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DOI:
10.1016/j.envint.2023.107991

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Aquilina, NJ & Harrison, RM 2023, 'Evaluation of the cancer risk from PAHs by inhalation: Are current methods fit for purpose?', *Environment International*, vol. 177, 107991. https://doi.org/10.1016/j.envint.2023.107991

Environment International 177 (2023) 107991

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Evaluation of the cancer risk from PAHs by inhalation: Are current methods fit for purpose?

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ARTICLE INFO

Handling Editor: Marti Nadal

Keywords:
Polycyclic Aromatic Hydrocarbons (PAHs)
Exposure
Lung cancer risk
Unit Risk

ABSTRACT

There is ample evidence from occupational studies that exposure to a mixture of Polycyclic Aromatic Hydrocarbons (PAHs) is causally associated with an increased incidence of lung cancers. In both occupational atmospheres and ambient air, PAHs are present as a mixture of many compounds, but the composition of the mixture in ambient air differs from that in the occupational atmosphere, and varies in time and space in ambient air. Estimates of cancer risk for PAH mixtures are based upon unit risks which derive from extrapolation of occupational exposure data or animal model data, and in the case of the WHO use one compound, benzo[a]pyrene as a marker for the entire mixture, irrespective of composition. The U.S. EPA has used an animal exposure study to derive a unit risk for inhalation exposure to benzo[a]pyrene alone, and there have been a number of rankings of relative carcinogenic potency for other PAHs which many studies have used to calculate a cancer risk from the PAHs mixture, frequently incorrectly by adding the estimated relative risks of individual compounds, and applying the total "B[a]P equivalent" to the WHO unit risk, which already applies to the entire mixture. Such studies are often based upon data solely for the historic US EPA group of 16 compounds which do not include many of the apparently more potent carcinogens. There are no data for human cancer risk of individual PAHs, and conflicting evidence of additivity of PAH carcinogenicity in mixtures. This paper finds large divergences between risk estimates deriving from the WHO and U.S. EPA methods, as well as considerable sensitivity to the mixture composition, and assumed PAH relative potencies. Of the two methods, the WHO approach appears more likely to provide reliable risk estimates, but recently proposed mixture-based approaches using *in vitro* toxicity data may offer some advantages.

1. Introduction

Polycyclic Aromatic Hydrocarbons (PAHs) in the atmosphere are present as a highly complex mixture containing both compounds of known carcinogenic activity, and compounds which in pure form do not exhibit carcinogenicity. Every year, hundreds of research papers are published which report measurements of airborne concentrations of PAHs, many also including some PAH derivatives such as nitro-PAHs and oxy-PAHs, mostly quinones. A substantial proportion of those papers include an estimation of the cancer risk associated with inhalation exposure. Most such estimates are derived by repetition of methods used in earlier published papers, and in many cases, these are based upon incorrect assumptions. As pointed out recently by a WHO expert group (WHO, 2020), there are different ways of estimating the cancer risk associated with PAHs exposure, and it is a very complex matter to determine the most suitable method. In this article, we consider the possible approaches, highlight some of the pitfalls associated with each, and consider which approach is most likely to provide a plausible estimate of carcinogenic risk in the general population.

Most methods of estimating carcinogenicity of PAHs require measurements of benzo(a)pyrene (B[a]P). In the early 1930s a few grams of B[a]P were isolated from 2 tons of pitch and shown to cause tumors in rodents (Carl-Elis et al., 2002). The frequent use of B[a]P as an index compound for PAHs followed from this observation. Nowadays, the justification of using B[a]P as an index PAH is attributed to: i) it has been the most studied individual PAH (Phillips, 1983) ii) it is routinely

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https://doi.org/10.1016/j.envint.2023.107991
Received 29 March 2023; Received in revised form 17 May 2023; Accepted 22 May 2023
Available online 23 May 2023

measured in environmental matrices which contain PAHs; iii) its dose–response data involving chronic exposures is robust and available and iv) several studies have compared the carcinogenic potency of B[a]P with the potency of other PAHs in various assays.

When the United States Environmental Protection Agency (U.S. EPA) was set up in 1970, following several commissioned reports on organics in water, in the 1976 consent decree, a list of "65 toxic pollutants" was presented for regulation. However, there were some shortcomings, including that the list could contain only representatives of large groups of compounds such as the PAHs, no minimum levels of detection were specified, and no standard methods were yet available for collecting, preserving and analyzing these chemicals at low concentrations. Also, the analytical facilities were crude and more importantly few QA/QC requirements were in place when compared to today's standards.

Three PAHs were in the original list, 7 more were selected because an analytical standard was then available, another 3 were chosen because they were suspected carcinogens in water and an additional 3 were included because they were easily found in tars or dyes. These 16 criteria PAHs were considered the best to represent PAHs at the time, and were enshrined in US law soon after, and thus recommended by the U.S. EPA for monitoring (Phillips, 1983). In fact, following these recommendations, many studies have sought only to measure this PAH group. In the four decades that followed, collection and extraction methods have been improved, more analytical standards have become available and advanced analytical instruments have been developed. These advancements led to the discovery of a whole class of polycyclic aromatic compounds (PAC), namely more PAHs, their alkylated derivatives, and keto-, hydroxy-, oxy-, nitro-, amino- and cyano-PAHs to mention a few. Simultaneously more toxicity studies were carried out, indicating that some PACs, in addition to B[a]P were highly carcinogenic and/or genotoxic, mutagenic and eco-toxic (Sun et al., 2020; Sun et al., 2021; Ren et al., 2021; Alves et al., 2017; Zhang et al., 2022; Li et al., 2020; Fernández, 2020; Famiyeh et al., 2021; Mallah et al., 2022; Wang et al., 2022; Lawal, 2017; Patel et al., 2020; Caumo et al., 2022; Alegbeleye et al., 2017). These compounds go well beyond the U.S. EPA-16. Andersson and Achten (Andersson and Achten, 2015) have reviewed the history behind the adoption of the EPA-16 and highlight that it takes no account of many other relevant compounds. Zhuo et al. (Zhuo et al., 2017) and Iakovides at al. (Iakovides et al., 2021) demonstrate that consideration only of the 16 compounds is liable to underestimate carcinogenicity, and to give a false outcome to source attribution of carcinogenic activity.

As B[a]P is only one of at least 100 PAHs which have been identified in airborne particulate matter (PM) (Finlayson-Pitts and Pitts Jr., 1986; Lee et al., 1981) different approaches have been tested to quantify the relevant exposure to the PAH mixture, such as studying the benzene soluble material, total PAH levels and using the concentration of B[a]P as a marker of a complex mixture (EPAQS, 1999). The choice of B[a]P as a marker was based on occupational exposure studies of workers occurring predominantly through inhalation and by dermal contact (IARC, 2010; IARC, 2014).

Epidemiological studies of occupational exposure to a PAH mixture by different pathways demonstrated a considerable range of acute health effects (Delgado-Saborit et al., 2011). The exposure to airborne PAHs by the inhalation pathway and the corresponding health impact of most concern, lung cancer, has been historically addressed at an occupational level, in coke oven workers (Lloyd and Ciocco, 1969; Lloyd et al., 1970; Lloyd, 1971; Redmond et al., 1972; Mazumdar et al., 1975; Redmond et al., 1976; Gibbs and Labrèche, 2014), workers in aluminium reduction plants (Gibbs and Labrèche, 2014) and other industries (Lindstedt and Sollenberg, 1982). Studies by Lao et al., Bjørseth et al. and Aries et al., amongst others, have collected airborne samples and tested gaseous + particle phases of PAHs and their derivatives in coke plants. The results indicate that normally the gaseous PAHs, which are of lesser carcinogenicity, are in much higher proportion compared to the particle-phase PAHs. From the latter group, typically of higher molecular weight (>250), B[a]P stands out to be the most representative individual PAH. This led to B[a]P being used for derivation of unit risk (Lao et al., 1975; Bjørseth et al., 1978; Aries et al., 2007).

