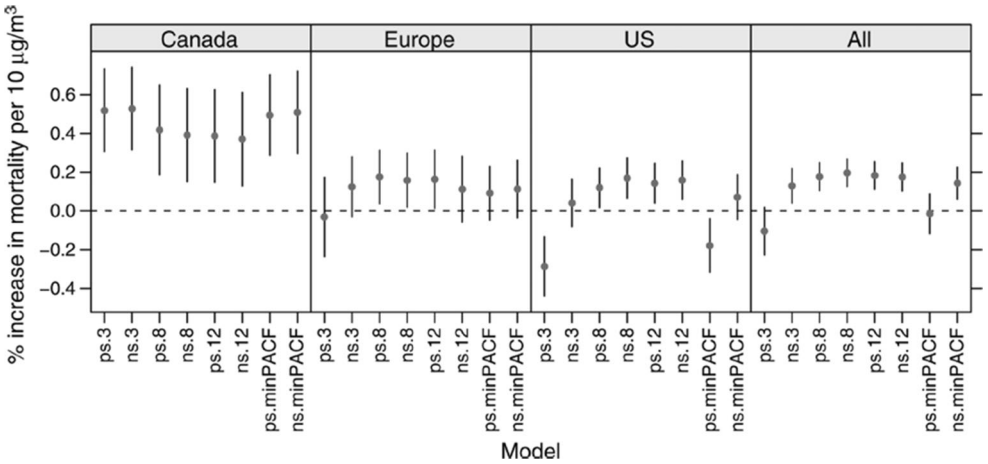


Fig. 2 Effects of a 10 μg/m^3 increase on mortality. *NS* natural spline, *PS* penalized regression spline, *PACF* partial autocorrelation function (source: Peng et al. 2013)

conducted in animals or in vitro, which generally use very high level of pollutant to evaluate underlying biological mechanisms.

The induction of transient decrements in lung function is one of the most studied respiratory acute end-points. Studies were more frequently conducted in healthy young subjects, usually non-smokers, exposed to a wide range of ozone levels (40–600 ppb[1]), during physical activity (McDonnell et al. 2012; EPA 2012). Since the 2005 WHO global update of the air quality guidelines (WHO 2006), a growing scientific interest was addressed to produce predictive models for lung function decrements (FEV1) related to inhaled ozone dose, with the aim to evaluate risk and produce response thresholds (McDonnell et al. 2012; Schelegle et al. 2009). Main results show that subjects exposed to high outdoor ozone levels (outdoor workers, children in summer camps, exercising adults), but lower than those used in chamber studies, experience acute lung function decrements (Kinney et al. 1996; Brunekreef et al. 1994; Thaller et al. 2008; Chan and Wu 2005).

Results from epidemiological studies show robust, positive and significant associations between fluctuations in ambient ozone levels and increased morbidity. The most frequently studied health end-points or proxy of them are hospital admissions or emergency department visits for asthma, respiratory tract infections and exacerbation of other respiratory diseases, school absenteeism. The effects were frequently observed in children, elderly people, asthmatics and subjects with chronic obstructive pulmonary disease (COPD), and during warmer months. As in mortality studies, there are large multicity analyses relating variations of ozone levels with the hospital admissions for respiratory diseases (Burnett et al. 1997; Anderson et al. 1997). Such associations are still significative when introducing in the models' time-related variables, such as day of the week, seasonal effects, other air pollutants and meteorological factors.

[1] 1 ppb = 1.96 μg/m^3 at standard temperature and pressure

Cardiovascular system effects

Results from experimental studies on animals have produced some evidence for cardiovascular effects of ozone, such as increased heart rate and diastolic pressure, vascular oxidative stress, inflammation and decreased heart rate variability (Chuang et al. 2009; Perepu et al. 2010; Tankersley et al. 2010). On the other hand, experimental studies on human are less conclusive and have provided inconsistent associations with ozone (Kusha et al. 2012; Fakhri et al. 2009; Rudez et al. 2009; Thompson et al. 2010; Chuang et al. 2007; Liao et al. 2005; Steinvil et al. 2008).

Park et al. (2005) conducted a study on 603 men in the Boston area who participated in the Veterans Administration Normative Ageing Study. Electrocardiographic monitoring was performed, including measurement of heart rate variability (HRV). Authors observed a 11.5% (95% CI 0.4–21.3) reduction of low-frequency HRV associated to 2.6 μg/m^3 ozone increase in the previous 4 h, and stronger effects resulted in men affected by ischemic heart disease and hypertension.

Rich et al. (2006) followed patients with implanted defibrillators in the Boston area and observed an increased risk (OR = 2.1, 95% CI 1.2–3.5) of paroxysmal atrial fibrillation episodes associated with short-term fluctuations of ozone concentrations.

Observational studies have found positive associations between exposure to ambient ozone and some cardiovascular alterations, such as oxidative stress, inflammation, alteration of heart rate variability, imbalance of autonomic components, arterial pressure control, coagulation and myocardial infarction (Jia et al. 2011; Chuang et al. 2007).

In Italy, Nuvolone et al. (2013) found a 6.3% (95% CI 1.2–11.7%) increase in out-of-hospital coronary deaths for a 10 μg/m^3 increase in ozone, suggesting higher risks for females, elderly and patients previously hospitalized for cerebrovascular and artery diseases.

