HBM4EU science and policy for a healthy future

HORIZON2020 Programme
Contract No. 733032 HBM4EU

SCOPING DOCUMENTS

(1st round of prioritization)

Prioritized substance group: PAHs and air pollutants

Chemical Group leader: AUTH

Date: 20/12/2018 **Document version: 1.0**

Table of contents

1. Introduction

HBM4EU has established Chemical Working Groups during the proposal phase for the nine prioritized substance groups that HBM4EU will work on in 2017 and 2018. Additional substance groups will be identified by late 2018 through the implementation of a refined prioritization strategy.

For each substance group, scoping documents are produced under Workpackage 4.4 of HBM4EU. The scoping document will contain a review of the available evidence, will list policy-related questions, identify knowledge gaps and propose research activities. Proposed activities will be fed into the framework of work packages and tasks of HBM4EU in a coordinated and harmonized manner, and will constitute the basis for the annual work plans. The scoping documents are the linkage between policy questions and the research to be undertaken (broken down for single substances) in order to answer those questions. This methodology will optimize work on the different substances, avoid redundancies, ensure coordination and facilitate the calculation of budgets for each WP. The scoping documents do not contain a comprehensive literature review per substance group but are intended to provide information for the WP leaders who will draft the Annual Work Plans.

For the selected substance groups the availability of (toxicology or human biomarker) data is variable. A scheme was therefore developed to classify the compounds within each substance group into categories A, B, C, D and E based on the availability of data to answer research questions (see further). In direct response to the key project goal of exploiting HBM data in policy making to positively impact on human health, the research activities for each substance group will generate knowledge on exposure trends and associated health effects. Throughout the course of the project, we will generate knowledge that will shift substances towards to a higher level of knowledge category.

For further information see www.hbm4eu.eu

Template for Scoping document

Substance group: PAHs and air pollutants

2. Background Information

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants generated primarily during the incomplete combustion of organic materials (e.g. coal, oil, petrol, and wood). Emissions from anthropogenic activities predominate (automobile emissions and cigarette smoke); nevertheless, some PAHs in the environment originate from natural sources (e.g. open burning, natural losses or seepage of petroleum or coal deposits, and volcanic activities).

Particulate Matter is generally categorised on the basis of the size of the particles that reflects their aerodynamic diameter (e.g PM2.5 refers to particles with an aerodynamic diameter of less than 2.5µm). PM is made up of a wide range of components and are formed from a variety of sources and processes. Ambient air levels of PM comprise primary particles emitted directly into the atmosphere from combustion sources and secondary particles formed by chemical reactions in the air. Ambient air PM are released from both anthropogenic and natural sources (such as sea spray, Saharan dust or volcanos). The most common anthropogenic sources are stationary fuel combustion and transport. Road transport gives rise to primary particles from engine emissions, as well as various non-exhaust emissions such as tire and brake wear. Secondary PM is formed from emissions of ammonia, sulphur dioxide and oxides of nitrogen as well as from emissions of organic compounds from both combustion sources and vegetation.

Ozone is not emitted directly from anthropogenic sources; it is formed by photochemical reactions resulting from the interaction of sunlight on nitrogen dioxide (NO_2) and VOCs, typically emitted from transportation sources. Formation can take place over several hours or days and may have arisen from emissions many hundreds, or even thousands of kilometers away. Ozone is a secondary pollutant, which often impacts rural areas far from the original emission site as a result of long-range transport.

Sulphur dioxide (SO_2) emissions are dominated by combustion of fuels containing sulphur, such as coal and heavy oils by power stations and refineries. In some EU countries, coal for domestic use is a significant source. Carbon monoxide (CO) is mainly formed from incomplete combustion of carbon containing fuels. The most significant source is road transport, followed by residential and industrial combustion.

Nitrogen Dioxide (NO_2) is one of a group of gases called nitrogen oxides (NOx). While all of these gases are harmful to human health and the environment, NO_2 is of the greatest concern. NO_2 primarily gets in the air from the burning of fuel related to transport emissions, mainly from diesel vehicles (including cars, trucks and buses) and power plants.

Finally, benzene is an air toxic emitted from gasoline service stations, gasoline (mainly) motor vehicle exhaust and fuel evaporation, the burning of coal and oil, and to a lesser extend to various other combustion sources.

Hazardous properties

Many PAHs are known or suspected carcinogenic and mutagenic compounds (e.g., benzo(a)pyrene, dibenzo(a,h) anthracene, etc.). They are included in the candidate list under article 59 of REACH which contains a number of complex substances derived from petroleum and coal such as: coal tar pitch, high temperature (CTPHT) – EC 266-028-2; anthracene oil EC 292-602-7 and other anthracene related fractions. The reasons for inclusion are the Persistent Bioaccumulative Toxic (PBT), very Persistent very Bioaccumulative (vPvB) and carcinogenic properties of the PAHs which are present as constituents in these UVCB substances (substances of Unknown or Variable composition, Complex reaction products or Biological materials, ECHA)

Currently eight PAH congeners (Benzo[a]pyrene (BaP), benzo[e]pyrene (BeP), benzo[a]antracene (BaA), chrysene (CHR), benzo[b]fluoranthene, (BbF), benzo[j]fluoranthene (BjF), benzo[k]fluoranthene (BkF), dibenzo[a,h]antracene (DBAhA)) are classified as known carcinogens in Annex VI of Regulation (EC) 1272/2008 (Classification Labelling and Packaging, CLP regulation). These are legally classified carcinogens of Category 1B acc. to the CLP regulation.

Benzo[a]pyrene (BaP) and chrysene (CHR) are also legally classified mutagens (CLP Cat. 1B; CHR: CLP Cat. 2). In addition, BaP is a classified reprotoxicant (CLP: Cat. 1B). Lack of 'CMR (Carcinogenic Mutagenic Reprotoxic)' classification1 for the other PAH congeners may rather be attributed to the comparatively limited database available for these compounds. There are indications that the carcinogenic potency of some further PAH congeners, e.g. some of the dibenzopyrenes, may even be considerably higher than that of the lead compound BaP.

The mechanism of toxicity is considered to be interference with the function of cellular membranes as well as with enzyme systems which are associated with the membrane. It has been proven that PAHs can cause carcinogenic and mutagenic effects and are potent immune-suppressants. Effects have been documented on immune system development, humoral immunity and on host resistance [1, 2]. PAH-induced carcinogenesis can result when a PAH-DNA adduct forms at a site critical to the regulation of cell differentiation or growth. A mutation occurs during cell replication if the aberration remains unrepaired. Cells affected most significantly by acute PAH exposure appear to be those with rapid replicative turnover, such as those in bone marrow, skin, and lung tissue. Tissues with slower turnover rates, such as liver tissue, are less susceptible. Target organs identified in animal studies with some of the PAHs were the skin, the liver, the hemolymphatic and the respiratory system [3-5]. Many PAHs are aryl hydrocarbon receptor (AhR) ligands and several recent studies have suggested that PAHs or their metabolites may activate estrogen receptors (ER). Activation of ER signaling in endocrine cancer prone tissues, such as breast epithelium, might thus further contribute to their known carcinogenicity [6]. PAHs have been shown to exert endocrine and developmental toxicity in experimental animals, including decreased weight of reproductive organs, damage to growing ovarian follicles, decreased fertility, embryonic damage and lethality or developmental defects of testis and spermatogenesis in males [7-9].

PAHs can be formed both during biological processes and as products of incomplete combustion from either natural combustion sources (forest and brush fires) or man-made combustion sources (automobile emissions and cigarette smoke). Thus, PAHs are commonly detected in air, soil, and water. Therefore, PAHs are considered ubiquitous in the environment [10, 11]. PAHs are highly lipid soluble and thus readily absorbed from the gastrointestinal tract of mammals. They are absorbed through ingestion, inhalation, and dermal contact, according to animal study data. The percentage absorbed varies in these studies for several reasons, including the vehicle (transport medium) in which the PAHs are found [12]. In general, PAHs not bound to particulate matter may be absorbed in the lungs better than the same dose found on the surface of airborne particulate matter [13, 14]. They are rapidly distributed in a wide variety of tissues with a marked tendency for localization in

body fat. Metabolism of PAHs occurs via the cytochrome P450-mediated mixed function oxidase system with oxidation or hydroxylation as the first step. Because of their lipophilic nature, PAHs can accumulate in breast milk and adipose tissue. However, biliary and urinary excretion of PAHs is relatively efficient because of the wide distribution of enzymes that transform PAHs into polar metabolites.