From a skin painting animal study conducted by Warshawsky and colleagues it was noted that low dose levels of B[a]P can alter the carcinogenic potential of mixtures. It was also noticed that the presence or absence of B[a]P in a mixture, is not always able to account for the observed potency and the synergistic effects of other pollutants which might be present (Warshawsky et al., 1993). Whether these findings are also applicable to an airborne, inhaled PAH mixture is still an open question, because the interactions of the different PAHs within the mixture are still not well understood (Bruce et al., 2009), and not a simple task to deal with.

The International Agency for Research on Cancer (IARC) considers some mixtures containing PAHs as known human carcinogens (Group 1) (Supplementary Material, Table S1). It also considers several PAHs and PAH derivatives to be probable (Group 2A) or possible (Group 2B) human carcinogens (IARC, 2010; IARC, 1987). The IARC has also classified approximately 45 PAHs as a class of chemicals for which there are no human data on carcinogenesis and limited or inadequate data from animal studies (Group 3) (IARC, 1987; IARC, 2014). On the other hand, the U.S. EPA classification of PAHs varies slightly when compared to that in Table S1, by considering benz[a]anthracene (B[a]A) and dibenz [a,h]anthracene (DB[a,h]A) in Group B2 and B[a]P as a human carcinogen (Group A) (IRIS, 2017).

In recent years the PAH mixture has been measured in many different microenvironments such as urban, trafficked, industrial and marine areas and biomass burning to mention a few (Ceratti et al., 2021; Elzein et al., 2020; Iakovides et al., 2021; Liu et al., 2015; Nowakowski et al., 2021; Pietrogrande et al., 2022; Samburova et al., 2016; Zhang et al., 2022; Zhuo et al., 2017; Alves et al., 2017; Alves et al. 2023; Zhang et al., 2018) and also in the indoor environment, typically dominated by infiltration of PAHs, cooking, tobacco smoking and other indoor combustion processes (Dubowsky et al., 1999; Lin et al., 2022; Zhang et al., 2021). In many studies, PAHs have been better characterized in terms of the chemical composition and the individual compounds' toxicology (Achten and Andersson, 2015; Mueller et al., 2019; Zhuo et al., 2017). A persistent problem associated with the exposure (for whichever pathway is considered) to PAHs is that they are composed of a complex mixture of compounds including many derivatives, leading to a highly variable composition (De Rosa et al., 2004). Through various animal studies, it has been shown that several components of this mixture are carcinogenic, yet to varying degrees (IARC, 2010; WHO 2021; IARC, 1983; U.S. EPA, 2010), and thus the implications of human exposure to such a variable mixture on health cannot be ignored and should not be underestimated (EPAQS, 1999).

Both the World Health Organisation (WHO) and the U.S. EPA have estimated unit risk factors for lung cancer from exposure to PAHs. The former was estimated using data from occupational exposure to coke-oven emissions, whilst the latter uses an animal inhalation study. Over the years several approaches have been proposed to estimate the cancer risk associated with the exposure to PAHs mixtures, such as the use of Toxicity Equivalent Factors (TEFs), Potency Equivalency Factors (PEFs), Relative Potency Factors (RPFs) and Mixture Potency Factors (MPFs) (Yousefi et al., 2022).

This paper will explore the issues involved with the use of the unit risk for B[a]P as a marker of PAHs exposure in ambient air, and methods which seek to sum the risks associated with other compounds in a mixture, and seeks to clarify what is known with confidence regarding the associated cancer risk by the inhalation route.

2. Quantitative assessment of carcinogenicity

The most widely accepted quantitative risk assessment is based on an increased risk of lung cancer among coke-oven workers, because that was the most important occupational exposure in the 1970s and

numerous epidemiological studies were associated with that microenvironment (Lloyd and Ciocco, 1969; Lloyd et al., 1970; Lloyd, 1971; Redmond et al., 1972; Mazumdar et al., 1975; Redmond et al., 1976). These studies found that an excess of total cancer mortality and respiratory organ cancer mortality among workers were both PAH dose related. As no information was available on smoking habits, tobacco smoking, as a balanced covariate rather than a confounder could still be a modifier of the effect of coke oven emissions (Moolgavkar et al., 1998; U.S. EPA, 1984). The profile of the coke-oven emissions with regards to the relative contribution of B[a]P and other PAH is outlined in the Supplementary Material, Table S2. As the mechanism of co-carcinogenesis is not fully understood, if additivity is assumed, the presence of many carcinogenic compounds in the coke oven emissions or other complex mixtures increases the likelihood of an additional risk for humans above that associated with B[a]P (Petry et al., 1996).

The U.S. EPA considers that a linear non-threshold model is feasible for any carcinogen and can be used as the primary basis for risk extrapolation to low levels of exposure unless there is evidence that shows otherwise. It is also widely accepted that the estimation of cancer risk to humans at low levels of exposure is uncertain. If the linear extrapolation model provides a reasonable estimate of the upper limit of risk, the true risk could very well be considerably lower. This implies that even if exposures are accurately defined, the risk estimates should not be regarded as accurate representations of the true cancer risks.

A number of approaches have been used to estimate the human lifetime respiratory cancer death rate due to a continuous exposure to 1 $\mu g/m^3$ of the benzene soluble organics extracted from the particulate phase of coal tar pitch volatiles from the coke ovens emissions. Application of a Weibull-type model estimated that the risk due to a 1 $\mu g/m^3$ unit exposure to benzene-soluble organics ranges from 1.30×10^{-8} for the 95% lower-bound zero lag-time assumption to 1.05×10^{-3} for the 95% upper-bound 15-year lag-time assumption (IARC, 2010). On the other hand, using a multistage-type model, the maximum likelihood estimates for the risk due to the same exposure range from 1.76×10^{-6} for the zero lag-time case to 6.29×10^{-4} if a 15-year lag-time is considered (U.S. EPA, 1984). Since it is not known whether either of these models reflects the true dose–response relationship at low doses, a range of estimates from zero (lower bound) to an upper bound is a more appropriate indicator of potential risk. To obtain this upper bound, a linearized modification of the multistage model was used, giving a unit risk value of 1.26×10^{-3} as the highest potency amongst the different lag-time data sets used (U.S. EPA, 1984).

A composite unit risk estimate for exposed workers was obtained from the multistage 95% upper-bound estimates for each of the lag-times by taking their geometric mean. This resulted in a composite estimate of 6.17×10^{-4} per 1 $\mu g/m^3$ of benzene soluble organics extracted from the particulate phase of coal tar pitch volatiles, which is regarded as the most reasonable upper-bound estimate.

Given the uncertainties in calculating these estimates, partly derived from lack of information such as the true composition of the complex mixture, not accounting for cigarette smoking patterns, race and/or sex differences, the range of these results does not reflect the total uncertainty associated with these estimates.

2.1. WHO unit risk

In 1987, the WHO published the Air Quality Guidelines (AQGs) for Europe (WHO, 1987) and adopted the estimated unit risk for lung cancer from exposure to PAHs as the upperbound individual lifetime unit risk of 6.2×10^{-4} obtained from the occupational exposure of coke-oven workers (for continuous exposure to 1 $\mu g/m^3$ of benzene soluble coke oven emissions) (Lloyd, 1971; Lloyd and Ciocco, 1969; Redmond et al., 1972; Redmond, 1983). The AQGs were updated in 2000 (WHO, 2017; WHO, 2000) and the abovementioned unit risk was revised to 8.7×10^{-5} per ng/m^3 B[a]P using this compound as an indicator of PAHs and representing 0.71% of the coke oven emissions (Lindstedt and Sollenberg, 1982). The same value was also adopted by the 2010 *WHO guidelines for indoor air quality* (WHO, 2010).

2.2. U.S. EPA unit risk

The latest toxicological review of B[a]P issued by the U.S. EPA (IRIS, 2017), derives risk estimates from the Thyssen et al. bioassay, which is a study of lifetime, chronic exposure to inhaled B[a]P by Syrian male hamsters (Thyssen et al., 1981). Supportive evidence for the carcinogenicity of inhaled B[a]P comes from additional studies with hamsters exposed to the carcinogen via intratracheal instillation (Saffiotti et al., 1972; Feron et al., 1965; Feron and Kruysse, 1978; Henry et al., 1973; Ketkar et al., 1978). Such studies however are not as useful for the quantitative extrapolation of cancer risk from the inhalation of B[a]P in the environment because this exposure method alters the deposition, clearance, and retention of substances (Driscoll et al., 2000; Pufulete et al., 2004).

