SCOEL/REC/404
Polycyclic Aromatic Hydrocarbon mixtures containing benzo[a]pyrene (PAH)

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B —Employment
Unit B.3 — Health and safety

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RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR POLYCYCLIC AROMATIC HYDROCARBON MIXTURES CONTAINING BENZO[A]PYRENE (PAH)

8-hour TWA:	no health-based OEL applicable
STEL:	not applicable
BLV/BGV:	BLV: no health-based limit value applicable BGV: 0.5 µg 1-hydroxypyrene in urine [determined after conjugate hydrolysis]
Additional categorisation:	carcinogen(s) group A [genotoxic carcinogen(s)]
Notation:	Skin

For cancer risk assessments, see chapter 7.7.3

The present Recommendation was adopted by SCOEL 2016-12-13.

RECOMMENDATION EXECUTIVE SUMMARY

Outcome Considerations

Complex polycyclic aromatic hydrocarbon mixtures (PAH) containing benzo[a]pyrene or low molecular weight PAH mixtures, are not produced and used as such, but are specifically and ubiquitously formed during combustion and pyrolysis processes of organic materials. Occupational exposure to PAH primarily occurs through inhalation and skin contact. The most extensively studied PAH as surrogate for total airborne PAH exposure is benzo[a]pyrene. It is released from a great variety of different PAH-sources. Benzo[a]pyrene is considered as one of the strongest genotoxic carcinogens, which significantly contributes to the carcinogenic potency of PAH-rich mixtures. Polycyclic aromatic hydrocarbons are of concern on account of carcinogenicity. After metabolism within the body, PAH may have various toxic effects. The carcinogenicity of individual PAH has been demonstrated by many animal studies using different exposure models. Genotoxic effects of PAH were observed in numerous animal studies and also in human cells in vitro and in vivo. The pathway leading to genotoxicity and carcinogenicity has been well investigated. Carcinogenic PAH, such as benzo[a]pyrene can be converted to highly reactive dihydrodiol epoxides during mammalian metabolism. These diol epoxides react with double strand and single strand DNA, preferably with the N^6 position of guanine and the N^2 position of adenine.

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.

Derived Limit Values /Carcinogenic Risk Assessment

Polycyclic aromatic hydrocarbon mixtures containing benzo[a]pyrene (PAH), PAH mixtures and benzo[a]pyrene are *genotoxic carcinogens (SCOEL Group A)* for which safe health-based exposure limits cannot be derived. In consequence, no OEL is recommended. Quantitative risk assessment procedures may be used to approximate the carcinogenic risk, dependent on the dose of PAH, by using benzo[a]pyrene as indicator substance.

As discussed in chapter 6.7.3, two more recent risk assessments by DECOS (2006) and by AGS (2011), both based on the same extensive metaanalysis of Armstrong et al (2003, 2004), lead to practically identical figures in excess human lung cancer risk mortality, related to PAH exposure with benzo[a]pyrene as indicator compound. According to these assessments, a mean airborne 8h-TWA PAH exposure over 40 working years in the order of 6 ng benzo[a]pyrene per m^3 would lead to an excess lung cancer mortality rate of 4×10^{-5}.

Skin notation

Occupational exposure studies, in which the urinary excretion of 1-hydroxypyrene 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 is supported by experimentation in animals (see 7.1.). Therefore, a *skin notation* is warrented. 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.

Biological Monitoring

The permeability of the human skin for benzo[a]pyrene and for PAH compounds in general has triggered a great number of studies on biological monitoring. Analytically validated methods are available for biological monitoring of urinary PAH metabolites.

1-Hydroxypyrene excretion in urine has been used as a parameter for assessing systemic PAH exposure in most field studies. Analytical approaches are also developed and used for a number of metabolites of other relevant constituents of PAH-mixtures. These include 3-hydroxybenzo[a]pyrene as a metabolite of the carcinogenic benzo[a]pyrene, as well as metabolites of benzo[a]anthracene, benzo[a]phenanthrene, chrysene, fluorene, fluoroanthene and naphthalene. Diverse approaches for sample preparation and analytical methods for the different constituents are discussed and further developed as addressed under 6.2.

In conclusion, 1-hydroxypyrene represents the main metabolite of pyrene in mammals and has become accepted as a sensitive and specific parameter of PAH exposure, for which reliable and robust analytical methods are described. As shown in the *Annex Tables*, in general the urinary excretion of 1-hydroxypyrene does not exceed 0.5 µg 1-hydroxypyrene per g creatinine (determined after conjugate hydrolysis) in 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 proposes this value of *0.5 µg 1-hydroxypyrene per g creatinine* as a Biological Guidance Value (BGV). As the BGV is derived from the background of the general population, the sampling time is not critical as such. For instance, sampling may be performed before the following shift.

Recent analytical developments allow a specific and sensitive determination of the relatively small amounts of 3-hydroxybenzo[a]pyrene occurring in the urine as exposure markers for the carcinogenic benzo[a]pyrene. This approach may, when more studies will be available, lead to the development of an additional BGV for 3-hydroxy-benzo[a]pyrene.

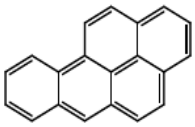
RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR POLYCYCLIC AROMATIC HYDROCARBON MIXTURES CONTAINING BENZO[A]PYRENE (PAH)

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	benzo[a]pyrene
Synonyms:	3,4-benzopyrene; benzo[def]chrysene
Molecular formula:	$C_{20}H_{12}$

Structural formula:



Fp: 178.1°C; Kp: 496°C

EC No.:	
CAS No.:	50-32-8
Molecular weight:	252.3
Conversion factors: (20 °C, 101.3kPa)	[*not volatile*]

Benzo[a]pyrene is commonly used as a quantitative indicator compound within complex mixtures of polycyclic aromatic hydrocarbons (PAH). These mixtures of polycyclic aromatic hydrocarbons containing benzo[a]pyrene as indicator are addressed by the present Recommendation. PAH are formed by processes of combustion/pyrolysis of organic materials and represent a large class of organic compounds consisting of two or more fused aromatic rings of carbon and hydrogen atoms. Numerous configurations of conjugated aromatic rings are possible.

Benzo[a]pyrene is a PAH that consists of five aromatic benzene rings. In the literature, various terms are used for PAH and related compounds, which may be confusing. Both IPCS (1998) and IARC (2010) refer to the term PAH as unsubstituted non-heterocyclic PAH (including alkyl-substituted derivates). 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. This evaluation considers only unsubstituted non-heterocyclic PAH. At the moment there are more than 100 single PAH identified. Outstanding examples are given in *Table 1*. Only a minor fraction of all PAH has been studied toxicologically. 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 in which these are naturally or artificially produced or processed (DECOS 2006).

Table 1: Chemical properties of typical constituents of PAH mixtures (from DFG 2012)

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

This Recommendation is based on previous compilations performed by ATSDR (1995, 2002), IPCS (1998), DECOS (2006), IARC (1983, 2010), AGS (2011) and DFG (2012). An additional literature search has been conducted in 2016 by the Joint Research Centre of the European Commission.

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for benzo[a]pyrene/ benzo[def]chrysene (CAS number 50-32-8; EC Number 200-028-5; Index 601-032-00-3) is provided by ECHA (2016), as summarised in Table 2.

Table 2: Classification according to Regulation (EC) No 1272/2008, Annex VI, Table 3.1 "List of harmonised classification and labelling of hazardous substances" (ECHA, 2016).

Classification		Labelling			Spec. Conc. Limits, M-factors
Hazard Class & Category Code(s)*	**Hazard statement code(s)***	**Hazard statement code(s)***	**Suppl. Hazard statement code(s)**	**Pictograms, Signal Word Code(s)**	
Skin Sens.1	H317	H317		GHS07 GHS09 GHS08 Dgr**	Carc.1B; H350:C≥0.01%
Muta. 1B	H340	H340			
Carc.1B	H350	H350			
Repr. 1B	H360FD	H360FD			
Aquatic Acute 1	H400				
Aquatic Chronic 1	H410	H410			

* *Skin Sens.1,H317* — *May cause an allergic skin reaction*
Muta. 1B, H340 — *May cause genetic defects*
Carc. 1B, H350 — *May cause cancer*
Repr. 1B, H360FD — *May damage fertility. May damage the unborn child*
Aquatic Acute 1, H400 — *Very toxic to aquatic life*
Aquatic Chronic 1, H410 — *Very toxic to aquatic life with long-lasting effects*

** *Signal word code 'Dgr' for 'Danger*

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Benzo[a]pyrene as pure chemical is not of occupational relevance; it is commonly used as a quantitative indicator compound within complex mixtures of polycyclic aromatic hydrocarbons (PAH). Such 'PAH mixtures' are specifically formed by processes of combustion/pyrolysis of organic materials and represent a large class of organic compounds consisting of two or more fused aromatic rings of carbon and hydrogen atoms. Numerous configurations of conjugated aromatic rings are possible.

Polycyclic aromatic hydrocarbon mixtures containing benzo[a]pyrene (PAH), PAH mixtures, are process-generated substances that are hazardous chemical agents in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Polycyclic aromatic hydrocarbon (PAH) mixtures containing benzo[a]pyrene are process-generated substances that are carcinogens or mutagens for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

At EU level, no OEL has been adopted for benzo[a]pyrene or polycyclic aromatic hydrocarbon mixtures containing benzo[a]pyrene (PAH). However, OELs do exist in various EU Member States as well as outside the EU. OELs for PAH mixtures are presented in Table 3 and OELs for the single PAH; benzo[a]pyrene are represented in Table 4. These lists should not be considered as exhaustive.

There are no Biological Limit Values (BLVs) for benzo[a]pyrene or for PAH mixtures containing benzo[a]pyrene available to date. There is however a BAR (Biologischer Arbeitsstoff-Referenzwert / biological reference value) by DFG of 0.3 µg 1-hydroxypyrene (after hydrolysis) /g creatinine in urine (DFG 2015). The UK has a biological monitoring guidance value of 4 µmol 1-hydroxypyrene/mol creatinine (approx. 8 µg 1-hydroxypyrene (after hydrolysis) /g creatinine) based on the 90th percentile value of a survey of workplaces with exposure to PAH (HSE 2011, Unwin et al 2006). The ACGIH have proposed a Biological Exposure Index (BEI) of 2.5 µg/l (adjusted for the pyrene to benzo(a)pyrene ratio of the PAH mixture to which workers are exposed) (ACGIH 2016)

Table 3: Existing OELs for PAH mixtures

EU	TWA (8 hrs)		STEL (15 min)		Remarks	References
	ppm	mg/m³	ppm	mg/m³		
Denmark	-	0.2	-	-	PAH, benzene soluble fraction	DK DWEA (2007)
Germany	-	-	-	-	NO OEL because PAH is classified as carcinogenic	-
Latvia **	-	0.2	-	-	*Coal tar pitch sublimates, with average content of benzopyrene* (Less than 0.075% of benzopyrene)	GESTIS (2016)
	-	0.1	-	-	*Coal tar pitch sublimates, with average content of benzopyrene* (0.075-0.15% of benzopyrene)	GESTIS (2016)
	-	0.05	-	-	*Coal tar pitch sublimates, with average content of benzopyrene (*0.15-0.3 % of benzopyrene)	GESTIS (2016)
The Netherlands	-	0.2	-	-	Administrative OEL, PAH as soluble in cyclohexane, only valid for non-carcinogenic PAH	-

Non-EU						
USA (ACGIH)	-	0.2	-	-	TLV; coal tar pitch volatiles as benzene soluble aerosol	USA ACGIH (2012)
USA (NIOSH)	-	0.1	-	-	REL; coal tar pitch volatiles as cyclohexane extractable fraction	USA NIOSH (2007)
USA (OSHA)	-	0.2	-	-	PEL; coal tar pitch volatiles as benzene soluble aerosol	USA OSHA (2006)

TLV: Threshold Limit Value
REL: Recommended Exposure Limit
PEL: Permissible Exposure Limits