PAHs are predominantly metabolized in the liver, via CYP enzymes (enzymes in the P-450 mixed-function oxidase system) [15-17].

In addition to the liver and kidneys, metabolism of PAHs occurs in the adrenal glands, testes, thyroid, lungs, skin, sebaceous glands, and small intestines [18].

PAHs are transformed initially to epoxides, which are converted to dihydrodiol derivatives and phenols. Glucuronide and sulfate conjugates of these metabolites are excreted in the bile and urine. Glutathione conjugates are further metabolized to mercapturic acids in the kidney and are excreted in the urine.

The hydroxylated metabolites of the PAHs are excreted in human urine both as free hydroxylated metabolites and as hydroxylated metabolites conjugated to glucuronic acid and sulfate [19]. A commonly measured urinary metabolite is 1-hydroxypyrene [20-22].

Metabolism is a prerequisite for hepatobiliary excretion and elimination through the feces, regardless of route of entry. Excretion half-lives in feces and urine have been reported in animal studies as 22 hours and 28 hours, respectively [21].

Pyrene is commonly found in PAH mixtures, and its urinary metabolite, 1-hydroxypyrene, has been used as an indicator of exposure to PAH chemicals [19-22].

Exposure to PAHs is almost always to mixtures that pose a challenge in developing conclusions [23]. Several epidemiologic studies have shown increased cancer mortality in workers exposed to PAHs.

Carbon Monoxide is a colourless, odourless, tasteless gas that is slightly lighter than air. Natural background levels of CO fall in the range of 10-200 ppb. Levels in urban areas are highly variable, depending upon weather conditions and traffic density. 8-hour mean values are generally less than 10 ppm (12 mgm^{-3}) but have been known to be as high as 500 ppm (600 mgm^{-3}). The European limit value for the maximum daily 8-hour mean concentrations of CO is set to 10 mg/m^3 [24]. Based on the available measurements, it can be concluded that in EU the CO ambient concentrations above the limit value is very localised and infrequent, and is limited to a very few areas near traffic and industry. The only concentration above the limit value was registered at an urban industrial station in the former Yugoslav Republic of Macedonia [25].

CO is an intermediate product through which all carbon species must pass when combusted in oxygen (O_2). In the presence of an adequate supply of O_2 most CO produced during combustion is immediately oxidised to carbon dioxide (CO_2). However, this is not the case in spark ignition engines, especially under idling and deceleration conditions. Thus, the major source of atmospheric CO is the spark ignition combustion engine. Smaller contributions come from processes involving the combustion of organic matter, for example in power stations and waste incineration.

The main health effects related to exposure to CO are: headaches, dizziness, slows mental processes, and at high levels can lead to death. CO prevents the normal transport of oxygen by the blood. This can lead to a significant reduction in the supply of oxygen to the heart, particularly in people suffering from heart disease.

SO_2 is a colourless gas. It reacts on the surface of a variety of airborne solid particles, is soluble in water and can be oxidised within airborne water droplets.

Annual mean concentrations in most major UK cities are now well below 35 ppb (100 µgm^{-3}) with typical mean values in the range of 5-20 ppb (15-50 µgm^{-3}). Hourly peak values can be 400-750 ppb (1000-2000 µgm-3) on infrequent occasions. Natural background levels are about 2 ppb (5 µgm^{-3}). The European air quality standards for SO_2 are defined by the Ambient Air Quality Directive [26] for SO_2. The limit value for 24-hour average SO_2 concentration is set at 125 µg/m^3 and can be exceeded on up to 3 days per year. The 1-hour limit value threshold of 350 µg/m^3 can be exceeded on up to 24 hours per year. EU countries were obliged to meet both public health protection limits by 2005. There is also an 'alert' threshold value of 500 µg/m^3. When this alert threshold is exceeded over three consecutive hours, authorities have to implement action plans to lower the high levels of SO_2. SO_2 concentrations are generally well below the limit values for the protection of human health. Only one industrial station in Bulgaria, out of some 1 350 stations measuring SO_2 in 34 European countries (EU‑28, Albania, FYROM, Iceland, Montenegro, Norway and Serbia), registered concentrations of SO_2 above this limit value.

The most important sources of SO_2 are fossil fuel combustion, smelting, manufacture of sulphuric acid, conversion of wood pulp to paper, incineration of refuse and production of elemental sulphur. Coal burning is the single largest man-made source of SO2 accounting for about 50% of annual global emissions, with oil burning accounting for a further 25-30%.

Even moderate concentrations may result in constriction of the lung airways. This effect is particularly likely to occur in people suffering from asthma and chronic lung disease. Tightness in the chest and coughing occur at high levels, and lung function of asthmatics may be impaired to the extent that medical help is required. Sulphur dioxide pollution is considered more harmful when particulate and other pollution concentrations are high.

NOx is a collective term used to refer to two species of oxides of nitrogen: nitric oxide (NO) and nitrogen dioxide (NO_2). Annual mean concentrations of NO_2 in urban areas are generally in the range 10-45 ppb (20-90 µgm-3). Levels vary significantly throughout the day, with peaks generally occurring twice daily as a consequence of "rush hour" traffic. Maximum daily and one hourly means can be as high as 200 ppb (400 µgm^{-3}) and 600 ppb (1200 µgm^{-3}) respectively. The Ambient Air Quality directive [26] sets short-term (1-hour) and long-term (annual mean) limit values for the protection of human health. The limit value for the annual mean NO_2 concentration is set at 40 µg/m^3. The 1-hour limit value threshold of 200 µg/m^3 can be exceeded on up to 18 days per year (corresponding to the 99.8 percentile of hourly concentrations in one year) before the limit value is breached.

In 17 (Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, the Netherlands, Poland, Portugal, Slovakia, Spain, Sweden and the United Kingdom) of the 28 EU Member States recorded concentrations above the annual limit value at one or more stations. Concentrations above 55 µg/m^3 were also measured at one urban background station in Serbia and another in the United Kingdom. These findings demonstrate that NO_2 concentrations still need to be substantially reduced in large areas of Europe (focusing on traffic and urban locations) for the annual limit value to be met. The hourly limit value threshold for NO_2 is less stringent. Concentrations above this limit value were observed in 0.5 % of all the reporting stations, mostly at urban traffic stations except for two (urban and suburban) background stations. They were observed in seven (Spain (five stations), Germany (three) and France, Hungary, Italy, Portugal and the United Kingdom (one station each)) Member States.

Globally, quantities of nitrogen oxides produced naturally (by bacterial and volcanic action and lightning) far outweigh anthropogenic (man-made) emissions. Anthropogenic emissions are mainly due to fossil fuel combustion from both stationary sources, i.e. power generation (21%), and mobile sources, i.e. transport (44%). Other atmospheric contributions come from non-combustion processes, for example nitric acid manufacture, welding processes and the use of explosives.

The main health effects associated to exposure to NO_x are: shortness of breath or coughing and enhanced risk of respiratory disease. NO_2 is associated with several respiratory adverse effects on human health. At high levels NO_2 causes inflammation of the airways. Long term exposure may affect lung function and respiratory symptoms. NO_2 also enhances the response to allergens in sensitive individuals. Nitrogen dioxide can irritate the lungs and lower resistance to respiratory infections such as influenza. Continued or frequent exposure to concentrations that are typically much higher than those normally found in the ambient air may cause increased incidence of acute respiratory illness in children.

O_3 is the tri-atomic form of molecular oxygen. It is a strong oxidising agent, and hence highly reactive. Background levels of O_3 in Europe are usually less than 15 ppb but can be as 100 ppb during summer time photochemical smog episodes. In the UK ozone occurs in higher concentrations during summer than winter, in the south rather than the north and in rural rather than urban areas. According to the Ambient Air Quality Directive [26], a maximum daily 8-hour mean threshold of 120 µg/m^3 has been established. The target applied by EU Member States (starting from January 1, 2010), is that the threshold should not be exceeded at a monitoring station more than 25 day per year (corresponding to the 93.2 percentile), determined as a 3-year average starting from 2010. The long-term objective is no exceedance of the threshold level at all. For public health protection, there are also two other types of thresholds: 'public information' (180 µg/m^3) and 'alert' thresholds (240 µg/m^3). When the public information threshold is breached, the authorities in that country are obliged to notify their citizens, using a public information notice. When the alert threshold is exceeded for three consecutive hours, a short‑term action plan has to be drawn up, in accordance with the specific provisions established in the Ambient Air Quality Directive [26].

