ANNEX 1

in support of the Committee for Risk Assessment (RAC) for evaluation of limit values for

polycyclic aromatic hydrocarbons at the workplace

ECHA/RAC/OEL-O-0000007198-66-01/F

1 December2022

Telakkakatu 6, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

Table of Contents

List of Figures

List of Tables

List of abbreviations

Abbreviation	Definition
ADME	Absorption, distribution, metabolism and excretion
AGS	Ausschuss für Gefahrstoffe (German Committee on Hazardous Substances)
AHH	Aryl hydrocarbon hydroxylase
AhR	Aryl hydrocarbon receptor
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BaA	Benzo[a]anthracene
BaP	Benzo[a]pyrene
BAR	Biologische Arbeitsstoff-Referenzwerte (Biological reference value; corresponds to the background level present concurrently, in a reference population of persons of working age who are not occupationally exposed to this substance).
BbFA	Benzo[b]fluoranthene
BeP	Benzo[e]pyrene
BGV	Biological Guidance Value
BjFA	Benzo[j]fluoranthene
BkFA	Benzo[k]fluoranthene
BLV	Biological Limit Value
BPDE	Benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide
CAREX	CARcinogen EXposure database
CEFIC	European Chemical Industry Council
CHR	Chrysene
CMRD	Carcinogens and Mutagens Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. The amendment of the CMD, Directive 2022/431/EU also brought reprotoxic substances within the scope of the directive, changing the original title on the protection of workers from the risks related to exposure to carcinogens or mutagens at work to the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD).
COE	Coke oven emissions
CSR	Chemical Safety Report
CTPHT	Coal Tar Pitch High Temperature
DBAhA	Dibenzo[a,h]anthracene
DECOS	Dutch Expert Committee on Occupational Safety
DFG	Deutsche Forschungsgemeinschaft, German Research Foundation
EC	European Commission
ECHA	European Chemicals Agency
EKA	Expositionsäquivalente für krebserzeugende Arbeitsstoffe (Exposure equivalents for carcinogenic substances; an exposure equivalent, correlation between external and internal exposure.)
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPA	U.S. Environmental Protection Agency
ERR	Exposure-risk relationship
EU	European Union
FIOH	The Finnish Institute of Occupational Health
GC-APLI-MS	Gas chromatography (GC) coupled to atmospheric pressure laser ionization-mass spectrometry (APLI-MS)
GC-MS	Gas chromatography-mass spectrometry

Abbreviation	Definition
GC-NICI-MS/MS	Gas chromatography/negative-ion chemical-ionization tandem mass spectrometry
GESTIS Substance Database	GEfahrSToffInformationsSystem (German information system for the safe handling of hazardous substances and other chemical substances at work) Substance Database
GM	Geometric mean
HBC-OCRV	Health-based calculated occupational cancer risk values
HMW PAH	High molecular weight polycyclic aromatic hydrocarbon (PAH)
HPLC-FLD	High-performance liquid chromatography with fluorescence detection
IFA	Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung
IPCS	The International Programme on Chemical Safety, World Health Organization
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LMW PAH	Low molecular weight polycyclic aromatic hydrocarbon (PAH)
LOAEL	Lowest observed adverse effect level
LOD	Limit of detection
LOQ	Limit of quantification
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEL	No observed adverse effect level
NOGEL	No observed genotoxic effect level
OEL	Occupational exposure limit
OHN(s)	Hydroxy metabolites of naphthalene
OH-Phen(s)	Hydroxy metabolites of phenanthrene
3-OHBaP	3-Hydroxybenzo-a-pyrene
1-OHP	1-Hydroxypyrene
OSHA	Occupational Safety and Health Administration (USA)
PAH	Polycyclic aromatic hydrocarbon(s)
PBPK modelling	Physiologically based pharmacokinetic modelling
PBTK-TD model	Physiologically based toxicokinetic and toxicodynamic model
RAC	Committee for Risk Assessment
REACH	Regulation (EC) No 1907/2006 of the European Union concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
RR	Relative risk
SCOEL	Scientific Committee on Occupational Exposure Limits (former committee of the European Commission)
SLA	Service Level Agreement
SPE	Solid phase extraction
STEL	Short term exposure limit
TEQ	Toxic equivalency value
TLC/HPLC	Thin Layer Chromatography/High Performance Liquid Chromatography.
TWA	Time-Weighted Average
URR	Unit Relative Risk
WHO	World Health Organization
WPC	Working Party on Chemicals

Literature search

This report is based on national and international assessments, including those of AGS (2011), AGS (2015), ATSDR (1995), DECOS (2006), DFG (2012), (DFG, 2021), ECHA (2018), ECHA (2019), EPA (2017), IARC (2010), IARC (2012), IPCS (1998) and SCOEL (2016). The report is further supported by a literature search of published papers from 2017 to date, for topics of relevance to this report.

ECHA prepared a scoping study, as requested by the Commission, to identify and assess approaches to monitoring exposure to combinations of different polycyclic aromatic hydrocarbons (PAH) and to recommend the most appropriate approach and to include a recommendation on, whether an airborne occupational exposure limit for benzo-a-pyrene (CAS RN 50-32-8) (and/or other substance (s)) is a suitable marker of overall PAH exposure. The scoping study recommended that benzo-a-pyrene (CAS RN 50-32-8) was a suitable marker of overall PAH exposure and was presented to the Working Party on Chemicals (WPC) for commenting and approval: there were no comments and the report was approved and is published on the ECHA website[1]. ECHA has subsequently prepared this report, using the scoping study to evaluate occupational limit values for polycyclic aromatic hydrocarbons at the workplace.

ECHA evaluation and recommendation

Benzo-a-pyrene (BaP) is considered as a marker substance for carcinogenic PAH mixtures. BaP is a non-threshold carcinogen. Consequently, no health-based occupational exposure limit (OEL) can be identified. An exposure-risk relationship (ERR) expressing the excess risk for lung cancer in function of air concentration of BaP is derived.

The tables below present the outcome of the scientific evaluation to derive limit values for BaP. It is proposed to use BaP as a marker of cancer risk for carcinogenic PAH mixtures, i.e the ERR is not calculated for BaP alone but for (combustion/pyrolysis-derived) PAH mixtures using BaP as an exposure indicator.

Derived Limit Values

OEL as 8-hour TWA:	No proposal
STEL:	No proposal
BLV:	No proposal yet, but recommended to be set based on the OEL set (see text after ERR table below)
BGV:	No proposal yet, but recommended to be set based on the OEL set (see text after ERR table below)

Notations

Notations:	Skin

[1] https://echa.europa.eu/documents/10162/7399806/scoping_study_pah_report_en.pdf/e4cc1ef4-610d-feb7-8b68-89b2ba50cc97?t=1653474170416

Cancer exposure-risk relationship *

Air concentration of BaP (ng/m^3)	Excess life-time lung cancer risk (cases per 100 000 exposed)
1	0.56
2	1.1
5	2.8
10	5.6
20	11
50	28
100	56
200	110
500	280
1000	560

* Assuming exposure 8 hours per day and 5 days per week, over a 40-year working life period. The air concentration values refer to inhalable particles.

Biomonitoring of PAH metabolites in urine is also recommended. However, it is not possible to derive a safe level for such biomonitoring markers for non-threshold carcinogen PAH. It is noted that the actual OEL will be set later in the legislative process taking also into account socio-economic aspects. It is recommended that after the OEL has been defined, the correlations between BaP in air and 1-hydroxypyrene (1-OHP) and 3-hydroxybenzo-a-pyrene (3-OHBaP) in urine, described in section 6.2.2 are used to set BLVs for either 1-OHP and 3-OHBaP that correspond to the decided OEL for BaP. As an alternative, a BGV could be defined 1-OHP based on the general population reference concentrations observed for these biomarkers and described in section 6.2.1. As for the air monitoring of BaP, these biomonitoring markers are proposed to be used as marker substances for carcinogenic PAH mixtures.

Annex I of the CMRD currently has the following entry:

> *"Work involving exposure to polycyclic aromatic hydrocarbons present in coal soot, coal tar or coal pitch"*

It is recommended to review this entry and it may be necessary to revise this in a way that covers more comprehensively the carcinogenic PAH exposures (see section 9.1.5 for some considerations).

1. Chemical Agent Identification and Physico-Chemical Properties

1.1 Polycyclic aromatic hydrocarbons compounds

Polycyclic aromatic hydrocarbons (PAH: the abbreviation is used as both plural and singular) constitute a large class of compounds. Hundreds of individual substances may be released during incomplete combustion or pyrolysis (thermal degradation) of organic matter, an important source of human exposure. Studies of various environmentally relevant matrices, such as coal combustion effluents, motor vehicle exhaust, used motor lubricating oil, and tobacco smoke, have shown that the PAH in these mixtures are mainly responsible for their carcinogenic potential (IPCS (1998), IARC (1973), IARC (1983), IARC (1984a), IARC (1984b), IARC (1985), IARC (1986), IARC (1987), IARC (1989a), IARC (1989b), IARC (2010), IARC (2012)). There are more than 100 single PAH identified (ATSDR (1995), IPCS (1998), SCOEL (2016)). Only a minor fraction of these have been studied in environmental research and toxicology. Furthermore, PAH occur almost always in mixtures of several PAH. Because the composition of such mixtures is complex and varies with the generating process, it is impossible to test all mixtures in animal models and even in cultured cell lines, let alone to conduct epidemiological studies in human populations exposed to all such mixtures.

Polycyclic aromatic hydrocarbons consist of two or more fused aromatic rings of carbon and hydrogen atoms. Besides aromatic rings, some PAH also contain pentacyclic rings. The simplest PAH is the rather volatile solid naphthalene, consisting of two fused aromatic rings. However, the number of rings may be larger and the molecules can form large graphite-like aggregates (Blumer, 1976). Between these two extremes, numerous configurations of conjugated aromatic (and pentacyclic) rings are possible. Benzo-a-pyrene (BaP) is a PAH that consists of five aromatic benzene rings.

As reviewed by DECOS (2006), various terms are used for PAH and related compounds, and this may be confusing. IPCS (1998) and IARC (1983) refer to the term PAH as unsubstituted non-heterocyclic PAH (including alkyl-substituted derivatives), i.e., they contain only hydrogen and carbon atoms. The general terms 'polycyclic aromatic compounds', 'polycyclic organic matter' or 'polynuclear aromatic compounds', not only include PAH, but also functional PAH derivates, in which hydrogen atoms are replaced by other atoms or functional groups (e.g., chlorine, alkyl, nitro and amino groups); and/or, heterocyclic analogues, in which one or more carbon atoms in the rings are replaced by nitrogen, oxygen or sulphur atoms. DECOS (2006) and SCOEL (2016) followed the IPCS and IARC definition of PAH and did not assess PAH derivatives substituted with functional groups other than alkyls which may obviously differ importantly as regards toxicological properties due to the modifying effects/characteristics stemming from these additional functional groups. Similar considerations apply to this report as well. The toxicity of compounds with derivatives substituted with functional groups other than alkyl groups is not in the scope of this report and consequently the risk estimates produced do not apply to substances with such constituents.

The names, molecular weights, structural formulae and some physicochemical properties of some PAH are described in **Figure 8** and **Table 19** in Appendix 1. As reviewed by DECOS (2006), the physical and chemical properties of PAH vary and are largely determined by the number of rings and molecular masses (Zander, 1983). Overall, PAH are solids (at room temperature) with relatively high melting (66-439 °C) and boiling (218–596 °C) points (DECOS 2006). In particular, high molecular PAH are very little to moderately volatile. In addition, they can occur in the air in particle and in vapour phase. Their water solubility is low and tends to decrease with increasing molecular mass. However, PAH are highly lipophilic and, therefore, soluble in many organic solvents. Finally, PAH are chemically rather inert, although they show chemical and photochemical reactions in the atmosphere (IPCS 1998, ATSDR 1995).

As mentioned already, in practice, PAH do not exist isolated, but as components of complex mixtures that contain many different PAH and related compounds. This is due to the way

they are naturally or artificially produced or processed (see Section 5). A number of these mixtures, which may exist in an industrial or occupational environment, are also described in **Table 20** of Appendix 1.

2. EU Harmonised Classification and Labelling - CLP (EC) 1272/2008

As pointed out in Section 1, PAH is a complex entity covering hundreds of substances, some monoconstituent but many of them multiconstituent or UVCB substances containing numerous constituents[2]. Consequently, the harmonised classifications of PAH vary and a systematic description is beyond the scope of this document. There are numerous PAH, either monoconstituent or more complex mixtures, classified as Carc. 1A (e.g., coal tar, coal tar pitch high temperature) or Carc. 1B (e.g,. BaP, benzo(a)anthracene, benzo(a)fluoranthene), creosote oil), Muta. 1B (e.g,. BaP, benzo(d,e,f)chrysene, Tar oils, brown-coal).

Such substances are listed e.g., in Appendixes 1, 2 and 4 of Annex XVII of REACH.

An exposure risk relationship (ERR) is derived for BaP as a marker substance recommended to be used for carcinogenic PAH substances, including PAH mixtures resulting from incomplete combustion and pyrolysis or organic material (see section 9.1.3). The harmonised classification for BaP is presented in **Table 1** below.

Table 1: EU classification: Benzo[a]pyrene

Index No	International chemical ID	EC No	CAS RN	Annex VI of CLP hazard class and category	Hazard statement code
601-032-00-3	benzo[a]pyrene benzo[def]chrysene	200-028-5	50-32-8	Carc. 1B Muta. 1B Repr. 1B Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H340 H360FD H317 H400 H410

3. Chemical Agent and Scope of Legislation - Regulated uses of polycyclic aromatic hydrocarbons in the EU

3.1 Directive 98/24/EC and Directive 2004/37/EC

Annex 1 of Directive 2004/37/EC includes the entry: "Work involving exposure to polycyclic aromatic hydrocarbons present in coal soot, coal tar or coal pitch". However, no binding OEL is included for any PAH substance under that Directive.

Under Directive 98/24/EC, an indicative OEL of 50 mg/m^3 (8-hr TWA) or 10 ppm has been set for naphthalene via the first Indicative Limit Value Directive (91/322/EEC). Naphthalene, however, has for carcinogenicity a harmonised classification of Carc. 2, while many PAH have a harmonised classification as Carc. 1B or 1A (See section 2).

3.2 REACH Registrations

Although some PAH are commercially-produced industrial chemicals, many are process-generated and thus not subject to REACH registration. Much of the PAH occupational safety and health problem results from the process-generated PAH. It is not relevant for this report to describe the REACH registration data for PAH.

[2] UVCB stands for unknown or variable composition, complex reaction products or of biological materials, see further definitions in https://echa.europa.eu/support/substance-identification/what-is-a-substance

3.3 Authorised uses under Annex XIV of REACH

Anthracene oil (EC 292-602-7) and Pitch, coal tar, high temp. (CTPHT) (EC number 266-028-2) are listed in Annex XIV or REACH.

3.4 Restricted uses under Annex XVII of REACH

Entry 31 of Annex XVII concerns restrictions of the following PAH containing substances:

a) Creosote; wash oil (EC No 232-287-5, CAS RN 8001-58-9)

b) Creosote oil; wash oil (EC No 263-047-8, CAS RN 61789-28-4)

c) Distillates (coal tar), naphthalene oils; naphthalene oil (EC No 283-484-8, CAS RN 84650-04-4)

d) Creosote oil, acenaphthene fraction; wash oil (EC No 283-484-8, EC No 292-605-3, CAS RN 90640-84-9)

e) Distillates (coal tar), upper; heavy anthracene oil (EC No 266-026-1, CAS RN 65996-91-0;)

f) Anthracene oil (EC No 292-602-7, CAS RN 90640-80-5)

g) Tar acids, coal, crude; crude phenols (EC No 266-019-3, CAS RN 65996-85-2)

h) Creosote, wood (EC No 232-419-1, CAS RN 8021-39-4)

i) Low temperature tar oil, alkaline; extract residues (coal), low temperature coal tar alkaline (EC No 310-191-5, CAS RN 122384-78-5;)

The restrictions concern the use of these substances in wood treatment and specify that these substances shall not be placed on the market, or used, as substances or in mixtures where the substance or mixture is intended for the treatment of wood. Furthermore, wood so treated shall not be placed on the market.

However, some further derogations in Entry 31 specify that under certain conditions these substances can be used in wood treatment, among others (see Entry 31 for full legal text):

a) The substances and mixtures may be used for wood treatment in industrial installations or by professionals covered by Community legislation on the protection of workers for *in situ* retreatment only if they contain:

   (i) benzo[a]pyrene at a concentration of less than 50 mg/kg (0,005% by weight), and

   (ii) water extractable phenols at a concentration of less than 3% by weight.

b) Wood treated in industrial installations or by professionals according to subparagraph (a) which is placed on the market for the first time or retreated *in situ*, may be used for professional and industrial use only, for example on railways, in electric power transmission and telecommunications, for fencing, for agricultural purposes (for example stakes for tree support) and in harbours and waterways.

c) Section 3 of entry 31 further specifies uses where such treated wood cannot be used.

Entry 50 of Annex XVII concerns restrictions of the following PAH substances:

a) Benzo[a]pyrene (BaP)

b) Benzo[e]pyrene (BeP)

c) Benzo[a]anthracene (BaA)

d) Chrysene (CHR)

e) Benzo[b]fluoranthene (BbFA)

f) Benzo[j]fluoranthene (BjFA)

g) Benzo[k]fluoranthene (BkFA)

h) Dibenzo[a,h]anthracene (DBAhA)

The restrictions concern the use of certain products that may contain one or more of the above PAH substances. These include, among others, the following (see entry 50 of Annex XVII for full legal text):

a) 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, or

   - more than 10 mg/kg (0,001% by weight) of the sum of all listed PAH.

b) Articles shall not be placed on the market for supply to the general public, if any of their rubber or plastic components that come into direct as well as prolonged or short-term repetitive contact with the human skin or the oral cavity, under normal or reasonably foreseeable conditions of use, contain more than 1 mg/kg (0,0001% by weight of this component) of any of the listed PAH.

c) Toys, including activity toys, and childcare articles, shall not be placed on the market, if any of their rubber or plastic components that come into direct as well as prolonged or short-term repetitive contact with the human skin or the oral cavity, under normal or reasonably foreseeable conditions of use, contain more than 0,5 mg/kg (0,00005% by weight of this component) of any of the listed PAH.

d) Granules or mulches shall not be placed on the market for use as infill material in synthetic turf pitches or in loose form on playgrounds or in sport applications, if they contain more than 20 mg/kg (0,002 % by weight) of the sum of all listed PAH.

e) Granules or mulches shall not be used as infill material in synthetic turf pitches or in loose form on playgrounds or in sport applications if they contain more than 20 mg/kg (0,002% by weight) of the sum of all listed PAH.

In addition to the above, the group entries 28, 29 and 30 of Annex XVII concern restrictions of substances which are, respectively, classified as carcinogen, germ cell mutagen or reproductive toxicant category 1A or 1B in Part 3 of Annex VI to Regulation (EC) No 1272/2008. Such substances:

- Shall not be placed on the market, or used, as substances, as constituents of other substances, or, in mixtures, for supply to the general public when the individual concentration in the substance or mixture is equal to or greater than either the relevant specific or generic concentration limit in Part 3 of Annex VI to Regulation (EC) No 1272/2008.
- Without prejudice to the implementation of other Community provisions relating to the classification, packaging and labelling of substances and mixtures, suppliers shall ensure before the placing on the market that the packaging of such substances and mixtures is marked visibly, legibly and indelibly as follows: 'Restricted to professional users'.
- Certain derogations for these restrictions are listed in paragraph 2 of entries 28 to 30.

Such substances are also listed in Appendixes 1 to 6 of Annex XVII. A number of PAH substances and PAH containing substances are listed there.

3.5 Plant Protection Products Regulation (EC) 1107/2009

PAH are used in pesticides; for further details check the EFSA website under plant protection products and the specific PAH.

3.6 Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC respectively

PAH are used in some medicines based on coal tar; for further details check the EMA website and the specific PAH.

3.7 Biocidal Products Regulation (EU) 528/2012

PAH are not used in Biocidal products and not listed as an active substance in Annex I to the Biocides Regulation.

3.8 Other legislation

According to Annex II of the EU Regulation (EC) No 1223/2009[3] on cosmetic products, a number of PAH or PAH containing substances are prohibited in cosmetic products. These include:

- E.g. benzo[a]pyrene, dibenz[a,h]anthracene, benz[a]anthracene, benzo[e]pyrene, benzo[j]fluoranthene, benz(e)acephenanthrylene, benzo(k)fluoranthene, chrysene, anthracene oil.
- An important number of PAH mixtures with benzo[a]pyrene >0,005% w/w (e.g., entries 613-636, 1123, 1205-1211, 1540-1541 of Annex II of Regulation (EC) No 1223/2009.

4. Existing Occupational Exposure Limits

At EU level, no OEL has been adopted for BaP or PAH mixtures containing BaP. However, OELs exist in various EU Member States as well as outside the EU.
National OELs for PAH as benzene soluble fraction in EU are presented in **Table 2.**

National OELs for the BaP and naphthalene (ie single PAH) are presented in

Table 3 and

Table 4, respectively. The values are collected from the GESTIS International Limit Values Database (GESTIS, 2022).

Table 2: Existing Occupational Exposure Limits (OELs) indicated as 8-h Time-Weighted Average (TWA) and as 15 min short-term exposure limit (STEL) for PAH (benzene soluble fraction)

Country	TWA (8 hrs) ppm	mg/m³	STEL (15 min) ppm	mg/m³	Remarks
Denmark		0.2		0.4	
Norway		0.04			
Poland		0.002			skin
Romania		0.2			

Table 3: Existing Occupational Exposure Limits (OELs) indicated as 8-h Time-Weighted Average (TWA) and as 15 min short-term exposure limit (STEL) for BaP

Country	TWA (8 hrs) ppm	mg/m³	STEL (15 min) ppm	mg/m³	Remarks
Austria		0.002		0.008	Based on technical
Finland		0.01			
Germany Risk 4:1 000		0.0007		0.0056	Tolerable cancer risk,
Germany Risk 4:10 000		0.00007			Acceptable cancer risk, inhalable

[3] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R1223&from=EN

Country	TWA (8 hrs)		STEL (15 min)		Remarks
	ppm	mg/m³	ppm	mg/m³	
Hungary		0.002			
Latvia		0.00015			
Poland		0.002			
Sweden		0.002		0.02	
Switzerland		0.002			
The Netherlands		0.0005507[a]			skin

[a] The Netherlands has the same value also for Polycyclic Aromatic Hydrocarbons derived from coal (as BaP)

Table 4: Existing Occupational Exposure Limits (OELs) indicated as 8-h Time-Weighted Average (TWA), and as 15 min short-term exposure limit (STEL) for naphthalene

Country	TWA (8 hrs)		STEL (15 min)		Remarks
	ppm	mg/m³	ppm	mg/m³	
Austria, France, Ireland, Italy, Latvia, Norway, Romania, Switzerland, Turkey	10	50			
Finland	1	5	2	10	
Germany	0.4	2	1.6	8	Inhalable fraction and vapour, skin
Hungary		50			
Poland		20		50	
Belgium	10	53	15	80	
Denmark	10	50	20	100	
Spain	10	53	15	80	skin
Sweden	10	50	15	80	
The Netherlands		50		80	
United Kingdom	(10)	(53)	(15)	(80)	1

1. The UK Advisory Committee on Toxic Substances has expressed concern that, for the OELs shown in parentheses, health may not be adequately protected because of doubts that the limit was not soundly-based. These OELs were included in the published UK 2002 list and its 2003 supplement, but are omitted from the published 2005 list

There are no legally binding Biological Limit Values (BLVs) for PAH metabolites. SCOEL and some countries have recommended biomonitoring of PAH exposure and have set a guidance or reference value for urinary 1-OHP, which has been considered as indicator for PAH exposure.

SCOEL proposed the value of 0.5 µg 1-OHP per g creatinine as a Biological Guidance Value (BGV). SCOEL noted that in general, the urinary excretion of 1-OHP does not exceed 0.5 µg 1-OHP per g creatinine (determined after conjugate hydrolysis) in the urine of people not occupationally exposed to PAH. This value also includes smokers, who are not occupationally exposed. Exceeding this value points to occupational PAH exposure, by any route of entrance into the body. SCOEL also noted the recent development in the biomonitoring of 3-OHBaP in urine and considered that when more studies will be available, it might lead to the development of an additional BGV for 3-OHBaP.

DFG has set a BAR (Biologischer Arbeitsstoff-Referenzwert/biological reference value) of 0.3 µg 1-OHP (after hydrolysis)/g creatinine in urine (DFG 2015).

The UK has a biological monitoring guidance value of 4 µmol 1-OHP/mol creatinine (approx. 8 µg 1-OHP (after hydrolysis)/g creatinine) based on the 90th percentile value of a survey of workplaces with exposure to PAH (Unwin et al., 2006, HSE, 2020).

FIOH recommends using 1-OHP in urine as the marker for biomonitoring PAH exposure. A biological limit value ("action limit") of 12 nmol 1-OHP/l urine (approx. 2.3 µg 1-OHP/g creatinine) was identified. The value is based on the 90th percentile from the biomonitoring results, measured for coke oven workers (N=32) with good industrial practices in 2008, in Finland (FIOH, 2011).

5. Occurrence, Use and Occupational Exposure

5.1 Occurrence

PAH are formed by incomplete combustion of organic material, such as coal and wood and they are released to the environment via natural and man-made sources.

The main natural, non-anthropogenic sources of PAH release in the environment include forest fires and volcanic activity. Primary man-made sources of environmental exposure include industrial emissions, vehicle exhaust, domestical heating, gas cooking, smoke from open fireplaces and cigarette smoking. Man-made sources provide a much greater release volume than natural sources; the largest single source is the burning of wood in homes (SCOEL, 2016).

Ambient air concentrations of BaP are high across large parts of Europe, mostly as a result of emissions from the domestic combustion of coal and wood. Exceedances of the target value of 1 ng/m^3 for BaP set by the Air Quality Directive (EU, 2004) were measured mainly at urban and suburban stations. About 20% of the European population was exposed to BaP annual mean concentrations above the target value of 1 ng/m^3 in 2012, and only about 12% of the European population live in areas in which concentrations are below the estimated reference level of 0.12 ng/m^3 (European Environment Agency: Air Quality in Europe – 2015 report EEA Report No 5/2015)(EEA, 2015).

Hazardous waste sites can be concentrated sources of PAH on a local scale. Examples of such sites are abandoned wood-treatment plants (sources of creosote) and former manufactured-gas sites (sources of coal tar). PAH can enter surface water through atmospheric deposition and from discharges of industrial effluents (including wood-treatment plants), municipal wastewater, and improper disposal of used motor oil. Several of the PAH have been detected at hazardous waste sites at elevated levels. In the air, PAH are found sorbed (both absorbed into the particulate matter and adsorbed to the particulate surfaces) to particulates and as gases. Particle-bound PAH can be transported long distances and are removed from the atmosphere through precipitation and dry deposition (SCOEL, 2016).

Important sources of individual exposure to PAH are inhalation of tobacco smoke and contaminated air and ingestion of contaminated food and drinking water (ATSDR, 1995).

5.2 Production and Use Information

As discussed, PAH mixtures are formed in incomplete combustion and pyrolysis (thermal degradation) processes of organic material. Some PAH are also intentionally manufactured. In this section (5.2), the main processes where workers may experience exposure to PAH are described. The exposure levels are further described in section 5.3.

5.2.1 Monoconstituent PAH

Some single PAH are commercially produced in Western Europe, Japan and the USA (SCOEL, 2016). These include: naphthalene, acenaphthene, acenaphthylene, fluorene, anthracene, phenanthrene, fluoranthene and pyrene. Of those, only naphthalene,

acenaphthene, acenaphthylene and anthracene are produced in significant quantities. Commercially produced PAH are mainly used for research goals. In addition, some PAH are used as (chemical) intermediates, such as: anthracene in dye production and in the synthesis of the chemotherapeutic agent Amsacrine; acenaphtalene in the manufacture of pharmaceuticals and plastics; and fluorene in resin production.

5.2.2 Main PAH mixtures

The main industrial sectors where workers are exposed to various PAH formed in incomplete combustion processes of organic materials are described below.

5.2.2.1 Coke production (coke oven workers)

Coke was first produced commercially in England in the early eighteenth century. Coal carbonization is a process that yields metallurgical coke for use in iron-making blast furnaces and other metal-smelting processes. Carbonization entails heating the coal to temperatures as high as 1300 °C in the absence of oxygen to distil out tars and light oils. A gaseous by-product, referred to as coke-oven gas, together with ammonia, water and sulphur compounds are also removed thermally from the coal. Worker exposure to PAH is from the coke oven itself and from associated maintenance activities.

The coke that remains after this distillation largely consists of carbon in various crystallographic forms, but also contains the thermally modified minerals that were in the original coal. These mineral residues, commonly referred to as coke ash, are not combustible and are left after the coke is burned. Coke also contains part of the sulphur from the coal. Coke is principally used as a fuel, as a reducing agent and support for other raw materials in iron-making blast furnaces. A smaller amount of coke is used similarly in cupola furnaces in the foundry industry. The carbonization by-products are usually refined within the coke plant to commodity chemicals such as elemental sulphur, ammonium sulphate, benzene, toluene, xylene and naphthalene. Subsequent processing of these chemicals produces a large number of other chemicals and materials. Coke-oven gas is a valuable heating fuel that is used mainly within steel plants, for example, to fire blast-furnace stoves, to soak furnaces for semi-finished steel, to anneal furnaces and lime kilns, as well as to heat the coke ovens themselves.

Coke is mostly produced from slot-type, by-product coke ovens. Above the ovens is a roof system from which coal is discharged into each oven. Modern technology includes telescopic charging chutes to minimize dust emissions during charging. Many facilities also include automatic removal and replacement of the charging-hole lid. Volatile gases generated from the coal during carbonization flow to the top of the oven, into the free space and out through standpipes connected to large collecting mains that transport the gases to the by-product plant, in which they are processed into various materials. Water is sprayed into the mains to cool the Coke production gases and to condense out some of the tar. At the end of the coking cycle, which ranges from about 15 to 30 hours, the coke is pushed into a hot car (quench car). The hot car may or may not have a moveable roof or partial roof to minimize gaseous and particulate emissions. The hot coke is then quenched before being dropped onto a conveyor system for transportation to a blast furnace, storage pile or out of the plant (IARC, 2012).

Figure 1 describes the coke production and the various other PAH containing products formed during it e.g., coal tar pitch, creosote and chemical oil. These products are used or have been used in various processes resulting in PAH emissions (see next sections e.g. 5.2.2.2, 5.2.2.4 and 5.2.2.5).

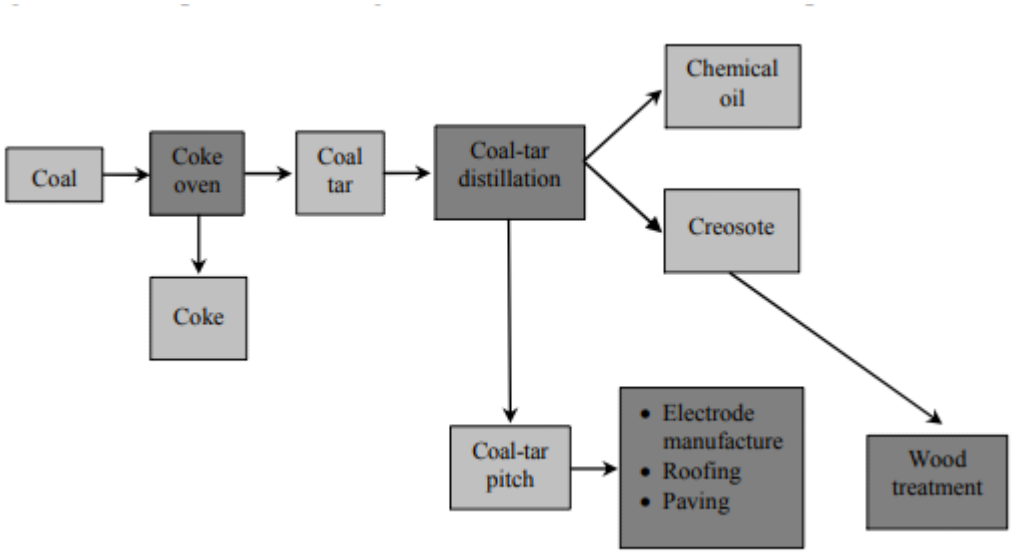


Figure 1: Simple schema for coke production and generation of different products from it (IARC, 2010)

5.2.2.2 Graphite electrode production

Graphite electrode is made of high-quality calcined needle coke. Medium crushing and sieving take place, entailing the needle coke being broken in a machine and sifted, then proportioned according to the recipe requirements. This is sometimes referred to as batching. After batching, the raw material is mixed with a certain proportion of asphalt by heating and kneading to make a plastic paste. After mixing and kneading, the paste is cooled to the process temperature and then pressed into the press according to the product specifications.

The next step is roasting. In the roasting furnace, the "raw embryo" electrode is roasted to the specified temperature according to the technological requirements, and the roasted product is impregnated with special impregnated asphalt according to the specific technological process to improve the product density and mechanical strength, and then the impregnated product is re-roasted to improve the product performance.

The next step is graphitization. The secondary roasted products are electrified in the graphitized resistance furnace and heated to 3000 °C, so that the carbon atom structure is rearranged in a specific crystal form, and the carbon is converted into graphite.

Some of these stages result in significant release of PAH into the atmosphere, with total-PAH concentrations in flue gases similar to those found in coke drying and calcination.

5.2.2.3 Aluminium production

Since 1886, nearly all aluminium has been produced by electrolysis of alumina dissolved in a molten cryolite (Na_3AlF_6)-based bath (also known as the Hall–Héroult process). Molten aluminium is deposited on the carbon cathode, which also serves as the melt container, and oxygen is simultaneously deposited on and consumes the carbon–carbon anode(s) of the electrolytic cell.

A modern alumina-smelting cell consists of a rectangular steel shell lined with refractory insulation surrounding an inner lining of baked carbon. Electric current enters the cell through the anode (either pre-baked or continuously self-baking Søderberg anode) and leaves through steel (collector) bars connected to the carbon cathode at the bottom. Pre-baked anodes are produced by moulding petroleum coke and coal-tar pitch binder into blocks which are baked at 1000–1200 °C. Søderberg anodes are formed continuously from a paste of petroleum coke and coal-tar pitch. The paste is typically added to the top of the rectangular steel shell and bakes to form carbon as it passes through the casing, replacing

the anode that is being consumed. Molten aluminium is generally removed from the cells daily by siphoning into a crucible.

Workers in aluminium production are primarily exposed to PAH. Occupational exposures in this and the related carbon electrode manufacturing industry have been monitored most intensively with respect to PAH. Biomonitoring studies have focused primarily on exposures in the aluminium industry itself and in anode-manufacturing for the aluminium industry. Other potential exposures in these occupational settings include: sulphur dioxide and fluorides; aluminium fluoride; fibrous sodium aluminium tetrafluoride particles; fluorspar; alumina; carbon monoxide; carbon dioxide; various trace metals, such as vanadium, chromium and nickel; asbestos; extreme heat; and high static magnetic fields. Exposures to PAH, sulphur dioxide and fluorides have decreased over time. The decrease in exposure can be attributed to the improvements in control technology and technical processes , increased use of effective devices for personal protection, and the increasing predominance of pre-bake pot-rooms, although this may only apply to the anode pre-baking plants. (IARC, 2012).

In Europe, there is only one Søderberg plant in use anymore, hence the PAH exposure in aluminium plants is currently mainly related to paste plants and anode baking plants in pre-bake smelters [4].

5.2.2.4 Wood impregnating process/Creosote

Historically, railway sleepers, telegraph poles and other similar wooden articles were often treated with Creosote in order to protect them from the elements and from insect infestation. Creosote extends the life of the wood. Nowadays, used railway sleepers are sometimes used to retain vegetable gardens, even though the use is forbidden for growing purposes and if there is a risk of frequent skin contact (see REACH Annex XVII Entry 31).

Commercial processing of coal leads first to coal-tars (see **Figure 1**), which are further processed to yield pitch, coal tar based binders, impregnating oils (creosotes for the preservation of wood), and residue oils, such as anthracene oil. The concentration of PAH in coal-tars is generally 0.75-1%; Comparable levels were detected in high-temperature coal-tar pitches. The PAH content of soot is about one order of magnitude lower, and that of carbon and furnace blacks ranges from about 1 to 500 mg/kg, with pyrene being present at the highest concentration.

The European standard EN 13991:2003 categorises creosote oils used for impregnation to three WEI grades. WEI grades B and C are restricted to 0.005% (v/v) BaP, whereas WEI A may contain up to 0.05% BaP. For wood impregnation, only grades B and C are currently allowed in the EU (see section 3.4), and vacuum processes and hot-and-cold dipping are the mostly applied techniques (Hebisch et al., 2020).

Further details of exposure concentrations during manufacturing operations are provided in section 5.3.2.

5.2.2.5 Products derived from crude oil

Crude oil is transformed in oil refineries into products such as gasoline or petrol, kerosene, diesel oil, fuel oil and bitumen (see **Figure 2**). Depending on the manufacturing process, all these different products contain various PAH. The concentrations of PAH in petrol and diesel fuels for vehicles and in heating oils are several parts per million. Almost all individual compounds are present at <1 mg/kg; only phenanthrene, anthracene, and fluoranthene are sometimes found at >10 mg/kg. The PAH levels in unused engine lubricating oils are of the same order of magnitude. During the use of petrol-fuelled engine oils, the PAH content rises dramatically by 30-500 times; in comparison, the total PAH levels in used diesel-fuelled engine oils were only 1.4-6.1 times greater than that in an unused sample. The major constituents of used oils are pyrene and fluoranthene, although

[4] Information received from "European-aluminium.eu"

benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, and dibenz[a,h]anthracene were also detected at considerable concentrations. PAH have also been found in machine lubricating and cutting oils, which is of interest for the estimation of exposure in the workplace. The concentrations were <7 mg/kg, although phenanthrene may have been present at a higher level. PAH were detected in coloured printing oils, the concentrations of individual compounds varying between <0.0001 and 63 mg/kg. By far the most abundant compounds were fluoranthene and pyrene (>1 mg/kg); benzo[ghi]fluoranthene, cyclopenta[cd]pyrene, benz[a]anthracene, benz[c]phenanthrene, chrysene, triphenylene, benzo[b+j+k]fluoranthenes, benzo[a]pyrene, benzo[e]pyrene, anthanthrene, benzo[ghi]perylene, indeno[1,2,3-cd]pyrene, dibenz[a,h]anthracene, and coronene were found at concentrations of <0.5 mg/kg.

Bitumen is produced in oil-refining. It is used to bind the mineral aggregates in asphalt and in roofing. In Europe, road paving accounts for about 80% of the total use of bitumen, other remaining part is used in roofing, waterproofing, flooring and paints (IARC, 2013). Chemical composition of bitumen depends on the original crude petroleum and the manufacturing process. In general, small amounts of PAH, alkylated PAH and sulphur-containing PAH are found from bitumen. The laying/process temperature is an important parameter that affects the composition and the amount of emissions during work with bitumen. Earlier, coal-tar pitch was used in roofing, flooring and road paving. However, coal-tar has been phased out in many countries starting in Finland, already in 1965. In Germany, the use of coal tar in asphalt paving ended in 1995. Even after the cessation of use of coal tar, workers may have been exposed to coal tar due to the use of recycled asphalt or during tearing off old roofing material that still contained coal tar. Coal tar contains much higher concentrations of PAH than bitumen, and particularly in the three- and seven-ring range. Exposure to coal tar among roofers was associated with a 35-times increase in dermal exposure to BaP and a 6-times increase to PAH. Similarly, exposure among pavers was estimated to be 5-times higher via inhalation when coal tar was present in the mixture (IARC, 2010, IARC, 2013).

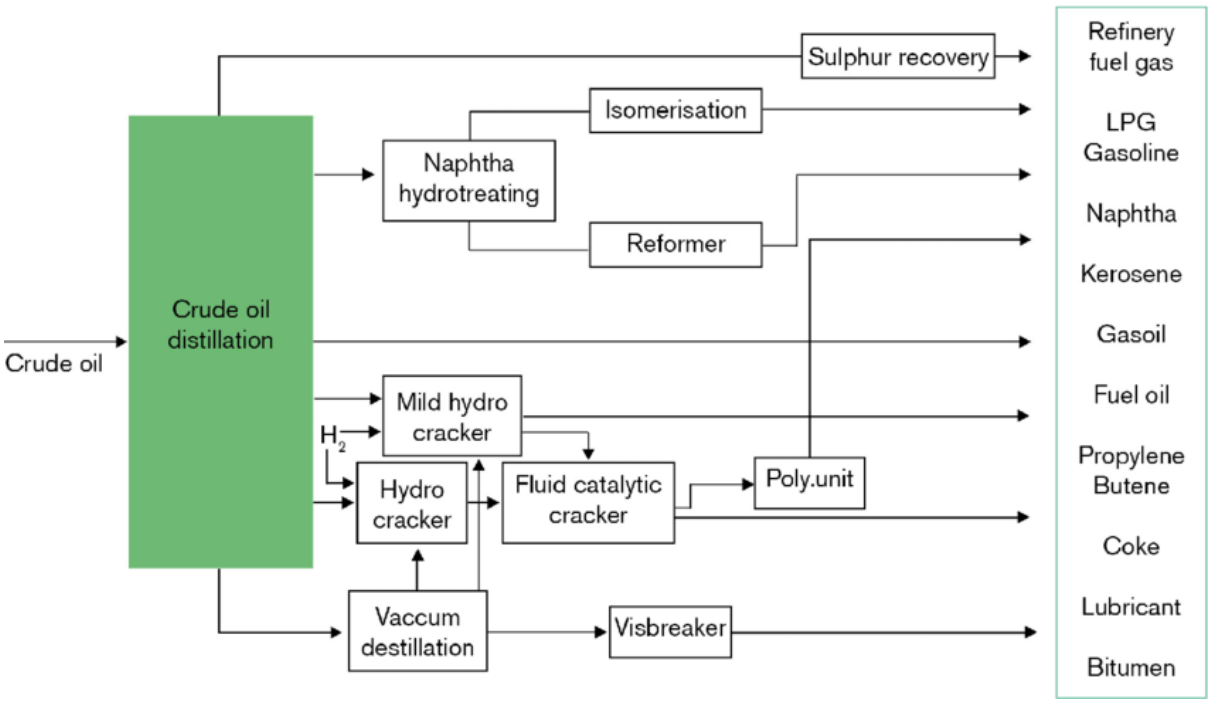


Figure 2: Schematic of products derived from crude oil (Berntsson et al., 2014)

5.2.2.6 Steel and iron foundries

Foundries produce shaped castings from re-melted metal ingots and scrap. Although foundry work is assumed to start with re-melting of ingots and scrap and to end with the

fettling of castings, the industry is often so integrated that the distinction is not obvious. Machine shops are not normally part of the work environment where castings are produced; however, simple and accessory machining may be carried out, and these activities may be part of small foundry operations. The processes in iron and steel founding generally comprise pattern-making, moulding and core-making, melting, pouring and shake-out, and fettling.