Using the data from Thyssen et al. (Redmond et al., 1976), a time-to-tumor dose–response model was fit to the time-weighted average continuous exposure concentrations and the individual animal incidence data for the overall incidence of tumors in the upper respiratory tract or pharynx. The inhalation unit risk (IUR) of 6.4×10^{-4} per $\mu g/m^3$ of B[a]P was calculated by linear extrapolation (slope factor = $0.1/BMCL_{10}$) from a $BMCL_{10}$ of 0.16 mg/m^3 ($BMCL_{10}$ is the lower 95% confidence limit on the benchmark concentration associated with a benchmark response of 10%) for the occurrence of upper respiratory and upper digestive tract (forestomach) tumors in male hamsters chronically exposed by inhalation to B[a]P (IRIS, 2017; Thyssen et al., 1981).

Although the study design of the Thyssen et al. bioassay had certain limitations and issues associated with the particle size distribution and composition of the carrier particles, exposure variability, and deposition, the robust tumour response following B[a]P inhalation exposure could not be ignored. This meant that the U.S. EPA concluded that the strengths of the study supported the use of this data to derive an inhalation unit risk for B[a]P.

2.3. Comparison of WHO and U.S. EPA unit risk factors

Whilst acknowledging the very different means of estimation, and the differing basis for application, it is possible to make a crude comparison. The WHO value of $8.7 \times 10^{-2}/\mu g/m^3$ refers to B[a]P as a marker of the mixture. If B[a]P represents respectively 50% or 10% of the carcinogenic potency of the mixture, the unit risk for B[a]P alone would be 4.3×10^{-2} or $8.7 \times 10^{-3}/\mu g/m^3$. This compares with a unit risk determined by U.S. EPA of $6.4 \times 10^{-4}/\mu g/m^3$. It may be argued that as both represent upper bound estimates and are determined in different ways from very different datasets and are also dependent upon the contribution to the total carcinogenic effect of other PAH in the coke oven emissions, they are within reasonable agreement. Nonetheless, their divergence by more than order of magnitude serves to emphasise the uncertainties in quantitative estimates of lung cancer risk from PAH exposure.

2.4. Relative carcinogenic potency

B[a]P is the only PAH for which a complete quantitative risk assessment has been conducted (Collins et al., 1998; Collins et al., 1991). From different environments, the contribution of the carcinogenic potency of B[a]P alone ranges from 27 to 67% of the activity of the different PAH mixtures according to Petry et al., confirming the importance of B[a]P as an index compound for PAH mixtures in air (Petry et al., 1996).

The Toxicity Equivalent Factors (TEFs) approach proposed by Nisbet and LaGoy and applied to 17 PAHs was based on the core assumptions that an index chemical which is well characterized can be used as a surrogate for all compounds considered in a complex mixture provided

the toxic mechanisms of the compounds within a mixture are qualitatively similar to those of the index chemical and hence can be characterized by means of a relative potency or TEF. Furthermore, it was assumed that the TEFs for different toxic end points are similar, so that limited information on relative toxic potencies in one or a few assay systems can be used to assign TEFs to single compounds or subclasses for other end points and that the toxic effects of different compounds of the mixtures are additive (Nisbet and LaGoy, 1992).

These assumptions may be satisfied for PAHs in the context of using B[a]P as the index chemical because many PAHs cause similar carcinogenic effects to B[a]P, albeit to different extents. Although studies have shown reasonably close concordance between relative potencies for different end points, further research is necessary. Whilst the additivity of effects when considering PAHs has not been studied systematically, there is evidence that this assumption applies to mixtures of PAHs which are not necessarily the 16 U.S. EPA PAHs or a well-defined complex mixture, as long as the toxicity of the individual PAH considered is well characterized (Boström et al., 2002; Nisbet and LaGoy, 1992), although the WHO (WHO 2021; Kortenkamp et al., 2009; U.S. EPA, 2010), questioned this proposition. Also, interactions between compounds can lead to synergistic or antagonist effects that make risk assessment more challenging than simple additivity (Tarantini et al., 2011; Carpenter et al., 2002). The work of Misaki et al. is indicative of mechanisms beyond direct genotoxicity by which PAH promote tumour growth, and may invalidate simple assumptions of additivity (Misaki et al., 2016).

When doing a risk assessment for environmental settings using the WHO unit risk, it must be taken into account that the B[a]P concentration represents the carcinogenic potency of the PAH mixture occurring in coke plants. Mueller et al. summarized the TEFs proposed by Nisbet and Lagoy to indicate the carcinogenic potency of each PAH relative to B[a]P. Multiplying the measured concentration of the individual PAH by the TEF would indicate the concentration of the PAH in terms of B[a]P equivalents ($B[a]P_{eq}$) (Mueller et al., 2019). The application of TEFs to the PAH mixture allows the determination of a relative potency factor (RPF) defined as the ratio between the airborne concentration of $B[a]P_{eq}$ to the concentration of B[a]P alone ($RPF_{env} = B[a]P_{eq} / B[a]P$. The RPF values make it possible to compare the carcinogenic activity of the PAH mixture in different environments. If this ratio is further divided by that calculated for coke plants (RPF_{env} / RPF_{coke}), the obtained value would indicate the variability of the risk for the different environments when risk assessment is strictly performed on the basis of the epidemiological results for coke oven workers.

A very common error which appears throughout the literature is to estimate cancer risk by multiplication of a $B[a]P_{eq}$ concentration by the WHO Unit Risk (e.g. (Goudarzi et al., 2018; Pongpiachan et al., 2015). This can vastly overestimate risk as the correct procedure is to use the concentration of B[a]P alone as a surrogate for the entire mixture, as adopted by WHO when deriving the Unit Risk.

However, some limitations are worth mentioning. For the range of environmental exposures, it is still debatable if potency factors derived from carcinogenicity tests are valid because the unit risks for the different PAHs will not necessarily show a similar dependence upon concentration if the shapes of the dose response curves differ. Secondly, the TEF approach depends upon the expectation that all carcinogens in the PAH mixture have been accounted for, and it is well known that the 16 priority PAH specified by U.S. EPA do not necessarily represent the carcinogenic activity of all emission sources, as has been shown for diesel exhausts, cigarette smoke or wood smoke to mention a few (Heinrich, 1986; Iakovides et al., 2021; Lewtas, 1993; Andersson and Achten, 2015). The presence of other carcinogenic or co-carcinogenic compounds including other PAH, nitrated PAHs, aromatic amines, or aza-arenes in the aerosol could be confounding factors as they may potentially add to or modify the carcinogenic activity of the complex PAH mixture (Andersson and Achten, 2015; Iakovides et al., 2021).

It has been shown that PAHs of MW > 300 in urban airborne particulate PAHs may contribute 33% or more to the total mutagenicity and toxic potential of the PAH fraction due to isomers of dibenzopyrene (Boström et al., 2002; Cavalieri et al., 1991; Durant et al., 1998; Menichini and Merli, 2012; Platt et al., 2004). A high level of uncertainty will always be associated with evaluation of the toxicity of PAHs because of the diversity of possible PAH mixtures.

As chronic inhalation studies of PAH are not available, the Office of Environmental Health Hazard Assessment (OEHHA) of the California EPA has developed a Potency Equivalency Factor (PEF) procedure to assess the relative potencies of PAH and their derivatives as a group with the scope of allowing the assessment of the impact of carcinogenic PAHs in ambient air (Collins et al., 1998). Using a hierarchy of preference of available data on carcinogenicity and mutagenicity of PAHs, described by Collins et al., PEFs were assigned to 18 PAH, of which some are listed in Table 1. The PEF is determined by dividing the inhalation unit risk factor for that PAH by the inhalation unit risk factor for B[a]P (CARB, 1994).