Since the formation of O_3 requires sunlight, O_3 levels increase as one moves from the northern to the southern parts of Europe, with the highest levels observed in some Mediterranean countries. The O_3 typical concentrations in 16 EU countries (Austria, Bulgaria, Croatia, Cyprus, the Czech Republic, France, Germany, Greece, Hungary, Italy, Luxembourg, Malta, Poland, Slovakia, Slovenia and Spain) of the EU-28 [25] were above the O_3 target value more than 25 times.

Most O_3 in the troposphere (lower atmosphere) is formed indirectly by the action of sunlight on nitrogen dioxide - there are no direct emissions of O3 to the atmosphere. About 10 - 15% of tropospheric O_3 is transported from the stratosphere where it is formed by the action of ultraviolet (UV) radiation on O_2. In addition to O_3, photochemical reactions involving sunlight produce a number of oxidants including peroxyacetyl nitrate (PAN), nitric acid and hydrogen peroxide, as well as secondary aldehydes, formic acid, fine particulates and an array of short lived radicals. As a result of the various reactions that take place, O_3 tends to build up downwind of urban centres where most of NO_x is emitted from vehicles. Exposure to high levels of O_3 may result in irritation to eyes and nose. Very high levels can damage airways leading to inflammatory responses. Ozone reduces lung function and increases incidence of respiratory symptoms, respiratory hospital admissions and mortality. Ground level ozone can also cause damage to many plant species leading to loss of yield and quality of crops, damage to forests and impacts on biodiversity.

Particulate matter is a complex mixture of organic and inorganic substances, present in the atmosphere as both liquids and solids. Coarse particulates can be regarded as those with an aerodynamic diameter greater than 2.5 µm (micrometres), and fine particles less than 2.5 µm. Coarse particles usually contain earth crustal materials and fugitive dust from roads and industries. Fine particles contain the secondarily formed aerosols, combustion particles and re-condensed organic and metallic vapours. The acid component of particulate matter generally occurs as fine particles. A further distinction that can be made is to classify particulates as either primary or secondary, according to their origin. Primary particulates are those emitted directly to the atmosphere while secondary particulates are those formed by reactions involving other pollutants.

In the urban context, most secondary particulate matter occurs as sulphates and nitrates formed in reactions involving SO_2 and NOx.

Reported concentrations vary according to the sampling technique. In urban areas typical annual mean values are 10 - 40 µg/m^3 (gravimetric sampling) although short-lived pollution episodes such as Bonfire night can cause particulate concentrations to rise to several hundred µg/m^3. Background levels in rural areas range form 0-10 µgm^{-3}. The Ambient Air Quality Directive [26] sets limit values for long‑term (annual) $PM_{2.5}$ concentrations. The deadline for meeting the target value for PM2.5 (25 µg/m^3) was 1 January 2010, and the deadline for meeting the limit value (25 µg/m^3) and the exposure concentration obligation for $PM_{2.5}$ (20 µg/m^3) was 2015. The typical concentrations of PM2.5 in EU is above the EU limit value in large parts of Europe according to the data of the European air-quality database ([25]. Nevertheless, there were stations with PM2.5 concentrations higher than the target value (annual mean, which has been the limit value for PM2.5 from 2015 on) in four Member States of EU. These concentrations were observed in Bulgaria (ranged from 25 to 30 µg/m^3), Czech Republic, Italy and Poland, as well as in one station in the former Yugoslav Republic of Macedonia [25]. The PM2.5 concentrations in these countries ranged from 25 to 30 µg/m^3.

Particulate matter is emitted from a wide range of sources, the most significant primary sources being road transport (20%), homes (20%), construction, mining and quarrying (13%), industrial combustion plants and processes (10%) and public power generation (10%). Natural sources are less important; these include volcanoes and dust storms. Particulate matter can also be formed by the transformation of gaseous emissions such as oxides of sulphur and nitrogen and VOCs.

Both short-term and longterm exposure to ambient levels of PM are consistently associated with respiratory and cardiovascular illness and mortality as well as other adverse health effects. It is not currently possible to discern a threshold concentration below which there are no effects on public health. Fine particles are deposited in the lowest part of the human respiratory tract, where they can cause inflammation and a worsening of the condition of people with heart and lung diseases. In addition, they may carry surface-absorbed carcinogenic compounds into the lungs.

Benzene is a colourless, clear liquid compound. It is fairly stable but highly volatile, i.e. it readily evaporates. Ambient concentrations of benzene are typically between 1 - 50 ppb. Levels close to major emission sources can be as high as several hundred ppb. The urban background mean concentration of benzene is 1 to 2 ppb (3 to 6 µg/m^3); rural areas average 0.5 to 1 ppb (1.5 to 3 µg/m^3). Mean annual concentration can be 5 ppb (15 µg/m^3) on urban roadsides. The limit value for benzene is set as an annual mean, given that C_6H_6 is a carcinogen with long-term effects. The target value for benzene is set at 5 µg/m^3. Nevertheless, C6H6 is measured at a relatively small number of stations in EU. The concentrations above the limit value is limited to a few local areas with higher concentrations (2 µg/m^3) which are often close to traffic or industrial sources. No exceedances of the limit value were observed [25].

About 80% of man-made emissions come from petrol-fueled vehicles. This results from both the benzene content of the fuel and partial combustion of the petrol. A further 5% comes from the handling, distribution and storage of petrol and approximately 1% comes from oil refining. Emissions also come from benzene-producing and handling industries, the burning of wood and other organic material, and the use of benzene as a laboratory reagent.

Human exposure to benzene has been associated with a range of acute and long-term adverse health effects and diseases, including cancer and aplastic anemia. Benzene is a recognized human carcinogen that interacts with the genetic material and, as such, no absolutely safe level can be specified in ambient air. Studies in workers exposed to high levels have shown an excessive risk of leukemia. Exposure can occur occupationally and domestically as a result of the ubiquitous use of benzene-containing petroleum products, including motor fuels and solvents. Active and passive

exposure to tobacco smoke is also a significant source of exposure. Benzene is highly volatile, and exposure occurs mostly through inhalation.

VOCs comprise a very wide range of individual substances, including hydrocarbons, halocarbons and oxygenates. All are organic compounds and of sufficient volatility to exist as vapour in the atmosphere. Methane is an important component of VOCs, its environmental impact principally related to its contribution to global warming and to the production of ozone in the troposphere. Regional effects derive from non-methane VOCs (NMVOCs), such as benzene and toluene.

Most measurements of total VOCs are in terms of their carbon content, without analysis as individual compounds. The major contributor to VOCs is normally methane with a local background concentration of 1.6 ppm. Whilst most other individual compounds (e.g. benzene) are present in urban air at concentrations of a few ppb, or less, total NMVOCs will amount to several hundred ppb concentrations.

Hydrocarbons are emitted from petrol evaporation and incomplete combustion, and from leakage of natural gas from distribution systems. Oxygenates arise in vehicle exhausts and via atmospheric chemical reactions. Evaporation of solvents, used in paints or industrial degreasing processes, cause a release of hydrocarbons, oxygenates and halocarbons to the atmosphere.

BaP is a potent carcinogen. The target value for BaP for the protection of human health is set at 1 ng/m^3 [27] as an annual mean. Ambient air concentrations of BaP are high across large parts of Europe, mostly as a result of emissions from domestic combustion of coal and wood. More than a third of the BaP measurement stations in Europe measured annual concentrations above 1.0 ng/m^3. Values above 1.0 ng/m^3 were measured mainly at urban and suburban stations. These values above 1.0 ng/m^3 (1.0 to 1.5 ng/m^3) are most predominant in central and eastern Europe (Austria, Bulgaria, Croatia, the Czech Republic, Hungary, Italy, Lithuania, and Poland), although they are also found in Finland, Germany, Ireland and the United Kingdom. The average concentration measured at Polish stations is 4.8 times as high as the target value (ranging from 0.8 to 10 ng/m^3).

Possible chronic health effects include cancer, central nervous system disorders, liver and kidney damage, reproductive disorders, and birth defects

Exposure characteristics

Combustion sources are thought to account for over 90% of the environmental concentrations of PAHs. Major anthropogenic sources of PAHs include residential heating, coal gasification and liquefying plants, carbon black, coal-tar pitch and asphalt production, coke and aluminum production, catalytic cracking towers and related activities in petroleum refineries as well as motor vehicle exhaust. In addition, there could be some other, mainly local/target group exposure from very defined uses of products emitting PAHs. Synthetic turf, made with an infill of rubber crumb from used tires or virgin rubber also contains PAHs.

