Airborne Aerosols and Human Health: Leapfrogging from Mass Concentration to Oxidative Potential

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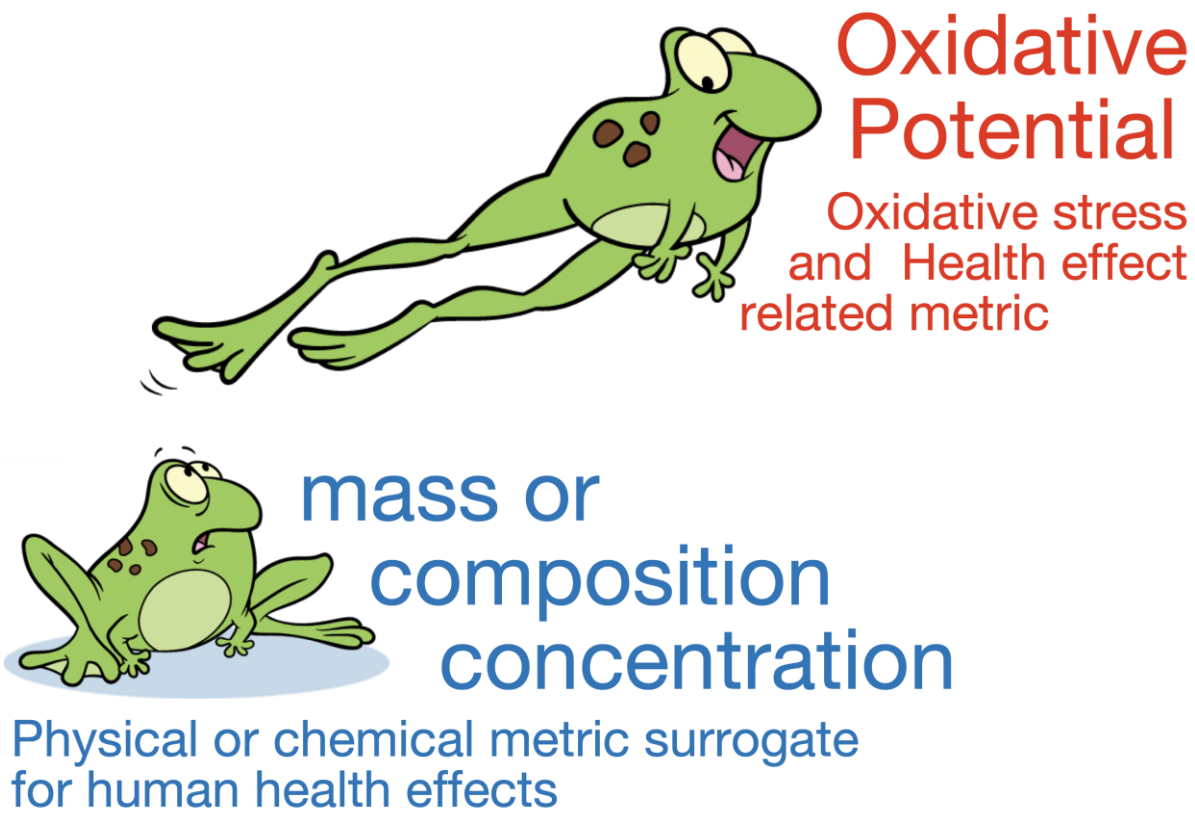
Abstract. The mass concentration of particulate matter (PM) has been systematically used in epidemiological studies as exposure indicator, to relate airborne concentrations with a wide variety of human health effects, which can be hardly explained by using this single parameter. In fact, PM is a "particle cocktail" that includes a complex mixture of compounds with a wide range of sizes, chemical compositions and emission sources. Current research hypothesizes that many of the adverse health effects are derived from oxidative stress in biological systems caused by the deposition of PM into the lungs. This emerging hypothesis is called the oxidative stress paradigm. In this commentary article we analize how this new paradigm could help to answer the as-of-yet unanswered questions related to the mechanism of action of PM pollution on human health. Acellular oxidative potential (OP) assays have been emerged as a promising approach to quantify the PM potential to induce oxidative stress and to relate it with the chemical composition and size distribution of PM. Recent researches have shown that the OP is related to the presence of metals, organic carbon, polyaromatic hydrocarbons and quinones. However, the association between PM and particle-induced toxicity is still largely unknown. Therefore, additional research is needed to identify the specific PM characteristic(s), such as its specific size, emission source or chemical content, which contribute the most to its redox activity. Thus, the OP measurements provide information that allows us to evaluate and integrate the toxic potential of PM in a unique parameter, whose relationships with emission sources, size distribution and/or chemical composition should be faced in the near future.

Keywords: Airborne aerosols; Reactive oxygen species (ROS); health effects; oxidative potential.