Table 4: Existing OELs for benzo[a]pyrene within PAH mixtures

EU	TWA (8 hrs)		STEL (15 min)		Remarks	References
	ppm	mg/m³	ppm	mg/m³		
Austria	-	0.002	-	0.008	-Other workplaces -TRK value (based on technical feasibility)	AU GKV (2011)
	-	0.005	-	0.02	-Cokeries, oven area -TRK value (based on technical feasibility)	AU GKV (2011)
Finland	-	0.01	-	-	-	FI MSAH (2012)
Germany (AGS)	-	0.0007	-	-	"Tolerable risk" (4:1000) The risk refers to the total PAH concentration using benzo[a]pyrene as exposure marker.	BAUA (2011), AGS (2011)
	-	0.000007	-	-	"Acceptable risk" (4:10000 in 2016; to be reduced to 4:100000 by 2018 at the latest) The risk refers to the total PAH concentration using benzo[a]pyrene as exposure marker.	BAUA (2011), AGS (2011)
Hungary	-	-	-	0.002	-	HU MHSFA (2000)
Latvia	-	0.00015	-	-	-	GESTIS (2016)
Poland	-	0.002	-	-	-	GESTIS (2016)
Sweden	-	0.002	-	0.02	15 min. average value	SWE SWEA (2011)
The Netherlands	-	0.00055	-	-	-	NL SZW (2008)
Non-EU						
Canada (Ontario)	-	L	-	-	L: Exposure by all routes should be carefully controlled to levels as low as possible.	CA OML (2013)
Canada (Québec)	-	0.005	-	-	TWAEV	CA IRSST (2010)
Switzerland	0.0002	0.002	-	-	-	CH SUVA (2016)
USA (ACGIH)	-	L	-	-	L: Exposure by all routes should be carefully controlled to levels as low as possible.	USA ACGIH (2012)

TWAEV: Time Weighted Average Exposure Values
TRK: Technische Richtkonzentration

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence and use

PAH are released to the environment through natural and synthetic sources with emissions largely to the atmosphere. Natural sources include emissions from volcanoes and forest fires. Man-made sources provide a much greater release volume than natural sources; the largest single source is the burning of wood in homes. Automobile and truck emissions are also major sources of PAH. Environmental tobacco smoke, unvented radiant and convective kerosene space heaters, and gas cooking and heating appliances may be significant sources of PAH in indoor air. Hazardous waste sites can be a 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 waste water, and improper disposal of used motor oil. Several of the PAH have been detected at hazardous waste sites at elevated levels. In air, PAHs are found sorbed to particulates and as gases. Particle-bound PAH can be transported long distances and are removed from the atmosphere through precipitation and dry deposition. PAH are transported from surface waters by volatilization and sorption to settling particles. The compounds are transformed in surface waters by photooxidation, chemical oxidation, and microbial metabolism. In soil and sediments, microbial metabolism is the major process for degradation of PAHs. Although PAHs are accumulated in terrestrial and aquatic plants, fish, and invertebrates, many animals are able to metabolize and eliminate these compounds. Important sources of individual exposure to PAH are inhalation of tobacco smoke and contaminated air and ingestion of the compounds in foodstuffs (ATSDR 1995).

5.2. Production and use information

Benzo[a]pyrene and complex PAH mixtures are not produced and used as such, but are ubiquously formed during combustion and pyrolysis processes of organic materials.

5.3. Occupational exposure

The processing and use of coal and coal-derived products is fundamental to many industries. Pyrolysis (also called thermolysis) is the thermal decomposition of organic substances such as coal during heating to more than 300°C in an oxygen-free atmosphere. It is the generic term for carbonisation, coking and devolatilisation. It is also the primary reaction in gasification, combustion and direct liquefaction. The decomposition products of pyrolysis are pyrolysis gas (mainly hydrogen, carbon monoxide, carbon dioxide, methane and C_2–C_5 hydrocarbons), liquid products (tar, oil, crude benzene and water) and coke as a solid residue and the main product. Depending on the properties of the coal, different sulfur and nitrogen compounds are formed during the pyrolysis process. Distribution and composition of pyrolysis products are mainly determined by the type of coal but can be influenced by parameters in the process such as heating rate, temperature, atmosphere and pressure.

Low-temperature carbonisation and coking involve the heating of coal with the exclusion of air. This process removes condensable hydrocarbons (pitch, tar and oil), gas and gas liquour, which leaves a solid residue of coke. Low-temperature carbonisation (up to 800°C) and coking (>900°C) are differentiated by the final temperature. The two processes also differ considerably in the rate of heating of the coal and the residence time in the reactor. These parameters have a direct effect on the product yields. Low temperature carbonization produces fine coke and fairly large quantities of liquid and

gaseous products, whereas high-temperature coking is used primarily for the production of a high-temperature lump coke for blast furnaces and cupola ovens. High-temperature coking of coal is carried out entirely in batch-operated coke ovens, the majority of which are of the horizontal chamber type. The feedstock is a coking coal of given size and composition. The coking properties depend chiefly on softening and resolidification temperatures and on swelling behaviour. Coking takes place at 1000–1300°C for 15–30 h. The coking time depends on the operating conditions and width of the oven. The main product is metallurgical coke that is required for the production of pig iron. Metallurgical coke is characterised by its suitable size and high resistance to abrasion even under the conditions of a blast furnace. Coke-oven gas and liquid byproducts are also produced. In Western Europe, these by-products influence the economy of coking and, therefore, are reprocessed. High-temperature coking is associated with higher levels of exposure to PAHs than low-temperature processes. Considerable technical improvements in coke production have led to greater cost-effectiveness. These include the mechanization and automation of oven operations, the reduction of coking time and an increase in specific throughput by the use of thinnerbricks of higher thermal conductivity and larger oven sizes (IARC 2010).

IARC (2010) has summarised the information available on exposures from 1983 to 2005 for 10 industrial sectors. Approximately one-third of the available studies reported measurements of urinary metabolites, usually 1-pyrenol (1-hydroxypyrene). Based on the CAREX database, it has been estimated that in 15 countries in Europe in 1990–93 almost 1 000 000 people were exposed to PAH above background levels through their occupations (Kauppinen et al 2000). A study in Costa Rica showed that 17700 men and women were occupationally exposed to PAH, excluding environmental tobacco smoke and Diesel exhaust (Partanen et al 2003). The production and use of coal tar and coal tar-derived products are major sources of occupational exposure to PAHs. Crude coal tar is a by-product of coke production and was formerly also a by-product of gas works. Crude coal tar is reported to be usually distilled, and blends of distillation fractions are used for various purposes, such as wood conservation, paints, road tars and roofing materials. PAH concentrations in coal-tar products may range from less than 1% up to 70% or more (Jongeneelen 2001, ATSDR 2002, IARC 2010). Relevant additional exposure data for the UK have been presented by Unwin et al (2006).

Benzo[a]pyrene as an analytical surrogate for PAH exposure
The most extensively studied PAH as surrogate for total PAH exposure is benzo[a]pyrene. It is released from a great variety of different PAH-sources. In the 1930s, benzo[a]pyrene was identified as the predominant carcinogenic compound in coal tar. Since then and up to now, exposure assessment and health effect studies were largely focussed on this particular compound. In addition, various national and international authorities have used benzo[a]pyrene as an indicator for total PAH exposure. At present, the compound is considered as one of the strongest genotoxic known carcinogens, which significantly contributes to the carcinogenic potency of PAH-rich mixtures.

5.4. Routes of exposure and uptake

Most PAH are relatively non-volatile compounds. Airborne PAH with fewer than four aromatic rings are sufficiently volatile to be present as gaseous compounds in the working environment. PAH with four rings may be present both in the gas phase and as adsorbed particulates. PAH with higher molecular weights (>228) are typically bound to airborne particulates (IARC 2010). Occupational exposure to PAH occurs primarily through inhalation and skin contact. Monitoring of workplace air and personal air sampling for individual PAH, sets of PAH or surrogates (*e.g*. coal-tar pitch volatiles) have been used to characterise inhalation exposures; more recently, biological monitoring methods have been applied to characterise the uptake of certain PAH (*e.g.* pyrene, benzo[a]pyrene) as biomarkers of total exposure (IARC 2010).

There is awareness that occupational uptake of PAHs through the skin is substantial

(Jongeneelen 2001). Thus, uptake of pyrene by the dermal route was estimated to account for as much as 75% of 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 1993b, IARC 2010).

6. MONITORING EXPOSURE

6.1 Monitoring airborne benzo[a]pyrene / PAH in the workplace

Benzo[a]pyrene / PAH can be monitored in the air of the workplace by applying the following fully or partially evaluated methods:

- **OSHA. Method number 58**
  (Coal tar Pitch volatiles (CTPV), Coke oven emissions (COE) and selected Polynuclear aromatic hydrocarbons (PAHs))
- **DFG (1991)**
  (particle bound Polycyclic Aromatic Hydrocarbons (PAHs))
- **DFG (2003a). Method number 2**
  (Polycyclic Aromatic Hydrocarbons (PAHs))
- **DFG (2003b). Method number 3**
  (Polycyclic Aromatic Hydrocarbons (PAHs))
- **NIOSH method 5800**
  (Polycyclic Aromatic Compounds, total (PACs))
- **NIOSH method 5515**
  (Polynuclear aromatic hydrocarbons (PAH))
- **NIOSH method 5506**
  (Polynuclear aromatic hydrocarbons (PAH))

An overview of these methods and their operational performance characteristics is presented in Table 5. In all seven methods PAH mixtures are sampled from the air in the workplace by adsorption onto a solid sorbent or absorption into solution, followed by extraction of PAH with an organic solvent. The PAH-containing extract can then be analysed by gas chromatography (GC), using flame ionisation detection (FID) or mass spectrometry (MS) or by liquid chromatography (LC) /high-pressure liquid chromatography (HPLC) or Flow injection followed by UV and or fluorescence detection, as shown in Table 5. UV light may degrade PAHs; therefore, it is recommended using yellow, UV-absorbing shields for fluorescent lights or use incandescent lighting.

Table 5: Overview of sampling and analytical methods for monitoring PAH mixtures in the air of the workplace, mostly applied to coal-tar derived PAH.

Method	Filters/ adsorbent	Desorption solution	Analysis	EE (%)	LOD/LOQ	Concentration range	Flow rate/ Sample volume/time	References
OSHA. Method number 58	Glass fiber filters	Benzene	HPLC-with fluorescence or ultraviolet detection	108.7	0.045µg/m^3(4ppt) for benzo[a]pyrene (LOD)	n.a	960L at 2L/min	OSHA
DFG (1991)	Glass fiber- or silver membrane filters	Cyclohexane or Toluene	GC-FID	n.a	Theoretical: 0.15 µg/m^3 Practical: 0.5 µg/m^3 (LOD) #	n.a	Personal sampling: 4-8 hour 480-960L Stationary sampling: 1 hour or less 22.5 m^3 or less	DFG (1991)
DFG (2003a). Method number 2	Teflon filter and a glass tube filled with purified XAD-2	Acetonitrile / methanol and dichloromethane	LC with UV and fluorescence detection	98.4**	0.012 µg/mL or 0.20 µg/m^3 for benzo[a]pyrene (LOQ)	0.1-2 times the threshold value in air for Benzo[a]pyrene (in 2002)*	At least 1 hour 2L/min 120 L	DFG (2003a)
DFG (2003b). Method number 3	XAD-2 resin	Toluene	GC/MS	n.a	0.023 µg/mL or 0.064 µg/m^3 for benzo[a]pyrene (LOQ)	0.02-300 µg/m^3PAH	Personal sampling: 4-8 hour 240-480L Stationary sampling: 1 hour or less 60 L	DFG (2003b)
NIOSH method 5515	Filter + sorbent PTFE+ XAD-2	Organic solvent appropriate to sample matrix	GC-FID	n.a	Ca. 0.3-0.5 µg/sample (LOD)	3-150 µg/m^3 (for a 400 L air sample)	2 L/min 200-1000L	NIOSH 1994
NIOSH method 5506	Filter + sorbent PTFE and XAD-2	Acetonitrile	HPLC with fluorescence and UV detection	0.002-0.1 µg/sample (LOD) 0.0051-0.33 µg/sample (LOQ)	50-101 (depending on the filters/sorbent tubes)	2 L/min 200L to max 1000L	2 L/min 200-1000L	NIOSH 1998a
NIOSH method 5800	Filter + sorbent PTFE and XAD-2	Hexane	Flow injection, fluorescence detection	90-95***	Detector 1 ^:0.012 µg/sample (LOD) Detector 2 ^: 0.05 µg/sample (LOD)	Detector 1 ^: 0.04 to 250 µg/sample Detector 2 ^: 0.15 to 250 µg/sample	1 to 2 L/min 5 to 1000L	NIOSH 1998b

n.a *not available*
LOD: *Limit of Detection (for the overall procedure)*
LOQ: *Limit of Quantification*
EE: *Extraction efficiencies (average)*
PTFE: *Polytetrafluoroethylene*