The following three types: *pyrogenic*, *petrogenic*, and *biological* are the major PAH sources to the environment. In pyrolysis processes pyrogenic PAHs are formed whenever organic substances are exposed to high temperatures under low oxygen or no oxygen conditions. The destructive distillation of coal into coke and coal tar, or the thermal cracking of petroleum residuals into lighter hydrocarbons are pyrolytic processes that occur intentionally. Meanwhile, other unintentionally processes occur during the incomplete combustion of motor fuels in cars and trucks, the incomplete combustion of wood in forest fires and fireplaces, and the incomplete combustion of fuel oils in heating systems.

The temperatures at which the pyrogenic processes occur are ranging from about (350 °C to more than 1200 °C). Pyrogenic PAHs are generally found in greater concentrations in urban areas and in locations close to major sources of PAHs.

PAHs formed during crude oil maturation and similar processes are called petrogenic. Such petrogenic PAHs are common due to the widespread transportation, storage, and use of crude oil and crude oil products. Some of the major sources of petrogenic PAHs include oceanic and freshwater oil spills, underground and above ground storage tank leaks, and the accumulation of vast numbers of small releases of gasoline, motor oil, and related substances associated with transportation. It is well-known that PAHs can be formed during the incomplete combustion of organic substances. PAHs are also found in petroleum products.

On the other hand, it is not well-known that PAHs can be produced biologically. For example, they can be synthesized by certain plants and bacteria or formed during the degradation of vegetative matter.

PAHs are also found in a multitude of consumer articles and mixtures. Although they are not produced intentionally for this purpose, they are present in these products due to the use of plasticisers (e.g. extender oils) or carbon black (soot) in the manufacture of rubber or other elastomers.

The atmosphere is the most important means of PAH dispersal, it receives the bulk of the PAH environmental load resulting in PAHs being ubiquitous in the environment.

Once released to the atmosphere, PAHs are found in two separate phases, a vapor phase and a solid phase in which the PAHs are sorbed onto particulate matter [28-30]. Hydrophobic organic chemicals with low vapor pressures, such as PAHs, are sorbet to atmospheric particulates more readily than chemicals with higher vapor pressures. The variability in vapor pressures of different PAH compounds cause the individual PAHs to distribute in different concentrations in the vapor [8] and other sorbet phases [31]. Low-molecular-weight PAHs (two and three rings) occur in the atmosphere predominantly in the vapour phase, whereas multi-ringed PAHs (five rings or more) are largely bound to particles. Intermediate-molecular-weight PAHs (four rings) are partitioned between the vapour and particulate phases, depending on the atmospheric temperature [32].

The removal of PAHs from the atmosphere by dry and wet deposition processes are strongly influenced by their gas/particle partitioning. Atmospheric deposition is a major source for PAHs in soil.

Background levels of some representative PAHs in the air are reported to be 0.02-1.2 ng/m^3 in rural areas and 0.15-19.3 ng/m^3 in urban areas. Background levels of PAHs in drinking water range from 4 to 24 ng/L.

Humans are exposed to PAH through several routes, namely inhalation of air and re-suspended soil and dust, consumption of food and water, and dermal contact with soil and dust [33]. All these sources are relevant to global human exposure

There is no sufficient evidence that exposure to PAHs has declined during the last ten years in Europe. In terms of spatial differentiation, exposure to PAHs is expected to be higher in areas with intense traffic and industrial activity.

Personal lifestyle factors, such as smoking and the use of indoor biomass combustion for heating and cooking, are also important determinants of exposure.

Since certain PAHs are considered carcinogens, there is no threshold under which exposure is safe. Thus, there are no BE values for PAHs. The maximum levels of benzo(a)pyrene and the sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene are regulated in food stuff according to Commission Regulation (EU) No 835/2011 [34]. In addition, Entry 50 of Annex XVII of the REACH regulation also stipulates limits for PAH containing extender oils in car tyres [35]. According to the regulation the extender oils shall not be placed on the market, or used for the

production of tyres or parts of tyres if they contain more than 1 mg/kg (0,0001 % by weight) BaP and more than 10 mg/kg (0,001 % by weight) of the sum of all listed PAHs.

In the Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons [36], United States EPA recommends using toxicity equivalency factors (TEFs) to convert concentrations of 19 carcinogenic PAHs (cPAHs) to an equivalent concentration of benzo(a)pyrene (B[a]P). In this scheme the TEF for B[a]P is set equal to one.

Urinary levels of PAHs and their respective metabolites are associated with proximity to combustion sources such as municipal solid waste incinerators [37]. Levels of 1-hydroxypyrene (1-OHP) (a major urinary PAH metabolite) were found to be higher for smokers (0.14 μg/g creatinine) than for non-smokers (0.08 μg/g creatinine) in the study by Lafontaine et al. [38], but not in the study by Leroyer et al. [39]. Proximity to industrial sites hot-spots in Germany was found to significantly affect PAH exposure levels with the mean urinary 1-OH-P level of 0.31 μg/g creatinine in the children living close to the hot spots, compared to 0.15 μg/g creatinine compared to children living far from hot spots [40]. In all cases, the 1-OH-P levels were lower than the reference value (RV) of 0.5 μg/L [41].

Studies in the Czech Republic [42, 43] found that levels of B[a]P-like DNA adducts were similar in the Ostrava and Prague regions, although B[a] P levels in the Ostrava region were more than eight times higher. This was attributed to the more efficient DNA repair capacity in the continuously highly exposed population. The nonlinear association between exposure levels and the formation of DNA-adducts, or the occurrence of oxidative stress, highlights the need to use advanced multi-omics approaches that can help to explain the observed pattern and reveal the mechanisms of interaction between environmental toxicants and human systems, which are modified by genetic make-up and other intrinsic factors.

Exposure to PAHs is affected by proximity to intense combustion sources, such as heavily trafficked roads, municipal waste incinerators and industrial sites. An additional source of PAHs is combustion of solid fuel for space heating. In this regard, special attention ought to be paid to the use of biomass in large urban and metropolitan areas, which, if not controlled, may contribute substantially to the overall PAH exposure of the urban population. Biomass combustion for heating is expected to contribute to indoor exposure as well.

For the rest of air pollutants, the only relevant route of exposure is inhalation. In practice, people are exposed to various levels of air pollutants during their daily activity, depending on a) the levels of these pollutants in the various microenvironments and b) the inhalation rate which is related to age, gender and the respective activity performed in the microenvironment. The concentration levels of the pollutants are clearly linked to the proximity to major sources, e.g. proximity to heavily trafficked roads results in increased levels of traffic related pollutants such as PM, NO_x and benzene, but not for VOCs like acetaldehyde and formaldehyde that are explicitly associated with indoor sources [44]. In this case, the levels of exposure are associated with the presence of building materials and furniture containing the respective compounds and the air exchange levels of the respective microenvironment. Air exchange rate is a key determinant of indoor air pollution, affecting both the processes of outdoor infiltration (e.g. outdoor PM infiltrate indoors) or accumulation of compounds emitted indoors (e.g. emission of formaldehyde from furniture). In practice, for compounds that significant sources occur both outdoors and indoors, indoor levels are defined by the overall interaction of indoor and outdoor air contamination [45]. Finally, regarding the mixture effects, people are always exposed to the mixture of PAHs and not to a single compound, although there are differences in the relative composition based on their origin, which is also reflected in their toxicity [46]. An efficient way to deal with the characterization of these mixtures is the use of the Toxic Equivalent Quotient (TEQ), where for every component of the mixture, a Toxic Equivalent Factor (TEF) is given, based on its relative toxicity to benzo[a]pyrene; the overall toxicity of the mixture (TEQ) is the sum of the individual components concentration multiplied to the respective TEF. With

regard to the quaternary mixture of benzene, toluene, ethylbenzene and xylene (BTEX), interactions have been identified at the level of metabolism (competitive inhibition acting upon the same CYP substrate). Thus, co-exposure to the BTEX mixture results in slower metabolism of benzene, compared to the metabolic rate of benzene when individual exposure to that substance occurs [47].