Zhao et al. (2017) recently reviewed available literature on the impact of short-term exposure to air pollutants on the onset

of out-of-hospital cardiac arrest, and pooled results confirmed the positive and significant association with ozone exposure (RR = 1.016, 95% CI 1.008–1.024).

Chronic health effects

In contrast to the well-established evidence from short-term studies, evidence for the chronic effects of ozone is less conclusive. Epidemiological studies face with some methodological limitations, mostly in long-term exposure assessment, and there is a lack of studies specifically designed to evaluate the long-term effects of ozone exposure. The most robust association observed in well-designed approaches focuses on the effects on asthma and asthma-like symptoms. However, further investigations are needed to better describe relationship between ozone and chronic health end-points.

Death or reduction of life expectancy, effects on lung function and atherosclerosis and the onset of asthma are the most common health outcome taken into account in studies aiming to assess the health effects of long-term exposure to ozone.

In the 2005 WHO global update of air quality guidelines (WHO 2006), experts reported sufficient evidence only for a short-term effect of ozone on mortality. In large studies conducted in USA, such as a study from California, the Loma Linda University Adventist Health and Smog (AHSMOG) study (Abbey et al. 1999) and a re-analysis of the US Veterans study (Lipfert et al. 2006), no statistically significant relation between long-term ozone exposure and mortality was reported.

But since 2005, results from several cohort studies conducted in recent years provided a suggestive association between long-term exposure and mortality, mostly respiratory and cardiorespiratory mortality and in people affected by predisposing conditions (Lipfert et al. 2006; Krewski et al. 2009; Jerrett et al. 2009; Smith et al. 2009; Zanobetti and Schwartz 2011). The American Cancer Society Cancer Prevention Study II (CPS II) was the most informative and relevant study on this issue. The CPS II cohort study enrolled more than 1.2 million participants between September 1982 and February 1983 in all 50 US states. A questionnaire on demographic characteristics, smoking habits and history, alcohol, diet, education and other individual information was administered. Findings reported a statistically significant association between long-term exposure to ozone and total mortality. Risk estimates were stronger for cardiopulmonary mortality (Krewski 2009). However, some uncertainty in interpreting these results is caused by the interaction between ozone and $PM_{2.5}$ levels, and it is not too easy to separate specific effects of the two pollutants. In a further analysis, in which robust adjustment methods were applied, long-term exposure to ozone remains associated only to respiratory mortality (Jerrett et al. 2009).

Atkinson et al. (2016) recently published a systematic review of the effects of ozone on long-term mortality. Authors highlighted the lack of population-based studies addressing this question: studies are predominantly conducted in USA, and epidemiological evidence is based mostly on the American Cancer Society CPS II cohort study. However, authors concluded that available findings report a suggestive, positive association between long-term ozone exposure, especially during warmer months, and cardiopulmonary and respiratory mortality.

No clear and consistent findings have been reported for the long-term effects on lung function. As regards to toxicological studies, the extrapolation of data observed in experimental studies on rodents is complicated by some qualitative and quantitative sources of uncertainty, such as the differences between rodent and human respiratory physiology, cellular makeup, dosimetry and morphometry (EPA 2012). However, studies conducted on non-human primates allow better interpretation of results because of the similarity between primates and human respiratory system. A wide range of studies conducted by Poppler and colleagues using primates have shown a clear relation between exposure to ozone concentrations and changes in airway morphology and pulmonary function (Schelegle et al. 2003; Larson et al. 2004; Plopper et al. 2007; Fanucchi et al. 2006; Reiser et al. 1987). Among epidemiological studies, one of the most well-designed study was the Children's Health Study, which was conducted in 12 cohorts from communities in southern California (Peters et al. 1999). Authors reported significant associations between lung function and ozone annual means only among children spending more time outdoors. The lung function growth rates resulted significantly associated with a series of common pollutants in urban areas, such as $PM_{2.5}$ and nitrogen dioxide, but exposure to ozone did not provide any conclusive results (Gauderman et al. 2000, 2002, 2004). Other two studies performed by the University of California at Berkeley (UCB) reported positive results. University freshmen who had lived all their lives in California were enrolled, and for each participant, a long-term exposure was estimated (Künzli et al. 1997; Tager et al. 2005). Both studies reported consistent and significant associations between reduced airway function and long-term ozone exposure. Galizia and Kinney (1999) carried out a similar study, as regards to design and exposure assessment, on Yale college freshmen who had different residential histories. Effects on lung function, in terms of FEV1 and FEF25–75, resulted significantly associated with individual long-term ozone exposure. Another study in Europe by Ihorst et al. (2004) collected data on lung function measurements twice a year on 2153 schoolchildren in 15 towns in Austria and Germany. Authors highlighted a suggestive association between ozone exposure and seasonal changes in lung function growth. However, these changes were not observed over 3.5 years probably because of the partial reversibility of the effects or the relatively low levels of ozone.

A recent systematic review (Götschi et al. 2008) and a conference report on the evidence of health effects of ozone by McClellan et al. (2009) do not provide any conclusive results for lung function effects due to long-term ozone exposure.

As regards to atherosclerosis, one of the common biomarkers used in studies investigating the effects of pollutants is the carotid intima-media thickness (CIMT) (Künzli et al. 2005). In a cross-sectional study conducted in Los Angeles, CIMT resulted significantly associated with residential outdoor $PM_{2.5}$ levels, whereas exposure to ozone provided weak and statistically not significant association (Brook et al. 2002).

