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Methods for the assessment of health risk induced by contaminants in atmospheric particulate matter: a review

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Abstract:

Air pollution is a major issue for human health with more than 7 million premature deaths per year due to indoor and outdoor air pollution. Exposure to particulate matter is correlated with adverse health effects in the short and long run. Evaluating the health risk from exposure to particulate matter is challenging because particulate matter contains many contaminants and observed diseases result from multiple causes. Here we review advanced methods for the evaluation of cancer and non-cancer risks induced by exposure to contaminants in particulate matter. Contaminants include polycyclic aromatic hydrocarbons, phthalates, dioxins, furans, dioxin-like polychlorobiphenyls, and major and trace elements. We discuss risk assessment by ingestion, inhalation, and dermal contact, and for population age categories. We observe that the highest contributions to cancer risk come from benzo[a]pyrene, indeno[1,2,3-c,d]pyrene, benzo[k]fluoranthene, dibenz[a,h]anthracene, chromium, arsenic, cadmium, and cobalt.

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38 Abbreviation list:

ABS	Dermal adsorption factor
ADD	Average daily dose
ADI	Acceptable daily intake
AF	Dermal adherence factor
AT	Average timing
BW	Body weight
C_i	Concentration of species i in air
CR	Cancer risk
CSF	Cancer slope factor
DL-PCBs	Dioxin-like polychlorobiphenyls
EC	Exposure concentration in air
ED	Exposure duration
EF	Exposure frequency
ET	Exposure time
GIABS	Gastrointestinal absorption factor
HI	Hazard index
HQ	Hazard quotient
ILCR	Incremental lifetime cancer risk
IR_{ing}	Soil intake rate
IR_{inh}	Inhalation intake rate
IUR	Inhalation unit risk
LADD	Lifetime average daily dose
LCR	Lifetime cancer risk
MRL	Minimal risk level
PAHs	Polycyclic aromatic hydrocarbons
PCDD	Dioxins
PCDF	Furans
RBA	Relative bioaccessibility
RfC	Reference concentration
RfD	Reference dose
SA	Exposed skin surface area
SBET	Simple bioavailability extraction test
TEF	Toxic equivalent factor
TEQ	Toxic equivalent concentration
USEPA	United States environmental protection agency
WHO	World health organization

1 Introduction

Rapid industrialization around the world has led to an important economic prosperity and an increase in the living standards. This evolution was also accompanied by the deterioration of the environmental balance and a drastic decrease in air quality (Fowler *et al.* 2020). The effects of air pollution on human health have returned as a top priority at the end of the XXth and at the beginning of the XXIst century as new epidemiological evidence emerged (Fowler *et al.* 2020). According to the world health organization, air pollution was responsible for about 7 million premature deaths worldwide in 2016 (WHO 2016). In 2013, the international agency for research on cancer (IARC) has classified outdoor air pollution and particularly particulate matter as Group 1 “carcinogenic to humans” (Loomis *et al.* 2013). Particulate matter is nowadays considered as one of the most challenging issues in the environmental field because of its effect on human health (Mark Goldberg 2008, Anderson *et al.* 2012, Thurston *et al.* 2017, Cochard *et al.* 2020). Epidemiological, biomedical, and clinical studies indicate that long-term exposure to particulate matter will increase the probability of having strokes, myocardial infarcts, vascular dysfunction, hypertension, heart insufficiency and heart failure (Du *et al.* 2016, Lelieveld and Münzel 2020, Manisalidis *et al.* 2020, Manojkumar and Srimuruganandam 2021). Long-term exposure to air pollution can be also related to chronic asthma, pulmonary insufficiency, and might even promote lung cancer (Xing *et al.* 2016, Manisalidis *et al.* 2020). As for the respiratory system, short-term exposure to particulate matter is closely correlated to cough, shortness of breath, asthma, and chronic obstructive pulmonary disease (Manisalidis *et al.* 2020).

Atmospheric particles represent a complex mixture of inorganic species such as elements, water-soluble ions, etc., organic species such as polycyclic aromatic hydrocarbons (PAHs), alkanes, hopanes, etc., and a biological fraction including pollen, spores, etc. The composition of these particles varies strongly and depends on the source of emissions (Sitaras and Siskos 2008, Mukherjee and Agrawal 2017, Yu and Park 2021), the reactivity of the atmosphere and the atmospheric lifetime (**Fig. 1**). The exposure to the different atmospheric contaminants can happen via three major routes: inhalation, ingestion and dermal absorption (**Fig. 1**). However, the physical and chemical properties of the substance will dictate the manner in which the substance enters the human body. Airborne particles might enter the human body via the respiratory system. The penetration and the interaction of these particles with the human respiratory tract are controlled by the size, the shape and the composition of the particles as well as the geometry of the airways (Schwartz and Neas 2000, Bell *et al.* 2009, Cochard *et al.*

2020). Once inhaled, particulate matter and associated chemicals are either exhaled or deposited in the respiratory tract. Large particles, that have a diameter higher than 10 μm , can be retained in the oro-pharyngeal region due to impaction. Coarse particles, having a diameter between 2.5 and 10 μm can be deposited in the tracheobronchial region. Fine and ultrafine particles, having a diameter below 2.5 μm and 0.1 μm respectively, can reach the alveoli and small conducting airways due to gravitational sedimentation (Thakur *et al.* 2020). Additionally, particulate matter deposition and accumulation might also occur at carinal ridges due to inertial impact and lower clearance efficiency (Martonen *et al.* 1994). On the other hand, the non-respirable particulate matter can enter the human body via the oral route. The absorption of the particulate matter chemical components, leading to the introduction into the vascular system is the most important in the small intestine compared to other organs in the gastrointestinal tract (Asante-Duah 2019). As for the dermal route, the skin provides a major interface between the body and the environment. However, the most common route of a toxicant via the skin is a passive diffusion through the epidermis into the dermis where the toxicant might enter a blood vessel (Asante-Duah 2019). Upon contact with skin or organs in the human body, chemicals may cause different health effects from a simple irritation to a severe tissue destruction (Anderson and Meade 2014).

Health risk assessment studies aim at estimating the nature and the probability of adverse health effects in humans who may be exposed to chemicals in contaminated media (USEPA 2022a). These studies differ from epidemiological by their objectives. Epidemiological studies evaluate if past chemical exposures may be responsible for documented health problems in a specific group of the population. On the other hand, health risk assessment studies estimate whether current or future exposures will pose risks to a broad population (OEHHA 2001). The latter studies are based on the evaluation of the cancer and the non-cancer health risks. According to the national air toxics assessment glossary, the cancer risk represents the incremental probability that an individual might develop cancer over a lifetime as a result of a specific exposure to a carcinogenic chemical (USEPA 2022b). On the other hand, the non-cancer risk represents the probability to develop health complications other than cancer such as cardiovascular and respiratory diseases as a result of exposure to chemical pollutants. The evaluation of the health risks associated with the exposure to pollutants is an important step leading to the development of effective risk management policies in a population.

Health risk assessment tools such as the environmental benefits mapping and analysis program-community edition (BenMap-CE), the CO-benefits risk assessment (COBRA), the air quality+

(Air Q+), the household air pollution intervention tool (HAPIT), and others are widely used (Glorennec and Monroux 2007, Gao *et al.* 2015, Farzaneh 2017, 2019). However, these tools only assess the health risks of major pollutants such as sulfur oxides, nitrogen oxides, ozone and particulate matter (Hassan Bhat *et al.* 2021). The present paper is a comprehensive review of the published methods for the assessment of the health risks due to the exposure to different classes of compounds in particulate matter. This paper also develops the methodology for the evaluation of the cancer and the non-cancer risks for the different exposure pathways and for different age categories. The review also aims to further understand which species and/or classes of compounds appears as the most problematic to human health, and to understand the limitations of health risk evaluation methods.