Policy relevance

PAHs are regulated on the basis of the National Emission Ceilings Directive 2001/81/EC. Moreover, Regulation (EU) 1272/2013 on PAHs in articles for supply to the general public, amended entry 50 of Annex XVII to REACH. According to this regulation, the use of PAHs has been restricted by a limit of 1 mg/kg (0,0001 % by weight) of BaP and 10 mg/kg (0,001 % by weight) for each of 8 PAHs for extender oils used for the production of tires or parts of tires. This regulation entered into force in January 2010. In addition, subject to the detailed scope of the restriction, a limit of 1 mg/kg is established for the rubber and plastic parts of many types of consumer articles. In the case of toys and childcare articles the limit is lowered to 0.5 mg/kg for each of 8 carcinogenic PAHs. The restriction entered into force in December 2015. Anthracene oil and coal tar pitch are included in the 6th recommendation of the European Chemicals Agency, of 1 July 2015 for the inclusion of substances in Annex XIV to REACH.
The main policy instrument regarding air pollutants within the EU is the Ambient Air Quality Directive [26, 27] and the National Emission Ceilings (NEC) Directive [48]. In 2011-2013 the Commission conducted a review of the EU air policies which resulted in the adoption of the Clean Air Policy Package in which the EU proposed a Clean Air Programme for Europe, updating the 2005 Thematic Strategy on Air Pollution in order to set new objectives for EU air policy for 2020 and 2030. The main legislative instrument towards 2030 objectives of the Clean Air Programme is Directive 2016/2284/EU on on the reduction of national emissions of certain atmospheric pollutants which entered into force on 31 December 2016. This Directive sets national reduction commitments for the five pollutants (sulphur dioxide, nitrogen oxides, volatile organic compounds, ammonia and fine particulate matter) responsible for acidification, eutrophication and ground-level ozone pollution which leads to significant negative impacts on human health and the environment.

Table 1. Legislative framework regarding PAHs and other air pollutants

Legislative reference	Matrix	ML[1] (Y/N)	Compound
Commission Regulation (EC) No 1881/2006 Amended by Commission Regulation (EU) No 835/2011	Food	N[2]	16 EPA PAHs (mentioned as generic carcinogenic PAHs at point 58) Not included in other lists: Acenaphthene, Acenaphthylene, Anthracene, Fluoranthene, Fluorene, Naphthalene, Phenanthrene, Pyrene 15+1 EU PAHs:Benzo[*a*]anthracene, Benzo[*b*]fluoranthene, Benzo[*j*]fluoranthene, Benzo[*k*]fluoranthene, Benzo[*c*]fluorene, Benzo[*ghi*]perylene, Chrysene, Cyclopental[*cd*]pyrene, Dibenzo[*a,h*]anthracene, Dibenzo[*a,e*]pyrene, Dibenzo[*a,h*]pyrene, Dibenzo[*a,i*]pyrene, Dibenzo[*a,l*]pyrene, Indeno[1,2,3-*cd*]pyrene, 5-Methylchrysene
		Y	Benzo[*a*]pyrene plus the sum of the 4 marker PAHs (Benzo[*a*]pyrene, Benzo[*a*]anthracene, Benzo[*b*]fluoranthene and Chrysene)
Commission Regulation (EC) No 333/2007 Amended by Commission Regulation (EU) No 836/2011	Food	N	Benzo[*a*]pyrene Plus Benzo[*a*]anthracene, Benzo[*b*]fluoranthene and Chrysene
Commission Recommendation (2005/108/EC) of 4 Faburary 2005 on the further investigation into the levels of polycyclic aromatic hydrocarbons in certain foods	Food	N	15 SCF PAHs: Benzo[*a*]pyrene , Benzo[*a*]anthracene, Benzo[*b*]fluoranthene, Benzo[*j*]fluoranthene, Benzo[*k*]fluoranthene, Benzo[*c*]fluorene, Benzo[*ghi*]perylene, Chrysene, Cyclopental[*cd*]pyrene, Dibenzo[*a,h*]anthracene, Dibenzo[*a,e*]pyrene, Dibenzo[*a,h*]pyrene, Dibenzo[*a,i*]pyrene, Dibenzo[*a,l*]pyrene, Indeno[1,2,3-*cd*]pyrene, 5-Methylchrysene
Commission Regulation (EC) No 672/2006	Primary Smoke products	N	15 SCF PAHs, Benzo[*a*]pyrene, Benzo[*a*]anthracene

[1] Maximum level (Y=yes; N=no)
[2] Benzo[a]pyrene is considered a marker for PAHs

Legislative reference	Matrix	ML1 (Y/N)	Compound
Regulation (EC) No 2065/2003 of the European Parliament and of the Council	Primary Smoke products	Y	Benzo*[a]*pyrene, Benzo[*a*]anthracene
Directive 2000/76/EC of the European Parliament and the Council	Emissions from incineration plants	N	PAHs (Mentioned as carcinogenic compounds that might be subject to limitations in Member States' regulations)
Decision No 2455/2001/EC of the European Parliament and rhe Council	Water	N	PAHs (Annex: Identified as priority hazardous substance), Benzo[*a*]pyrene, Benzo[*b*]fluoranthene, Benzo[*ghi*]perylene, Benzo[*k*]fluoranthene, Indeno[1,2,3-*cd*]pyrene
ANNEX XVII to REACH restriction Entry 50 Restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles	Oil, Toys, Articles, Tyres	Y	8 PAHs (mentioned as generic carcinogenic PAHs): Benzo[a]pyrene, Benzo[e]pyrene, Benzo[a]anthracene, Chrysen, Benzo[b]fluoranthene, Benzo[j]fluoranthene, Benzo[k]fluoranthene, Dibenzo[a,h]anthracene
Directives regulating ambient air quality (2008/50/EC, 2004/107/EC)	Air	Y	PM, O_3, NO_2, SO_2, CO, Bap
Directives regulating emissions of air pollutants (2001/81/EC)	Air	Y	NO_2, SO_2, NMVOC
Directive regulating ambient air benzene 2000/69/EC	Air	Y	Benzene

Regulation on air pollutants is driven to a large extent by the data available with regard to their adverse health effects. Data come from the integration of epidemiological, controlled clinical studies, and animal toxicology. Epidemiological studies show statistical associations between health outcomes and exposure but they cannot establish a definite cause-effect relationship. However, the utility of toxicological studies lies in the possibility they provide to establish this relationship [49]. The European Union has developed an extensive body of legislation, based on the outcome of these studies, in order to establish health based standards and objectives for a number of pollutants present in the air. Each air quality standard has two elements: the maximum acceptable concentration and the period of time period over which the concentration is averaged. During the 1990s, there was a great surge of reports on time-series-based studies of associations between daily ambient air pollutant concentrations and daily rates of mortality and hospital admissions for respiratory diseases [50]. In terms of morbidity, there has been a rapid growth of the literature showing associations between air pollutants concentrations and exacerbation of asthma, increased symptom rates and decreased respiratory function. The statistical techniques used by modern epidemiologists have seen considerable evolution. The result was that associations were found implying that far lower levels of pollutants were possibly adversely affecting human health on a wide scale [51, 52]. In summary, epidemiological studies so far have found associations between short-term changes in particulate air pollution and acute mortality (cardiovascular and respiratory related) and acute morbidity (hospital admissions, emergency room visits, exacerbation of asthma, respiratory symptoms, lung function measures, restricted activity days in workers, and school absences). These studies have associated ill health effects with increases in PM_{10} by 10 $\mu g/m^3$ and in PM2.5 by 1 $\mu g/m^3$ over the previous day levels indicating thousands of annual deaths and other adverse effects [52]. Epidemiological evidence is overwhelming and strong enough on its own to support a particular standard (especially as results are replicated in several independent studies performed in different jurisdictions). Yet, toxicology offers the possibility to validate coherent mechanisms underlying the evidence upon which the standard is based. Toxicological studies also provide a basis for examining specific components within the complex ambient air mixture, such as PM; thereby they provide a basis for identifying the most toxic components of ambient air.