The iron and steel industry is very diverse in materials and processes, resulting in occupational exposures to a wide variety of substances. Substantial exposures to silica and carbon monoxide continue to occur in many foundries. Occupational exposures to airborne PAH are also present, resulting mainly from the thermal decomposition of carbonaceous ingredients commonly added to foundry sand. In addition, some steel foundry workers (e.g., fettlers) are exposed to airborne chromium and nickel compounds. The introduction of organic binder materials in the late 1950s has resulted in exposures of foundry workers to other chemicals, including phenol, formaldehyde, isocyanates and various amines.

Organic binder materials for cores and moulds include furan, phenol-formaldehyde, urea-formaldehyde and urethane resins, as well as oleo-resinous oils. These ingredients may volatilise into the workplace air during mixing, blowing, ramming, drying or baking operations. Curing reactions and thermal decomposition give rise to the formation of additional compounds, which are released during pouring and shakeout. When organic binders are subjected to high temperatures, pyrolysis may produce gases and smoke aerosols. Only a few components of these emissions have been identified: aliphatic components include methane, ethane, ethylene, acetylene, and smaller amounts of high molecular weight compounds; aromatic substances include benzene, toluene, xylenes, naphthalenes and a variety of PAH in lower concentrations.

PAH result from thermal decomposition of carbonaceous ingredients in foundry sand. During casting, PAH are formed and partly vapourised under the extremely hot and reducing conditions at the mould-metal interface. They are then adsorbed onto soot, fume or sand particles and spread throughout the workplace during shake-out and other dusty operations. Although the mechanism of PAH formation is complex and variable, the reactions proceed via pathways that involve free radicals. Various radical species containing carbon atoms combine in rapid fashion at the temperature range of 500–800 °C. This pyro-synthesis is influenced by many variables, such as the composition of the gaseous atmosphere and the chemical structure of the carbonaceous material. Organic binders, coal powder and other carbonaceous additives are the predominant sources of PAH in iron and steel foundries. In some cases, exhaust gases from engines, furnaces and ovens may increase the exposure of workers to these compounds (IARC, 2012).

5.2.2.7 Tyre manufacturing

While PAH are not directly used in the production of rubber goods, PAH are present as impurities in raw materials used for the production of several rubber articles. According to the information received during the published ‘Call for Evidence’, the potential presence of PAH in the work environment of rubber production sites may theoretically arise exclusively from two sources, from oils, which facilitate the processing of the rubbers compounds from which tyres are made, and carbon black, which is the most commonly used reinforcing filler in the production of rubber articles. Carbon Black contains PAH as impurities that could potentially be released in the workplace. PAH present in carbon black have very strong physical-chemical bonding to the matrix and they don’t extract easily from carbon black.

The limited bioavailability of PAH in Carbon Black, due to the strong adsorption on its surface, has also been confirmed from more recent studies. Additionally, PAH coming from Carbon Black, once incorporated into a rubber matrix, do not migrate to aqueous simulants representing typical human or environmental liquids like sweat, saliva or rainwater as described at the study STANPAH4 performed by the Joint Research Centre of the European Commission in 2018.

Since the 2000s, extender oils with a high level of PAH have been systematically replaced by very low PAH extender oils. Since 2010, entry 50 on Annex XVII of REACH restricts the presence of PAH in extender oils used for the production of tyres, contributing to ensuring the safety of consumers and workers (see section 3.4). Therefore, the PAH risk for workers exposure in industrial sites producing rubber articles is of low concern. PAH present in Carbon Black are hardly bioavailable and old extender oils have already been replaced by the new low-PAH content oils.

The use of End of Life Tyres (ELT) as infill material in synthetic turf in the sport fields has increased in the last 10-15 years in the EU. One of the concerns over the use of ELT granules are the PAH which are found in the rubber matrix. Granules and mulches are regarded as mixtures. Earlier rubber infill material did not fall within the scope of the REACH restriction entry 50, since this entry was only applicable to articles. While the general restriction in entry 28 applies to rubber granules meeting End-of-Waste status, it permits higher concentrations of PAH than those currently permitted in articles made from the same material. There was a concern that some individuals in the EU, like workers for installation and maintenance, professional athletes, amateur athletes and children playing at playgrounds are most likely to come into contact with granules. For this reason, on 20 July 2021, the entry 50 on Annex XVII of REACH was expanded to include granules or mulches used as infill material.

5.2.2.8 Combustion products

Various combustion processes from smoking fish to burning garden or industrial waste, generate PAH, including BaP (Unwin et al., 2006, Maitre et al., 2018).

The small-scale industrial fires simulated in these experiments generated a wide range of combustion products including VOCs, acid gases, and PAH. Benzene concentrations of up to 23 mg/m^3 and total PAH concentrations (17 PAH) ranging from 1.7 to 8.6 mg/m^3, were observed in personal air samples collected outside the structural firefighting ensembles, as well as a variety of acid gases including hydrogen chloride and hydrogen cyanide. Similar combustion products are involved in firefighter exposures during residential and industrial fires, however deposition rates of PAH may be substantially higher during industrial firefighting (Kirk et al., 2021).

5.2.2.9 Others

PAH exposure occurs in many other processes e.g. vehicle exhausts. However, it is beyond the scope of this document to describe them all in detail. More detailed exposure data are compiled in Section 5.3.

5.3 Occupational exposure

The economic activity sectors in the EU, where exposure to PAH (excluding environmental tobacco) is most common, are construction (146 506), personal and household services (110 039; household is an employer)) and iron and steel basic industries (75 120) according to the CAREX (CARcinogen EXposure) database where exposure data are from the early 1990s. Total estimate for all 41 different industrial sectors of the workers exposed to PAH is 959 332 in Europe (FIOH, 2022).

High occupational exposure to PAH may occur in several industries, such as in coke ovens and power plants; petroleum refining; aluminium production using Søderberg anodes; manufacture of anodes; and steel and iron foundries. However, incomplete combustion in coal-derived processes are not the only source of PAH formation; other sources are wood, petroleum, and gas oil. Examples of processes involving heating include power plants heated with wood, coal and mineral oils, and waste incinerations. Combustion products of petroleum or gas oil (vehicle exhaust), and asphalting may contain other substituted PAHs in much greater quantities than unsubstituted PAH.

In occupational exposure assessment, different sets of PAH compounds have been monitored e.g., individual PAH, particle bound PAH, vaporous PAH or total PAH. For total PAH, the 16 US Environmental Protection Agency (EPA) PAH are often measured and they are included in numerous EN and national standards. The 16 USEPA priority PAH consist of unsubstituted polycyclic aromatic hydrocarbons including two to six aromatic rings substances such as: Naphthalene (CAS RN 91-20-3); Acenaphthene (CAS RN 83-32-9); Acenaphthylene (CAS No.208-96-8); Fluorene (CAS No.86-73-7); Anthracene (CAS RN 120-12-7); Phenanthrene (CAS RN 85-01-8); Fluoranthene (CAS RN 206-44-0); Pyrene (CAS RN 129-00-0); Benzo(a)anthracene (CAS RN 56-55-3); Chrysene (CAS RN 218-01-9); Benzo(b)fluoranthene (CAS RN 205-99-2); Benzo(k)fluoranthene (CAS RN 207-08-9); Benzo(a)pyrene (CAS RN 50-32-8); Indeno(1,2,3-cd)pyrene (CAS RN 193-39-5); Dibenzo(ah)anthracene (CAS RN 53-70-3); Benzo(ghi)perylene (CAS RN 191-24-2). The US EPA priority PAH are listed in Appendix 1, **Table 21**.

These particular PAH compounds were selected in the 1970's by US EPA due to historical reasons. The concept of selecting 16 EPA PAH compounds has enabled the development of improved quality analytical methods and reference materials. However, it is clear that the present list of the 16 EPA PAH does not cover the most toxic PAH that are found in environmental samples and therefore it cannot be used as a reliable proxy for a complete analysis of the polycyclic aromatic compounds when a good understanding of the toxicity of a certain sample is the goal (Andersson and Achten, 2015, Keith, 2015).

The most extensively studied PAH is BaP which has been identified as the predominant carcinogenic compound in coal tar and is present in various PAH emissions. As BaP is considered one of the strongest known genotoxic carcinogens, significantly contributing to the carcinogenic potential of PAH-rich mixtures, exposure assessment and health effect studies have largely focussed on this particular compound. In addition, various national and international authorities have used BaP as an indicator for total PAH exposure (SCOEL, 2016, AGS, 2011, DECOS, 2006).

5.3.1 PAH exposure profiles

French PAH occupational exposures spanning 20 years (1995-2014), have been recorded in the Exporisq-HAP database (Maitre et al., 2018). The database covers sectors like aluminium and silicon production, manufacturing of carbon products, foundries, use of lubricating oils, engine exhaust emissions, combustion processes, road paving and use of bitumen, and coke production. Maitre et al., 2018 have provided a thorough overview of the PAH exposures containing exposure levels and chemical compositions in different industrial sectors (see **Figure 3** and **Figure 4**). PAH exposure differs between industrial sectors. The highest exposure levels for total PAH (16 EPA-PAH) and for BaP occurred in industries that used coal or coal-derived products. BaP emissions resulting from petroleum-derived products were relatively low. The portion of particulate PAH ranged from 4 to 32% in emissions measured in industries of coal-derived products. The portion was much lower among petroleum-derived products and combustion processes, ranging from 1 to 4%. Also, the portion of carcinogenic PAH was higher in sectors using coke-derived products compared to sectors with engine exhaust, bitumen or combustion.

(Stec et al., 2018) studied exposure to PAH carcinogens in less traditional, non-industrial occupational settings, e.g., PAH exposure of firefighters in the UK. Wipe samples were collected from skin (jaw, neck, hands), personal protective equipment of firefighters, and the working environment (offices, fire stations and engines), in two UK Fire and Rescue Service Stations. The levels of 16 EPA PAH were determined on body surfaces (e.g., hands, throat), on PPE including helmets and clothing, and on work surfaces.

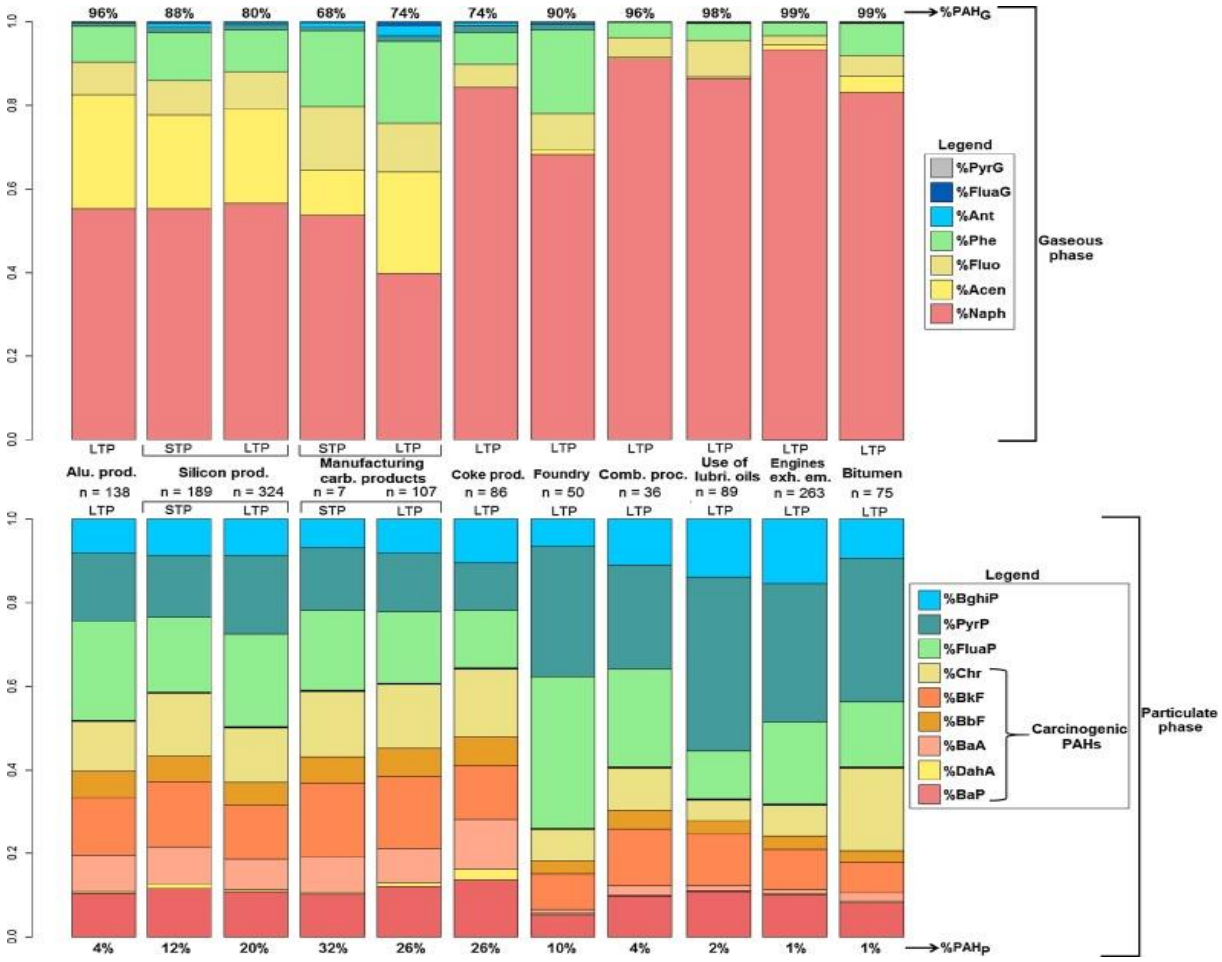


Figure 3: PAH chemical composition for different industries in France. Individual PAH compounds in gaseous (top) and particulate (bottom) phases are presented as geometric mean percentage (Maitre et al 2018)[5]

[5] Reprinted from International Journal of Hygiene and Environmental Health, 221, Maitre et al, Exporisq-HAP database: 20 years of monitoring French occupational exposure to polycyclic aromatic hydrocarbon mixtures and identification of exposure determinants, pages 334-346, 2018, with permission from Elsevier.

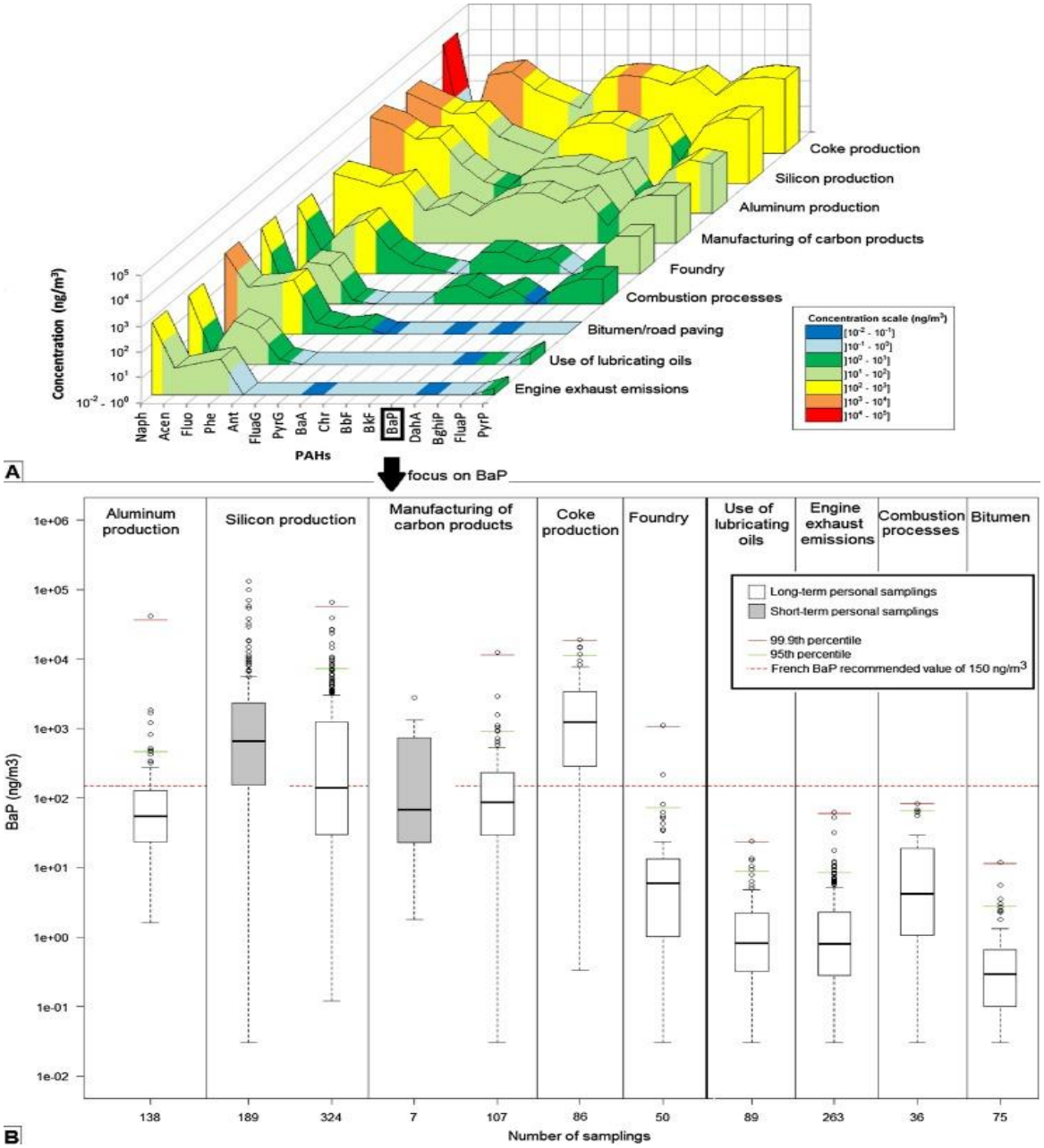


Figure 4: A) Panoramic view of the geometric mean PAH concentrations and B) BaP concentrations in the different industrial landscapes (Maitre et al 2018)[6]

The main exposure route was via skin absorption. A significantly elevated concentration of the majority of the studied PAH was noticeable on the four sampled locations, especially the hands and a similar profile was observed in the hand samples of most of the firefighters studied. Post-training, BaP was still found from almost all collected samples.

The PAH concentrations profile (see **Figure 5**) was also monitored from the wristbands worn by firefighters in a recent US study (Baum et al., 2020). The total number of firefighters was 71, with 47 of them reporting that they did not respond to fires, and 24

[6] Reprinted from International Journal of Hygiene and Environmental Health, 221, Maitre et al, Exporisq-HAP database: 20 years of monitoring French occupational exposure to polycyclic aromatic hydrocarbon mixtures and identification of exposure determinants, pages 334-346, 2018, with permission from Elsevier.

reporting response to fires. The average concentration of low molecular weight (LMW) PAH, defined as those with three aromatic rings or fewer, observed in fire-exposed wristbands was approximately 42% higher than in non-fire exposed wristbands. The average concentration of high molecular weight (HMW) PAH observed did not differ significantly between fire-exposed and non-fire-exposed wristbands, with average concentrations of 0.79 and 0.88 ppb, respectively. Wristband extracts from firefighters who responded to active fires showed greater concentrations for most LMW PAH than firefighters who did not respond to fires. These results are expected, since LMW PAH are both more volatile and present at higher concentrations in active fire situations. However, it should be noted that these results suggest that firefighters are exposed to PAH also outside of active fire situations, since firefighters who did not respond to fires had high concentrations of PAH during the sampling period and it was noticed that HMW PAH originated also from diesel fumes and particulate matter from activities involving the fire engine, which are not limited to active fire situations.

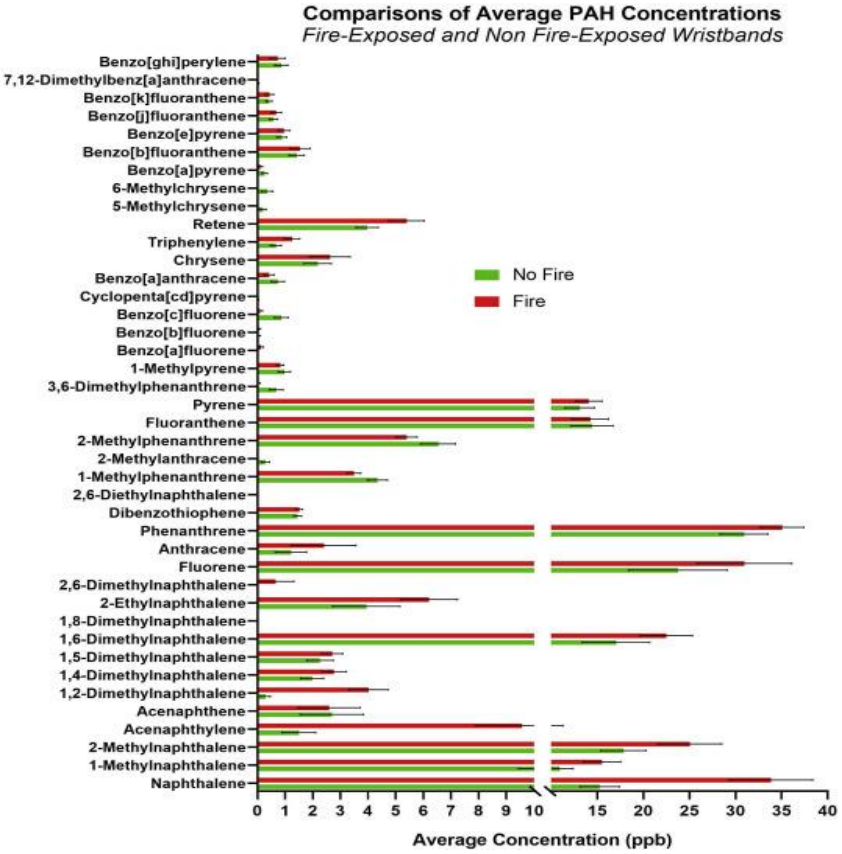


Figure 5: PAH profiles for firefighters monitored from fire-exposed and non-fire exposed workers' wristbands (Baum et al, 2020)

According to another US study, PAH concentrations were low in skin and neck wipes of firefighters, but many more PAH were detected in the wipe samples than in the air samples (Baxter et al., 2014). In the air samples, only three PAH (i.e., acenaphthylene, naphthalene and benzofluoranthene) were detected in this study. However, the sampling times (the longest time was 27 minutes) at the live overhaul events were very short. The only compounds found in both overhaul air and skin wipe samples were benzofluoranthene isomers. Pyrene was detected in 6 (30%) of the wipes, while benz[a]anthracene, chrysene, fluoranthene, phenanthrene, BaP, and benzo[e]pyrene were also detected. Finally, benzo[b,j,k]fluoranthene was found in all wipes where any PAH was found above the limit of detection.

5.3.2 Occupational exposure levels

Occupational exposure monitoring for PAH is performed by monitoring workplace air (static and personal air) but more and more frequently, biological monitoring is also applied. Most

commonly, 16 EPA PAHs and especially BaP are monitored from air samples and 1-OHP, which is a metabolite for pyrene, is monitored from the urine of workers. Biomonitoring is performed since dermal exposure significantly contributes to the total PAH exposure while taking into account the effectiveness of the applied PPE (respiratory protection and skin protection). Dermal exposure has been measured semi-quantitatively in some studies (Hebisch et al., 2020, Vaananen et al., 2005).

A decrease in occupational exposure levels to BaP is observed in various industrial workplaces in Europe, when BaP and PAH levels from 1995 to 2018 are compared to exposure levels gathered from the early 1980's and 1990's (see Table 4 of DFG 2012). There are various reasons for this decrease, e.g., changes in the production, composition and temperature of application, developments in the engines, improvements in occupational practices and new standards and legislations (Maitre et al., 2018). Some recent occupational exposure studies performed in different industrial fields in France, in the UK and in other part of Europe are gathered in Appendix 2, which include **Table 22** and **Table 23**, based on publications from Maitre and Unwin, and also **Table 24** summarising exposure and biomonitoring data from other studies gathered from open literature. This collection of the PAH exposure data is not based on an exhaustive review. Below is a summary of the data in the Appendix 2.

Based on the French Exporisq-HAP database described in section 5.3.1, Maitre et al. (2018), categorised available data to nine industrial exposure groups. The highest BaP exposure was observed in coke production followed by manufacturing of carbon products and silicon and aluminium productions. The lowest BaP concentrations were measured in road paving, from engine exhaust emissions and from use of lubricating oils were the P95 concentrations for BaP were less than 0.01 µg/m^3. Measurable BaP concentrations were also observed, resulting from combustion processes (firefighters, chimney sweeps, garbage incinerators). The median and P95 concentration for BaP in the different exposure groups are presented below:

- coke production (N=86): 1.2 and 11.3 µg/m^3;
- silicon production (N=324): 0.14 and 7.2 µg/m^3;
- manufacturing of carbon products (N=107): 0.09 and 0.92 µg/m^3;
- aluminium production (N=138): 0.06 and 0.46 µg/m^3;
- foundry (N=50): 0.006 and 0.07 µg/m^3;
- use of lubricating oils (N=89): <0.001 and 0.009 µg/m^3;
- engine exhaust emissions (N=263): <0.001 and 0.008 µg/m^3;
- combustion process (N=36): <0.001 and 0.07 µg/m^3;
- road paving (N=75): <0.001 and 0.003 µg/m^3, respectively.

Unwin et al. (2006) gathered PAH exposure measurements from different industrial sectors in the UK. 16 EPA PAHs and urinary 1-OHP were monitored in 25 workplaces. PAH concentrations ranged from 0.01 to 35 µg/m^3 (8 h TWA) with a median value of 0.12 µg/m^3 (8 h TWA). Naphthalene dominated the PAH profiles. BaP levels ranged from <0.01 to 6.21 µg/m^3 (8 h TWA), with a median value of 0.01 µg/m^3 (8 h TWA). The highest BaP levels were measured in coke ovens. The urinary 1-OHP levels ranged from <LOD (0.5 µmol/mol) to 60 µmol/mol with a mean value of 2.5 µmol/mol. Median value was below the LOD. The highest levels of urinary 1-OHP were found in timber impregnators using creosote and workers using coal tar, where both dermal and inhalation exposure exist.

(Förster et al., 2008) studied occupational PAH exposures (16 EPA PAH) in four industrial areas: converter infeed, production of fireproof materials (refractory), coking plant and production of graphite electrodes. Binding pitch was the source for PAH exposure in converter infeed plants, refractories and in the production of graphite electrodes. Coke oven gas was the source for PAH exposure in coking plants. Urinary metabolites for pyrene, phenanthrene and BaP (1-OHP, OH-Phens and 3-OHBaP) were measured together with airborne PAH exposure. Phenanthrene was the most abundant airborne PAH. For all industries (N=199), BaP concentrations ranged from LOD (0.04 µg/m^3) to 44.30 µg/m^3

and the median concentration was 0.6 µg/m^3. A highest BaP exposure occurred in converter infeed industries followed by production of graphite electrodes and coking plants. Relatively low BaP concentrations were observed in refractories. The median and P95 concentrations for BaP were as follows:

- converter infeed (N=12): 2.4 and 29.1 µg/m^3;
- graphite electrodes (N=24): 1.5 and 11.55 µg/m^3;
- coking plant (N=79): 0.89 and 6.19 µg/m^3;
- refractory (N=84): 0.14 and 5.6 µg/m^3, respectively.

A high correlation was observed between urinary 3-OHBaP and 1-OHP with correlation coefficients ranging from 0.618 to 0.867, at different workplaces. 1-OHP levels (N=225) ranged from LOD to 280 µg/g creatinine with a mean value of 11.8 µg/g creatinine, and a median and P95 value of 6.05 and 34.8 µg/g creatinine, respectively. The concentrations for 3-OHBaP reached up to 19.5 ng/g creatinine, with a median and P95 value of 0.8 and 6.7 ng/g creatinine, respectively. Only three samples were below the LOD of 3-OHBaP. Workers from converter infeed and refractories had the highest urinary 1-OHP and 3-OHBaP concentrations. A poor correlation of urinary 3-OHBaP and BaP in air was attributred to exposure routes other than inhalation (dermal or oral) (Förster et al., 2008).

PAH exposure during working activities in railway sleeper recycling and thermal soil remediation was investigated in Germany (Hagmann et al., 2017). Workplace measurements to determine inhalation exposure to BaP and other EPA PAH were carried out at two railway sleeper recycling companies and a thermal soil remediation company. Biomonitoring of internal exposure, using 1-OHP as a marker, was carried out simultaneously, with a total of 63 workers before and after the implementation of protective measures. The BaP concentrations varied from <0.02 to 2.09 µg/m^3. The highest BaP concentration was measured from the breathing zone of an inspector in the treatment hall of contaminated soils. Naphthalene was the most abundant PAH compound in the samples collected and its concentration regularly exceeded the German OEL value of 500 µg/m^3 in the thermal and treatment hall of contaminated soils. Overall, biomonitoring based on the 1-OHP marker did not show a good correlation with the workplace air measurements. One explanation for this was the dermal absorption of PAH, but also the variation of PAH profiles and the ratio between pyrene and other PAH (e.g., BaP) in different workplaces. However, with 1-OHP values up to 350 µg/g creatinine, it was possible to detect very high occupational PAH exposure in an individual case. The aim of the study was to define and implement measures to reduce both inhalation and dermal exposure to PAH. At the end of the study, the biomonitoring values were mostly within the range of the German BAR value ("Biologischer Arbeitsstoff-Referenzwert"-biological reference value for workplace substances). It was concluded that 1-OHP represented a suitable biomonitoring parameter together with workplace measurements to ensure the success of the preventive measures (e.g., respiratory protection, extraction devices, safety-ventilated cabins, disposable protective clothing, chemical protective gloves, daily change of work clothes), on a lasting basis.

PAH levels during handling of creosote-impregnated wood ranged from 0.05 µg/m^3 BaP to 650 µg/m^3 naphthalene (IPCS, 1998). When these levels are compared to the recent study by (Hebisch et al., 2020), it is noted that BaP levels have substantially decreased. PAH exposure levels were studied during wood impregnation work with creosote in 7 creosote treatment sites in Germany (Hebisch et al., 2020). Coal tar creosote oils are used as wood protectants for e.g., railway sleepers, utility poles and marine pilings. The European standard EN 13991:2003 categorises creosote oils used for impregnation to three WEI grades. WEI grades B and C are restricted to 0.005% (v/v) BaP, whereas WEI A may contain up to 0.05% BaP. For wood impregnation, only grades B and C are currently allowed in the EU. Vacuum processes and hot-and-cold dipping are the most applied techniques. Inhalation and dermal exposure and human biomonitoring were studied in six and four impregnation plants in Germany, respectively. 18 PAH and 1-OHP were measured from personal air and dermal samplers and in pre- and post-shift urine. Dermal exposure

was measured by using disposable chemical protective overalls and split leather gloves as a whole body dosimetry. Dermal exposure strongly affected the total exposure and the level of dermal exposure depended on the working processes. Up to 10 of the 16 EPA PAH (naphthalene, acenaphthylene, acenaphthene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, benzo(a)anthracene and chrysene) could be determined by personal air sampling and on the dermal samplers. Generally, no PAH with a higher boiling point than that for chrysene were found. The concentration of BaP was lower than the LoD (16 ng/m^3=0.016 µg/m^3) in all samples, consistent with the restriction of BaP content in the creosote grades used. Pyrene was found in all inhalation and dermal samplers. For inhalation, pyrene contributed between 1 to 3% of total PAH concentration. For dermal exposure, pyrene contributed with 6 - 10%.

PAH exposure among 73 roofers that were using soft-applied roofing with polymer-modified bitumen ("PMB"), hot-applied roofing with oxidized bitumen ("OB") and the tearing off of old roof coatings containing coal tar ("CT") were assessed in a study conducted between 2004 and 2017, in France (Persoons et al., 2020). Seventeen PAH from air samples and 14 urinary biomarkers, metabolites of pyrene (1-OHP), BaP (3-OHBaP and Tetraol-BaP), naphthalene (1- and 2-naphtols), fluorene (1- 2- 3- 9-fluorenols) and phenanthrene (1- 2- 3- 4- 9-phenanthrols), were analysed. Both inhalation and biomonitoring results showed that the PAH containing 2–3 rings were the most abundant ones. The highest exposure levels were observed in the "CT" group, where the airborne levels were around 10 times higher than in the other groups. However, mean BaP levels in the CT group were respectively around 100 times (outdoor) to 50000 times (confined) higher than in the PMB and OB groups. The geometric mean (GM) for the BaP concentration in the CT group exhibited large differences between outdoor activities (GM: 0.037 µg/m^3), and roofing in confined spaces (GM: 15.4 µg/m^3). The highest BaP levels (22.5 µg/m^3) were measured in 2011, when large surfaces of old coatings made of coal tar were removed in confined spaces. In contrast, BaP levels in the other exposure groups were below 0.010 µg/m^3. The levels of 1-OHP, 3-fluorenol and 2-phenanthrol better correlated with airborne levels and were less influenced by smoking, than the other metabolites. The levels of the BaP metabolites, 3-OHBaP and Tetraol-BaP, were very low when applying bitumen membranes, while much higher exposures were observed during tear-off activities.

Firefighters' exposure to combustion products has focused predominantly on real or simulated residential structure fires, with few investigations considering industrial fire scenarios. The atmospheric concentrations of PAH produced during fires in simulated industrial premises, as well as the deposition of PAH onto the structural firefighting ensembles worn by the firefighters involved in extinguishment activities have been measured. Total PAH concentrations (17 PAH) ranging from 1.7 to 8.6 mg/m^3 were observed in personal air samples collected outside the structural firefighting ensembles. Most combustion products detected outside the structural firefighting ensembles were also detected inside. Deposition of a variety of PAH compounds was observed on the outer surface of the ensembles, with total PAH concentrations ranging from 161 to 347 ng/cm^2. BaP accounted for between 1.2 and 4.9% by mass, to the PAH deposited on the structural firefighting ensembles. While similar combustion products are involved in firefighter exposures during residential and industrial fires, deposition rates of PAH, may be substantially higher during industrial firefighting. Fireground decontamination measures for the management of contamination of structural firefighting ensembles and equipment worn or carried by firefighters during firefighting activities is important to reduce exposures to PAH (Kirk et al., 2021).

A total of 101 environmental and occupational exposure studies using 1-OHP to assess occupational PAH exposure were reviewed by (Hansen et al., 2008). Studies covered activities conducted in or involving coke plants, foundries, soil remediation, combustion processes, working with asphalt and working in traffic. The highest concentrations of 1-OHP were found among coke oven workers and among workers in foundries. Occupational PAH exposure was the major factor determining high urinary concentration of 1-OHP.

However, it was concluded that at low level occupational exposure to PAH, it is crucial to provide information on intra- and inter-individual variations and other contributing factors like environmental tobacco smoke, country, cooking culture and behaviour, which can influence urinary 1-OHP levels.

5.4 Routes of exposure and uptake

Both human and animal studies clearly have showed that PAH penetrate the skin and reach the circulation (Dankovic et al., 1989, VanRooij et al., 1993b, DECOS, 2006).

The main routes for occupational exposure to PAH are inhalation and skin contact (Jongeneelen, 2001). Thus, uptake of pyrene by the dermal route was estimated to account for as much as 75% of the total body dose for coke-oven workers (Van Rooij et al 1993a); for creosote-impregnating workers, dermal pyrene uptake was on average 15-fold higher than the estimated respiratory uptake (Van Rooij et al 1993c, IARC 2010). The prominent extent of dermal PAH exposure in creosote wood impregnation processes was also observed in a recent study that compared four German plants (Hebisch et al., 2020). The study also observed marked differences in exposure, which could be explained, above all, by the technical and structural differences between the plants and the associated differences in the workflows. The relevance of inhalation and dermal routes are further described in sections 5.3.1 and 5.3.2.

5.5 General population exposure

The main sources of non-occupational exposure are: polluted ambient air, smoke from open fireplaces and cooking, environmental tobacco smoke, contaminated food and drinking-water, and the use of PAH-contaminated products.

Average concentrations of individual PAH in the ambient air of urban areas typically range from 1 to 30 ng/m^3 (excluding naphthalene), with the more volatile PAH generally being more abundant. However, concentrations up to several tens of nanograms per cubic metre have been reported in road tunnels or in large cities that extensively use coal or other biomasses as residential heating fuels (IPCS, 1998).

PAH can be found in indoor air as a result of residential heating and environmental tobacco smoke at average concentrations of 1-100 ng/m^3, with a maximum of 2300 ng/m^3. The intake of individual PAH from food has been estimated to be 0.10-10 µg/day, per person. The total daily intake of BaP from drinking-water was estimated to be 0.0002 µg/person. Cereals and cereal products are the main contributors to the intake of PAH from food because they are a major component of the total diet (IPCS, 1998).

Levels of total PAH in mainstream smoke ranged from 1 to 1.6 µg/cigarette. Side-stream smoke is a source of PAH in indoor air; levels of BaP in side-stream smoke have been reported to range from 52 to 95 ng/cigarette; more than three times that in mainstream smoke (IARC, 2010).

PAH is also produced in manufacturing and treatment processes where food is strongly heated or comes into contact with combustion gases or smoke. Smoked foods usually contain BaP residues below 1 pg/kg, and in individual cases also above 100 µg/kg. By comparison, high content of BaP can occur in grilled meat and sausage products, concentrations of up to 5 µg/kg BaP have been found in grilled meat (Kazerouni et al., 2001).

6. Monitoring Exposure

6.1 External exposure (monitoring methods)

Airborne PAH compounds with two and three aromatic rings are mainly in the vapour phase and PAH compounds with four of more aromatic rings are in particle phase. Fluoranthene and pyrene are often found in both phases.

Airborne PAH are collected using pumping systems, filters for particle-bound PAH and absorbents for gaseous PAH. When PAH compounds occur in both particulate and vapour phases, the sampling system must consist on both filters and absorbents. For the particle-bound PAH, the inhalable fraction should be collected. In some existing methods a sampler for inhalable fraction is not applied and it may create some uncertainty to the air concentrations. After solvent extraction and sample purification, single PAH compounds are analysed by chromatographic or spectrophotometric techniques.

In general, after sampling, the filters and the sorbents are extracted with organic solvents (e.g. toluene, cyclohexane, dichloromethane, acetone and methanol). Standard extraction techniques, such as ultrasonic techniques and solid-phase extraction may be used. Following extraction, samples are cleaned-up or purified. In case of complex samples from coal and petroleum streams e.g. tyre pyrolysis oil and asphalt, fractionation is needed after extraction and before analytical detection (UBA, 2022). The analytical methods routinely used to determine the concentrations of PAH in air samples include: separation by gas chromatography (GC) combined with flame ionisation detection (FID) and/or mass spectrometry (MS) for detection or/and identification; and, separation by reversed-phase high-performance chromatography (HPLC), combined with ultraviolet and/or fluorescence detection and/or MS for detection and identification.

Available standard methods for monitoring PAH in workplace air are described in **Table 5**. The methods are mainly validated according to the criteria set out in the standard *EN 482:* "*Workplace exposure. General requirements for the performance of procedures for the measurement of chemical agents*". However, some shortcomings in validation data (e.g., sampling and recovery efficiencies, expanded uncertainty) can be encountered. Due to the demands for achieving very low limit of detection and quantification, increase in sampling time and/or change to a sampler that allows higher flow rate for sampling and also more sophisticated analytical methods are applied.

BaP/PAH can be monitored in the air of the workplace by applying the following fully or partially evaluated methods:

- DFG (2017) Method number 1. Polycyclic aromatic hydrocarbons (PAHs) – Method for the determination of semi-volatile PAHs in work-place air using high performance liquid chromatography (HPLC) validated for six semi-volatile PAH including BaP
- IFA (2018) Method for Polycyclic Aromatic Hydrocarbons (PAHs) – particularly for BaP
- MetroPol Fiche 332 (2018) (Polynuclear aromatic hydrocarbons (PAH))
- MTA/MA 039 (2000) (Polynuclear aromatic hydrocarbons (PAH))
- DFG (2002) Method number 2 (Polycyclic Aromatic Hydrocarbons (PAH))
- DFG (2002) Method number 3 (Polycyclic Aromatic Hydrocarbons (PAH))
- NIOSH method 5515 (Polynuclear aromatic hydrocarbons (PAH))
- NIOSH method 5506 (Polynuclear aromatic hydrocarbons (PAH))

Table 5: Existing methods for monitoring PAH/BaP in the air of the workplace. Most of them are validated for 17 PAH.

Method	Suitable for	Filters/adsorbent	Desorption solution	Analytical technique	Flow rate/Sample volume/Time	LOD/LOQ/range
MétroPol Fiche 322 Hydrocarbures aromatiques polycycliques (HAP), 2018	Validated for 8 PAH	K7 Quartz fiber filter + tube containing XAD2.	Filter: CH_2Cl_2 and methanol Tube: toluene	HPLC/FLD	1 l/min (closed cassette), 2 l/min (open cassette) 240-480 l	LOQ: <10 ng/m^3 (480 l)
IFA - Arbeitsmappe, Kennzahl 8408, 2018	Particle bound PAH (semi-volatile PAH)	PTFE-Filter	Solvent extraction	HPLC/FLD		LOD for B(a)P: 0.003 µg/m^3 (1200 l)
DFG Method Nr 1, 2017	Particle bound PAH; Validated for six semi-volatile PAH	PTFE-Filter	Acetonitrile/methanol (60/40)	HPLC/FLD	10 l/min (sampler GSM/SG10 type), at least 2 h	LOQ for B(a)P: 0.0016 µg/m^3 (1200 l)
DFG Method Nr 2, 2002	Validated for 17 PAH	PTFE-Filter and sorbent tube containing washed XAD (100/50mg).	Filter: Acetonitrile/methanol (60/40) XAD-2: Acetonitrile/methanol (60/40) and dichloromethane	HPLC/UV/FLD	2 l/min, at least 1 h	LOQ 0.13 – 1.80 µg/m^3 (120 l); Range 0,8-40 µg/m³
DFG Method Nr 3, 2002	Validated for 16 PAH both as particles and in gaseous form	Sorbent tube containing washed XAD (100/50mg)	Toluene	GC/MS	≤1 l/min, 240-480 l	LOQ 0.017-0.195 µg/m^3 (360 l)
MTA/MA 039, 2000	Validated for 17 PAH	PTFE-filter + Orbo 43 tube	Carbon disulphide	HPLC/FLD	2 l/min 200 to 1000 l	LOQ 1.5 to 0.08 µg/m^3 (200 l)
NIOSH 5506, 1998	Validated for 17 PAH	PTFE filter+XAD-2 sorbent	Acetonitrile	HPLC/FLD/UV	2 l/min; 200-1000 l	0.001-0.2 µg/sample (LOD); 0.01-0.4 µg/sample (LOQ)
NIOSH 5515, 1994	Validated for 17 PAH	PTFE filter+XAD-2 sorbent	Organic solvent	GC-FID	2 l/min; 200-1000 l	0.3-0.5 µg/sample (LOD), 3-150 µg/m^3 (400 l)

Dermal exposure is often relevant for PAH which can also be absorbed through the skin. Skin contamination can be measured (semi)quantitatively e.g., with skin wiping, pads, silicon bands or washing methods. Even though there are studies where the dermal exposure to PAH has been investigated (Hebisch et al., 2020), quantification is particularly difficult because of lack of standardised and validated measurement methods (Strandberg et al., 2018, IPCS, 2014). For these reasons, dermal exposure to PAH is often assessed indirectly, by comparison of personal air samples with corresponding biomonitoring data.