Graphical abstract



Introduction

Given the growth in the number, size, and geographical distribution of urban centres around the world in the last 50 years, it can be stated that our world is an urban world (HEI 2019; Katsouyanni 2013; van den Bergh 2003; WHO 2018, 2019). By the middle of the 21st century, the urban population will almost double, increasing from approximately 3.4 billion in 2009 to 8.5 billion in 2030 (World-Gazetteer 2013). This agglomeration of people and activity in urban areas exerts increasing amounts of stress on the natural environment (Benton-Short and Short 2008; Grantz et al. 2003; Newman 2006). One of the major problems associated with the urbanized world is air pollution and its impact on human health (Cohen et al. 2005; Dockery 2009), specifically the impacts associated with airborne particulate matter (PM) (Anderson et al. 2012; Kim et al. 2015; USEPA 2010).

Particles less than 10 microns (PM_{10}) or 2.5 microns ($PM_{2.5}$) in size have been linked to adverse respiratory health effects (Bruckmann and Eikmann 2007; Incecik et al. 2014; McDonald 2012; Sacks et al. 2011), even at low concentrations (Dockery et al. 1993; USEPA 2010). In 2013, the World Health Organization (WHO) catalogued PM as a human carcinogen (IARC 2013). The relationship between PM concentrations and human health has been studied using time series in traditional epidemiological population-based studies (Anderson 2006; Anderson et al. 2012; Bhaskaran et al. 2013; Bonetto and Bellini 2000; Leiva et al. 2013) and by measuring the effect of certain components of PM on live organisms (Akhtar et al. 2010; Maier et al. 2008; Piacentini et al. 2019; Unfried et al. 2005).

The chemical composition of PM varies greatly, depending on the geography, meteorological factors and emission source (Zereini and Wiseman 2010). In general, PM contains a large number of chemical species that can be divided into two major classes. *Macro-components*: inorganic ions, elements and carbon-containing compounds that exceed more than 1% of the PM mass and *Micro-components*: elements and organic compounds present in trace amount (< 1% of PM mass). Typically, the *fine* fraction of PM is mostly constituted by chemical components such as elemental carbon (EC), sulphates (normally present as ammonium salts) and various organic compounds of primary and secondary origin. On the contrary, the *coarse*

fraction is mainly formed by elements coming from the earth's crust (Ca, Al, Si, Mg, Fe) and some bio-organic materials such as pollen, spores, plants and animal wastes. These components, either alone or as part of a mixture, can induce negative effects on human health (Morales and Leiva 2006). Epidemiologists have documented statistically significant associations between PM concentrations and an increase in the incidences of several diseases and mortality rates (Akhtar et al. 2010; Anderson 2006; Bhaskaran et al. 2013; Bonetto and Bellini 2000; Goldman et al. 2011; Kappos 2010; Wilson 2001). These studies show a correlation between exposure to PM and adverse effects on human health (Diaz-Robles et al. 2008; Leiva et al. 2013; Sanhueza et al. 2009; Valdes et al. 2012).

The mass concentration of PM has been systematically used in epidemiological studies to relate PM concentrations with a wide variety of human health problems (Kappos 2010). The relative estimated risk based on the U.S. Environmental Protection Agency Criteria Document's review of PM_{10} studies advises an increased all-age mortality of 2.5-5.0% for each 10 μg m^{-3} or 25 μg m^{-3} increase in the PM_{10} or $PM_{2.5}$ concentration, respectively (USEPA 1996). Some key epidemiological studies, including The Harvard Six Cities Study (Dockery 2009; Krewski et al. 2003), the study of the American Cancer Society (Krewski et al. 2003; Pope et al. 1995) and The Adventist Health Study of Smog (Abbey et al. 1999; McDonald 2012), have shown an association between PM mass concentration and health effects. In the first study, approximately 8,000 adults were monitored over 14 years in six U.S. cities with varying amounts of air pollution to explore the influence of the total suspended particulates, $PM_{2.5}$ and other air pollutants on different health indicators (Dockery 2009). The result showed that the $PM_{2.5}$ had the strongest association with mortality. In the second key study (Pope et al. 1995), 550,000 adults were monitored for a period of 8 years in 154 U.S. cities; this was later was extended to 16 years of follow-up. The authors found the strongest association between $PM_{2.5}$ and mortality, the highest among the key studies cited here. The third key study (Abbey et al. 1999) followed mortality for 15 years among 34,000 non-smoking, white, Seventh Day Adventists aged 27–95 years living in California. They found a strong association of PM_{10} with mortality due to respiratory disease and lung cancer. Based on

the results of these studies, it can be inferred that there is a positive relationship between PM exposure and negative health effects on humans.