A draft document describing a new Relative Potency Factor (RPF) approach for PAHs in mixtures, based on tumor bioassay data was published by the U.S. EPA in 2010. The list, summarised in Table 1, shows compounds with higher RPF values than B[a]P, most notable among which is dibenzo[a,l]pyrene (DB[a,l]P; RPF = 30) (Mueller et al., 2019; U.S. EPA, 2010). Schneider et al. suggested that ideally RPF estimates should be derived separately for oral, dermal, and inhalation exposure using studies with the relevant exposure pathway (Schneider et al., 2002).

The U.S. EPA recommended a component-based approach, involving an analysis of the toxicity of components of the mixture, when appropriate toxicity data on a complex mixture or a "sufficiently similar" mixture, are unavailable (U.S. EPA, 1986; U.S. EPA, 2000). The RPF approach involves weighted dose addition as long as the components in the mixture are considered to act in a toxicologically similar way. If the behaviour of the components is such, their doses are added together after scaling them relative to the potency of B[a]P and using the dose–response curve of B[a]P, and then the response to the total equivalent dose in the mixture is estimated (U.S. EPA, 1986; U.S. EPA, 2000).

The RPF approach involves two important assumptions related to the application of a dose-additivity model. The first assumption is of similar toxicological action of the components and the second is that interactions among PAH mixture components do not occur at low levels of exposure typically encountered in the environment. The first important limitation to the RPF approach is that RPFs have been derived for a limited number of PAHs and secondly cancer risks from non-PAH components, unidentified PAHs, and heterocyclic and substituted PAHs in PAH mixtures are not included.

The abovementioned comparative potency approaches are mainly used by US and European authorities, but a whole-mixture approach would be ideal to understand possible interaction effects (Flowers et al., 2002; WHO, 2021; U.S. EPA, 2000). An alternative approach was proposed by Dreij et al., to use mixture potency factors (MPFs). This approach although somewhat similar to the previously discussed ones, uses B[a]P as a suitable reference compound and does not require a well-characterized and a sufficiently similar reference mixture, of known component-specific potencies. The potency of whole-mixture samples would be expressed as MPFs relative to B[a]P by comparing these samples on a relevant biological end-point (Dreij et al., 2017).

The study by Dreij et al. has shown that the relative potency of individual PAH can activate proportionate DNA damage signalling *in vitro*, and is supported by other studies (Audebert et al., 2012; Khoury et al., 2013; Tsamou et al., 2012) and is in good agreement with published RPFs based on *in vivo* studies. This approach is claimed to improve the way to assess whole-mixture samples of airborne PAHs, and hence the health risk assessment (Jarvis et al., 2014). Further studies are however needed to evaluate the validity of this approach from samples of complex PAH composition, obtained in different microenvironments when exposed to highly variable meteorological conditions during sampling, as compared to Standard Reference Materials (SRM) associated with

Table 1
IARC classification and toxicity (TEF/PEF/RPFs) of the 16 EPA PAH and other PAH.

16 EPA PAH	CAS No.	Abbreviation	TEF	PEF	RPF	IARC
Naphthalene	91–20-3	Naph	0.001			
Acenaphthylene	208–96-8	Acy	0.001			
Acenaphthene	83–32-9	Ace	0.001			
Fluorene	86–73-7	Flo	0.001			3
Phenanthrene	85–01-8	Phen	0.0005[a]/0.001[b]			3
Anthracene	120–12-7	Ant	0.0005[a]/0.01			3
Fluoranthene	206–44-0	Flt	0.001/0.05[a]/0.08[b]		0.08	3
Pyrene	129–00-0	Pyr	0.001			3
Benz[a]anthracene	56–55-3	B[a]A	0.1	0.1	0.2	2B
Chrysene	218–01-9	Chry	0.01/0.017[c]	0.01	0.1	2B
Benzo[b]fluoranthene	205–99-2	B[b]F	0.1[b]/0.25	0.1	0.8	2B
Benzo[k]fluoranthene	207–08-9	B[k]F	0.03[d]/0.1	0.1	0.03	2B
Benzo[a]pyrene	50–32-8	B[a]P	1	1	1	1
Benzo[g,h,i]perylene	191–24-2	B[ghi]P	0.01/0.02[b]		0.009	3
Indeno[1,2,3-cd)pyrene	193–39-5	IndP	0.07[d]/0.1	0.1	0.07	2B
Dibenz[a,h]anthracene	53–70-3	DB[ah]A	0.4[f]/1.1/5[e]/10[d]	0.4	10	2A
Other PAH						
Dibenzo[a,e]pyrene	192–65-4	DB[ae]P	0.4[d]/1[b]	1	0.4	3
Dibenzo[a,h]pyrene	189–64-0	DB[ah]P	0.9[d]/10[b]	10	0.9	2B
Dibenzo[a,i]pyrene	189–55-9	DB[ai]P	0.6[d]/10[b]	10	0.6	2B
Dibenzo[a,l]pyrene	191–30-0	DB[al]P	30[d]/10[b]	10	30	2A
Benzo[c]fluorene	205–12-9	B[c]F	20			3
7,12-Dimethylbenz(a)anthracene	57–97-6	DMBA	10 [g]	10 [h]		3
Dibenzo[a,c]anthracene	215–58-7	DB[ac]A	10 [g]			3
5-Methylchrysene	3697–24-3	5-MC	1[b]	1		3

[a]: (Elzein et al., 2019); [b]: (Richter-Brockmann and Achten, 2018); [c]: (Durant et al., 1998); [d]: (Lim et al., 2022); [e]: (Mueller et al., 2019); [f]: (Wei et al., 2011); [g]: (U.S. EPA, 2010); [h]: (Collins et al., 1998).

coal tar (SRM1597a), urban dust (SRM1649b), and diesel PM (SRM1650b), which have been already tested (de Oliveira Galvão et al., 2022).

3. Analysis of carcinogenic PAH concentrations and risk

Table 1, adapted from Mueller et al. (Mueller et al., 2019), compares the relative carcinogenicity (according to the IARC classification) and the toxicity of the 16 EPA and other PAH generally with molecular weight > 300 based on TEFs or PEFs or RPFs as described earlier. Petry et al. had characterized the 16 EPA PAH emitted in various occupational environments linked with high levels of PAH as summarized in Table S2. By far, coke ovens are the occupational environment which represents the highest emissions of all PAH and hence its use in the development of the IUR.

Table 1 indicates that the low molecular weight subgroup of PAH from Naph to Pyr is potentially problematic to include in the assessment of carcinogenicity of a PAH mixture. It is well established that this subgroup tends to be found primarily in the gaseous phase (and hence is always underestimated in the routine measurements of the particulate-phase 16 EPA PAH, using filters), and these PAH are classified as Class 3 carcinogens by the IARC and their TEF values indicate that their contribution to the overall carcinogenicity of the 16 EPA PAH is almost negligible (Elzein et al., 2019).

Recent studies have questioned the suitability of using the 16 EPA PAH as representative of more complex PAH mixtures (Achten and Andersson, 2015; Mueller et al., 2019; Andersson and Achten, 2015). For these reasons, the carcinogenicity of the more carcinogenic sub-group, termed as ΣC-PAH (which comprises the group (B[a]A – D[a,h]A)) will be considered. Few studies have attempted to characterise complex PAH mixtures in different microenvironments probably due to sampling and analytical challenges (Bjørseth et al., 1978; Delgado-Saborit et al., 2011; Iakovides et al., 2021; Khalili et al., 1995; Lao et al., 1975; Lim et al., 2015; Mueller et al., 2019; Petry et al., 1996; Zhuo et al., 2017; Andersson and Achten, 2015; Bergvall and Westerholm, 2007). Problems with understanding how the carcinogenicity of the PAH mixture is influenced by the different components and their concentration levels are compounded by the lack of knowledge of toxicity data of some of the detected compounds, some of which are possibly more carcinogenic than the B[a]P marker (Bergvall and Westerholm, 2006; Bjørseth and Bjørseth, 1981; Collins et al., 1998; Samburova et al., 2017) but yet are still classified as Class 3 carcinogens by IARC (see Table 1). One of the PAH sub-groups for which there is evidence of carcinogenic potency are dibenzopyrenes (DBPs) (refer to Table 1). To date, the individual PAH exhibiting the highest known carcinogenicity is one of the four isomers, dibenzo[a,l]pyrene (Bergvall and Westerholm, 2006; Boström et al., 2002; Cavalieri et al., 1991; Devanesan et al., 1990; Lim et al., 2015; Sadiktsis et al., 2012) and thus this sub-group is potentially important to be monitored. Given their typically low levels in the atmosphere and the associated sampling and analytical challenges, datasets reporting them are scarce. Over the years the quest for enhancing knowledge of this sub-group in PAH mixtures has probably been further hampered by the use of the 16 EPA PAHs as representative of all PAHs, at least from a regulatory perspective.