*For a sample air volume of 1 m^3 and a final solution volume of 50 µL a theoretical detection limit of 0.15 µg/m^3 for each individual substance can be achieved. In practice, however, this detection limit frequently remains unattainable and an actual detection limit of 0.5 µg/m^3 can be expected.*

* *For benzo[a]pyrene the TRK value (Technische RichtKonzentration) is 2 µg/m^3(production and loading/unloading of pencil pitch and near the ovens in coking plants: 5 µg/m^3)*
** *Mean recovery for benzo[a]pyrene over the whole calibration range*
*** *Recovery of 90 % was obtained for the 254 nm ex/370nm em analysis and about 95% for the 254 nm ex/400 nm em analysis*

^ *Detector 1 Fluorescence excitation 254 nm; emission 370nm*
Detector 2 Fluorescence excitation 254 nm; emission 400nm

In addition, the following ISO methods are relevant:
- ISO 16'000-12 (for indoor air);
- ISO 12'884 and 16'362 (for ambient air);

6.2 Biomonitoring methods for benzo[a]pyrene / PAH in the workplace

Biological monitoring of exposure to PAH is a complex issue:
- PAH always occur as complex mixtures of variable composition of complex reaction products (termed UVCB's under REACH).
- The individual compounds exert various adverse effects and their potency may vary.
- Biotransformation is specific as well as highly complex for individual compounds (see chapter 7.1) and results in metabolites with potentially different effects (i.e. to induce carcinogenic effects).

Several groups of PAHs-metabolites have been considered as biomarkers of exposure and current appraisals about their adequacy for bio-monitoring human exposures to PAHs are summarized in Table 6.

Table 6: Overview of biomarkers selected by DECOS, IARC and DFG for biomonitoring human exposures to PAHs

Reference	Selection of Markers
DECOS, 2006	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). However, since biological monitoring represents total body burden, and thus dermal, oral and inhalation exposure cannot be separated, it cannot readily be used for the risk estimation in this document, which is based on inhalation exposure alone.
IARC, 2010	**1-Hydroxypyrene**, a specific metabolite of pyrene in urine, has been suggested as a biomarker of human exposure to PAHs (Jongeneelen et al., 1985; Jongeneelen, 2001). At the present time it is the most reliable and practical marker for monitoring individual exposures or exposures of the 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 has been used to measure hydroxylated phenanthrenes and **3-hydroxybenzo[a]pyrene** (Gundel et al. 1996; Popp et al. 1997; Gendre et al. 2002). An attempt at **immunoaffinity 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 bio-monitor human exposures to PAHs the most commonly applied biomarkers are metabolites of pyrene and phenathrenes: **1-Hydroxypyrene** and **hydroxyphenanthrenes (**mostly 1-, 2-, 3-, 4- and 9 Hydroxy-phenanthrenes). However, due to their low toxicity, both types of these markers do not represent adequately the internal exposure to carcinogenic PAHs in quantitaqtive terms. Furthermore, they do not represent well the variability of the PAHs exposure mixtures. To tackle these drawbacks, metabolites of the toxicologically more relevant constituents of PAH-mixtures are taken into consideration. These include **3-hydroxybenzo[a]pyrene** as a metabolite of the carcinogenic benzo[a]pyrene, as well as 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 bio-chemical effect monitoring, but they are not considered to be sufficiently specific and sensitive for diagnostic purposes.

For the most promising biomarkers specified in the above table, according to DFG (2013), the following analytical techniques to support implementation of bio-monitoring approaches are available

a. Hydroxylated urinary metabolites of pyrenes and phenanthrenes
The applied analytical methods include:

Sample preparation:

- enzymatic hydrolysis with follow-up cleaning by liquid/liquid extraction (Jacob III et al. 2007; Li et al. 2006; Rossella et al. 2009; Serdar et al. 2003);
- a solid phase extraction (Hagedorn et al. 2009; Romanoff et al. 2006; Xu et al. 2004);
- a solid phase micro extraction (Gmeiner et al. 1998; Smith et al. 2002) or column switching techniques (Lintelmann et al. 1994).

Separation, analysis and quantification:

- High-performance liquid chromatography with fluorescent detection (HPLC-FD) (Hagedorn et al. 2009; Lintelmann et al. 1994; Simon et al. 1999);
- Liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Jacob III et al. 2007; Onyemauwa et al. 2009; Ramsauer et al. 2011; Xu et al. 2004)
- Gaschromatography with mass spectrometry (GC-MS) following derivatisation of the hydroxylated PAH metabolites (Li et al. 2006; Romanoff et al. 2006; Smith et al. 2002).

Based on the above analytical techniques a standard method has been developed and published by the Working Group "analysis in biological materials" of the DFG (Greim and Angerer 1999). This method allows monitoring of hydroxylated urinary metabolites of pyrenes (1-hydroxypyrene) and phenanthrenes (1-, 4- and 9 Hydroxy-phenanthrenes) up to a detection limit of 5 ng metabolite/ L urine (Heudorf und Angerer 2001).

b. 3-Hydroxybenzo[a]pyrene as urinary metabolite

Sample preparation:

- enzymatic hydrolysis by solid phase extraction (Barbeau et al. 2011; Romanoff et al. 2006; Sarkar et al. 2010) or column switching (Simon et al. 2000);

Separation, analysis and quantification:

- HPLC-FD (Barbeau et al. 2011; Simon et al. 2000), Gas Chromatography Coupled with High Resolution Mass Spectrometry (GC-HRMS) (Romanoff et al. 2006) o LC-MS/MS (Sarkar et al. 2010).

According to (DFG, 2013) the determination of 3-hydroxybenzo[a]pyrene, based on the above analytical technique, allows detection of the urinary metabolite up to very low detection limits, capturing thus not only the range of occupationally exposed workers but also the general population. However, according to (Boogaard 2012), this analytical methodology is sophisticated and has not yet allowed setting of a routine method with reference standards and external quality control.

In conclusion, it appears there is general agreement that *1-Hydroxypyrene* represents, at present, the best biomarker to bio-monitor human exposures to PAHs, despite several disadvantages (specified in Table 6).

7. HEALTH EFFECTS

Polycyclic aromatic hydrocarbons are highly relevant on account of carcinogenicity. After metabolism withing the body, PAH may have various toxic effects. The carcinogenicity of individual PAH has been demonstrated by animal studies using different exposure models (IARC 1973, 2010, WHO 1998). Genotoxic effects of PAH were observed in numerous animal studies; they were also detected in human cells in vitro and in vivo (WHO 1998, DFG 2012).

7.1. Toxicokinetics (absporption, distribution, metabolism, excretion)

The general principles of the toxicokinetics of PAH, in particular benzo[a]pyrene, are well covered in the published literature [for extensive overviews see IPCS (1998), ATSDR (1995), IARC (2010) and DFG (2012)]. Therefore, only a very brief summary is given here, mainly focussed on the relevant issues of dermal absorption and of the carcinogenic pathway (DECOS 2006).

The biotransformation of PAH starts at the moment they are absorbed through the epithelia of the lungs and the skin. The longer the retention time in the epithelium of the respiratory tract, the more PAH will be metabolised. The metabolism of PAH is complex. In a first step, PAH are oxidized to form epoxides, phenols and dihydrophenols (phase-I metabolites). In a second step, these metabolites are conjugated with either glutathione, sulphate or glucuronic acid to form much more polar and water-soluble metabolites (phase-II metabolites). Most PAH metabolised in this way are deactivated. However, some of them are activated to DNA-binding species, which can initiate cancer (DECOS 2006).

7.1.1. Human data

Occupational exposure studies, in which the urinary excretion of 1-hydroxypyrene 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 (DECOS 2006). For instance, Van Rooij et al (1993a) estimated that on average 75% of the total absorbed amount of pyrene (indicator: urinary 1-hydroxypyrene concentration) entered the body through the skin. In controlled studies, van Rooij et al (1993b) 109 applied coal-tar ointment to the skin of seven healthy volunteers. The ointments were applied three times for 6 hours on various anatomical sites (foreheads, shoulders, volar forearms, palms of the hands, groins, and ankles). Dermal absorption and urinary 1-hydroxypyrene levels were measured up to 72 hours after application. PAH were clearly absorbed through the skin (20-56%, 6 hours after application and dependent on anatomical site).

7.1.2. Animal data

Animal studies have confirmed that PAH are rapidly transported from the site of administration (gastrointestinal tract, lungs or skin) to other tissues via the blood and lymph (Mitchell 1982). This was also evident from the fact that high concentrations of DNA adducts were found in the lungs after application of PAH to the rodent skin (see DECOS 2006, DFG 2012).

Most information on the carcinogenic bioactivation of PAH is obtained from *in vivo* and *in vitro* studies with benzo[a]pyrene as model compound. Other carcinogenic PAH compounds are metabolised in a comparable way (see also IPCS 1998). In the first step, benzo[a]pyrene is oxidised by the enzyme aryl hydrocarbon hydroxylase (AHH, an enzyme of the CYP family) resulting in epoxide and phenol groups at several sites in its

ring structure. These epoxides may be hydrated by epoxide hydrolase to dihydrodiols, or spontaneously rearrange to phenols. Also quinone structures can be formed. The epoxides may be conjugated with glutathione, while the phenols are conjugated with glucuronate or sulfate. Most conjugates are detoxification products. After the initial formation of the (+)benzo[a]pyrene-7,8-epoxide and its subsequent epoxide hydrolase dihydrodiol product, it is activated to the ultimate reactive intermediate (+)anti-benzo[a]pyrene-7,8-dhydrodiol-9,10-epoxide. This is an extremely reactive species that covalently interacts with cellular DNA. The DNA adducts formed may lead to mutations. An additional complexity of PAH metabolism is the stereoselectivity in the metabolism. Depending on the location of the epoxide in de PAH ring system the epoxide displays more or less chemical reactivity towards DNA. Several investigators suggested that also other mechanisms than the diol-epoxide mechanism play a role. These include the radical-cation, the quinone and the benzylic oxidation mechanisms, which may occur simultaneously for the various PAH components (see IPCS 1998 for a detailed overview). The extent to which PAH will express carcinogenic effects in certain persons are thought to be partly genetically controlled. Although similar enzyme systems are involved in PAH metabolism, the inducibility and activity of these enzymes may differ per species, within one species and per organ. Since the inducibility determines the extent of the carcinogenic susceptibility, it is clear that the ultimate carcinogenic risk may vary per person. However, to what extent genetic variability may have contributed to the variations in cancer mortality ratios, which were found when epidemiological studies were compared, remains unclear (DECOS 2006).

7.1.3. In vitro data

An in vitro study using full-thickness monkey skin showed that the penetration of acenaphthene, anthracene, phenanthrene, fluoranthene, naphthalene, pyrene and fluorene from a lubricating oil is slower than from acetone and artificial sweat. For benzo[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene and benzo[a]pyrene, it was possible to demonstrate absorption through the skin only when the compounds were dissolved in acetone/artificial sweat (Sartorelli et al 1999). The penetration of radioactively labelled benzo[a]pyrene was detected in flow-through cells with human skin after up to 24-hour exposure. The study did not contain any quantitative data on the flux level. Treatment of the skin with two skin barrier creams did not reduce absorption; even increased absorption rates were observed in some cases (Van der Bijl et al 2002).