In the EPA report "Integrated Science Assessment of Ozone and Related Photochemical Oxidants—Second External Review Draft" (EPA 2012), experts concluded that the strongest epidemiological evidence relating long-term ozone exposure and respiratory morbidity refers to new-onset (new diagnosis) asthma in children and increased respiratory symptom effects in asthmatics. Two large US studies focused on this issue: the Children's Health Study (CHS) (McConnell et al. 2002) and in adults the University Adventist Health and Smog study (AHSMOG) (McDonnell et al. 1999). The CHS study prospectively followed more than 3500 non-asthmatic children aged 9–16 from 1993 to 1998. Overall results did not report a positive association between community mean ozone levels and new diagnosis of asthma. However, in communities with high levels of ozone, authors observed a significant association between developing asthma and the number of outdoor sports, with a relative risk of 3.3 (range 1.9–5.8).

In the AHSMOG study, 3091 non-smoking adults were followed for 15-year follow-up period and a 20-year ozone exposure history was assigned to each participant. Asthma onset resulted significantly associated with long-term ozone increases, with a twofold risk among men, and not among women.

As regards to ozone effects on other biological systems, different from respiratory and cardiovascular, results from toxicological studies suggested associations between exposure to ozone and some effects on central nervous systems, such as alterations in neurotransmitters, motor activity, short-term and long-term memory, sleep patterns and histological signs of neurodegeneration (EPA 2012). Limited evidence has been produced for a relationship between ozone exposure and birth-related health outcomes, including mortality, premature births, low birth weights and birth defects (EPA 2012).

Health impact assessment

HIA is a qualitative and quantitative set of methods useful to evaluate how any policy, programme or project may affect human health. In the framework of the health aspects of air pollution, HIA aims to evaluate health impacts of pollutants' exposure and the improvement in health that might be expected through the implementation of policies aiming to pollutants' reduction.

In order to quantitatively and qualitatively assess the health impacts of air pollutants, four main sets of data are needed: the air pollution levels, the population exposed, the background mortality and morbidity rates and the concentration–response functions (CRFs).

The main steps of a health impact assessment are summarized in Fig. 3.

Air pollution data, limits and guidelines for ozone

The most recent overview of air quality and ozone levels in Europe has been published by the European Environment Agency (EEA) (EEA 2016). The 2008 Ambient Air Quality Directive sets a maximum daily 8-h mean threshold of 120 $\mu g/m^3$ for health protection. The target value is that at each monitoring site, this threshold should not be exceeded more than 25 days per year (corresponding to the 93.2 percentile), calculated on 3-year average period starting from 1 January 2010. The directive also sets a long-term objective: at each station, no exceedance of the threshold value of 120 $\mu g/m^3$ is allowed. According to the well-established

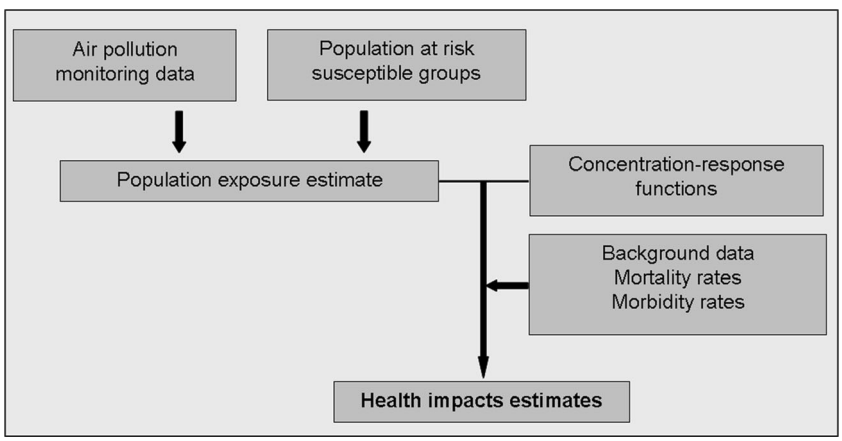


Fig. 3 Main steps of the health impact assessment (source: WHO 2008)

evidence of health effects related to ozone exposure, the more recent WHO Air Quality Guidelines set a more restrictive threshold for ozone, which is a daily maximum 8-h mean concentration of 100 μg/m^3 (WHO 2006).

Figure 4 represents concentration of ozone in 2014 in European countries. The map shows the 93.2 percentile of the ozone maximum daily 8-h mean, representing the 26th highest value. This value is related to the ozone target value, allowing 25 exceedances over the 120 μg/m^3 threshold.

As the formation of ozone occurs in the presence of sunlight, ozone concentrations show a clear geographical trend, with higher values observed in the southern parts of Europe, mostly in some Mediterranean countries. In 2014, in 16 countries of the EU-28 and in 11% of all monitoring stations, ozone levels were above the target value for the protection of human health. However, there was a significant reduction of the exceedences comparing with those observed in 2013. On the other hand, only in 14% of all stations, the long-term objective (no exceedances of the threshold level) was met and conformity with the WHO guidelines for ozone was observed only in fewer than 4% of all stations. WHO guidelines were respected only in 5 of the 503 rural background stations in 2014, 4 in Ireland and 1 in Norway. Luxembourg, Malta and Italy are the three states with the highest 93.2 percentile of the ozone maximum daily 8-h mean (Fig. 5).