Table 2 summarizes the details of the UK and other sites which report monthly mean ΣC-PAH and DBPs (2012–2021), alongside sites used in shorter campaigns that have reported concentrations of a wider range of airborne PAH and their derivatives, conducted in China (2009–2010) and (2014-2015), Colombia (2015), Sweden (2017), and around eastern Australia during a sea expedition (2018–2019).

The datasets available have been used to evaluate the contribution of specific PAHs, for which toxicity data are available, to the overall carcinogenicity in comparison to the routinely measured ΣC-PAH (Table 3). As information on the four DBPs is more widely available, these are considered as a separate sub-group termed as ΣDBPs. For this purpose, ΣPAH represents the sum of ΣC-PAH and ΣDBPs. In the studies carried out in Colombia and Sweden, a few compounds whose potency is known to be similar or higher than B[a]P (see Table 1) were recorded and are considered in the context of their possible contribution to greater carcinogenicity of the PAH mixture. In Colombia, 7H-benzo[c]fluorene (B[c]F), dibenzo[a,c]anthracene (DB[a,c]A) and 5-methylchrysene (5-MC) were reported. In Sweden, B[c]F and 7,12-dimethylbenzo[a]anthracene (DMBA) were measured. In the UK, DB[a,c]A and 5-MC were additionally monitored and in the China and the Asian campaigns, DMBA was

Table 2
Site description, sampling period and number of samples from studies collecting data on a wide range of PAH.

Country	Site Name	Site	Year	N	Site Description
UK	Brent London	BRL[1,*]	2011–2021	132	Urban Background
	Chilbolton Observatory	CBO[1,*]	2016–2021	72	Rural Background
	Derry Brandywell	DEB[1,*]	2011–2021	132	Urban Background
	Marylebone Road London	MRL[1,*]	2011–2021	132	Urban Traffic
	Port Talbot Margam	PTM[1,*]	2011–2021	132	Urban Industrial
	Scunthorpe Low Santon	SLS[1,*]	2011–2021	132	Urban Industrial
	Scunthorpe Town	STO[1,*]	2011–2021	132	Urban Industrial
China	Longtang Town, Qingyuan	LOT-A[2]	2009–2010	11	Industrial complex (winter)
	Nanjing	NAN[3]	2014–2015	24	Urban Industrial
Colombia	Aburrá valley	EST-MAGO[4]	2015	NR	Side Road
	Aburrá valley	ITA-PTR[4]	2015		Side Road
	Medellin	MED-PJIC[4]	2015		City Highway
	Medellin	MED-UNMF[4]	2015		Main Road
	Medellin	MED-MIRA[4]	2015		Main Road
	Caldas	CAL-PMER[4]	2015		Valley + Industry
Sweden	Enskede	EN[5]	2017	18	Urban + Residential roads
	Delsbo	DE[5]	2017	18	Villa area with low traffic
	Ytterjärna	YJ[5]	2017	13	Valley + Residential roads
	Torkel	TK[5]	2017	18	Urban background (24 m)
Asia	Snowdragon Expedition	SNO[6]	2018–2019	6	Expedition around Australia

1: This Study; **2**: (Wei et al., 2011); **3**: (Zhuo et al., 2017); **4**: (Mueller et al., 2019); **5**: (Lim et al., 2022) ; **6**: (Zhang et al., 2022); NR: Not reported.
*: These stations form part of the PAH UK network collecting particle-phase PAHs. Details of this network are found here: [https://uk-air.defra.gov.uk/networks/network-info?view=pah]; related data archives are found here at: [https://uk-air.defra.gov.uk/data/pah-data].

reported. These PAH are considered as ΣEx-PAH. The sum of the ΣDBPs and ΣEx-PAH are termed as ΣAllEx-PAH.

3.1. Summed carcinogenicity and cancer risk estimates

Table 3 summarizes information on a) the mean B[a]P, ΣC-PAH, ΣDBPs and ΣPAH concentrations in ng/m^3, b) their corresponding B[a]P$_{eq}$ calculated by summing all PAH concentrations that were multiplied with the corresponding maximum TEF (from Table 1) and c) shows the mean percentage contribution of B[a]P and ΣDBPs to the carcinogenicity of the different PAH mixes. The variability in the mean concentration of B[a]P reported in Table 3(a) could be associated with the activities occurring at the sites listed in Table 2, but for the industrial site in China (LOT-A) the level stands out to be particularly high. The ΣC-PAH concentrations are also congruent with the type of site, only in China (LOT-A) the levels are about five times higher than in SLS (in the UK) which is heavily industrialised with coke ovens operational nearby. The second site in China (NAN) is very different from LOT-A, but being urban industrial, data obtained is very similar to PTM (in the UK). Data from coke plants in different countries shows that levels of B[a]P, as for other C-PAH are high (Bieniek and Łusiak, 2012; Bigda et al., 2017; Bjørseth et al., 1978; Khalili et al., 1995; Lim et al., 2015; Aries et al., 2007; Liberti et al., 2006), and in the sites considered for this study, B[a]P typically represents 13.2–18.5% of the ΣC-PAH mass. The B[a]P contribution to the ΣC-PAH B[a]P$_{eq}$ varied from 18.4 to 38.9%, the latter in older plants. In Colombia, in some sites the contribution is from 24 to 29.3%.

In the expedition samples, SNO, most of the ΣC-PAH were not detected and that explains why B[a]P contributes 50% to carcinogenicity of the ΣC-PAH mix. Table 3(a),(b) also shows that ΣDBPs are in much smaller concentrations in the atmosphere compared to other PAHs and hence the contribution of B[a]P to the ΣPAH mass does not change drastically but due to the high potency of the DBPs, the ΣPAH B[a]P$_{eq}$ is substantially greater than the ΣC-PAH B[a]P$_{eq}$. Table 3(c) shows that the percentage B[a]P contribution to the carcinogenic potency decreases substantially if DBPs are included in the PAH mixture.

As a range of TEF values has been reported for some compounds, a sensitivity analysis on the change in the percentage contribution to carcinogenicity of B[a]P and the different sub-groups considered in this study, when applying a minimum and a maximum TEFs (if available, from Table 1) and if an additive scenario is assumed, is presented in Table S3. Table S4 refers to the individual PAH contribution to the carcinogenicity. The application of minimum and maximum TEFs show that the ΣC-PAH are highly influenced by the contribution of DB[a,h]A, an observation noted also by Collins et al. (Collins et al., 1991). In all sites, except for Colombia, the contribution of B[a]P to the total carcinogenic potential decreases once any extra PAH are considered in addition tothe 16 EPA PAH. The degree of contribution of each PAH subgroup varies across sites but is also sensitive to the TEFs applied. It is noticeable that the contribution of the ΣDBPs to carcinogenicity varies from 14.9 to 76.1% when minimum TEFs were applied and to 5.5 to 81.2% when maximum TEFs are applied. When any other extra PAH were considered together with ΣDBPs, their carcinogenic contribution to the PAH mixture, across the studies considered varied from 17.3 to 96.8% and from 5.5 to 92.4% when minimum and maximum TEF were applied respectively. In all cases apart from the Swedish sites, the contribution to carcinogenicity was predominantly due to the ΣDBPs rather than from the ΣEx-PAH. For the Swedish sites, the opposite appears to be true. It is not known if this is due to different PAH sources, which is unlikely given the variety of sites considered in the other studies, or due to different analytical methods employed and the commonly used NIST standard reference material 1649b – urban dust, does not give certified concentrations for all the other PAH mentioned in this paper.