7.1.4. Toxicokinetic modelling

With a specific ecotoxicological perspective, a physiologically based toxicokinetic and toxicodynamic (PBTK-TD) model was developed for benzo[a]pyrene 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 benzo[a]pyrene 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).

7.1.5. Biological monitoring

A detailed account of the present state of biological monitoring of workers exposed to PAH mixtures has been presented by DFG (2012). The following gives a brief summary. For details, the assessment by DFG (2012) should be consulted. 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-Hydroxypyrene 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). DFG (2012) has compailed the available data in PAH-exposed and non-exposed controls (*see Annex Tables*).

Apart from 1-hydroxypyrene, further metabolites of pyrene, such as trans-4,5-dihydroxy-4,5-dihydropyrene, 1,6- and 1,8-dihydroxypyrene, 1,6- and 1,8-pyrenequinone and dihydrodiol phenols, were detected in the urine. 1-Hydroxypyrene is not the end product of a metabolic pathway of pyrene, but is further oxidized enzymatically to 1,6-dihydroxypyrene and 1,8-dihydroxypyrene (DFG 2012).

A number of studies did not only determine 1-hydroxypyrene in the urine but also the excretion of further PAH metabolites – particularly of phenanthrene phenols (1-, 2-, 3-, 4- and 9-hydroxyphenanthrene). In the evaluation of the data, these were specified as sum parameters of all five isomers (sum of hydroxyphenanthrenes) in most cases and have the advantage that hydroxyphenanthrenes are influenced by individual smoking or eating habits to a much lesser extent than 1-hydroxypyrene in the urine. Determination of hydroxyphenanthrenes is a more sensitive and more specific method of recording occupationally induced PAH exposure than the determination of 1-hydroxypyrene in the urine. The lesser effect of smoking on the excretion of hydroxyphenanthrenes in the urine as compared with 1-hydroxypyrene had already been observed in earlier studies. Only a slight increase in hydroxyphenanthrenes was observed among smokers as compared with non-smokers, whereas no differences whatsoever were detected for passive smokers as compared with non-smokers (Martin et al 1989). Different eating habits have a minor influence on the urinary excretion of hydroxyphenanthrenes. In principle, human biomonitoring by determination of PAH-specific metabolites in the urine is much more suitable for assessing workplace exposure than airborne PAH measurements at the workplace on account of dermal PAH absorption.

Altogether, it may be stated that the results of the measurements of 1-hydroxypyrene 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. Also phenanthrenetetrol has been used as a good biomarker of systemic PAH exposure (DFG 2012).

The human biomonitoring described so far, based on the excretion of phenanthrene and pyrene metabolites in urine, reflects exposure to PAH but only indirectly reflects the risk posed by systemic exposure to carcinogenic PAH. Accordingly, more recent efforts are being made to develop and measure urinary metabolites of carcinogenic PAH like naphthalene, chrysene and benzo[a]pyrene. The results of the measurements of 1-hydroxypyrene and 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 (DFG 2012).

Analogous to 1-hydroxypyrene, individual differences observed for the excretion of hydroxyphenanthrenes can largely be explained by different levels of exposure (DFG 2012).

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 benzo[a]pyrene and dibenzopyrenes. The latter are almost completely bound to

particles. Therefore, metabolites covering a broad spectrum of exposure would be desireable. 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-hydroxybenzo[a]pyrene occurring in the urine as exposure markers for the carcinogenic benzo[a]pyrene. Based on the data of Lafontaine et al (2004), DFG (2013) has issued the following correlation between airborne benzo[a]pyrene exposure (8h TWA) and 3-hydroxybenzo[a]pyrene levels in urine (determined after hydrolysis). The sampling time is 16 h after last exposure, before following shift (Gendre et al 2002, 2004). This approach may, in future, lead to the development of a BGV for 3-hydroxy-benzo[a]pyrene.

Benzo[a]pyrene in air (µg/m^3)	3-Hydroxy-benzo[a]pyrene in urine (ng/g creatinine)
0.07	0.7
0.35	2
0.7	3.5
1.0	5
1.5	7

7.2. Acute toxicity

7.2.1. Human data

Data regarding acute toxicity of PAH in humans are scarce. 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 (DFG 2012).

7.2.2. Animal data

Values specified by WHO (1998) show that the acute toxicity of PAH compounds is relatively low. Reduced size of the spleen, cellular depletion, haemosiderosis and follicles with large lymphocytes were observed in mice after a single intraperitoneal injection of benzo[a]pyrene (dose not specified; WHO 1998). A single intraperitoneal injection of 30 mg chrysene per animal did not affect the growth in rats. One or 2 intraperitoneal injections of 3 to 90 mg dibenzo[a,h]anthracene into young rats led to an inhibition of growth within 2 days, and this persisted up to 15 weeks (DFG 2012).

7.2.3. In vitro data

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 benzo[a]pyrene in acetone to the intrascapular region (Elgjo 1968).

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. 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. The typical acute systemic effect after accidental dermal, oral or inhalation exposure to naphthalene is acute haemolytic anaemia. In addition, after dermal application, anthracene, fluoranthene and phenanthrene may induce specific skin reactions. 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. Only limited 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. In one study, workers in a rubber factory showed reduced lung function, abnormal chest X-ray, cough, and throat and chest irritation. However, the authors did not make clear whether the observed effects were due to PAH-exposure or to other toxic chemicals. In addition, coke oven workersshowed reduced levels of serum immunoglobulin and decreased immune function. However, the biological significance of these findings is uncertain (DECOS 2006).

7.3.2. Animal data (DFG 2012)

7.3.2.1. Inhalation

Male Syrian golden hamsters were exposed 4.5 hours daily on 5 days per week for 16 weeks to 9.8 or 44.8 mg/m^3 benzo[a]pyrene by inhalation. No neoplasms were observed in the respiratory tract (Thyssen et al. 1980) in the experimental timeframe. Fischer 344/Crl rats were exposed 2 hours per day on 5 days per week for 4 weeks to 7.7 mg benzo[a]pyrene dust/m^3. Lung lavage, clearance of radioactively labelled particles and histopathological examinations revealed no lesions of the respiratory tract (Wolff et al. 1989).

7.3.2.2. Oral exposure

DBA/2N mice having a low affinity Ah receptor (aryl hydrocarbon receptor) were given oral doses of 120 mg benzo[a]pyrene daily for 1 to 4 weeks. The animals died from the toxic effect on the bone marrow. No toxic effect on the bone marrow was observed in C57B1/6N mice with a high affinity Ah receptor; the animals survived 6 months under these conditions (Legraverend et al 1983). Reduced carboxylase activity was found in the intestinal mucosa of rats that were given 50 or 150 mg benzo[a]pyrene orally for 4 days. The NOAEL (no observed adverse effect level) for the effect on the stomach, liver or kidneys was 150 mg benzo[a]pyrene/kg body weight per day (Nousiainen et al. 1984). The growth of rats that were administered 1.1 g benzo[a]pyrene/kg diet for 100 days was inhibited (White and White 1939; WHO 1998). Ingestion of 100 mg phenanthrene/kg body weight per day for 4 days led to a 30% increase of the carboxylase activity in the intestinal mucosa (Nousiainen et al. 1984). The daily ingestion of benzo[a]anthracene by rats for 4 days resulted in a NOAEL of 150 mg/kg body weight for the effect on the stomach, liver or kidneys. The carboxylase activity in the intestinal mucosa was reduced (Nousiainen et al. 1984).

WHO (1998) listed studies of naphthalene in a table. In rats, 150 to 220 mg/kg body weight administered for 14 weeks led to enlarged liver with cellular oedema, damage to the liver parenchyma and signs of an inflammation of the kidneys. The administration of 1000 mg/kg in the diet for 46 to 60 days led to the formation of cataracts; 2000 mg/kg in the diet inhibited growth and induced enlargement and fatty degeneration of the liver. Mice were treated with 27, 53 and 267 mg/kg body weight on 7 days/week for 14 days. The findings observed in the animals of the highest dose group included weight reduction

of the thymus and spleen. In a second test (5.3, 53 and 133 mg/kg body weight on 7 days per week for 90 weeks), the relative spleen weights were reduced. In dogs, diarrhoea and anaemia occurred for 7 days after administration of 220 mg/kg body weight.

Groups of 20 male or 20 female CD-1 mice were given pyrene doses of 75, 125 or 250 mg/kg body weight by gavage for 13 weeks. Nephropathy was detected in all 4 male control animals, 1 male of the low dose group, 1 male of the middle dose group and 9 males of the high dose group and, correspondingly, in 2, 3, 7 and 10 females. The relative and absolute kidney weights were reduced in the animals of the middle and highest dose groups. A NOAEL of 75 mg/kg body weight per day and a LOAEL (lowest observed adverse effect level) of 125 mg/kg body weight per day were determined on the basis of nephropathy and reduced kidney weights (USEPA 1989; WHO 1998).

7.3.2.3. Dermal exposure

As already mentioned (7.1.1/7.1.2), there is substantial skin absorbtion of PAH compounds. However, this appears to be vehicle-dependent. Thus, the binding of benzo[a]-pyrene to DNA and proteins in the mouse skin was found 15 to 20 times higher if acetone was used as a vehicle instead of a low-viscosity oil (Ingram and Phillips 1993).

7.3.3. In vitro data

No relevant data upon repeated exposures were identified.

7.4. Irritancy and corrosivity

7.4.1. Human data

In the old literature, there is some notice on local dermal effects of PAH mixtures. This was compiled by ATSDR (1995) as follows. Mixtures of carcinogenic PAHs cause skin disorders in humans and animals; however, specific effects in humans of individual PAHs, except for benzo[a]pyrene, have not been reported. Mixtures of PAHs are also used to treat some skin disorders in humans. From these patients comes much of the data describing dermal effects of PAH exposure. Regressive verrucae (*i.e.,* warts) was reported following up to 120 dermal applications of 1% benzo[a]pyrene 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 benzo[a]pyrene in patients with the preexisting 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 discolorations, ulcers, and cutaneous and muscular atrophy) (Cottini and Mazzone 1939). A 1% benzo[a]pyrene solution topically applied to patients with pemphigus resulted in local bullous eruptions characteristic of the disease. Patients with xeroderma pigmentosum exposed to 1% benzo[a]pyrene slightly longer than the pemphigus patients exhibited only pigmentary and slight verrucous effects. Similarly treated patients with preexisting 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 preexisting skin lesions was noted.

7.4.2. Animal data

7.4.2.1. Skin

Benzo[a]pyrene was produced protracted irritation to the mouse ear (Brune et al. 1978). Adverse dermatological effects observed in animals after acute and mid-term dermal exposures to PAH included destruction of the sebaceous glands, dermal ulcers, hyperplasia, hyperkeratosis and alterations of epidermal cell growth. Perylene, benzo[e]pyrene, phenanthrene, pyrene, anthracene, naphthalene, acenaphthene, fluorene and fluoranthene generated no sebaceous gland suppression; benzo[a]anthracene, dibenzo[a,h]anthracene and benzo[a]pyrene increased the sebaceous gland index to >1 (Bock and Mund 1958). 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). In Swiss mice that were treated daily with benzo[a]pyrene solutions for 3 days, a concentration of 0.1% destroyed less than half and 0.2% more than 50% of the sebaceous glands (Suntzeff et al. 1955). Single doses of 6.25 to 200 nmol dibenzo[a,l]pyrene or its metabolites were applied once to the skin of female SENCAR mice. Dibenzo[a,l]pyrene and dibenzo[a,l]pyrene-11,12-dihydrodiol, a metabolic precursor of the highly active diol epoxide, caused erythema 5 to 6 days after treatment (Casale et al. 1997).

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).

7.4.3. In vitro data

No relevant data were identified.