Population exposure

Population exposure estimates rely on standardized methods using measured concentrations at stations classified as "urban and suburban background". Pollutant's levels measured at sites classified as "traffic stations" are used for exposure evaluation only for populations living within 100 m of major roads. Information on urban life are derived from Eurostat census statistics. Industrial monitoring sites are excluded from calculations.

In 2014, according to EEA estimates (EEA 2016), about 8% of the EU-28 population in urban areas was exposed to

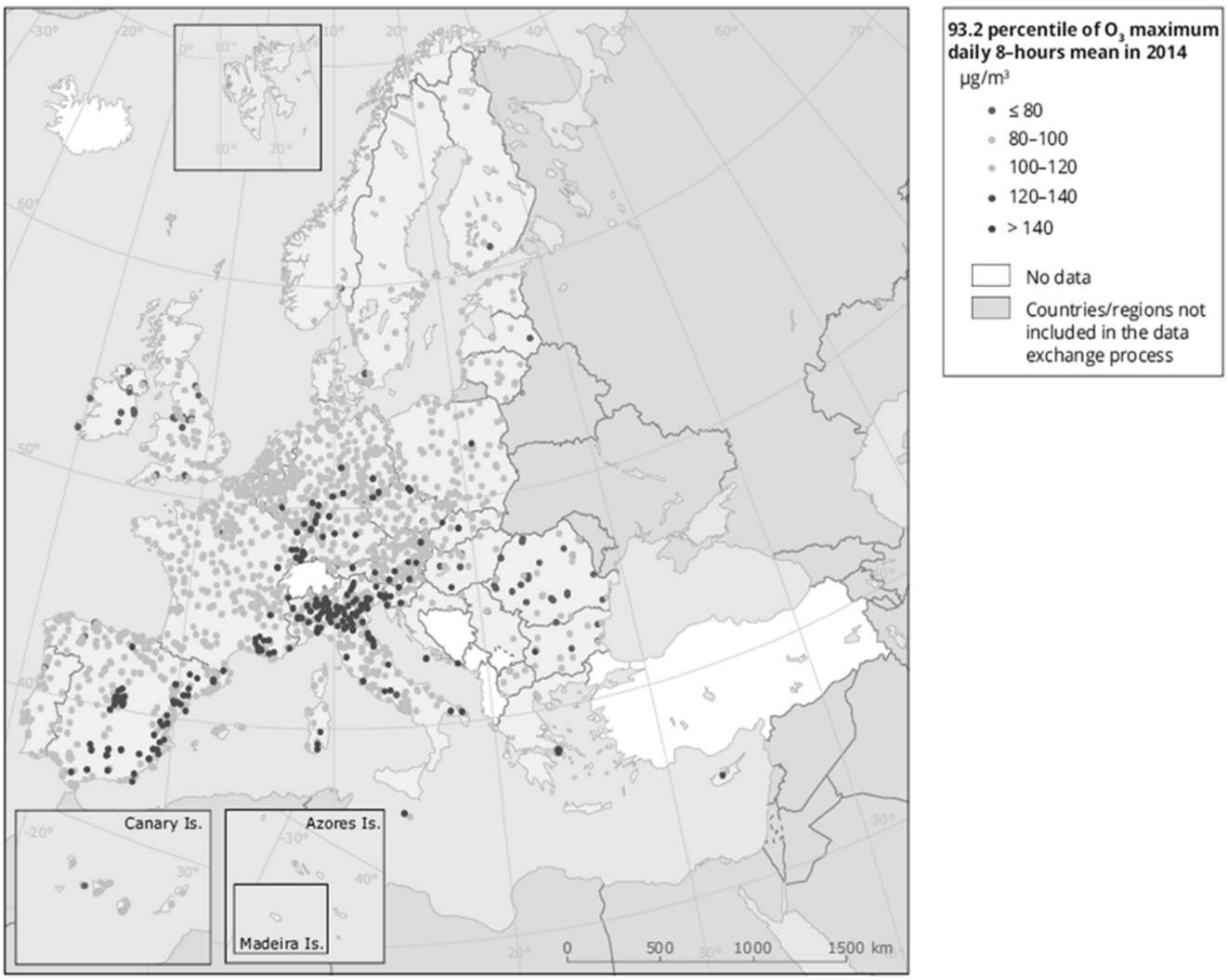
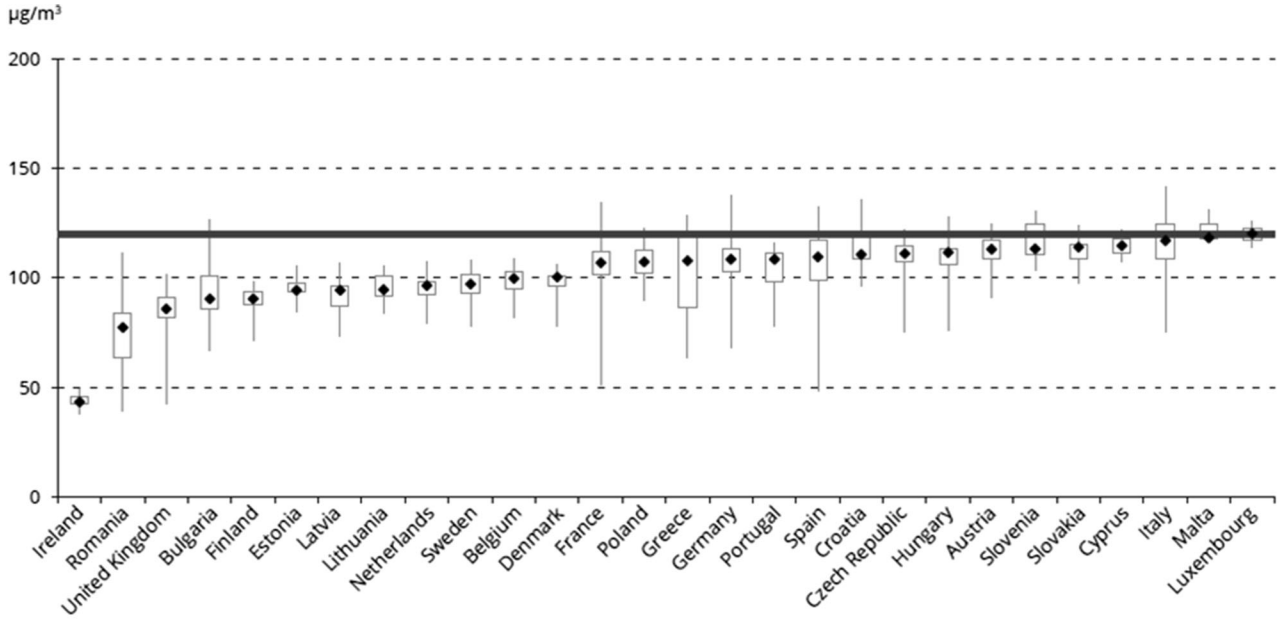