Leapfrogging to oxidative potential

Different studies have spotlighted strong correlations between PM mass concentration exposure and the onset of cardiovascular and respiratory diseases (Bruckmann and Eikmann 2007; Pope and Dockery 2006). However, PM mass concentration as exposure indicator, misestimates the overall impact of PM, since it does not take into account the different sizes, compositions and toxicological effects of the multiple pollutants that make up the PM. The negative health effects posed by the particles cannot be explained by a single parameter such as mass concentration (Bouwmeester et al. 2011). A significant empirical uncertainty of the results obtained from epidemiological studies is observed, which is mainly related to the presence of numerous confounding factors in the PM mass as a surrogate for the cause of human health effects. Particulate matter is a “particle cocktail” (Calvo et al. 2013; Grahame 2010) that includes a complex mixture of compounds with a wide range of sizes, chemical compositions and emission sources (Zereini and Wiseman 2010). Thus, it is possible that a specific major chemical component (i.e., contributing a large mass proportion) has low or very low toxicological activity, consequently inducing moderate or no negative effects on human health, while minority or trace chemical components may have high toxicological activity,thus inducing a significant deterioration in human health. In this sense, the PM mass concentration is a poor metric or explanatory variable for explaining mechanisms of PM exposure-induced human health deterioration (Wilson 2001). This limitation can be overcome by identifying possible relationships between PM toxicity and its specific physic-chemical properties (Piacentini et al., 2019). During the last years, the complex and variable composition of PM has been widely investigated and many studies have revealed that several PM properties influence its health and environmental effects, but they are not entirely conclusive (Hellack et al. 2017; Kelly et al. 2012; Ricci and Cirillo 1985; WHO 2013).

While the body of epidemiological studies is generally not as robust as an examination of the health effects of PM, new approaches are emerging to reduce the uncertainty of the results and to answer the following questions: (i) What concentration of PM is risk-free for human

health?, (ii) How does PM cause human health damage?, (iii) Is this damage caused by the particle itself or by a particular chemical constituent of PM?, (iv) Is the damage caused by the interaction between PM chemical constituents?, (v) Which chemical constituent or mixture of constituents is responsible for the effects? Finally, (vi) what is the best metric, other than PM mass concentration, for determining the association between the PM exposure and the adverse effects on human health? Answering these questions will help to us understand the mechanisms of action of PM pollution on human health.

The specific mechanisms of action by which exposure to PM may lead to adverse health effects are largely unknown (Miranda et al. 2014; Omaye and Yang 2009; Rohr and Wyzga 2012). However, substantial research has been dedicated to understanding the mechanisms (Delfino et al. 2013; Hoek et al. 2013) and oxidative stress has been suggested to be an important underlying mechanism of action. In many of these studies, a large number of PM health effects have been attributed to the oxidative or oxidant-generating properties of the ambient particles (Delfino et al. 2013; Li et al. 2009; Lin and Yu 2011). Current research hypothesizes that many of the adverse health effects are derived from oxidative stress in biological systems caused by the deposition of PM into the lungs (Omaye and Yang 2009; Valavanidis et al. 2013). This emerging hypothesis is called the oxidative stress paradigm (Clift and Rothen-Rutishauser). The hypothesis proposes that oxidative stress proceeds through two mechanisms. The first mechanism is related to intrinsic oxidation-reduction reactions resulting from redox-active substances in the PM (Charrier and Anastasio 2011, 2012). This mechanism may be caused by some chemical compounds, such as soluble transition metals, which reduce the dissolved oxygen into reactive oxygen species (ROS) and nitrogen-containing oxidants, such as nitric oxide ($NO^{\cdot}$), into reactive nitrogen species (RNS) (Frezzini et al. 2019; Piacentini et al. 2019). ROS is a collective term comprising chemically reactive oxygen radicals and/or oxygen-derived species, such as peroxide ($O_2^{\cdot-}$), hydroxyl ($\cdot OH$), peroxyl ($RO_2^{\cdot}$), and alkoxyl (RO^{-}) as well as hypochlorous acid (HOCl), ozone (O_3), singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2), which are non-radicals. These non-radicals are oxidizing agents and/or converted into radicals (ChaudièRe 1994; Pruchniak et al. 2016). In living organisms, ROS represent the most important class of radical species from a

biochemical processes point of view (Arnhold 2020; Di Meo et al. 2016; Pruchniak et al. 2016).

Although ROS and other radicals are continually formed in the human body as a natural by-product of aerobic metabolism, the enhanced generation of radicals by PM in living organisms can overwhelm the antioxidant defenses (Clift and Rothen-Rutishauser 2013). The second mechanism is a biological response to inhaled PM or cell-mediated oxidant generating capacity. This mechanism is believed to be associated with oxidative phosphorylation in cells, which occurs through the sequential addition of electrons to dissolved oxygen (Chio et al. 2007; Valavanidis et al. 2013; Venkatachari et al. 2007; Zhang et al. 2008). The amount of ROS formed by PM is several orders of magnitude higher than the concentrations that cause oxidative stress, which is the main cause of the inflammatory response. Figure 1 summarizes these mechanistic pathways of PM producing oxidative stress and inflammatory response. Thus, oxidative stress represents a relevant mechanism of toxicity from PM, and the oxidative potential (OP) measurement in PM is a first step in the elucidation of the subsequent downstream processes. However, the relatively complex measurement processes in biological systems make it difficult to monitor the ROS parameter in the environment.