6.2 Biomonitoring of exposure (internal exposure)

Biomonitoring options for PAH exposure include the measurement of PAH metabolites in urine, and DNA- and protein adducts of PAH in blood and tissues (Angerer et al., 1997). However, the latter are not considered to be sufficiently specific and sensitive for diagnostic purposes (DFG, 2013).

Recently a comprehensive review of the use of human biomonitoring to assess occupational exposure to PAHs in Europe has been performed (Louro et al., 2022). The review was developed under the Human Biomonitoring for Europe (HBM4EU) Initiative, and it was based on the literature available from 2008-2022. It aimed to present and discuss the information on occupational exposure to PAHs, in order to identify the strengths and limitations of exposure and effect biomarkers and the knowledge needs for regulation in the workplace. The review showed that the most frequently used exposure biomarker is urinary 1-hydroxypyrene (1-OHP), a metabolite of pyrene and as effect biomarkers, those based on the measurement of oxidative stress (urinary 8-oxo-dG adducts) and genotoxicity (blood DNA strand-breaks) are the most common.

The most widely and routinely used biomonitoring method for assessing occupational PAH exposure is to measure urinary 1-OHP, which is a major metabolite of pyrene (Jongeneelen et al., 1988, Louro et al., 2022). 1-OHP was originally selected as the most promising biomarker for two reasons. Firstly, the highly symmetric pyrene has a high thermodynamic stability making it one of the most predominant PAH in virtually any PAH mixture. As a consequence, it can serve as a universal marker for exposure to PAH. Secondly, due to the high rotational symmetry of pyrene, only a single monohydroxy metabolite, 1-OHP, can be formed, which therefore is not only more abundant but also limits interindividual variations due to genetic make-up compared with most other PAH which can form various monohydroxy metabolites. This feature also means that a relatively large proportion of pyrene is excreted in the urine as 1-OHP, which facilitates its detection. A limitation is that pyrene is not carcinogenic and therefore for risk assessment purposes, the ratio of pyrene to a carcinogenic PAH, such as BaP, should be known (Boogaard, 2008).

More recent studies also used other PAH metabolites for biomonitoring, particularly the sum of the 1-, 2-, 3-, 4- and 9-hydroxy-phenanthrenes which have well-established methods (Campo et al., 2016, Pesch et al., 2011). Among the monohydroxylated phenanthrene metabolites, 3- or 1-OH-Phen are the most abundant in human urine (Angerer et al., 1997). In comparison to 1-OHP, (the sum of) hydroxylated phenanthrenes are less influenced by smoking and eating habits and are therefore less susceptible to errors in the determination of occupational PAH exposure (TRGS-910-BaP).

Urinary 1- and 2-naphthols (OHN) which are metabolites of naphthalene have been measured for the assessment of respiratory PAH exposure, especially in those cases when the main PAH compounds consist of two and three aromatic rings (Bieniek, 1997, Rappaport et al., 2004). Smoking significantly increases the level of OHNs, and particularly 2-OHN (Pesch et al., 2011, Persoons et al., 2020).

Biological monitoring of 3-OHBaP in urine can also be utilised for assessing PAH exposure (Barbeau et al., 2014, Barbeau et al., 2015). BaP is the most potent carcinogenic substance in PAH mixtures and thus 3-OHBaP in urine would be more closely related to the internal genotoxic entity than 1-OHP. The shortcoming of this biomarker is that only a small fraction is excreted as 3-OHBaP in the urine and the elimination of 3-OHBaP is slow

compared to 1-OHP which may then require another sampling time than end-shift. (Barbeau et al., 2015) proposed that urine samples should be collected at the beginning of the shift at the end of the working week for the 3-OHBaP quantification, especially in cases of high exposure variability. Modern and sophisticated analytical procedures and methods are needed for analysing 3-OHBaP in urine. 3-OHBaP has been determined reliably in the urine of workers exposed to PAH in different industries (Förster et al., 2008). In this study, 3-OHBaP showed to be a diagnostically specific and sensitive marker for biomonitoring purposes, exhibiting a good correlation to 1-OHP, with correlation coefficients ranging from 0.618 to 0.867, at different workplaces (converter infeed, coking plants and production of graphite electrodes). A new method using GC-APLI-MS with high sensitivity has been developed for 3-OHBaP, which would allow human biomonitoring of carcinogenic PAH exposure using biomarkers excreted in the urine at very low levels (LOD of 0.6 pg/l) (Richter-Brockmann et al., 2019). However, there have been stability problems with the metabolite in the lower concentration range (Weiss et al., 2019), while there are still uncertainties regarding the elimination kinetics (Hagmann et al., 2017). Another advanced analytical procedure for the more sensitive and specific determination of 3-OH-BaP in human urine has been published and validated according to the US Food and Drug Administration (FDA) guideline (Rögner et al., 2021). This method is based on enzymatic hydrolysis, solid-phase extraction, derivatisation with 2-fluoromethylpyridinium-p-toluene sulfonate, and LC-MS/MS analysis. Both the calibration reference substance and the isotope-labelled internal standards (IS) were used as glucuronide conjugates (3-OH-BaP-glucuronide, 3-OH-BaP-$^{13}C_6$-glucuronide). In native urine samples, 3-OH-BaP was found to be present in its conjugated form in urine at almost 100% ; thus, instability of the analyte would not present an issue in real samples. Another advantage is that $^{13}C_6$-3-OH-BaP-Gluc also compensates for losses during enzymatic hydrolysis. The method is suitable for the quantification of occupationally and non-occupationally exposed populations and it can differentiate smokers from non-smokers as well as from users of new generation tobacco/nicotine products.

Recently, an alternative to 3-OHBaP has been introduced as a promising biomarker of BaP exposure: urinary trans-anti-7,8,9,10- tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene (7,8,9,10-OHBaP=Tetraol-BaP) (Barbeau et al., 2018). This biomarker represents the carcinogenic mechanism of BaP, but it is excreted in significantly higher concentrations than 3-OHBaP. In addition, no stability problems were observed for tetraol-BaP. Urinary tetraol-BaP levels seem easier to interpret than those of 3-OHBaP because inter-individual variability mainly stems from differences in occupational exposure. The method based on the Barbeau et al. (2018) published procedure, was slightly modified by IPA. The quantification after capillary gas chromatographic separation is performed on a tandem mass spectrometer with large-volume injection using isotope-labelled tetraol-BaP as the internal standard. The method has a limit of determination of 0.05 ng tetraol-BaP/L of urine (Weiss et al., 2019).

In **Table 6** (below), SCOEL has listed the potential markers for the biomonitoring of PAH exposure as proposed by DECOS (2006), IARC (2010) and DFG (2013). In this listing the new alternative for 3-OHBaP, tetraol-BaP, was not yet available/considered.

Table 6: The potential markers for biomonitoring of PAH exposure (SCOEL 2016)

Reference	Selection of markers
DECOS* (2006)	Internal BaP and PAH exposure can be assessed using biological monitoring techniques (e.g., **1-hydroxypyrene** in urine, and **DNA- and protein adducts** in blood and tissues). However, biological monitoring represents total body burden, and thus dermal, oral and inhalation exposure cannot be separated.
IARC (2010)*	**1-Hydroxypyrene**, a specific metabolite of pyrene in urine, has been suggested as a biomarker of human exposure to PAH (Jongeneelen et al., 1985; Jongeneelen, 2001). At the time it was considered the most reliable and practical marker for

Reference	Selection of markers
	monitoring individual exposures or exposures of the general population (IARC, 2010, Dor at al. 1999). **The glucuronide of 1-hydroxypyrene** has also been used as an indicator of exposure, since the majority of 1-hydroxypyrene is conjugated and the fluorescence intensity of the conjugate is higher, but its additional value has not yet been assessed (Strickland et al. 1996). The measurement of various **hydroxylated phenanthrenes** have also been reported as a biomarkers of exposure; analysis by GC–MS (Grimmer et al. 1991, 1993) and HPLC have been used to measure hydroxylated phenanthrenes and **3-OHBaP** (Gundel et al. 1996; Popp et al. 1997; Gendre et al. 2002). I**mmunoaffinity separation of PAH metabolites** from the urine of exposed workers showed the presence of both 1-hydroxypyrene and several hydroxyphenanthrenes (Bentsen-Farmen et al. 1999).
DFG (2013)*	To biomonitor human exposures to PAH the most commonly applied biomarkers are metabolites of pyrene and phenathrenes: **1-Hydroxypyrene** and **hydroxyphenanthrenes** (mostly 1-, 2-, 3-, 4- and 9 Hydroxyphenanthrenes). However, due to the low toxicity of the parent compounds, neither type of these markers represent adequately the internal exposure to carcinogenic PAH in quantitative terms. Furthermore, they do not represent well the variability of the PAH exposure mixtures. To tackle these drawbacks, metabolites of the toxicologically more relevant constituents of PAH mixtures are taken into consideration. These include **3-OHBaP** as a metabolite of the carcinogenic BaP, and metabolites of benzo[a]anthracene, benzo[a]phenanthrene, chrysene, fluorene, fluoroanthene and naphthalene. A complicating issue related to these markers is the fact that they are preferably metabolised and excreted in faeces. **Protein and DNA adducts** have been proposed for biochemical effect monitoring, but they are not considered to be sufficiently specific and sensitive for diagnostic purposes.

*Reports and references therein, are cited in SCOEL, 2016

SCOEL (2016) noted:

"In principle, human biomonitoring by determination of PAH-specific metabolites in the urine would be more suitable for assessing workplace exposure than airborne PAH measurements at the workplace on account of dermal PAH absorption (Jongeneelen 1997). 1-OHP excretion in urine was used as a parameter for measuring systemic PAH exposure in most field studies. It represents the main metabolite of pyrene in mammals and has become accepted as a sensitive and specific parameter of PAH exposure; a review has been presented by Jongeneelen (1997). ….A number of studies did not only determine 1-OHP in the urine but also the excretion of further PAH metabolites – particularly of phenanthrene phenols (1-, 2-, 3-, 4- and 9-hydroxyphenanthrene)……Altogether, it may be stated that the results of the measurements of 1-OHP and the sum of hydroxyphenanthrenes in the urine of PAH-exposed workers demonstrate higher exposures to PAH mainly in the production and further processing of fireproof materials and graphite electrodes as well as in coking plants and tar distillation, whereas fire damage restoration and hydraulic engineering have lower exposure to PAH. Only low level exposures were demonstrated in the latter branches of industry by determinations of both 1-hydroxypyrene and hydroxyphenanthrenes (DFG 2012).

SCOEL (2016) further notes *"…that human PAH exposure at different workplaces in various trades is always characterized by substantial differences in PAH compositions, the spectrum ranging from low-molecular representatives, such as the volatile naphthalene, to higher-molecular representatives, such as BaP and dibenzopyrenes. The latter are almost completely bound to particles. Therefore, metabolites covering a broad spectrum of exposure would be desirable. However, the proportion of PAH metabolites excreted in the urine generally decreases with an increasing molecular weight due to increasing biliary*

excretion. Taking into account the ease of urine sample collection and the well-established methods of determination, phenolic metabolites naphthalene, pyrene and phenanthrene are biomarkers that have been most widely used. Recent analytical developments now allow a specific and sensitive determination of the relatively small amounts of 3-OHBaP occurring in the urine as exposure markers for the carcinogenic BaP. Based on the data of Lafontaine et al (2004), DFG (2013) has issued the following correlation between airborne BaP exposure (8h TWA) and 3-OHBaP levels in urine (determined after hydrolysis). The sampling time is 16 h after last exposure, before following shift (Gendre et al 2002, 2004). SCOEL noted that this approach may, in future, lead to the development of a BGV for 3-OHBaP."

6.2.1 Background levels

PAH are everywhere in the environment. Tobacco smoke, smoked and grilled food, traffic exhaust, mineral oil products, domestic combustion and industrial emissions contain PAH. Background PAH levels are further described in sections 5.1 and 5.2.

DFG has compiled the available biomonitoring data (1-hydroxypyrene and hydroxyphenantrenes) in PAH-exposed and non-exposed controls (DFG, 2012, DFG, 2013). In Germany, the urinary 1-OHP has a biological agent reference value (BAR value) of 0.3 µg/g of creatinine for non-smokers (MAK). The BAR value, which is the 95th percentile value, was based on two German studies (Becker et al, 2002 and Heudorf and Angerer 2001, as cited in DFG, 2013) of non-occupationally exposed people (18-69 years old), where the number of non-smokers was 389 and 288, respectively. In Italy, the 95th percentile value for non-smoking general population (22-81 years old) was higher than the BAR value in Germany, being 0.65 µg/g creatinine. The maximum values for 1-OHP of non-occupationally exposed non-smokers in two studies from France were comparable to the BAR value in Germany, being 0.29 and 0.32 µg/g creatinine (DFG, 2013).

According the recent data collected in the HBM4EU, the range for 95 percentile values for non-smoking general population is from 0.085 – 0.74 µg/g creatinine based on data from 8 EU and 2 non-EU countries. The lowest concentration is from Iceland (sampled from 2019-2021, N=186) and the highest concentrations from Poland (sampled 2017, N=198). In Portugal and Luxemburg the 95 percentiles for non-smoking general population were 0.6 µg/g creatinine (Portugal 2019-2020, N= 186; Luxemburg 2016-2018, N=174). In Switzerland (2020, N=218) and Czech Republic (2019, N=261) the 95 percentile concentrations were 0.2 µg/g creatinine and in Croatia (2019-2020, N=209) 0.14 µg/g creatinine [7].

The urinary 1-OHP levels are about 2 to 3 times higher for smokers than for non-smokers (DGF, 2013). In the US NHANES study, 1-hydroxypyrene concentrations are about 3-fold higher in smokers compared to non-smokers (Huang et al., 2004). The geometric mean concentration for the general US population of 20 years and older was 0.025 µmol/mol creatinine (0.048 µg/g creatinine) for non-smokers, and 0.080 µmol/mol creatinine (0.15 µg/g creatinine) for smokers. The 95th percentile concentration for both non-smokers and smokers of 20 years of age or older was 0.28 µmol/mol creatinine (0.54 µg/g creatinine) (95% CI 0.23-0.34) (Huang et al., 2004). The review of Jongeneelen (2001) reported the 95th percentiles of creatinine adjusted urinary 1-OHP values for non-occupationally exposed controls, being 0.24 µmol/mol (0.46 µg/g creatinine) for non-smokers and 0.76 µmol/mol (1.47 µg/g creatinine) for smokers (Jongeneelen, 2001). Based on 20 samples, Kim et al. (2005) reported pre-exposure mean 1-OHP concentrations of 0.20 µg/g creatinine in non-smokers and 0.51 µg/g creatinine in smokers, and post-exposure values of 0.39 µg/g creatinine in non-smokers and 0.73 µg/g creatinine in smokers (Kim et al., 2005).

[7] https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/; accessed 4.10.2022

Lafontaine et al (2006) has proposed, based on their own study and taking into account the pre-shift data of occupationally exposed workers, a mean value for 3-OHBaP for non-smoker, non-occupationally exposed people of 0.014 nmol/mol creatinine (0.03 ng/g creatinine) and a mean value for smokers, non-occupationally exposed people of 0.03 nmol/mol creatinine (0.07 ng/g creatinine), with an upper limit of about 0.1 nmol/mol creatinine (0.24 ng/g creatinine). The influence of smoking to the concentration of 3-OHBaP in the urine makes the assessment of occupational exposure to low levels of BaP (<100 ng/m^3) difficult (Lafontaine et al., 2006).

Initial tests of urine samples from the general population show internal BaP exposures with tetraol-BaP in the range up to 0.1 ng/L. In about 90% of the samples examined, values above the limit of determination could be found. Occupational exposures were generally above 0.1 and up to about 4 ng/L of urine (Weiss et al., 2019).

6.2.2 Correlations between external and internal exposure

6.2.2.1 Hydroxypyrene (1-OHP)

Post-shift urinary 1-OHP and airborne BaP levels correlated well (r^2 = 0.768) when samples from workers with known use of respiratory protection and with significant dermal exposure were excluded (Unwin et al., 2006). The relationship between BaP (=x) and 1-OHP (=y) was determined to be y=11.1x + 1.13, at sites without use of respiratory protection or significant dermal exposure (**Figure 6**).

RAC (ECHA, 2018) noted that the study by Unwin et al. (2006) involved 25 sites using both airborne monitoring of 17 individual PAH and biological monitoring and set the relationship between airborne BaP and urinary 1-OHP.

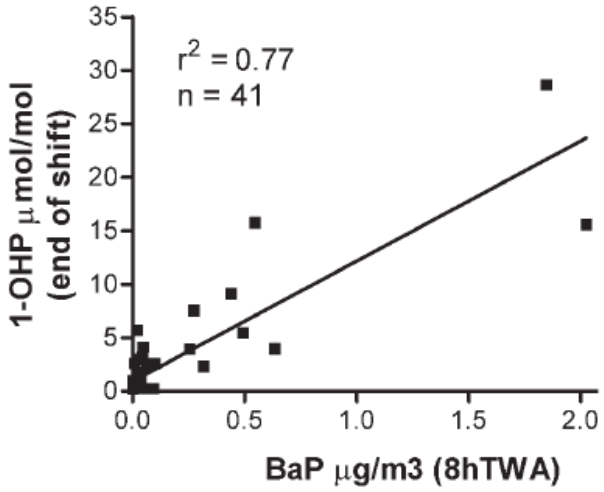


Figure 6: Relationship between BaP in air and urinary 1-OHP (y = 11.1x + 1.13) for sites without respiratory protection or significant dermal exposure (Unwin et al., 2006)

The industrial sites selected in the survey published by Unwin et al. (2006) involved PAH originating from coal tar pitch, oil and bitumen, rubber fume, foundries and wood smoke. RAC (ECHA, 2018) further noted that *"…airborne BaP correlated well (r^2 = 0.971) with levels of carcinogenic 4–6 ring PAHs and was an effective indicator of exposure for all industries where significant particle bound PAH levels were found and, in particular, for CTPV exposure. Urine samples collected from different workers at the end of shift (n= 218) and pre-shift next day (n = 213) were analysed for 1-OHP. Levels of 1-OHP in end-of-shift samples were generally higher than those in pre-shift-next-day samples and showed a good correlation (r^2 = 0.768) to airborne BaP levels if samples from workers using respiratory protection or with significant dermal exposure were excluded. Urinary 1-OHP*

in end-of-shift samples ranged from the limit of detection (0.5 µmol/mol creatinine) to 60 µmol/mol creatinine with a mean of 2.49 µmol/mol creatinine and a 90th percentile value of 6.7 µmol/mol creatinine. The highest 1-OHP levels were found in samples from workers impregnating timber with creosote where exposure was dominated by naphthalene. If the 11 samples from these workers were excluded from the dataset, the 90% value for end-of-shift urine samples was 4 µmol/mol creatinine (n = 207). Using the observed relationship between urinary 1-OHP and airborne BaP, a level of 1-OHP of 4 µmol/mol creatinine is roughly equivalent to an airborne BaP level of 0.26 µg/m^3.

Exposure levels in µg/m^3 can be back-calculated from urinary 1-OHP as follows:

$$concentration\ of\ airborne\ B[a]P = \frac{(\text{concentration}_{1-OHP}) - 1.13)}{11.1}$$

where the concentration of airborne BaP is in µg/m^3 and the concentration of urinary 1-OHP in µmol/mol creatinine.

Urinary biomonitoring data may be expressed as µg 1-OHP/g creatinine. To convert µmol 1-OHP/mol creatinine into µg 1-OHP/g creatinine, a factor of 1.93 can be used."

Table 7: Correlation between urinary 1-hydroxypyrene and airborne BaP based on the study by Unwin et al 2006

Urinary 1-OHP (µmol/mol creatinine)	Urinary 1-OHP (µg/g creatinine)	Converted BaP (µg/m^3)
100	193	8.9
10	19.3	0.80
5	9.65	0.35
2	3.86	0.078
1.13	2.18	0.000

6.2.2.2 Hydroxybenzo(a)pyrene (3-OHBaP)

The relationship between airborne BaP (=x) and urinary 3-OHBaP (=y) was determined to be y=0.001835x + 0.1729 (r=0.89) (Lafontaine et al., 2004) (**Figure 7**). Measurements were performed in various industrial areas and urinary 3-OHBaP concentrations were highest in the carbon disk industry and lowest in creosoting places. Atmospheric and biological monitoring was carried out on 38 people exposed to PAH, in different workplaces. Only workers with mainly inhalation exposure were selected for the calculations of the correlation between external and internal exposure.

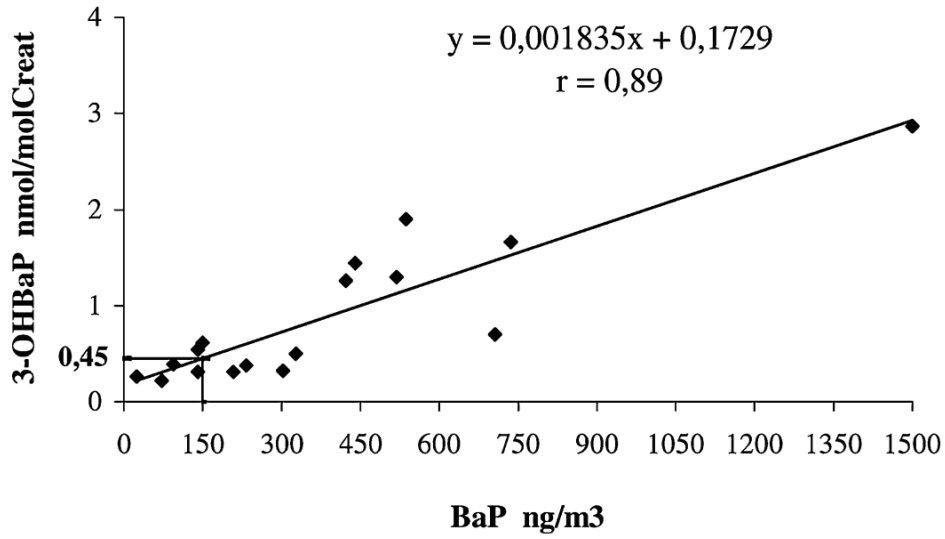


Figure 7: Relationship between atmospheric BaP and urinary 3-OHBaP (y = 0.001835x + 0.1729) (Lafontaine et al., 2004)

Exposure levels in ng/m^3 can be back-calculated from urinary 3-OHBaP as follows:

$$concentration\ of\ airborne\ B[a]P = \frac{(\text{concentration}_{3-OHBaP}) - 0.1729)}{0.001835}$$

where the concentration of airborne BaP is in ng/m^3 and the concentration of urinary 3-OHBaP in nmol/mol creatinine.

As noted by RAC (ECHA, 2018) "*… one limitation of this relationship is that it is also not accurate in the low exposure range and is not able to estimate exposure levels below urinary 3-OHBaP values below 0.1729 nmol/mol creatinine (0.41 µg/g creatinine) (below this level, the corresponding air concentration would be negative).*"

Based in the study of (Lafontaine et al., 2004), the German MAK Commission has derived 3-OHBaP in urine as an exposure equivalent (EKA) for BaP, in the air (**Table 8**).

Table 8: Correlation between airborne BaP and urinary 3-OHBaP (after hydrolysis) (DFG, 2021)

Airborne BaP (ng/m^3)	Urinary 3-OHBaP, post-shift (ng/g creatinine)	Urinary 3-OHBaP, post-shift (nmol/mol creatinine)[1]
70	0.7	0.295
350	2	0.84
700	3.5	1.5
1000	5	2.1
1500	7	2.9

[1] 1 nmol/mol creatinine = 2.372 ng/g creatinine, sampling time for biomonitoring at the beginning of the next shift

6.2.2.3 Other findings in correlations

In the study by Förster et al (2008), linear correlations between urinary 1-OHP and 3-OHBaP for workers from different work areas (converter infeed, coking plant, refractories

and graphite electrodes) were found (Förster et al., 2008). 3-OHBaP correlated well also with OH-Phens. However, airborne BaP did not correlate with urinary 3-OHBaP. This is not surprising, since very often no correlation has been found between external (inhalation) and internal (biomonitoring) exposure measurements. In this study, a poor correlation of urinary 3-OHBaP and BaP in air was explained with other exposure routes than inhalation (dermal or oral) (Förster et al 2008).

External and internal exposures are influenced by different factors. Firstly, the lack of correlation between inhalation and biomonitoring can be attributed to the fact that PAH are absorbed through the skin and dermal exposure can be even higher than exposure via inhalation. Van Rooij et al has shown that on average, 75% (range 28-95%) of the systemic exposure to pyrene occurred dermally for coke plant workers (VanRooij et al., 1993c, VanRooij et al., 1993a).

The second reason is that the PAH profile differs between different materials and processes and the ratios between different PAH can vary a lot. Reported pyrene/BaP ratios varied from 1.1 to 38 according the IARC Monograph 92. Most often the ratio ranged from 2 to 4 in mixtures used in aluminium work, electrode manufacturing and in road tars. The highest ratio of pyrene/BaP was measured in bulk creosote. In coke oven work, the ratio of pyrene and BaP is defined to be 2.5 (Jongeneelen, 2014). These differences in the PAH profile explain partly the lack of correlation between BaP and pyrene in the air and between airborne BaP and 1-OHP in urine (Hagmann et al., 2017). The ratio of pyrene and BaP in the air samples varied depending on the production plant and no correlation between 1-OHP and BaP was found in a recent study from different industrial workplaces (Kloslova et al., 2016). The pyrene/BaP ratio was 0.5 in the carbon material plant, 1.0 in the aluminium plant and 3.7 in the bitumen production and asphalting plant. The highest ratio (6.0) was in the rubber products production plant. However, 1-OHP concentrations in the post-shift urine samples correlated well with the total PAH and pyrene concentrations in the air among workers occupationally exposed to PAH in aluminium production, production of graphite electrodes, road construction and the rubber forming industry (Klöslova et al, 2016).

Valiere et al (2022) investigated consistency between air and biological monitoring for assessing PAH exposure and cancer risk of workers in a recent study which was based on French Exporisq-HAP database. In the assessment, the effectiveness of RPE was taken into account. It was found in the study that 3-OHBaP is not a relevant biomarker for low PAH exposure. The use of adjusted 1-OHP is more protective way to assess the exceedance of the current limit values than urinary -3-OHBaP and airborne BaP, but the concentration of 1-OHP should be corrected with the ratio of airborne Pyr and BaP (Valière et al., 2022).

Jongeneelen has proposed a limit value of 1 µmol/mol creatinine (1.93 µg/g creatinine) for 1-OHP in post-shift urine. The value is suggested to be the "no observed genotoxic effect level (NOGEL)", where the genotoxic endpoints are genotoxic effects in white blood cells of PAH-exposed workers (chromosomal aberrations, sister chromatid exchanges, micronuclei, DNA-adducts) (Jongeneelen, 2014). The values have been derived mainly based on studies among coke oven workers where the ratio of pyrene and BaP is defined to be 2.5.

6.2.3 Biomonitoring analytical methods

There are many potential biomarkers for PAH exposure available as described above in section 6.2. The methods for analysing urinary metabolites of pyrene and BaP are described below and in **Table 9**.

6.2.3.1 Methods for biomonitoring of 1-hydroxypyrene (and hydroxyphenanthrols)

For the metabolite of pyrene, 1-OHP, the urine sample analysis is based on the method of (Jongeneelen et al., 1988). Urinary 1-OHP should be collected at the end of the work shift

and at the end of the work week. Nowadays, the applied sample preparation includes enzymatic hydrolysis with follow-up cleaning procedures by liquid-liquid extraction, solid phase extraction, solid phase micro extraction or column switching technique. For separation, analysis and detection, high-performance liquid chromatography with fluorescent detection (HPLC/FLD); liquid chromatography with tandem mass spectrometry (LC-MS/MS); or gas chromatography with mass spectrometry (GC-MS) following derivatisation of the hydroxylated PAH metabolites can be utilized.

The limit of quantification for 1-OHP was 20 ng/l with the method based on enzymatic hydrolysis and direct analysis with HPLC/FLD (Barbeau et al., 2014). The method that uses enzymatic hydrolysis and column switching technique before analysing with HPLC/FLD, allows monitoring of hydroxylated urinary metabolites of pyrenes (1-OHP) and phenanthrenes (1-, 2-, 3- and 4- hydroxyphenanthrenes), down to a detection limit of 5 ng metabolite/L urine (Heudorf and Angerer, 2001).

6.2.3.2 Methods for biomonitoring 3-OHBaP and tetraol-BaP

The metabolite of BaP, 3-OHBaP, is quantified by using HPLC-FLD after enzymatic hydrolysis and automated solid phase extraction. The limit of quantification (LOQ) was 0.05 ng/l (Barbeau et al., 2011). Urine samples should be collected at the beginning of the shift at the end of the working week for 3-OHBaP quantification, especially in case of high exposure variability (Barbeau et al., 2015).

More sophisticated analytical methods with multiple sample preparation steps have been recently developed. A new method using GC-APLI-MS with high sensitivity has been developed for 3-OHBaP. The detailed description of the sample preparation and analytical setup has been reported by (Richter-Brockmann et al., 2019). Briefly, 10 ml of urine sample is adjusted with a sodium acetate buffer to pH 5.4. After addition of the internal standard, beta-glucuronidase/arylsulfatase (50 µl) and ascorbic acid are added and shaken at 37 °C, for 16 hours, followed by several steps of solvent extraction and sample purification. The new method allows human biomonitoring of carcinogenic PAH exposure using 3-OHBaP excreted in urine at very low levels (LOQ of 1.8 pg/l).

Another advanced analytical procedure for the more sensitive and specific determination of 3-OH-BaP in human urine has been published and validated according to the US Food and Drug Administration (FDA) guideline (Rögner et al., 2021). The method is based on enzymatic hydrolysis, solid-phase extraction, derivatisation with 2-fluoromethylpyridinium-p-toluene sulfonate, and LC-MS/MS analysis. Both the calibration reference substance and the isotope-labelled internal standards (IS) were used as glucuronide conjugates (3-OH-BaP-glucuronide, 3-OH-BaP-$^{13}C_6$-glucuronide). Using the glucuronides as standard and IS material proved to be superior to the unstable free analyte during method validation, calibration, and quality control procedures. In native urine samples, 3-OH-BaP was found to be present in its conjugated form in urine at almost 100% ; thus, instability of the analyte would not present an issue in real samples. Another advantage is that $^{13}C_6$-3-OH-BaP-Gluc also compensates for losses during enzymatic hydrolysis. The limit of quantification for the method is 50 pg/l urine. The method is suitable for the quantification of occupationally and non-occupationally exposed populations and it can differentiate smokers from non-smokers as well as from users of new generation tobacco/nicotine products. The method will soon be adopted by the working group "Analyses in Biological Materials" of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK commission) in Germany.

An alternative for 3-OHBaP is urinary trans-anti-7,8,9,10- tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene (7,8,9,10-OHBaP=Tetraol-BaP) (Barbeau et al., 2018). This method by Barbeau et al. is based on enzymatic hydrolysis involving only one step of solid phase extraction (SPE) before derivatisation and detection with GC-NICI-MS/MS. Limit of quantification (LOQ) is 0.02 ng/l urine. The best sampling time was determined to be the

post-shift at the end of week but samples should also be collected at pre-shift, in the beginning of week, for assessing background exposure levels.

IPA modified slightly the above method by Barbeau et al. The quantification after capillary gas chromatographic separation is performed on a tandem mass spectrometer with large-volume injection using isotope-labelled tetraol-BaP as the internal standard. The method has a limit of determination of 0.05 ng tetraol-BaP/l urine (Weiss et al., 2019).

The determination of 3-OHBaP and tetraol-OHBaP, based on the above analytical techniques, allows the detection of the urinary metabolite down to very low detection limits, thus capturing not only the range of occupationally exposed workers but also the general population. However, the applied analytical methodologies are very sophisticated.

Table 9: Biomonitoring methods for 1-OHP, 3-OHBaP and Tetraol-BaP

Method	Hydrolysis	Analytical method	LOD	LOQ	Reference
1-OHP (and OH-Phens)	Enzymatic hydrolysis	HPLC/FLD; LC-MS/MS; GC-MS	5 ng/l (LC-MS/MS)	20 ng/l (HPLC/FLD)	Heudorf and Angerer 2001; Barbeau et al 2014
3-OHBaP	Enzymatic hydrolysis	HPLC/FLD		0.05 ng/l	Barbeau et al 2011
3-OHBaP	Enzymatic hydrolysis	GC-APLI-MS	0.6 pg/l	1.8 pg/l	Richter-brockmann et al 2019
3-OHBaP	Enzymatic hydrolysis	LC-MS/MS	17 pg/l	50 pg/l	Rögner et al 2021
Tetraol-BaP	Enzymatic hydrolysis	GC-NICI-MS/MS		0.02 ng/l	Barbeau et al 2018
Tetraol-BaP		GC-MS	0.05 ng/l		IPA Journal 1/2019

HPLC/FLD = high performance liquid chromatography with fluorescence detection
LC-MS/MS = liquid chromatography with tandem mass spectrometry
GC-MS = chromatography with mass spectrometry
GC-APLI-MS = gas chromatography coupled to atmospheric pressure laser ionization-mass spectrometry
GC-NICI-MS/MS=gas chromatography coupled with tandem mass spectrometry with negative chemical ionization source

7. Health Effects

The focus of hazard assessment in this section is on carcinogenicity although genotoxicity and reproductive toxicity are also addressed in some detail. Non-cancer endpoints are described mostly based on reviews and existing national and international PAH assessments; this is for two reasons: first there are hundreds of individual PAH and PAH mixtures and second, for many hazard endpoints, very little specific information is available. A similar approach has been followed in existing assessments, as briefly described below.

DECOS referred to the assessments of IPCS (1998) and ATSDR (1995) and summarised as follows:

- *Human data*: Reliable health-based information on the non-carcinogenic toxicity of single PAH compounds is very limited, because in the environment, PAH occur as mixtures and not as single compounds. Although a considerable number of epidemiological studies on complex PAH mixtures have been published, the end-

point of most of these studies has been carcinogenicity. No data are available on human death and on systemic effects, such as cardiovascular, gastrointestinal, hepatic effects, dermal effects, and effects on reproduction, following inhalation exposure to PAH.

- *Animal data*: Most of the experiments have addressed the carcinogenicity of PAH. The number of studies on the non-carcinogenic short- and long-term toxicity are limited. Moreover, these studies are for a large part restricted to non-carcinogenic PAH, such as acenaphthene, anthracene, fluoranthene, fluorene, and pyrene. Furthermore, data on the non-carcinogenic effects are only available for single PAH and not for complex PAH mixtures.

AGS (2011) stated that the most significant endpoint for the effects of PAH mixtures containing BaP is their carcinogenicity. Other endpoints have rarely been studied either in humans or in laboratory animals.

SCOEL referred to the DECOS, DFG, ATSDR and IPCS documents and acknowledged the incompleteness of data on non-cancer endpoints.

7.1 Toxicokinetics (Absorption, distribution, metabolism and excretion - ADME)

The number of PAH and PAH mixtures is huge and comprehensive international and national assessments are available. The toxicokinetics of PAH are described below, only at a general level and not separately for each PAH, and without indicating for each observation/conclusion if it is based on human, animal and/or *in vitro* data. The AGS (2011) comprehensive summary of toxicokinetics is directly quoted:

Like other PAH, BaP is easily absorbed by inhalation, through the skin and the gastrointestinal tract. The Air Quality Guidelines for Europe (WHO, 2000) contain a comparison of the half-life of free and particle-bound BaP and other PAH. These half-lives were obtained using various application pathways and after various initial pulmonary doses. This basis is thus not suitable to arrive at valid conclusions concerning the elimination rate for free or particle-bound BaP.

In case of occupational exposure, dermal absorption may obviously play a considerable role. It was found in coking plant workers that 28 to 95% (75% on average) of total pyrene absorption - measured as urine excretion of 1-hydroxypyrene – had occurred through the skin. In animal studies with male Wistar rats, 50% of the pyrene applied to the skin in an acetone solution was excreted with the urine. Other studies showed that the dermal absorption route for BaP from high-viscosity oils is lower than the BaP absorption from low-viscosity oils (DECOS 2006). In vitro studies of monkey skin showed that BaP - just as benzo[a]anthracene, benzo[b]fluoranthene and benzo[k]fluoranthene - does not permeate the skin from the lubricant, but only from acetone/artificial sweat, while permeation from both liquids could be proven for other PAH (acenaphthene, anthracene, phenanthrene, fluoranthene, naphthalene, pyrene and fluorene). The in vitro BaP permeation of human skin was not reduced by using skin protection creams; in some cases it even increased (Greim, 2008).

Irrespective of the place of absorption, absorbed PAH are quickly transported by blood and lymph to other tissues and especially to tissues with high lipid content. PAH cross the placenta barrier. Tissues with high lipid content may represent a short term depot, from which PAH are released again after the exposure has ended, but an accumulation in the proper sense does not occur because of the rapid metabolism (WHO 2000). Compared to other organs, the gastrointestinal tract shows a high concentration of PAH and PAH metabolites, even though there was no oral route of exposure (Greim 2008).

The glucuronised or sulphatised phenols and dioles, which are metabolised from BaP and other PAH, are excreted with urine and with the bile contained in the faeces. In laboratory animals (rats), the excretion as mercapturic acid was also observed, after the arenoxides

formed in an initial step are conjugated with glutathione (GSH), and these GSH conjugates are converted in a later stage. The significance of this metabolic pathway and elimination route for PAH in humans is unknown (Greim 2008).

For occupationally exposed workers of a coking plant, a renal PAH elimination with a half-life of 6 to 35 hours was found, when it was measured as the excretion of 1-hydroxypyrene (DECOS 2006); for workers of an aluminium plant, the half-life of PAH elimination was 9.8 hours and therefore in the same range (Greim 2008).

BaP and other non-substituted PAH are initially metabolised by microsomal cytochrome-P450-monooxygenases. As many other PAH, BaP enhances its own oxidative metabolism by an induction of the respective P450-monooxygenases and epoxide-hydrolases. In this process, the induction of the most important enzymes (CYPIA1 and A2) is started by binding to a special cytosolic protein, the Ah-receptor, (WHO 2000). The highest biotransformative capacity is found in the liver, followed by the lung, the intestinal mucosa, the skin and the kidneys, but the corresponding enzymatic systems are found in most cells and tissues of humans and animals. Foetal cells can also metabolise PAH, albeit less quickly than the cells of adult tissue (IPCS 1998, WHO 2000). The epoxides formed in the first reactive step form isomers – depending on the place of oxidation in the molecule - at different rates, and react spontaneously to form phenols or they hydrolyse to dihydrodiols with the help of epoxide hydrolases, and they are then oxidised by mono-oxygenases and form dihydrodiol-epoxides and their derivatives. The phenolised derivatives may also react to form quinones. Resulting from the hydrolysis of the dihydrodiol-epoxides, tetrols may also be formed. The hydrolysed compounds are also esterified by glucuronyltransferases and sulphate-transferases or transformed with glutathione (see above). An oxidative metabolism of BaP-7,8-diole may also occur - at least in vitro -via prostaglandin synthase, myeloperoxidase and lipoxygenase, when diol-epoxides and tetrols are formed (IPCS 1998).

The large variety of metabolites is further increased by the occurrence of optical isomers. In the case of BaP, the main metabolic pathway runs from the initially formed BaP-7,8-dihydrodiol to BaP-7,8-dihydrodiol-9,10-epoxide (BPDE), which has four optical isomers. In most tissue, the (+)-anti-BPDE-isomer is primarily formed. This reactive metabolite has the strongest tumourigenic effect and also represents the isomer, which is most active in forming covalent DNA adducts (WHO 2000). BPDE hydrolysis to tetrolene represents a deactivating reaction. The formation of dihydrodiols, phenols and quinones was found in in vitro experiments for all analysed human tissue and cell types; in most cells and tissues, these analyses also found other metabolites such as tetrols and conjugates. The same metabolites were also found in these types of experiments using tissues of animal studies. Degradation by opening of the ring system involving a release of carbon dioxide does not play any role for higher organisms (IPCS 1998).

It should be noted that highly differentiated dermal penetration rates are exhibited among single PAH, based on their molecular weight (reviewed by (DECOS, 2006)). (VanRooij et al., 1995) investigated the dermal absorption of a series of single PAH in the blood-perfused pig ear model and showed that that lower molecular weight PAH (e.g., phenanthrene) are absorbed in larger quantities than pyrene, while higher molecular weight PAH (e.g., BaP) are absorbed in smaller quantities. In *in vitro* studies on monkey abdominal skin specimens, (Sartorelli et al., 1999) reported the penetration constant and steady-state absorption rate of pyrene to be approximately 18-fold and 28-fold higher than those of a 1.5-fold lower BaP dose, respectively, in a vehicle of acetone solution with artificial sweat. It is expected therefore that BaP and likewise high-molecular weight PAHs exhibit lower systemic bioavailability by the dermal route, compared to low molecular weight PAHs. As described in section 9.1.2.1 DECOS (2006) considered that although skin absorption of PAH occurs to significant amounts there was no clear evidence that BaP or other PAH compounds add substantially to systemic non-carcinogenic adverse health effects by dermal exposure. However, as a positive association between dermal exposures

to PAH and skin cancer was observed, by direct contact on the skin, DECOS considered that a skin notation is justified.

7.1.1 Toxicokinetic modelling

Physiologically based pharmacokinetic (PBPK) modelling is very limited for PAH in general, as it requires information on individual components to define the properties of the whole mixture and for this reason no PBPK models have been proposed for PAH. However, SCOEL (2016) reported that with a specific ecotoxicological perspective, a physiologically based toxicokinetic and toxicodynamic (PBTK-TD) model was developed for BaP in the scallop *Chlamys farreri*. Aryl hydrocarbon hydroxylase AHH activity, comet assay results, protein carbonyl measurements and lipid peroxidation data were integrated. The model predicted the BaP concentrations within each organ compartment and the effects in the digestive gland. Predicted and measured data in different organs were found in good agreement, and the comet assay was considered as the best effect biomarker (Liu et al 2014[8]).

7.1.2 Biological monitoring

Biomonitoring of PAH is described in section 6.2.

7.1.3 Summary

Both human and animal studies clearly showed that PAH is readily absorbed through inhalation, dermal and gastrointestinal routes. Although there are no human data for distribution of PAH in the body following dermal exposure, from the limited animal data that are available, it is reasonable to conclude that PAH after dermal exposure is distributed through various internal organs, including the lungs.