Fig. 4 Concentrations of ozone in 2014 in the EU-28 (source: EEA 2016)



Notes: The graph is based, for each Member State, on the 93.2 percentile of maximum daily 8-hour mean concentration values, corresponding to the 26th highest daily maximum of the running 8-hour mean. For each country, the lowest, highest and median values (in µg/m³) at the stations are given. The rectangles mark the 25th and 75th percentiles. At 25 % of the stations, levels are below the lower percentile; at 25 % of the stations, concentrations are above the upper percentile. The target value threshold set by the EU legislation is marked by the red line.

Source: EEA, 2016a.

Fig. 5 Ozone concentrations in relation to the target value in 2014 in the EU-28 (source: EEA 2016)

ozone concentrations above the EU target value threshold, and about 96% of the total EU-28 urban population was exposed to ozone levels exceeding the WHO AQG, with values ranging between 94 and 99%.

Health impacts

One of the key points in health impact assessment is the selection of health end-points for which impact estimates are produced. The selection of appropriate health end-point is based on the robustness of the available evidence from literature, the availability and accessibility of health data and the relevance of health impact assessment from public health and economic points of view.

The methodology was reviewed by WHO working groups in recent years. In the framework of the European Union declaration of 2013 as the Year of Air, two great multidisciplinary international projects were promoted by the WHO Regional Office for Europe: the "Review of Evidence on Health Aspects of Air Pollution (REVIHAAP)" (WHO 2013a, b) and the "Health Risks of Air Pollution in Europe (HRAPIE)" (WHO 2013b) projects. The aim of these projects was to provide an updated overview of the health consequences of air pollution and standardized methodologies useful to political decision makers and other stakeholders to promote policies for air pollution reduction, in the framework of cost-benefit analyses.

One of the main activities of the WHO working groups was to provide recommended concentration–response functions for common pollutants, such as particulate matter, ozone and nitrogen dioxide. Concentration–response functions are the results of an extensive review of available epidemiological studies, mainly derived from published meta-analyses, from large multicentre studies involving a great number of participating subjects or from single studies whose relevance has been verified from scientific community. They come from statistical models and are generally expressed in terms of the relative risk (RR) for a specified change in pollutant level.

The WHO experts agreed that, following the actual state of knowledge produced by the REVIHAAP project (WHO 2013a, b), for each recommended CRF, there is sufficient evidence for a causal association between pollutant outcome. According to the strength of the causal relation, the WHO experts classified the pollutant–outcome pairs into two groups:

- Group A: comprises the ozone–outcome pairs for which evidence allows a quantitative estimate of effects.
- Group B: comprises the ozone–outcome pairs for which quantitative estimates are affected by more uncertainty.

The recommended concentration–response functions for short-term and long-term ozone exposure are summarized in Table 1 and refer to three main health outcomes: mortality (all causes, respiratory and cardiovascular), hospital admissions for respiratory and cardiovascular diseases and minor restricted activity days (MRADs).