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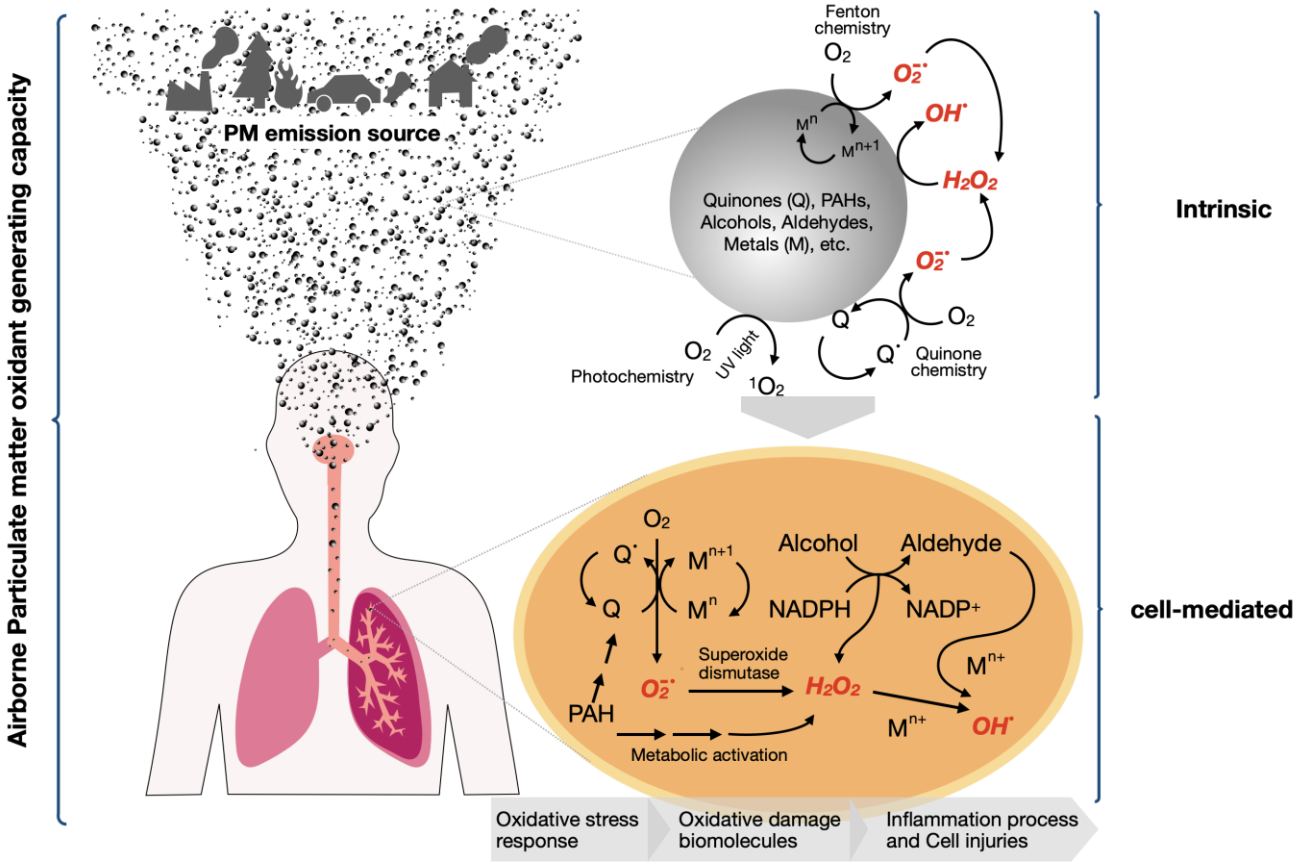

Figure 1. Schematic mechanistic pathways of PM producing oxidative stress and inflammatory response.