7.2 Acute toxicity

7.2.1 Human data

Data regarding acute toxicity of PAH in humans are scarce (SCOEL 2016). As reviewed by DFG (2012), several accidental intoxications were reported only with naphthalene. Lethal oral doses in cases of poisonings with naphthalene were specified to be 5-15 g for adults and 2 g for a 6-year-old child. Between 1949 and 1959, 10 cases of poisonings with naphthalene caused by mothballs (sucking or ingestion) were described in the United States. Some of the children were found to have haemolytic anaemia.

The signs of naphthalene ingestion became manifest after one or several days in the form of nausea, vomiting and convulsions, often followed by diarrhoea. Other symptoms included disturbances of consciousness, lethargy, incoordination, coma and hemiplegia. Haemolytic anaemia with haemoglobin concentrations of up to 40% was often followed by haemoglobinuria. More or less pronounced jaundice was also observed, and there was liver necrosis in one lethal case.

7.2.2 Animal data

Few studies are available on the acute toxicity of PAH, except for naphthalene. The main routes of exposure in the available studies are oral, intraperitoneal and dermal. In general, single doses of PAH (e.g., anthracene, BaP, naphthalene) have moderate to low toxicity (LD50 values >500 mg/kg bw after oral administration).

SCOEL (2016) and DFG (2012) reported that values specified by IPCS (1998) showed that the acute toxicity of PAH compounds is relatively low. The studies on BaP reported by IPCS, SCOEL and DFG are summarised in **Table 10** below.

[8] Reference cited by SCOEL (2016)

Table 10: Summary table of acute toxicity studies on BaP

Method, route	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference*
LD50 oral	mouse	BaP		LD50 <1600 (mg/kg b.w.)	Awogi and Sato 1989
LD50 i.p.	mouse	BaP		LD50 ~250 (mg/kg b.w.) LD50 <1600 (mg/kg b.w.)	Salamone et al. 1981 Awogi and Sato 1989
LD50 s.c.	rat	BaP		LD50 50 (mg/kg b.w.)	Montizaan et al. 1989
Single ip injection	young rats	BaP	10 mg	Inhibition of growth	Haddow et al. 1937
Single ip injection	young rats	dibenzo[a,h]anthracene	3 to 90 mg	Inhibition of growth within 2 days, lasted for up to 15 weeks	Haddow et al. 1937
Single ip injection	rats	chrysene	30 mg	No effect on growth	Haddow et al. 1937
Single ip injection	mice	BaP	dose not specified	Reduced size of the spleen, cellular depletion, haemosiderosis and follicles with large lymphocytes	Shubik and Della Porta 1957; WHO 1998

* References are taken from IPCS (1998), SCOEL (2016) and DFG (2012)

7.2.3 *In vitro* data

SCOEL (2016) reported a study (Elgjo 1968[9]) where the mitosis rate in the epidermal cells of hairless mice (hr/hr strain) was reduced after a single application of 0.05 ml of a 15% solution of BaP in acetone.

7.2.4 Summary

Acute toxicity of PAH compounds is relatively low as reported in animal studies and human data.

7.3 Specific target organ toxicity/Repeated dose toxicity

7.3.1 Human data

DECOS (2006) summarized the findings in epidemiological studies of workers exposed to PAH. For workers with PAH exposure from coal processing, there are no data on the inhalation pathway with respect to non-carcinogenic systemic effects of the cardiovascular system, the gastrointestinal tract, the liver, the skin and reproduction. In a study of workers in a rubber plant, an impairment of pulmonary function was reported with abnormal X-rays of the chest cavity and coughing, pharyngeal irritation and chest pains. The BaP concentration stated in this study was only 0.1 µg/m³. But it is not known whether the effects described were caused by PAH or other, simultaneously present toxic chemicals or suspended particulate matters (Gupta et al., 1993).

[9] Reference cited by SCOEL (2016) and DFG (2012)

Workers at coking ovens showed a reduced immunoglobulin level in the serum and various reduced immune functions, but the biological significance of these changes is unclear (Lei (1993), Szczeklik et al. (1994)).

DECOS (2006) also referred to a new cohort study that examined the mortality from ischaemic heart disease in 12 000 male workers from five countries, employed in asphalt processing since 1953 (Burstyn et al., 2005). The amount of the BaP exposure was examined with database models, the exposure to coal was calculated in a semi-quantitative assessment based on company data. The average exposure to BAP showed a positive correlation to the mortality induced by ischaemic heart disease (significant positive trend across all five exposure categories).

For an average BaP concentration ≥ 273 ng/m³ (group with the highest exposure), the RR was 1.64 (95% CI 1.13 – 2.38); in the lower exposure categories, the RR was >1, but the increase was not significant. There were similar results with respect to cumulative BaP exposure and with respect to the exposure to coal tar. Even taking into account potential realistic influences resulting from smoking behaviour, it was estimated that the risk of ischaemic heart disease is increased by approximately 20 to 40% in the highest exposure category. With respect to other factors (diet, physical activity, body-mass-index) and the exposure to other noxious agents, especially diesel motor emissions and fine dust, there were insufficient data so that these potential factors could not be taken into account in the analysis.

More recently Mallah et al. (2021) reviewed the studies on PAH exposure and risk of cardiovascular disease. Twenty studies were identified, having assessed the effect of PAH exposure on either risk of cardiovascular diseases like atherosclerotic cardiovascular disease and blood pressure, or on levels of known risk factors of cardiovascular disease like obesity or serum cholesterol levels. Although positive associations were observed, the results were not consistent. Furthermore, the risks were not associated to quantitative levels of airborne concentrations of specific PAH, but either on semiquantitative metrics or on a variety of generic biomarkers of PAH exposure.

Sjogren et al. (2020) reviewed the literature concerning occupational chemical exposures and cardiovascular disease. For BaP they identified the study of Friesen et al. (2010) which analysed ischaemic heart disease morality among 6000 Canadian aluminium smelter workers and found a statistically significantly increased risk in the highest exposure category (≥ 66.7 µg/m^3 BaP-years, calculated with a 5-year lag). Sjogren et al. (2020) estimated an average exposure of 111 µg/m^3 BaP-years in this open ended exposure category, which corresponds to 2.78 µg/m^3 BaP assuming a 40-year career. It is noted that Friesen et al. (2010) adjusted for potential confounding by smoking, calendar year, employment status and time since first employed, but not for any occupational co-exposures.

7.3.2 Animal data

There are a number of animal studies although almost all of the repeat dose studies reported were designed to assess the carcinogenic potency of PAH. SCOEL (2016), DFG (2012), EPA (2017) and IPCS (1998) reported several studies by inhalation, oral and dermal routes for BaP and these are summarised in **Table 11**. Subacute and sub-chronic toxicity of various PAH compounds were mainly described in animals that were exposed by gavage.

Table 11: Summary table of repeat dose studies on BaP [IPCS (1998), SCOEL (2016), DFG (2012), EPA (2017)]

Method, route	Species, strain, sex	Dose levels duration of exposure	Results	Reference*
Inhalation	Male Syrian	9.8 or 44.8 mg/m^3	No neoplasms were observed	Thyssen et al.

Method, route	Species, strain, sex	Dose levels duration of exposure	Results	Reference*
	golden hamsters	4.5 hours daily on 5 days per week for 16 weeks	in the respiratory tract	1980
Inhalation	Fischer 344/Crl rats	7.7 mg bBaP dust/m^3 2 hours per day on 5 days per week for 4 weeks	Lung lavage, clearance of radioactively labelled particles and histopathological examinations revealed no lesions of the respiratory tract	Wolff et al. 1989
Feeding study-diet enriched by BaP	Rats	1.1 g/kg for 100 days	Inhibited growth	White & White 1939
Oral admin	DBA/2N mice (poor-affinity to Ah receptor) C57 Bl/6N mice (high affinity)	120 mg/kg bw; daily; 1-4 weeks 120 mg/kg bw; daily; 6 months	Death due to myelotoxicity No myelotoxicity	Legraverend et al., 1983
Oral	rats	50 or 150 mg for 4 days	NOAEL 150 mg/kg bw /day. Reduced carboxylase activity was found in the intestinal mucosa	Nousiainen et al. 1984
Oral gavage	Wistar rats 10/sex/ dose	0, 3, 10, or 30 mg/kg/d; 5 d/wk; 90 d 0, 1.5, 5, 15, or 50 mg/kg/d; 5 d/wk ; 35 d	↑ liver weight Liver histopathology: no effects reported ↑ liver weight Liver histopathology: no effects reported. Kidney weight: no change (data not reported)	Kroese et al (2001)
Oral in diet	F344 rats, 20/sex/ dose	0, 5, 50, or 100 mg/kg/d 90 d	↑ liver: body weight ratio Females: no change (numerical data not reported) Males (% change from control): 23% change reported at 100 mg/kg/d (numerical data not reported) ↑ abnormal tubular casts Females: not statistically significant (numerical data not reported) Males: apparent dose-dependent increase (numerical data not reported)	Knuckles et al (2001)
Oral gavage	Wistar rats, 8 males/dose	0, 3, 10, 30, or 90 mg/kg/d; 5 d/wk; 35 d	↑ liver weight ↑ liver oval cell hyperplasia (numerical data not reported) reported as significant at 90	De Jong et al (1999)

Method, route	Species, strain, sex	Dose levels duration of exposure	Results	Reference*
			mg/kg/d ↓ kidney weight	
Oral in diet	C57BL/6J mice male	0 or 12.5 mg/kg-d in diet	"Modest" increase in atherosclerotic lesions were seen in the aorta (numerical data not reported)	Uno et al (2014)
Dermal,	mouse		the binding of BaP to DNA and proteins was found 15 to 20 times higher if acetone was used as a vehicle instead of a low-viscosity oil	Ingram and Phillips 1993
Dermal-neck area Dermal absorption and excretion	mouse	1.25 to 125 µg/cm^2	6% and 40% of the amount applied were no longer detected within 1 hour and 24 hours After 7 days, 7% was still detected at the application site excreted via the hepatobiliary system and in the faeces, i.e., 35% after 24 hours, 58% after 48 hours and 80% after 7 days 10% of the radioactivity was found in the urine absorption showed a saturation effect at >15 µg/cm^2: this was regarded as evidence of an increased risk of tumour induction in the epithelium of the skin	Sanders et al. 1986

* References are taken from IPCS (1998), EPA (2017), SCOEL (2016) and DFG (2012).

Summary of effects observed

EPA (2017) reported that there is some evidence that BaP can produce non-cancer effects in the liver, kidney, cardiovascular system, and nervous system in animals.

Liver effects other than cancer, associated with BaP exposure primarily include changes in liver weight, which provide some evidence of the liver as a target for BaP exposure; however, these changes in liver weight do not appear to be substantially supported by histological findings or other indicators of hepatoxicity.

There is minimal evidence of kidney toxicity following exposure to BaP, but overall the studies are so few, conclusions on kidney toxicity cannot be drawn.

Several studies of cardiovascular effects in populations highly exposed to BaP, as a component of complex PAH mixtures are available; however, it is difficult to attribute effects of these exposures to any one component of the mixture. Very limited information is available that evaluates the potential cardiovascular toxicity from subchronic or chronic exposure to BaP in animal models, but overall, the available studies provide suggestive evidence of cardiovascular toxicity. There are no chronic exposure studies in animal models that evaluate nervous system effects.

7.3.3 *In vitro* data

DFG (2012) reported an *in vitro* study of the dermal penetration of BaP or pyrene in guinea pigs which showed that pyrene mainly diffuses passively, whereas BaP undergoes biotransformation during absorption and 7,8,9,10-tetrol is found as a metabolite in the receptor fluid of the diffusion cells (Ng et al. 1992[10]). Both the parent substance and a wide spectrum of metabolites were found in the receptor fluid in *in vitro* studies with skin samples from mice, rats, rabbits, guinea pigs, marmosets and humans that had been treated with BaP (Kao et al. 1985[11])

7.3.4 Summary

There is some evidence that BaP can produce effects in the liver, kidney, cardiovascular system, and nervous system but overall this is less robust evidence than that for other endpoints and conclusions cannot be drawn.

7.4 Irritancy and corrosivity

7.4.1 Human data

Data regarding irritation effects of PAH in humans are scarce. As reviewed by DFG (2012), skin contact with small amounts of naphthalene (wearing clothes that had been treated with mothballs) induced irritation up to severe dermatitis (Gerarde, 1960). Contact with clothes that were exposed to mothballs may cause severe erythema. Workers had inflammation of the skin on the hands, arms, legs and lower abdomen after contact with mineral oil containing 1% to 1.5% naphthalene or developed dermatitis after skin contact with naphthalene. Eye irritation was found at airborne naphthalene concentrations of 15 ml/m^3 and above (Grant, 1986).

Healing occurred in a man with exfoliative dermatitis after all contact with naphthalene had been eliminated (Fanburg, 1940). Cases of haemolytic anaemia were observed in newborn whose nappies had previously been stored together with mothballs (Anziulewicz et al., 1959). Repeated exposure to naphthalene vapours or naphthalene dust led to ulceration of the cornea, lenticular opacity and cataracts (Sandmeyer, 1981).

SCOEL (2016) also referred to observations made when mixtures of PAH had been used to treat some skin disorders in humans. Regressive verrucae (i.e., warts) was reported following up to 120 dermal applications of 1% BaP in benzene to human skin, over 4 months (Cottini and Mazzone, 1939). Although reversible and apparently benign, the changes were thought to represent neoplastic proliferation. Adverse dermal effects have been noted in humans following intermediate-duration dermal exposure to BaP in patients with the pre-existing dermal conditions of pemphigus vulgaris (acute or chronic disease characterized by occurrence of successive crops of blisters) and xeroderma pigmentosum (a rare disease of the skin marked by disseminated pigment discolourations, ulcers, and cutaneous and muscular atrophy) (Cottini and Mazzone 1939). A 1% BaP solution topically applied to patients with pemphigus resulted in local bullous eruptions characteristic of the disease. Patients with xeroderma pigmentosum exposed to 1% BaP slightly longer than the pemphigus patients exhibited only pigmentary and slight verrucous effects. Similarly treated patients with pre-existing active skin lesions due to squamous cell cancer showed a general improvement and/or retardation of the lesion. The severity of abnormal skin lesions appeared to be related to age; those in the lowest age range exhibited fewer and less-severe effects than those in the mid-range groups. No such age relationship of effects involving those patients with normal or pre-existing skin lesions was noted.

[10] Reference cited by DFG (2012)
[11] Reference cited by DFG (2012)

7.4.2 Animal data

7.4.2.1 Skin

The adverse dermatological effects observed in animals after acute and subchronic dermal exposure to PAH included destruction of sebaceous glands, dermal ulceration, hyperplasia, hyperkeratosis, and alterations in epidermal cell growth.

The sebaceous gland index is used to compare the number of active sebaceous glands in the skin of animals treated with a carcinogenic substance with the number of active sebaceous glands in the skin of animals treated with a non-carcinogenic substance. Index 3 means complete destruction of the sebaceous glands after application of the carcinogenic substance; index 2 refers to degeneration of more than half and index 1 to less than half of the sebaceous glands. Index 0 describes the intact skin (Smith 1956, Suntzeff et al. 1955). Studies are summarised in **Table 12**

Table 12: Summary table of dermal irritation studies on BaP

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference*
Daily dose for 3 days to skin	Swiss mouse	BaP	0.1% 0.2%	destroyed sebaceous glands <half; destroyed > 50%	Suntzeff et al 1955
Dermal irritancy index	Mouse	BaP		Sebaceous gland indices > 1	Bock and Mund 1958
Dermal irritancy - Irritant Dose 50	Mouse ear	BaP	24 hrs	Id_{50} = 5.6 x 10^{-5} mmol	Brune et al 1978
Dermal application	female SENCAR mice	dibenzo[a,l]pyrene; dibenzo[a,l]pyrene-11,12-dihydrodiol	Single doses of 6.25 to 200 nmol	erythema 5 to 6 days after treatment	Casale et al. 1997

* References are taken from IPCS (1998), SCOEL (2016) and DFG (2012)

7.4.2.2 Eyes

A single dose of 100 mg naphthalene had a slightly irritant effect on the rabbit eye (Sax and Lewis 1984[12]).

7.4.3 *In vitro* data

No relevant data identified.

7.4.4 Summary

Mixtures of carcinogenic PAH cause skin disorders in humans and animals; however, specific effects in humans of individual PAH, except for BaP, have not been reported. There is old literature that reports local dermal effects of PAH mixtures (ATSDR 1995). Adverse dermatological effects are observed in animals after acute and sub-chronic dermal exposure to PAH and a sebaceous index of 1 has been reported indicating the destruction

[12] Reference cited by SCOEL (2016) and DFG (2012)

of less than half of the sebaceous glands by carcinogenic substances. It is also reported to be a slight eye irritant.

7.5 Sensitisation

7.5.1 Human data

7.5.1.1 Respiratory sensitisation

There are no human data on respiratory sensitisation of PAH.

7.5.1.2 Skin sensitisation

Data regarding skin sensitisation effects of PAH in humans are scarce. As reviewed by DFG (2012), anthracene increases the sensitivity of the skin to sunlight (Gerarde, 1960). A positive reaction to naphthalene was observed in the patch test carried out in a 43 year-old patient who suffered from acute recurrent dermatitis (Wagner and Wezel, 1966). One of 598 patients who were examined because of dermatoses reacted to naphthalene in the patch test. A frequency of 0.13% is specified for allergy to naphthalene (Kaschka and Vossmann, 1994).

7.5.2 Animal data

7.5.2.1 Respiratory sensitisation

There are no animal data on respiratory sensitisation of PAH.

7.5.2.2 Skin sensitisation

SCOEL (2016) and DFG (20112) both reported positive skin sensitisation effects from several studies as summarised in **Table 13**, below.

Table 13: Summary table of skin sensitisation studies on BaP (IPCS 1998)

Method, guideline, deviations if any	Species, strain, sex, no/group	Dose levels duration of exposure	Results	Reference*
Single injection & two to three weeks later were tested for contact sensitivity	guinea-pigs 4 adult females	250 µg in Freund's adjuvant: Challenge with solutions of 0.001, 0.01, 0.1 BaP or 1% BaP in acetone and olive oil	After 24 h, a slight to severe (0.001-1%) contact hypersensitivity was observed	Old et al., 1963
LLNA Epicutaneous administration into the abdominal skin - 5 days later apply to dorsal aspect of the ear	C3H mice	100 µg BaP in 0.1% acetone solution Challenge: 20 µg BaP	The response was quantified by ear thickness, which reached a maximum three to five days after challenge. The LOAEL for allergic contact sensitivity was thus 120 µg	Klemme et al., 1987
LLNA 3H-thymidine was injected into the animals and lymphocyte	mouse	0.5, 1.0 and 2.5% BaP in acetone/olive oil. Admin to for 3 consecutive days; Challenge after 5 days	Positive result: determined to be sensitising	Ashby et al. (1995)

Method, guideline, deviations if any	Species, strain, sex, no/group	Dose levels duration of exposure	Results	Reference*
proliferation as compared with the control animals was determined				

* References are taken from IPCS (1998)

7.5.3 *In vitro* data

No *in vitro* data identified.

7.5.4 Summary

SCOEL (2016) and DFG (20112) both reported positive skin sensitisation effects in humans and animals for certain PAH and these can be considered to be causing skin sensitisation. However, data are not comprehensively available for various types of PAH.

7.6 Genotoxicity

Genotoxicity of some single PAH is summarised below.

RAC summarised the genotoxicity conclusions of various international assessments as regards the eight PAH included in entry 50 of Annex XVII of REACH (ECHA, 2019b) (see **Table 14**, below). RAC also noted that metabolic activation is seen as a prerequisite for the carcinogenic potential of these PAH.

As mentioned in section 8.1.1 (see **Table 17**, section 8.1.1) DECOS (2006) referred to the study of Collins et al. (1991) comparing the carcinogenicity and genotoxicity of a number of PAH in comparison to BaP. According to this comparison, BaP is the most potent genotoxicant of the PAH assessed in that study.

Table 14: Mutagenicity of certain polycyclic aromatic hydrocarbons: overall overview of regulatory evaluations (ECHA, 2019b)

Chemical (CAS RN)	Mutagenicity EC 1272/2008	WHO/IPCS (1998)	EC (2002)	FAO/WHO (2006)
Benzo[a]pyrene (50-32-8)	Muta. 1B (H340)	Genotoxic	Genotoxic (positive results in vitro and in vivo for multiple end-points; positive also at germ cell level)	Genotoxic, both *in vitro* and *in vivo*
Benzo[e]pyrene (192-97-2)	no	Genotoxic	Equivocal (mixed results in vitro, inconsistent results in vivo)	-
Benzo[a]anthracene (56-55-3)	no	Genotoxic	Genotoxic (positive results in vitro and in vivo for multiple end-points; positive also at germ cell level)	Genotoxic, both *in vitro* and *in vivo*
Dibenzo[a,h]anthracene (53-70-3)	no	Genotoxic	Genotoxic (positive results in assays in vitro and in vivo for multiple end-points)	Genotoxic, both *in vitro* and *in vivo*
Benzo[b]fluoranthene (205-99-2)	no	Genotoxic	Genotoxic (positive results in assays in vitro and in vivo for different end-points)	Genotoxic, both *in vitro* and *in vivo*
Benzo[j]fluoranthene (205-82-3)	no	Genotoxic	Genotoxic (positive results in assays in vitro and for DNA binding in vivo)	Genotoxic, both *in vitro* and *in vivo*
Benzo[k]fluoranthene (207-08-9)	no	Genotoxic	Genotoxic (positive results in assays in vitro and for DNA binding in vivo)	Genotoxic, both *in vitro* and *in vivo*
Chrysene (218-01-9)	Muta. 2 (H341)	Genotoxic	Genotoxic (positive results in vitro and in vivo for multiple end-points; positive also at germ cell level)	Genotoxic, both *in vitro* and *in vivo*

7.6.1 Human data

DFG (2012) summarised the human data as follows: genotoxic effects induced by PAH were found in human cells *in vitro* and *in vivo* (Glatt, 2005).

SCOEL (2016) noted the following studies. Urine samples from some non-smoking psoriasis patients treated with coal tar and UV light were mutagenic in *S. typhimurium* TA98 in the presence of an Aroclor 1254-induced rat liver metabolic system (Wheeler et al., 1981). The urine of all 15 non-smoking patients who were treated with a 2% coal tar ointment and who had avoided a high-temperature cooked meat diet was mutagenic in *S. typhimurium* YG1024 with exogenous metabolic activation. GSTM1-0/0 patients had higher levels of mutagens in their urine than GSTM1-positive patients (Gabbani et al., 1999). The skin and white blood cells (monocytes, lymphocytes and granulocytes) of a group of eczema patients treated topically with coal tar ointments showed the presence of aromatic DNA adducts by ^{32}P-postlabelling (Godschalk et al., 1998). Analysis of benzo[a]pyrene-7,8-diol-9,10-oxide–DNA adduct levels by an HPLC/fluorescence method in a group of 26 psoriasis patients showed that the percentage of subjects with adduct levels that exceeded the 95th percentile of the control value was not significant (Pavanello et al., 1999). The white blood cells of 23 psoriasis patients who were undergoing clinical coal tar therapy were examined for benzo[a]pyrene-7,8-diol-9,10-oxide–DNA adducts by an enzyme-linked immunosorbent (ELISA) method. Although these adducts were detected and their levels decreased with time after treatment, no relationship could be ascertained between the level of exposure and the amount of adducts. Also, no difference in the level of DNA adducts was found between smoking and non-smoking patients (Paleologo et al., 1992). PAH diol epoxide–DNA adducts and GSTM1 genotype in the white blood cells of 57 psoriasis patients and 53 controls were determined by ELISA methods and polymerase chain reaction, respectively. PAH diol epoxide–DNA adducts were slightly elevated in patients compared with controls, but there was no relationship between the presence of the GSTM1 gene and DNA adducts (Santella et al., 1995). Skin biopsy samples from 12 psoriasis patients who received therapy with coal tar ointment, contained aromatic DNA adducts as measured by ^{32}P-postlabelling analysis (Schoket et al., 1990). No significant effect of coal tar treatment of psoriasis patients on the levels of benzo[a]pyrene-7,8-diol-9,10-oxide–DNA adducts was detected by ^{32}P-postlabelling analysis in peripheral blood lymphocytes (Pavanello and Levis, 1994). In a study of 111 Korean coal tar-based paint workers, the levels of aromatic DNA adducts measured by ^{32}P-postlabelling analysis were slightly higher than those of 27 on-site control workers (Lee et al., 2003). The lymphocytes of 49 coal-tar workers exhibited a significant increase in the frequency of chromosomal aberrations, sister chromatid exchange and satellite associations compared with controls (Yadav and Seth, 1998). Increased levels of p53 were found in skin biopsies of atopic eczema patients treated topically with coal tar. A correlation was also observed between p53 and levels of aromatic DNA adducts measured in the same tissue by ^{32}P-postlabelling analysis (Godschalk et al., 2001).

7.6.2 Animal data (*in vivo*)

SCOEL (2016) reported that extensive summaries of the animal *in vivo* genotoxicity data are available from IPCS (1998) and DFG (2012) and tabulated summaries of the test data can be referenced in these reports.

Database[13]

Studies were made on a number of PAH including: benzo[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[b]naphtho-[2,1-d]thiophene (not listed in WHO 1998), BaP, chrysene, dibenzo[a,h]anthracene, dibenzo[a,e]pyrene, indeno[1,2,3-cd]pyrene, naphthalene, phenanthrene and pyrene.

Study data for *in vivo* studies are tabulated by DFG (2012) in Annex 1 in Tables A10 & A11, based on Tables 88 & 87 in IPCS (1998):

Tables A10 & A11 in DFG (2012)

- A10 Chromosomal effects of PAH in mammalian cell systems *in vivo* including DNA binding and adducts, as well as sperm abnormalities (IPCS 1998)
- A11 Effect of PAH on morphological transformation of mammalian cells *in vivo*

Tables 87 & 88 in IPCS (1998)

- Table 87: Chromosomal effects of polycyclic aromatic hydrocarbons in mammalian cell systems *in vivo*, including DNA binding and adducts and sperm abnormalities
- Table 88: Effects of polycyclic aromatic hydrocarbons on morphological transformation of mammalian cells *in vivo*

Results

SCOEL (2016) and DFG (2012) reported on the extensive summaries as follows: possible chromosomal effects of PAH in mammalian cell systems *in vivo*, including DNA binding, adduct as well as sperm abnormality studies; evidence of DNA adducts or DNA binding was provided for all compounds listed by IPCS (1998) except pyrene; BaP and trans benzo[a]pyrene-4,5-diol led to damage to the DNA in C3H10T1/2 cells; no stable DNA adducts were demonstrated in cells treated with trans-benzo[a]pyrene-4,5-diol (Nesnow et al 2002) and sister chromatid exchanges (SCE) were induced after administration of benzo[a]anthracene, benzo[b]fluoranthene, BaP, chrysene, dibenzo[a,h]anthracene and phenanthrene, but not after administration of pyrene.

Studies of the *in vivo* genotoxicity of naphthalene showed no increase in unscheduled DNA synthesis in rat hepatocytes. Although benzo[a]anthracene increased the number of chromosome aberrations in the bone marrow of hamsters and the oocytes of mice, it failed to do so in the bone marrow of rats and hamsters in a different study. Both negative and positive findings are available for BaP. Benzo[b]fluoranthene, dibenzo[a,h]anthracene and phenanthrene induced no increase in chromosome aberrations *in vivo*. No increased number of chromosome aberrations was found in bone marrow cells or spermatogonia of Chinese hamsters, whereas a weak increase of chromosome aberrations was observed in the oocytes of mice (Basler et al 1977).

An elevated number of micronuclei was detected in rat bone marrow cells and spleen cells after administration of benzo[a]anthracene, in mouse bone marrow after administration of benzo[b]fluoranthene and benzo[b]naphtho[2,1-d]thiophene, and in the lungs, blood lymphocytes and bone marrow of rats and in the mouse skin after administration of dibenzo[a,h]anthracene. Chrysene induced both a positive (Nishikawa et al 2005) and a negative finding (He and Baker 1991) in the micronucleus test in keratinocytes. For the induction of micronuclei, numerous positive findings in various tissues of mice, rats and Chinese hamsters and negative findings in mice and hamsters are available for BaP. No increase in the number of micronuclei was caused by naphthalene, phenanthrene or pyrene. BaP induced dominant lethal mutations.

Evidence of DNA adducts was provided in the lung cells of the mouse strain A/J after administration of cyclopenta[c,d]pyrene by means of ^{32}P-labelling (Nelson et al 2002).

[13] References cited by IPCS (1998), SCOEL (2016) and DFG (2012)

7.6.3 *In vitro* data

SCOEL (2016) reported that extensive summaries of the animal *in vitro* genotoxicity data are available from IPCS (1998) and DFG (2012) and tabulated summaries of the test data can be referenced.

Database[14]

Studies were made on a number of PAH including: anthanthrene, benzo[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[b]naphtho[2,1-d]thiophene, BaP, chrysene, cyclopenta[cd]pyrene, dibenzo[a,h]anthracene, dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,l]pyrene, indeno[l,2,3-cd]pyrene, naphthalene, phenanthrene and pyrene.

The purity of the test substances and details of the test conditions were not listed because of the great deal of available data. Differences in the S9 fractions with regard to the age, sex and strain of the rats used for this purpose and the use of different enzyme inducers might have had a considerable impact on the established results and might also explain discrepancies.

Study data for *in vitro* studies are tabulated by DFG (2012) in Annex 1 in Tables A7-A9, based on Tables 81-86 in IPCS (1998):

Tables A7-A9 in DFG (2012)

- A7 Mutagenicity of PAH in *Salmonella* (IPCS 1998
- A8 DNA damage induced by PAH in eukaryotes (IPCS 1998)
- A9 Effect of PAH in *Drosophila melanogaster* (IPCS 1998)

Tables 81-86 in IPCS (1998)

- Table 81 Mutagenicity of polycyclic aromatic hydrocarbons to *Salmonella typhimurium*
- Table 82 DNA damage induced by polycyclic aromatic hydrocarbons *in vitro*
- Table 83 Mutagenicity of polycyclic aromatic hydrocarbons in yeasts and other eukaryotes, host-mediated mutagenicity, and mutagenicity in *Drosophila*
- Table 84 Mutagenicity of polycyclic aromatic hydrocarbons in mammalian cells *in vitro*
- Table 85 Chromosomal effects of polycyclic aromatic hydrocarbons in mammalian cells *in vitro*
- Table 86 Morphological transformation of mammalian cell *in vitro* by polycyclic aromatic hydrocarbons

Results

SCOEL and DFG reported on the extensive summaries as follows: no DNA damage was detected for chrysene, phenanthrene or pyrene (with one exception); evidence of induction of DNA damage was provided for all other compounds; and in mouse embryos naphthalene an elevated incidence of chromosome aberrations *in vitro*, only with S9 mix.

A significantly increased number of CREST-negative micronuclei was found in the micronucleus test. Naphthalene caused a significant increase of superoxide anions and hydroxyl radicals in J774A.1 macrophages and an increase of DNA fragmentation. DNA adducts of dibenzo[a,l]pyrene were detected in C3H10T1/2 cells by means of TLC/HPLC and ^{32}P-labelling (Nesnow et al 1997).

Evidence of DNA adducts was provided in C3H10T1/2CL8 cells after administration of cyclopenta[c,d]pyrene by means of ^{32}P-labelling (Nelson et al 2002). DNA adducts were also recorded in a study of the metabolism of dibenzo[a,h]anthracene in C3H10T1/2 cells. It was possible to detect DNA adducts of the parent substance and some possible

[14] References cited by IPCS (1998), SCOEL (2016) and DFG (2012)

intermediate compounds via ^{32}P-labelling (Nesnow et al. 1994). Following exposure of C3H10T1/2 cells to ^{3}H-dihydroxyepoxy-tetrahydrobenzo[a]pyrene and ^{3}H- benzo[a]-pyrene, it was demonstrated after processing of the lysate that the major fraction of adducts is contained in mitochondrial DNA rather than in nuclear DNA (Backer and Weinstein 1982).

As an example for studies on a complex mixture (Billet et al 2008), the metabolic activation of PAH within PM2.5 and PAH-DNA bulky stable adduct patterns in human alveolar macrophage and/or human lung epithelial L132 cells, in mono- and cocultures were studied. In the coculture system, only human AM were exposed to air pollution PM2.5, unlike L132 cells. Particles, inorganic fraction and positive controls [i.e., TiO2, thermally desorbed PM and BaP, respectively] were included in the experimental design. Cytochrome P450 (CYP) 1A1 gene expression, CYP1A1 catalytic activity and PAH–DNA bulky stable adducts were studied after 24, 48 and/or 72 h. Relatively low doses of PAH within PM2.5 induced CYP1A1 gene expression and CYP1A1 catalytic activity in human alveolar macrophages and, thereafter, PAH–DNA bulky stable adduct formation. Adduct spots in PM2.5-exposed human AM were higher than those in desorbed PM-exposed ones, thereby showing the incomplete removal of PAH by thermal desorption. PAH within air pollution PM2.5 induced CYP1A1 gene expression but not CYP1A1 catalytic activity in L132 cells. However, despite the absence of PAH-DNA bulky stable adduct in L132 cells from human alveolar macrophage/L132 cell cocultures exposed to desorbed PM2.5 or PM2.5, reliable quantifiable PAH-DNA bulky stable adducts were observed in L132 cells from human alveolar macrophage/L132 cell coculture exposed to BaP. These data were interpreted to highlight the genotoxicity of highly reactive BaP-derived metabolites produced within human alveolar macrophages and lung epithelial cells (Abbas et al 2011).

7.6.4 Summary

BaP is classified as a Muta. 1B. It has been extensively studied in various *in vitro* and *in vivo* mutagenicity tests. It scored positive in many endpoints, such as: bacterial DNA repair and mutation; mutations in *Drosophila melanogaster*; DNA binding in various species; DNA repair; sister chromatid exchange; chromosomal aberration; point mutation; transformation in mammalian cells *in vitro*; *in vivo* sperm abnormalities; and *in vivo* somatic mutations at specific loci.

Regarding other PAH, IPCS (1998) reported that anthracene, fluorene and naphthalene were inactive in various short-term mutagenicity tests and inconsistent results were found for phenanthrene and pyrene. In addition, data on acenaphene, acenaphthylene, benzo[a]fluorene, and coronene were inadequate. Other PAH were positive or showed a tendency for mutagenic activity.

7.7 Carcinogenicity

7.7.1 Human data

Exposure to PAH mixtures in various occupational settings has been consistently linked to increased risk of cancer at site of contact, lung and skin. Some studies have also observed increased risks of bladder cancer. For this cancer site, the findings have not been consistent and have concerned only certain occupational settings, raising the possibility of confounding by established occupational bladder cancer carcinogens that have occurred in these settings. These aspects are discussed more in detail.

ATSDR (1995) reviewed data on 17 individual PAH substances and concluded that no human cancer studies were available following inhalation exposure to any of these. ATSDR further concluded that while epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to various PAH mixtures, it was impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens.

Later on, data has been published assessing the available human epidemiological cancer database and producing cancer risk estimates by level of BaP in workplace air (Armstrong et al. 2003 and 2004). No epidemiological studies were identified having assessed cancer risk by level of any other individual indicator PAH in workplace air.

7.7.1.1 Lung cancer

In the report to Health and Safety Executive, Armstrong et al. (2003) reviewed the literature and performed a meta-analysis to obtain estimates of the relationship of PAH exposure with lung cancer. The study was also published in a scientific journal (Armstrong et al., 2004). There were 39 cohorts identified that could be used to estimate unit relative risk (URR) of lung cancer by cumulative exposure to PAH. The cohorts from various industries, included exposure from nine occupational settings, coke ovens, coal gas production, aluminum smelting, carbon anode plants, asphalt work, tar distillation, chimney sweeping, thermoelectric plant and carbon black industries. The overall mean URR for lung cancer was 1.20 (95% CI, 1.11-1.29, $p<0.001$) for cumulative exposure of 100 µg/m^3 BaP years. As pointed out by DECOS (2006) none of the cohorts dominated the estimate. In addition, it was little changed after removal of less precise cohorts. The above-mentioned URR by Armstrong et al. (2003, 2004) was based on a log-linear model. However, it was reported that at moderate to low relative risks, log-linear interpolation was close to linear interpolation. Furthermore, meta-regression analysis revealed that the URRs for coke ovens, gas works and aluminium production were consistent and relatively precisely estimated (combined URR 1.17; 95% CI 1.12-1.22), whereas mean URRs for other industries (e.g., chimney sweeps, asphalt, carbon black) were rather imprecise. After allowing for differences across industries by including industry in the meta-regression analysis, no difference more than could be explained by chance ($p > 0.20$) was found when studies were grouped according to several heterogenic factors (e.g., source of exposure, smoking habits, study design, duration, dust exposure). It is noted that although not explicitly mentioned, the exposure data used by Armstrong et al. (2003, 2004) refers to (total) inhalable fraction of particles. Among the 39 cohorts exposures to PAHs measured as BaP had been measured in 10 cohorts, while in 6 cohorts a proxy measure (benzene soluble matter, total PAH, carbon black) had been measured and could be converted to BaP. In 23 cohorts no exposure measures were available but could be estimated by Armstrong et al. (2003, 2004) for each worker group based on published estimates in the same industries. Armstrong et al. (2003, 2004) performed sensitivity analyses calculating the lung cancer URR separately for those cohorts where BaP, proxy or no exposure estimates were provided in the original study. There was no statistically significant difference between those URRs ($p > 0.20$).

Since the Armstrong et al. (2003, 2004) studies, IARC (2012) updated the carcinogenicity assessments of some PAH related processes/substances. When human data was considered to indicate sufficient evidence of carcinogenicity in humans, the overall evaluation statement is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. The PAH processes/substances assessed by IARC (2012) were (1) coal tar distillation, (2) coal tar pitch, (3) coke production, (4) soot, as found in occupational exposure of chimney sweep, sand (5) exposures during aluminum production. In addition, (6) coal gasification was assessed, but IARC noted that in addition to PAH, workers in coal gasification may be exposed to many compounds, including asbestos, silica, amines, arsenic, cadmium, lead, nickel, vanadium, hydrocarbons, sulfur dioxide, sulfuric acid and aldehydes. IARC also assessed (7) BaP, but as there was no human data, IARC did not conclude on cancer sites or target tissues in humans.

For lung cancer, IARC concluded as follows:

- *The following were considered to cause lung cancer: Coal-tar pitch as encountered in paving and roofing, Coke production, Soot, as found in occupational exposure of chimney sweeps, Exposures during aluminum production, Coal gasification*.

Later, meta-analyses have also reported an increased risk in a variety of industries/occupations with exposure to PAH. However, these reports did not present meta-risk estimates by air concentration level or cumulative exposure to BaP or any other marker PAH. Rota et al. (2014) reported the following statistically significant or non-significant meta-RRs: aluminum production (RR = 1.07, 95% CI 0.93 – 1.23, 10 cohorts), iron and steel foundries (RR = 1.31, 95% CI 1.07 – 1.61, 13 cohorts), asphalt workers (RR = 1.59 95% CI 0.68 – 3.76, 3 cohorts) and carbon black production (RR = 1.52, 95% CI 0.91 – 2.52, 3 cohorts). There was significant heterogeneity in risk estimates for each industry ($p < 0.001$ in each industry). Singh et al. (2018) reported a statistically significantly increased meta-RR for coal and coke and related industry (RR = 1.55, 95% CI 1.02–2.37, 7 cohorts) and for iron/steel foundries (RR = 1.52, 95% CI 1.05 – 2.21, 3 cohorts) and non-significant meta RRs for aluminum production (RR = 1.13, 95% CI 0.96–1.33, 9 cohorts) and for "other industries" (RR = 1.29, 95% CI 0.88 – 1.89, 5 cohorts). There was a wide variation in smoking habits among workers in each study and exposure to PAHs in the work place. Only 10 studies reported smoking adjusted data and due to this limited number of studies Singh et al. (2018) did not perform a meta-analysis based on smoking-adjusted data.

7.7.1.2 Skin cancer

Boffetta et al. (1997) reviewed the PAH related risk of various cancer sites based on cohort and case-control studies and concluded that heavy occupational exposure to mixtures of PAH entails a substantial risk of skin cancer and that the increased risk is restricted to settings entailing substantial dermal exposure.

The IARC (2012) assessment looking at 5 PAH related industries, described above for lung cancer, concluded for skin cancer:

- *The following were considered to cause skin cancer: Exposures during coal-tar distillation, Soot, as found in occupational exposure of chimney sweeps.*

7.7.1.3 Bladder cancer

In the report to the Health and Safety Executive, Armstrong et al. (2003) also performed a meta-analysis to obtain estimates of the relationship of PAH exposure with bladder cancer. This part of the study was not published in the Armstrong et al. (2004) scientific paper but follows the same methods. For bladder cancer, there were 27 cohorts for which risk estimates were published. Mean numbers of cases per cohort were much lower than for lung cancer (19 vs 74), and a much higher proportion (16/27) reported only single-group SMRs (instead of reporting risk estimates for several exposure categories). Some large cohorts reporting full lung cancer results reported only partial results for bladder cancer; often only a single group SMR was reported.

Nineteen (70%) unit relative risks were above one, though only one (Tremblay et al., 1995) statistically significantly so. The mean URR was 1.33 (95% CI; 1.16 - 1.52), and this changed little on excluding less precise URRs. Neither a general test of heterogeneity ($p>0.20$), nor specific tests for variation in URRs over industries ($p=0.20$) or other potential modifiers ($p>0.20$) showed evidence for variation more than could be easily explained by chance.

The overall mean was strongly dependent on results for the aluminum production industry, in particular two large studies (Romundstad et al. (2000) in Norway and especially Tremblay et al. (1995) in Canada). Although the URRs from other industries were statistically compatible with those for aluminum, there was little independent evidence for an association of bladder cancer with PAH in coke ovens or in other industries. However, small numbers of cases, especially for mortality studies, limited power.

As with lung cancer, there was no evidence for publication bias, nor did analysis with contrasts chosen by alternative criteria change overall patterns substantially.

Armstrong et al. (2003) cited the review of Negri and La Vecchia (2001) which noted specifically that the evidence of bladder cancer risk from exposure to PAH was confined to the aluminum production industry and that other co-exposures, in particular aromatic amines and nitro-PAH (Tremblay et al., 1995) known to have been present in small concentrations in aluminum pot rooms, have been suggested as alternative causal agents. It is noted that aromatic amines like 4-aminophenyl, 2-naphtylamine and ortho-toluidine have long been established causative agents for bladder cancer (IARC 2012). Tremblay et al. (1995) reported that in the plant they studied, exposure to BaP may be closely related to suspected bladder carcinogenic agents such as aromatic amines (arylamines). In 1990, the presence of 2-naphthylamine and 4-aminobiphenyl was reported in the Soderberg pot room atmosphere in the plant. Also nitro-PAH compounds had been detected in the Soderberg pot room air.