The percentage contribution of each PAH, *i* to the total carcinogenicity of the PAH mixture was calculated following the approach by Elzein et al., as given by (Elzein et al., 2020):

$$(\%Carc.Potential)_i = \frac{(RC \times TEF)_i}{\sum_{i=1}^{N}(RC \times TEF)_i} \times 100$$

where RC is the relative abundance marker of an individual PAH, *i* to the carcinogenic index marker, B[a]P given by $(RC = (PAH)_i/(B[a]P)$.

More importantly, apart for the Chinese site, LOT-A, Table S3 shows that the percentage contribution to carcinogenicity coming from the additional potent PAH considered (ΣAllEx-PAH) is > 50%.

The lifetime excess cancer risk (LECR), calculated by multiplying the B[a]P concentration with the IUR gives a statistical estimate of the potential of developing cancer from inhalation after a lifetime exposure to particle-bound PAH (Elzein et al., 2020). It represents the number of people per 100,000 people who may develop lung cancer when exposed to an average concentration of 1 ng/m^3 of B[a]P over an adult lifetime of 70 years. In Table 4, the LECR is shown for each site considered in this

Table 3
(a) Mean concentrations (in ng/m^3) of B[a]P, ΣC-PAH, ΣDBPs and ΣPAH, (b) their corresponding B[a]P_{eq} concentrations (in ng/m^3) and (c) the mean %B[a]P in ΣC-PAH B[a]P_{eq} and in ΣPAH B[a]P_{eq} and the mean % ΣDBPs B[a]P_{eq} in ΣPAH B[a]P_{eq} for various sites considered. The maximum values of TEFs listed in Table 1 were used to calculate the B[a]P_{eq}.

	(a)					(b)			(c)		
Site	**B[a]P**	**ΣC-PAH[1]**	**ΣDBPs[2]**	**ΣPAH[3]**	**% B[a]P in ΣC-PAH**	**% B[a]P in ΣPAH**	**ΣC-PAH B[a]P_{eq}**	**ΣDBPs B[a]P_{eq}**	**ΣPAH B[a]P_{eq}**	**% B[a]P in ΣC-PAH B[a]P_{eq}**	**% B[a]P in ΣPAH B[a]P_{eq}**	**% ΣDBPs B[a]P_{eq} in ΣPAH B[a]P_{eq}**
BRL	0.15	1.16	0.09	1.25	14.1	13.0	0.41	0.60	1.01	39.9	15.5	59.8
CBO	0.08	0.54	0.07	0.61	14.4	12.8	0.22	0.50	0.72	35.8	11.1	68.3
DEB	0.85	4.68	0.48	5.16	19.0	17.3	1.97	3.28	5.24	45.8	18.1	61.1
MRL	0.17	1.35	0.08	1.42	14.2	13.4	0.40	0.53	0.94	45.2	20.9	54.7
PTM	0.55	4.02	0.40	4.42	14.2	12.9	1.50	2.70	4.20	39.1	14.6	63.0
SLS	1.93	12.38	1.10	13.48	15.9	14.5	4.66	7.04	11.70	33.0	16.5	61.0
STO	1.66	10.93	0.90	11.83	16.3	15.0	4.03	5.86	9.90	44.0	17.6	59.8
LOT-A	7.50	57.20	0.64	57.84	13.1	13.0	34.74	3.53	38.28	21.6	19.6	9.2
NAN	0.64	8.97	0.22	9.19	7.1	7.0	1.89	1.66	3.55	33.8	18.0	46.7
EST-MAGO	0.18	0.75	0.05	0.78	24.0	23.1	0.31	0.41	0.72	58.8	25.5	56.6
ITA-PTR	0.36	1.14	0.14	1.22	10.3	29.5	0.61	1.16	1.77	59.2	20.3	65.6
MED-PJC	0.43	2.62	0.28	2.77	16.4	15.5	0.90	2.22	3.11	48.1	13.8	71.2
MED-UNMF	0.48	3.04	0.32	3.20	15.8	15.0	0.97	2.49	3.45	49.9	14.0	72.0
MED-MIRA	1.08	3.72	0.37	3.89	29.0	27.8	1.85	2.95	4.80	58.7	22.6	61.5
CAL-PMER	0.98	3.35	0.36	3.50	29.3	28.0	1.58	2.69	4.27	61.8	22.9	62.9
DE	0.14	1.23	0.03	1.26	10.3	10.0	0.34	0.12	0.46	33.6	25.4	29.8
EN	0.09	0.83	0.02	0.85	11.0	10.7	0.24	0.09	0.33	32.9	24.4	30.6
TK	0.04	0.45	0.02	0.47	9.5	9.2	0.13	0.06	0.19	32.9	22.7	31.0
YJ	0.11	1.00	0.03	1.03	10.4	10.1	0.29	0.11	0.40	31.1	23.0	31.2
SNO	0.01	0.02	0.00	0.02	50.0	50.0	0.03	0.001	0.03	27.7	27.2	1.9

[1] : ΣC-PAH – Sum of carcinogenic PAH (B[a]A-DB[ah]A); [2]: ΣDBPs – Sum of dibenzopyrenes; [3]: ΣPAH – Sum of ΣC-PAH and ΣDBPs

study using the mean B[a]P concentration as representative of the mixture and the WHO Unit Risk, and the U.S. EPA IUR to together with different measures of B[a]P-equivalent concentration. Several points arise. The application of the U.S. EPA IUR resulted in the number of people possibly developing lung cancer by exposure to B[a]P to be two orders of magnitude lower than when using the WHO UR. Focussing on the results using the WHO UR, it could be noted that as expected, the LECR were highest in the following order: urban and industrial > traffic roads > urban background > rural background, independent of the country. The number of cancers per 100,000 people in the UK ranged from 0.7 to 16.8, in Mexico from 1.6 to 9.4, in Sweden from 0.3 to 1.2, at NAN and LOT-A in China were 5.6 and 65.3 respectively, whilst in SNO in Asia was 0.1. LECR calculations were repeated using the (ΣC-PAH)B[a]P_{eq}, (ΣPAH)B[a]P_{eq} and (ΣAll-PAH)B[a]P_{eq} (from Table 3(b)), when applying the maximum TEFs as reported in Table 1 and multiplying by the U.S. EPA UR, a common approach used by several researchers. Our results in Table 4 show that across all sites, considering ΣDBPE and other toxic PAH increases the number of people per 100,000 who can develop cancer typically by > 100%.

Data from Table S3 and S4 confirm that more extensive characterisation of the chemical composition of the PAH mixture and increased knowledge of the toxicity of more PAH can greatly influence the estimated contribution of B[a]P to the overall carcinogenicity of the PAH mixture. Also, the B[a]P_{eq} approach using the U.S. EPA UR is markedly sensitive to the extent of compounds included in the evaluation, and can far exceed the risk estimates obtained if only the EPA-16 compounds are considered.

It is also instructive to compare the profile of PAH at different sites, as shown in Figs. 1 and 2. Fig. 1 shows average profiles for compounds within the ΣC-PAH group, i.e. the carcinogens with in the U.S. EPA 16 PAH. Overall differences between the site types, including coke oven samples are quite small.

Based on mean monthly data measured in various sites across the UK in 2018, Fig. 2(a) represents the ΣC-PAH profile across different sites. The sites SLS to DEB are the same as defined in Table 2, whilst Glasgow Townhead (GLT) and Birmingham Ladywood (BLW) are two extra urban background sites. Fig. 2(b) shows the profile of the DBPs and other "extra" PAH discussed in Table S3. Fig. 2(c) shows an 80–90% contribution of the ΣC-PAH, whilst ΣDBPs and ΣExtraPAH represent 5–12% and 2–5% of the PAH mixture considered respectively. The sites PTM, STO and SLS are all close to steelworks, and likely to be influenced by coke oven emissions. It is notable that all of these three sites show an elevated proportion of DB[ai]P, but not of DB[al]P, for which evidence of elevated carcinogenicity is greater (see Table 1). As concentrations are low, these are not sufficient to impact heavily upon carcinogenicity of the mixture if an additive approach is taken.