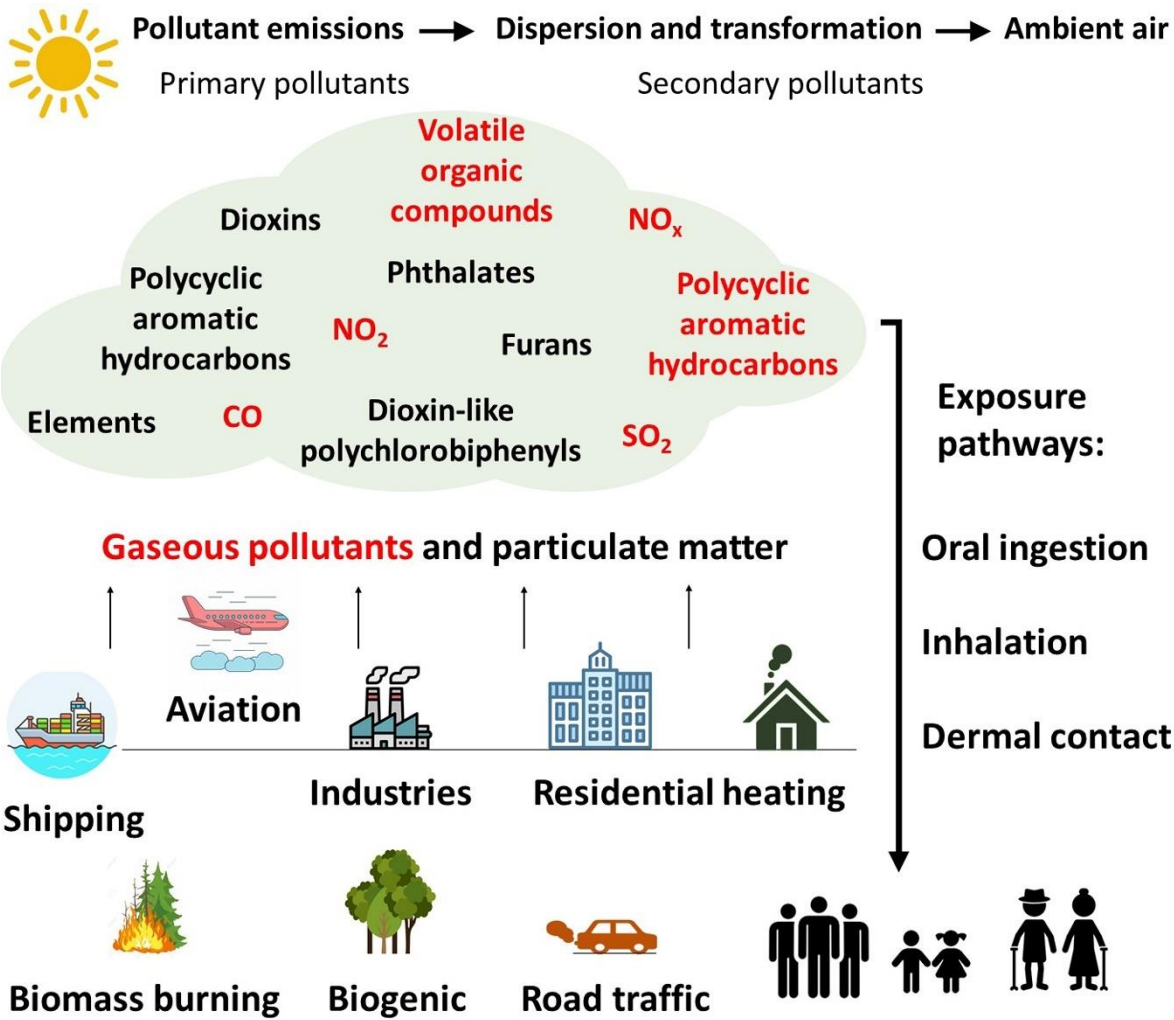


Fig. 1: Exposure cycle to air pollutants emitted by different natural and anthropogenic sources, dispersed in ambient air while undergoing transformations before reaching humans and impacting their health.

2 Health risk assessment and epidemiological studies

Health risk assessment and epidemiological studies are both important but have different aims. The scientists that are searching for relationships between the exposure to chemicals and observed health problems in a population usually conduct an epidemiology study (OEHHA 2001). On the other hand, health risk assessment methodologies are used to estimate if a current or a future exposure to chemicals might pose a health risk to a population. The epidemiological study has the advantage to be based on a known illness while the health risk assessment is a probabilistic method for occurrence of pathologies and is used as a preventive tool. The methods used in the health risk evaluation cannot be used to link health problems to past chemical exposures. As well, both epidemiological or health risk assessment studies cannot prove that a specific chemical caused an individual's illness (OEHHA 2001).

Since the early 1980s, health risk assessment methods began to develop and is increasingly being used to inform major policy decisions (McClellan 1999). In the same period, toxicological data have formed the foundation for many hazard and dose-response assessments (Krewski *et al.* 1990, Déglin *et al.* 2021). In parallel, health risks in human population were increasingly being assessed by the use of empirical data for epidemiological studies (Nurminen *et al.* 1999). The latter studies are considered important for the interpretation of relationships between putative causal agents and health outcomes in human populations (Déglin *et al.* 2021). These studies can yield more defensible estimates of likely human health risk than those obtained from biologic models based on animal studies (Nurminen *et al.* 1999). That is why risk assessors rely on both toxicological and epidemiological studies when investigating the association between the chemical exposure and the adverse health effects. Epidemiological studies can also contribute to update and modify exposure data due to continuous surveillance of animal and human data, both in terms of exposure and associated health outcomes (Maffini *et al.* 2021). Conversely, epidemiological and risk assessment studies operate in parallel lines due to the inherent limitations and challenges of observational epidemiological studies (Déglin *et al.* 2021).

3 Steps for risk assessment evaluation

The risk assessment process is described by four steps: hazard identification, exposure assessment, dose-response assessment, and risk characterization (USEPA 1991c, OEHHA 2001, WHO 2021). In the first step of the risk assessment process, scientists determine the types

of health problems caused by the exposure to a specific chemical. This step can be accomplished by reviewing studies investigating the effects of the considered species on humans and laboratory animals (OEHHA 2001). "Hazard identification" also includes the determination of hazardousness of a species by international organizations and to which extent (WHO 2021). Then, "exposure assessment" is considered as the process of estimating the magnitude, the frequency, and the duration of the exposure as well as the exposure pathway of a chemical present in the atmosphere (USEPA 1991c). All of this information is combined with factors related to individuals such as body weight, breathing rates or daily activity patterns in order to estimate the quantity of the chemical that is entered into the body. Some of these parameters also differ by age and sex. Hence, the relationship between the likelihood and the severity of adverse health effects, and the amount of the exposure to the chemical is described by the "dose-response assessment". The dose-response relationship often differs between chemicals in general and between the ones that can cause cancer compared to those that can cause other kinds of health problems (OEHHA 2001). Finally, the risk characterization step combines the information developed in the previous steps in order to estimate the risk in an exposed population.

4 Cancer and non-cancer risk assessment

4.1 Cancer risk assessment

According to the United States environmental protection agency, there is no exposure that have "zero risk" while evaluating cancer risk unless there is a clear evidence otherwise (USEPA 1991a). Even an exposure to a very low concentration of cancer-causing pollutant can increase the risk of cancer assuming a linear correlation between dose and response.

The cancer risk evaluation is based on carcinogenic chemicals where risk estimates are assigned to a probability that an individual might develop a cancer over a lifetime as a result of an exposure to a carcinogenic chemical. By that, the cancer risk is usually expressed as the maximum number of cases of cancer projected to occur in a population of 1 million due to the exposure to the cancer-causing substances over a 70-years lifetime (OEHHA 2001). The cancer risk associated with a chemical in a specific exposure pathway will be the product of a lifetime average daily dose by a carcinogenic slope factor (USEPA 1989a).

4.2 Non-cancer risk assessment

Historically, scientists have assumed that some molecular events can evoke mutagenic changes in a cell that leads to damage multiplication and carcinogenicity (Haber *et al.* 2012). This phenomenon is considered as a non-threshold effect because response generation is probable at all exposure levels. The non-cancer risk represents the risk of developing health problems other than cancer. The non-cancer effect is assumed to have a certain threshold or a certain value below which no response is generated. This is mainly due to adaptive protective mechanisms in the cells against toxic effects (Haber *et al.* 2012). Non cancer health effects, such as asthma, nervous system disorders, birth defects, cardiovascular diseases and problems in the development of children, become more severe as the exposure to chemical increases (OEHHA 2001).

The safe threshold doses, which are used for the non-cancer risk evaluation, are designated differently by a number of health agencies worldwide. This threshold dose is reported as a reference dose (RfD) or reference concentration (RfC) by the United States environmental protection agency (USEPA 1994), or an acceptable daily intake (ADI) by the world health organization (Lu 1988). Other agencies reported this threshold dose as a tolerable intake (TI) such as the international program on chemical safety (IPCS 1994), or a minimal risk level (MRL) such as the United States agency for toxic substances and disease registry (ATSDR) (Pohl and Abadin 1995).

According to the United States environmental protection agency, the calculated hazard for a non-cancer health effect is not a probability but a measured ratio of the magnitude of a receptor's potential exposure usually called the average daily dose (ADD) to a standard exposure level such as the reference concentration (RfC) or the reference dose (RfD) (USEPA 1989b). This ratio is also called "Hazard quotient" (HQ) and is calculated for a specific species in a specified exposure pathway. Additionally, the hazard index (HI) is defined as the sum of more than one hazard quotient for multiple substances considering one pathway or multiple exposure pathways considering one substance (USEPA 1991c).

5 Risk assessment methodology

Health risk assessment methods consider several parameters in order to evaluate the severity of the exposure. These factors include the dose or the intake rate, the characteristics of the exposed individuals the concentrations of the pollutant and other parameters related to the harmfulness

of the compounds on human health. The characteristics of the exposed individuals are mainly the body weight, the duration and the frequency of the exposure. In this section, the methodology for the evaluation of the risk related to the exposure to different classes of compounds will be presented, also taking into consideration the three major exposure pathways: inhalation, ingestion, and dermal contact.

5.1 Method developed by the United States environmental protection agency

The health risk assessment presented by the United States environmental protection agency was first developed and published in 1989 and 1991 (USEPA 1989c, 1991c). This method was applied since then to different classes of compounds in particulate matter depending on the availability of reference values for the different species and the different exposure pathways. Both non-cancer and cancer risk evaluation need to consider a daily exposure dose, expressed in mg/kg/day, or a daily exposure concentration, expressed in mg/m³. For the non-cancer risk, the daily exposure dose is referred to as an average daily dose (ADD_i) and the daily exposure concentration is referred to as an exposure concentration in air (EC_i).

The average daily dose (ADD_i) for the different exposure pathways, and the exposure concentration (EC_i) for inhalation are estimated as follows (Eq. 1 to Eq. 4):

$$ADD_{i-inhalation} = \frac{C_i \times IR_{inh} \times ED \times EF \times 10^{-6}}{BW \times AT} \quad (Eq. 1)$$

$$ADD_{i-ingestion} = \frac{C_i \times IR_{ing} \times ED \times EF \times 10^{-6}}{BW \times AT} \quad (Eq. 2)$$

$$ADD_{i-dermal} = \frac{C_i \times SA \times AF \times ABS \times ED \times EF \times 10^{-6}}{BW \times AT} \quad (Eq. 3)$$

$$EC_i = \frac{C_i \times ET \times ED \times EF \times 10^{-6}}{AT} \quad (Eq. 4)$$

Detailed information of each parameter used in the different formulas is given in **Table 1**. The concentration of the species (C_i) is usually considered as the average concentration during the sampling or exposure period. Some of the parameters presented in the formulas are related to the exposed individual such as the inhalation (IR_{inh}) and ingestion (IR_{ing}) rates and the body weight (BW) while other parameters are more related to the frequency (EF) and the duration of the exposure (ED) to an agent (**Table 1**). However, for the evaluation of the cancer risk, the exposure period during which the dose is averaged is usually lifetime or 70 years (USEPA

2011). Accordingly, the lifetime average daily dose ($LADD_i$) for the different exposure pathways can be calculated using Eq. 1 to 4 with lifetime that corresponds to 25500 days replacing the average timing calculated as $AT = ED \times 365$ days (USEPA 1989c, 2011) (**Table 1**).