Since the Armstrong et al. (2003) study, IARC (2012) updated carcinogenicity assessments of some PAH related processes/substances. When human data was considered to indicate sufficient evidence of carcinogenicity in humans, the overall evaluation statement is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. The PAH processes/substances assessed were (1) coal tar distillation, (2) coal tar pitch, (3) coke production, (4) soot, as found in occupational exposure of chimney sweep, sand (5) exposures during aluminum production. In addition, (6) coal gasification was assessed, but IARC noted that in addition to PAH, workers in coal gasification may be exposed to many compounds, including asbestos, silica, amines, arsenic, cadmium, lead, nickel, vanadium, hydrocarbons, sulfur dioxide, sulfuric acid and aldehydes. IARC also assessed (7) BaP, but as there was no human data, IARC did not conclude on cancer sites or target tissues in humans.

For bladder cancer, IARC concluded as follows

- *The following were considered to cause bladder cancer: Exposures during aluminum production. In addition, IARC noted that a positive association has been observed between exposure to coal-tar pitch as encountered in paving and roofing and risk of bladder cancer.*

Rota et al. (2014) performed an updated review and meta-analysis by also including cohort studies that had been published between 2006 and January 2014, i.e., those that were published since the review and meta-analysis of Bosetti et al. (2007) that had covered cohort studies published until 2005. The search was focused on studies investigating the effects of PAH on respiratory and urinary tract cancers in workers employed in selected industries (i.e., those covered by Boffetta et al. (1997), Bosetti et al. (2007), Baan et al. (2009), IARC 2010 and, IARC 2012). There were 13 new eligible cohort studies and were included in the updated meta-analysis together with those older studies previously included. Seven studies were on aluminum production workers, two on iron and steel foundries, two on asphalt workers and two of carbon black production. There were no new cohort studies identified for coal gasification workers, coke production workers and carbon electrode manufacture.

- For aluminum production there were 10 cohort studies available with altogether 279 bladder cancer cases and a pooled RR of 1.28 (95% CI 0.98-1.68). The cumulative meta-analysis did not substantially show any meaningful changes in RRs over time. There was no indication of publication bias (p for Egger's test = 0.22, p for Begg and Mazumdar's test=0.93).
- For iron and steel foundries there were 9 cohort studies available with altogether 151 bladder cancer cases and a pooled RR of 1.38 (95% CI 1.00-1.91). A significant heterogeneity between studies was observed (p=0.001). The cumulative meta-analysis showed a decreased RR of bladder cancer for studies published after 1990. There was no indication of publication bias (p for Egger's test=0.30, p for Begg and Mazumdar's test=0.17). It is noted that workers in iron and steel foundries were

exposed, mainly in the past, to various other known or potential carcinogenic substances, including several heavy metals, crystalline silica and asbestos.

- With reference to bladder cancer in asphalt workers, the pooled RR was 1.03 (95% CI 0.82-1.30) based on 109 cancers from two studies only. The limited number of studies did not allow the investigation of publication bias for bladder cancer.
- As regards carbon black production, no excess risk of bladder cancer was found from three studies, with a pooled RR of 1.10 (95% CI 0.61-2.00), based on 15 cases. No evidence of publication bias emerged (p for Egger's test=0.61, p for Begg and Mazumdar's test=0.61).

Overall, Rota et al. (2014) concluded that for bladder cancer and exposure to PAH the available data, although suggesting a possible increased risk, were still too limited to draw any definite conclusion.

It is noted that in addition to the reviews and meta-analyses described above, a number of similar studies have also assessed the role of occupational exposures, including PAH related ones, and risk of bladder cancer (Mannetje et al. (1999), Kogevinas et al. (2003), Reulen et al. (2008)). However, as the cut-off date for inclusion of individual studies was earlier than for IARC (2012) evaluation and the review of Rota et al. (2014), they were only explored to see if they had assessed specific PAH related processes (without concomitant exposure to known bladder carcinogens), other than those assessed by these latest reviews. This was not the case.

In a recent systematic review and meta-analysis, Cumberbatch et al. (2015) studied bladder cancer risk by occupation. Increased risks were observed also in occupations with exposure to PAH, e.g., workers in manufacture of metals, aluminum or glass. However, the study used only occupational codes without consideration of which other carcinogens than PAH, the workers in these occupations might have been exposed to.

7.7.1.4 Other cancer sites

As explained above, IARC (2012) updated carcinogenicity assessments of some PAH related processes/substances. When human data was considered to indicate sufficient evidence of carcinogenicity in humans, the overall evaluation statement is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. The PAH processes/substances assessed were (1) coal tar distillation, (2) coal tar pitch. (3) coke production, (4) soot, as found in occupational exposure of chimney sweep, sand (5) exposures during aluminum production. In addition, (6) coal gasification was assessed, but IARC noted that in addition to PAH, workers in coal gasification may be exposed to many compounds, including asbestos, silica, amines, arsenic, cadmium, lead, nickel, vanadium, hydrocarbons, sulfur dioxide, sulfuric acid and aldehydes. IARC also assessed (7) BaP, but as there was no human data, IARC did not conclude on cancer sites or target tissues in humans. IARC did not find sufficient human evidence of those PAH increasing the risk of cancer of sites other than those discussed above. IARC (2010) assessed earlier a number of PAH but assessed only if the overall human evidence was sufficient without separately pointing out the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans.

DECOS (2006) concluded that data on cancer at cancer sites other than those discussed above, were inconclusive, due to limitations in data presentation and the low number of cases. DECOS (2006) also concluded that the numerous human and animal studies have revealed that PAH act mainly as local carcinogens (e.g., lung cancer by inhalation, skin cancer by dermal exposure).

AGS (2011) relied on the review of Greim (2008) when assessing PAH related risk of renal cancer, oral cancer, pharyngeal cancer, laryngeal cancer and "other cancers" and concluded that there is no convincing evidence of increased risk from PAH exposure for any of these cancer sites.

SCOEL (2016) relied mostly on the DECOS (2006) review but noted additionally that "*a few cohort-based studies reported on cancer in the liver, kidneys, the larynx and stomach. However, as Boffetta et al (1997) indicated these data were limited and inconclusive. Therefore, it is unclear whether inhalation or dermal exposure of PAH may lead to tumours at other sites of the body than the lungs or skin, respectively, or possibly the bladder*".

For cancer sites other than lung, bladder or skin, RAC (ECHA 2018) relied on IARC (2010) and some studies published later. However, only case-control studies with significantly increased risk were described by RAC in that previous RAC assessment. The case-control studies with non-significant results were not described and no results from PAH exposed cohorts were presented.

7.7.2 Animal data

There is a vast amount of studies available in which animals were exposed to a single PAH, however, most of these animal studies were addressed to BaP and to dermal and oral exposure; only a few have been published on inhalation exposure. It is beyond the scope of this report to discuss all these studies in detail. Extensive summaries of these studies are available from IPCS (1998), IARC (1973, 2012) and DFG (2012).

Various complex PAH-containing mixtures to which humans can be exposed during work have been investigated for carcinogenic properties with experimental animals and SCOEL (2016) and DFG (2012) reported on the carcinogenicity of these complex PAH mixtures as described below; in most of these studies the animals were dermally exposed to extracts, tars or condensates but in a small number, exposure via the respiratory tract was applied.

Inhalation

Heinrich et al (1986) exposed female Wistar rats (n=108/group) to coal oven exhaust gas (containing 0.3 µg/m^3 BaP) for 9 months, followed by exposure to a combination of pyrolized pitch and coal oven exhaust gas (containing approximately 90 µg/m^3 BaP) for another 12 months, with a gap of one month between the two exposures. Exposure was on average 16 h per day and 5 days per week. After exposure, about 50% of the exposed animals had died, which was comparable with the mortality in the clean air exposed control group. Furthermore, preliminary results showed that of the exposed animals that died, 12 developed lung tumours (mainly squamous cell carcinomas), whereas no lung tumours were detected in the control group. In the same study and with the same exposure regimen, also female NMRI mice (n=28-31/group) were exposed to clean air or pyrolized pitch/coal oven exhaust (month 1-9, average 0.3 µg/m^3 BaP; from 10 months, average ca. 60 µg/m^3 BaP) for 16 h/day, 5 d/week for 2 years. Macroscopic evaluation revealed lung tumour incidences of 32% and 79% for control and exposed animals, respectively. In addition, the tumour multiplicity (average number of tumours ± SD per lung) was 0.7 ± 1.7 and 7.0 ± 7.9, respectively. Tumours in organs other than the lung were not studied.

Schulte et al (1994) used newborn female NMRI/BR mice to study carcinogenesis of PAH-rich exhausts. The authors explained the use of newborn animals by the lower spontaneous lung tumour incidence of newborn and a greater susceptibility to tumour induction. Exposure started at the first day after birth. The animals (n=40/group) were exposed to filtered room air or coal tar pitch volatile aerosols (mass median aerodynamic diameter of 0.55 ± 0.03 µm), containing 50 or 90 µg/m^3 BaP, for 16 hours per day, 5 days per week during 44 weeks. Exposure to PAH-rich exhausts caused a dose-dependent increase in lung tumours. As in the previous study, tumours in organs other than the lung were not investigated.

In another study, Heinrich et al (1994) exposed rats to coal tar/pitch condensation aerosols, free of any carbon black carrier particles, to estimate lifetime unit lung cancer risk for BaP. Female Wistar rats (n=72/group) were exposed to filtered clean air or the aerosols, with a concentration of BaP of 20 or 46 µg/m^3, for 17 hours per day, 5 days per week for 10 or 20 months. After exposure, the animals were left in a clean air room for 20

or 10 months, respectively, making a total experimental time of 30 months for all groups. A clear dose-dependent increase in lung tumour incidence was observed. Most tumours were classified as keratinising squamous cell tumours, but also some broncho-alveolar adenomas and adenocarcinomas were found. No exposure-related tumours were observed in organs other than the lung.

Intratracheal instillation

A few studies comprised intratracheal instillation of PAH-rich mixtures in Syrian golden hamsters. In the Pott and Stöber (1983) study, hamsters received 30 intratracheal instillations of PAH fraction of extracts of urban particulate air pollution, containing 12.5 µg BaP. Nine out of the 46 examined animals showed tumours in the respiratory tract. The authors stated that when pure BaP would be given at the same concentration as in the extract, the tumour incidence rate would have been considerably lower.

In another study, performed by Künstler (1983), hamsters (n=25-30/group) received intratracheal instillations with different doses of automobile exhaust condensate fractions. Some of these fractions were recombined with a synthetic mixture of pure carcinogenic PAH, resulting in doses between 5.3 and 42.8 µg BaP equivalents. The instillations took place at 2-week intervals until their natural death. The treatments did not result in any malignant neoplasia in the respiratory tract.

However, Reznik-Schüller and Mohr (1977) found multiple pulmonary adenomas in Syrian golden hamsters, which were exposed by intratracheal instillations to automobile exhaust condensates containing 340 µg/g BaP, once every two weeks for life.

Concerning the choice of animals, DECOS (2006) noted the comment of Pott and Stöber (1983) that for unknown reasons, strains of Syrian golden hamster may differ in response to PAH exposure. Furthermore, DECOS (2006) noted that for intratracheal instillations, PAH was always applied as particles or extracts. This means that effects of PAH may be influenced by possible effects of particles themselves. Therefore, DECOS (2006) considered these types of studies not relevant for estimating additional lifetime risks of PAH.

Dermal application

A number of chronic animal studies used dermal application of condensates containing various PAH compounds. These condensates included those obtained from tobacco smoking, diesel and gasoline engine exhaust, carbon blacks, coal tar and coal gasification derived products, etc. Overall, these mixtures caused dermal tumours, mainly of benign origin, after repeated dermal exposure. However, for estimating additional lifetime cancer risk values for PAH, these studies are not useful for several reasons. Firstly, the mixtures and condensates contain also potential carcinogenic substances other than PAH. Furthermore, not always the amount of substance applied could be reproduced (DECOS 2006).

Oral application

Culp et al (1998) fed coal tar mixtures to female B6C3F1 mice (n= 48/group) for 2 years. Mixture one (coal tar from seven coal gasification plant waste sites) was given at doses of 0.0, 0.01, 0.03, 0.1, 0.3, 0.6 and 1.0% in diet; mixture two (coal tar from two of the seven waste sites plus another site having a high BaP content) at doses of 0.0, 0.03, 0.1, and 0.3% in diet. A significant decrease in food consumption was observed in animals fed the highest doses. In addition, the body weights of these animals were significantly less than those of the control animals fed normal diets without coal tar mixtures. Also the survival period in the group of animals fed the highest amounts of coal tar mixtures was shortened; none of the animals fed a diet with 1% of mixture one survived the two-year period. The coal tar mixtures induced a variety of tumours. The incidence of the following neoplasms were statistically significantly increased: hepatocellular adenomas and/or carcinomas (mix one, 0.3%; mix two, 0.3%); alveolar/bronchiolar adenomas and or carcinomas (mix one, 0.3, 0.6, and 1.0%; mix two, 0.1 and 0.3%); papillomas and/or

carcinomas in the forestomach (mix one, 0.3 and 0.6%; mix two, 0.3%); adenocarcinomas in the small intestines (mix one, 0.6 and 1.0%); haemangiosarcomas in various organs (mix one, 0.3 and 0.6%; mix two, 0.3%) and histiocytic sarcomas (mix two, 0.3%). The p-values for dose-related trends for these tumours were 0.006 or lower.

Weyand et al (1995) reported on the tumorigenic activity of manufactured gas plant residues (MGP) in female A/J mice (n=30/group) using a F0927 basal gel diet system. These animals were chosen because of their sensitivity to chemical induction of pulmonary adenomas. The mice were fed the diets, containing 0.0, 0.1 or 0.25% of MGP, for 260 days. After the last exposure day, the animals were sacrificed and their lungs and stomach removed for histologic examination. The investigators observed an unexpected and unexplained lower intake of diet and body weight in control animals. Also the intake of diet and body weight of animals fed the highest amount of MGP was lower compared to the other exposed group. The percentage of mice with lung tumours was statistically significantly increased in groups fed MGP compared to controls [29/29 (0.25% MGP), 19/27 (0.1% MGP), 4/21 (controls)]. However in none of the animals fed MGP or in controls, forestomach tumours were found.

7.7.3 Summary

IARC concluded that there is sufficient evidence for the carcinogenicity of BaP in experimental animals. IARC (1973, 2012) reported that BaP produced tumours in all species tested (mouse, rat, hamster, guinea-pig, rabbit, duck, newt, monkey) for which data were reported following exposure by many different routes (oral, dermal, inhalation, intratracheal, intrabronchial, subcutaneous, intraperitoneal, intravenous). BaP had both a local and a systemic carcinogenic effect, was an initiator of skin carcinogenesis in mice, and was carcinogenic in single-dose studies and following prenatal and transplacental exposures.

Overall, these animal data clearly showed that carcinogenic PAH act as local carcinogens. Thus, concerning occupational exposure, cancer in the lungs and skin presents the main risks.

In humans, there is consistent evidence of PAH-related risk of lung cancer. There is also consistent human evidence of PAH-related risk of skin cancer after substantial dermal exposure to PAH. The human evidence of PAH-related risk of bladder cancer is not consistent. An increased risk in workers has been observed only in a limited number of PAH-related processes and confounding by other, established bladder carcinogens remains a possibility. There is no consistent human evidence of PAH-related risk for other cancer sites.

Quantitative estimates have been published for cancer risk by BaP concentration in the air, based on a meta-analysis of 39 cohort studies representing 9 main occupational settings with PAH exposure. Quantitative risk estimates were not identified from human data for any other specific PAH compound.

Section 9.1.2 further describes how this human evidence has been assessed and used by national and international bodies, in cancer risk assessments concerning PAH, overall.

7.8 Reproductive toxicity

RAC (ECHA, 2019b) noted that in its criteria document, the IPCS/WHO discussed the reproductive toxicity of several individual PAH, which included BaP. It was concluded that this PAH had adverse effects on female fertility and reproduction (IPCS, 1998) (see below).

When analysing non-cancer effects EPA (2017) reported specifically for reproductive effects that there is weight of the evidence from human and animal studies indicating human hazards following BaP exposure for developmental toxicity (including neurodevelopmental toxicity) and reproductive toxicity. Some supporting studies in humans exposed to PAH mixtures are available, which utilise BaP air monitoring data or report associations between particular health endpoints and concentrations of BaP-DNA

adducts in blood or tissue. In general, the available human studies report effects that are analogous to the effects observed in animal toxicological studies (especially those regarding developmental and reproductive effects).

7.8.1 Human data

No epidemiological studies on developmental or fertility effects of PAH were reported by DFG (2012) or SCOEL (2012).

DFG (2012) cited two reports on transplacental naphthalene poisoning (Anziulewicz et al. 1959; Zinkham and Childs (1958)). In both cases, expectant mothers had sucked or chewed naphthalene-containing mothballs for a prolonged period in the last trimester of pregnancy. Haemolytic anaemia with jaundice was observed in the newborn, 7 hours and 3 days after birth, respectively.

EPA (2017) reviewed studies potentially available for oral reference dose of BaP. EPA (2017) summarised that human studies of environmental PAH mixtures across multiple cohorts have observed effects following exposure to complex mixtures of PAH. The available data suggest that BaP exposure may pose health hazards other than cancer, including reproductive and developmental effects such as infertility, miscarriage, and reduced birth weight and effects on the developing nervous system. However, EPA (2017) concluded that the available human studies that utilised benzo[a]pyrene-deoxyribonucleic acid (DNA) adducts as the exposure metric, do not provide external exposure levels of BaP from which to derive a value, and exposure is likely to have occurred by multiple routes. In addition, EPA (2017) noted that uncertainty exists due to concurrent exposure to other PAH and other components of the mixture (such as metals).

7.8.2 Animal data

DECOS (2006) reported that the main routes of exposure in evaluating reprotoxicity were by diet, intraperitoneal or subcutaneous injections. It was noted that whether PAH compounds express reproductive and embryotoxic effects depends on the genotype of mice (induction of the cytochrome P450 monooxygenase receptor) and the ability to transform PAH into active PAH metabolites. These metabolites can cross the placenta and, therefore, may produce adverse effects in the embryo and foetus. Indeed, in female mice, which can induce monooxygenase receptors, BaP as well as benz[a]anthracene, dibenz[a,h]anthracene, and naphthalene were found to be embryotoxic. Concerning BaP, it is suggested that the route of exposure affects also the magnitude of effects; the teratogenicity being worse in orally exposed animals than in animals exposed intraperitoneally. Further, a single intraperitoneal injection of BaP in mice reduced fertility and destroyed primordial oocytes in a dose-dependent manner.

7.8.2.1 Developmental reprotoxicity

SCOEL (2016) and DFG (2012) reported the results of studies on the embryotoxicity in rats and mice; they are included in **Table 15**.

Table 15: Summary table of developmental reprotoxicity studies on BaP (IPCS 1998)

Species, strain	No/ group	Route	Dose levels duration of exposure	Results	Reference
Mouse white Swiss	9	diet	50 mg/kg bw Day 5 or 10 of gestation until delivery	F1: no malformations	Rigdon and Neal 1965*
Mouse C57BI/6N, AKR/J & back-crosses	6-17	diet	120 mg/kg/day Day 2-10 of gestation	F1: increased intrauterine toxicity and malformations in $Ah^d/Ah7^d$ embryos compared with Ah^b/Ah^d embryos in	Legraverend et al. (1984)*

Species, strain	No/ group	Route	Dose levels duration of exposure	Results	Reference
(reciprocal)				pregnant Ah^d/Ah^d mice (effect not seen in pregnant Ah^b/Ah^d mice)	
Mouse C57BI/6, AKR & back-crosses (reciprocal)	5-30	i.p	50-300 mg/kg bw Day 7, 10 or 12 of gestation	200 mg/kg bw: F1: increase in stillbirths, resorptions, malformations (4-fold higher in pregnant C57BI than in AKR mice)	Shum et al. (1979)*
Mouse C57BI/6, DBA/2 & back-crosses (reciprocal)	20	i.p.	150 or 300 mg/kg Day 8 of gestation	150 and 300 mg/kg bw: F0: increased fetal mortality (except DBA/2 × DBA/2 offspring); reduced fetal body weight; increased number of cervical ribs. 300 mg/kg: F1: increased malformations (C57BI/6 × C57BI/6)	Hoshino et al. (1981)*
Mouse CIT1	-	gavage	10, 40, 160 mg/kg bw/day Day 7-16 of gestation	F0: no toxicity F1: no toxicity	MacKenzie & Angevine (1981)*
Rat	17	s.c	5 mg/ animal/ day Day 1-11 or 16 of gestation	F0: Days 10 and 12: profuse vaginal haemorrhage; day 14: intraplacental haemorrhage; F1: fetal death and resorption up to day 18	Wolfe & Bryan (1939)*
Rat Sprague-Dawley	-	gavage	60 mg/kg Day 19 of gestation	F1: induction of BaP-hydroxylase in liver 20 vs < 0.2 units in controls)	Welch al al. (1972)*
Sprague-Dawley	10-15	s.c	50 mg/kg bw/day Day 6-8 or 6-11 of gestation	F1: significant increase in number of resorptions and fetal wastage (dead fetuses plus resorption); fetal weight reduced	Bui et al. (1986)*
Chrysene rat, Sprague Dawley	-	gavage	60 mg/kg bw/day Day 19 of gestation	F1: induction of BaP hydroxylase in liver (6 vs <0.2 units in controls)	Welsh et al. (1972)*
F-344 rats (pregnant)	10	Inhalation (nose-only)	25, 75, and 100 $\mu g/m^3$, 4 h daily for 10 days (Day 11-20 of gestation)	Dose-dependent decrease in pups per litter and in fetal survival compared to unexposed controls (survival: 78.3%, 38% and 33.8% per litter in the 25, 75 and 100 $\mu g/m^3$ dose groups, respectively); decrease in mean pup weight (in the 75, and 100 $\mu g/m^3$ dose groups); significant decrease in plasma progesterone, estradiol, and prolactin concentrations in the 75 $\mu g/m^3$ exposed group	(Archibong et al., 2002)

Species, strain	No/ group	Route	Dose levels duration of exposure	Results	Reference
				compared to unexposed controls (on day 17 of gestation)	
Long Evans rats (pregnant)	194 F1 pups were utilised	gavage	0, 25 and 150 µg/kg bw (Day 14-17 of gestation)	Significant disposition to the hippocampus and cortex of offspring, downregulation of developmental glutamate receptor mRNA and protein subunit expression and voltage-dependent decreases in the amplitude of inward currents at negative potentials in B(a)P-treated cortical neuronal membranes	(Brown et al., 2007)
Long Evans rats (pregnant)	15	gavage	300 µg/kg bw (Day 14-17 of gestation)	no significant effect on the number of pups born per litter, the pre-weaning growth curves and the initial and final brain to body weight ratios; deficits in cortical neuronal activity in offspring	(McCallister et al., 2008)
Pregnant Long Evans Hooded (LEH) rats	6-17	gavage	150, 300, 600 and 1200 µg/kg/bw, (day 14-17 of gestation)	No significant effects to number of pups born per litter, or pre-weaning growth curves	(Jules et al., 2012)

* References are taken from IPCS (1998)

The effects of subacute inhaled BaP-exposure of pregnant rats on post-implantation fetal survival was reported by(Archibong et al., 2002). Reduced fetal survival rates in the mid and high dose groups (75 and 100 µg/m^3) compared to unexposed controls was linked to significant declines in hormones necessary for pregnancy maintenance and possibly attributed to a decrease in luteotropin activity, BaP interference with estrogen receptor signalling and a consequent reduction in uterine progesterone receptors.

7.8.2.2 Reproductive toxicity

SCOEL (2016) and DFG (2012) reported that BaP displayed adverse effects on the fertility of female mice and on the postnatal development of the offspring. The studies are summarised in **Table 16**. (Archibong et al., 2008) (Inyang et al., 2003) (Liang et al., 2012) also reported male reproductive toxicity manifesting as reduced epididymal and testicular endocrine and spermatogenic function in exposed rats (**Table 16).**

Table 16: Summary table of reproductive toxicity studies on BaP (IPCS 1998)

Species, strain	Sex/ No/ group	Route	Dose levels duration of exposure	Results	Reference
Mouse white Swiss	M 5	diet	37.5, 75, or 150 mg/kg bw /day Up to 30 days before mating	NOEL: 150 mg/kg bw per day Parameters: sperm in lumen of testes; number of offspring, malformations	Rigdon & Neal (1965)*

Species, strain	Sex/ No/ group	Route	Dose levels duration of exposure	Results	Reference
Mouse white Swiss	F 5-65	diet	37.5, 75, or 150 mg/kg bw /day 20 days before mating	NOEL: 150 mg/kg bw per day Parameter: number of offspring	Rigdon & Neal (1965)*
Mouse DBA/2N	F 15	i.p.	10, 100, 200, or 500 mg/kg bw once Day 14 before mating,	10, 100 mg/kg bw: dose-dependent decrease in number of pups 200, 500 mg/kg bw: completely infertile; threshold: 3.4 mg/kg bw; 50% effect dose: 25.5 mg/kg bw	Mattison et al. (1980)*
Mouse DBX2N	F	i.p.	5, 10, 50, 100, or 500 mg/kg bw once Day 21 before sacrifice	Dose-dependent increase in primordial oocyte destruction; 500 mg/kg: 100% destruction; threshold: 2.7 mg/kg bw; 50% effect dose: 24.5 mg/kg bw	Mattison et al. (1980)*
Mouse B6 & D2	F 5	i.p.	100 mg/kg bw once Day 13 before mating	100 mg/kg bw: significant increase in primordial oocyte destruction in both genotypes; effects in B6 mice greater than in D2 mice	Mattison & Nightingale (1980)*
Mouse CD-1	F 30-60/dose (F0)	gavage	10, 40, 160 mg/kg bw/day Day 7-16 of gestation	F0: no toxicity; F1: total sterility in 97% of mice exposed to 40 or 160 mg/kg bw/day; fertility markedly impaired in 10 mg/kg bw/day group; impaired fertility in F1 was associated with marked alterations in gametogenesis and folliculogenesis and a dramatic decrease in the size of the gonads; germ aplasia, reduction in the size of seminiferous tubules, increase in interstitial tissue in M; marked hypoplasia with very few corpora lutea or follicles in F	(MacKenzie and Angevine, 1981)
Mouse C57BI/6N (136), DBA/2N (D2), D2B6F_1 (F_1)	F	Intra-ovarian injection	10 µg/right ovary once Day 14 before mating	10 µg/ ovary: decreased ovarian weight (D2); decreased ovarian volume (D2 and F1); decreased antral follicles (F1) decreased number of small follicles (D2 and F1)	Mattison et al. (1989)*
Mouse C57BI/6N	F 5	i.p.	1, 5, 10, 50, 100, or 500 mg/kg bw 1, 2, 3, and 4 weeks before sacrifice	500 mg/kg: 35% mortality; 1-500 mg/kg bw: dose & time dependent decrease in ovarian volume, total volume & number of corpora lutea/ovary (for last parameter, after 1 week threshold was about 1 mg/kq bw and ED_{50} 1.6 mg/kg	Swartz & Mattison, (1985)* Miller et al. (1992)*

Species, strain	Sex/ No/ group	Route	Dose levels duration of exposure	Results	Reference
				bw); effect transitory in low-dose groups, but not reversible in two highest by four weeks	
NMRI mice	F 9	Oral intubation	10 mg/kg bw/day (Day 7-16 of F0 pregnancy)	F1: significantly reduced fertility; significantly lower weights and depletion of follicles and corpora lutea compared to controls,	(Kristensen et al., 1995)
F-344 rats	M 10	inhalation	25, 75, and 100 µg BaP/m^3, 4 h daily for 10 days	No effect on testis weight and density of stored sperm; Reduced stored sperm progressive motility in rats in the mid and high dose groups, compared to the low dose and untreated counterparts; in the 75 µg BaP/m^3 group: significant decline in plasma testosterone concentrations up to 48 h post cessation of exposure, followed by compensatory increase at 72 h; significant increases in mean plasma luteinizing hormone (LH) compared to controls, at 24, 48 and 72 h post exposure.	(Inyang et al., 2003)
F-344 rats (adult male)	M 10	Inhalation (nose-only)	75 µg BaP/m^3, 4 h daily for 60 days	Significant decreases in mean testis weight (33%), total weight of tubules (27%) and total tubular length (39%) per paired testes in exposed rats, compared with unexposed controls; significant reduction in daily sperm production; significant decrease in plasma and intra-testicular testosterone concentrations (assessed on last day of exposure (day 60) persisting up to 72 hours therafter), concurrent increase in LH levels (significant at 72 h post-cassation of exposure).	(Archibong et al., 2008)
Sprague-Dawley rats (neonate)	M	gavage	0, 5, 10, or 25 mg/kg day; postnatal day 1 (PND 1) to PND 7	Significant reduction in testicular daily sperm production, sperm counts of the epididymis cauda at PND 90 and serum testosterone levels at PND 8, 35 and 90, at ≥10 mg/kg bw compared to controls; attributed to persistent decrease in mRNA levels of St*AR*	(Liang et al., 2012)

Species, strain	Sex/ No/ group	Route	Dose levels duration of exposure	Results	Reference
F-344 rats	F 20	Inhalation (nose-only)	50, 75, 100 µg BaP/m^3, 4 h a day, for 14 days	No effect on ability of all exposed animals to cycle, non-significant decreases in ovarian weights of exposed animals compared to controls; High dose group only (compared to other dose levels and untreated counterparts): 24 h extension of length of estrous cycle (proestrous); significantly reduced ovulation rates, fetal survival and fetal losses; significant reductions in plasma estradiol and progesterone concentrations (by 34% and 44%, respectively) at proestrus and diestrus I, respectively FSH concentration significantly increased; significant reduction in LH concentrations in exposed animals in proestrus; induction of AHH via activation of AhR in ovaries	(Archibong et al., 2012)

* References are taken from IPCS (1998)

7.8.2.3 Other postnatal effects and immunological effects

IPCS (1998) reported three studies in mice administered BaP dermally intraperitoneally, or orally which showed adverse postnatal effects, including an increased incidence of tumours, immunological suppression, and reduced fertility.

BaP given to pregnant rats on day 15 or 19 of gestation, caused alterations at the thymic glucocorticoid receptors in the offspring, suggesting binding to the pre-encoded hormone receptors and interference with receptor maturation (Csaba et al., 1991; Csaba & Inczefi-Gonda, 1992[15]). Strong suppression of immunological parameters was found in the progeny of mice that had been treated intraperitoneally with BaP at mid-gestation (Urso & Johnson, 1987[15]).

Transplacental deposition of desorbed BaP to the fetus following maternal inhalation (acute BaP:carbon black aerosol (100 µg/m^3) 4 h exposure, on gestation day 15 of a 21-day gestation period) resulted in *in utero* neurotoxicity which manifested postnatally as enhanced, premature DNA binding of the transcription factor Sp1 in the postnatally developing cerebellum, peaking on postnatal day 3 (Hood et al., 2000). The modulation of gene expression via the altered binding of key transcription factors involved in growth and differentiation in the developing brain presents a molecular mechanism for the adverse

[15] Reference cited by IPCS (1998)

neurobehavioral effects observed in other studies (Saunders et al., 2001). Behavioural impairments (e.g. locomotor activity, spatial learning functions) in adult life, resulting from postnatal exposure via the oral route of up to 2 mg/kg/day BaP were noted in Sprague-Dawley rats ((Chen et al., 2011). Parental exposure of Long Evans rats to low-level BaP (300 µg/kg/bw), resulted in significant deficits in cortical neuronal responses of the offspring, mediated by an exposure-related diminished cerebrocortical mRNA expression of the glutamatergic NMDA receptor subunit (NR2B) (McCallister et al., 2008). Oral delivery of BaP to pregnant LEH rats was shown to predispose offspring to functional deficits in cardiovascular development, manifesting as significantly elevated systolic blood pressure postnatally, in the middle and high exposure groups of offspring (600 and 1200 µg/kg/BW) compared to controls (Jules et al., 2012).

7.8.3 Summary

EPA (2017) reported that human and animal studies provided evidence for PAH and BaP induced developmental effects (including developmental neurotoxicity). Effects on embryo/foetal survival, postnatal growth, neurobehavioral function, and development have been demonstrated in human populations exposed to PAH mixtures during gestation. Animal studies demonstrated various effects including changes in embryo/foetal survival, pup weight, blood pressure, fertility, reproductive organ weight and histology, and nervous system function in gestationally and/or early postnatally treated animals.

They also reported that human and animal studies provided evidence for BaP induced male and female reproductive toxicity. Effects on sperm quality and male fertility have been demonstrated in human populations highly exposed to PAH mixtures. The use of internal biomarkers of exposure in humans (e.g., BPDE-DNA adducts) supports associations between BaP exposure and these effects. In females, numerous epidemiological studies indicate that cigarette smoking reduces fertility, however few studies have specifically examined levels of BaP exposure and female reproductive outcomes. Animal studies demonstrate decrements in sperm quality, changes in testicular histology, and hormone alterations following BaP exposure in adult male animals, and decreased fertility and ovotoxic effects in adult females following exposure to BaP. As described by the EPA (2017), from human data it is not possible to identify external exposure metrics allowing to assess effect levels for the reproductive toxicity effects of PAH.

BaP is classified as Repro. 1B for effects on fertility and developmental toxicity, according to Regulation (EC) No 1272/2008. However, RAC (ECHA, 2019b) further noted that the observed effects are threshold effects and it is considered that these thresholds will be orders of magnitude higher than potential DMELs for carcinogenicity.

8. Other considerations

8.1 Mode of action (MoA) considerations

RAC recently reviewed the mechanisms of carcinogenic action of PAH (ECHA, 2018) and the assessment is directly cited: *"Many PAHs share the same genotoxic mechanism of action, i.e., metabolic activation to electrophilic dihydrodiol epoxides and/or quinones which are capable of covalent binding to DNA (IPCS 1998). The DNA adducts thus formed may cause mutations.*

The variation in carcinogenic potencies of PAHs is most probably associated with the structural differences between adducts and the subsequent effects on removal by DNA repair mechanisms. However, it could also be a result of changes in DNA polymerase activity and incorrect base-pair insertion resulting from post-lesion DNA synthesis. Mutations can activate oncogenes or inactivate tumour suppressor genes, i.e. p53 gene. Many PAHs are ligands for the aryl hydrocarbon receptor (AhR), which has different roles involved in metabolism including induction of bioactivating enzymes. Epigenetic changes

including DNA methylation and telomere dysfunction have been also reported after exposure to complex PAH mixtures in human workers and following in vivo mouse exposure.

Experiments on interactions of PAH in both binary and complex mixtures on DNA adduct levels reported both less-than-additive and more-than-additive effects. In a dose-response study performed in mice (Jarvis et al., 2014), it was found that mixtures of 5 PAHs exhibited more-than-additive effects at low doses and less-than-additive effects at high doses compared to individual PAH exposure. This paradoxical finding (i.e. non-linear dose-effect relationship) probably resulted from competitive inhibition of the metabolising enzymes at higher doses and hence decreased amounts of DNA-reactive metabolites, and is in accordance with the findings of studies on binary and complex PAH mixtures (Jarvis et al., 2014).

The carcinogenicity of BaP, the most extensively studied PAH, is well documented in animal models (IARC (2010); Xu et al. (2009); Jiang et al. (2007); Jiang et al. (2005); Xue and Warshawsky (2005); Ramesh et al. (2004); Boström et al. (2002); Penning et al. (1999); Harvey (1996); ATSDR (1995); Cavalieri and Rogan (1995)). The primary mode of action by which BaP induces carcinogenicity is genotoxicity. This mode of action is presumed to apply to all tumour types and is relevant for all routes of exposure. The general sequence of key events (KEs) associated with genotoxic mode of action for BaP is as follows:

1. *Bioactivation of BaP to DNA-reactive metabolites via three possible metabolic activation pathways: a diol epoxide pathway, a radical cation pathway, and an o-quinone pathway;*
2. *Direct DNA damage by reactive metabolites, including the formation of DNA adducts and ROS-mediated damage;*
3. *Formation and fixation of DNA mutations, particularly in tumour suppressor genes or oncogenes associated with tumour initiation; and*
4. *Clonal expansion of mutated cells during the promotion and progression phases of cancer development.*

BaP can act as both an initiator and a promoter of carcinogenesis. Initiation by direct DNA damage (key event 2) can occur via all three metabolic pathways of BaP. DNA damage that is not adequately repaired may lead to mutations (key event 3). These mutations can undergo clonal expansion (key event 4) enabled by multiple mechanisms which are also induced by BaP. These latter include AhR binding leading to an upregulation of genes related to biotransformation, growth, and differentiation, and regenerative cell proliferation resulting from cytotoxicity and a sustained inflammatory response. However, there is insufficient evidence that these mechanisms, which contribute to the promotion and progression phases of cancer development, act independently of DNA damage and mutation to produce BaP-induced tumours. The available human, animal, and in vitro evidence all supports mutagenicity as the primary mode of action by which BaP induces carcinogenesis (EPA, 2017).

Bitumen and coal tar fume condensates obtained at various temperatures[16] were all found to be mutagenic in the Ames test (Binet et al., 2002). Metabolic activation was needed to obtain positive results.

In addition to genotoxicity, there are suspected interactions of BaP with various constituents of the proteome. Such non-genotoxic pathways are a matter of recent research (Verma et al., 2012). For example, BaP and its metabolites are implicated in oxidative stress-mediated pathways (formation of orthoquinone/ reactive oxygen species,

[16] The vapour production from the two bitumen samples considered in the study was performed at 160°C and 200°C, and that from the coal-tar at 110°C and 160°C.

and AhR mechanism), immunosuppression through AhR-mediated CYP-derived metabolites (diolepoxides, quinones), as well as epigenic mechanisms involving cell proliferation, PAH-induced apoptosis and DNA methylation (IARC, 2012).”

Overall, a non-threshold mode of action has been assumed by regulatory bodies for BaP, some specific PAH (e.g., CTPHT) and more generally for carcinogenic PAH or PAH mixtures (AGS (2011), DECOS (2006), SCOEL (2016), ECHA (2018), ECHA (2019a).

8.1.1 Potency of PAH constituents

Numerous PAH have been investigated for their carcinogenic potency. The structural characteristics of PAH understandably influence both their metabolic activation and the stereochemistry of DNA binding (ECHA, 2018).

Comparisons of the potencies of PAH molecules show that the genotoxic potency increases with the number of rings; the carcinogenic 3- or 4-ring PAH are clearly less potent than their 5- and 6-ring counterparts (see IARC 1983, 2010). Compounds with a bay region-an indentation caused by an angular benzene ring attached-are strong carcinogens. Compounds with a fjord region-a distortion caused when a bay region is methylated or closed by an additional benzo ring-are even more potent carcinogens (SCOEL, 2016).

DECOS (2006) referred to the study of Collins et al. (1991) comparing the carcinogenicity (and genotoxicity) of a number of PAH in comparison to BaP. According to this comparison, dibenz[*a,h*]anthracene (a 5-ring PAH) appears to be equipotent or somewhat more potent than BaP, whereas other 5-ring PAH tested (e.g., benzofluoranthenes, benzo[*e*]pyrene) are less or much less potent, indicating that the BaP is the most potent genotoxicant of the PAH assessed in that study (**Table 17**).

Table 17: Relative carcinogenic and mutagenic of single PAH (DECOS (2006) adapted from Collins et al. (1991)

PAH	Carcinogenicity[a]	Mutagenicity[a]
Dibenz[a,h]anthracene	1.11	0.47
Benzo[a]pyrene	1.00	1.00
Anthanthrene	0.320	0.06
Indeno[1,2,3,-cd]pyrene	0.232	0.14
Benz[a]anthracene	0.145	0.62
Benzo[b]fluoranthene	0.141	0.20
Benzo[k]fluoranthene	0.066	
Benzo[j]fluoranthene	0.061	
Pyrene	0.081	0.20
Cyclopentadieno[cd]pyrene	0.023	0.26
Benzo[ghi]perylene	0.022	0.08
Chrysene	0.0044	0.37
Benzo[e]pyrene	0.004	0.42

[a] BaP set equal to 1.00, other PAH were scaled to BaP. Adapted from Collins *et al.* (1991)[26].

8.2 Lack of specific scientific information

The toxicological and epidemiological data on PAH mixtures and single PAH is focused on the carcinogenic effects of PAH. There is only limited information on dose-response between PAH exposure and effects other than cancer. This limited evidence, however, indicates that cancer is the critical hazard at low levels of exposure.

As regards quantitative cancer risk, human epidemiological data on PAH mixture cancer risk is limited to risk estimates by air concentration of BaP. Non-human data indicate that other single PAH are less potent or at maximum of similar potency compared to BaP, however, such non-human data are available only for a number of PAH (see **Table 17**).

8.3 Groups at Extra Risk

No groups at extra risk were identified. However, it is noted that tobacco smoke contains PAH and thus under similar working conditions, smokers would have a higher overall PAH exposure than non-smokers.

9. Evaluation and recommendations

9.1 Cancer risk assessment

As described in Section 5, occupational exposure to PAH concerns almost exclusively exposure to PAH mixtures. These mixtures have a varying content of different PAH and those different PAH have different carcinogenic potencies. Moreover, only a minor fraction of all PAH or of all PAH mixtures have been tested in standard toxicological assays, let alone having been investigated in epidemiological studies. Due to this, the cancer risk assessment of PAH is complex.

The options identified and the one selected as the preferred option by recent OEL setting regulatory frameworks are first described in section 9.1.1. Thereafter, in section 9.1.2, the actual quantifications of cancer risk calculated by these bodies are described. The ECHA approach is described in section 9.1.3.

9.1.1 Consideration of possible exposure indicators for cancer risk assessment

The options identified by recent OEL setting regulatory frameworks are described below.

9.1.1.1 Inhalation route

RAC recently reviewed the alternative approaches that could be applied for assessing cancer risk after occupational inhalation exposure to coal tar pitch high temperature (CTPHT) (RAC, 2018). This assessment is directly cited: "*For occupational and environmental air measurements, BaP is usually chosen as the key indicator for PAH mixtures (e.g., Petry et al. (1996); Pufulete et al. (2004); Okona-Mensah et al. (2005)) because of (i) the large amount of available data on exposure and toxic effects of BaP, (ii) the availability of air-monitoring techniques for BaP, and (iii) the known and frequent human exposure to BaP in airborne PAHs.*

According to Petry et al. (1996), who tested and analysed various samples from coke plants, graphite production plants, carbon anode production plants, silicon carbide production plants, bitumen paving work and worksites of metal recycling process, the contribution of the carcinogenic potency of BaP alone is in the range of 27 – 67% of the activity of the different PAH mixtures. Petry et al. (1996) concluded that using BaP as an indicator of exposure (surrogate), and not considering the PAH profile variability, was justified as a practical tool for the assessment of health risks from both occupational and environmental exposure to PAHs in air.