Table 1 Recommended concentration–response functions (CRFs) for ozone exposure (source: WHO 2013b)

Ozone metric	Health outcome	Group	CRF: RR (95% CI) per 10 μg/m^3 ozone increase
Ozone short-term exposure			
O_3 daily maximum 8-h mean	Mortality, all natural causes	A	1.0029 (1.0014–1.0043)
O_3 daily maximum 8-h mean	Mortality, respiratory causes	A	1.0029 (1.0014–1.0043)
O_3 daily maximum 8-h mean	Mortality, cardiovascular causes	A	1.0049 (1.0013–1.0085)
O_3 daily maximum 8-h mean	Hospital admissions, respiratory causes	A	1.0044 (1.0007–1.0083)
O_3 daily maximum 8-h mean	Hospital admissions, cardiovascular causes	A	1.0089 (1.0050–1.0127)
O_3 daily maximum 8-h mean	MRADs	B	1.0154 (1.0060–1.0249)
Ozone long-term exposure			
O_3 summer months (April–September), average of daily maximum 8-h mean over 35 ppb	Mortality, respiratory causes	B	1.014 (1.005–1.024)

RR relative risk, *CI* confidence intervals, *MRADs* minor restricted activity days

The confidence intervals (CIs) associated with the relative risks are a measure of the random error and the variability attributed to heterogeneity in the epidemiologic effect estimates used for health impact assessment. Uncertainty is a relevant issue in health impact assessment. Despite the improvements in new research which are expected to reduce actual uncertainty, any estimate will always be affected by bias. The main issue to be addressed is if the relation between pollutant and health outcome is causal. In observational epidemiological study, researchers evaluate if there is an association between pollutant and outcome, but it is much more difficult to establish if this relation is causal. Other unmeasured factors correlated to the pollutant may play a role in confounding the association under study. However, the uncertainty may be reduced and the probability of a causal relation may be strengthened depending on some factors, such as the strength of the association, the consistency and the internal coherence, the presence of a biological gradient and a dose–response relationship, the biological plausibility, the coherence with previous knowledge and the lack of bias and confounding.

WHO experts agreed that the mortality is the most robust and significant indicator of the overall health effects related to ozone exposure. The evidence produced by a large number of time series studies conducted worldwide in the last decades is strong, and findings show an elevated degree of internal and external coherence towards an association between mortality and short-term exposure to ozone. In the case of mortality, the end-point under study is well defined and it is routinely measured in all countries. Baseline mortality standardized rates are available and comparable worldwide, and the data can be easily accessed. All these conditions are not easily satisfied for other relevant morbidity end-points, such as the number of asthma attacks or the use of drugs for respiratory diseases.

The most recent estimates at European level of mortality indicators attributable to ozone exposure have been produced by EEA (2016). They used two common epidemiological mortality indicators: the "premature deaths", i.e. the deaths that occur before the age of standard life expectancy, and the "years of life lost" (YLLs), which are defined as the years of potential life lost because of premature death (Table 2).

In 2013, across all 41 European countries, 17,000 premature deaths are estimated to be attributable to ozone exposure. In the EU-28, ozone is considered responsible of 16,000 premature deaths. The estimated number of YLLs related to ozone exposure is 192,000 in EU-41 and 179,000 in EU-28. In Italy, Germany, France, Spain and Poland, the largest mortality impacts are observed, and in relative terms considering the YLL per 100,000 inhabitants, the countries with the highest rates are Greece, Italy, most of the countries in the Western Balkans and Hungary.

Concentration–response functions for hospital admission for respiratory and cardiovascular diseases mainly come from APHENA study (Katsouyanni et al. 2009) which has been extensively reviewed in previous sections.

The other outcome for which WHO experts provide a recommended CRF is the number of MRAD. This definition implies to take into account the days in which there is no work loss or bed disability but include less serious restrictions on normal activity. The recommended CRF for MRADs comes from the study by Ostro and Rothschild (1989), which consists of six separate analyses of annual data of the US National Health Interview Survey 1976–1981. Perhaps surprisingly, there was no clear association between ozone and respiratory RADs, which are the days in which any alteration of normal activity is considered, including stay in bed and work or school loss. There was, however, a strong and consistent relationship between ozone and MRADs.

Table 2 Premature deaths (PDs) and years of life lost (YLLs) attributable to ozone in Europe in 2013 (source: EEA 2016)

Country	Population	PD	YLL	YLL/100,000 inhab.
Austria	8,451,860	330	3600	43
Belgium	11,161,642	210	2300	21
Bulgaria	7,284,552	330	3500	48
Croatia	4,262,140	240	2500	58
Cyprus	865,878	30	300	37
Czech Republic	10,516,125	370	4100	39
Denmark	5,602,628	110	1300	23
Estonia	1,320,174	30	300	25
Finland	5,426,674	80	900	16
France	63,697,865	1780	20,900	33
Germany	80,523,746	2500	27,200	33
Greece	11,003,615	840	8600	78
Hungary	9,908,798	460	5100	51
Ireland	4,591,087	50	600	12
Italy	59,685,227	3380	36,500	61
Latvia	2,023,825	60	600	32
Lithuania	2,971,905	90	900	30
Luxembourg	537,039	10	100	19
Malta	421,364	20	200	50
Netherlands	16,779,575	270	3100	18
Poland	38,062,535	1150	14,400	38
Portugal	9,918,548	420	4500	45
Romania	20,020,074	430	4800	24
Slovakia	5,410,836	200	2400	45
Slovenia	2,058,821	100	1200	56
Spain	44,454,505	1760	19,300	43
Sweden	9,555,893	160	1600	17
UK	63,905,297	710	8100	13
Albania	2,874,545	100	1200	43
Andorra	76,246	<5	<100	59
Bosnia and Herzegovina	3,839,265	180	2000	52
Republic of Macedonia	2,062,294	100	1200	57
Iceland	321,857	<5	<100	9
Kosovo	1,815,606	100	1100	60
Liechtenstein	36,838	<5	<100	42
Monaco	36,136	<5	<100	62
Montenegro	620,893	30	400	64
Norway	5,051,275	70	800	16
San Marino	33,562	<5	<100	47
Serbia	7,181,505	320	3400	47
Switzerland	8,039,060	240	2700	33
Total		17,000	192,000	
EU-28		16,000	179,000	