Additionally, exposure parameters also vary depending on the exposure pathway, the age group chosen such as newborns, children, adolescents, or adults, the sex, and the exposed population, e.g. residents, indoor workers, outdoor workers, etc.. These parameters should be site-specific and should be chosen based on demographic data and exposure factors related to the country or the region. If no data available, default values can be used. For instance, the default body weight (BW) for a newborn between 0 and 1 year is 7.8 kg, while for a child between 1 and 11 years, the body weight is 25 kg, for an adolescent between 12 and 18 years, the body weight is 61 kg, and for an adult, the body weight is 70 kg (**Table 1**). The United States environmental protection agency has published an exposure factor handbook that was updated in 2011 in order to provide statistical data on the various factors used in the assessment of the exposure to air contaminants for assessors inside the agency as well as outside (USEPA 1997a, 2011). The handbook also contain data for the assessment of the exposure to soil and water contaminants.

Furthermore, the Chinese research academy of environmental sciences (CRAES) has also published a Chinese exposure factors handbook for children and adults for the Chinese population (Duan *et al.* 2015, Duan 2016). This data is mainly used by assessors in China since the exposure parameters highly reflects the Chinese population.

5.1.1 Non-cancer risk assessment

The non-cancer risk assessment is based on the comparison between the average daily dose (ADD_i) representing the exposure estimate and the reference dose (RfD_i) or the comparison between the exposure concentration in air (EC_i) to the reference concentration for inhalation (RfC_i). The reference dose (RfD_i), expressed in mg/kg/day, is defined as an estimate of a daily exposure of the human population including sensitive groups that is likely to be without an appreciable risk of deleterious effects during a lifetime (USEPA 2022a). Additionally, the reference concentration (RfC_i) is a similar term that is used to assess inhalation risks and is expressed in mg/m^3 . The ratios between ADD_i and RfD_i or RfC_i are called hazard quotients (HQ_i) and are calculated following either Eq. 5a or Eq. 5b (USEPA 1989c, 1991c, 2011):

$$HQ_i = \frac{ADD_i}{RfD_i} \text{ (Eq. 5a)}$$

$$\text{or } HQ_i = \frac{EC_i}{RfC_i} \text{ (Eq. 5b)}$$

The reference dose (RfD_i) and the reference concentration (RfC_i) values found in the literature for different species in various classes such as PAHs, elements, phthalates, dioxins, furans and dioxin-like polychlorobiphenyls and different exposure pathways are presented in **Table 2**. For non-standard populations, no correction is needed for the reference dose and the reference concentration values (USEPA 2011). This is due to the idea that the integrated risk information system (IRIS) does not consider a 70 kg body weight assumption in the determination of RfD_i and RfC_i. Additionally, the dermal reference dose (RfD_{dermal}) can be determined from oral reference dose (RfD_{oral}) values if a gastrointestinal absorption factor (GIABS) is available as follows:

$$RfD_{dermal} = RfD_{oral} \times GIABS \text{ (Eq. 6)}$$

A default value for gastrointestinal absorption factor of 1 is used except for inorganic compounds such as Sb, Ba, Be, Cd, Cr(VI), Mn, Ni, Ag and V that were assigned values of 0.15, 0.07, 0.007, 0.025, 0.025, 0.04, 0.04, 0.04 and 0.026, respectively (USEPA 2004b).

A receptor might also be exposed to different chemicals associated with non-cancer effects. By that, the non-cancer risk values can be presented either by species for the different exposure pathways, or by the sum of species for a specific exposure pathway, or by the sum of species for all exposure pathways (USEPA 1989c, 1991c, 2011). In order to distinguish between the different definitions, we will describe each one separately.

The total hazard quotient (total HQ_i) is defined as the non-cancer risk for a species in the different exposure pathways assuming additive effects and is calculated as follows (Eq.7):

$$Total HQ_i = HQ_{i-inhalation} + HQ_{i-ingestion} + HQ_{i-dermal} \text{ (Eq. 7)}$$

In order to calculate the non-cancer risk for a family of chemicals in a specific exposure pathway, the hazard index (HI) is used and will be calculated as follows (Eq.8):

$$HI_{inhalation/ingestion/dermal} = \sum_i HQ_{i-inhalation/ingestion/dermal} \text{ (Eq. 8)}$$

Finally, in order to evaluate the total non-cancer risk for a specific family for the combined exposure pathways, the total hazard index (THI) is calculated as follows (Eq. 9):

$$Total\ HI = THI = HI_{inhalation} + HI_{ingestion} + HI_{dermal} \quad (Eq. 9)$$

Generally, the higher hazard quotient, total hazard quotient, hazard index and total hazard index values above 1, the greater is the level of concern and the higher the probability of occurrence for hazardous non-cancer effects (USEPA 2011).

5.1.2 Cancer risk assessment

The cancer risk (CR_i) for a specific chemical in one exposure pathway is calculated as follows (Eq. 10a and Eq. 10b), considering the exposure concentration (EC_i) or the lifetime average daily dose ($LADD_i$):

$$CR_{i-inhalation} = EC_i \times IUR_i \quad (Eq. 10a)$$

$$or \quad CR_{i-inhalation/ingestion/dermal} = LADD_i \times CSF_i \quad (Eq. 10b)$$

IUR_i is the inhalation unit risk for a chemical expressed in m^3/mg used to calculate the cancer risk associated with the inhalation pathway (USEPA 1997a). CSF_i is the cancer slope factor for a chemical in a specific exposure pathway expressed in $kg \cdot day/mg$. Cancer slope factors (CSF) and inhalation unit risk (IUR) values found in the literature for different species and classes of compounds in particulate matter are presented in Table 2. According to USEPA (1997a), cancer slope factors and inhalation unit risk values are corrected for non-standard populations, i.e. body weight (BW) different than 70 kg, by multiplying the values by $\sqrt[3]{\frac{BW}{70}}$.

323 Table 1: Exposure parameters through inhalation, ingestion, and dermal contact (*USEPA: *United States environmental protection agency*)

Exposure parameters		Unit	Availability of data	Reference
Concentration in air	C_i	ng/m ³		
Inhalation intake rate	IR_{inh}	m ³ /day	Short-term and long-term exposure values for inhalation are available for different age groups in the USEPA* exposure handbook 20 m ³ /day for an adult and 10 m ³ /day for a child	(USEPA 2011)
Soil intake rate	IR_{ing}	mg/day	Data is available for different age groups in the USEPA* exposure handbook 100 mg/day for a child and 50 mg/day for and adult	(USEPA 2011)
Body weight	BW	kg	Body weight is considered a demographic parameter. The use of specific data for the country or the region is recommended. If no data available, default body weight values for different age groups and sex found in the USEPA* exposure handbooks: 7.8 kg for newborns (0 to <1 year), 25 kg for children (1 to <12 years), 61 kg for adolescents (12 to <18 years) and 70 for adults (18 to 70 years)	(USEPA 1991c, 1997a, 2011)
Exposure frequency	EF	days/year	225 days for outdoor workers, 250 days for indoor workers and 350 days for residents	(USEPA 2002, 2004b)
Exposure time	ET	h/day	6 hours for a child, and 8 hours for an adult	(Liu <i>et al.</i> 2018, Dahmardeh Behrooz <i>et al.</i> 2021)
Exposure duration	ED	years	Exposure durations can be found in the USEPA* exposure handbook for different age groups: 1 for newborns (0 to <1 year), 11 for children (1 to <12 years), 6 for adolescents (12 to <18 years) and 52 for adults (18 to 70 years)	(USEPA 2011)
Average timing	AT	days	AT = ED x 365(days) for non-carcinogens AT = 70 years x 365 for carcinogens	(USEPA 1989c)
Exposed skin surface area	SA	cm ²	Exposed skin surface area can be found in the exposure handbook. The default exposed surface area is 2800 cm ² for a child, 5700 cm ² for an adult, 3300 cm ² for an outdoor worker and 3300 cm ² for a construction worker	(USEPA 2002, 2011)
Dermal adherence factor	AF	mg/cm ²	0.2 mg/cm ² for a child, 0.07 mg/cm ² for an adult resident, and 0.2 mg/cm ² for an adult worker	(USEPA 2002)
Dermal adsorption factor	ABS	-	0.13 for polycyclic aromatic hydrocarbons 0.03 for As 0.001 for Cd 0.01 for other elements	(USEPA 2002, 2011)

325 Table 2: Values of the reference dose (RfD), reference concentration (RfC), cancer slope factor (CSF), and inhalation unit risk (IUR) reported in
326 the literature for the different species