Technical aspects

Relevant individual PAHs to biomonitor, where feasible via their specific metabolites, include:

- 8 carcinogenic PAHs in entry 50 of Annex XVII to REACH: Benzo[a]pyrene, Benzo[e]pyrene, Benzo[a]anthracene, Chrysen, Benzo[b]fluoranthene, Benzo[j]fluoranthene, Benzo[k]fluoranthene and Dibenzo[a,h]anthracene
- 16 USEPA priority PAHs, included in numerous EN and national standards:
    - Naphthalene (CAS No. 91-20-3); Acenaphthene (CAS No.83-32-9); Acenaphthylene (CAS No.208-96-8); Fluorene (CAS No.86-73-7); Anthracene (CAS No.120-12-7); Phenanthrene (CAS No. 85-01-8); Fluoranthene (CAS No.206-44-0); Pyrene (CAS No.129-00-0); Benzo(a)anthracene (CAS No.56-55-3); Chrysene (CAS.No.218-01-9); Benzo(b)fluoranthene (CAS No. 205-99-2); Benzo(k)fluoranthene (CAS No.207-08-9); Benzo(a)pyrene (CAS No.50-32-8); Indeno(1,2,3-cd)pyrene (CAS No.193-39-5); Dibenzo(ah)anthracene (CAS No.53-70-3); Benzo(ghi)perylene (CAS No.191-24-2)
- Potentially also alkylated PAHs: 7,12-dimethylbenzo(a)anthracene; 1-methylphenanthrene; 2,3,5-trimethylnaphthalene; 1-methylnaphthalene; 2-methylnaphthalene and 2,6-dimethylnaphthalene.

To study the exposure to PAHs, urinary mono-hydroxylated PAHs (OH-PAHs), a group of PAH metabolites, are commonly used as biomarkers (39). Among the OH-PAHs, 1-hydroxypyrene (1-

PYR) is the most commonly used PAH biomarker in both occupational as well as in the general population from various countries (40).

From the technical point of view, methods already exist for the determination of some PAHs (such as BaP) in urine. Further methodological developments may be necessary however; solutions to this may be found by the European Human Biomonitoring Initiative cost-effectively. Considering that exposure to PAHs may occur from multiple sources and through multiple exposure routes, further understanding on the determination of the overall exposure levels is necessary. HBM information would be extremely useful in determining the overall exposure of the general population or of sensitive sub-populations, particularly children and specific target groups, to carcinogenic PAHs. HBM data would also help us determine whether the existing restrictions and limitations (in articles, in certain foods, in water, in ambient air) have a positive effect in reducing exposure to this ubiquitous family of chemicals or not. Finally, the HBM4EU work can also be very relevant in assessing worker exposure to these chemicals in certain activities (petrochemical plants, manufacture of anodes, etc.).

With regard to the other air pollutants, actual biomarkers of exposure have been established only for benzene. These include either major benzene metabolites such as S-phenylmercapturic acid (S-PMA) and trans,trans-muconic acid (t,t-MA). However, due to their low sensitivity in common environmental settings, unmetabolized urinary benzene has also been suggested as a low exposure sensitive biomarker [53, 54]. With regard to other air pollutants, at the moment there are no well-established exposure biomarkers. Previous efforts have associated exposure to high levels of exposure to SO_2 with S-sulfonates in nasal lavage [55], and exhaled breath CO [56], while in the case of the main air pollutants exposure is usually associated with markers of inflammation [57].

Societal concern

PAHs are ubiquitous pollutants frequently found in a variety of environments such as oil, toys, food and atmosphere, increasing the exposure of humans to this chemical carcinogen even if in low concentrations. Due to their widespread distribution, the environmental pollution due to PAHs has aroused global concern. Many PAHs and their epoxides are highly toxic, mutagenic and/or carcinogenic to humans. Increased incidences of lung and skin cancers are associated with exposure to PAHs.

Benzene has been recognized as a carcinogen and the latest years focus is on the effects of prolonged exposure to low environmental levels. Although, the C_6H_6 emissions have declined sharply across the European Countries since the introduction of the Fuel Quality Directive [58], there is still concern raised from studies which show that the atmosphere around petrol stations contains significantly higher levels of benzene [59]. This has been strengthened by epidemiological studies, showing that children living close to a gasoline station, are subject to higher risk of leukemia [60].

PM is a widespread air pollutant, present wherever people live. The health effects of PM2.5 even at relatively low concentrations on health are significant. Effective management of air quality aiming to achieve low levels is necessary in order to minimize health risks. There is evidence that decreased levels of particulate air pollution following a sustained intervention result in health benefits for the population assessed. These benefits come into place with almost any decrease in the PM levels. In many European Counties the PM2.5 concentrations, on average, tended to go down in the last decade [25]. However, in countries such as Croatia, Greece, Hungary and Spain a change in residential fuel consumption practices resulted in an increased use of biomass since 2005. This could be the combined result of the economic recession and/or the implementation of local policies such as incentivizing the installation of biomass stoves in newly built or refurbished homes. As a result, biomass burning has turned into a major contributor to the atmospheric PM levels during wintertime [61] for a number of countries and major urban centers in the EU.

Overall, the importance of poor air quality has been recently highlighted by WHO, where it is mentioned that worldwide, ambient air pollution contributes to 5.4% of all-cause mortality [62].

3. Categorization of Substances

Table 2: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C, D, E substances (see general introduction)

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
A	NO2	Nitrogen dioxide	10102-44-0	Directive 2008/50/EC
	SO2	Sulphur dioxide	7446-09-5	Directive 2008/50/EC
	O3	Ozone	10028-15-6	Directive 2008/50/EC
	CO	Carbon monoxide	630-08-0	Directive 2008/50/EC
B		Acenaphthene	83-32-9	According to the notifications provided by companies to ECHA in REACH registrations no hazards have been classified.
		Acenaphthylene	208-96-8	
		Antracene	120-12-7	Substance of very high concern (SVHC) and included in the candidate list for authorisation.
	BaA	Benzo(a)anthracene	56-55-3	Entry 50 of Annex XVII to REACH
	BaP	Benzo(a)pyrene	50-32-8	Entry 50 of Annex XVII to REACH
	BbFA	Benzo(b)fluoranthene	205-99-2	Entry 50 of Annex XVII to REACH
	BeP	Benzo(e)pyrene	192-97-2	Entry 50 of Annex XVII to REACH
		Benzo(ghi)perylene	191-24-2	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects.
	BjFA	Benzo(j)fluoranthene	205-82-3	Entry 50 of Annex XVII to REACH
	BkFA	Benzo(k)fluoranthene	207-08-9	Entry 50 of Annex XVII to REACH
		Dibenzo(ah)anthracene	53-70-3	Entry 50 of Annex XVII to REACH

		Fluoranthene	206-44-0	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects, is harmful if swallowed and causes serious eye irritation
		Fluorene	86-73-7	According to the classification provided by companies to ECHA in REACH registrations this substance is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects. ECHA has no data from registration dossiers on the precautionary measures for using this substance.
		Chrysene/Benzo(a)phenanthrene	218-01-9	Entry 50 of Annex XVII to REACH
		Indeno(123-cd)pyrene	193-39-5	According to the classification provided by companies to ECHA in CLP notifications this substance is suspected of causing cancer.
		Naphthalene	91-20-3	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects, is harmful if swallowed and is suspected of causing cancer. Substance included in the Community Rolling Action Plan (CoRAP).
		Phenantrene	85-01-8	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects and is harmful if swallowed.
		Pyrene	129-00-0	According to the notifications provided by companies to ECHA in REACH registrations no hazards have been classified.
		1-Methylnapthalene	90-12-0	According to the classification provided by companies to ECHA in CLP notifications this substance may be fatal if swallowed and enters airways, is toxic to aquatic life with long lasting effects and is harmful if swallowed. ECHA has no data from registration dossiers on the precautionary measures for using this substance.
		1-Methylphenanthrene	832-69-9	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life, is very toxic to

				aquatic life with long lasting effects, is harmful if swallowed and is suspected of causing cancer.
		2,6-Dimethylnapthalene	581-42-0	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects
		2-Methylnapthalene	91-57-6	According to the classification provided by companies to ECHA in CLP notifications this substance is toxic to aquatic life with long lasting effects and is harmful if swallowed. ECHA has no data from registration dossiers on the precautionary measures for using this substance.
		7.12-Dimethylbenz(a)anthracene	57-97-6	According to the classification provided by companies to ECHA in CLP notifications this substance may cause cancer and is harmful if swallowed.
	235TMNPT	2,3,5-trimethylnaphthalene	2245-38-7	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects and is harmful if swallowed
		Benzene	71-43-2	Entry 5 of Annex XVII to REACH
		Toluene	108-88-3	Entry 48 of Annex XVII to REACH
		Ethylbenzene	100-41-4	According to the harmonised classification and labelling (ATP06) approved by the European Union, this substance may be fatal if swallowed and enters airways, is a highly flammable liquid and vapour, is harmful if inhaled and may cause damage to organs through prolonged or repeated exposure.
		Xylene	1330-20-7	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is a flammable liquid and vapour, is harmful in contact with skin, is harmful if inhaled and causes skin irritation. Substance included in the Community Rolling Action Plan (CoRAP).
		o-Xylene	95-47-6	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is a flammable liquid and vapour, is harmful in contact with skin, is harmful if inhaled and