The Italian situation

As described in previous paragraphs, Italy, together with Malta and Luxembourg, shows the highest values of ozone concentration among EU countries. According to data by the Italian National Institute for Environmental Protection and Research (ISPRA 2016), in 2013 and 2014, long-term target value for human health protection was exceeded in almost all monitoring stations (94%). In 2014, the percentage of stations in which

conformity with the EU legislation was not met was 33%, lower than in 2013 (61%).

The public information threshold was exceeded in 45% of the stations in 2014, in 50% of them in 2013. In 3% of monitoring sites, the alert threshold was exceeded. The highest ozone concentrations were measured in Northern Italy.

The study by Dimitriou et al. (2013) compared air quality levels in Europe using data from 14 monitoring stations in eight EU countries: Belgium, Germany, Denmark, Spain, UK, Portugal, Romania and one background station in Rome. Authors used two different air quality indexes: the pollution index (PI), which considers each pollutant separately, and the air pollution index (API), which considers the combined effects of a mixture of pollutants. For ozone, results showed a quite variable contribution to the calculated API index among countries, depending on the type of monitoring site and on geographical location. In Italy, ozone showed the highest percentage (41%) compared to PM (26%) and NO_2 (29%). As expected, the greatest contributions of ozone were estimated in background and rural stations, confirming the reactivity of ozone with its traffic-related precursors.

A multicity study aiming to estimate the association between ozone exposure and acute cause-specific mortality in Italy was conducted by an extensive research network, the Air Pollution and Health, Epidemiological Surveillance and Prevention (EPIAIR) (Stafoggia et al. 2010). A case–crossover analysis was conducted in 10 Italian cities. Data on mortality were collected for the period 2001–2005 (April to September), for 127.860 deceased subjects. Authors estimated a 1.5% (95% CI 0.9–2.1) increase in total mortality for a 10 μg/m^3 increase in ozone. The effect resulted more pronounced in elderly people over 85 years of age (3.5%, 95% CI 2.4–4.6), in women (2.2%, 95% CI 1.4–3.1) and for out-of-hospital deaths (2.1%, 95% CI 1.0–3.2), especially among diabetics (5.5%, 95% CI 1.4–9.8).

One of first projects aiming to produce national health impact estimates attributable to ozone exposure was that performed by WHO (Martuzzi et al. 2006) in 13 Italian cities. Impact analysis was allowed by the increasing availability of routinely collected data on air pollutant concentration and on health statistics. Authors used health end-points and concentration–response functions according to the available epidemiological evidence in that time. For ozone, in the 13 cities, a total of 516 premature deaths (0.6% of total acute mortality), equivalent to almost 6000 YLLs, were estimated. A total of 1710 days of bronchodilator usage for asthma in children between 6 and 7 and 13–14 years of age and more than a half a million days in adults were attributable to levels of ozone exceeding 70 μg/m^3. Two humdred twenty-eight respiratory-related hospital admissions for people older than 64 years of age and more than a million MRADs in people 18–64 years were estimated, too.

As already described, more recent estimates on mortality attributable to ozone exposure are those produced by EEA (2016). In Italy in 2013, 3380 premature deaths, equivalent to 36,500 years of life lost, are estimated to be attributable to ozone exposure, the highest values among the 41 European countries. In relative terms, with its 61 years of life lost per 100,000 inhabitants, Italy shows the highest values, the same as Greece and Western Balkans.

Discussion

The evidence produced by an extensive volume of literature shows that the levels of ozone which are routinely measured in several areas of the world may cause significant functional and biochemical alterations. Integrated findings from toxicological animal studies, human-controlled exposure studies and epidemiological studies allow to state that there is a consistent evidence for a causal relationship between short-term exposure to ozone and respiratory effects. Coherent and solid observations across different scientific disciplines show a clear association between short-term exposure and lung function decrements, lung inflammation, lung permeability, mild bronchoconstriction, symptoms of cough and pain on deep inspiration, immune system activation and epithelial injury. Numerous experimental studies, both animal and human, have provided evidence for a biological plausibility for the associations observed in epidemiological studies relating short-term variations in ozone levels with respiratory symptoms and respiratory-related hospitalizations and emergency department visits.

Although some studies indicate a certain degree of adaptive measures facing with sequential ozone exposures, it is likely that multiple acute alterations may lead to permanent damage. A wide series of epidemiological studies conducted in large communities and/or analysing long series of daily environmental and health data show a clear and consistent association between ozone and acute adverse health effects, expressed as mortality or morbidity indicators. The majority of epidemiological results presented in the present review come from the largest and robust multicity studies conducted all over the world. Most of the extensive research networks, such as APHEA, US UNMAPS, PAPA, the Canadian study and the American Cancer Society study, analysed millions of health events correlated to ozone exposure. Many sensitivity analyses on these huge databases have been carried out to test the robustness of results on different statistical protocols to control for confounding. Results from international projects promoted by WHO expert groups and findings from systematic reviews on specific health outcome are cited, too.