Compound	Reference dose (RfD) (mg/kg/day)			Reference concentration (RfC) (mg/m ³)	Cancer slope factor (CSF) (kg·day/mg)			Inhalation unit risk (IUR) (m ³ /mg)
	Dermal	Ingestion	Inhalation		Dermal	Ingestion	Inhalation	
Polycyclic aromatic hydrocarbons								
benzo[a]pyrene	-	3 x 10 ⁻⁴ ^c	-	2 x 10 ⁻⁶ ^c	25 ^a	7.3 ^a	3.85 ^a	6 x 10 ⁻¹ ^c
Dioxins, furans, dioxin-like polychlorobiphenyls								
2,3,7,8-tetrachlorinated dibenzo-p-dioxin	-	7 x 10 ⁻¹⁰ ^c	-	4 x 10 ⁻⁸ ^c	-	1.3 x 10 ⁵ ^c	-	3.8 x 10 ⁴ ^c
Phthalates								
bis(2-ethylhexyl)phthalate	-	2 x 10 ⁻² ^c	-	-	-	1.4 x 10 ⁻² ^c	8.4 x 10 ⁻³ ^b	2.4 x 10 ⁻³ ^c
butyl benzyl phthalate	-	2 x 10 ⁻¹ ^c	-	-	-	1.9 x 10 ⁻² ^c	-	-
diethylphthalate	-	8 x 10 ⁻¹ ^c	-	-	-	-	-	-
dibutylphthalate	-	1 x 10 ⁻¹ ^c	-	-	-	-	-	-
Elements								
aluminum	-	1 ^c	-	5 x 10 ⁻³ ^c	-	-	-	-
antimony metallic	-	4 x 10 ⁻⁴ ^c	-	3 x 10 ⁻⁴ ^c	-	-	-	-
arsenic, inorganic	1.23 x 10 ⁻⁴ ^d	3 x 10 ⁻⁴ ^{c,d}	3.01 x 10 ⁻⁴ ^d	1.5 x 10 ⁻⁵ ^c	1.5 ^{e,g}	1.5 ^c	15.1 ^{c,d}	4.3 ^c
barium	-	2 x 10 ⁻¹ ^c	-	5 x 10 ⁻⁴ ^c	-	-	-	-
cadmium	1 x 10 ⁻⁵ ^d	1 x 10 ⁻³ ^c	1 x 10 ⁻⁵ ^d	1 x 10 ⁻⁵ ^c	-	-	6.3 ^e	1.8 ^c
chromium (VI)	6 x 10 ⁻⁵ ^d	3x 10 ⁻³ ^{c,d}	2.86 x 10 ⁻⁵ ^d	1 x 10 ⁻⁴ ^c	20 ^g	5 x 10 ⁻¹ ^c	41 ^c	84 ^c
cobalt	1.6 x 10 ⁻² ^d	3 x 10 ⁻³ ^c	5.71 x 10 ⁻⁶ ^d	6 x 10 ⁻⁶ ^c	-	-	9.8 ^e	9 ^c
copper	1.2 x 10 ⁻² ^d	4 x 10 ⁻² ^{c,d}	6.9 x 10 ⁻⁴ ^d	-	-	-	-	-
iron	-	7 x 10 ⁻¹ ^c	-	-	-	-	-	-
lanthanum	-	5 x 10 ⁻⁵ ^c	-	-	-	-	-	-
lead	5.2 x 10 ⁻⁴ ^d	3.52 x 10 ⁻³ ^d	3.5 x 10 ⁻⁵ ^d	-	8.5 x 10 ⁻³ ^g	8.5 x 10 ⁻³ ^e	4.2 x 10 ⁻² ^e	1.2 x 10 ⁻⁵ ^h
manganese	1.84 x 10 ⁻³ ^d	1.4 x 10 ⁻¹ ^c	1.43 x 10 ⁻⁵ ^d	5 x 10 ⁻⁵ ^c	-	-	-	-
mercury	3 x 10 ⁻⁴ ^c	3 x 10 ⁻⁴ ^c	3 x 10 ⁻⁴ ^c	3 x 10 ⁻⁴ ^c	-	-	-	-
nickel	9 x 10 ⁻⁵ ^d	2 x 10 ⁻² ^{c,d}	9 x 10 ⁻⁵ ^d	9 x 10 ⁻⁵ ^c	-	-	0.84 ^d	0.26 ^c
strontium	-	6 x 10 ⁻¹ ^c	-	-	-	-	-	-
thallium (soluble salts)	-	1 x 10 ⁻⁵ ^c	-	-	-	-	-	-
tin	-	6 x 10 ⁻¹ ^c	-	-	-	-	-	-
vanadium	-	5 x 10 ⁻³ ^c	-	1 x 10 ⁻⁴ ^c	-	-	-	8.3 ⁱ
zinc	6 x 10 ⁻² ^d	3 x 10 ⁻¹ ^{c,d}	3 x 10 ⁻¹ ^d	-	-	-	-	-

327 ^a(Peng *et al.* 2011); ^b(OEHHA 2011); ^c(USEPA-IRIS 2022); ^d(Hao *et al.* 2020); ^e(Bello *et al.* 2017); ^f(USEPA 2009);
328 ^g(USEPA 2004b); ^h(CalEPA 2022); ⁱ(PPRTV 2022); ^j(USEPA 1997b); ^k(RAIS 2022).

Additionally, dermal cancer slope factor can be determined from oral cancer slope factor values if a gastrointestinal absorption factor (GIABS) is available (Eq.11):

$$CSF_{dermal} = \frac{CSF_{oral}}{GIABS} \quad (Eq. 11)$$

The total cancer risk for a species is calculated as the sum of the different risks associated with the different exposure pathways and is presented as follows (Eq.12):

$$Total\ CR_i = CR_{i-inhalation} + CR_{i-ingestion} + CR_{i-dermal} \quad (Eq. 12)$$

The cancer risk for a family of chemicals associated with a specific exposure pathway is estimated as follows (Eq.13):

$$CR_{inhalation/ingestion/dermal} = \sum_i CR_{i\ inhalation/ingestion/dermal} \quad (Eq. 13)$$

The cumulative cancer risk (CCR) as the risk attributed to a family of compounds in the combined three exposure pathways is calculated as follows (Eq.14):

$$Cumulative\ CR = CCR = CR_{inhalation} + CR_{ingestion} + CR_{dermal} \quad (Eq. 14)$$

The United States environmental protection agency considers a risk level of 10^{-6} (one additional case per one million people) as the threshold limit (USEPA 1991b). More concern should be given regarding these chemicals when the risk level exceeds the threshold. Additionally, values between 10^{-6} and 10^{-4} denote a potential risk and values higher than 10^{-4} indicate a high potential cancer risk (Chiang *et al.* 2009).

Furthermore, the cancer risk can be calculated for different age categories and summed together in order to obtain an average lifetime cancer risk (LCR) or an incremental lifetime cancer risk (ILCR) (OEHHA 2012):

$$\begin{aligned} LCR = & Cumulative\ CR_{Newborn} \times \frac{ED_{newborn}}{70} + Cumulative\ CR_{child} \times \frac{ED_{child}}{70} \\ & + Cumulative\ CR_{adolescent} \times \frac{ED_{adolescent}}{70} \\ & + Cumulative\ CR_{adult} \times \frac{ED_{adult}}{70} \quad (Eq. 15) \end{aligned}$$

5.1.3 Concentration of the species in the risk assessment evaluation

The risk assessment in air samples can be evaluated for the exposure to the gas-phase compounds as well as the particulate phase. Therefore, several classes of compounds are usually used for the assessment of the cancer and the non-cancer risk such as elements, PAHs, phthalates, dioxins, furans, and dioxin-like polychlorobiphenyls.

PAHs refer to lipophilic chemical compounds that are formed by two or more aromatic rings that are environmentally persistent with various structures and toxicity (Halek *et al.* 2010, Abdel-Shafy and Mansour 2016). Phthalates are a class of human-made chemicals that are commonly used to increase the flexibility of plastic products, especially in poly(chloride)vinyl (PVC) products (USEPA 2012). Dioxins, furans, and dioxin-like polychlorobiphenyls are semi-volatile persistent organic pollutants that can be transported far from their emission sources (Srogi 2008, Koukoulakis *et al.* 2020). Even if these organic and inorganic species are found in low amounts in particulate matter, it has been shown that they largely contribute to the particulate matter toxicity (Akhtar *et al.* 2010, Fortoul *et al.* 2015, Bandowe and Meusel 2017). On the other hand, ammonium, sulfate, sea salts, and crustal elements that contribute largely to particulate matter mass contribute the least to the toxicity (Borm *et al.* 2007). The assessment for elements and phthalates is usually done by evaluating the risk of each species. The reason is that some of them are considered carcinogenic while others can only be evaluated for their non-cancer risks. For example, diethylphthalate and dibutylphthalate are only evaluated for their non-cancer risks due the fact that no cancer slope factor or inhalation unit risk values were found for these species in order to assess their cancer risk. On the other hand, bis(2-ethylhexyl)phthalate and butyl benzyl phthalate are evaluated for both cancer and non-cancer risks due to the availability of reference coefficients in the literature (**Table 2**).

Among PAHs, dioxins, and furans, benzo[a]pyrene (B[a]P) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) are known to be carcinogenic to humans (IARC 2021). A toxic equivalent factor (TEF) was introduced to assign toxicity values for the different congeners based on the toxicity of either B[a]P or 2,3,7,8-TCDD reported as 1 (Nisbet and LaGoy 1992, Van den Berg *et al.* 2006).

Table 3: Toxic equivalent factor (TEF) values for the different polycyclic aromatic hydrocarbons (PAHs) and their derivatives

Compound name	Toxic equivalent factor (TEF) value
acenaphthylene	0.001 ^a
1-methylnaphthalene	0.0025 ^b
2-methylnaphthalene	0.001 ^a
acenaphthene	0.001 ^a
fluorene	0.001 ^a
7H-benzo[c]fluorene	20 ^e
anthracene	0.01 ^a
phenanthrene	0.001 ^a
1-methylphenanthrene	0.001 ^e
fluoranthene	0.001 ^a
pyrene	0.001 ^a
cyclopenta[c,d]pyrene	0.01 ^e
1-methylpyrene	0.001 ^e
benz[a]anthracene	0.1 ^a
chrysene/triphenylene	0.01 ^a
5-methylchrysene	1 ^e
benzo[b]fluoranthene	0.1 ^a
benzo[k]fluoranthene	0.1 ^a
benzo[a]pyrene	1 ^a
benzo[e]pyrene	0.002 ^d
dibenz[a,h]anthracene	5 ^a
benzo[g,h,i]perylene	0.01 ^a
indeno(1,2,3-C,D)pyrene	0.1 ^a
dibenzo[a,l]pyrene	0.001 ^e
dibenzo[a,e]pyrene	10 ^e
dibenzo[e,l]pyrene	1 ^e
dibenzo[a,i]pyrene	10 ^e
dibenzo[a,h]pyrene	10 ^e
5-nitroacenaphthene	0.01 ^d
2-nitrofluorene	0.01 ^b
9-nitroanthracene	0.0032 ^c
3-nitrofluoranthene	0.0026 ^c
1-nitropyrene	0.1 ^b
6-nitrochrysene	10 ^b

^a(Nisbet and LaGoy 1992), ^b(Collins *et al.* 1998), ^c(Durant *et al.* 1996), ^d(Hester and Harrison 1998), ^e(Iakovides *et al.* 2021)

The health risk evaluation for the PAHs and dioxins/furans classes of compounds is conducted using the benz[a]pyrene equivalent concentration (B[a]P_{eq}) and the toxic equivalent concentration of 2,3,7,8-tetrachlorinated dibenzo-p-dioxin (WHO-TEQ) using the following formulas (Eq.16a and Eq.16b):

$$\text{WHO - TEQ} = \sum_{i=1}^n C_i \times \text{TEF}_i \quad (\text{Eq. 16a})$$

$$\text{B[a]P}_{\text{eq}} = \sum_{j=1}^n C_j \times \text{TEF}_j \quad (\text{Eq. 16b})$$

C_i and C_j , expressed in ng/m^3 , are the concentrations of the dioxins, furans and dioxin-like polychlorobiphenyls congeners, and PAHs and their derivatives, respectively. TEF_i and TEF_j correspond to the toxic equivalent factor compared to 2,3,7,8-TCDD and B[a]P, respectively (Nisbet and LaGoy 1992, Collins *et al.* 1998, Van den Berg *et al.* 2006). The values of toxic equivalent factors, TEF_i and TEF_j are found in **Table 3** and **Table 4**. The calculated B[a]P_{eq} or WHO-TEQ are added in Equations 1 to 4 to calculate the daily dose or exposure concentration and then the non-cancer or cancer risks.