7.5. Sensitisation

As outlined by IARC (2010), PAH exert effects on the immune system of many species. The dose and route of exposure determine the nature of the effect of specific and adaptive immune responses. Studies with pure PAH suggest that Ah receptors play a critical role in the activation of immunotoxic PAH, such as benzo[a]pyrene, *via* diol epoxide mechanisms which lead to DNA interactions that cause genotoxicity and suppress immunity by p53-dependent pathways. Benzo[a]pyrene diol epoxide may also affect protein targets and modulate lymphocyte signalling pathways via non-genotoxic (epigenetic) mechanisms. Certain oxidative PAHs, such as benzo[a]pyrene quinones, may be formed *via* CYP-dependent and -independent (peroxidase) pathways. Redox-cycling PAH quinones may exert oxidative stress in lymphoid cells. Human exposures to PAHs are usually in the form of complex mixtures, and it is difficult to attribute the relative contributions of individual PAHs to the overall immunotoxic effects. Some evidence suggests that environmental exposures to PAH may produce immunotoxicity, but further epidemiological studies are needed (IARC 2010).

7.5.1. Human data

Anthracene was reported to increase the sensitivity of the skin to sunlight. 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. One of 598 patients who were examined because of dermatosis reacted to naphthalene in the patch test. A frequency of 0.13% was specified for allergy to naphthalene (DFG 2012).

7.5.2. Animal data

A total dose of 250 µg benzo[a]pyrene in complete Freund's adjuvant was injected into 4 adult female guinea pigs; 2 or 3 weeks later, they were treated with solutions of 0.001, 0.01, 0.1 or 1% benzo[a]pyrene in acetone and olive oil to investigate contact sensitization. After 24 hours, slight to marked hypersensitivity was observed (Old et al. 1963). C3H mice were treated with an epicutaneous application of 100 µg benzo[a]pyrene in 0.1% acetone solution. Contact hypersensitivity was achieved 5 days later by applying 20 µg benzo[a]pyrene to the ear dorsum. The response was determined via ear swelling, which reached its maximum 3 to 5 days after application. The LOAEL for contact sensitization was 120 µg (Klemme et al. 1987). A positive result was also observed for benzo[a]pyrene in the local lymph node assay (LLNA). Various concentrations of the test substance (0.5, 1.0 and 2.5% benzo[a]pyrene in acetone/olive oil) or the vehicle were applied to the dorsum of both ears of mice (no other details) on 3 consecutive days. After 5 days, ^{3}H-thymidine was injected into the animals and lymphocyte proliferation as compared with the control animals was determined via incorporated ^{3}H-thymidine. Based on this data, Ashby et al. (1995) classified benzo[a]pyrene as sensitising.

7.5.3. In vitro data

No specific data on sensitisation were identified.

In a broader sense, *in vitro* data on effects of PAH on the immune system in general were reviewed by IARC (2010), to which reference can be made. In summary, PAH exert many important effects on the immune system of many species. The dose and route of exposure determine the nature of the effect of specific and adaptive immune responses. Studies with pure PAHs suggest that AhRs play a critical role in the activation of immunotoxic PAHs, such as benzo[a]pyrene, via diol epoxide mechanisms which lead to DNA interactions that cause genotoxicity and suppress immunity by p53-dependent pathways. B[a]P diol epoxide may also affect protein targets and modulate lymphocyte signalling pathways via non-genotoxic (epigenetic) mechanisms. Certain oxidative PAHs, such as benzo[a]pyrene quinones, may be formed via CYP-dependent and -independent (peroxidase) pathways. Redox-cycling PAH quinones may exert oxidative stress in lymphoid cells.

7.6. Genotoxicity

7.6.1. Human data (IARC 2010)

Urine samples from some nonsmoking 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 nonsmoking 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 DNA adduct (Godschalk et al 1998). Analysis of anti-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 immunsorbent

(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 nonsmoking 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 analyses 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 32P-postlabelling analysis (Godschalk et al 2001).

7.6.2. Animal data

Extensive summaries are available from WHO (1998), IARC (2010) and DFG (2012), to which reference can be made.

As summarised by DFG (2012), existing studies of benzo[a]anthracene, benzo[a]pyrene and pyrene in *Drosophila melanogaster* were listed in detail by WHO (1998). Studies of benzo[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[b]naphtho-[2,1-d]thiophene (not listed in WHO 1998), benzo[a]pyrene, chrysene, dibenzo[a,h]anthracene, dibenzo[a,e]pyrene, indeno[1,2,3-cd]pyrene, naphthalene, phenanthrene and pyrene for possible chromosomal effects of PAH in mammalian cell systems in vivo are summarized by DFG 2012), including DNA binding, adduct as well as sperm abnormality studies. Evidence of DNA adducts or DNA binding was provided for all listed compounds listed by WHO (1998) except pyrene. Benzo[a]pyrene 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 the cells treated with trans-benzo[a]pyrene-4,5-diol (Nesnow et al 2002). Sister chromatid exchanges (SCE) were induced after administration of benzo[a]anthracene, benzo[b]fluoranthene, benzo[a]pyrene, 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 benzo[a]pyrene. 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 benzo[a]pyrene. No increase in the number of micronuclei was caused by naphthalene, phenanthrene or pyrene. Benzo[a]pyrene 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).

7.6.3. **In vitro** (DFG 2012)

The results of studies in *Salmonella typhimurium* with anthanthrene, benzo[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[b]naphtho[2,1-d]thiophene, benzo[a]pyrene, 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 were listed in detail by WHO (1998) and DFG (2012). 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.

In an evaluation of short-term tests carried out by WHO, benzo[a]pyrene and pyrene were used as carcinogenic and non-carcinogenic structurally related test substances, respectively (IPCS 1998). 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. More recent studies on the in vitro genotoxicity of naphthalene are included in DFG (2012). In CHO cells, naphthalene induced an increase of sister chromatid exchanges in the presence and absence of a metabolic system as well as an elevated incidence of chromosome aberrations 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 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 benzo[a]pyrene, 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 benzo[a]pyrene. These data were interpreted to highlight the genotoxicity of

highly reactive benzo[a]pyrene-derived metabolites produced within human alveolar macrophages and lung epithelial cells (Abbas et al 2011).

7.7. Carcinogenicity

Experimentally, Yamagiwa and Ichikawa (1915) demonstrated for the first time the carcinogenic effect of coal tar on rabbit skin. A large number of studies followed that showed this effect for numerous coal tar products (mixtures) the mouse skin (IARC 1985). Cook et al. (1932) was the first to apply benzo[a]pyrene to mouse skin, and numerous PAH started later to be investigated in this test system.

7.7.1. **Human data** (DECOS 2006)

No human data were available on exposure to benzo[a]pyrene or other single PAH compounds.

A number of epidemiological studies have been performed on the carcinogenesis of complex PAH mixtures due to occupational exposure. These include cohort and case-control studies with various PAH-rich sources (*e.g.*, evaporation of carbon electrode materials, coal tar distillation and purification, coke production, thermal decomposition of organic materials) in various industries (*e.g.*, aluminium production, coal gasification, coke production, iron and steel foundry). It is evident that in none of these industries PAH is the only substance to which workers are exposed. This not only concerns organic solvents, nitro-PAH, aromatic amines and metals, but also dust particles and in some cases asbestos. Some of these substances are carcinogens, such as 2-naphthylamine and 4-aminobiphenyl, which are known to cause bladder cancer. Also airborne particles are suspected to elicit genotoxicity and carcinogenicity by directly generating reactive oxygen (ROS) and nitrogen species (RNS), and indirectly by activating pathways of inflammation and proliferation. Particle induced ROS and RNS may interfere with the carcinogenic potency of PAH.

Cohort studies
Armstrong et al (2003, 2004) published a well-performed meta-analysis on lung and bladder cancer risk following PAH exposure. The meta-analysis was based on published reports, in which relationships between occupational PAH exposure and lung and bladder cancer was studied quantitatively. The exposures concerned airborne PAH, emitted from incomplete combustion of organic matter. Risk estimates on lung and bladder cancer were determined because of the clearly positive or highly suggestive association between these cancers and occupational PAH exposure. In the analysis only studies were included that did meet certain criteria. These criteria included: original epidemiological studies of occupational exposure by inhalation; studies of workplaces in which PAH was considered the predominant carcinogen (this meant exclusion of rubber industry, Diesel exhaust, foundries and part of steel works); studies in which misclassification of exposure was not to be likely; and, only the most recently reported results from the same workforce reported in several papers. From the 744 references screened, only 36 papers fully met these criteria. These papers covered 39 distinct cohorts (35 cohorts, 1 case-cohort and 3 nested case-control samples from within a cohort). For the meta-analysis, it is essential that the PAH exposures in the included studies were determined or estimated by the same exposure parameter. For this reason, Armstrong and colleagues converted total PAH and BSM concentrations to benzo[a]pyrene concentrations by using conversion ratios. These conversion ratios differed for each study (for details see the original publications). Furthermore, for those studies with no exposure measurements, a job-exposure matrix indicating estimated mean concentrations of benzo[a]pyrene exposure for each industry and occupation was estimated with the collaboration of industrial hygienists and by using published reviews on workplace exposure (proxy measures). Concerning studies with cumulative exposure, the mean cumulative exposure in each group or the midpoint of interval was chosen as an estimate for the average cumulative benzo[a]pyrene exposure. Overall, the cumulative exposure in the highest exposure

groups ranged across three orders of magnitude, from 0.75 to 805 μg/m^3 benzo[a]pyrene years (≈average air concentration of 0.04 to 40 μg/m^3 benzo[a]pyrene). For each cohort, unit relative risks (URRs) were calculated. URRs refer to increments in relative risk per 100 μg/m^3 benzo[a]pyrene years, in which 100 μg/m^3 benzo[a]pyrene years corresponds to a concentration of 2.5 μg/m^3 Benzo[a]pyrene over 40 years. For determining URRs two models were used: the log-linear relative risk model (RR=exp(bloglin x) and the linear relative risk model (RR=1+blin x), where 'x' is cumulative exposure (μg/m^3-years) and 'b' the slope of the exposure-response relationship. Concerning data on effects, the authors preferred mortality outcomes over morbidity outcomes within a same study. Furthermore, other preferences were formulated, such as smoking-adjusted data over unadjusted data. The meta-analysis was performed with standard methods. These methods allow for variation in precision by which URRs are estimated in different studies, but allow also for random effects. To obtain an average URR, weights were implicitly given to each study reflecting these two effects. In addition, to identify cohort or exposure characteristics that explained variation in URRs (*e.g.*, industry, source of exposure information), each was considered as a dependent variable in a meta-regression analysis. The relative risks for lung cancer, predicted at 100 μg/m^3 benzo[a]pyrene years from the log-linear models, ranged from 0 to over 1,000 among the studies, with standard errors ranging between 0.02 and 1,000. This is a substantial variation in precision, which is well explained by variations in the degree of exposure in the studies (some studies have only low exposures) and by variations in size of cohort populations and duration of follow-up. The overall mean URR for lung cancer was 1.20 (95% CI, 1.11-1.29, p< 0.001). In general, repeating analyses using the linear model revealed similar rankings of URRs for lung cancer as those obtained from the log-linear model, with some acceptable variation in URRs of the cohorts. None of the cohorts dominated the estimate. In addition, it was little changed after removal of less precise cohorts. 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<0.02) was found when studies were grouped according to several heterogenic factors (*e.g.*, source of exposure, smoking habits, study design, duration, dust exposure). However, whether the differences between industries are caused by chance or by true unknown variations is not exactly known, because scientific data that reported on the presence of true variations is not available or insufficient to draw conclusions. Overall, lung cancer risk at other exposures can be estimated from URRs under log-linear model assumptions: URRcum exp X = [URRcum exp 100](x/100) . In the United Kingdom, the lifetime lung cancer risk in males from the general population is 8% (year 1997). This means a lifetime excess risk for coke oven workers (URR 1.17), who were 40 years exposed to 1.5 μg/m^3 benzo[a]pyrene of 1.9x10-4 (8 cases among 1,000 coke oven workers). The use of the study of Armstrong et al (2003, 2004) for the derivation of lung cancer risk assessments is further described in chapter 6.7.4.