Oxidative potential measurement assays

Based on this possible mechanistic route linking aerosol chemistry to health, numerous studies initiated in the past several years have been focused on measuring the oxidative properties of ambient particles. Some studies (Schaumann et al. 2004; Wessels et al. 2008) have demonstrated a relationship between the intrinsic (cell-free assay) PM-induced generation of hydroxyl radicals ($OH^{\cdot}$) and the adverse biological effects (cell assay). In another study (Li et al. 2003), a positive correlation between the ROS activities of PM collected in central Beijing and the *in vivo* inflammatory responses in cells was found. Meanwhile, Delfino et al. (2013) found a strong association between the intrinsic particle-induced ROS generation potential and the fractional exhaled nitric oxide, a biomarker of airway inflammation, in school children

with persistent asthma in southern California (Delfino et al. 2013). However, they found that the ambient $PM_{2.5}$ mass concentration was not associated with biomarkers of airway inflammation. Li et al. (2003) found that a quantitative measure of in vitro ROS formation was correlated with the polycyclic aromatic hydrocarbon (PAH) content and cellular heme oxygenase-1 expression, a sensitive marker for oxidative stress (Li et al. 2003). Therefore, the PM-OP (i.e., intrinsic cell-free particle-induced ROS generation potency) is discussed as a promising additional metric that links environmental monitoring and adverse health effects (Ayres et al. 2008; Borm et al. 2007; Groso et al. 2010; Koike and Kobayashi 2006; Künzli et al. 2006a). Cell-free tests are helpful for rapid initial hazard screening, require less controlled environments, are simpler measurements than those using biological systems, and allow OP environmental monitoring. Finally, the OP results allow researchers to identify specific properties of aerosols (such as the chemical and biological composition; size and/or surface area of airborne particles) as the main responsible for the oxidative stress generation in living organisms (e.g., cellular or animal tests) (Mirowsky et al. 2015; Piacentini et al. 2019).

The formation of ROS and oxidative stress can be assessed by different cell-free assays (Bates et al. 2019; Hedayat et al. 2015; Hellack et al. 2017; Øvrevik 2019; Pietrogrande et al. 2019b). Common acellular OP assays include electron spin (or paramagnetic) resonance (ESR) (Calas et al. 2018; Gomes et al. 2005; Hellack et al. 2017; Schins et al. 2004; Valavanidis et al. 2013), dithiothreitol (DTT) assay (Berg et al. 2020; Borlaza et al. 2018; Lin and Yu 2019; Molina et al. 2020) , ascorbic acid (AA) assay (Pietrogrande et al. 2019a) and dichlorofluorescin (DCFH) assay (Karlsson et al. 2010; Myhre et al. 2003; Rota et al. 1999). ESR measures the generation of hydroxyl radicals via electron spin resonance, while DTT and AA measure the depletion rate of chemical proxies for cellular reductants (DTT) or antioxidants (AA), which is proportional to the generation rate of ROS. On the contrary, particle-bound ROS measurements, such as DCFH assay, use fluorescent-based techniques to measure concentrations of specific ROS, usually the hydroxyl radical or hydrogen peroxide, on and/or within a PM sample (Bates et al. 2019). These methods usually reveal a different response to different chemical constituents of PM. In recent studies (Piacentini et al. 2019; Simonetti et al. 2018), the DTT, AA and DCFH assays were applied to seven types of

widespread atmospheric dusts (brake dust, pellet ash, road dust, soil dust, coke dust and Saharan dust) characterized by very different chemical compositions, which can be associated with different adverse health effects. The three oxidative potential assays have provided very different results for each dust, confirming that none of the examined methods can be *a-priori* considered as representative of ROS and RNS generation pathways in biological organisms.

OP environmental monitoring

Noticeable OP results have been obtained using the methods described above, which can be expressed as the OP normalized to volume of air containing a certain concentration of PM or as the OP normalized to mass of particles, representing the intrinsic OP of the PM analyzed. ESR studies have demonstrated that the formation of •OH is promoted by $PM_{2.5}$, which is comparable to the concentrations found in cigarette smoke particles (Valavanidis et al. 2013; Zhao and Hopke 2012). In a study conducted in six cities (Baltimore, Chicago, Los Angeles, New York, St. Paul and Winston-Salem) over a one-year period (Sverre et al. 2013), DTT measurements were found to vary over time. The OP (in mass) from DTT assay in the PM winter samples was found to be between 1 and 3-fold higher than in the summer samples; this is mainly due to the major strength of typical winter sources such as domestic biomass heating. In fact, DTT assay is deemed to be specifically sensitive toward particles released by biomass burning during the colder season. Other studies showed that PM_{10}-OP, as measured by ESR spectroscopy, was 4.5 times higher in an industrial city compared to a rural neighboring town, despite the similar PM_{10} mass levels in the air (Boogaard et al. 2012). Similarly, in the Netherlands, the highest OP values of PM_{10} and $PM_{2.5}$, as measured by EPR, were found at locations close to highways and roads compared to urban background locations and suburban background locations; furthermore, the values were 3.6 to 6.5 times higher at urban locations compared to suburban locations (Sverre et al. 2013; Yang et al. 2014). Likewise, significantly higher OP values were found in the PM_{10} compared to the $PM_{2.5}$ samples, which were analyzed on an equal mass basis. This variability is not explained by the variability in the absolute particle mass collected. In Los Angeles, USA, the redox activity (measured by DTT assay) of the PM size-segregated samples collected in various

environments (road tunnel, freeway, background sites) revealed a maximum $PM_{0.15}$ value in the road tunnel samples, which were directly influenced by the source emissions (Fang et al. 2016).