5.2 Other parameters and formulas included in the assessment of the health risk

5.2.1 Cancer risk for phthalates

In the evaluation of the cancer risks for phthalates, Zhang *et al.* (2019b) applied the same formulas presented in section 3.1.2 to calculate the lifetime average daily dose for inhalation. However, an additional factor related to the age sensitivity factor was added to the calculations of the 70-years lifetime cancer risk when considering different age categories in the calculations. The authors have added an age sensitivity factor (ASF) of 10 for infants between the age of 0 and 2, 3 for toddlers between the age of 3 and 6, 3 for adolescents between the age of 7 and 16, and 1 for adults between the age of 17 and 70 based on the reported of the office of environmental health hazard assessment (OEHHA). OEHHA developed these ASF to take into account the higher sensitivity to carcinogens during early-life exposure (OEHHA 2015) but are not highly used in the literature to calculate the health risk for the different age categories.

5.2.2 Cancer risk for polycyclic aromatic hydrocarbons

Several papers estimating the health risk due to the exposure to PAHs only consider the inhalation pathway and calculate a lifetime excess cancer risk (ECR). The formula used for the calculation of excess cancer risk related to PAHs exposure is the same as Eq.10a but instead of

422 multiplying an exposure concentration by the inhalation unit risk, the assessors directly use the
 423 B[a]P_{eq} (Yang *et al.* 2017, Song *et al.* 2019, Pateraki *et al.* 2020, Tsai *et al.* 2020).

424
 425 Table 4: Available toxic equivalent factor (TEF) values presented by the world health
 426 organization (WHO) in 1998 and re-evaluated in 2005 for dioxins, furans and dioxin-like
 427 polychlorobiphenyls (Van den Berg *et al.* (2006)

	WHO 1998	WHO 2005
Dioxins (PCDDs)		
2,3,7,8-tetrachlorinated dibenzo-p-dioxin	1	1
1,2,3,7,8-pentachlorinated dibenzo-p-dioxin	1	1
1,2,3,4,7,8-hexachlorinated dibenzo-p-dioxin	0.1	0.1
1,2,3,6,7,8-hexachlorinated dibenzo-p-dioxin	0.1	0.1
1,2,3,7,8,9-hexachlorinated dibenzo-p-dioxin	0.1	0.1
1,2,3,4,6,7,8-heptachlorinated dibenzo-p-dioxin	0.01	0.01
octachlorinated dibenzo-p-dioxin	0.0001	0.0003
Furans (PCDFs)		
2,3,7,8 tetrachlorinated dibenzofuran	0.1	0.1
1,2,3,7,8 pentachlorinated dibenzofuran	0.05	0.03
2,3,4,7,8 pentachlorinated dibenzofuran	0.5	0.3
1,2,3,4,7,8 hexachlorinated dibenzofuran	0.1	0.1
1,2,3,6,7,8 hexachlorinated dibenzofuran	0.1	0.1
2,3,4,6,7,8 hexachlorinated dibenzofuran	0.1	0.1
1,2,3,7,8,9 hexachlorinated dibenzofuran	0.1	0.1
1,2,3,4,6,7,8-heptachlorinated dibenzofuran	0.01	0.01
1,2,3,4,7,8,9-heptachlorinated dibenzofuran	0.01	0.01
octachlorinated dibenzofuran	0.0001	0.0003
Dioxin-like polychlorobiphenyls (DL-PCBs)		
3,4,4',5-tetrachlorobiphenyl	0.0001	0.0003
3,3',4,4'-tetrachlorobiphenyl	0.0001	0.0001
2,3',4,4',5'-pentachlorobiphenyl	0.0001	0.00003
2,3',4,4',5-pentachlorobiphenyl	0.0001	0.00003
2,3,4,4',5-pentachlorobiphenyl	0.0005	0.00003
2,3,3',4,4'-pentachlorobiphenyl	0.0001	0.00003
3,3',4,4',5-pentachlorobiphenyl	0.1	0.1
2,3',4,4',5,5'-hexachlorobiphenyl	0.00001	0.00003
2,3,3',4,4',5-hexachlorobiphenyl	0.0005	0.00003
2,3,3',4,4',5'-hexachlorobiphenyl	0.0005	0.00003
3,3',4,4',5,5'-hexachlorobiphenyl	0.01	0.03
2,3,3',4,4',5,5'-heptachlorobiphenyl	0.0001	0.00003

428
 429 The United States environmental protection agency proposed $6 \times 10^{-7} (\text{ng}/\text{m}^3)^{-1}$ as the inhalation
 430 unit risk value for B[a]P_{eq}. However, inhalation unit risk value was reported as 8.7×10^{-5}

(ng/m³)⁻¹ by the world health organization (WHO 2000), and 1.1 x 10⁻⁶ (ng/m³)⁻¹ by the office of environmental health hazard assessment (OEHHA 2009). The two latter agency used a method that does not take into consideration the different exposure parameters but only considers the pollutant concentration and a fixed unit risk leading to an overestimation or an underestimation of the real risk. Consequently, the United States environmental protection agency method can contribute to more accurate results based on the different exposure pathways and the age categories.

5.2.3 Non-cancer and cancer risks for elements

For the elements, a dimensionless average annual excess risk for an individual (R) can be used to calculate the cancer and the non-cancer risks using the average daily dose (ADD_i) and the lifetime daily dose (70 x RfD_i), respectively, as follows (Eq. 17-18) (Chen *et al.* 2015, Wang *et al.* 2018):

$$R(\text{non} - \text{carcinogenic}) = \frac{10^{-6} \times ADD_i}{70 \times RfD_i} \quad (\text{Eq. 17})$$

$$R(\text{carcinogenic}) = \frac{1 - e^{-\frac{LADD}{CSF}}}{70} \quad (\text{Eq. 18})$$

In this calculation, the threshold value above which the risk is unacceptable for cancer risk is also 10⁻⁶, whereas the risk level of 10⁻³ per year or higher is considered serious and a high priority for attention (Wang *et al.* 2018). The acceptable value for the non-cancer risk is lower than one.

Other papers integrated the bioaccessibility of the elements in the health risk evaluation. The bioaccessibility represents the fraction of the species concentration that is released from the environmental matrix into a synthetic biological fluid and becomes available for absorption (Expósito *et al.* 2021). Therefore, the bioavailability, considered as the fraction of the species in the exposure media absorbed by the organism, is influenced by the bioaccessibility since solubilization is required for crossing membranes in the body (USEPA 2007). By that, the bioaccessible fraction represents the maximum amount of the species that can be absorbed (Manjón *et al.* 2020). Hu *et al.* (2011) estimated the relative bioaccessibility (RBA) of the elements using a simple bioavailability extraction test (SBET) and integrated them to the

estimation of the cancer risk and the hazard quotient through ingestion pathway as follows (Eq.19a and Eq.19b):

$$HQ_{ingestion} = \frac{ADD_i \times RBA}{RfD_i} \quad (Eq. 19a)$$

$$CR_{i-ingestion} = LADD_i \times RBA \times CSF_i \quad (Eq. 19b)$$

Where RBA is the relative bioaccessibility corresponding to the ratio of the elements' contents extracted using the simple bioavailability extraction test method to their total contents in the study. According to the study, the highest bioaccessibility rates were observed for Cd, Zn and Pb with values exceeding 60%. On the other hand, the lowest values were attributed for Cr, Co, and Ni with mean values of bioaccessibility ranging between 12 and 19%. These values were also applied by Iakovides *et al.* (2021) that added the relative bioaccessibility parameter to the different formulas used for the calculations of the cancer risk in the three exposure pathways.

Furthermore, Nie *et al.* (2018) evaluated the bioaccessibility of the elements through different simulated body fluids in order to have different contact interfaces between human body and particulate elements. Nie *et al.* (2018) used artificial lung fluid, artificial sweat, and artificial gastric juice, and phosphate buffered saline solution. The trace elements that have the highest bioaccessibility in artificial lung fluid and in artificial sweat were As, Cu, Pb and V (60-80%). V, Cu, As, and Mn had the highest values in phosphate buffered saline solution (62-82%), and V, Pb, Cu, and Mn in artificial gastric juice (67-84%). According to Mishra *et al.* (2021), the concentration of the bioaccessible fraction is more relevant than the total concentration of the element for a better and more accurate risk assessment of the element toxicity. Up to our knowledge, there were no other study using the bioaccessible fraction of other species in the risk assessment evaluation.

6 Risk assessment studies

The health risk related to particulate matter exposure is generally evaluated by studying the cancer and non-cancer risks of one or several classes of compounds such as PAHs, phthalates, dioxins, furans, dioxin-like polychlorobiphenyls, and elements as mentioned earlier.