Another well-established approach is the relative potency approach, i.e. to estimate the cancer risk related to exposure of a PAH mixture based on measured exposure to several constituents of the mixture and based on the carcinogenic potency of these constituents relative to the carcinogenic potency of BaP (Petry et al., 1996; Pufulete et al., 2004; Sidorov (2013); Purcaro et al. (2013); Jarvis et al., 2014; Lemieux et al. (2015)). This component-based approach requires analytical determination of the carcinogenic constituents in the mixture. The quantitative estimate of the carcinogenic potency of selected individual components of the mixture is then expressed as the toxic equivalency value (TEQ) in relation to the potency of BaP (expressed as BaP equivalents). Petry et al. (1996) reported that the approach using BaP alone underestimated risks by a factor of 1.1 to 2 in comparison with a relative potency approach for several occupational environments and one city environment.

Overall, it seems appropriate to assess occupational risks by using airborne BaP as an indicator of exposure to coal tar derived products including PAH mixtures released when CTPHT is heated to high temperatures (coal tar pitch volatiles). This pragmatic approach allows epidemiologic data to be used, where exposure is expressed using BaP as an exposure indicator as well."

DECOS (2006) noted that the complex composition of PAH mixtures raises the question of the best indicator for PAH exposure in ambient air. DECOS considered the options of (1) BaP as unique indicator, (2) a selection of PAH and (3) total PAH (benzene soluble matter).

> For option 2, DECOS concluded that "*a main disadvantage in using a selection of PAH is that at present no accepted selection of PAH is available as a marker for PAH exposure. Furthermore, only a limited number of data is available in which a selection of PAH is used for health risk assessment. Consequently, comparisons among different investigations are hampered".*
>
> For option 3, DECOS concluded that *a "main disadvantage of using BSM as exposure parameter is that it may include non-PAH substances released from sources other than the typical PAH-sources. As a result, BSM values are source dependent and may strongly be influenced by additional non-PAH sources in the vicinity of the sampling site. This makes the marker less attractive for risk assessment."*
>
> DECOS concluded that among options 1 to 3, option 1 (BaP as unique indicator) was the preferred option, because i) validated and standardised analysis techniques are available, ii) in the past thirty years, most exposure data have been presented with BaP as exposure indicator, and iii) BaP is considered as one of the more potent PAH carcinogens. As a result, the excess cancer risk estimated for PAH exposure is expressed as the concentration of BaP in the air.

DECOS further noted that their recommendation is valid for BaP and other PAH derived from coal. Various measurements have pointed out that by current industrial use of coal, the variation between BaP and other PAH contributes to a limited degree in the whole set of uncertainties. However, this relationship will be disturbed when, for instance, BaP (but not the other PAH) is filtered out before the PAH mixture is emitted in the air. In those cases, a readjustment of the recommendation is advised.

AGS (2011) concluded that "*the decisive effect for risk assessment purposes is the carcinogenic effect of BaP as an individual substance in animal studies as well as its carcinogenic effect in humans for PAH mixtures containing BaP. The carcinogenic effect of such PAH mixtures is primarily attributed to the polycyclic aromatics with 4 to 7 rings, and BaP - as representative of this fraction with relatively high carcinogenicity - is used as exposure marker for the assessment of the carcinogenic potency of these complex mixtures. This presupposes, however, that these mixtures do not contain any substantial amounts of other carcinogenic substances in addition to PAH (such as aromatic amines or diesel soot particles). Furthermore, a risk quantification based on the BaP content only applies to PAH mixtures of similar composition. As an alternative to a quantitative risk assessment based on a single substance acting as an exposure marker, an assessment has been repeatedly proposed using equivalence factors for various carcinogenic PAH. This approach is not pursued in this context. On the contrary, the exposure-risk relationships and the tolerable risks and acceptable risks derived from them are related to "total PAH" with a given BaP concentration and a given PAH profile (similar to coking plant emissions)."*

SCOEL (2006) did not discuss extensively approaches other than BaP as unique indicator but concluded "*Although it might be desirable to monitor total PAH or a selection of PAH, considering the vast and consistent amount of data presented for benzo[a]pyrene and the fact that benzo[a]pyrene is considered as one of the more potent PAH carcinogens, most available studies have preferred the use of benzo[a]pyrene as a marker substance for overall airborne PAH exposure for practical reasons. Validated analytic techniques are available to measure benzo[a]pyrene in air. Therefore, SCOEL considers benzo[a]pyrene*

as a quantitative indicator for general airborne PAH exposure to be an acceptable procedure in practice."

9.1.1.2 Dermal route

Exposure via the dermal route contributes to systemic exposure and thus may contribute to the dose-response relationship derived from epidemiological studies for air concentrations. However, the predominant route of exposure will depend on the occupational setting, and, although cancers occur from systemic exposure, the route of exposure influences significantly the site where local cancers occur (i.e., lung cancers can be expected to arise mainly from exposure via inhalation and skin cancers from dermal exposure).

RAC recently reviewed the alternative approaches that could be applied for assessing cancer risk after occupational dermal exposure to coal tar pitch high temperature (CTPHT) (RAC 2018). This assessment is directly cited below.

"In certain cases, dermal absorption of PAHs is of special concern and may be a significant or even the main route of exposure (ATSDR, 1995). A group of coke workers underwent an intensive skin monitoring program combined with personal air sampling and biological monitoring based on 1-OHP as a biomarker of exposure (VanRooij et al., 1993b). Mean total skin contamination of 12 workers ranged between 21 and 166 µg pyrene per day. The dermal uptake of pyrene ranged between 4 and 34 µg/day, which was about 20% of the pyrene contamination of the skin. The mean respiratory uptake of pyrene varied between 0.5 and 32.2 µg/day. It was estimated that an average of 75% of the total absorbed pyrene enters the body through the skin. Therefore, dermal absorption was responsible for the main portion of pyrene intake as measured by 1 OHP excretion (VanRooij et al., 1993b).

IARC (2010) expressed the growing awareness that occupational uptake of PAHs through the skin is substantial (Jongeneelen, 2001). For example, uptake of pyrene by the dermal route was estimated to account for as much as 75% of total body dose for coke-oven workers (VanRooij et al., 1993b); for creosote-impregnating workers, dermal pyrene uptake was on average 15-fold higher than the estimated respiratory uptake (VanRooij et al., 1993c). Urinary levels of 1-hydroxypyrene also reflect dermal uptake and therefore should be interpreted as a measure of uptake via both inhalation and the skin. Creosote applied topically to mouse skin in vivo or human skin in short-term organ culture produced a complex pattern of aromatic DNA adducts with similar levels in both systems (Schoket et al. (1988a), Schoket et al. (1988b)). Multiple topical treatments of mice with creosote resulted in accumulation of DNA adducts in lung tissues (Schoket et al., 1988a). Extracts of soil samples from a wood-preserving waste site known to contain creosote and pentachlorophenol were topically applied to mouse skin. Aromatic DNA adducts were detected in distal organs (lung, liver, kidney and heart) as well as the skin. The anti-benzo[a]pyrene-7,8-diol-9,10-oxide–deoxyguanosine adduct was detected in all organs (Randerath et al. (1996), Randerath et al. (1997)).

Other findings as for distal target organs were confirmed by the study of Letzel and Drexler (1998) that described an extended case series of skin tumours among German tar-refinery workers. Among the various histologies, 380 squamous-cell carcinomas, 218 basal-cell carcinomas and 182 keratoacanthomas were reported. Some cases had multiple tumours. The authors noted that the ratio of squamous- to basal-cell carcinomas was 1.7:1 in contrast to a ratio of 1:10 in the German population. Most of the tumours occurred in areas that had been in contact with the tar or tar fumes, notably the facial area, forearms and hands.

Based on current knowledge dermal exposure in humans is related with cancers in areas of first contact with the body and its effect is rather local than systemic.

Dermal exposure to PAHs and absorption through the skin may contribute to exposure of workers in aluminium plants and related carbon electrode-manufacturing (IARC, 2012)

Exposures have been intensively (bio)monitored and have been shown to have decreased over time for some activities, such as in anode pre-baking plants (Benke et al., 1998), but less so in anode manufacturing (Hopf et al., 2009).

(VanRooij et al., 1992) showed that, in pot-rooms and anode pre-bake plants, dermal exposures do not always correlate with inhalation exposure. Measured levels of BaP were two-times higher on the wrists of workers in a bake-oven area, than the wrists of workers from a paste plant. However, exposure of bake-oven workers to BaP by inhalation was four times lower than for workers in the paste plant, while exposure to pyrene by both inhalation and dermal contact was higher in the paste plant.

Professional workers may be dermally exposed to CTPHT in mixtures or articles. Professional, wide-dispersive uses include paints, coatings, sealants and waterproofing materials, and use of clay pigeons. Exposure of professional workers is decreasing, as uses in coatings, paints and sealants are being phased out with suitable alternatives now available. Uses in roofing and road construction (which accounts for < 2% of sales according to CSRs submitted by registrants) are being phased-out in preference for petroleum pitch products where the PAH level is significantly lower than coal tar pitch without considerable lowering of the carbon content. Only specialised applications such as anti-kerosene coating for parking lots, airfields, taxi ways and fuel stations still use pitch emulsions (RIVM, 2008).

Similarly, some uses in heavy-duty corrosion protection and waterproof coatings are being phased-out (e.g. ships and quays), but some remain (e.g. coating of pipelines and nuclear waste containers). This market, together with CTPHT-containing kerosene proof coatings represents ca. 2 000 tonnes of CTPHT per year according to information from the public consultation on economic impacts of inclusion of CTPHT in REACH Annex XIV as submitted by the Coal Chemicals Sector Group at CEFIC (European Chemical Industry Council).

Use as a binding agent in clay pigeons is also decreasing as manufacturers move towards more environmentally friendly products that use petroleum-based binders or none at all (RIVM, 2008).

Overall, it can be concluded that dermal exposure may be significant to both local (skin) and systemic cancers in occupational settings. For local cancers from direct dermal contact with CTPHT in articles, BaP may again be chosen as the relevant indicator of exposure. Any contribution from dermal exposure to bladder cancer (and possibly lung cancer) risks is inherently accounted for in the dose-response relationships derived for bladder (and lung) cancers from epidemiological studies for air concentrations."

It is noted that RAC (2018) finally derived ERRs also by urine concentration of 1-hydroxypyrene and for urine concentration of 3-hydroxybenzo(a)pyrene. The ERRs were derived from correlation of airborne BaP and these two biomarkers and then applying that to the ERR by airborne BaP (see section 9.1.2.4).

As regards biomonitoring DECOS (2006) concluded that "*Internal benzo[a]pyrene and PAH exposure can be assessed using biological monitoring techniques (e.g., 1-hydroxypyrene in urine, and DNA- and protein adducts in blood and tissues). Biological monitoring is not only useful in protecting worker health and minimising exposure, but also for quantitative occupational cancer risk estimation. However, since biological monitoring represents total body burden, and thus dermal, oral and inhalation exposure cannot be separated, it cannot readily used for the risk estimation in this document, which is based on inhalation exposure alone."* DECOS (2006) also assigned a skin notation to PAH (see section 9.1.2.1).

The German MAK Commission derived a correlation between the BaP metabolite 3-OHBaP in urine (ng/g creatinine) and BaP in the air (µg/m³). There is also a biological reference value (Biologische Arbeitsstoff-Referenzwerte) of 0,3 µg/g creatinine for 1-OHP derived for non-smokers (DFG, 2021). A skin notation (Hautres) is also assigned to PAH (DFG, 2021).

SCOEL (2006) reviewed the biomonitoring data and methods for 1-OHP and other PAH metabolites (see section 9.1.2.1) and proposed a Biological Guidance Value (BGV) of 0.5

µg 1-OHP/g creatinine. SCOEL also noted the recent development for biomonitoring of 3-OHBaP in urine and considered that when more studies will be available, it might lead to the development of an additional BGV for 3-OHBaP. SCOEL also assigned a skin notation to PAH containing BaP (See section 9.1.2).

9.1.1.3 Conclusion

It is noted that national and international bodies, after having considered various options, including approaches based on toxicological equivalency of several marker PAH compared to BaP, concluded that BaP is the most robust marker of PAH-related cancer risk via inhalation route. This is mainly due to the abundance of quantitative data on the level of cancer risk and the fact that BaP is considered as one of the most potent genotoxic carcinogens and thus a conservative surrogate for the overall PAH risk. BaP may, however, not be a suitable marker in settings where its presence is low, either due to restrictions that are in place or due do its physicochemical properties (not very volatile in low temperature processes). As regards systemic exposure via dermal route, the urine concentration of 1-hydroxypyrene and for urine concentration of 3-hydroxybenzo(a)pyrene have been recommended as suitable indicators by some, but not all bodies.

9.1.2 Published approaches for cancer risk assessment

The carcinogenic PAH are considered non-threshold carcinogens and consequently no health-based OELs have been recommended by national and European assessments. Instead, excess risk relationships have been derived to set regulatory standards. These approaches are quite consistent as regards main choices, while some differences exist as regards how the scope in terms of PAH covered has been defined, how different cancer sites have been considered and as regards the role of biomonitoring.

9.1.2.1 The Netherlands

DECOS (2006) derived health-based calculated - occupational cancer risk values (HBC-OCRV) of BaP. The scope of the evaluation was restricted to BaP and unsubstituted non-heterocyclic PAH from coal-derived sources. DECOS noted that coal-derived sources are not the only source at which PAH may be formed by incomplete combustion; other examples are wood, petroleum, and gas oil. However, DECOS considered that the main problem with these sources is that they contain relatively high concentrations of other substances than PAH. Some of these are carcinogenic, just as PAH. Therefore, DECOS was not able to combine data from these different sources to estimate reliable cancer risk values for PAH, and thus left these data aside the evaluation.

DECOS (2006) derived an exposure-risk relationship (ERR) based on BaP from the unit relative lung cancer risk of the meta-analysis of Armstrong et al. (2003, 2004). The unit relative risk of all studies, i.e., RR=1.20 per 100 µg/m^3 BaP years was taken as the point of departure. DECOS used the Dutch male population rates when converting the relative risk estimate to absolute excess cases of lung cancer. The following BaP HBC-OCRVs associated with excess mortality levels of 4 per 1000 and 4 per 100000 as a result of working life exposure (40 years) are:

- 550 ng/m^3 of BaP, excess risk 4 per 1000
- 5.7 ng/m^3 of BaP, excess risk 4 per 100000

DECOS considered only lung cancer when deriving the cancer risk values. Concerning bladder cancer, DECOS noted that possible co-exposure to other carcinogenic compounds, such as 2-naphtylamine, which are known to induce bladder cancer could not be ruled out in epidemiological studies having assessed bladder cancer risk from exposure to PAH. Overall, DECOS considered the evidence inconclusive as regards increased risk for cancer in humans in organs other than lung and the skin. Therefore, DECOS considered that it is unclear whether inhalation or dermal exposure of PAH may lead to tumours at other sites of the body than the lungs or skin, respectively.

DECOS noted that skin absorption of PAH occurs to significant amounts but did not find proof that BaP or other PAH compounds add substantially to systemic non-carcinogenic adverse health effects by dermal exposure. However, as both human and animal studies have clearly shown a positive association between dermal exposures to PAH, by direct contact on the skin, and skin cancer risk, DECOS considered that a skin notation is justified.

DECOS noted that the internal BaP and PAH exposure can be assessed using biological monitoring techniques (e.g., 1-OHP in urine, and DNA- and protein-adducts in blood and tissues). DECOS further noted that biological monitoring would not only be useful in protecting worker health and minimising exposure, but also for quantitative occupational cancer risk estimation. However, since biological monitoring represents total body burden, and thus dermal, oral and inhalation exposure cannot be separated, DECOS considered that it cannot readily be used for the risk estimation in their evaluation, which was based on inhalation exposure alone.

9.1.2.2 Germany

AGS (2011) derived an exposure-risk relationship (ERR) based on BaP from the unit relative lung cancer risk of the meta-analysis of Armstrong et al. (2003, 2004). The unit relative risk of all studies, i.e,. RR=1.20 per 100 µg/m^3 BaP years was taken as the point of departure. AGS noted that the lung cancer rates are higher in men than in women and decided to use German male population rates when converting the relative risk estimate to absolute excess cases of lung cancer. The following BaP levels associated with excess mortality levels of 4 per 1000, 4 per 10000 and 4 per 100000 as a result of working life exposure (40 years) are:

- 700 ng/m^3 of BaP, excess risk 4 per 1000
- 70 ng/m^3 of BaP, excess risk 4 per 10000
- 7 ng/m^3 of BaP, excess risk 4 per 100000

AGS (2011) also did two alternative calculations. When using reference rates of the entire German population (instead of males only), the reference excess risk levels of 4 per 1000 or 4 per 10 000 corresponded to about 50% higher BaP levels (1050 and 109 ng/m^3, respectively). When using a rat cancer bioassay as the basis of risk calculations, the reference excess risk level of 4 per 1000 corresponded again to an about 50% higher BaP level (1116 ng/m^3).

Concerning bladder cancer, AGS noted that in their meta-analysis, Armstrong et al. (2003, 2004) also studied the relationship between occupational PAH exposure and cancer of the bladder. The database was generally poorer, and the average number of cases was considerably lower than for lung cancer. The overall results and the significance depended to a large extent on two major studies from the aluminum industry. Without these studies, there was no clear evidence for a correlation between the incidence of bladder cancer and PAH exposure in coking plants or other industrial sectors. AGS also reviewed a number of other studies on PAH exposure and bladder cancer risk. After the review AGS considered only lung cancer when deriving the cancer risk values.

The German MAK Commission derived a correlation between the BaP metabolite 3-OHBaP in urine (ng/g creatinine) and BaP in the air (µg/m³) (See section 6.2.2). There is also a biological reference value (Biologische Arbeitsstoff-Referenzwerte) of 0,3 µg/g creatinine for 1-OHP derived for non-smokers (DFG, 2021). A skin notation (Hautres) is also assigned to PAH (DFG, 2021).

In TRGS 551 "Tar and other pyrolysis products from organic material" AGS (2015) specifies how the derived BaP levels apply to the protection of employees and other persons during activities with pyrolysis products made of organic material that have a BaP concentration of 50 mg/kg and more. The above excess risk estimates by BaP are referred as regards tolerable and acceptable risk and with reference to the tiered approach of risk reduction

of TRGS 910 that were taken into account when defining the protective measures of PAH covered by TRGS 551. TRGS 551 further states that "*depending on the risk assessment, other PAHs may also be used for the exposure assessment. As a rule, the 16 PAHs are then determined according to U.S. EPA (United States Environmental Protection Agency)*."

As regards the scope, TRGS describes that "*activities involving organic pyrolysis products with a concentration of BaP of 50 mg/kg or more*", TRGS 551 gives a list of products and processes which, in particular, are concerned. These include the ones listed in points 2 to 6 (see TRGS 551 for exact wording):

2. Technically produced pyrolysis products made of organic material include:

1. Coal tar and coal tar-pitch from the pyrolysis (coking) of hard coal,

2. Tar distilled from lignite and lignite tar pitch from the pyrolysis (coking) of lignite,

3. Pyrolysis oils from the pyrolysis of oil fractions to olefins, diolefins, acetylene and homologues (cracking process),

4. Pyrolysis oils from the pyrolysis of methane and products similar to natural gas,

5. Gasification tars from pyrolysis of coal and petroleum fractions into synthesis gas,

6. Liquid products from processes for the transfer of solid organic matter (e.g. carbon hydrogenation),

7. Coke oils from the carbonisation process of petroleum fractions,

8. Wood tar from the pyrolysis of wood,

9. Pyrolysis oils from pyrolytic recycling processes of scrap tires and plastics waste,

10. Technical soot from the transfer of suitable petrochemical and coal-chemical raw materials.

3. Some technically produced pyrolysis products are separated into distillates and distillation residues by distillation which are technically utilised.

4. Pitch used in the refractory industry for the production of heat-resistant products, in the steel and iron industry for the use of special refractory products and in the optical industry as a sealant agent for the production of lenses.

5. Processes in which pyrolysis products from organic material are unintentionally produced as a by-product or intermediate product under the special conditions of handling from other substances, e.g. during the course of a desired chemical reaction. These include, but are not limited to

(i). Casting of iron and steel in the presence of organic materials,

(ii). Combustion processes in heating installations with incomplete combustion.

6. Unintentionally produced pyrolysis products from organic material contained in e.g., used engine oil or are adsorbed on soot from combustion installations. In particular, when heating with brown or hard coal and burning wood with poor burn-up, the resulting soot can have BaP content of more than 50 mg/kg.

9.1.2.3 SCOEL

SCOEL (2016) recommendation 404 addressed "Polycyclic Aromatic Hydrocarbon mixtures containing BaP (PAH)". SCOEL considered that the most extensively studied PAH as surrogate for total airborne PAH exposure is BaP which is released from a great variety of different PAH sources. SCOEL noted that BaP is considered as one of the strongest genotoxic carcinogens, which significantly contributes to the carcinogenic potency of PAH-rich mixtures. SCOEL considered BaP as a quantitative indicator for general airborne PAH exposure to be an acceptable procedure in practice.

SCOEL noted that the ERRs derived by DECOS and AGS were almost identical and took the mean of them as ERR for risk of lung cancer by airborne level of BaP:

- 6 ng/m^3 of BaP, excess risk 4 per 100000

It is noted that as DECOS and AGS both assumed a 40-year occupational career, that was also assumed by SCOEL. SCOEL did not find the data robust enough to consider also bladder cancer in the risk calculations.

SCOEL noted that occupational exposure studies, in which the urinary excretion of 1-OHP was determined together with external exposure to pyrene, clearly indicate that a large part of the amount excreted had entered the body through the skin. This was supported by experimentation in animals. Therefore, SCOEL considered a skin notation warranted. SCOEL also noted that exposure of the skin to PAH should also be avoided because it is known that dermal exposure to PAH leads to an increased risk of skin cancer.

SCOEL also reviewed the biomonitoring data and methods for 1-OHP and other PAH metabolites. SCOEL noted that in general, the urinary excretion of 1-OHP does not exceed 0.5 µg 1-OHP/g creatinine (determined after conjugate hydrolysis) in the urine of people not occupationally exposed to PAH. This value also includes smokers, who are not occupationally exposed. Exceeding this value points to occupational PAH exposure, by any route of entrance into the body. Therefore, SCOEL proposed this value of 0.5 µg 1-OHP/g creatinine as a Biological Guidance Value (BGV). SCOEL also noted the recent development for biomonitoring of 3-OHBaP in urine and considered that when more studies will be available, it might lead to the development of an additional BGV for 3-OHBaP. SCOEL did not propose a BLV.

9.1.2.4 ECHA/RAC

In the context of the authorisation process of Coal Tar Pitch High Temperature (CTPHT) RAC (ECHA, 2018) derived an exposure-risk relationship (ERR) based on BaP from the meta-analyses of Armstrong et al. (2003, 2004). The ERR was derived separately for lung cancer and for bladder cancer. Although the ERR was derived for CTPHT, the unit relative risk of all studies, i.e., RR=1.20 per 100 µg/m^3 BaP years for lung cancer and RR=1.33 per 100 µg/m^3 BaP years for bladder cancer were taken as the point of departure. Male population rates of EU were used for both cancer sites when converting the relative risk estimates to absolute excess cases of cancer. The (linear) lung cancer ERR is very similar to the ones derived by DECOS, DFG and SCOEL, just reflecting differences in lung cancer reference rates over time and population (national vs EU). For example, the following BaP levels would correspond to the 4 per 1000, 4 per 10000 and 4 per 10 000 excess lung cancer risks (assuming 40 year occupational career):

- 710 ng/m^3 of BaP, excess risk 4 per 1000
- 71 ng/m^3 of BaP, excess risk 4 per 10000
- 7.1 ng/m^3 of BaP, excess risk 4 per 100000

RAC considered also bladder cancer as an established CTPHT-related cancer site, the following BaP levels would correspond to the 4 per 1000, 4 per 10000 and 4 per 10 000 excess bladder cancer risks:

- 1000 ng/m^3 of BaP, excess risk 4 per 1000
- 100 ng/m^3 of BaP, excess risk 4 per 10000
- 10 ng/m^3 of BaP, excess risk 4 per 100000

As RAC considered both lung cancer and bladder cancer as established CTPHT-related cancer sites, it can be estimated that the following BaP levels would correspond to the 4 per 1000, 4 per 10000 and 4 per 10 000 excess lung+bladder cancer risks, when arithmetically just adding lung cancer and bladder cancer risk functions:

- 420 ng/m^3 of BaP, excess risk 4 per 1000
- 42 ng/m^3 of BaP, excess risk 4 per 10000
- 4.2 ng/m^3 of BaP, excess risk 4 per 100000

RAC further derived, from animal data, an excess risk relationship between dermal exposure to BaP (µg BaP/cm^2/day) and excess risk of skin cancer.

In the CTPHT authorisation process, RAC also derived a correlation between airborne BaP and 1-OHP in urine as well as between airborne BaP and 3-OHBaP in urine. Both correlations were derived from studies having included only workers with mainly inhalation exposure (Unwin et al. (2006) and Lafontaine et al. (2004), respectively). The correlation between BaP in air and 3-OHBaP in urine is identical to the one derived by the German MAK Commission (see section 6.2.2), apart from urine concentrations being expressed as nmol/mol creatinine by RAC and ng/g creatinine by MAK.

The Armstrong lung cancer studies were also selected as key studies for human inhalation exposure in the RAC opinion on Restriction of use of polycyclic aromatic hydrocarbons in granules or mulches used as infill material in synthetic turf pitches or in loose form on playgrounds and in sport applications (ECHA 2019a). The restriction covered the eight PAH substances of Entry 50 of Annex XVII (see section 3.4). The above-mentioned ERR for lung cancer risk by BaP concentration in air was reiterated in that RAC Opinion.

9.1.2.5 France

In France there is no official OEL for PAH. However, there is a recommendation by the national health insurance fund CNAM (Caisse Nationale d'Assurance Maladie) for a provisional target level below 150 ng/m^3 BaP in certain industries with exposure to PAH (INRS, 2016).

9.1.2.6 Finland

An OEL of 10 µg/m^3 for BaP, accompanied by a skin notation, was set in 2005 (STM, 2005). A weight-of evidence approach was used when the value was set, using animal carcinogenicity data and risk estimates presented by IPCS (1998), as key sources. The OEL from 2007 for naphthalene is 1 ppm (8h TWA), and the short-term value 2 ppm (15 minutes) (STM, 2007). The values are based on respiratory tract irritation.

The Finnish Institute of Occupational Health (FIOH) has introduced, so called target levels for PAH (FIOH, 2016). Target levels are voluntarily applied guideline values intended to improve the conditions beyond the OEL-defined levels. They represent exposure levels which are achievable by good working practices and advanced control technology, with minimal health or comfort effects, but are not health-based, as such. The target levels for PAH use BaP as the indicator substance for hot processes and naphthalene as the indicator substance for creosote wood preservation and for indoor air.

The following values were introduced for BaP in hot processes:

OEL for BaP 10 µg/m^3

- Target level for BaP
  - Coke oven plants: <0.1 µg/m^3
  - Other workplaces: <0.01 µg/m^3

The following values were introduced for naphthalene in creosote wood preservation and for indoor air:

OEL for naphthalene 5 mg/m^3

- Target level for naphthalene
  - Creosote wood preservation and processing preserved wood: <0.05 mg/m^3
  - Ambient indoor air: <0.002 mg/m^3

FIOH recommends using 1-OHP in urine as the marker for biomonitoring PAH exposure. A biological limit value ("action limit") of 12 nmol 1-OHP/l urine was identified (FIOH, 2011). As reliable dose-response data were not available, the basis for the recommended value was the 90th percentile of urine 1-OHP concentrations in 2008, among workers of a Finnish coke oven plant which applied good occupational hygiene practice. The value was also recommended for any other sectors as samples collected in 8 other risk industries in 2005-2007 showed 90th percentiles below 12 nmol 1-OHP/l urine.

9.1.3 Cancer risk assessment

Although not all PAH mixtures have been investigated in experimental or (observational) epidemiological studies, it is concluded based on general mode of action considerations that PAH should be considered non-threshold carcinogens. BaP is a potent PAH with an abundant human database on cancer risk. Thus an exposure risk relationship (ERR) is derived to characterise the excess cancer risk by concentration of airborne BaP. It is noted that the ERR will be applied to a variety of PAH resulting from incomplete combustion and pyrolysis (thermal degradation) processes of organic material. A PAH-related excess of lung cancer has been quite consistently observed following exposure to PAH mixtures in various industries. The ERR is thus derived for lung cancer risk.

As explained in section 9.1.2.4, in the context of the authorisation process of Coal Tar Pitch High Temperature (CTPHT), RAC (ECHA, 2018) derived an exposure-risk relationship (ERR) based on BaP from meta-analyses of Armstrong et al. (2003, 2004). The (linear) lung cancer ERR used the unit relative risk of all studies, i.e., RR=1.20 for lung cancer from cumulative exposure of 100 µg BaP/m^3-years. This cumulative exposure was distributed over a 40-year working career (i.e., a yearly average airborne concentration equalling 2.5 µg BaP/m^3). The relative risk was converted to absolute excess cases of lung cancer using a life-table approach and EU male population reference rates for lung cancer (**Table 18**). It is noted that as lung cancer rates are higher among males than females, using the male population rates results in more conservative excess risk estimates in comparison to calculations using data on both genders. It is noted that male rates were used both by DECOS (2006) and AGS (2011) and consequently also by SCOEL (2016) which used the average of DECOS and AGS.

It is noted that the meta-RR from Armstrong et al. (2003,2004) is based on 39 cohorts representing 9 different main occupational settings with PAH exposure, and the variety of jobs and tasks therein. Thus, they represent an average and quite comprehensive view on published real-life exposures. It is proposed to use the ERR already established by RAC (2018) which is based on this representative meta-RR converted to absolute excess risk estimates using EU male population reference rates. As explained in Section 7.7.1 the exposure metric refers to inhalable fraction of particles. It is proposed to use BaP as a marker of cancer risk for carcinogenic PAH mixtures, i.e the ERR is not calculated for BaP alone but for (combustion/pyrolysis-derived) PAH mixtures using BaP as an exposure indicator

Table 18: Lung cancer exposure-risk relationship after a 40-year working life exposure to a given 8-hour air concentration for five working days a week

Air concentration of BaP (ng/m^3)	Excess life-time lung cancer risk (cases per 100 000 exposed)
1	0.56
2	1.1
5	2.8
10	5.6
20	11
50	28

Air concentration of BaP (ng/m^3)	Excess life-time lung cancer risk (cases per 100 000 exposed)
100	56
200	110
500	280
1000	560

In Section 9.1.2.4, for the ease with comparison with AGS, DECOS and SCOEL, the same ERR was presented for BaP levels that would correspond to excess life-time cancer risks of 4 per 1000 etc. Instead, in **Table 18** it is presented for some rounded levels of BaP content.

9.1.4 Uncertainties

The proposed approach is based on a single indicator substance, BaP, which would be applied to control cancer risk from a variety of PAH mixtures. BaP is a very potent carcinogenic PAH. Therefore the ERR which is derived from a large number of human epidemiological studies representing exposure from a large variety of processes and industries and using the potent BaP as risk marker is considered a representative proxy of the overall cancer risk of PAH exposure from various combustion and pyrolysis sources. It is noted that in epidemiological stuides related to occupational PAH exposure and using BaP as exposure measure, the total effects recorded always include all other (less carcinogenic) PAHs. Therefore it is considered to be a valid strategy to use the carcinogen BaP as a reference (Petry et al. 1996). However, in some occupational settings, the exposure results from PAH contained in the materials used and the content of certain single PAH, including BaP in those products, is already heavily restricted. This results in low workplace concentrations of these restricted PAH while leaving the possibility of exposure to other non-regulated PAH (see e.g., creosote wood impregnation and tyre manufacturing in sections 5.2 and 5.3). In such settings it would be preferable to monitor exposure to a wider variety of PAH, e.g., the 16 EPA PAH, even if they were less carcinogenic than BaP. However, the available toxicological and epidemiological data does not allow deriving quantitative ERRs or other benchmarks for such an approach. It is noted, however, that the exposure minimisation principle of CMRD would apply to any carcinogenic PAH.

The ERR is derived for lung cancer. There are also indications of an elevated risk of bladder cancer in some industries with PAH exposure. However, the evidence is less consistent than for lung cancer and limited to only a few specific industries some of which also entailed exposure to known bladder carcinogens, i.e., aromatic amines. Therefore confounding from such exposures cannot be excluded. This would mean that an ERR derived for bladder cancer risk by BaP as a proxy of exposure would be confounded and would not correctly describe the cancer risk in all PAH related exposures. The calculations made by RAC (see section 9.1.2.4) allow to estimate that if, instead, this association actually would not be a result of confounding in any of the cohorts included in the meta-analysis used and would thus apply to all industries and processes with PAH exposure (in addition to the lung cancer risk), it would influence the overall cancer ERR with a factor of 1.7. That can be considered as a maximum of such an effect as the estimation based on simple addition of the two ERRs does not take into account any effect of reduction of survival in individuals already contracting one of the two cancers.

9.1.5 Observations regarding Annex I of Directive 2004/37/EC

Article 2 of Directive 2004/37/EC defines carcinogens and mutagens. In addition to carcinogenic substances covered by Art 2 (a) (i) and (ii), the section (iii) defines as carcinogens substances, preparations and processes listed in Annex I of CMRD. Annex I

currently has the following entry:

- Work involving exposure to polycyclic aromatic hydrocarbons present in coal soot, coal tar or coal pitch

It seems necessary to revise that entry in a way that covers more comprehensively the carcinogenic PAH exposures. One way would be analogous to the hard wood dust entry in the same Annex which refers to the related IARC monograph listing "some" of them. However, PAH are covered by various IARC monographs (see section 1 for references) and there would be a need to refer to several of them. A second way would be similar to the ones used in the titles of some recent national documentations, e.g., "PAH from tar and other pyrolytic products made of organic material" or "BaP and PAH from coal-derived sources" by analogy to TRGS 551 (AGS 2015) and DECOS (2006), respectively. A more comprehensive listing of relevant similar processes is used by TRGS 551 (see section 9.1.2.2).

It is noted that the selection of level of detail for the above definition is also a question of legal certainty and clarity and thus rather a legal wording issue than a scientific question.

9.1.6 Other observations

It is noted that naphthalene is a monoconstituent PAH substance. Naphthalene has also been linked to human cases of haemolytic anaemia (HSE, 2018). In addition, naphthalene has a harmonised classification as Carc. 2, and is thus not in the scope of CMRD.

As described in section 3.1, naphthalene has an indicative OEL under CAD and it has been suggested it may need a revision (HSE, 2018). Although monitoring of naphthalene may also contribute to the risk management of PAH mixtures in general, a revision of the OEL specifically for naphthalene would be in the scope of CAD and would require focusing also on non-cancer endpoints and an approach not following the same principles as an OEL setting for non-threshold carcinogenic PAH that fall under CMRD. Consequently, naphthalene has not been further assessed in this report.

9.2 Derived Occupational Exposure Limit (OEL) Values

9.2.1 Published approaches to establishing OELs

As explained in section 9.1.1, PAH are considered non-threshold carcinogens and consequently no health-based OELs have been recommended by national and European assessments. Instead, excess risk relationships have been derived to set regulatory standards according to national practices, e.g., concerning predefined excess cancer risk levels agreed at national level.

9.2.2 Occupational Exposure Limits (OELs) - 8h TWA

BaP and PAH containing BaP are considered non-threshold carcinogens and consequently no health-based OELs can be recommended. Instead, an ERR for lung cancer has been derived in section 9.1.3.

As described in section 7.8.2 inhalation studies in rats identified LOAECs of 25 µg BaP/m³ for foetal survival (Archibong et al., 2002), 75 µg BaP/m³ for reduced testis weight (Archibong et al., 2008) and 100 µg BaP/m³ for ovulation rate effects and reduced pups/litter number (NOAEC 75 µg BaP/m³). It is noted that these studies are unique, there are no other inhalation studies on reproductive toxicity. All other studies either find no impact on fetal mortality or testes weight and/or used far higher doses via different exposure pathways.that other studies via different exposure routes found higher effect levels. OELs could be based on the described LOAECs (i.e. 25 µg/m³ resp. 75 µg/m³) or NOAEC (75 µg/m³) for effects on reproduction/development. The mentioned studies would provide OELs for the respirable fraction, while the ERR is related to the inhalable fraction. As no mass median aerodynamic diameters (MMAD) are given in these studies, the respirable and deposited fraction in rats and humans cannot precisely be derived. As a

result, OEL derivation from the studies by Archibong et al. must be considered with caution. The lowest respirable fraction OEL from the Archibong studies would be derived as follows:

A LOAEC of 25 µg BaP/m³ for foetal survival was provided from Archibong et al. 2002. Using default factors for inter- and intraspecies differences, 4 h/d to 8 h/d, LOAEC to NAEC (i.e. 2.5 × 5 × 2 × 3) x 6.7 m³/10 m³ results in a human NAEC of 223 ng BaP/m³ for the respirable dust fraction. A time extrapolation factor is not needed as the exposure time covered pregnancy/foetal development periods.

Assuming a 20% proportion of respirable fraction of the inhalable fraction, would mean that a putative OEL for reproductive toxicity related to respirable dust would be complied with levels of up to 1 µg BaP/m³ (= 1000 in ng BaP/m³) inhalable dust. This corresponds to the upper end of the cancer ERR and thus a high residual cancer risk. Therefore, there seems to be no need to establish a separate OEL for respirable dust based on non-cancer effects, as prevention of such risks would be expected to be covered by the putative risk-based OELs based on carcinogenic effects.

9.2.3 Short Term Exposure Limits (STELs)

As described in Sections 7 and 9, most of the available toxicological and epidemiological evidence concerns hazardous effects from long-term exposure, especially lung cancer. There is no obvious evidence indicating a particular hazard from short-term exposure. It is concluded that it is not justified to recommend a STEL for BaP as an indicator substance or for any other specific PAH.

9.2.4 Biological Limit Value (BLV)

As BaP and PAH are considered non-threshold carcinogens, an ERR is derived in section 9.1.3 describing the excess lung cancer risk by level of airborne BaP.

The actual OEL will be set later in the legislative process taking also into account socio-economic aspects. It is recommended that after the OEL has been defined, the correlations between BaP in the air and 1-OHP and 3-OHBaP in urine, described in section 6, are used to set BLVs for either 1-OHP or 3-OHBaP that correspond to the decided OEL for BaP. As an alternative, BGVs could be defined either based on the general population reference concentrations observed for 1-OHP described in section 6. More specifically, a BGV for 1-OHP could be defined as an overall PAH exposure control trigger with further argumentation presented in section 9.2.5.

9.2.5 Biological Guidance Value (BGV)

The most widely and routinely used biomonitoring method for assessing occupational PAH exposure is to measure urinary 1-OHP, a major metabolite of pyrene (see section 6.2). Pyrene has a high thermodynamic stability rendering it one of the most predominant PAH in virtually any mixture of PAHs. As a consequence, it can serve as a universal marker for exposure to PAH. Due to its structure, its metabolism is also less prone to interindividual genetic variation compared to many other PAH. A relatively large proportion of pyrene is excreted in the urine as 1-OHP, which facilitates its detection. A limitation is that pyrene is not carcinogenic and therefore not a direct indicator of cancer risk. 1-OHP background levels in urine of occupationally unexposed adults are available for some European countries (see section 6.2.1). These indicate 95th percentiles around 0.085-0.74 µg/g of creatinine, however, with indications of a 2-3-fold difference between non-smokers and smokers. Such data could be used to define a BGV value contributing to the overall risk management of PAH mixtures. However, it is noted that currently no BGVs have been set under CMRD for any substance, neither at general level nor separated by smoking habits.

9.3 Notations

PAH is a complex group of substances with variation by size and other characteristics of the molecule. Furthermore, PAH usually occur as mixtures of several PAH. Consequently,

dermal absorption of PAH varies, but can be high in certain industries and processes, e.g., creosote wood impregnation. Therefore a skin notation is recommended.

The PAH entry in CMRD Annex I covers a wide variety of PAH. It is not possible to tailor the assignment of skin notation in another way than to use it for all PAH exposures where there is possibility of significant dermal contact. Such tailor-made assignment would require knowledge not only on the type of PAH but also the way of using it. It is recommended to assign skin notation to all PAH as a precautionary measure.

BaP has a harmonised classification for skin sensitisation. However, there is no comprehensive information indicating skin or respiratory sensitisation from most of PAH and notation for these properties are not recommended for PAH overall.

References

AGS 2011. *Exposure-risk relationship for benzo[a]pyrene in BekGS 910. Committee on Hazardous Substances (AGS).*

https://www.baua.de/EN/Service/Legislative-texts-and-technical-rules/Rules/TRGS/pdf/910/910-benzo-a-pyrene.pdf?__blob=publicationFile&v=2.

AGS 2015. *Technische Regeln für Gefahrstoffe. TRGS 551. Teer und andere Pyrolyseprodukte aus organischem Material. Ausschuss für Gefahrstoffe. BAuA.*

https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/TRGS-551.html.

ANDERSEN, M. H. G., SABER, A. T., FREDERIKSEN, M., CLAUSEN, P. A., SEJBAEK, C. S., HEMMINGSEN, C. H., EBBEHØJ, N. E., CATALÁN, J., AIMONEN, K., KOIVISTO, J., LOFT, S., MØLLER, P. & VOGEL, U. 2021. Occupational exposure and markers of genetic damage, systemic inflammation and lung function: a Danish cross-sectional study among air force personnel. *Scientific reports,* 11**,** 17998-17998.

ANDERSSON, J. T. & ACHTEN, C. 2015. Time to Say Goodbye to the 16 EPA PAHs? Toward an Up-to-Date Use of PACs for Environmental Purposes. *Polycycl Aromat Compd,* 35**,** 330-354.

ANGERER, J., MANNSCHRECK, C. & GUNDEL, J. 1997. Biological monitoring and biochemical effect monitoring of exposure to polycyclic aromatic hydrocarbons. *Int Arch Occup Environ Health,* 70**,** 365-77.

ANZIULEWICZ, J. A., DICK, H. J. & CHIARULLI, E. E. 1959. Transplacental naphthalene poisoning. *American Journal of Obstetrics and Gynecology,* 78**,** 519-521.

ARCHIBONG, A. E., INYANG, F., RAMESH, A., GREENWOOD, M., NAYYAR, T., KOPSOMBUT, P., HOOD, D. B. & NYANDA, A. M. 2002. Alteration of pregnancy related hormones and fetal survival in F-344 rats exposed by inhalation to benzo(a)pyrene. *Reprod Toxicol,* 16**,** 801-8.

ARCHIBONG, A. E., RAMESH, A., INYANG, F., NIAZ, M. S., HOOD, D. B. & KOPSOMBUT, P. 2012. Endocrine disruptive actions of inhaled benzo(a)pyrene on ovarian function and fetal survival in fisher F-344 adult rats. *Reprod Toxicol,* 34**,** 635-43.

ARCHIBONG, A. E., RAMESH, A., NIAZ, M. S., BROOKS, C. M., ROBERSON, S. I. & LUNSTRA, D. D. 2008. Effects of benzo(a)pyrene on intra-testicular function in F-344 rats. *Int J Environ Res Public Health,* 5**,** 32-40.