Among epidemiologic studies, studies focusing on individuals potentially exposed to high levels of ozone, such as people engaged in outdoor physical activity, children attending

summer camps and outdoor workers, are more comparable to human-controlled exposure studies (McDonnell et al. 2012; Kinney et al. 1996; Chan and Wu 2005; Schelegle et al. 2009). These studies are based on improved ozone exposure estimates, measurement of lung function before and after periods of outdoor activity and evaluation of the effects when the dose of ozone reaching the lungs may be higher because of higher ventilation and inhalation of larger volumes of air.

Evidence for short-term effects of ozone exposure on cardiovascular systems is less conclusive and robust. Findings from toxicological studies are more supportive of ozone-related cardiovascular effects, such as increased heart rate and diastolic pressure, decreased heart rate variability and vascular oxidative stress, if compared with epidemiological evidence. Despite the evidence for a biological plausibility, results from epidemiological studies do not show conclusive associations between short-term exposure and cardiovascular morbidity.

As regards to long-term effects of ozone exposure, toxicological studies in primates show that structural changes in the respiratory tract are caused by ozone exposure, and they also suggest cumulative impacts associated to such exposures. The strongest epidemiological evidence for a relationship between long-term ozone exposure and respiratory morbidity is provided by studies focusing on new-onset asthma in children and on increased respiratory symptom effects in asthmatics.

HIA procedures presented in the second part of the present review provided the most updated estimates of health impacts attributable to ozone exposure. Using the most consistent evidence from epidemiological literature, HIA provides a summary overview of the health impacts associated to short-term and long-term ozone exposure, in terms of mortality and morbidity indicators. These estimates are particularly relevant for decision makers when evaluating some policies, programmes or interventions. Producing a quantitative estimate of the health impacts needs the knowledge of various measures such as concentration–response functions, size of the population exposed and the level of exposure of the affected population. These requirements may lead to some limitations because of the lack of this information or the lack of evidence for the causal relationship between exposure and health effects. These limitations are critical sources of uncertainty in definitive health impact assessment, and evaluation of uncertainty in HIA is a fundamental issue to be addressed.

Another key point in the evaluation of ozone health effects and attributable health impacts is the confounding effects of other pollutants and of meteorological conditions.

Ozone, particulate matter, nitrogen dioxide and other air pollutants share a wide variety of effects on human health, such as acute mortality, morbidity, respiratory and cardiovascular symptoms and damages. Thus, controlling for the confounding effects of these pollutants is a critical issue in evaluating ozone-specific health effects. The correlations between ozone and other harmful substances show differential pattern, depending on season and location. During summer, when ozone concentrations are higher, a positive correlation with the other pollutants has been often observed. High-pressure systems during the warmer seasons lead to stable conditions near the surface. In this condition, the vertical mixing of precursors and the dispersion of pollutants are very limited, and the photochemical reactions for the formation of ozone are enhanced because of higher temperatures and the availability of sunlight. The common result that ozone effects are mainly observed during the summer may be a result of the higher concentrations measured during warmer months, but also, it may be due to the longer time spent outdoors, probably exercising, resulting in higher exposures. On the other hand, during winter when ozone production is limited, negative correlations between ozone and primary pollutants emitted from vehicles and heating are observed. Thus, the apparent absence of adverse effects of ozone in winter may be a consequence of the confounding effects of the other pollutants. For this reason, fitting adjusting models taking into account the confounding effects is widely recommended (Gryparis et al. 2004).

Temperature and meteorological conditions may also play a significative role in confounding the relation between ozone and health outcome. High temperatures (Gronlund et al. 2014; Basu 2008, Baccini et al. 2008) and heat waves in particular (Robine et al. 2012; Kovats and Hajat 2008) have shown associations with increased mortality. In order to evaluate the specific and independent effect of ozone, studies of short-term exposure, such as time series studies, include temperature as a confounder factor in statistical models.

Overall, the evidence from literature shows that most ozone effect estimates remained robust in models adjusted for temperature, humidity and co-pollutants such as PM, NO_2 or SO_2 (EPA 2012).

There is a great variability in the individual response to ozone exposure: biological and external factors, such as gender, age, deficiencies of the antioxidant defences, pre-existing pulmonary diseases and high-intensity exercise, may influence the individual susceptibility and the disease burden associated to ozone. For these reasons, a better characterization of the more sensitive groups is a key point for preventing the impacts and reducing the number of people affected by ozone-related health effects.

However, all policies aiming to pollutants' reduction have to face with the great issue of climate change, which is expected to directly and indirectly influence future ozone concentrations. Changes in meteorological conditions, variation of the emissions of ozone precursors, atmospheric chemistry, dispersion and transport and loss of ozone by dry deposition to vegetation are only some of the mechanisms implicated. Despite difficulties in producing quantitative estimates of future levels of ground-level ozone, because of the interaction of the processes involved, modelling available studies (EEA

2015; Heal et al. 2013; Wu et al. 2008) show that projected mid-century climate change (2041–2070) will increase ambient ozone levels over the vast majority of continental Europe and in densely populated area worldwide.

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