486 Table 5: Selection of health risk assessment studies reported in the literature for polycyclic aromatic hydrocarbons (PAHs), elements, phthalates,
487 dioxins and furans (PCDD/Fs), and dioxin-like polychlorobiphenyls (DL-PCBs)

Site (Country)	Risk evaluation	Class of compounds	Total cancer risk values	Total non-cancer risk values	Exposure pathways	Age categories	Problematic species	Reference
Zouk Mikael and Fiaa (Lebanon)	Cancer and non-cancer risk	PAHs Elements Phthalates PCDD/Fs and DL-PCBs	$0.4 - 1.4 \times 10^{-5}$ $2.5 - 4.4 \times 10^{-5}$ $3.8 - 5.1 \times 10^{-7}$ 4×10^{-7}	$0.1 - 0.4$ $0.3 - 1.2$ $0.001 - 0.1$ $0.01 - 0.06$	Inhalation, ingestion, and dermal contact	Newborns, children, adolescents, and adults	Sum of PAHs reported to benzo[a]pyrene, As, Co, Cr(VI), Ni and V	Fadel <i>et al.</i> (2022)
Thohoyandou (South Africa)	Cancer and non-cancer risk	Elements	3.4×10^{-6}	$0.54 - 1.18$	Inhalation	Lifetime	Ni	Edlund <i>et al.</i> (2021)
Tangshan (China)	Cancer and non-cancer risk	Elements	$0.4 - 1.5 \times 10^{-4}$	$2.8 - 2.81$	Inhalation	Children and adults	Mn, As, Cd, and Cr(VI)	Fang <i>et al.</i> (2021)
Abuja (Nigeria)	Cancer and non-cancer risk	Elements	$1.4 - 4.0 \times 10^{-10}$	$10^{-5} - 10^{-4}$	Inhalation, ingestion, and dermal contact	Children and adults	-	Sulaymon <i>et al.</i> (2020)
Sha-Lu area (Taiwan)	Cancer risk using a unit risk for inhalation	Elements	8.2×10^{-5}	-	Inhalation	Lifetime	As and Cr(VI)	Tsai <i>et al.</i> (2020)
Iasi (Romania)	Cancer and non-cancer risk	Elements	$6.3 - 8.0 \times 10^{-6}$	$0.2 - 0.3$	Inhalation	Lifetime	As and Cr(VI)	Galon-Negru <i>et al.</i> (2019)
Barcelona (Spain)	Cancer and non-cancer risk	Elements	$2.3 - 3.1 \times 10^{-5}$	below 1	Inhalation	Lifetime	Cr(VI)	Sánchez-Soberón <i>et al.</i> (2015)
Nicosia (Cyprus)	Cancer risk	PAHs Elements	7.1×10^{-4} 7.7×10^{-4}	-	Inhalation, ingestion, and	Lifetime	Sum of PAHs As, Ni, and Pb	Iakovides <i>et al.</i> (2021)

					dermal contact			
Penteli, Votanikos, and Tourlos (Greece)	Cancer risk using a unit risk for inhalation	PAHs	$0.3 - 2.6 \times 10^{-7}$	-	Inhalation	Lifetime	benzo[a]pyrene	Pateraki <i>et al.</i> (2020)
Harbin (China)	Cancer and non-cancer risk	PAHs	4.1×10^{-4}	-	Inhalation, ingestion, and dermal contact	Children, adolescents, and adults	Benzo[a]pyrene, indeno(1,2,3-c,d)pyrene, and benzo(k)fluoranthene	Ma <i>et al.</i> (2020b)
Beijing (China)	Cancer risk	PAHs	8.7×10^{-6}	-	Inhalation	Lifetime	Benzo[a]pyrene	Chang <i>et al.</i> (2019)
Jamshedpur (India)	Cancer risk	PAHs	$1.0 - 2.3 \times 10^{-5}$	-	Inhalation	Lifetime	Benzo[a]pyrene, dibenz[a,h]anthracene	Kumar <i>et al.</i> (2019)
Beijing (China)	Cancer risk using a unit risk for inhalation	PAHs	3.0×10^{-4}	-	Inhalation	Lifetime	Sum of PAHs reported to benzo[a]pyrene	Song <i>et al.</i> (2019)
Northern Thailand	Cancer risk	PAHs	$0.8 - 2.6 \times 10^{-3}$	-	Inhalation, ingestion, and dermal contact	Lifetime	Sum of PAHs reported to benzo[a]pyrene	Pongpiachan (2015)
Eleusis (Greece)	Cancer risk	PAHs PCDD/Fs and DL-PCBs	2.4×10^{-5} 1.2×10^{-5}	-	Inhalation	Lifetime	Sum of PAHs reported to benzo[a]pyrene and the sum of PCDD/Fs	Koukoulakis <i>et al.</i> (2020)
Suzhou of Jiangsu province (China)	Cancer risk	PCDD/Fs	$0.2 - 2.7 \times 10^{-5}$	-	Inhalation	Lifetime	Sum of PCDD/Fs reported to 2,3,7,8-TCDD	Sun <i>et al.</i> (2017)
Around metallurgical plants in China	Cancer risk using a unit risk for inhalation	PCDD/Fs, DL-PCBs	Sintering plants: $0.1 - 4 \times 10^{-5}$ Copper plants: $0.05 - 1.1 \times 10^{-4}$	-	Inhalation	Lifetime	Sum of PCDD/Fs reported to 2,3,7,8-TCDD	Yang <i>et al.</i> (2017)

			Aluminum plants: $0.04 - 7.1 \times 10^{-4}$ Lead plant: 2.1×10^{-6}					
Beirut (Lebanon)	Cancer risk	PCDD/Fs	6.5×10^{-5}	-	Inhalation	Different age categories	Sum of PCDD/Fs reported to 2,3,7,8- TCDD	Baalbaki <i>et al.</i> (2016)
Xi'an (China)	Cancer and non-cancer risk	Phthalates	$10^{-12} - 10^{-10}$	$10^{-7} - 10^{-3}$	Inhalation	Lifetime	bis-2- ethylhexylphthalate, and butyl benzyl phthalate	Ma <i>et al.</i> (2020a)
Guangzhou, Shanghai, Beijing, and Harbin (China)	Cancer and non-cancer risk	Phthalates	$10^{-10} - 10^{-7}$	0.01 – 0.02	Inhalation	Infants (0-2 years), toddlers (3-6 years), adolescents (7- 17 years), and adults (17- 0 years)	bis-2- ethylhexylphthalate	Zhang <i>et al.</i> (2019b)

6.1 Search methodology for risk assessment publications

For this review, the authors conducted a literature search using several online literature databases such as Google scholar, Web of Science; ScienceDirect, PubMed, etc.). The keywords searched for were “health risk assessment in particulate matter”, “risk evaluation in particulate matter” as well as the “health risk assessment” for the different classes of compounds in particulate matter such as elements, PAHs, phthalates, dioxins and furans, and dioxin-like polychlorobiphenyls. After obtaining articles using the aforementioned keywords, the articles were then filtered based on the title and the abstract of the research. The authors did not take into consideration publications related to the health risk assessment of PAHs, phthalates, dioxins and furans, and dioxin-like polychlorobiphenyls in the gaseous phase as well as the evaluation of the risk due to the exposure to volatile organic compounds.

Number of publications

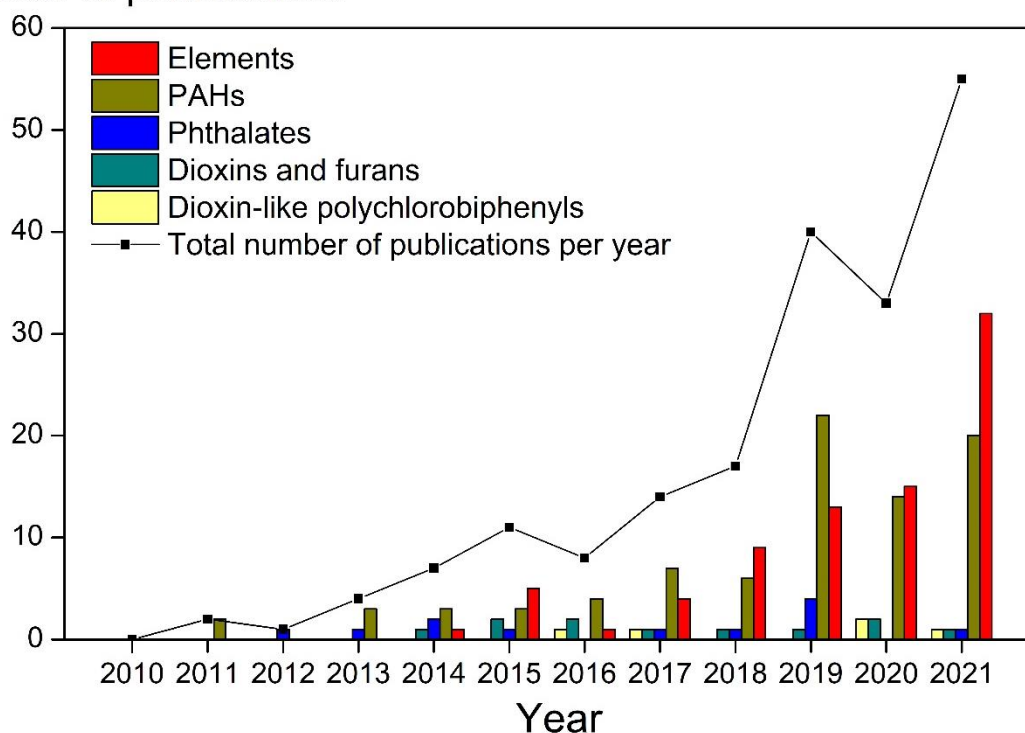


Fig. 2: Number of articles published related to the health risk evaluation for different classes of compounds in particulate matter (elements, polycyclic aromatic hydrocarbons (PAHs), phthalates, dioxins and furans, and dioxin-like polychlorobiphenyls).

The evolution of the number of publications between 2010 and 2021 dealing with health risk assessment for the different classes of compounds in particulate matter is presented in **Fig. 2**. Additionally, more details can be found regarding these publications in the supplementary information. The figure shows that the number of publications including the health risk evaluation is highly increasing especially for elements and PAHs in particulate matter. However, few studies were found for phthalates, dioxins, furans, and dioxin-like polychlorobiphenyls.