Bladder cancer was reported in 27 cohorts. The overall mean URR was 1.33 (95% CI: 1.16-1.52), with no statistically significant variation by industry or other putative determinants. In addition, the mean URR was strongly dependent on results of two large aluminium production industries, one that was performed by Tremblay et al (1995) and the other by Romunstad et al (2000); only the Tremblay results were statistically significant. There was little evidence of a relationship between bladder cancer and PAH exposure in coke ovens and other industries. Though the URR of bladder cancer (URR 1.33) is higher than that for lung cancer (URR 1.17) Armstrong et al (2003, 2004) considered the causal relationship between PAH exposure and bladder cancer weak. Armstrong et al (2003, 2004) discussed in detail the uncertainties as to the exposure-response relationship. In summary, by comparing their results with those of others, the authors concluded that the results for coke-ovens, gasworks, and aluminium production are relatively well supported by others, although potential biases should be considered. These biases include; smoking, which was uncontrolled in most studies; confounding by other occupationalexposures, although the authors excluded studies in which PAH was

judged unlikely to be the predominant carcinogen (except dust); and inaccurate exposuremeasurement estimates (uncertainty in past exposure). Regarding smoking habits, data from four cohorts were adjusted for smokinghabits. Pooling data of these cohorts revealed a higher unit relative risk for lung cancer than the pooled data from the other cohorts (1.31 (95%CI 1.16-1.48), and 1.16 (95%CI 1.11-1.21), respectively). Comparable results were found for bladder cancer risk. However, Armstrong et al considered the data on smoking habits too small to base the meta-analysis on these four studies only, and thus theyincluded all other cohorts as well. True variations in URRs between industries were explained by confounding, such as: inaccurate exposure estimation; smoking habits; uncertainty about the right metric (cumulative versus average exposure); and, variations in carcinogenic potency of the PAH mixture across industries.

DECOS has evaluated the meta-analysis to assess its usefulness for risk assessment and deriving cancer risk values. A critical point was whether inclusion of all cohorts was acceptable, since not always exposure measurements were available, nor exposure duration was known, and not all cohort-studies concerned exposure to PAH only. In the meta-analysis, cohorts without exposure data could have been excluded from the evaluation. In that case the unit relative risks for lung cancer increases (URR 1.29 (95%CI, 1.11-1.49) versus URR 1.17 (95%CI, 1.03-1.33) for cohorts with and without exposure data on benzo[a]pyrene, respectively). It also means that 16 cohorts with limited exposure data remained for the analysis, whereas 23 cohorts with useful data on cancer would have been excluded. To take this into account, Armstrong et al used supplementary exposure estimates for the studies for which no exposure data were available, and included the respective cohorts in the meta-analysis. For the estimates they used a large database of exposure measurements and data obtained from industrial hygienists. These data showed rather stable exposure patterns by job title and type of industry. However, as a consequence of using exposure estimates, not all studies are completely independent with respect to exposure, and this may have influenced the outcome (smaller exposure variation among studies). On the other hand, they are independent concerning effect data, and observations showed merely a marginal heterogeneity among the studies. Therefore, according to DECOS, the use of supplementary exposure estimates was justified. DECOS noticed that for some studies no data on exposure duration were available. This was overcome by Armstrong et al by estimating exposure duration by using an average value from external data. In general, this could have led to an overestimation as well as to an underestimation of the relative risk in the duration-response analysis.

In a few cohorts, co-exposure was likely (*i.e.*, bitumen (asphalt) industry, power plants). It is therefore well possible that in those studies other substances have contributed to the observed excesses in lung cancer. On the other hand, Boffetta et al (2001, 2003) did not find associations between lung cancer risk among asphalt road pavers and roofers, and co-exposure to other substances (*i.e.*, silica, organ vapour, diesel exhaust). Furthermore, in the majority of the cohorts (*i.e.*, coke-ovens, gas works, carbon black, and aluminium industry) co-exposure to other substances than PAH was marginal, and PAH is the predominant exposure leading to lung cancer. Based on this information, DECOS took the position that co-exposure only played a minor role in the overall uncertainties introduced by performing a meta-analysis.

In conclusion, DECOS considered the meta-analysis study of Armstrong et al (2003, 2004) as well performed and useful for estimating cancer risk values (see 6.7.3). Taking into account both the uncertainties and the strength of this meta-analysis, no serious constraints were found to exclude certain cohorts with no or limited exposure data.

In an earlier publication, Armstrong et al (1994) estimated the quantitative lung cancer risk for aluminium production workers from a large cohort study in Quebec, Canada. The study was performed in one plant that used two types of pots to melt aluminium, namely Söderberg and prebake pots. In particular, in the Söderberg process high amounts of coal tar pitch volatiles are emitted. The workers were exposed to substantial quantities of

coal tar pitch volatiles, expressed as cumulative exposure to benzene-soluble material (BSM) or benzo[a]pyrene. The follow-up period started in 1950 and continued through 1988. Both linear and (supra-linear) curved relationships were computed between rate ratios and cumulative exposure. As a result, the best fit was obtained using the supra-linear curve model. The model predicted a rate ratio for lung cancer in aluminium production workers of 1.42 and a lifelong excess risk of 3.8% after 40 years exposure to 0.2 mg/m^3 BSM. The authors advised to be cautious in extrapolating their results to modern aluminium plants, because exposure to coal tar pitch volatiles have been substantially reduced in this industry.

In the review by Boffetta et al (1997), several industries and occupations were included of which data were published before 1997. According to these, heavy exposure to PAH entailed a substantial risk for lung, skin and bladder cancer. These substantial risks were not likely to be explained by other carcinogenic exposure present in the same industries. The major target organ of PAH carcinogenicity was the lung. The increased risk for lung cancer was present in most industries and occupations studied. Furthermore, they concluded that an increased risk for skin cancer among asphalt road pavers and roofers, and co-exposure to other substances (*i.e.*, silica, organ vapour, diesel exhaust). Furthermore, in the majority of the cohorts (*i.e.*, coke-ovens, gas works, carbon black, and aluminium industry) co-exposure to other substances than PAH was marginal, and PAH is the predominant exposure leading to lung cancer. Based on this information, DECOS took the position that co-exposure only played a minor role in the overall uncertainties introduced by performing a meta-analysis.

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 othersites of the body than the lungs or skin, respectively, or possibly the bladder.

A cohort study of workers in the US carbon black industry (5011 workers at 18 plants) showed no risk in overall cancer , lung cancer or non-malignant respiratory diseases (Dell et al. 2015)

Cancer mortality was studied in cohort of workers in the European Rubber manufacturing industry. No cancer mortality excess was observed entering the rubber manufacturing industry after 1975 (Boniol et al. 2016).

Case-control studies
The number of case-control studies on the relationship between cancer and PAH exposure is vast. IPCS (1998) and Boffetta et al (1997) summarized most of these studies. Overall, the same conclusions follow from case-control studies as from cohort studies: increased risk for lung cancer and skin cancer following inhalation and dermal exposure, respectively, and inconclusive results on the relation between bladder cancer and other types of cancer.

7.7.2. Animal data (DECOS 2006)

As far as carcinogenicity of PAH in experimental animals is concerned, both the effects of single PAH and effects of various complex PAH-containing mixtures, to which humans can be exposed during their work, have been investigated. In a great number of animal studies, the carcinogenic properties of single PAH have been investigated. There is a strong preponderance of studies with benzo[a]pyrene and of studies with dermal exposure. Such studies were described in detail by ATSDR (1995) and IARC (2010).

Carcinogenicity of complex PAH mixtures
Various complex PAH-containing mixtures, to which humans can be exposed during work, have been investigated for carcinogenic properties with experimental animals. In most of

these studies the animals were dermally exposed to extracts, tars or condensates. Exposure *via* the respiratory tract was applied in a much smaller number of studies.

Inhalation
Heinrich et al (1986) exposed female Wistar rats (n=108/group) to coal oven exhaust gas (containing 0.3 µg/m^3 benzo[a]pyrene) for 9 months, followed by exposure to a combination of pyrolized pitch and coal oven exhaust gas (containing approximately 90 µg/m^3 benzo[a]pyrene) 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 benzo[a]pyrene; from 10 months, average ca. 60 µg/m^3 benzo[a]pyrene) for 16 h/day, 5 d/week for 2 years. Macroscopically 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 µ g/m^3 benzo[a]pyrene, 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 benzo[a]pyrene. Female Wistar rats (n=72/group) were exposed to filtered clean air or the aerosols, with a concentration of benzo[a]pyrene of 20 or 46 µ g/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 benzo[a]pyrene. Nine out of the 46 examined animals showed tumours in the respiratory tract. The authors stated that when pure benzo[a]pyrene 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 benzo[a]pyrene 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 (1077) found multiple pulmonary adenomas in Syrian golden hamsters, which were exposed by intratracheal instillations to automobile exhaust condensates containing 340 µg/g benzo[a]pyrene, 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 benzo[a]pyrene 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. Carcinogenic risk assessment

As human data from exposed workers are available, a numerical carcinogenic risk assessment should be based on an aggregation of such data.

DECOS et al (2006) and AGS (2011) independently based their assessments on the large meta-analysis by Armstrong et al (2003, 2004) that was performed for the Britisch Health and Safety Executive (see 6.7.1). In this well-performed study, unit relative risks

and lifetime excess lung cancer risks for workers, who were mainly exposed to PAH, were calculated. [Unit relative risk values refer to increments in relative lung cancer risk per 100 µg/m^3 benzo[a]pyrene-years, in which 100 µg/m^3 benzo[a]pyrene-years corresponds to a concentration of 2.5 g/m^3 benzo[a]pyrene over 40 years – see *Table 1 in Annex 2*.] Based on data obtained from 39 distinct cohorts, the overall mean unit relative risk for lung cancer was calculated at 1.20 (95% CI, 1.11-1.29; p< 0.001; log-linear model). The cohorts included various industries in which PAH were considered the predominant carcinogens. All these industries concerned coal-derived PAH. Although none of the cohorts dominated the estimate, significant differences across industries were found. After allowing for these differences in the analysis, differences could only be explained by chance or by unknown true variations. Differences across industries could be explained by problems of exposure estimation and small number of cases in some studies. For both DECOS (2006) and AGS (2011), such uncertainties and variability within the cohorts were no reason to reject any of the included cohorts. The overall consideration of all cohorts from all industrial sectors resulted in a significantly increased risk of lung cancer (*Table 1 in Annex 2*). In addition, recent data point to positive association between PAH exposure and larynx cancer (Wagner et al. 2015). As the database for larynx cancer is less robust compared to the database for lung cancer, the present evaluation is based on lung cancer.

Evaluation by DECOS (2006)

A „HBC-OCRV" was defined as the additional lifetime cancer risk value, usually expressed per ng/m^3, under occupational conditions. To derive an HBC-OCRV for lung cancer in humans under workplace exposure conditions, it was assumed that the average man lives 75 years, is exposed 8 hours per day during 5 days per week, 48 weeks per year, for 40 years, and inhales 10 m^3 air per 8-hour-working day. These assumptions were taken into account in the meta-analysis (Armstrong et al 2003, 2004). Furthermore, the analysis showed that the relationship between exposure and cancer risk was best described by a log-linear model instead of a linear model. Therefore, DECOS used the formula obtained from this log-linear model to derive HBCOCRVs. The log-linear equation was expressed as follows:

$$\text{URRcum exp } X = [\text{URRcum exp } 100](X/100)$$

in which X represents the exposure concentration of benzo[a]pyrene, 100 the benchmark of 100 µg/m^3 benzo[a]pyrene-years, the URRcum exp X the relative risk on exposure to X, and URRcum exp 100 the relative risk of 1.20 on exposure to 100 µg/m^3 benzo[a]pyrene-years (2.5 µg benzo[a]pyrene /m^3 per 40 years). According to Armstrong et al (2003, 2004), at moderate or lowrelative risks, the log-linear interpolation is close to the linear interpolation. The excess lifetime cancer risk depends on the background rate of lung cancer. In the Netherlands, of the 250 death cases in the general male population (age>15 years), on average 24.21 are caused by lung cancer (source: Statline, a databank of Statistics Netherlands, period 1996-2002). For the derivation of an HBC-OCRV, an additional risk of one extra cancer death due to occupational exposure per 250 death cases is taken into account (= $4x10^{-3}$; corresponds to 1 excess death per 1,000). As a result, the unit relative risk was calculated at 1.041 (calculation: (24.21+1)/24.21). Using the non-linear formula, this corresponds with a concentration of 22.03 µg benzo[a]pyrene/m^3 per 40 years [1.041 = [1.20](X/100)]. This means over a period of 40 working years an average exposure of 550 ng/m^3 benzo[a]pyrene. In case of an additional risk of one cancer death per 250,000 death cases, the unit relative risk is 1.0004131 [(2421+1)/2421], and the equivalent concentration 0.227 µg benzo[a]pyrene/m^3 per 40 years. This corresponds to an average exposure of 5.7 ng/m^3 benzo[a]pyrene over 40 working years. Comparable results were obtained with two chronic animal studies.