ARMSTRONG, B., HUTCHINSON, E. & FLETCHER, T. 2003. *Cancer risk following exposure to polycyclic aromatic hydrocarbons (PAHs): a meta-analysis. Research Report 068. Health and Safety Executive, United Kingdom.*

ARMSTRONG, B., HUTCHINSON, E., UNWIN, J. & FLETCHER, T. 2004. Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: a review and meta-analysis. *Environ Health Perspect,* 112**,** 970-8.

ATSDR 1995. *TOXICOLOGICAL PROFILE FOR POLYCYCLIC AROMATIC HYDROCARBONS. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Public Health Service. Agency for Toxic Substances and Disease Registry.*

BAAN, R., GROSSE, Y., STRAIF, K., SECRETAN, B., EL GHISSASSI, F., BOUVARD, V., BENBRAHIM-TALLAA, L., GUHA, N., FREEMAN, C., GALICHET, L. & COGLIANO, V. 2009. A review of human carcinogens--Part F: chemical agents and related occupations. *Lancet Oncol,* 10**,** 1143-4.

BARBEAU, D., LUTIER, S., BONNETERRE, V., PERSOONS, R., MARQUES, M., HERVE, C. & MAITRE, A. 2015. Occupational exposure to polycyclic aromatic hydrocarbons: relations between atmospheric mixtures, urinary metabolites and sampling times. *International Archives of Occupational and Environmental Health,* 88**,** 1119-1129.

BARBEAU, D., LUTIER, S., CHOISNARD, L., MARQUES, M., PERSOONS, R. & MAITRE, A. 2018. Urinary trans-anti-7,8,9,10-tetrahydroxy-7,8,9,10-tetrahydrobenzo(a)pyrene as the most relevant biomarker for assessing carcinogenic polycyclic aromatic hydrocarbons exposure. *Environ Int,* 112**,** 147-155.

BARBEAU, D., MAITRE, A. & MARQUES, M. 2011. Highly sensitive routine method for urinary 3-hydroxybenzo[a]pyrene quantitation using liquid chromatography-fluorescence detection and automated off-line solid phase extraction. *Analyst,* 136**,** 1183-91.

BARBEAU, D., PERSOONS, R., MARQUES, M., HERVE, C., LAFFITTE-RIGAUD, G. & MAITRE, A. 2014. Relevance of urinary 3-hydroxybenzo(a)pyrene and 1-hydroxypyrene to assess exposure to carcinogenic polycyclic aromatic hydrocarbon mixtures in metallurgy workers. *Ann Occup Hyg,* 58**,** 579-90.

BAUM, J. L. R., BAKALI, U., KILLAWALA, C., SANTIAGO, K. M., DIKICI, E., KOBETZ, E. N., SOLLE, N. S., DEO, S., BACHAS, L. & DAUNERT, S. 2020. Evaluation of silicone-based wristbands as passive sampling systems using PAHs as an exposure proxy for carcinogen monitoring in firefighters: Evidence from the firefighter cancer initiative. *Ecotoxicology and Environmental Safety,* 205**,** 111100.

BAXTER, C. S., HOFFMAN, J. D., KNIPP, M. J., REPONEN, T. & HAYNES, E. N. 2014. Exposure of Firefighters to Particulates and Polycyclic Aromatic Hydrocarbons. *Journal of Occupational and Environmental Hygiene,* 11**,** D85-D91.

BENKE, G., ABRAMSON, M. & SIM, M. 1998. Exposures in the alumina and primary aluminium industry: an historical review. *Ann Occup Hyg,* 42**,** 173-89.

BERNTSSON, T., SANDEN, B., OLSSON, L. & ASBLAD, A. 2014. *What is a biorefinery? In: Systems perspectives on biorefineries. Sanden B, Petterson K (Eds). Chalmers 2014.*

BIENIEK, G. 1997. Urinary naphthols as an indicator of exposure to naphthalene. *Scandinavian Journal of Work Environment & Health,* 23**,** 414-420.

BINET, S., PFOHL-LESZKOWICZ, A., BRANDT, H., LAFONTAINE, M. & CASTEGNARO, M. 2002. Bitumen fumes: review of work on the potential risk to workers and the present knowledge on its origin. *Sci Total Environ,* 300**,** 37-49.

BLUMER, M. 1976. Polycyclic aromatic compounds in nature. *Sci Am,* 234**,** 35-45.

BOFFETTA, P., JOURENKOVA, N. & GUSTAVSSON, P. 1997. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. *Cancer Causes Control,* 8**,** 444-72.

BOOGAARD, P. J. 2008. Urinary biomarkers in the risk assessment of PAHs. *Occup Environ Med,* 65**,** 221-2.

BOSETTI, C., BOFFETTA, P. & LA VECCHIA, C. 2007. Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. *Ann Oncol,* 18**,** 431-46.

BOSTRÖM, C. E., GERDE, P., HANBERG, A., JERNSTRÖM, B., JOHANSSON, C., KYRKLUND, T., RANNUG, A., TÖRNQVIST, M., VICTORIN, K. & WESTERHOLM, R. 2002. Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. *Environ Health Perspect,* 110 Suppl 3**,** 451-88.

BREUER, D., HAHN, J.-U., HÖBER, D., EMMEL, C., MUSANKE, U., RÜHL, R., SPICKENHEUER, A., RAULF-HEIMSOTH, M., BRAMER, R., SEIDEL, A., SCHILLING, B., HEINZE, E., KENDZIA, B., MARCZYNSKI, B., WELGE, P., ANGERER, J., BRÜNING, T. & PESCH, B. 2011. Air sampling and determination of vapours and aerosols of bitumen and polycyclic aromatic hydrocarbons in the Human Bitumen Study. *Archives of Toxicology,* 85**,** 11-20.

BROWN, L. N. A., KHOUSBOUEI, H., GOODWIN, J. S., IRVIN-WILSON, C. V., RAMESH, A., SHENG, L., MCCALLISTER, M. M., JIANG, G. C. T., ASCHNER, M. & HOOD, D. B. 2007. Down-regulation of early ionotrophic glutamate receptor subunit developmental expression as a mechanism for observed plasticity deficits following gestational exposure to benzo(a)pyrene. *NeuroToxicology,* 28**,** 965-978.

BURSTYN, I., KROMHOUT, H., PARTANEN, T., SVANE, O., LANGÅRD, S., AHRENS, W., KAUPPINEN, T., STÜCKER, I., SHAHAM, J., HEEDERIK, D., FERRO, G., HEIKKILÄ, P., HOOIVELD, M., JOHANSEN, C., RANDEM, B. G. & BOFFETTA, P. 2005. Polycyclic aromatic hydrocarbons and fatal ischemic heart disease. *Epidemiology,* 16**,** 744-50.

CAMPO, L., HANCHI, M., OLGIATI, L., POLLEDRI, E., CONSONNI, D., ZRAFI, I., SAIDANE-MOSBAHI, D. & FUSTINONI, S. 2016. Biological Monitoring of Occupational Exposure to Polycyclic Aromatic Hydrocarbons at an Electric Steel Foundry in Tunisia. *Ann Occup Hyg,* 60**,** 700-16.

CAVALIERI, E. L. & ROGAN, E. G. 1995. Central role of radical cations in metabolic activation of polycyclic aromatic hydrocarbons. *Xenobiotica,* 25**,** 677-88.

CHEN, C., TANG, Y., JIANG, X., QI, Y., CHENG, S., QIU, C., PENG, B. & TU, B. 2011. Early Postnatal Benzo(a)pyrene Exposure in Sprague-Dawley Rats Causes Persistent Neurobehavioral Impairments that Emerge Postnatally and Continue into Adolescence and Adulthood. *Toxicological Sciences,* 125**,** 248-261.

COLLINS, J. F., BROWN, J. P., DAWSON, S. V. & MARTY, M. A. 1991. Risk assessment for benzo[a]pyrene. *Regul Toxicol Pharmacol,* 13**,** 170-84.

COTTINI, G. B. & MAZZONE, G. B. 1939. The Effects of 3: 4—Benzpyrene on Human Skin. *The American Journal of Cancer,* 37**,** 186-195.

CUMBERBATCH, M. G., COX, A., TEARE, D. & CATTO, J. W. 2015. Contemporary Occupational Carcinogen Exposure and Bladder Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol,* 1**,** 1282-90.

DANKOVIC, D. A., WRIGHT, C. W., ZANGAR, R. C. & SPRINGER, D. L. 1989. Complex mixture effects on the dermal absorption of benzo[a]pyrene and other polycyclic aromatic hydrocarbons from mouse skin. *Journal of Applied Toxicology,* 9**,** 239-244.

DECOS 2006. *BaP and PAH from coal-derived sources. Health-based calculated occupational cancer risk values of benzo[a]pyrene and unsubstituted non-heterocyclic polycyclic aromatic hydrocarbons from coal-derived sources. Dutch Expert Committee on Occupational Standards a committee of the Health Council of the Netherlands. The Hague.*

DFG 2012. *Polycyclic aromatic hydrocarbons (PAH). The MAK-Collection Part I: Occupational Toxicants, Vol. 27. DFG, Deutsche Forschungsgemeinschaft.*

DFG 2013. Grenzwerte in biologischem Material. Polycyclische aromatische Kohlenwasserstoffe (PAH). *BAT 20. Lieferung.*

DFG 2021. *MAK- und BAT-Werte-Liste 2021. Ständige Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. Mitteilung 57. DEUTSCHE FORSCHUNGSGEMEINSCHAFT. Düsseldorf, Germany.*

ECHA 2018. *Committee for Risk Assessment (RAC). Note on reference dose-response relationship for the carcinogenicity of pitch, coal tar, high temperature and on PBT and vPvB properties.* *https://echa.europa.eu/documents/10162/17229/ctpht_rac_note_en.pdf/a184ee42-0642-7454-2d18-63324688e13d?t=1544526560573*.

ECHA 2019a. *Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC). Opinion on an Annex XV dossier proposing a restriction on Polycyclic-aromatic hydrocarbons (PAHs). ECHA/RAC/RES-O-0000001412-86-279/F and ECHA/SEAC/RES-O-0000001412-86-292/F. https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e181d5746d*.

ECHA 2019b. *Committee for Risk Assessment (RAC), Committee for Socio-economic Analysis (SEAC). Annex to Background Document to the Opinion on the Annex XV dossier proposing a restriction on Polycyclic-aromatic hydrocarbons (PAHs). ECHA/RAC/RES-O-0000001412-86-279/F and ECHA/SEAC/RES-O-0000001412-86-292/F.*

EEA 2015. Air Quality in Europe - 2015 EEA Report No 5. European Environment Agency.

EPA 2001. *Guidance for reporting toxic chemicals: polycyclic aromatic compounds category: Emergency planning and community right-to-know act - section 313. The US EPA.*

EPA 2017. *Toxicological Review of Benzo[a]pyrene. EPA/635/R-17/003Fa. U.S. Environmental Protection Agency, Washington, DC. 234 pp.*

FANBURG, S. 1940. Exfoliative dermatitis due to naphthalene: Report of an eruption resembling mycosis fungoides. *Archives of Dermatology and Syphilology,* 42**,** 53-58.

FIOH 2011. Background document for setting a biological limit value for 1-pyrenol. Perustelumuistio 1-pyrenolin toimenpiderajaksi (in Finnish). Finnish Institute of Occupational Health, Finland. Link to the data: https://www.ttl.fi/sites/default/files/2022-01/PAH-Pyrenoli.pdf Last accessed 04.02.2022.

FIOH 2016. Background document for setting the target level for PAHs. PAH-yhdisteiden tavoitetasoperustelumuistio (in Finnish). Link to the data: https://www.ttl.fi/teemat/tyoturvallisuus/altistuminen-tyoympariston-haittatekijoille/tyoympariston-tavoitetasot Last accessed 11.02.2022. 2010. Updated 2012 and 2016. ed.: Finnish Institute of Occupational Health (FIOH).

FIOH 2022. CAREX (CARcinogen EXposure) database; FIOH (Finnish Institute of Occupational Health) link to the database https://www.ttl.fi/en/carex/.

FÖRSTER, K., PREUSS, R., ROSSBACH, B., BRUNING, T., ANGERER, J. & SIMON, P. 2008. 3-Hydroxybenzo[a]pyrene in the urine of workers with occupational exposure to polycyclic aromatic hydrocarbons in different industries. *Occup Environ Med,* 65**,** 224-9.

FRIESEN, M. C., DEMERS, P. A., SPINELLI, J. J., EISEN, E. A., LORENZI, M. F. & LE, N. D. 2010. Chronic and acute effects of coal tar pitch exposure and cardiopulmonary mortality among aluminum smelter workers. *Am J Epidemiol,* 172**,** 790-9.

GABBANI, G., PAVANELLO, S., NARDINI, B., TOGNATO, O., BORDIN, A., FORNASA, C. V., BEZZE, G. & CLONFERO, E. 1999. Influence of metabolic genotype GSTM1 on levels of urinary mutagens in patients treated topically with coal tar. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis,* 440**,** 27-33.

GERARDE, H. W. 1960. *Toxicology and biochemistry of aromatic hydrocarbons. Toxicological effects of the aromatic hydrocarbons. In: Browning E (Ed) Elsevier Monographs on Toxic Agents Elsevier Publishing, Amsterdam, 225–248.*

GESTIS 2022. GESTIS International Limit Values Database IFA Institut für Arbeitssicherheit der Deutschen Gesetzlichen Unfallversicherung, Germany. http://limitvalue.ifa.dguv.de/ Accessed on 03.02.2022.

GLATT, H. 2005. Indicator assays for polycyclic aromatic hydrocarbon-induced genotoxicity. In: Luch A (Ed) The Carcinogenic Effects of Polycyclic Aromatic Hydrocarbons, Imperial College Press, London, 283–314.

GODSCHALK, R., OSTERTAG, J., MOONEN, E., NEUMANN, H., KLEINJANS, J. & VAN SCHOOTEN, F. 1998. Aromatic DNA adducts in human white blood cells and skin after dermal application of coal tar. *Cancer Epidemiology and Prevention Biomarkers,* 7**,** 767-773.

GODSCHALK, R. W., OSTERTAG, J. U., ZANDSTEEG, A. M., VAN AGEN, B., NEUMAN, H. A., VAN STRAATEN, H. & VAN SCHOOTEN, F.-J. 2001. Impact of GSTM1 on aromatic-DNA adducts and p53 accumulation in human skin and lymphocytes. *Pharmacogenetics and Genomics,* 11**,** 537-543.

GRANT, W. M. 1986. *Toxicology of the eye. Charles C Thomas Publisher, Springfield, 650–655*.

GREIM, H. 2008. *Gesundheitsschädliche Arbeitsstoffe, Toxikologischarbeitsmedizinische Begründungen von MAK-Werten, Loseblattsammlung, 45. Lfg. DFG, Deutsche Forschungsgemeinschaft, WILEY-VCH Verlag, Weinheim, 2008.*

GUPTA, P., BANERJEE, D. K., BHARGAVA, S. K., KAUL, R. & RAVI SHANKAR, V. 1993. Prevalence of Impaired Lung Function in Rubber Manufacturing Factory Workers Exposed to Benzo(a)pyrene and Respirable Particulate Matter. *Indoor Environment,* 2**,** 26-31.

HAGMANN, M., HEBISCH, R., BAUMGÄRTEL, A., BEELTE, S., KARMANN, J., KRUG, M., PROTT, U., SONDERMANN, J., WESSELER, S., WILMS, L., WOLF, T. & WEISS, T. 2017. The operational implementation of the risk concept for carcinogenic hazardous substances. Exposure to polycyclic aromatic hydrocarbons during the recycling of railway sleepers and the remediation of contaminated soils. *ASU Arbeitsmed Sozialmed Umweltmed,* 52**,** 670-681.

HANSEN, A. M., MATHIESEN, L., PEDERSEN, M. & KNUDSEN, L. E. 2008. Urinary 1-hydroxypyrene (1-HP) in environmental and occupational studies-A review. *International Journal of Hygiene and Environmental Health,* 211**,** 471-503.

HARVEY, R. G. 1996. Mechanisms Of Carcinogenesis of Polycyclic Aromatic Hydrocarbons. *Polycyclic Aromatic Compounds,* 9**,** 1-23.

HEBISCH, R., KARMANN, J., SCHÄFERHENRICH, A., GÖEN, T., BERGER, M., POPPEK, U. & ROITZSCH, M. 2020. Inhalation and dermal exposure of workers during timber impregnation with creosote and subsequent processing of impregnated wood. *Environ Res,* 181**,** 108877.

HEUDORF, U. & ANGERER, J. 2001. Internal exposure to PAHs of children and adults living in homes with parquet flooring containing high levels of PAHs in the parquet glue. *International Archives of Occupational and Environmental Health,* 74**,** 91-101.

HOOD, D. B., NAYYAR, T., RAMESH, A., GREENWOOD, M. & INYANG, F. 2000. Modulation in the developmental expression profile of Sp1 subsequent to transplacental exposure of fetal rats to desorbed benzo[a]pyrene following maternal inhalation. *Inhal Toxicol,* 12**,** 511-35.

HOPF, N. B., CARREON, T. & TALASKA, G. 2009. Biological markers of carcinogenic exposure in the aluminum smelter industry--a systematic review. *J Occup Environ Hyg,* 6**,** 562-81.

HSE 2018. *Naphthalene - Substance evaluation conclusion as required by REACH Article 48 and Evaluation Report. https://echa.europa.eu/documents/10162/c5cb00e9-0ff4-ac35-3db1-24566967fea8*.

HSE 2020. EH40/2005 Workplace exposure limits. *In:* EXECUTIVE, T. H. A. S. (ed.) Fourth edition 2020 ed. London.

HUANG, W., GRAINGER, J., PATTERSON, D. G., JR., TURNER, W. E., CAUDILL, S. P., NEEDHAM, L. L., PIRKLE, J. L. & SAMPSON, E. J. 2004. Comparison of 1-hydroxypyrene exposure in the US population with that in occupational exposure studies. *Int Arch Occup Environ Health,* 77**,** 491-8.

IARC 1973. *Certain Polycyclic aromatic hydrocarbons and heterocyclic compounds. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 3. Lyon, France.*

IARC 1983. *Polynuclear Aromatic Compounds; Part 1; Chemical, Environmental and Experimental Data. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 32. Lyon, France.*

IARC 1984a. *Polynuclear aromatic compounds, Part 2, Carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 33. Lyon, France.*

IARC 1984b. *Polynuclear aromatic compounds, Part 3, Industrial exposures in aluminium production, coal gasification, coke production, and iron and steel founding. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 34. Lyon, France.*

IARC 1985. *Polynuclear aromatic compounds, Part 4, Bitumens, coal-tars, and derived products, shale oils and soots. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 35. Lyon, France.*

IARC 1986. *Tobacco smoking. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 38. Lyon, France.*

IARC 1987. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Supplement 7. Lyon, France.*

IARC 1989a. *Diesel and gasoling engine exhausts and some nitroarenes. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 46. Lyon, France.*

IARC 1989b. *Occupational exposures in petroleum refining: Crude oil and major petroleum fuels. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 45. Lyon, France.*

IARC 2010. *Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 92. Lyon, France.*

IARC 2012. *Chemical agents and related occupations. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100F, A review of human carcinogens. Lyon, France.*

IARC 2013. Bitumens and bitumen emissions, and some N- and S-heterocyclic polycyclic aromatic hydrocarbons. Volume 103. Lyon, France.

INRS 2016. *Valeurs limites d'exposition professionnelle aux agents chimiques en France. Aide mémoire technique ED 984.*

INYANG, F., RAMESH, A., KOPSOMBUT, P., NIAZ, M. S., HOOD, D. B., NYANDA, A. M. & ARCHIBONG, A. E. 2003. Disruption of testicular steroidogenesis and epididymal function by inhaled benzo(a)pyrene. *Reprod Toxicol,* 17**,** 527-37.

IPCS 1998. *Selected non-heterocyclic polycyclic aromatic hydrocarbons. Environmental health criteria 202. International Programme on Chemical Safety. World Health Organization, Geneva.*

IPCS 2014. Environmental Health Criteria 242. Dermal exposure. *In:* (IPCS), T. I. P. O. C. S. (ed.). WHO.

JARVIS, I. W., DREIJ, K., MATTSSON, Å., JERNSTRÖM, B. & STENIUS, U. 2014. Interactions between polycyclic aromatic hydrocarbons in complex mixtures and implications for cancer risk assessment. *Toxicology,* 321**,** 27-39.

JIANG, H., GELHAUS, S. L., MANGAL, D., HARVEY, R. G., BLAIR, I. A. & PENNING, T. M. 2007. Metabolism of benzo[a]pyrene in human bronchoalveolar H358 cells using liquid chromatography-mass spectrometry. *Chem Res Toxicol,* 20**,** 1331-41.

JIANG, H., SHEN, Y. M., QUINN, A. M. & PENNING, T. M. 2005. Competing roles of cytochrome P450 1A1/1B1 and aldo-keto reductase 1A1 in the metabolic activation of (+/-)-7,8-dihydroxy-7,8-dihydro-benzo[a]pyrene in human bronchoalveolar cell extracts. *Chem Res Toxicol,* 18**,** 365-74.

JONGENEELEN, F. J. 2001. Benchmark guideline for urinary 1-hydroxypyrene as biomarker of occupational exposure to polycyclic aromatic hydrocarbons. *Ann Occup Hyg,* 45**,** 3-13.

JONGENEELEN, F. J. 2014. A guidance value of 1-hydroxypyrene in urine in view of acceptable occupational exposure to polycyclic aromatic hydrocarbons. *Toxicology Letters,* 231**,** 239-248.

JONGENEELEN, F. J., ANZION, R. B., SCHEEPERS, P. T., BOS, R. P., HENDERSON, P. T., NIJENHUIS, E. H., VEENSTRA, S. J., BROUNS, R. M. & WINKES, A. 1988. 1-Hydroxypyrene in urine as a biological indicator of exposure to polycyclic aromatic hydrocarbons in several work environments. *Ann Occup Hyg,* 32**,** 35-43.

JULES, G. E., PRATAP, S., RAMESH, A. & HOOD, D. B. 2012. In utero exposure to benzo(a)pyrene predisposes offspring to cardiovascular dysfunction in later-life. *Toxicology,* 295**,** 56-67.

KASCHKA, F. & VOSSMANN, D. 1994. *Kontaktallergene: chemische, klinische und experimentelle Daten;(Allergen-Liste),* Schmidt.

KAZEROUNI, N., SINHA, R., HSU, C.-H., GREENBERG, A. & ROTHMAN, N. 2001. Analysis of 200 food items for benzo[a]pyrene and estimation of its intake in an epidemiologic study. *Food and Chemical Toxicology,* 39**,** 423-436.

KEITH, L. 2015. The Source of U.S. EPA's Sixteen PAH Priority Pollutants. *Polycyclic Aromatic Compounds,* 35**,** 147-160.

KIM, J. Y., HECHT, S. S., MUKHERJEE, S., CARMELLA, S. G., RODRIGUES, E. G. & CHRISTIANI, D. C. 2005. A Urinary Metabolite of Phenanthrene as a Biomarker of Polycyclic Aromatic Hydrocarbon Metabolic Activation in Workers Exposed to Residual Oil Fly Ash. *Cancer Epidemiology, Biomarkers & Prevention,* 14**,** 687-692.

KIRK, K. M., SPLAWINSKI, Z., BOTT, R. C. & LOGAN, M. B. 2021. Combustion products generated in simulated industrial fires. *J Occup Environ Hyg,* 18**,** 510-521.

KLOSLOVA, Z., DRIMAL, M., BALOG, K., KOPPOVA, K. & DUBAJOVA, J. 2016. The Relations between Polycyclic Aromatic Hydrocarbons Exposure and 1-OHP Levels as a Biomarker of the Exposure. *Cent Eur J Public Health,* 24**,** 302-307.

KOGEVINAS, M., T MANNETJE, A., CORDIER, S., RANFT, U., GONZÁLEZ, C. A., VINEIS, P., CHANG-CLAUDE, J., LYNGE, E., WAHRENDORF, J., TZONOU, A., JÖCKEL, K. H., SERRA, C., PORRU, S., HOURS, M., GREISER, E. & BOFFETTA, P. 2003. Occupation and bladder cancer among men in Western Europe. *Cancer Causes Control,* 14**,** 907-14.

KRISTENSEN, P., EILERTSEN, E., EINARSDOTTIR, E., HAUGEN, A., SKAUG, V. & OVREBO, S. 1995. Fertility in mice after prenatal exposure to benzo[a]pyrene and inorganic lead. *Environ Health Perspect,* 103**,** 588-90.

LAFONTAINE, M., CHAMPMARTIN, C., SIMON, P., DELSAUT, P. & FUNCK-BRENTANO, C. 2006. 3-Hydroxybenzo[a]pyrene in the urine of smokers and non-smokers. *Toxicol Lett,* 162**,** 181-5.

LAFONTAINE, M., GENDRE, C., DELSAUT, P. & SIMON, P. 2004. URINARY 3-HYDROXYBENZO[A]PYRENE AS A BIOMARKER OF EXPOSURE TO

POLYCYCLIC AROMATIC HYDROCARBONS: AN APPROACH FOR DETERMINING A BIOLOGICAL LIMIT VALUE. *Polycyclic Aromatic Compounds,* 24**,** 441-450.

LEE, K.-H., ICHIBA, M., ZHANG, J., TOMOKUNI, K., HONG, Y.-C., HA, M., KWON, H. J., KOH, S.-B., CHOI, H.-R. & LEE, K.-H. 2003. Multiple biomarkers study in painters in a shipyard in Korea. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis,* 540**,** 89-98.

LEI, Z. M. 1993. [The relationship between concentrations of B(a)P in blood, urine and immune function of coking workers]. *Zhonghua Yu Fang Yi Xue Za Zhi,* 27**,** 212-4.

LEMIEUX, C. L., LONG, A. S., LAMBERT, I. B., LUNDSTEDT, S., TYSKLIND, M. & WHITE, P. A. 2015. Cancer risk assessment of polycyclic aromatic hydrocarbon contaminated soils determined using bioassay-derived levels of benzo[a]pyrene equivalents. *Environ Sci Technol,* 49**,** 1797-805.

LETZEL, S. & DREXLER, H. 1998. Occupationally related tumors in tar refinery workers. *J Am Acad Dermatol,* 39**,** 712-20.

LIANG, J., ZHU, H., LI, C., DING, Y., ZHOU, Z. & WU, Q. 2012. Neonatal exposure to benzo[a]pyrene decreases the levels of serum testosterone and histone H3K14 acetylation of the StAR promoter in the testes of SD rats. *Toxicology,* 302**,** 285-91.

LOURO, H., GOMES, B. C., SABER, A. T., IAMICELI, A. L., GÖEN, T., JONES, K., KATSONOURI, A., NEOPHYTOU, C. M., VOGEL, U., VENTURA, C., OBEREMM, A., DUCA, R. C., FERNANDEZ, M. F., OLEA, N., SANTONEN, T., VIEGAS, S. & SILVA, M. J. 2022. The Use of Human Biomonitoring to Assess Occupational Exposure to PAHs in Europe: A Comprehensive Review. *Toxics,* 10.

MACKENZIE, K. M. & ANGEVINE, D. M. 1981. Infertility in mice exposed in utero to benzo(a)pyrene. *Biol Reprod,* 24**,** 183-91.

MAITRE, A., PETIT, P., MARQUES, M., HERVÉ, C., MONTLEVIER, S., PERSOONS, R. & BICOUT, D. J. 2018. Exporisq-HAP database: 20 years of monitoring French occupational exposure to polycyclic aromatic hydrocarbon mixtures and identification of exposure determinants. *International Journal of Hygiene and Environmental Health,* 221**,** 334-346.

MALLAH, M. A., MALLAH, M. A., LIU, Y., XI, H., WANG, W., FENG, F. & ZHANG, Q. 2021. Relationship Between Polycyclic Aromatic Hydrocarbons and Cardiovascular Diseases: A Systematic Review. *Front Public Health,* 9**,** 763706.

MANNETJE, A., KOGEVINAS, M., CHANG-CLAUDE, J., CORDIER, S., GONZÁLEZ, C. A., HOURS, M., JÖCKEL, K. H., BOLM-AUDORFF, U., LYNGE, E., PORRU, S., DONATO, F., RANFT, U., SERRA, C., TZONOU, A., VINEIS, P., WAHRENDORF, J. & BOFFETTA, P. 1999. Occupation and bladder cancer in European women. *Cancer Causes Control,* 10**,** 209-17.

MCCALLISTER, M. M., MAGUIRE, M., RAMESH, A., AIMIN, Q., LIU, S., KHOSHBOUEI, H., ASCHNER, M., EBNER, F. F. & HOOD, D. B. 2008. Prenatal

exposure to benzo(a)pyrene impairs later-life cortical neuronal function. *Neurotoxicology,* 29**,** 846-54.

NEGRI, E. & LA VECCHIA, C. 2001. Epidemiology and prevention of bladder cancer. *Eur J Cancer Prev,* 10**,** 7-14.

OKONA-MENSAH, K. B., BATTERSHILL, J., BOOBIS, A. & FIELDER, R. 2005. An approach to investigating the importance of high potency polycyclic aromatic hydrocarbons (PAHs) in the induction of lung cancer by air pollution. *Food Chem Toxicol,* 43**,** 1103-16.

PALEOLOGO, M., VAN SCHOOTEN, F., PAVANELLO, S., KRIEK, E., ZORDAN, M., CLONFERO, E., BEZZE, C. & LEVIS, A. 1992. Detection of benzo [a] pyrene-diol-epoxide-DNA adducts in white blood cells of psoriatic patients treated with coal tar. *Mutation Research Letters,* 281**,** 11-16.

PAVANELLO, S., FAVRETTO, D., BRUGNONE, F., MASTRANGELO, G., PRA, G. D. & CLONFERO, E. 1999. HPLC/fluorescence determination of anti-BPDE–DNA adducts in mononuclear white blood cells from PAH-exposed humans. *Carcinogenesis,* 20**,** 431-435.

PAVANELLO, S. & LEVIS, A. G. 1994. Human peripheral blood lymphocytes as a cell model to evaluate the genotoxic effect of coal tar treatment. *Environmental health perspectives,* 102**,** 95-99.

PENNING, T. M., BURCZYNSKI, M. E., HUNG, C. F., MCCOULL, K. D., PALACKAL, N. T. & TSURUDA, L. S. 1999. Dihydrodiol dehydrogenases and polycyclic aromatic hydrocarbon activation: generation of reactive and redox active o-quinones. *Chem Res Toxicol,* 12**,** 1-18.

PERSOONS, R., ROSEAU, L., PETIT, P., HOGRAINDLEUR, C., MONTLEVIER, S., MARQUES, M., OTTONI, G. & MAITRE, A. 2020. Towards a recommended biomonitoring strategy for assessing the occupational exposure of roofers to PAHs. *Toxicol Lett,* 324**,** 54-64.

PESCH, B., SPICKENHEUER, A., KENDZIA, B., SCHINDLER, B. K., WELGE, P., MARCZYNSKI, B., RIHS, H. P., RAULF-HEIMSOTH, M., ANGERER, J. & BRÜNING, T. 2011. Urinary metabolites of polycyclic aromatic hydrocarbons in workers exposed to vapours and aerosols of bitumen. *Arch Toxicol,* 85 Suppl 1**,** S29-39.

PETRY, T., SCHMID, P. & SCHLATTER, C. 1996. The use of toxic equivalency factors in assessing occupational and environmental health risk associated with exposure to airborne mixtures of polycyclic aromatic hydrocarbons (PAHs). *Chemosphere,* 32**,** 639-48.

PUFULETE, M., BATTERSHILL, J., BOOBIS, A. & FIELDER, R. 2004. Approaches to carcinogenic risk assessment for polycyclic aromatic hydrocarbons: a UK perspective. *Regul Toxicol Pharmacol,* 40**,** 54-66.

PURCARO, G., MORET, S. & CONTE, L. S. 2013. Overview on polycyclic aromatic hydrocarbons: occurrence, legislation and innovative determination in foods. *Talanta,* 105**,** 292-305.

RAMESH, A., WALKER, S. A., HOOD, D. B., GUILLÉN, M. D., SCHNEIDER, K. & WEYAND, E. H. 2004. Bioavailability and risk assessment of orally ingested polycyclic aromatic hydrocarbons. *Int J Toxicol,* 23**,** 301-33.

RANDERATH, E., ZHOU, G. D., DONNELLY, K. C., SAFE, S. H. & RANDERATH, K. 1996. DNA damage induced in mouse tissues by organic wood preserving waste extracts as assayed by 32P-postlabeling. *Arch Toxicol,* 70**,** 683-95.

RANDERATH, K., ZHOU, G. D., RANDERATH, E., SAFE, S. H. & DONNELLY, K. C. 1997. Comparative 32P-postlabeling analysis of exogenous and endogenous DNA adducts in mouse skin exposed to a wood-preserving waste extract, a complex mixture of polycyclic and polychlorinated chemicals. *Environ Mol Mutagen,* 29**,** 372-8.

RAPPAPORT, S. M., WAIDYANATHA, S. & SERDAR, B. 2004. Naphthalene and its biomarkers as measures of occupational exposure to polycyclic aromatic hydrocarbons. *Journal of Environmental Monitoring,* 6**,** 413-416.

REULEN, R. C., KELLEN, E., BUNTINX, F., BRINKMAN, M. & ZEEGERS, M. P. 2008. A meta-analysis on the association between bladder cancer and occupation. *Scand J Urol Nephrol Suppl***,** 64-78.

RICHTER-BROCKMANN, S., DETTBARN, G., JESSEL, S., JOHN, A., SEIDEL, A. & ACHTEN, C. 2019. Ultra-high sensitive analysis of 3-hydroxybenzo[a]pyrene in human urine using GC-APLI-MS. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences,* 1118**,** 187-193.

RIECHERT, F., BERGER, M. & KERSTEN, N. 2011. Biological Monitoring in wood impregnation with creosote - Urinary 1-hydroxypyrene as a marker for internal exposure to polycyclic aromatic hydrocarbons. *Zbl Arbeitsmed,* 61**,** 4-12.

RIVM 2008. *Coal-tar pitch high temperature (CTPHT), transitional arrangements and way forward under REACH: REACH-SEA report of scoping study. RIVM Report 601780001/2008. 40 pp.*

RÖGNER, N., HAGEDORN, H.-W., SCHERER, G., SCHERER, M. & PLUYM, N. 2021. A Sensitive LC–MS/MS Method for the Quantification of 3-Hydroxybenzo[a]pyrene in Urine-Exposure Assessment in Smokers and Users of Potentially Reduced-Risk Products. *Separations,* 8**,** 171.

ROMUNDSTAD, P., ANDERSEN, A. & HALDORSEN, T. 2000. Cancer incidence among workers in six Norwegian aluminum plants. *Scand J Work Environ Health,* 26**,** 461-9.

ROTA, M., BOSETTI, C., BOCCIA, S., BOFFETTA, P. & LA VECCHIA, C. 2014. Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014. *Arch Toxicol,* 88**,** 1479-90.

SANDMEYER, E. 1981. *Aromatic hydrocarbons. In: Clayton GD, Clayton FE (Eds) Patty's Industrial Hygiene and Toxicolgy, John Wiley and Sons, New York, pages 3333–3339.*

SANTELLA, R. M., PERERA, F. P., YOUNG, T. L., ZHANG, Y.-J., CHIAMPRASERT, S., TANG, D., WANG, L. W., BEACHMAN, A., LIN, J.-H. & DELEO, V. A. 1995. Polycyclic aromatic hydrocarbon-DNA and protein adducts in coal tar treated patients and controls and their relationship to gluthathione S-transferase genotype. *Mutation Research/Environmental Mutagenesis and Related Subjects,* 334**,** 117-124.

SARTORELLI, P., CENNI, A., MATTEUCCI, G., MONTOMOLI, L., NOVELLI, M. T. & PALMI, S. 1999. Dermal exposure assessment of polycyclic aromatic hydrocarbons: in vitro percutaneous penetration from lubricating oil. *Int Arch Occup Environ Health,* 72**,** 528-32.

SAUNDERS, C. R., SHOCKLEY, D. C. & KNUCKLES, M. E. 2001. Behavioral effects induced by acute exposure to benzo(a)pyrene in F-344 rats. *Neurotox Res,* 3**,** 557-79.

SCHOKET, B., HEWER, A., GROVER, P. L. & PHILLIPS, D. H. 1988a. Covalent binding of components of coal-tar, creosote and bitumen to the DNA of the skin and lungs of mice following topical application. *Carcinogenesis,* 9**,** 1253-8.

SCHOKET, B., HEWER, A., GROVER, P. L. & PHILLIPS, D. H. 1988b. Formation of DNA adducts in human skin maintained in short-term organ culture and treated with coal-tar, creosote or bitumen. *Int J Cancer,* 42**,** 622-6.

SCHOKET, B., HORKAY, I., KÓSA, A., PÁLDEÁK, L., HEWER, A., GROVER, P. L. & PHILLIPS, D. H. 1990. Formation of DNA adducts in the skin of psoriasis patients, in human skin in organ culture, and in mouse skin and lung following topical application of coal-tar and juniper tar. *J Invest Dermatol,* 94**,** 241-6.

SCOEL 2016. *Polycyclic Aromatic Hydrocarbon mixtures containing benzo[a]pyrene (PAH). Recommendation from the Scientific Committee on Occupational Exposure Limits. SCOEL/REC/404. European Commission, Luxembourg.*

SIDOROV, O. F. 2013. Reducing the carcinogenic impact of pitch processing. *Coke and Chemistry,* 56**,** 63-69.

SINGH, A., KAMAL, R., AHAMED, I., WAGH, M., BIHARI, V., SATHIAN, B. & KESAVACHANDRAN, C. N. 2018. PAH exposure-associated lung cancer: an updated meta-analysis. *Occup Med (Lond),* 68**,** 255-261.

SJOGREN, B., BIGERT, C. & GUSTAVSSON, B. 2020. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 153.Occupational chemical exposures and cardiovascular disease. *Arbete Hälsa,* 54**,** 1-437.

STEC, A. A., DICKENS, K. E., SALDEN, M., HEWITT, F. E., WATTS, D. P., HOULDSWORTH, P. E. & MARTIN, F. L. 2018. Occupational Exposure to Polycyclic Aromatic Hydrocarbons and Elevated Cancer Incidence in Firefighters. *Scientific reports,* 8**,** 2476-2476.

STM 2005. Background document for setting OEL for benzo(a)pyrene. HTP-arvoperustelumuistio benzo(a)pyreenille (in Finnish). Link to the data: : https://www.tyosuojelu.fi/documents/14660/6121605/Bentso%5Ba%5Dpyreeni2005.pdf/84f84111-11eb-ef00-bf7f-7e975e1cf2d6 Last accessed 11.02.2022. 2005 ed.: Ministry of Social Affairs and Health (STM).

STM 2007. Background document for setting OEL for naphthalene. HTP-arvoperustelumuistio naftaleenille (in Finnish). Link to the data: https://www.tyosuojelu.fi/documents/14660/6121636/Naftaleeni2007.pdf/6fc03ebf-f8c0-62dc-34af-90a124568128 Last accessed 11.02.2022. Ministry of Social Affairs and Health (STM).

STRANDBERG, B., JULANDER, A., SJÖSTRÖM, M., LEWNÉ, M., HATICE, K. A. & BIGERT, C. 2018. An improved method for determining dermal exposure to polycyclic aromatic hydrocarbons. *Chemosphere,* 198**,** 274-280.

SZCZEKLIK, A., SZCZEKLIK, J., GALUSZKA, Z., MUSIAL, J., KOLARZYK, E. & TARGOSZ, D. 1994. Humoral immunosuppression in men exposed to polycyclic aromatic hydrocarbons and related carcinogens in polluted environments. *Environ Health Perspect,* 102**,** 302-4.

TREMBLAY, C., ARMSTRONG, B., THÉRIAULT, G. & BRODEUR, J. 1995. Estimation of risk of developing bladder cancer among workers exposed to coal tar pitch volatiles in the primary aluminum industry. *Am J Ind Med,* 27**,** 335-48.

UBA 2022. TEXTE 63/2022 Final report. Development of a chemical analysis concept for substances derived from coal and petroleum stream. German Environment Agency.

UNWIN, J., COCKER, J., SCOBBIE, E. & CHAMBERS, H. 2006. An assessment of occupational exposure to polycyclic aromatic hydrocarbons in the UK. *Ann Occup Hyg,* 50**,** 395-403.

VAANANEN, V., ELOVAARA, E., NYKYRI, E., SANTONEN, T. & HEIKKILA, P. 2006. Road pavers' occupational exposure to asphalt containing waste plastic and tall oil pitch. *J Environ Monit,* 8**,** 89-99.

VAANANEN, V., HAMEILA, M., KALLIOKOSKI, P., NYKYRI, E. & HEIKKILA, P. 2005. Dermal exposure to polycyclic aromatic hydrocarbons among road pavers. *Ann Occup Hyg,* 49**,** 167-78.

VAANANEN, V., HAMEILA, M., KONTSAS, H., PELTONEN, K. & HEIKKILA, P. 2003. Air concentrations and urinary metabolites of polycyclic aromatic hydrocarbons among paving and remixing workers. *J Environ Monit,* 5**,** 739-46.

VALIÈRE, M., PETIT, P., PERSOONS, R., DEMEILLIERS, C. & MAÎTRE, A. 2022. Consistency between air and biological monitoring for assessing polycyclic aromatic hydrocarbon exposure and cancer risk of workers. *Environmental Research,* 207**,** 112268.

VANROOIJ, J. G., BODELIER-BADE, M. M., DE LOOFF, A. J., DIJKMANS, A. P. & JONGENEELEN, F. J. 1992. Dermal exposure to polycyclic aromatic hydrocarbons among primary aluminium workers. *Med Lav,* 83**,** 519-29.

VANROOIJ, J. G., BODELIER-BADE, M. M. & JONGENEELEN, F. J. 1993a. Estimation of individual dermal and respiratory uptake of polycyclic aromatic hydrocarbons in 12 coke oven workers. *British Journal of Industrial Medicine,* 50**,** 623-632.

VANROOIJ, J. G., DE ROOS, J. H., BODELIER-BADE, M. M. & JONGENEELEN, F. J. 1993b. Absorption of polycyclic aromatic hydrocarbons through human skin: differences between anatomical sites and individuals. *J Toxicol Environ Health,* 38**,** 355-68.

VANROOIJ, J. G., VAN LIESHOUT, E. M., BODELIER-BADE, M. M. & JONGENEELEN, F. J. 1993c. Effect of the reduction of skin contamination on the internal dose of creosote workers exposed to polycyclic aromatic hydrocarbons. *Scand J Work Environ Health,* 19**,** 200-7.

VANROOIJ, J. G., VINKE, E., DE LANGE, J., BRUIJNZEEL, P. L., BODELIER-BADE, M. M., NOORDHOEK, J. & JONGENEELEN, F. J. 1995. Dermal absorption of polycyclic aromatic hydrocarbons in the blood-perfused pig ear. *J Appl Toxicol,* 15**,** 193-200.

VERMA, N., PINK, M., RETTENMEIER, A. W. & SCHMITZ-SPANKE, S. 2012. Review on proteomic analyses of benzo[a]pyrene toxicity. *Proteomics,* 12**,** 1731-55.