6.2 Risk assessment studies per class of compounds

Table 5 presents a selection of papers dealing with the evaluation of the health risk for particulate matter components. In general, most of the studies found in the literature include both the chemical characterization of particulate matter as well as source apportionment and health risk evaluation. Furthermore, most of the studies focus on the exposure through one pathway that is inhalation and one class of compounds as shown in **Table 5**. Literature regarding the comparison of the health risks between different classes of compounds in particulate matter is scarce and more effort should be done in order to further understand the mechanism of interactions between species. Therefore, the presentation and the analysis of the different studies found in the literature will be discussed by class of species.

6.2.1 Polycyclic aromatic hydrocarbons

PAHs, oxygenated-PAHs, and nitrated-PAHs are mainly emitted from petrogenic, pyrogenic, and biogenic sources and are formed during the incomplete combustion of fossil fuels, natural gas, wood, coke, and organic waste (Abbas *et al.* 2018). PAHs can enter the human body through ingestion, inhalation, and dermal contact. The general population is usually exposed to a mixture of PAHs. The latter are present in the indoor or outdoor air as well as associated to cigarette and wood smokes, biomass and fossil fuels burning. The short-term exposure to PAHs might cause impaired lung function in asthmatics and thrombotic effects for people with coronary heart disease (Kim *et al.* 2013). Additionally, the exposure to high concentrations of pollutant mixtures containing PAHs might result in eye irritation, nausea, vomiting, etc. (Abdel-Shafy and Mansour 2016). On the other hand, some studies have shown that the long-term exposure to PAHs is linked to several health problems such as skin, lung bladder, and gastrointestinal cancers in workers (Abbas *et al.* 2018). Like many carcinogens, PAHs are metabolized enzymatically to various metabolites, of which some are reactive (Rengarajan *et*

al. 2015). The toxicity, mutagenicity and/or carcinogenic properties of the PAHs have made 16 of them listed as priority pollutants (Srogi 2007, Hussar *et al.* 2012): naphthalene, acenaphthylene, acenaphthene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, indeno[1,2,3-c,d]pyrene, dibenz[a,h]anthracene and benzo[g,h,i]perylene.

Most of the studies in the literature reported the concentrations of the 16 PAHs to an equivalent concentration of B[a]P considered as a key carcinogenic marker belonging to PAH species. Few studies in the literature added the oxygenated and nitrated derivatives of PAHs in the B[a]P_{eq} calculations (Bandowe *et al.* 2014, de Oliveira Galvão *et al.* 2018, Gao *et al.* 2018, Wei *et al.* 2021).

As observed in **Table 5**, benzo[a]pyrene, indeno(1,2,3-c,d)pyrene, benzo(k)fluoranthene, and dibenz[a,h]anthracene generally contribute the most to the calculated cancer risk. This is mainly due to their high toxic equivalent factor corresponding values compared to other PAHs (**Table 3**). These species along with benz[a]anthracene, chrysene, and benzo(b)fluoranthene are classified by the international agency for research on cancer as group 1, 2A, or 2B (IARC 2021). Several studies have reported that adults exhibited a greater cancer risk than children (Gong *et al.* 2019, Sulong *et al.* 2019, Wang *et al.* 2019, Bai *et al.* 2020). According to Chang *et al.* (2019), Bai *et al.* (2020), a greater cancer risk was observed for male adults due to inhalation exposure while female adults were at higher risk due to ingestion and dermal contact compared to inhalation. Furthermore, several studies have reported that when comparing exposure pathways, higher risk values were observed for dermal contact, then ingestion, and finally inhalation (Tarafdar and Sinha 2019, Iakovides *et al.* 2021, Fadel *et al.* 2022). This observation shows the importance of the evaluation of the three exposure pathways rather than only working on the inhalation pathway. According to Tarafdar and Sinha (2019), the most influential parameter found by sensitivity analysis in the assessment of health risk is the relative skin adherence factor followed by the exposure duration.

Anthropogenic activities in urban and industrial areas play an important role in governing cancer risk of human exposure to particulate matter (Pongpiachan 2015). Several studies tried to link the cancer risk values to PAHs emission sources. Chao *et al.* (2019) conducted a source apportionment exercise with only PAHs and concluded that vehicular emissions produce a high cancer risk contribution due to the high proportion of toxic PAHs such as benzo[a]pyrene, indeno(1,2,3-c,d)pyrene, benzo(k)fluoranthene, and dibenz[a,h]anthracene. The same conclusion was also presented by Chen *et al.* (2016), Song *et al.* (2019), Zhang *et al.* (2019c),

Mehmood *et al.* (2020), Iakovides *et al.* (2021), Fadel *et al.* (2022). Most of the latter studies also underlined the additional contribution of other sources such as coal combustion from industrial activities, biomass burning, and power plants. According to Ma *et al.* (2020b), the incremental lifetime cancer risk was at least 4 times higher in the heating period using coal as a source of heating compared to the non-heating period.

6.2.2 Phthalates

Phthalates are physically bound to the materials, hence and they can migrate from the matrix into the environment (Xie *et al.* 2005). These compounds are generally emitted into the atmosphere during plastic burning (Simoneit *et al.* 2005, Fadel *et al.* 2021). The major route of exposure for most phthalates is ingestion while inhalation and dermal absorption are considered minor routes (NRC 2008, Boberg *et al.* 2018, Chen *et al.* 2019). The critical age group for this class of chemicals is mainly small children and infants from the mouthing of toys, and other children's products manufactured from polyvinyl chloride (Babich *et al.* 2004). The United States environmental protection agency and several agencies in other countries have classified some of the phthalates as priority pollutants and endocrine disruptors compounds (Xie *et al.* 2005). They might interfere with the biosynthesis, secretion, action, or metabolism of naturally occurring hormones (Kavlock *et al.* 1996, Diamanti-Kandarakis *et al.* 2009). The exposure to phthalates might also affect the reproductive systems and children's intelligence (Lu *et al.* 2018). Additionally, Hauser *et al.* (2006) found that the DNA damage in human sperm might be related to urinary levels of some phthalates. On an environmental level, dibutylphthalate, bis(2-ethylhexyl)phthalate, and butyl benzyl phthalate have higher toxicity compared to other phthalates to terrestrial organisms, fish, and aquatic invertebrates (USEPA 2012).

Other than the reference dose values (RfD) presented by the United States environmental protection agency and presented in **Table 2**, the European food safety authority (EFSA) defined values for tolerable daily intake of phthalates as 0.01 mg/kg for dibutylphthalate and 0.05 mg/kg for bis(2-ethylhexyl)phthalate. On the other hand, the scientific committee on toxicity, ecotoxicity, and the environment (CSTEE) specified that the tolerable daily intake values for the exposure of infants and young children to some phthalates from toys are 37 µg/kg/day for bis(2-ethylhexyl)phthalate, 200 µg/kg/day for butyl benzyl phthalate, and 100 for dibutylphthalate (Ji *et al.* 2014). The daily intake, or the average daily dose, of phthalates to the reference dose showed negligible non-cancer risks since the hazard index values were below the threshold limit

of 1 (Sampath *et al.* 2017, Zhang *et al.* 2019b, Ma *et al.* 2020a, Fadel *et al.* 2022). However, it is worth noting that even at doses lower than the reference dose, phthalate exposure might be linked to interrupted semen quality and reproductive hormones in the human population. According to Chen *et al.* (2017) and Maffini *et al.* (2021), the values of reference doses (RfD) for phthalates proposed by the United States environmental protection agency were based on inadequate studies and did not take into consideration the male reproductive toxicity. However, these effects might decrease when the exposure decreases. The latter idea emphasizes on the importance of setting more stringent regulations on phthalates.

As for the cancer risk, most of the studies focused on the inhalation pathway (**Table 5**) and found no significant human health risk from particulate matter-bounded phthalates exposure specifically from the exposure to bis(2-ethylhexyl)phthalate (Lu *et al.* 2018, Gadi *et al.* 2019, Li *et al.* 2019, Ma *et al.* 2020a). However, the assessment of the health risk from the inhalation pathway only leads to an underestimation of the risk. Fadel *et al.* (2022) found that cancer risk values for ingestion due to the exposure to bis(2-ethylhexyl)phthalate is at least 6 times higher compared to inhalation, emphasizing on the importance of considering the different exposure pathways. Additionally, several studies have reported that children were subjected to greater phthalates exposure than adults (Zhang *et al.* 2014, Sampath *et al.* 2017), while no significant differences were observed between adult males and females (Lu *et al.* 2018). Monte Carlo simulation was applied by Li *et al.* (2019) in order to estimate the incremental lifetime cancer risk from inhalation on the basis of bis(2-ethylhexyl)phthalate concentrations. They found by sensitivity analysis that the phthalate concentration, the exposure frequency, and the inhalation rate have great contribution on the estimation of the risk while body weight is a less significant parameter. All of these findings were based on the few health risk assessment studies implicating phthalates (**Fig. 2**). That is why it is important to increase phthalate studies in particulate matter as well as the health risk evaluation.

6.2.3 Dioxins, furans and dioxin-like polychlorobiphenyls

Dioxins and furans are generally emitted by vehicular emissions and industrial processes especially industries producing compounds such as chlorophenols and phenoxy herbicides, chlorine bleaching of paper pulp and smelting (Cortés *et al.* 2014). Additionally, these compounds are emitted from high temperature processes such as waste incineration and sintering in iron and steel industries (Anderson and Fisher 2002). Dioxin-like

polychlorobiphenyls are not natural substances but were manufactured for use as dielectric fluids, in larger-scale electrical products such as transformers and capacitors, in heat transfer and hydraulic systems and in industrial oils and lubricants (WHO 2010). Several compounds have toxicological effects and can have a significant dioxin-like-toxicity. These agents have the ability to bind to the aryl hydrocarbon receptor or known as AhR. This protein is well known for its role in mediating toxicity and regulating enzymes and other proteins. The aryl hydrocarbon receptor was originally characterized as a regulator of xenobiotic metabolism. In the presence of dioxin-like compounds, this protein also mediates a variety of biological responses leading to hepatocellular damage, thymic involution, immune suppression, and/or tumor promotion (Stevens *et al.* 2009). Other than the reference dose values proposed by the United States environmental protection agency, the world health organization European centre of environment and health formulated tolerable daily intake value between 1 and 4 pg WHO-TEQ/kg/day. On the other hand, the United Kingdom committee on the toxicity of chemicals in food, consumer products and the environment recommended the value of 2 pg WHO-TEQ/kg/day (López *et al.* 2021). While the ingestion is the main pathway for the exposure to dioxins and furans and dioxin-like polychlorobiphenyls, studies in the literature mainly focused on the exposure by inhalation (**Table 5**). Fadel *et al.* (2022) showed that the cancer risk by ingestion is 7-fold higher for adults and 100-fold higher for newborns compared to inhalation and dermal contact. Considering the inhalation pathway, Barbas *et al.* (2018) and López *et al.* (2021) found that the risk assessment due to the exposure of dioxins, furans and dioxin-like polychlorobiphenyls pose a low cancer risk in Madrid and Valencia, two regions in Spain. On the other hand, several other studies found a considerable cancer risk due to the exposure to these pollutants especially in industrial areas and near waste burning activities. The health risk induced by dioxins and furans was worthy of attention as their values exceed the United States environmental protection agency limit in a Chinese and a Greek industrialized sites (Bi *et al.* 2020, Koukoulakis *et al.* 2020). Sun *et al.* (2017) evaluated the health risk near different types of factories and found that cancer risk values were the highest near municipal waste incinerators and the lowest near inorganic chemical factories. Yang *et al.* (2017) found that high cancer risk values were observed in sites near secondary aluminum and copper smelters.