				causes skin irritation. Substance included in the Community Rolling Action Plan (CoRAP).
		m-Xylene	108-38-3	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is a flammable liquid and vapour, is harmful in contact with skin, is harmful if inhaled and causes skin irritation. Substance included in the Community Rolling Action Plan (CoRAP).
		p-Xylene	106-42-3	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is a flammable liquid and vapour, is harmful in contact with skin, is harmful if inhaled and causes skin irritation. Substance included in the Community Rolling Action Plan (CoRAP).
		Formaldehyde	50-00-0	ccording to the harmonised classification and labelling (ATP06) approved by the European Union, this substance is toxic if swallowed, is toxic in contact with skin, causes severe skin burns and eye damage, is toxic if inhaled, may cause cancer, is suspected of causing genetic defects and may cause an allergic skin reaction. Substance included in the Community Rolling Action Plan (CoRAP).
		Acetaldehyde	75-07-0	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is an extremely flammable liquid and vapour, causes serious eye irritation, is suspected of causing cancer and may cause respiratory irritation.
C		Biologicals (mould, pollen)		
	PM	Particulate matter (PM1)		
	UFP	Ultra-fine particles (UFP)		

4. Policy-related questions

- What is the current exposure of the EU population to PAHs?
- What is the current exposure of different occupational groups?
- Does exposure differ between countries? Why?
- Is there an association between air quality and human exposure to PAHs??
- Can we see a decline in exposure to the eight PAHs restricted under REACH?
- Can HBM4EU data inform the development of legislation specifically targeting exposure to PAHs through ambient air?

5. Research Activities to be undertaken

*While completing this table please think of data and gaps concerning toxicology (and exposure [in three dimensions: **location** (differences between the countries), **time** (trends) and **age** (data available for which age group)]. If no HBM method is available or the method has to be harmonized within partner countries, please indicate this too.*

Table 3: Listing of research activities to be carried out to answer the policy questions summed up in 1.3

Policy question	Substance	Available knowledge	Knowledge gaps and activities needed
What is the current exposure of the EU population to PAHs?	PAHs	Data available for various European countries, but not for all of them – collected in different years	Collect, combine, harmonize and compare existing HBM and exposure data on PAHs relevant to the European population.
What is the current exposure of different occupational groups?	PAHs	Data available for various European countries, but not for various age groups	Collect, combine, harmonize and compare existing HBM and exposure data on PAHs and compare the data between different countries and population groups. Establish reference values for selected PAHs parent metabolites in urine for general population (adults/children, smokers/non-smokers) and for worker's populations (smokers/non-smokers).
Is there an association between air quality and human exposure to PAHs	PAHs	Limited data available for various European countries, lack of continuous monitoring	Collect, combine, harmonize and compare existing and new HBM and exposure data on PAHs and associate the data with air pollution levels.
Can we see a decline in exposure to the eight PAHs restricted under REACH?	PAHs	Limited data available for various European countries, lack of continuous monitoring	Collect, combine, harmonize and compare existing and new HBM and exposure data on PAHs and compare the data before and after the implementation of the REACH restriction.

Does exposure differ between countries? Why?	PAHs	Limited data available for various European countries	Collect, combine, harmonize and compare existing and new HBM and exposure data on PAHs and compare the data between different countries and associate these with exposure determinants.
Can HBM4EU data inform the development of legislation specifically targeting exposure to PAHs through ambient air?	PAHs		Collect new harmonised data that will fill the gaps related to various spatiotemporal scales and different population groups and associate these with exposure to PAHs through air

6. Results Report

In Year 2 (M18) a short overview of the results achieved within the HBM4EU programme shall be depicted here. Please, briefly state the main results answering the corresponding policy questions in a general understandably manner.

Table 3: Short overview of results of the activities carried out within HBM4EU to answer the policy questions with reference to corresponding deliverables

In Year 2 (M18) a short overview of the results achieved within the HBM4EU programme shall be depicted here. Please, briefly state the main results answering the corresponding policy questions in a general understandably manner.

Table 3: Short overview of results of the activities carried out within HBM4EU to answer the policy questions with reference to corresponding deliverables

Policy Question		**Short Summary of Results**
No	**Question**	*Extract the main findings of the deliverable that answers (part) of the policy question, mention the deliverable*
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		

7. References

1. Armstrong, B., et al., *Lung Cancer Risk after Exposure to Polycyclic Aromatic Hydrocarbons: A Review and Meta-Analysis.* Environmental Health Perspectives, 2004. **112**(9): p. 970-978.
2. CCME, *Canadian soil quality guidelines for potentially carcinogenic and other PAHs: scientific criteria document*. 2010: Winnipeg.
3. Legraverend, C., et al., *Bone marrow toxicity induced by oral benzo[a]pyrene: protection resides at the level of the intestine and liver.* Toxicol Appl Pharmacol, 1983. **70**(3): p. 390-401.
4. Old, L.J., B. Benacerraf, and E. Carswell, *Contact reactivity to carcinogenic polycyclic hydrocarbons.* Nature, 1963. **198**: p. 1215-6.
5. Robinson, J.R., et al., *Relationship between "aromatic hydrocarbon responsiveness" and the survival times in mice treated with various drugs and environmental compounds.* Mol Pharmacol, 1975. **11**(6): p. 850-65.
6. Santodonato, J., *Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity.* Chemosphere, 1997. **34**(4): p. 835-48.
7. Borman, S.M., et al., *Ovotoxicity in female Fischer rats and B6 mice induced by low-dose exposure to three polycyclic aromatic hydrocarbons: comparison through calculation of an ovotoxic index.* Toxicol Appl Pharmacol, 2000. **167**(3): p. 191-8.
8. MacKenzie, K.M. and D.M. Angevine, *Infertility in mice exposed in utero to benzo(a)pyrene.* Biol Reprod, 1981. **24**(1): p. 183-91.
9. Rigdon, R.H. and E.G. Rennels, *Effect of feeding benzpyrene on reproduction in the rat.* Experientia, 1964. **20**(4): p. 224-6.
10. Baklanov, A., et al., *Integrated systems for forecasting urban meteorology, air pollution and population exposure.* Atmospheric Chemistry and Physics, 2007. **7**(3): p. 855-874.
11. Latimer, J.S. and J. Zheng, *The Sources, Transport, and Fate of PAHs in the Marine Environment*, in *PAHs: An Ecotoxicological Perspective*. 2003, John Wiley & Sons, Ltd. p. 7-33.
12. Kawamura, Y., et al., *The effect of various foods on the intestinal absorption of benzo(a)pyrene in rats.* Shokohin Eiseigaku Zasshi / Journal of the Food Hygienic Society of Japan, 1988. **29**(1): p. 21-25.
13. Seto, H., et al., *Determination of polycyclic aromatic hydrocarbons in the lung.* Arch Environ Contam Toxicol, 1993. **24**(4): p. 498-503.
14. Creasia, D.A., J.K. Poggenburg, and P. Nettesheim, *Elution of benzo[a]pyrene from carbon particles in the respiratory tract of mice.* Journal of Toxicology and Environmental Health, 1976. **1**(6): p. 967-975.
15. Monteith, D.K., et al., *Metabolism of benzo[a]pyrene in primary cultures of human hepatocytes: dose-response over a four-log range.* Carcinogenesis, 1987. **8**(7): p. 983-8.
16. Kapitulnik, J., et al., *Hydration of arene and alkene oxides by epoxide hydrase in human liver microsomes.* Clin Pharmacol Ther, 1977. **21**(2): p. 158-65.
17. Kiefer, F., O. Cumpelik, and F.J. Wiebel, *Metabolism and cytotoxicity of benzo(a)pyrene in the human lung tumour cell line NCI-H322.* Xenobiotica, 1988. **18**(6): p. 747-55.
18. ATSDR, *Agency for Toxic Substances and Disease Registry. Toxicological profile for polycyclic aromatic hydrocarbons (PAHs) (update)*. 1995, US Department of Health and Human Services: Atlanta.
19. CDC, *Centers for Disease Control and Prevention. Third National Report on Human Exposure to Environmental Chemicals*. 2005: Atlanta GA.
20. Santella, R.M., et al., *Polycyclic aromatic hydrocarbon-DNA adducts in white blood cells and urinary 1-hydroxypyrene in foundry workers.* Cancer Epidemiol Biomarkers Prev, 1993. **2**(1): p. 59-62.
21. Becher, G. and A. Bjorseth, *Determination of exposure to polycyclic aromatic hydrocarbons by analysis of human urine.* Cancer Lett, 1983. **17**(3): p. 301-11.