4. Synthesis and conclusions

The WHO approach, when properly applied, and U.S. EPA approach to calculating ILCR give estimates which differ widely, even when including a wide range of compounds in calculating B[a]P-equivalent for the latter method. If only the U.S. EPA 16 PAH compounds are considered, the divergence becomes even greater. The simplicity of the WHO method and its risk derivation from human rather than animal model data makes it appealing. It is dependent upon the assumption that B[a]P represents a similar proportion of the carcinogenic activity in the sample in question to that in the coke oven samples used to establish the Unit Risk. The calculations presented above suggest that within reasonable limits this is a fair assumption, even when including a wide range of compounds, some of which only have an IARC 2B (possibly carcinogenic) assessment, and differing estimates of relative potency. The U.S. EPA method suffers more in this regard, as it is markedly sensitive both to which compounds are included in the calculation of B[a]P-equivalent, and to the relative potency values adopted. The simple additive approach used in the U.S. EPA method may also fail to account

Table 4
Lifetime Excess Cancer Risk (LECR) calculations using the WHO IUR and the U.S. EPA IUR for different PAH subgroups.

Site	[B[a]P]	LECR	No of people	ΣC-PAH[a]	LECR-EPA	No of people	ΣPAH[b]	LECR-EPA	No of people	ΣAll-PAH[c]	LECR-EPA	No of people	% Increase	% Increase	Difference
	ng/m3	WHO	per 100,000 WHO	[B[a]P]eq ng/m^3	ΣC-PAH	per 100,000 EPA	[B[a]P]eq ng/m^3	ΣPAH	per 100,000 EPA	[B[a]P]eq ng/m^3	ΣAll-PAH	per 100,000 EPA	in risk from ΣC-PAH to ΣPAH	in risk from ΣC-PAH to ΣAll-PAH	from ΣPAH to ΣAll-PAH
BRL	0.15	1.31×10^{-5}	1.3	0.41	2.6×10^{-7}	0.03	1.01	6.5×10^{-7}	0.06	1.30	8.3×10^{-7}	0.08	**146**	**217**	**71**
CBO	0.08	6.96×10^{-6}	0.7	0.22	1.4×10^{-7}	0.01	0.72	4.6×10^{-7}	0.05	0.86	5.5×10^{-7}	0.06	**227**	**291**	**64**
DEB	0.85	7.40×10^{-5}	7.4	1.97	1.3×10^{-6}	0.13	5.24	3.4×10^{-6}	0.34	6.19	4.0×10^{-6}	0.40	**166**	**214**	**48**
MRL	0.17	1.48×10^{-5}	1.5	0.40	2.6×10^{-7}	0.03	0.94	6.0×10^{-7}	0.06	1.17	7.5×10^{-7}	0.07	**135**	**193**	**58**
PTM	0.55	4.79×10^{-5}	4.8	1.50	9.6×10^{-7}	0.10	4.20	2.7×10^{-6}	0.27	5.06	3.2×10^{-6}	0.32	**180**	**237**	**57**
SLS	1.93	1.68×10^{-4}	16.8	4.66	3.0×10^{-6}	0.30	11.70	7.5×10^{-6}	0.75	14.09	9.0×10^{-6}	0.90	**151**	**202**	**51**
STO	1.66	1.44×10^{-4}	14.4	4.03	2.6×10^{-6}	0.26	9.90	6.3×10^{-6}	0.63	12.04	7.7×10^{-6}	0.77	**146**	**199**	**53**
LOT-A	7.50	6.53×10^{-4}	65.3	34.74	2.2×10^{-5}	2.22	38.28	2.4×10^{-5}	2.45	38.28	2.4×10^{-5}	2.45	**10**	**10**	**0**
NAN	0.64	5.57×10^{-5}	5.6	1.89	1.2×10^{-6}	0.12	3.55	2.3×10^{-6}	0.23	3.55	2.3×10^{-6}	0.23	**88**	**88**	**0**
EST-MAGO	0.18	1.57×10^{-5}	1.6	0.31	2.0×10^{-7}	0.02	0.72	4.6×10^{-7}	0.05	0.82	5.3×10^{-7}	0.05	**132**	**165**	**33**
ITA-PTR	0.36	3.13×10^{-5}	3.1	0.61	3.9×10^{-7}	0.04	1.77	1.1×10^{-6}	0.11	1.90	1.2×10^{-6}	0.12	**190**	**211**	**21**
MED-PJC	0.43	3.74×10^{-5}	3.7	0.90	5.8×10^{-7}	0.06	3.11	2.0×10^{-6}	0.20	3.93	2.5×10^{-6}	0.25	**246**	**337**	**92**
MED-UNFM	0.48	4.18×10^{-5}	4.2	0.97	6.2×10^{-7}	0.06	3.45	2.2×10^{-6}	0.22	4.64	3.0×10^{-6}	0.30	**256**	**378**	**122**
MED-MIRA	1.08	9.40×10^{-5}	9.4	1.85	1.2×10^{-6}	0.12	4.80	3.1×10^{-6}	0.31	5.25	3.4×10^{-6}	0.34	**159**	**184**	**24**
CAL-PMER	0.98	8.53×10^{-5}	8.5	1.58	1.0×10^{-6}	0.10	4.27	2.7×10^{-6}	0.27	4.99	3.2×10^{-6}	0.32	**170**	**216**	**46**
EN	0.14	1.22×10^{-5}	1.2	0.24	1.5×10^{-7}	0.02	0.33	2.1×10^{-7}	0.02	0.56	3.6×10^{-7}	0.04	**38**	**133**	**96**
DE	0.09	7.83×10^{-6}	0.8	0.34	2.2×10^{-7}	0.02	0.46	2.9×10^{-7}	0.03	0.77	4.9×10^{-7}	0.05	**35**	**126**	**91**
YJ	0.04	3.48×10^{-6}	0.3	0.29	1.9×10^{-7}	0.02	0.40	2.6×10^{-7}	0.03	0.68	4.4×10^{-7}	0.04	**38**	**134**	**97**
TK	0.11	9.57×10^{-6}	1.0	0.13	8.3×10^{-8}	0.01	0.19	1.2×10^{-7}	0.01	0.27	1.7×10^{-7}	0.02	**46**	**108**	**62**
SNO	0.01	8.70×10^{-7}	0.1	0.03	1.9×10^{-8}	0.00	0.03	1.9×10^{-8}	0.00	0.60	3.8×10^{-7}	0.04	**0**	**1900**	**1900**

WHO-UR = 8.70×10^{-5} (ng/m^3)$^{-1}$; U.S. EPA-UR = 6.4×10^{-7} (ng/m^3)$^{-1}$; [a]: ΣC-PAH = 8 Carcinogenic EPA PAH; [b]: ΣPAH = ΣC-PAH + ΣDBPs; [c]: ΣAll-PAH = ΣC-PAH + ΣDBPs + ΣExtra PAH.

Fig. 1. ΣC-PAH profile in different microenvironments (numbers in brackets represent the mean of the various studies considered). Note: the contribution from all individual compounds is normalized with the ΣAll-PAH.

for interactions between components within the PAH mixture. The lower estimates of risk deriving from the U.S. EPA method could arise for a number of reasons. These include inter-species differences in the susceptibility to lung cancers, the artificial exposure regime in the animal experiments, interactions between PAH in the mixture, or the possible omission of highly carcinogenic species in the calculation of $B[a]P_{eq}$. The *in vitro* studies of Dreij et al (Driscoll et al., 2000) strongly suggest that the carcinogenic potency of mixtures is not well described by application of relative potency factors to individual components of the mixture.

Although some variability in the concentration of the 16 U.S. EPA PAH from coke oven emissions may be explained by evaporative losses from filters (Kirton and Crisp, 1990), it is well known that sampling in a coke plant is technically challenging and also dependent on where the air is sampled. Locations include the oven battery top, by the charging hole lid, by the door (Bjørseth et al., 1978; Li et al., 2012; Mu et al., 2014; Aries et al., 2007), by the pusher machine, by the pusher machine side, by the charging car (Mu et al., 2013; Liberti et al., 2006), and from the combustion of the coke-oven gas in the process (Mu et al., 2013). Bieniek and Łusiak reported that PAH concentrations obtained during personal monitoring of different worker groups within a coke plant are highly variable and depend mainly on the sampling location (Bieniek and Łusiak, 2012).