6.2.4 Major and trace elements

Major and trace elements constitute a major concern due to the adverse effects associated with ambient exposure and their deposition (Dahmardeh Behrooz *et al.* 2021). They enter the human body through inhalation, ingestion and dermal contact with potentially damaging and altering the functioning of organs such as the brain, kidney, lungs and also blood (Godwill Azeh Engwa 2019). For instance, the exposure to high levels of arsenic might lead to the destruction of vessels, gastrointestinal tissues and can affect the heart and the brain (Martin and Griswold 2009). Additionally, the exposure to manganese might lead to neurological disorders (O'Neal and Zheng 2015). The exposure to lead is mainly related to the gastrointestinal tract and central nervous system in adults and children (Martin and Griswold 2009). Also according to Jaishankar *et al.* (2014), the exposure to elevated levels of mercury can damage the kidney, the brain, and developing fetus. The health effects due to the exposure to cadmium are mainly related to the fact that the human body cannot excrete cadmium because cadmium is re-absorbed by the kidney (Godwill Azeh Engwa 2019). Chromium (VI) can cause lung and upper respiratory cancers (Balali-Mood *et al.* 2021). The IARC has classified chromium (VI) compounds, arsenic, cadmium, and nickel as group I carcinogenic to humans (IARC 2021).

It has been also reported that children are more susceptible to hazardous metal substances compared to adults (Zhang *et al.* 2019a). The evaluation of the risk due to the exposure to major and trace elements is generally done for the three exposure pathways. The reference dose (RfD), reference concentration (RfC), inhalation unit risk (IUR), and cancer slope factors (CSF) values are available for a large number of elements (Jiang *et al.* 2018, Nirmalkar *et al.* 2021, Fadel *et al.* 2022, Priyan R *et al.* 2022). It is worth noting that the toxicity of chromium is reported to its hexavalent state. Therefore, the chromium concentration is generally divided by 7 to estimate Cr(VI) concentration, given the assumed Cr(VI)/Cr(III) concentration ratio of 1 to 6 (USEPA 2004a, Farahmandkia *et al.* 2017, Kermani *et al.* 2018, Dahmardeh Behrooz *et al.* 2021). Additionally, it is also assumed that the measured arsenic is totally inorganic (Huang *et al.* 2014).

For the non-cancer risk, several elements can be included in the evaluation such as Al, As, Ba, Cd, Co, Cr, Cu, Fe, Hg, La, Mn, Ni, Pb, Sb, Sn, Sr, Tl, V and Zn due to the availability of reference concentrations and reference doses values in the literature (**Table 2**). Several studies have reported that Mn, As and Ni contribute the most to the non-cancer values (Zhang *et al.* 2019a, Hao *et al.* 2020, Sulaymon *et al.* 2020, Dahmardeh Behrooz *et al.* 2021, Duan *et al.* 2021, Fang *et al.* 2021). This might be mainly due to the low values of the reference doses

leading to high values of hazard quotient and hazard index. Studies show that the non-cancer value of an element in one or/and several exposure pathways is usually below the threshold limit of 1. However, when considering the total risk for all the elements, it has been shown that the population near the sampling sites were at high risk of having non-cancer health effects (Díaz and Rosa Dominguez 2009, Zhang *et al.* 2018, Fadel *et al.* 2022). The non-cancer risk has been found higher for children compared to adults in some studies (Dahmardeh Behrooz *et al.* 2021, Fadel *et al.* 2022).

As for the cancer risk, Cr (VI) and As generally show the highest proportion of the total cancer risk value followed by Cd and Co (Wang *et al.* 2018, Galon-Negru *et al.* 2019, Liu *et al.* 2019, Hao *et al.* 2020, Duan *et al.* 2021, Fang *et al.* 2021). These elements show high values of the cancer slope factors especially for the inhalation pathway leading to high values of cancer risk (**Table 2**). Consequently, when trying to attribute cancer risk values for the different emission sources, the sources that emit Cr, As, Cd and Co are the ones that show the highest contributions. Major sources related to significant cancer risk values obtained are mainly road traffic and industrial sources, and more specifically coal combustion plants (Duan *et al.* (2021), Fang *et al.* (2021), Liu *et al.* (2018), Galon-Negru *et al.* (2019), Tsai *et al.* (2020), (Chen *et al.* 2021)). Sensitivity analysis using tornado plots were examined by Roy *et al.* (2019) for the ingestion and the inhalation pathways. The results of this analysis showed that the dermal adherence factor and the exposure duration were recognized as the predominant factors for cancer risk values. Additionally, a negative correlation was found with body weight for cancer risk calculations via inhalation pathway.

7 Strengths and limitations of the health risk evaluation

The main goal of a health risk assessment is to apply a transparent procedure to analyze the consequences of exposures to potentially harmful agents (Glorennec *et al.* 2012). Health risk assessment might aid policy makers in implementing new strategies to prevent from adverse health effects related to particulate matter exposure. The method is cost-efficient, standardized, and requires no health data (Edlund *et al.* 2021). Health risk assessment allows to easily assess the potential consequences of a given exposure situation (Glorennec *et al.* 2012) and to point out the most problematic species for risk management.

However, this assessment presents limitations and uncertainties. Health risk assessment methods assume independence between toxic actions within and across compounds. Actually,

the interactions between the different contaminants on health, defined as cocktail effect reflecting synergism or antagonism action is not well defined (Edlund *et al.* 2021, Fadel *et al.* 2022). Then, there is no available method for the calculation of health risk hazards due to exposure to a combination of several air contaminants. Consequently, the total cancer and non-cancer risks cannot be calculated when considering exposure to several classes of compounds since.. . Additionally, these studies do not account for the variability in the toxicity of a certain exposure depending on particle composition or differences in population sensitivity (Edlund *et al.* 2021). Furthermore, uncertainties accompany risk assessment studies especially in the choice of exposure parameters and reference values (Hao *et al.* 2020). Due to the lack of local data for exposure parameters in a considerable number of countries, the evaluation is based on the standard parameters proposed by different agencies and that might not be suitable to the studied population. That is why, exposure parameters should be carefully chosen in order to reflect the characterization of the population.

8 Conclusion and future directions

Health risk assessment studies estimate the health impact from exposure to pollutants and chemicals that affect air quality. This review presents the published methods used for the evaluation of the cancer and non-cancer risks due to the exposure to different classes of compounds in atmospheric particles. The most employed method is the one developed by the United States environmental protection agency (USEPA). Furthermore, several parameters can be added to this method such as the bioaccessibility of the species, age sensitivity factor, etc.

Most of the published papers in the literature regarding the human health risk evaluation in particulate matter focused on the following classes of compounds: PAHs, phthalates, dioxins, furans, dioxin-like polychlorobiphenyls, and major and trace elements. For some of these classes, the assessment was only based on the inhalation pathway while it is important to note that ingestion and dermal pathway might highly contribute to the risk values. Among PAHs, benzo[a]pyrene, indeno(1,2,3-c,d)pyrene, benzo(k)fluoranthene, and dibenz[a,h]anthracene contribute the most to the cancer risk calculated. On the other hand, the evaluation of the cancer risk is based on the bis(2-ethylhexyl)phthalate for phthalates, on the equivalent concentration of 2,3,7,8-tetrachlorinated dibenzo-p-dioxin for dioxins, furans, and dioxin-like polychlorobiphenyls, and the equivalent concentration of benzo[a]pyrene for PAHs. As for

elements, the most problematic species are Cr, As, Cd, and Co that show a high contribution to the cancer risk in different studies.

Despite the limitations, the results of health risk assessment studies are of utmost importance and might facilitate policy-decision making by focusing on the most problematic species. Since chromium (VI) is considered as one of the species leading to high cancer risk values, efforts should be made in order to analyze chromium (VI) rather than estimating the concentration of chromium (VI) from the total chromium concentration. On the other hand, several attempts were made in a qualitative way in order to link health risk values and the emission sources. Endeavors were also done in a quantitative way to link source apportionment results applied to one class of compounds, such as PAHs or elements, to the cancer and non-cancer risks. However, additional efforts should be made regarding this matter by including much more problematic species and emission source markers in order to better relate the health impact to the different sources. Additionally, more work should be done to determine local exposure parameters and local demographic data in order to reduce the uncertainty of the evaluation. Efforts should be also made to have a better knowledge on the toxicity of several species in the above-mentioned classes of compounds in order to add them to the global assessment. Reference doses or concentrations for the different exposure pathways are still missing especially for phthalates. Furthermore, since studies started adding the bioaccessibility values to the calculations of the health risk, future studies should be focalized on the determination of bioaccessibility values for different classes of compounds in particulate matter. Finally, future toxicological studies should be focused on the evaluation of the cocktail effect between the different classes of compounds. Such researches could contribute to the improvement of the health risk assessment model for a better estimation of the cumulative cancer and non-cancer risks, especially in population exposed to a mixture of contaminants.

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