Overall, despite the efforts of many research groups to understand the spatiotemporal variability of the OP between different cities, environmental conditions and emission sources, few studies provided long-term OP-PM systematic measurements in polluted urban areas (referencias).

OP and chemical composition of PM

Particle compounds implicated in ROS formation include heavy metals, organic carbon (OC), Polycyclic aromatic hydrocarbons (PAHs) and quinones (Charrier et al. 2015; Cho et al. 2005; Squadrito et al. 2001). Heavy metals may act as catalysts through Fenton-type chemistry (Charrier and Anastasio 2011, 2012; Jomova and Valko 2011) and promote ROS production. OP is attributed, in part, to the presence of transition metals such as Fe, V, Cr, Mn, Co, Ni, Cu, Zn, and Ti (CARB 2009). Metals such as Fe, Cu and V can initiate ROS formation both directly and indirectly through redox-mediated mechanisms (Frank et al. 2019; Hedayat et al. 2015; Saffari et al. 2014c; Verma et al. 2009). The importance of the role of metals in ROS activity is supported by a study by California Air Resources Board (CARB 2009), which found that the removal of metals from diesel PM via metal chelation treatment reduced the ROS activity by an average of 77%. Similarly, ultra-fine particles with metallic components were found to produce increased ROS activity, and differing metal compositions were linked to different levels of ROS activity and inflammation (CARB 2009). Direct correlations between ROS generation and the total metal content and different concentrations of V, Fe, and Co in PM have been observed (Jomova and Valko 2011). OP is related to the PM content of soluble transition metal species (Charrier et al. 2015; Mirowsky et al. 2015; Saffari et al. 2014c; Verma et al. 2014). For example, based on a correlation analysis of the particulate concentrations of soluble metals and the redox activity of the samples evaluated by the DTT assay, Charrier and Anastasio (Charrier et al. 2015) found that approximately 80% of DTT consumption can be attributed to metals (especially Cu and Mn) for typical $PM_{2.5}$ samples. The

association of transition metals, which are often used as robust source tracers (Massimi et al. 2020a; 2020b), with ROS activity, highlights the importance of identifying the PM emission sources. The potential sources of heavy metals (Fe, Cr, and Mn) in PM include a variety of high energy/combustion sources, such as vehicle exhaust, coal and fuel oil burning, welding fumes and steel processing, and waste incineration (Künzli et al. 2006b). An example of the impact of emission sources can be found in a study of PM emitted from oil combustion, in which the PM-induced redox activity was associated with residual oil combustion tracers (e.g., V and Ni) (Saffari et al. 2014c) at multiple locations and size ranges. The DTT loss is higher when the samples are exposed to the urban atmospheric particles than in the case of diesel and wood burning (wildfire) PM (Saffari et al. 2014c). It is important to mention here that different oxidative potential assays have different responses to metals (Bates et al. 2019). Generally, AA is deemed to be particularly sensitive to transition metals and has been strongly positively correlated with the main elements tracing non-exhaust traffic emission, such as Cu, Fe and Mn. On the other hand, various chemical components in atmospheric aerosols have been demonstrated to be well-correlated with DTT, including water-soluble transition metal ions, water-soluble organic compounds and quinones. Numerous studies have shown strong correlations of DTT with robust biomass burning tracers, such as K and organic compounds like levoglucosan. For DCFH assay, positive correlations between ROS and both transition metals (including Fe) and organic concentrations have been found (Massimi 2020).

The oxidative potential of particulate matter has also been attributed to certain organic compounds. A wide variety of organic compounds in PM (such as quinones and PAHs) induce oxidative stress (Risom et al. 2003; Sørensen et al. 2003). Moreover, organic extracts from wood smoke particles generate higher levels of OP compared to native particles (Danielsen et al. 2009). Particles generated by combustion processes, such as particles from the emission of wood smoke particles and diesel exhaust, contain quinones and nitro-derivatives of PAH, oxygenated PAH, and halogenated aromatic hydrocarbons that are related to the redox activity of PM (Risom et al. 2003; Sørensen et al. 2003) and can be involved in the redox cycle, resulting in the formation of ROS (Penning et al. 1999; Squadrito et al. 2001) . Semiquinone-like compounds in the PM samples may be responsible for radical production, which is similar

to that observed in the reduction of dioxygen by hydroquinone and semi-quinone radicals (Cheng et al. 2012; Taguchi et al. 2007). Further research will be undertaken to identify the quinone species and the relationship between these compounds and the redox potential that leads to the generation of ROS. The organic carbon (OC) and water-soluble organic carbon (WSOC) content in PM has been correlated with redox activity (Saffari et al. 2014b; Verma et al. 2012). In Prague, the $PM_{0.2\text{-}2.5}$ samples collected in winter displayed a relationship between redox activity and the high content (>50%) of carbonaceous materials, such as elemental carbon and organic matter (including PAH), which originated from local incomplete combustion (Happo et al. 2008). The inflammatory and cytotoxic activities of the samples were largely associated with the water-insoluble particulate fraction. PAHs tended to correlate with redox activity, although this was not consistent. The redox activity may be more strongly correlated with higher or lower molecular weight PAHs (McWhinney et al. 2013). Charrier and Anastasio (Charrier et al. 2015) found that approximately 20% of the redox activity could be attributed to quinone species when budgeting redox activity to measured species in particles collected from the San Joaquin Valley of California.