In conclusion, DECOS derived HBC-OCRVs corresponding to an *excess cancer mortality level* of:

• 4 per 1,000 ($4x10^{-3}$) for 40 years of occupational exposure to benzo[a]pyrene and polycyclic aromatic hydrocarbons from coal-derived sources of 550 ng benzo[a]pyrene/m^3 ;
• 4 per 100,000 ($4x10^{-5}$) for 40 years of occupational exposure to benzo[a]pyrene and polycyclic aromatic hydrocarbons from coal-derived sources of 5,7 ng benzo[a]pyrene/m^3.

Evaluation by AGS (2011)

The meta-analysis of Armstrong et al (2003, 2004) arrived at a URR (Unit Relative Risk) of 1.20 (95 % CI 1.11 – 1.29) for all industries or occupations studied. Broken down into industrial sectors or occupations, there were differences in the risk level which are - at least partly - attributable to the fact that the PAH mixtures may have different compositions in specific industries and may therefore have different effects. The URR determined for coking plants, gasworks and aluminium production are practically identical; for the overall assessment, a significantly increased URR of 1.17 (95 % CI 1.12 – 1.22) was determined at these workplaces, and it is in line with the overall risk of 1.20, when the uncertainties of such assessments are taken into account.

The point of departure for deriving the exposure-risk relationship by AGS (2011) was a URR ("unit relative risk") of 1.20. This URR specifies the increase of the RR, when the cumulative exposure increases by 100 µg/m^3 benzo[a]pyrene-years (corresponding to an average benzo[a]pyrene concentration of 2.5 µg/m^3 and 40 years of occupation).

The methodology of further derivation was described and discussed in detail by AGS (2011). This finally resulted, for an excess lung cancer mortality risk of 4:1000, in an average benzo[a]pyrene exposure concentration over 40 working years of 700 ng/m^3. The corresponding figures for a risk of 4:10,000 and 4:100,000 were 70 and 7 ng/m^3, respectively.

Conclusion

The two risk assessments by DECOS (2006) and by AGS (2011), both departing from the same extensive metaanalysis of Armstrong et al (2003, 2004), lead to practically identical figures in excess human lung cancer risk mortality, related to PAH exposure with benzo[a]pyrene as indicator compound. Taking both assessments together, a mean 8h-TWA PAH exposure over 40 working years of about 6 ng benzo[a]pyrene per m^3 would lead to an excess lung cancer mortality rate 4 x 10^{-5}.

A number of earlier cancer risk assessments has been summarised by AGS (2011), to which reference can be made.

7.8. Reproductive toxicity

7.8.1. Human data

Two reports are available on transplacental naphthalene poisoning. 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 (DFG 2012).

7.8.2. Animal data

The results of studies on the embryotoxicity of benzo[a]anthracene, chrysene and dibenzo[a,h]anthracene in rats and of benzo[a]pyrene and naphthalene in mice and rats, on the effect of benzo[a]pyrene on fertility and on the effect of benzo[a]pyrene on the postnatal development of mice were compiled in detail WHO (1998) and later

summarized by DFG (2012), to which reference can be made. In essence, benzo[a]pyrene displayed adverse effects on the fertility of female mice and on the postnatal development of the offspring. In a study in young mice, a *NOEL (no observed effect level) of 150 mg/kg body weight per day* was established for benzo[a]pyrene on the basis of the effects on fertility (sperm in the testicular lumen; litter size) and of embryotoxicity (malformations) (Rigdon and Neal 1965).

7.8.3. In vitro data

No relevant in vitro data were identified.

7.9. Mode of action and adverse outcome pathway considerations

One of the biggest issues for understanding complex PAH mixture toxicity is that it is impossible to test all mixtures in animal models and even in cultured cell lines. It is widely accepted that both approaches have limitations that restrict their extrapolation to human exposures, but at present they remain preferred best tools for experimental research. It is evident that the responses to complex PAH mixtures are heavily dependent on the modeling system used (Jarvis et al 2014). At present, there is noticable development towards use of new strategies such as toxicogenomics (Chepelev et al 2015), molecular fingerprints (Ceccaroli et al 2015) and proteomics (Verma et al 2012), in order to implement mechanistic knowledge applicable to hazard isentifiication, dose-response analysis and quantitative risk assessment.

PAH are relatively inert hydrophobic compounds that can be converted to highly reactive dihydrodiol epoxides during metabolism in mammals. These diol epoxides react with double strand and single strand DNA, preferably with the N^6 position of guanine and the N^2 position of adenine, with cis and trans adducts being formed for every syn and anti enantiomer (Jerina et al 1991, Scicchitano 2005). Depending on their reactivity and structure, activated PAH can form further adducts. The example of DNA adducts of anti-dihydrodiol epoxides was used to demonstrate that certain changes in the conformation of the DNA are associated with the covalent binding. Thus, the aromatic ligand may become positioned in the minor DNA groove without inducing any major changes in conformation, it may intercalate between base pairs in such a way that the double helix is only stretched or it may push between base pairs in such a way that their hydrogen bonds break and individual DNA bases are displaced from the double-helix structure into the outer section of the helix (Geacintov et al 1997; DFG 2012).

Numerous PAH were investigated for their carcinogenicity. Observations were made that compounds that have a bay region, an indentation caused by an angular benzene ring, are severe carcinogens; however, compounds with a fjord region are even more carcinogenic. The structural characteristics of PAH understandably influence both their metabolic activation and the stereochemistry after DNA binding. Many investigators have ranked the carcinogenic and mutagenic potencies of single PAH compared to benzo[a]pyrene in order to provide more reliable estimates of the carcinogenicity of PAH mixtures. To rank, a toxicity equivalence factor approach was used. Examples are those made by Collins et al (1991; see *Table 6*) and by the IPCS (1998). These rankings are based on comparative studies, in which benzo[a]pyrene and other PAH were assayed by the same protocol and within the same time frame. Overall, these comparisons 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). Concerning dibenz[a,h]anthracene, this 5-ring PAH appears to be equipotent or somewhat more potent than benzo[a]pyrene, whereas other 5-ring PAH tested (*e.g.*, benzofluoranthenes, benzo[e]pyrene) are less or much less potent. In addition, Pufulete et al (2004) reported on the high carcinogenic potency (higher than benzo[a]pyrene) of dibenzo[a,l]pyrene, dibenzo[a,i]pyrene, dibenzo[a,h]pyrene, dibenz[a,h]anthracene, and 5-methylchrysene. As a result, in estimating cancer risk of complex PAH mixtures in which benzo[a]pyrene is used as exposure indicator for PAH, values may be over- or

underestimated. However, at the present time benzo[a]pyrene may serve as an acceptable genotoxic indicator for PAH mixtures (DECOS 2006).

In addition to the genotoxicity, there are interactions of benzo[a]pyrene with various constituents of the proteome. Such non-genotoxic pathways are a matter of current research (Verma et al 2012).

Table 6: Ranking of carcinogenic and mutagenic properties of single PAH (Collins et al 1991, DECOS 2006)

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]Benzo[a]pyrene set to 1.0; other PAH were scaled to benzo[a]pyrene

7.10. Lack of specific scientific information

The toxicology of benzo[a]pyrene and of PAH in general has been well investigated. There is no specific lack of scientific information.

8. GROUPS AT EXTRA RISK

Interindividual differences in the excretion of PAH metabolites have been attributed to several sequence variants in genes that are involved in PAH metabolism. Modified genes may affect the catalytic properties or the amount of the coded enzyme. However, investigations into practical consequences for workplace situations are scarce, and investigations in human cell lines in vitro are complicated by an extreme variety in the genotoxic response to benzo[a]pyrene (Genies et al 2013). Observed interindividual differences in the excretion of 1-hydroxypyrene may vary considerably (factors between 10 and 100; Petry et al. 1996). However, these variations may mostly be explained by substantial dermal PAH absorption at individual workplaces or by different hygiene measures of the workers in the trade examined (McClean et al 2004). At present, it is difficult to explain observed interindividual differences in the excretion of 1-hydroxypyrene by genetic polymorphisms in PAH-metabolizing genes. The analysis of 11 polymorphisms in a total of eight enzymes involved in the xenobiotic metabolism of PAH (CYP1A1, CYP1A2, CYP1B1, CYP3A4, microsomal epoxide hydrolase, GSTM1, GSTT1 and GSTP) in a group of 170 workers exposed to PAH yielded an impact on the urinary excretion of 1-hydroxypyrene for only three polymorphisms but this was only small, resulting in factors between 1.4 and 1.6 (Rihs et al. 2005; DFG 2012). Similar results were reported by Molina et al (2013) when looking at a coherence of bulky DNA-adduct levels of PAH with a series of genetic polymorphisms in persons living in Mecico City.

Thus, specific sub-populations of workers at extra risk cannot be clearly defined at present.

8. REFERENCES

Abbas I, Garçon G, Saint-Georges F, Andre V, Gosset P, Billet S, Le Groff J, Verdin A, Mulliez P, Sichel F, Shirali P (2011) Polycyclic aromatic hydrocarbons within airborne particulate matter (PM2.5) produced DANN bulky stable adducts in a human lung cell coculture model. J Appl Toxicol 33: 109-119.

ACGIH [American Conference of Governmental Industriel Hygienists] (2016) TLVs and BEIs based on the documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. Published by ACGIH, Cincinatti, OH, USA

AGS [Ausschuß für Gefahrstoffe] (2011) ERB (Exposition-Risiko-Beziehung) Begründung zu Benzo[a]pyren. Ausgabe April 2011, Stand Mai 2010. BAuA, Dortmund. http://WWW.baua.de/ags English translation: http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/pdf/910/910-benzo-a-pyrene.pdf? blob=publicationFile&v=2

Armstrong B, Hutchinson E, Fletcher T (2003) Cancer risk following exposure to polycyclic aromatic hydrocarbons (PAHs): a meta-analysis. Prepared by the London School of Hygiene and Tropical Medicine for the Health & Safety Executive; 2003: Research Report no. 068.

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(9): 970-978.

Armstrong B, Tremblay C, Baris D, Theriault G (1994) Lung cancer mortality and polynuclear aromatic hydrocarbons: a case-cohort study of aluminum production workers in Arvida, Quebec, Canada. Am J Epidemiol 139(3): 250-262.