WAGNER, G. & WEZEL, G. 1966. Art und Häufigkeit hautschädigender Berufsnoxen in Schleswig-Holstein. *Berufsdermatosen,* 14**,** 1-40.

WEISS, T., KOSLITZ, S., COOK, H. & BRUNING, T. 2019. Human biomonitoring of PAH. A new procedure at IPA allows the determination of the internal load with benzo(a)pyrene. *IPA Journal,* 1**,** 15-19.

WHEELER, L. A., SAPERSTEIN, M. D. & LOWE, N. J. 1981. Mutagenicity of urine from psoriatic patients undergoing treatment with coal tar and ultraviolet light. *J Invest Dermatol,* 77**,** 181-5.

WHO, W. H. O. 2000. *Air Quality Guidelines for Europe. Chapter 5.9 WHO Regional Publications, European Series, No. 91, 2nd ed., Copenhagen, 2000.*

XU, D., PENNING, T. M., BLAIR, I. A. & HARVEY, R. G. 2009. Synthesis of phenol and quinone metabolites of benzo[a]pyrene, a carcinogenic component of tobacco smoke implicated in lung cancer. *J Org Chem,* 74**,** 597-604.

XU, Y., KÅREDAL, M., NIELSEN, J., ADLERCREUTZ, M., BERGENDORF, U., STRANDBERG, B., ANTONSSON, A.-B., TINNERBERG, H. & ALBIN, M. 2018a. Exposure, respiratory symptoms, lung function and inflammation response of road-paving asphalt workers. *Occupational and environmental medicine,* 75**,** 494-500.

XU, Y., LINDH, C. H., JÖNSSON, B. A. G., BROBERG, K. & ALBIN, M. 2018b. Occupational exposure to asphalt mixture during road paving is related to increased

mitochondria DNA copy number: a cross-sectional study. *Environmental health : a global access science source,* 17**,** 29-29.

XUE, W. & WARSHAWSKY, D. 2005. Metabolic activation of polycyclic and heterocyclic aromatic hydrocarbons and DNA damage: a review. *Toxicol Appl Pharmacol,* 206**,** 73-93.

YADAV, J. S. & SETH, N. 1998. Effect of polycyclic aromatic hydrocarbons on somatic chromosomes of coal tar workers. *Cytobios,* 93**,** 165-73.

ZANDER, M. 1983. *Physical and chemical properties of polycyclic aromatic hydrocarbons. In: Bjørseth A, editor. Handbook of Polycyclic Aromatic Hydrocarbons. New York: Marcel Dekker; 1983.*

ZINKHAM, W. H. & CHILDS, B. 1958. A defect of glutathione metabolism in erythrocytes from patients with a naphthalene-induced hemolytic anemia. *Pediatrics,* 22**,** 461-71.

Appendix 1. Structural formulae and physicochemical properties of some PAH

Figure 8: Structural formulae of some PAH molecules (IPCS 1998)

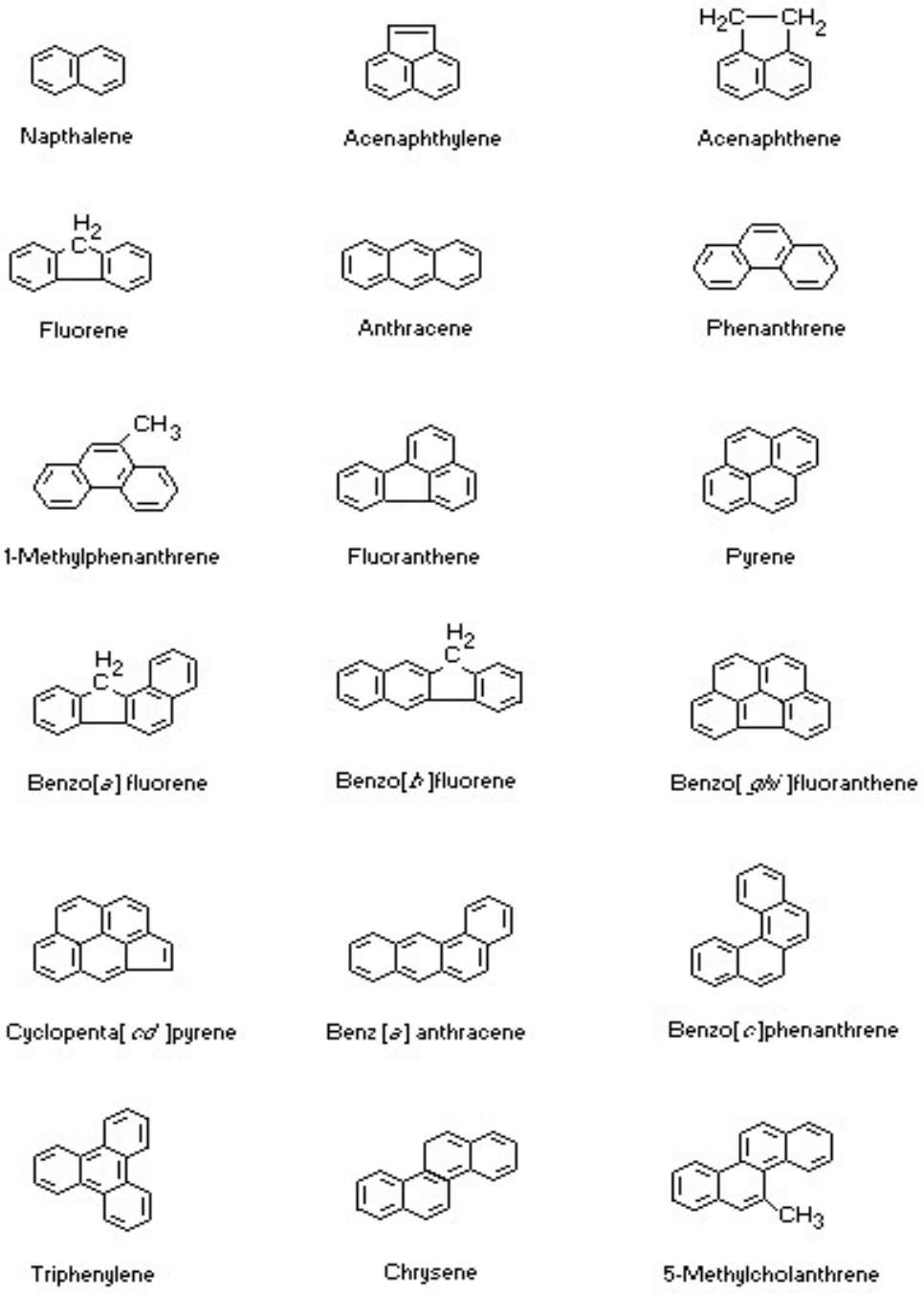
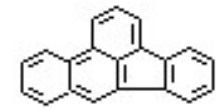
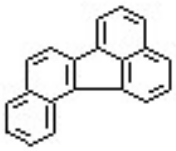


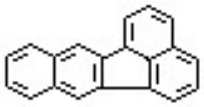
Figure 8 continues



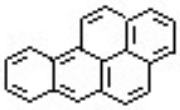
Benzo[*b*] fluoranthene



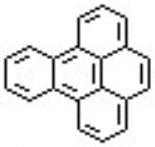
Benzo[*j*] fluoranthene



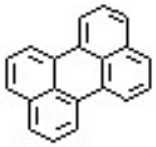
Benzo[*k*] fluoranthene



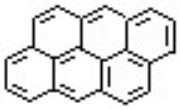
Benzo[*a*]pyrene



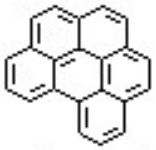
Benzo[*e*]pyrene



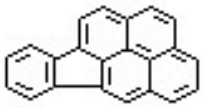
Perylene



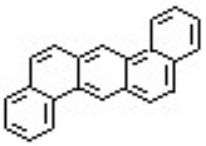
Anthanthrene



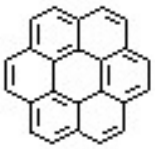
Benzo[*ghi*]perylene



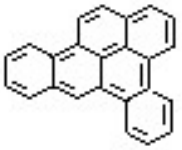
Indeno[1,2,3-*cd*]pyrene



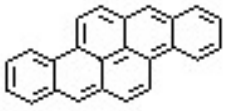
Dibenz[*a,h*]anthracene



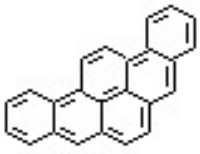
Coronene



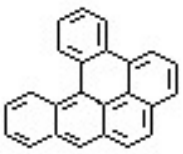
Dibenzo[*a,e*]pyrene



Dibenzo[*a,h*]pyrene



Dibenzo[*a,i*]pyrene



Dibenzo[*a,l*]pyrene

Table 19: Chemical properties of typical PAH mixtures (DFG 2012 and SCOEL 2016)

Name	CAS No.	Molecular formula	Molecular mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (Pa at 25 °C)	log K_{ow}	Genotoxicity (WHO 1998)	Carcinogenicity (WHO 1998)
anthanthrene	191-26-4	$C_{22}H_{12}$	276.3	264	547			(+)	+
benzo[*b*]fluoranthene	205-99-2	$C_{20}H_{12}$	252.3	168.3	481	6.7×10^{-5}	6.12	+	+
benzo[*a*]anthracene	56-55-3	$C_{18}H_{12}$	228.3	160.7	400	2.8×10^{-5}	5.61	+	+
benzo[*j*]fluoranthene	205-82-3	$C_{20}H_{12}$	252.3	165.4	480	2.0×10^{-6}	6.12	+	+
benzo[*k*]fluoranthene	207-08-9	$C_{20}H_{12}$	252.3	215.7	480	1.3×10^{-8}	6.84	+	+
benzo[*b*]naphtho[2,1-*d*]-thiophene[a]	239-35-0	$C_{16}H_{10}S$	234.3	185–188	160–180 (3 torr)	–	–	+	+
benzo[*a*]pyrene	50-32-8	$C_{20}H_{12}$	252.3	178.1	496	7.3×10^{-7}	6.50	+	+
chrysene	218-01-9	$C_{18}H_{12}$	228.3	253.8	448	8.4×10^{-5}	5.91	+	+
cyclopenta[*cd*]pyrene	27208-37-3	$C_{18}H_{10}$	226.3	170	439	–	–	+	+
dibenzo[*a*,*h*]anthracene	53-70-3	$C_{22}H_{14}$	278.4	266.6	524	1.3×10^{-8}	6.50	+	+
dibenzo[*a*,*l*]pyrene	191-30-0	$C_{24}H_{14}$	302.4	162.4	595	–	–	(+)	+
dibenzo[*a*,*e*]pyrene	192-65-4	$C_{24}H_{14}$	302.4	244.4	592	–	–	+	+
dibenzo[*a*,*h*]pyrene	189-64-0	$C_{24}H_{14}$	302.4	317	596	–	–	(+)	+
dibenzo[*a*,*i*]pyrene	189-55-9	$C_{24}H_{14}$	302.4	282	594	3.2×10^{-10}	7.3	+	+
indeno[1,2,3-*cd*]pyrene	193-39-5	$C_{22}H_{12}$	276.3	163.6	536	1.3×10^{-8}	6.58	+	+
naphthalene[b]	91-20-3	$C_{10}H_8$	128.2	81	217.9	10.4	3.4	–	
phenanthrene	85-01-8	$C_{14}H_{10}$	178.2	100.5	340	1.6×10^{-2}	4.6		
pyrene	129-00-0	$C_{16}H_{10}$	202.3	150.4	393	6.0×10^{-4}	5.18		
1-methylpyrene[c]	2381-21-7	$C_{17}H_{12}$	216.3	70–71	410				

+: positive; –: negative; (+): results are based on a small database

[a] not contained in WHO 1998; included because of its carcinogenicity in Osborne-Mendel rats after intratracheal instillation (Wenzel-Hartung et al. 1990; Wenzel-Hartung 1992)

[b] The studies with B6C3F1 mice (NTP 1992) and F344 rats (NTP 2000) showed carcinogenicity; there was a significantly increased incidence of pulmonary alveolar and bronchial adenomas in female mice (NTP 1992) and tumours of the olfactory epithelium in rats (NTP 2000).

[c] included as a representative of alkylated PAH

Table 20: Industrial mixtures of PAH (DECOS (2006), EPA (2001))

CAS Reg. No.	Industrial mixtures with polycyclic aromatic hydrocarbons
101794-76-7	Aromatic hydrocarbons, C-20-28, polycyclic, mixed coal-tar pitch-polystyrene pyrolysis-derived. Definition: A complex combination of hydrocarbons obtained from mixed coal tar pitch-polystyrene pyrolysis. Composed primarily of polycyclic aromatic hydrocarbons having carbon numbers predominantly in the range of C20 through C28 and having a softening point of 100°C to 220°C (212°F to 428°F) according to DIN 52025.
101794-75-6	Aromatic hydrocarbons, C20-28, polycyclic, mixed coal-tar pitch-polyethylene pyrolysis-derived. Definition: A complex combination of hydrocarbons obtained from mixed coal tar pitch-polyethylene pyrolysis. Combined primarily of polycyclic aromatic hydrocarbons having carbon numbers predominantly in the range of C20 through C28 and having a sof tening point of 100°C to 220°C (212°F to 428°F) according to DIN 52025.
101794-74-5	Aromatic hydrocarbons, C20-28, polycyclic, mixed coal-tar pitch-polyethylene-polypropylene pyrolysis-derived. Definition: A complex combination of hydrocarbons obtained from mixed coal tar pitch-polyethylene-polypropylene pyrolysis. Composed primarily of polycyclic aromatic hydrocarbons having a sof tening point of 100°C to 220°C (212°F to 428°F) according to DIN 52025.
94113-85-6	Aromatic hydrocarbons, polycyclic, from decompn. of solvent extd. coal tar pitch-2,4,6-tricnitrophenol-reaction products. Definition: A complex combination of organic compounds obtained by addition of a picric acid solution to the solvent extract of a bitumineus coal tar pitch and decomposition of the precipitated pitch-picric acid reaction product with bases. Composed primarily of high molecular weight polycyclic aromatic compounds.
94113-84-5	Aromatic hydrocarbons, polycyclic, from decompn. of iodine-solvent extd. coal-tar pitch cargo-transfer complexes. Definition: A complex combination of organic compounds obtained by addition of iodine solution to the solvent extract of a bitumineus coal tar pitch and decomposition of the precipitated pitch iodine reaction products. Composed primarily of high molecular weight polycyclic aromatic compounds.
68409-74-5	Aromatic hydrocarbons, polycyclic, cyclohexanone, ext. residues. Definition: A complex residuum from the cyclohexanone extraction of anthracene salts. It consists predominantly of polynuclear aromatic hydrocarbons such as anthracene.
90640-80-5	Anthracene oil. Definition: A complex combination of polycyclic aromatic hydrocarbons obtained from coal tar having an approximate distillation range of 300°C to 400°C (572°F to 752°F). Composed primarily of phenanthrene, anthracene, and carbazole.
141785-66-2	Tar bases, coal, low-temperature, crude. Definition: The reaction product obtained by neutralizing the acidic extract of alkali-washed low-temperature coal tar middie oil with an alkaline solution, such as aqueous sodium hydroxide, to obtain the free bases. Composed primarily of a complex mixture of aromatic nitrogen bases.
130576-63-5	Extracts (coal), coal tar pitch solvent. Definition: Solvent extract of bituminous coal tar pitch. Composed primarily of polycyclic aromatic hydrocarbons.
94113-98-1	Extracts (coal), coal tar pitch solvent, reaction products with 2,4,6-trinitrophenol.Definition: Insoluble reaction product obtained by addition of apicric acid solution to the solvent extract of a bitumineus coal tar pitch. Composed primarily of polycyclic aromatic hydrocarbons.
94113-97-0	Extracts (coal), coal tar pitch solvent, reaction products with iodine. Definition: Extract obtained by adding an iodine solution to the solvent extract of a bitumineus coal tar pitch. Composed primarily of polycyclic aromatic hydrocarbons.
94113-96-9	Extract residues (coal), liquefaction heavy acid, alkaline extracts. Definition: The neutral oil obtained by debasing and dephenolating the heavy oil from the high pressure hydrogenation of bituminous coal. Composed primarily of unsubstituted and alkyl-substituted aromatic polynuclear hydrocarbons that are partially hydrogenated and may contain heteroatoms.
94113-95-8	Extract residues (coal), naphthalene oil acid, alkaline extracts. Definition: The neutral oil obtained by debasing and dephenolating the middie oil from the low temperature carbonization of bituminous coal. Composed primarily of a mixture of mono- and polynuclear, substituted and unsubstituted aromatic and naphthenic hydrocarbons and heterocycles as well as paraffinic hydrocarbons.

Table 20 continues

CAS Reg. No.	Industrial mixtures with polycyclic aromatic hydrocarbons
101794-76-7	Aromatic hydrocarbons, C-20-28, polycyclic, mixed coal-tar pitch-polystyrene pyrolysis-derived. Definition: A complex combination of hydrocarbons obtained from mixed coal tar pitch-polystyrene pyrolysis. Composed primarily of polycyclic aromatic hydrocarbons having carbon numbers predominantly in the range of C20 through C28 and having a softening point of 100°C to 220°C (212°F to 428°F) according to DIN 52025.
140413-63-4	Distillates (coal tar), low-temperature, pitch. Definition: The distillate obtained during the heat treatment of low temperature coal tar pitch having an approximate distillation range of 100°C to 400°C (212°F to 752°F). Composed primarily of a complex mixture of aromatic compounds.
140203-27-6	Distillates (coal tar), upper, fluorene-low. Definition: A complex combination of hydrocarbons obtained by the crystallization of the fractional distillates from tar oil. It consists of aromatic polycyclic hydrocarbons, primarily diphenyl, dibenzof üran, and acenaphthene.
140203-21-0	Distillates (coal tar), gasification, pitch, full range. Definition: The distillate obtained during the heat treatment of pitch obtained from coal gasification tar having an approximate distillation range of 100°C to 400°C (212°F to 752°F). Composed primarily of aromatic and other hydrocarbons, phenolic compounds, and aromatic nitrogen compounds.
140203-19-6	Distillates (coal tar), gasification, heavy oils, pyrene fraction. Definition: The distillate from the fractional distillation of coal gasification tar having an approximate boiling range of 350°C to 450°C (662°F to 842°F). Composed primarily of phenanthrene and anthracene homologs, tetranuclear aromatic hydrocarbons which may also contain heteroatoms, high-boiling aliphatic and naphthenic hydrocarbons, and polynuclear phenols.
91995-52-7	Distillates (coal tar), pitch, pyrene fraction. Definition: The redistillate obtained from the fractional distillation of pitch distillate and boiling in the range of approximately 380°C to 410°C (716°F to 770°F). Composed primarily of tri- and polynuclear aromatic hydrocarbons and heterocyclic compounds.
91995-51-6	Distillates (coal tar), pitch, heavy oils. Definition: The distillate from the distillation of the pitch obtained from bitumineus high temperature tar. Composed primarily of tri- and polynuclear aromatic hydrocarbons and boiling in the range of approximately 300°C to 470°C (572°F to 878°F). The product may also contain heteroatoms.
91995-42-5	Distillates (coal tar), heavy oils, pyrene fraction. Definition: The redistillate obtained from the fractional distillation of pitch distillate boiling in the range of approximately 350°C to 400°C (662°F to 752°F). Consists predominantly of tri- and polynuclear aromatics and heterocyclic hydrocarbons.
91995-25-4	Distillates (coal), liquefaction, heavy. Definition: the heavy oil obtained by distillation in the range of approximately 300°C to 550°C (572°F to 1022°F) of coal oil from the catalytic hydrogenation of coal and coal-derived products. Composed primarily of polynuclear aromatics and naphthenes. The product contains sulfür, oxygen, and nitrogen compounds.
90640-86-1	Distillates (coal tar), heavy oils. Definition: The distillate from the fractional distillation of coal tar having an approximate distillation range of 300°C to 400°C (572°F to 752°F). Composed primarily of tri-and polynuclear aromatic hydrocarbons and heterocyclic compounds.
84989-11-7	Distillates (coal tar), upper, fluorene-rich. Definition: A complex combination of hydrocarbons obtained by the crystallization of the fractional distillates from coal tar. It consists of aromatic and polycyclic hydrocarbons, primarily fluorene and acenaphthene.
84989-10-6	Distillates (coal tar), upper, fluorene-free. Definition: A complex combination of hydrocarbons obtained by the crystallization of tar oil. It consists of aromatic polycyclic hydrocarbons, primarily diphenyl, dibenzof üran, and acenaphthene.
121575-60-8	Pitch, coal tar, high-temperature, heat-treated. Definition: The heat-treated residue from the distillation of high temperature coal tar. A black solid with an approximate sof tening point from 80°C to 180°C (176°F to 356°F). Composed primarily of a complex mixture of three or more membered condensed ring aromatic hydrocarbons.
100403-59-6	Pitch, mixed brown-coal tar-ethylene manufacturing pyrolysis oil distillation. Definition: The residue from the joint distillation of brown coal tar and pyrolysis residu^ oil from ethylene plants. Composed primarily of polynuclear aromatic and naphthenic hydrocarbons, which can be alkyl- and vinyl-substituted and can contain heteroatoms, paraffin hydrocarbons, and high-boiling mono- and dinuclear phenols. It is a black solid with a sof tening point of 60°C (140°F) according to DIN 52025.

Table 21: Overview of EPA PAH compounds determined in the NIOSH method 5506

POLYNUCLEAR AROMATIC HYDROCARBONS by HPLC: METHOD 5506, Issue 3, dated 15 January 1998 - Page 6 of 9

TABLE 1. FORMULAS AND PHYSICAL PROPERTIES.

COMPOUND (by M.W.)	FORMULA	WEIGHT	DETECTOR	MELTING POINT (°C)	BOILING POINT (°C)	REFERENCE
1. NAPHTHALENE	$C_{10}H_8$	128.17	UV	80.2	218	[6]
2. ACENAPHTHYLENE	$C_{12}H_8$	152.20	UV	92.5	280	[6]
3. ACENAPHTHENE	$C_{12}H_{10}$	154.21	UV	93.4	279	[6]
4. FLUORENE	$C_{13}H_{10}$	166.22	UV	115	295	[6]
5. ANTHRACENE	$C_{14}H_{10}$	178.23	UV	215	340	[6]
6. PHENANTHRENE	$C_{14}H_{10}$	178.23	UV	99.2	340	[6
7. FLUORANTHENE	$C_{16}H_{10}$	202.26	FL	108	384	[6]
8. PYRENE	$C_{16}H_{10}$	202.26	FL	151	404	[6]
9. BENZ[a]ANTHRACENE	$C_{18}H_{12}$	228.29	FL	167	435	[7]
10. CHRYSENE	$C_{18}H_{12}$	228.29	UV	258	448	[6]
11. BENZO[b]FLUORANTHENE	$C_{20}H_{12}$	252.32	FL	168	--	[7]
12. BENZO[k]FLUORANTHENE	$C_{20}H_{12}$	252.32	FL	217	480	[6]
13. BENZO[a]PYRENE	$C_{20}H_{12}$	252.32	FL	177	495	[6, 8]
14. BENZO[e]PYRENE	$C_{20}H_{12}$	252.32	FL	178	311	[6]
15. BENZO[ghi]PERYLENE	$C_{22}H_{12}$	276.34	FL	278	--	[7]
16. INDENO[1,2,3-cd]PYRENE	$C_{22}H_{12}$	276.34	FL	164	--	[7]
17. DIBENZ[a,h]ANTHRACENE	$C_{22}H_{14}$	278.35	FL	270	524	[7, 8]

Appendix 2. PAH exposures in different industrial sectors

Table 22: BaP exposure characteristics for different industries in France (Maitre et al 2018)[17]

Level groups	N	GM (ng/m³)	Med (ng/m³)	Min (ng/m³)	Max (ng/m³)	95th p. (ng/m³)	99.9th p. (ng/m³)	OEL exceedance? Fr	Dutch	SSP	Fin
1. Aluminum production	138	55	55	1.6	41891	484	36401	Y	NC	NC	NC
1.1 Prebaked anode production – paste tower	30	74	68	1.6	41891	1156	40729	Y	Y	NC	NC
*1.1.1 Manufacture operator**	7	84	84	35	320	285	319	Y	N	N	N
1.1.2 Watchman, heat attendant	18	43	28	1.6	1823	486	1796	Y	NC	N	N
1.2 Prebaked anode production – furnace*	24	24	29	6.0	88	67	87	N	N	N	N
*1.2.1 Gas attendant, Overhead crane man**	16	24	29	6.0	88	73	87	N	N	N	N
*1.2.2 Heat attendant mason**	8	25	29	8.2	57	54	57	N	N	N	N
1.3 Maintenance of the paste tower and furnace	22	94	101	16	819	511	812	Y	NC	N	N
*1.3.1 Maintenance operator**	6	73	55	24	426	345	424	Y	N	N	N
*1.3.2 Mechanic**	9	207	193	64	819	696	816	Y	Y	N	N
*1.3.3 Electrician**	6	48	43	16	206	183	206	Y	N	N	N
1.4 Ramming: electrolysis construction and furnace restoration	57	48	70	2.3	461	201	451	Y	N	N	N
1.4.1 Tank construction: using small seals	14	23	25	2.3	187	148	187	NC	N	N	N
1.4.2 Tank construction: using big seals	13	33	24	7.0	170	151	169	Y	N	N	N
*1.4.3 Tank construction: using both seals**	30	78	94	10	461	249	456	Y	N	N	N
2. Silicon production	324	184	140	0.12	64874	7167	56362	Y	Y	Y	NC
2.1 Composite electrodes	108	732	883	6.5	38521	8535	35954	Y	Y	Y	NC
2.1.1 Paste loading in the electrode	37	1399	1945	35	38521	11899	37657	Y	Y	Y	Y
2.1.2 Casing welding of the electrode	55	914	1036	18	9556	5882	9485	Y	Y	Y	N
2.2 Söderberg electrodes	13	131	126	12	1536	1097	1527	Y	Y	N	N
2.2.1 Casing welding of the electrode	8	174	191	26	1536	1187	1529	Y	Y	N	N
2.3 Manufacture	112	23	21	0.12	329	202	328	Y	N	N	N
2.3.1 Post's Chief	15	24	22	0.57	206	148	204	NC	N	N	N
2.3.2 Raw material loading	42	27	22	1.1	318	260	316	Y	N	N	N
2.3.3 Caster	54	20	20	0.12	329	179	324	Y	N	N	N
2.4 Heat attendant mason	25	868	3218	2.6	26573	23026	26564	Y	Y	Y	Y
2.4.1 Intervention in furnace	19	3448	3934	135	26573	26244	26566	Y	Y	Y	Y
2.5 Annual maintenance	62	497	474	18	64874	16219	62540	Y	Y	Y	Y
2.5.1 Plate and / or ring dismantling	27	2480	2449	218	64874	25713	63879	Y	Y	Y	Y
2.5.2 Resistors dismantling	7	513	609	88	4509	3731	4493	Y	Y	Y	N
*2.5.3 Fluke damage**	22	101	84	33	601	449	598	Y	NC	N	N
3. Manufacturing of carbon products	107	67	87	0.03	12562	921	11539	Y	Y	NC	NC
3.1 Cathodes production	107	67	87	0.03	12562	921	11539	Y	Y	NC	NC
3.1.1 Raw cathode extruding	52	161	131	8.8	12562	1006	12070	Y	Y	NC	NC
3.1.2 Cathode baking	18	47	98	0.03	1579	1130	1570	Y	Y	N	N
*3.1.3 Cathode graphitization**	8	8.7	9.5	1.7	36	34	36	N	N	N	N
3.1.4 Laboratory analysis	7	50	81	3.8	287	256	286	Y	N	N	N
4. Foundry	50	4.6	5.9	0.03	1109	72	1066	NC	NC	N	N
4.1 Aluminum	15	0.58	0.80	0.03	3.2	2.6	3.2	N	N	N	N
4.1.1 Driver, smelter	8	0.72	0.75	0.03	3.2	2.9	3.2	N	N	N	N
4.1.2 Caster	7	0.46	0.80	0.03	1.5	2.3	1.5	N	N	N	N
4.2 Steel	35	11	11	0.44	1109	121	1079	NC	NC	N	N
4.2.1 Fusion furnace operator	6	22	12	3.7	1109	837	1104	Y	Y	N	N
4.2.2 Crucible activity	6	19	29	2.6	63	61	63	N	N	N	N
4.2.3 Heat attendant mason	21	6.7	7.7	0.44	216	43	212	NC	N	N	N
5. Use of lubricating oils	89	0.80	0.81	0.03	24	8.7	23	N	N	N	N
5.1 Undercutting*	14	0.65	0.68	0.25	2.0	1.7	2.0	N	N	N	N
*5.1.1 Undercutting, help-undercutting**	7	0.71	0.95	0.25	2.0	1.8	2.0	N	N	N	N
5.2 Turning	43	0.48	0.48	0.03	5.1	3.2	5.1	N	N	N	N
*5.2.1 Mechanic**	30	0.27	0.30	0.03	0.78	0.62	0.78	N	N	N	N
5.3 Discharge mold*	13	4.9	4.3	1.5	24	18	24	N	N	N	N
5.4 Vehicles*	13	2.4	3.8	0.56	7.8	6.5	7.8	N	N	N	N
*5.4.1 Mechanic driver**	9	1.7	1.5	0.56	4.7	4.5	4.7	N	N	N	N
6. Engine exhaust emissions	263	0.70	0.80	0.03	62	8.4	59	N	N	N	N
6.1 Highways	43	0.11	0.15	0.03	2.9	0.78	2.9	N	N	N	N
6.1.1 Administration, Toll collector	23	0.09	0.03	0.03	0.67	0.66	0.67	N	N	N	N
6.1.2 Highway services	15	0.18	0.29	0.03	2.2	1.2	2.2	N	N	N	N
6.2 Heavy Truck (HT) garage + Roadwork + 2-Stroke engines	50	1.3	1.1	0.03	52	9.8	50	N	N	N	N
6.2.1 HT mechanic	28	1.3	1.2	0.03	10	8.5	10	N	N	N	N
6.2.2 Roadwork mechanic	9	0.96	0.35	0.12	52	36	52	N	N	N	N
*6.2.3 Agricultural mechanic**	12	1.5	1.3	0.43	6.5	6.1	6.5	N	N	N	N
6.3 Light Vehicles garage	70	1.0	0.98	0.03	10	6.6	10	N	N	N	N
*6.3.1 Mechanic (all engines)**	56	0.97	0.93	0.11	10	6.8	10	N	N	N	N
6.4 Driver: HT, delivery, roadwork, bus*	15	0.54	0.58	0.19	1.9	1.5	1.9	N	N	N	N
6.5 Downtown*	11	2.1	2.2	0.74	4.1	4.0	4.1	N	N	N	N
*6.5.1 Sewage worker**	6	1.9	1.9	0.74	4.1	4.0	4.1	N	N	N	N
6.6 Use of 2-Stroke and 4-Stroke engines*	30	2.5	2.4	0.71	18	11	18	N	N	N	N
*6.6.1 Brushwood clearer**	7	1.6	1.3	0.78	5.2	4.4	5.2	N	N	N	N
*6.6.2 Hedge trimmer**	8	3.1	3.2	0.95	18	15	18	N	N	N	N
6.7 Generator	8	0.95	0.84	0.16	8.5	8.3	8.4	N	N	N	N
6.8 Closed environment	35	0.33	0.19	0.03	62	18	61	N	N	N	N
6.8.1 Underground – driver	9	2.4	3.5	0.19	8.2	8.2	8.2	N	N	N	N
6.8.2 Work in tunnel	21	0.05	0.03	0.03	0.75	0.68	0.75	N	N	N	N
7. Combustion processes	36	4.2	4.2	0.03	83	65	82	N	N	N	N
7.1 Firefighter*	7	28	25	4.4	83	77	83	N	N	N	N
7.2 Chimney sweeper*	10	12	13	2.6	69	51	68	N	N	N	N
7.3 Household garbage incinerator	17	1.2	0.81	0.03	56	25	56	N	N	N	N
7.3.1 Operating household garbage incinerator	13	1.2	1.3	0.03	17	10	17	N	N	N	N
8. Road paving / Bitumen	75	0.27	0.29	0.03	12	2.8	11	N	N	N	N
8.1 Road paving: application of hot bitumen(>150°C)	61	0.28	0.28	0.03	12	3.0	12	N	N	N	N
8.1.1 Tar application	27	0.18	0.25	0.03	12	2.5	12	N	N	N	N
*8.1.2 Coating application**	11	0.14	0.19	0.03	0.25	0.25	0.25	N	N	N	N
8.1.3 Work in tunnel	17	0.80	0.72	0.03	5.5	3.9	5.5	N	N	N	N
8.2 Application of warm bitumen (≤150°C) in tunnel	8	0.18	0.26	0.03	2.4	1.8	2.3	N	N	N	N
9. Coke production	86	932	1242	0.33	18911	11310	18571	Y	Y	Y	Y
9.1 Coke pusher	14	872	2412	0.33	6338	5945	6330	Y	Y	Y	N
9.2 Furnace door settings	10	412	201	96	4770	4184	4758	Y	Y	Y	N
9.3 Coke withdrawn*	8	531	435	238	1395	1384	1394	Y	Y	N	N
9.4 Furnace battery cleaning-up	16	1035	2193	89	9471	4912	9380	Y	Y	Y	N
9.5 Watchman	12	499	779	5.0	18911	16428	18862	Y	Y	Y	Y
9.6 Mason	18	1544	1290	201	14807	12317	14757	Y	Y	Y	Y
*9.6.1 Furnace**	12	822	732	201	2889	2540	2882	Y	Y	Y	N
*9.6.2 Work in gallery**	6	7013	7982	1540	14807	14029	14791	Y	Y	Y	Y

[17] Reprinted from International Journal of Hygiene and Environmental Health, 221, Maitre et al, Exporisq-HAP database: 20 years of monitoring French occupational exposure to polycyclic aromatic hydrocarbon mixtures and identification of exposure determinants, pages 334-346, 2018, with permission from Elsevier.

Table 23: Summary of personal PAH exposure (8 h TWA, µg/m3) in different industrial sectors in the UK (Unwin et al 2006)

Site	Industry		Total PAH		Total 4–6 ring PAH		BaP		1-OHP µmol mol^{-1}	
		n	Mean	Range	Mean	Range	Mean	Range	Mean	Range
11	Coke oven	11	79.17	8.80–184.55	16.36	1.17–35.93	2.14	0.13–6.21	1.85	0.25–5.4
14	Coke oven	13	70.66	9.93–294.63	5.69	0.21–29.09	0.79	0.02–4.08	2.1	0.25–7.1
2	Coke oven (low T)	13	49.87	5.88–131.64	6.87	0.01–19.44	1.13	0.01–2.91	2.63	0.41–6.9
3	Tar distillation (high T)	12	278.82	51.9–1130.21	0.725	0.11–4.54	0.06	0.01–0.32	2.6	0.78–5.7
4	Tar distillation (low T)	8	12.17	5.20–38.59	0.01	0.01	0.01	0.01	0.36	0.25–1.1
1	Aluminium (green carbon)	9	60.88	10.45–138.38	0.31	0.01–0.85	0.03	0.03–0.10	0.72	0.25–2.6
6	Clay targets	8	24.67	13.39–38.69	5.44	1.91–12.84	0.82	0.26–2.02	11.3	3.9–11.3
7	Pipeline coating and wrap	11	263.64	73.34–758.22	3.78	0.4–18.30	0.32	0.04–1.65	10.6	1.7–21.3
15	Coal fired power station	12	1.37	0.40–2.11	0.20	0.04–0.79	0.02	<0.01–0.10	0.25	0.25
5	Timber impregnation	11	835.06	29.93–1912.6	0.05	0.01–0.11	0.01	0.01–0.011	16.0	1.4–60
24	Electrical carbon	1	12.79	—	1.72	—	0.24	—	0.25	0.25
9	Integrated oil refinery	12	5.24	0.77–20.34	0.01	0.01–0.03	0.01	0.01	0.25	0.25
13	Petroleum tar distillation	8	68.94	15.21–280.03	0.13	0.04–0.35	0.02	0.01–0.04	0.88	0.25–3.8
10	Petroleum coke	9	5.83	0.74–16.80	2.58	0.10–12.26	0.374	0.01–1.78	0.48	0.25–1.2
8	Bitumen refinery	12	2.38	0.08–7.01	0.02	0.01–0.06	0.01	0.01	0.25	0.25
22	Asphalt roofing	3	1.51	1.23–1.94	0.34	0.23–0.47	0.02	0.01–0.02	0.25	0.25
25	Asphalt road surfacing	7	3.21	1.83–4.63	0.01	0.01	0.01	0.01	0.25	0.25
23	Road construction (base)	5	9.56	3.83–17.60	0.38	0.07–0.72	0.01	0.01	0.25	0.25
17	Carbon black	11	10.70	1.98–69.09	0.52	0.03–4.49	0.05	0.01–0.41	0.63	0.25–0.31
16	Motor tyre	12	3.22	1.82–6.55	0.06	0.02–0.11	0.01	0.01–0.02	0.32	0.25–0.8
12	Motor tyre	11	3.22	1.63–4.54	0.03	0.01–0.11	0.01	0.01	0.25	0.25
18	Foundry	11	65.75	26.97–120.13	0.211	0.03–0.33	0.02	0.01–0.05	0.29	0.25–0.66
19	Foundry	7	21.12	8.88–47.38	0.09	0.05–0.13	0.01	0.01–0.02	0.25	0.25
20	Fish smokehouse	2	2.31	2.06–2.55	0.07	0.06–0.07	0.01	0.01	0.25	0.25
21	Fish smokehouse	1	—	17.24	—	1.55	—	0.22	0.25	0.25

Table 24: Occupational PAH exposure data mainly in EU collected from the recent publications. The list is not comprehensive.

Industry sector/occupation, Number of workers	Country	Year	Air monitoring, µg/m³, median				Biomonitoring, post-shift	Reference
			Sum of total PAHs (16EPA PAHs)	BaP	Pyrene	Naphthalene	1-OHP, median, post-shift (µg/g creatinine)	
Electric steel foundry, N=93*	Tunisia	2013					0.29 µg/g creat	Campo et al 2016
Bitumen applications in construction, N=317	Germany	2001-2008	2.47	0.045	0.095	1		(Breuer et al., 2011)
Bitumen applications in construction, N=321**	Germany	2001-2008					0.28 (NS); 0.52 µg/g creat (S)	Pesch et al 2011
Road construction, N=7	Slovak Republic		0.79	0.04			2.55 (1.32 µmol/mol create)	Klöslova et al 2016
Road paving asphalt workers, conventional asphalt N1=19; crumb rubber asphalt N2=18	Sweden		1. 2.75 (P95 6.24); 2. 2.55 (P95 9.81) [b]				1. 0.13 µg/g creat 0.068 µmol/mol creat (P95 0.24); 2. 0.11 (P95 0.76)	(Xu et al., 2018a, Xu et al., 2018b)
Road paving and remixing of asphalt, N=35**	Finland	1999-2000	All: GM 5.7, max 46 [c]	GM 0.02, max 0.22 road paving; GM 0.03, max 0.32 remixing	All: GM 0.08, max 1.2	All: GM 2.3, max 13	All pavers (N=29): GM 0.24, max 2.2 µmol/mol creat (NS);GM 0.18, max 0.29 µmol/mol creat (S)	(Vaananen et al., 2006, Vaananen et al., 2003)
Road paving (N=20) **	Finland	2003	GM 1.4, max 3.5	<0.01	GM <0.015, max 0.04	GM 0.75, max 2.2	All pavers: max 0.64 µmol/mol creat (NS); 2.05 µmol/mol creat (S)	(Vaananen et al., 2006)
Impregnation /creosote facility workers, n=27-44	Germany	2005-2017	Median 580, P95 1660 [a]	<LOQ (16 ng/m³)	Median 4, P95 10	30 median, P95 170	9 µg/g creat, P95 50 µg/g creat	Hebisch et al 2020
Wood impregnation with creosote, N=68	Germany	2005-2006					Range 2.2 – 105 µg/g creat	(Riechert et al., 2011)
Recycling of railway sleepers, N=90	Germany	2013-2015	176.9	0.13	1.4	90.5	Range for medians 1.6 -8.0 µg/g creat; P95 5.7 – 59 µg/g creat	Hagmann et al 2017
Recycling of railway sleepers, N=31	Germany	2013-2016	6.1	0.045	0.43	18.7	Range for medians 0.6 - 6.1 µg/g creat; P95 21-24 µg/g create	Hagmann et al 2017
Remediation of contaminated soil, N=51	Germany	2013-2015	637.2	0.17	1.15	553.5	Range for medians 0.3 - 8.4 µg/g creat;	Hagmann et al 2017

							P95 1.8 – 142 µg/g creat	
Production of rubber products, N=27	Slovak Republic		17.9	0.46			1.78 µmol/mol creat	Klöslova et al 2016
Aluminium production, N=19	Slovak Republic		0.5	0.04			1.20 µmol/mol creat	Klöslova et al 2016
Production of carbon and graphite electrodes, N=64	Slovak Republic		44.7	1.25			2.85 µmol/mol creat	Klöslova et al 2016
Graphite electrodes, N=24* **	Germany	1999-2004		1.50	2.24		2.05 µg/g creat	Förster et al 2008
Coke Oven workers, N=104	Italy	1993/94	11.7-46.7	0.05-1.1				Vimercati et al 2020
Coking plants, N=79* **	Germany	1999-2004		0.89	1.07		4.30 µg/g creat	Förster et al 2008
Converter infeed, N=12* **	Germany	1999-2004		2.40	9.28		9.40 µg/g creat	Förster et al 2008
Refractories, N=84* **	Germany	1999-2004		0.14	1.40		8.29 µg/g creat	Förster et al 2008
Firefighters, simulated fires	Australia		1700-8600 outside ensembles; 110-740 inside ensembles	20-95 outside; <LoR – 16 inside	120-900 outside; 6-30 inside	180-4700 outside; 80-580 inside		Kirk et al 2021
Air force ground crew personnel, N=79	Denmark	2018	Dermal exposure: 479 (±683) ng/g of silicone band per day; 473 (±503) ng/g for reference group 2.05 ng/cm^2 per 1 h skin wipes; 2.10 (±3.2) ng/cm^2 for reference group				Average 3.29 (±1.7 SD) µmol/mol creat workers; Average 4.76 (±3.9 SD) µmol/mol creat for reference group	(Andersen et al., 2021)

N = number of workers, LOD = limit of detection, LOQ = limit of quantification; LOR = limit of reporting; [a] 16 EPA PAHs + 2 methylnaphthalenes; [b] sum of 32 PAHs; [c] sum of 17 PAHs (EPA PAH and perylene);

*Urinary naphthols, phenanthrols and urinary unmetabolized PAHs were measured in addition to 1-OHP;

**Urinary naphthols and phenanhtrols were measured in addition to 1-OHP;

***Urinary 3-OHBaP and OH-Phens were measured in addition to 1-OHP