Oxidative potential and size segregated PM

Particle size can also be critical in mediating PM oxidative stress (Linak et al. 2007; Weichenthal et al. 2016). Because of their increased concentration, large surface area and high pulmonary deposition efficiency (Groso et al. 2010; Mirowsky et al. 2015; Saffari et al. 2014c), ultrafine particles may be more biologically active than larger coarse or fine particles (Ohlwein et al. 2019). It is likely that chemical composition of particles with different size, is responsible for differences in the oxidative potential responses to fine and coarse PM.AA assay was found to be particularly sensitive to coarse particles (mainly released by mechanical and abrasive processes) while DTT and DCFH assays resulted to be more sensitive toward fine particles (mainly originated by condensation and accumulation of ultrafine particles released by combustion processes (Simonetti et al. 2018; Manigrasso et al. 2020; Massimi et al., 2020c). In fact, transition metals, to whom AA is deemed to be more sensitive, are especially present in the coarse fraction, since they are mostly released by mechanical and

abrasive processes, such as brake abrasion. On the contrary, water-soluble metals and organics, which are generally associated with higher intrinsic ROS activity, and to whom DTT and DCFH seem to be more sensitive, are mainly released by combustion processes in ultrafine particles that generate the fine fraction of PM by condensation/coagulation processes. We can thus assume that relationships between PM size and oxidative potential mainly depend by the different chemical composition of particles released in different size fractions.

A higher activity has been found for smaller particles. Using particles collected in Los Angeles from November 2001 to March 2002, Li et al. (2003) found that the DTT decay rate per µg of PM was 8.7 times greater for ultrafine particles (defined as $PM_{0.15}$) than for fine particles and 21.7 times greater than for coarse particles (Li et al. 2003). Likewise, Cho et al. (2005) reported a similar trend examining particles collected in Los Angeles over a longer time scale; the redox activity, when normalized to the particle mass, decreased moving from ultrafine to fine and from fine to coarse particles (Cho et al. 2005).

The effect of PM size on OP in samples collected in an urban setting using a Micro Orifice Uniform Deposit Impactor (MOUDI) (Venkatachari et al. 2007) was determined by the DCFH assay. The results showed that the OP was higher for particles in the ultra-fine size range. This finding may be explained by the fact that ROS can be produced by photochemical reactions or vapor phase condensation on the particles. Similarly, other studies using DTT assays also showed a higher redox activity for PM samples in the ultrafine mode, while the activity decreased for PM samples in the fine and coarse modes (Venkatachari et al. 2007). A significant correlation was shown between particle numbers (but not particle mass) and the oxidative potential of diesel exhaust, again indicating that the particle size and composition strongly influence particle toxicity (Cheung et al. 2009; Saffari et al. 2014a). Despite these results, other studies have shown that the coarse fraction of PM has a higher oxidative potential than the fine fraction of PM (Murr and Garza 2009; Ntziachristos et al. 2007; Valavanidis et al. 2008; Venkatachari et al. 2007). These results suggest that there is no simple relationship between the dominant size of the air pollution particles and OP.

Oxidative potential and PM source

Efforts have also been made to associate specific sources of PM with oxidative stress (Zhang et al. 2008). Studies conducted to date have examined the toxicity of PM collected at urban areas of interest, including locations impacted by nearby airports, harbours, power plants and refineries. For example, in some studies (Saffari et al. 2014a; Saffari et al. 2014b) fuel oil combustion and vehicular sources (abrasion as well as tailpipe emissions) were found to be two major contributors to ROS activity, as indicated by the association of their metallic tracers with ROS activity at Los Angeles (USA), Long Beach (USA), Beirut (Lebanon), Milan (Italy), Thessaloniki (Greece), Denver (USA) and Lahore (Pakistan). The water-soluble fraction of organic aerosols is also another major contributor to ROS activity, with a more dominant effect at the locations with higher SOA formation at Riverside (USA), Milan (Italy) and Denver (USA). Additionally, Saffari et al. (2014c) found that the intrinsic PM-induced ROS activity levels as well as the exposure to redox-active PM are higher in locations with permissive air quality regulations compared with locations with stringent regulations (Saffari et al. 2014b).