Studies involving coke oven emissions have also shown that the contribution from individual PAH or different PAH groups varies substantially (Bigda et al., 2017; Kozielska and Konieczyński, 2015; Lim et al., 2015; Mu et al., 2013; Aries et al., 2007). The percentage of B[a]P in the U.S. EPA 16 PAH varied from 1.0% to 20.5% as a mole fraction. Fewer studies have provided insight of the PAH composition beyond the U.S. EPA 16 PAH (Bjørseth et al., 1978; Lao et al., 1975; Lim et al., 2015; Aries et al., 2007). In these studies, the PAH mixtures were diverse and the percentage of B[a]P in them was typically in the range 3.2–9.5% whilst the proportion of the U.S. EPA 16 PAH in the PAH mixtures considered was 40.4–93.2%.

Studies in different microenvironments such as industrial areas (Harrison et al., 2016; Kamal et al., 2015; Mueller et al., 2019; Smith et al., 1996; Wu et al., 2014), street canyons (Lim et al., 2015; Ren et al., 2017; Wu et al., 2014), subway stations (Bergvall and Westerholm, 2007) and tunnels (Demir et al., 2019; Keyte et al., 2016; Khalili et al., 1995) and urban background roads (Bari et al., 2010; Mueller et al., 2019; Smith et al., 1996; Wu et al., 2014) also show similar variability in the individual PAH contribution to the overall total measured ΣC-PAH concentration, when compared to coke ovens (Bieniek and Łusiak, 2012; Bjørseth et al., 1978; Khalili et al., 1995; Mu et al., 2013) as can be observed in Fig. 1. While Fig. 2 shows some compositional differences

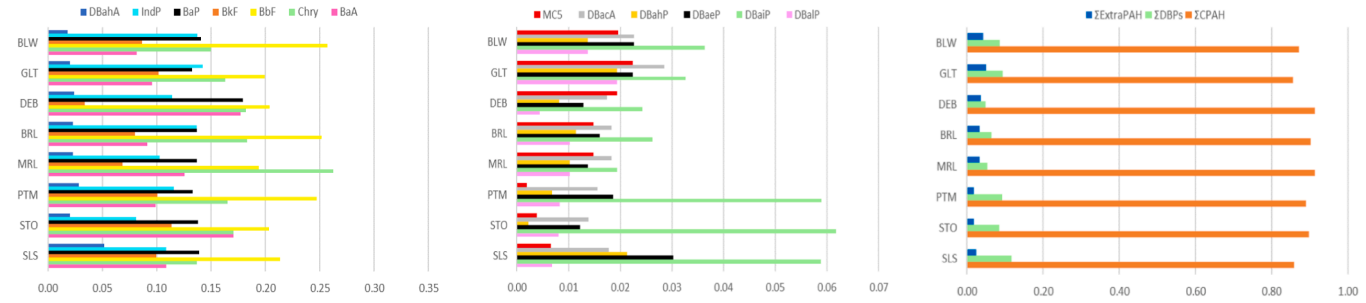

Fig. 2. (a) C-PAH profile; (b) DBP and Extra PAH profile and (c) contribution from each group to the PAH mixture considered across different sites in the UK. Note: For all sites, the contribution from all individual or groups of compounds is normalized with the ΣAll-PAH.

between sites, and especially those with a steelworks (coke oven) influence, the differences are not major, which adds confidence to use of the WHO approach of using the coke oven mixture as a proxy for other PAH mixtures based upon its B[a]P concentration. This line of analysis however omits consideration of PAH derivatives which may influence the mixture toxicity, but for which few data are available.

All the above mentioned issues serve to emphasise that the use of B[a]P as an index compound of the PAH mixture, or of the U.S. EPA 16 PAH to derive the risk attributable to PAH exposure is open to high uncertainty, beyond that resulting from application of very different types of data used as the starting point for the methods.

Several studies have put forward the argument that a cancer risk assessment associated with exposure to environmental PAH carried out using either a single marker as representative of the PAH mixture or a component-based factors approach, by applying TEFs to each PAH would probably misrepresent the actual health risk of exposure to a complex PAH mixture (Dreij et al., 2017; Layshock et al., 2010; Okona-Mensah et al., 2005; Yuling et al., 2011). Inferences from the sensitivity analysis and LECR calculations presented in this study, considering a range of compounds and applying a range of TEFs available in the literature support this line of argument. Recently, both the WHO and U.S. EPA have suggested a move towards a better approach (WHO, 2021). Backhaus et al. suggested use of a whole mixture potency evaluation approach which would have the least uncertainty when it comes to the impact of interaction effects between PAH and unknown mixture components. The major drawbacks of this approach are that it is dependent on-site specific data on the PAH mixture, which are not always available and would require extensive and expensive *in vivo* testing (Backhaus et al., 2010).

Studies have shown that potent PAH such as benz[j]aceanthrylene and DB[a,l]P can activate DNA damage signaling *in vitro* through the proteins checkpoint kinase 1 (Chk1) and H2A histone family, member X (H2AX) relative to that of B[a]P, results being in very good agreement with published *in vivo*-based RPFs (Jarvis et al., 2013; Lim et al., 2015). It is claimed that the activation of DNA damage signaling could be a relevant endpoint *in vitro* for developing mixture potency factors for environmental PAH samples (Jarvis et al., 2013, 2014). The validity of such an approach was further tested, with some degree of confidence, by comparing the *in vitro*-based system with RPFs obtained from cancer data *in vivo* (Dreij et al., 2017). The methodology to assign mixture potency factors for whole mixture airborne PAH and their derivatives, and to refine the WHO and U.S. EPA methods could be improved if specific research gaps are addressed, namely,

i) improve analytical methods to deal with challenging PAH and their derivatives and develop standard reference materials to support quality assurance.
ii) characterize better the chemical composition of the complex PAH mixtures found in different microenvironments, including analysis of PAH derivatives,
iii) identify those size fractions of particulate matter in which the most toxic PAH are found, to allow better estimation of the daily dose of PAH that deposits within the different parts of the respiratory system,
iv) further develop new approach methodologies for risk assessment applicable to complex environmental PAH mixtures, for which mixture potency factors can be assigned, possibly accounting for interactions between PAH, and such methodologies to be validated beyond available SRMs.

In the meantime, the WHO approach to risk assessment seems likely to offer more realistic estimates than the U.S. EPA approach based upon B[a]P equivalents as it implicitly takes account of interactions within a mixture with some similarity to those encountered in the urban atmosphere.

Ideally, predictions from the WHO and EPA approaches would be tested against lung cancer prevalence rates in the general population. This is not readily possible for two reasons. Firstly, prevalence rates are heavily influenced by the impacts of tobacco smoking which can only be controlled for very approximately at a population level. Secondly, PAHs are not the only carcinogens present in ambient air to which the general public is exposed; several metals and metalloids, as well as other trace organic compounds have carcinogenic activity. Harrison et al. (Harrison et al., 2004) posed the question of whether exposures to known chemical carcinogens could explain the cancer risks in residents of US cities, as revealed by the ACS cohort study of the chronic effects of $PM_{2.5}$ exposures, in which confounders were controlled at an individual level. Allowing for a latency period of 20 years, exposures to airborne Ni, As, Cr(VI) and PAH were found to plausibly explain the excess lung cancer risk, with PAH accounting for almost one half of the total risk. This study used the WHO approach to risk estimation and provides some, albeit limited, confidence in the approach. Application of the US EPA method in such a context, or in any study of large populations is likely to be precluded by the lack of suitably comprehensive PAH monitoring data.

CRediT authorship contribution statement

Noel J. Aquilina: Data curation, Methodology, Formal analysis, Investigation, Writing – original draft. **Roy M. Harrison:** Conceptualization, Methodology, Funding acquisition, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Acknowledgments

Hwanmi Lim from the Department of Materials and Environmental Chemistry, Stockholm University, 106 91 Stockholm, Sweden for the provision of PAH data from Sweden.

Funding

This work was supported by the National Centre for Atmospheric Science funded by the U.K. Natural Environment Research Council (R8/H12/83/011).

Data availability

Data supporting this publication are openly available from the UBIRA eData repository at https://doi.org/10.25500/edata.bham.00000938

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.107991.

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