22. Granella, M. and E. Clonfero, *Urinary excretion of 1-pyrenol in automotive repair workers.* International Archives of Occupational and Environmental Health, 1993. **65**(4): p. 241-245.
23. Samet, J.M., *What can we expect from epidemiologic studies of chemical mixtures?* Toxicology, 1995. **105**(2): p. 307-314.
24. EU, *Directive 2000/69/EC of the European Parliament and of the Council of 16 November 2000 relating to limit values for benzene and carbon monoxide in ambient air*. 2000.
25. EEA, *Air Quality e-Reporting Database. Accessed 26 October 2016.* 2016.
26. EU, *Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe*. 2008.
27. EU, *Directive 2004/107/EC of the European Parliament and of the Council of 15 December 2004 relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air. Accessed 21 July 2016*. 2004.
28. Zhang, Y. and S. Tao, *Global atmospheric emission inventory of polycyclic aromatic hydrocarbons (PAHs) for 2004.* Atmospheric Environment, 2009. **43**(4): p. 812-819.
29. Ravindra, K., R. Sokhi, and R. Van Grieken, *Atmospheric polycyclic aromatic hydrocarbons: Source attribution, emission factors and regulation.* Atmospheric Environment, 2008. **42**(13): p. 2895-2921.
30. Wang, Z., et al., *Gas/particle partitioning of polycyclic aromatic hydrocarbons in coastal atmosphere of the north Yellow Sea, China.* Environ Sci Pollut Res Int, 2013. **20**(8): p. 5753-63.
31. Kuo, C.Y., et al., *Comparison of polycyclic aromatic hydrocarbon emissions on gasoline- and diesel-dominated routes.* Environ Monit Assess, 2013. **185**(7): p. 5749-61.
32. Srogi, K., *Monitoring of environmental exposure to polycyclic aromatic hydrocarbons: a review.* Environmental Chemistry Letters, 2007. **5**(4): p. 169-195.
33. Menzie, C.A., B.B. Potocki, and J. Santodonato, *Exposure to carcinogenic PAHs in the environment.* Environmental Science & Technology, 1992. **26**(7): p. 1278-1284.
34. EC, *Commission Regulation (EU) No 835/2011 of 19 August 2011 amending Regulation (EC) No 1881/2006 as regards maximum levels for polycyclic aromatic hydrocarbons in foodstuffs. Official Journal of the European Union, L215:4–8* 2011.
35. ECHA, *ANNEX XVII TO REACH – Conditions of restriction*. 2018.
36. Schoeny, R. and K. Poirier, *Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons*. 1993, United States Environmental Protection Agency Washington, DC.
37. Ranzi, A., et al., *Biomonitoring of the general population living near a modern solid waste incinerator: a pilot study in Modena, Italy.* Environ Int, 2013. **61**: p. 88-97.
38. Lafontaine, M., et al., *3-Hydroxybenzo[a]pyrene in the urine of smokers and non-smokers.* Toxicol Lett, 2006. **162**(2-3): p. 181-5.
39. Leroyer, A., et al., *1-Hydroxypyrene and 3-hydroxybenzo[a]pyrene as biomarkers of exposure to PAH in various environmental exposure situations.* Sci Total Environ, 2010. **408**(5): p. 1166-73.
40. Wilhelm, M., et al., *Influence of industrial sources on children's health – Hot spot studies in North Rhine Westphalia, Germany.* International Journal of Hygiene and Environmental Health, 2007. **210**(5): p. 591-599.
41. Schulz, C., et al., *Update of the reference and HBM values derived by the German Human Biomonitoring Commission.* Int J Hyg Environ Health, 2011. **215**(1): p. 26-35.
42. Rossner, P., Jr., et al., *Analysis of biomarkers in a Czech population exposed to heavy air pollution. Part II: chromosomal aberrations and oxidative stress.* Mutagenesis, 2013. **28**(1): p. 97-106.
43. Rossner, P., Jr., et al., *Expression of XRCC5 in peripheral blood lymphocytes is upregulated in subjects from a heavily polluted region in the Czech Republic.* Mutat Res, 2011. **713**(1-2): p. 76-82.
44. Sarigiannis, D.A., et al., *Exposure to major volatile organic compounds and carbonyls in European indoor environments and associated health risk.* Environment International, 2011. **37**(4): p. 743-765.
45. Sarigiannis, D.A., *Combined or multiple exposure to health stressors in indoor built environments*. 2014, WHO Regional Office for Europe: Copenhagen, Denmark.

46. Sarigiannis, D.A., et al., *Lung cancer risk from PAHs emitted from biomass combustion.* Environmental Research, 2015. **137**(0): p. 147-156.
47. Sarigiannis, D.A. and A. Gotti, *Biology-based dose-response models for health risk assessment of chemical mixtures.* Fresenius Environmental Bulletin, 2008. **17**(9 B): p. 1439-1451.
48. EU, *Directive 2001/81/EC of the European Parliament and of the Council of 23 October 2001 on national emission ceilings for certain atmospheric pollutants* 2001.
49. Lippmann, M. and R.B. Schlesinger, *Toxicological Bases for the Setting of Health-Related Air Pollution Standards.* Annual Review of Public Health, 2000. **21**(1): p. 309-333.
50. Phalen, R.F., *The Particulate Air Pollution Controversy.* Nonlinearity in Biology, Toxicology, Medicine, 2004. **2**(4): p. 259-292.
51. Pope, C.A., *Review: Epidemiological Basis for Particulate Air Pollution Health Standards.* Aerosol Science and Technology, 2000. **32**(1): p. 4-14.
52. Pope, C.A., D.W. Dockery, and J. Schwartz, *Review of Epidemiological Evidence of Health Effects of Particulate Air Pollution.* Inhalation Toxicology, 1995. **7**(1): p. 1-18.
53. Fustinoni, S., et al., *Monitoring low benzene exposure: Comparative evaluation of urinary biomarkers, influence of cigarette smoking, and genetic polymorphisms.* Cancer Epidemiology Biomarkers and Prevention, 2005. **14**(9): p. 2237-2244.
54. Fustinoni, S., et al., *Urinary t,t-muconic acid, S-phenylmercapturic acid and benzene as biomarkers of low benzene exposure.* Chemico-Biological Interactions, 2005. **153-154**: p. 253-256.
55. Bechtold, W.E., et al., *Biological markers of exposure to SO2: S-sulfonates in nasal lavage.* J Expo Anal Environ Epidemiol, 1993. **3**(4): p. 371-82.
56. Sandberg, A., et al., *Carbon monoxide levels in exhaled breath as a measure of recent smoking status.* The Clinical Respiratory Journal, 2011. **5**: p. 8-9.
57. Dadvand, P., et al., *Air pollution and biomarkers of systemic inflammation and tissue repair in COPD patients.* Eur Respir J, 2014. **44**(3): p. 603-13.
58. EU, *Directive 2009/126/EC of the European Parliament and of the Council of 21 October 2009 on Stage II petrol vapour recovery during refuelling of motor vehicles at service stations*. 2009.
59. Karakitsios, S.P., et al., *Contribution to ambient benzene concentrations in the vicinity of petrol stations: Estimation of the associated health risk.* Atmospheric Environment, 2007. **41**(9): p. 1889-1902.
60. Steffen, C., et al., *Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study.* Occupational and Environmental Medicine, 2004. **61**(9): p. 773-778.
61. Sarigiannis, D.A., et al., *Total exposure to airborne particulate matter in cities: The effect of biomass combustion.* Science of the Total Environment, 2014. **493**: p. 795-805.
62. WHO, *A global assessment of the burden of disease from environmental risks: A global assessment of the burden of disease from environmental risks. ISBN 978 92 4 156519 6*, in *WHO Library*. 2016, WHO: France.