Due to the different chemical composition and size distribution of PM, associations between PM mass and health effects are difficult to reproduce, and a number of experimental studies suggest that there is a link between the oxidative stress response and the PM source and chemical composition (Massimi 2020). The knowledge of the relative relevance of the single source contributions in building up OP values can be of great help for the identification of the emission sources mainly responsible for ROS generation. Source apportionment of OP results from field campaigns have been attempted in some studies, but conflicting results were found (Calas et al. 2018; Chirizzi et al. 2017; Fang et al. 2016; Perrone et al. 2016). Therefore, to help understand which PM sources could represent a significant health hazard, OP measurements using different emission sources and size fractions are needed.

Remarks

In summary, chemical radical mechanisms are relevant for environmental toxicology because can directly cause the initiation of radical reactions that damage all types of macromolecules

in cells. Further evaluations of the spatial and temporal characteristics of PM redox activity are underway, along with studies of relationships between oxidative potential and specific physic-chemical properties and sources of PM . In fact, the analysis of OP is a useful tool in determining the potential of particles with different size and chemical composition to induce oxidative stress and harmful effects on human health. The determination of an association between PM and particle-induced toxicity is complicated by the fact that airborne PM is composed of a complex mixture that originates from various sources, both primary and secondary. Therefore, additional research is needed to identify the specific PM characteristic(s), such as its size, emission source or chemical content, which contribute the most to its redox activity. Thus, the OP measurements provide information that allows us to evaluate and integrate the toxic potential of PM in a unique parameter, whose relationships with emission sources, size distribution and/or chemical composition should be faced in the near future.

Finally, the OP like a metric associated with health effects (oxidative stress) can play an important role in research associated with exposure assessment-risk management (see Figure 2). Under this conceptual scheme, the OP is a nexus between aspects of exposure and health impacts, since it provides information related to the doses and biological mechanisms of the health effects, which results in the knowledge needed to establish pollution control and prevention measures. These measures make it possible to evaluate progress in protecting public health. Moreover, the OP is configured as a link between the disciplines of atmospheric sciences (e.g. atmospheric chemistry), health sciences (e.g. environmental epidemiology, environmental geology, etc.) and social sciences (e.g. political sciences, economic sciences).

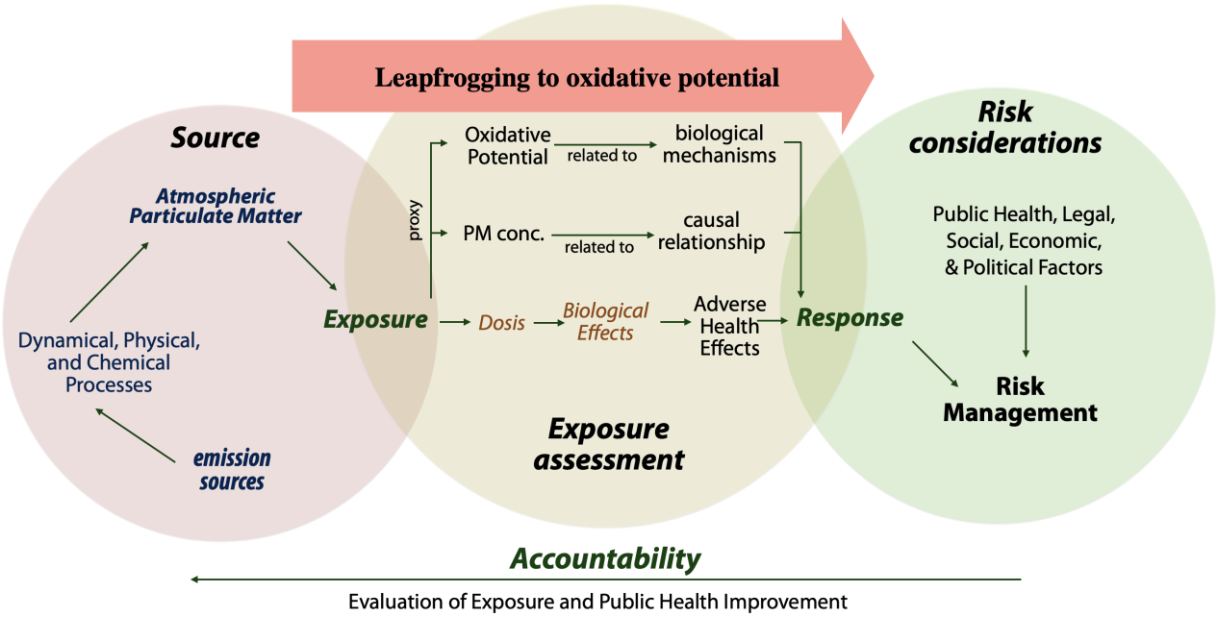

Figura 2. Conceptual an Integrated research across the exposure-risk assessment-risk management.

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Conflict of interest.

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