Ashby J, Basketter DA, Paton D, Kimber I (1995) Structure activity relationships in skin sensitizationusing the murine local lymph node assay. Toxicology 103: 177–194

ATSDR [Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services] (1995) Toxicological Profile for Polycyclic Aromatic Hydrocarbons. ATSDR, tp 69, August 1995. Atlanta, GA, USA

ATSDR [Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services] (2002) Toxicological Profile for Wood Creosote, Coal Tar Creosote, Coal Tar, Coal TarPitch, and Coal Tar Pitch Volatiles, Atlanta US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Atlanta,GA, USA

AU SWA [Safe Work Australia] (2011) Workplace exposure standards for airborne contaminants date of effect: 22 December 2011, Australia http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/639/Workplace_Exposure_Standards_for_Airborne_Contaminants.pdf. Accessed 2016.02.10

Backer JM, Weinstein IB (1982) Interaction of benzo[a]pyrene and its dihydrodiol-epoxide derivative with nuclear and mitochondrial DNA in C3H10T1/2 cell cultures. Cancer Res 42: 2764–2769

Basler A, Herbold B, Péter S, Röhrborn G (1977) Mutagenicity of polycyclic hydrocarbons. II. Monitoring genetic hazards of chrysene in vitro and in vivo. Mutat Res 48: 249–254

BAUA [Bundesanstalt für Arbeitsschutz und Arbeitsmedizin /Federal Institute for Occupational Safety and Health] (2011) Exposure-risk relationship for benzo[*a*]pyrene in BekGS 910 Issue: April 2011. http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/pdf/910/910-benzo-a-pyrene.pdf?__blob=publicationFile&v=2. Accessed 2016.02.10

Bentsen-Farmen RK, Botnen IV, Notø H, Jacob J, Vrebø S (1999) Detection of polycyclic aromatic hydrocarbon metabolites by high-pressure liquid chromatography after purification on immunoaffinity columns in urine from occupationally exposed workers. Int Arch Occup Environ Health 72: 161–168

Billet S, Abbas I, Le Goff J, Verdin A, André V, Lafargue PE, Hachimi A, Cazier F, Sichel F, Shirali P, Garçon G (2008) Genotoxic potential of polycyclic aromatic hydrocarbons - coted onto particulate matter (PM2.5) in human lung epithelial cells. Cancer Lett 270: 144-155

Bock FG, Mund R (1958) A survey of compounds for activity in suppression of mouse subaceous glands. Cancer Res 18: 887–892

Boogaard PJ (2012) Biomonitoring of exposure to polycyclic aromatic hydrocarbons. Shell Health, Shell International b.v., Chapter 3F, Issues in Toxicology No. 9, Biomarkers and Human Biomonitoring, Volume 1: Ongoing Programs and Exposures. Edited by Lisbeth E. Knudsen and Domenico Franco Merlo, Royal Society of Chemistry 2012 Published by the Royal Society of Chemistry, www.rsc.org

Boffetta P, Jourenkova N, Gustavsson P (1997) Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control 1997; 8(3): 444-472.

Boniol M, Koechlin A, Świątkowska B, Sorahan T, Wellmann J, Taeger D, Jakobsson K, Pira E, Boffetta P, La Vecchia C, Pizot C, Boyle P. (2016) Cancer mortality in cohorts of workers in the European rubber manufacturing industry first employed since 1975. Ann Oncol.;27(5):933-41. doi: 10.1093/annonc/mdw061

Borneff J, Kunte H (1969) Carcinogenic substance in water and soil. XXVI: A routine method for the determination of PAH in water. Arch Hyg (Berlin) 1969; 153: 220-229.

Bowman ED, Rothman N, Hackl C, Santella RM, Weston A (1997) Inter-individual variation in the levels of certain urinary polycyclic aromatic hydrocarbon metabolites following medicinal exposure to coal tar ointment. Biomarkers 2: 321–327

Brune K, Kalin H, Schmidt R, Hecker E (1978) Inflammatory, tumor initiating and promoting activities of polycyclic aromatic hydrocarbons and diterpene esters in mouse skin as compared with their prostaglandin releasing potency in vitro. Cancer Lett 4: 333–342

CA IRSST [Institut de Recherche Robert Sauvé en Santé et en Sécurité du Travail] (2010) Québec, Canada. http://www.irsst.qc.ca/en/laboratories/references-tools/guidestools/workplace-air-contaminant/substance/i/715. Accessed 2016.02.10

CA OML [Ontario Ministry of Labour] (2013) Current Occupational Exposure Limits for Ontario Workplaces Required under Regulation 833, Canada. http://www.labour.gov.on.ca/english/hs/pubs/oel_table.php. Accessed 2016.02.09

CAD (1998) Council Directive 98/24/EC of 7 April 1998 on the protection of safety workers from the risk related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC).

Casale GP, Higginbotham S, Johansson SL, Rogan EG, Cavalieri EL (1997) Inflammatory response of mouse skin exposed to the very potent carcinogen dibenzo[a,l]pyrene: a model for tumor promotion. Fundam Appl Toxicol 36: 71–78

Ceccaroli C, Pulliero A, Geretto M, Izzotti A (2015) Molecular fingerprints of environmental carcinogens in human cancer. J Evironmental Sci Health, Part C 33(2): 188-228

Chepelev NL, Moffat ID, Labin S, Bourdon-Lacombe J, Kuo B, Buick JK, Lemieux F, Malik AI, Halappanavar S, Williams A, Yauk CL (2015) Integrating toxicogenomics into human health risk assessment: lessons learned from the benzo[a]pyrene case study. Crit Rev Toxicol 45(1): 44-52

CH SUVA [Schweizerische Unfallversicherungsanstalt] (2015) Grenzwerte am Arbeitsplatz 2016. Suva, Bereich Arbeitsmedizin, Januar 2016 https://extra.suva.ch/suva/b2c/app/displayApp/%28cpgnum=1&layout=7.01-15_1_76_128_6_125&cquery=1903.D&cadvsearch=false&uiarea=0&carea=50328D134DA837E0E10080000A630358&citem=50328D134DA837E0E10080000A6303584BE36A0936148016E10080000A630387&cpgsize=10%29/.do;jsessionid=lenTwBBfurQ6Ze9THGFxmmmiqVRUUgFykRoe_SAPoWGzrscyyX3T40q-RuHjOuUa;saplb_*=%28J2EE505057620%29505057650?rf=y. Accessed 2016.02.10

CMD (2004) Directive 2004/37/EC of the European Parliament and the council of 29 april 2004 on the protection of workers from the risk related to exposure to carcinogens or mutagens at work (sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC)

Collins JF, Brown JP, Dawson SV, Marty MA (1991) Risk assessment for benzo[a]pyrene. Regul Toxicol Pharmacol 13(2): 170-184.

Cook JW, Hewett C, Hieger I (1932) Coal tar constituents and cancer. Nature 130: 926

Cottini GB, Mazzone GB (1939) The effects of 3,4-benzpyrene on human skin. Am J Cancer 37:186-195.

Culp SJ, Gaylor DW, Sheldon WG, Goldstein LS, Beland FA (1998) A comparison of the tumors induced by coal tar and benzo[a]pyrene in a 2-year bioassay. Carcinogenesis 19(1): 117-124

DECOS [Health Council of the Netherlands, Dutch Committee on Occupational Standards] (2006) Benzo[a]pyrene 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. No. 2006/01 OSH, The Hague, 21 Feb 2006

Dell LD, Gallagher AE, Crawford L, Jones RM, Mundt KA (2015) Cohort study of carbon black exposure and risk of malignant and nonmalignant respiratory disease mortality in the US Carbon Black Industry. J Occup Environ Med.;57(9):984-97

DFG [Deutsche Forschungsgemeinschaft] (1991) Polycyclic aromatic hydrocarbons (PAH) (particle-bound) Air Monitoring Methods, 1991 http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0pahse0001/pdf. Accessed 2016.02.09

DFG [Deutsche Forschungsgemeinschaft] (1999) PAH-Metabolite (1Hydroxyphenanthren, 4-Hydroxyphenanthren, 9-Hydroxyphenanthren, 1-Hydroxypyren). Analytische Methoden zur Pruüfung gesundheitsschädlicher Arbeitsstoffe, Band 2: Analysen in biologischem Material Greim H, Angerer J (Hrsg), 13. Lieferung, Wiley-VCH, Weinheim Available online via http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics

DFG [Deutsche Forschungsgemeinschaft] (2003a) Polycyclic aromatic hydrocarbons (PAH) Air Monitoring Methods, 2003. Method number 2 http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0223orge0008a/pdf. Accessed 2016.02.09

DFG [Deutsche Forschungsgemeinschaft] (2003b) Polycyclic aromatic hydrocarbons (PAH) Air Monitoring Methods, 2003. Method number 3 http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0223orge0008b/pdf. Accessed 2016.02.09

DFG [Deutsche Forschungsgemeinschaft] (2012) Polycyclic aromatic hydrocarbons (PAH). In : The MAK Collection Part I : Occupational Toxicants, Vol 27. Wiley-VCH, Weinheim. http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics. Accessed 2016.02.09

DFG [Deutsche Forschungsgemeinschaft] (2013) Polycyclische aromatische Kohlenwasserstoffe (PAH). In: Grenzwerte im biologischen Material, 20. Lieferung 2013, pp. 1-29 Wiley-VCH, Weinheim. Available online via http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics Accessed 2016.02.09

DFG [Deutsche Forschungsgemeinschaft] (2015) List of MAK and BAT values 2015 Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area Report 51

DFG [Deutsche Forschungsgemeinschaft] (2016) The MAK Collection for Occupational Health and Safety Benzo[a]pyrene and Polycyclic aromatic hydrocarbons (PAH) air monitoring methods. http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics?filter=AIRSmbe9882 Accessed 2016.02.09

DK DWEA [Danish Working Environment Authority] (2007) At-VEJLEDNING STOFFER OG MATERIALER Grænseværdier for stoffer og materialer August 2007 – Erstatter april 2005

Dor F, Dab W, Empereur-Bissonnet P, Zmirou D (1999) Validity of biomarkers in environmental health studies: The case of PAHs and benzene. Crit Rev Toxicol 29 : 129–168

ECHA [European Chemicals Agency] inventory database (2016). http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/20004. Accessed 02.09.2016.

Elgjo K (1968) Growth kinetics of the mouse epidermis after a single application of 3,4-benzopyrene, croton oil, or 1,2-benzopyrene. Acta Pathol Microbiol Scand 73: 183–190

Fan R, Dong Y, Zhang W, Wang Y, Yu Z, Sheng G, Fu J (2006) Fast simultaneous determination of urinary 1-hydroxypyrene and 3-hydroxybenzo[a]pyrene by liquid chromatography-tandem mass spectrometry. J Chromatogr B Biomed Sci Appl 836: 92–97

Farant J, Gariepy M (1998) Relationship between benzo(a)pyrene and individual polycyclic aromatic hydrocarbons in a Soderberg primary aluminum smelter. Am Ind Hyg Assoc J 58(11): 758-765.

FI MSAH [Ministry of Social Affairs and Health] (2012) HTP-värden 2012 Koncentrationer som befunnits skadliga. Social- och halso vardsministeriets publikationer 2012:6, Finland. http://www.ttk.fi/files/2610/STM_2012_6_HTP_SWE_web.pdf. Accessed 2016.02.10

Franco SS, Nardocci AC, Gunther WMR, (2008) PAH biomarkers for human health risk assessment: a review of the state-of-the-art. Cad.Saude Publica, Rio de Janiero, 24 Sup 4:S569-S580

Gabbani G, Pavanello S, Nardini B, Tognato O, Bordin A, Fornasa CV, Bezze G, Clonfero E (1999) Influence of metabolic genotype GSTM1 on levels of urinary mutagens in

Geacintov NE, Cosman M, Hingerty BE, Amin S, Broyde S, Patel DJ (1997) NMR solution structures of stereoisomeric covalent polycyclic aromatic carcinogen-DNA adducts: principles, patterns, and diversity. Chem Res Toxicol 10: 111–146

Gendre C, Lafontaine M, Delsaut P, Simon P (2004) Exposure to polycyclic aromatic hydrocarbons and excretion of urinary 3-hydroxybenzo[a]pyrene: assessment of an appropriate sampling time. Polycyclic Aromatic Compounds 24: 433–439

Gendre C, Lafontaine M, Morele Y, Payan JP, Simon P (2002) Relationship between urinary levels of 1-hydroxypyrene and 3-hydroxybenzo[a]pyrene for workers exposed to polycyclic aromatic hydrocarbons. Polycyclic Aromatic Compounds 22: 761–769

Genies C, Maitre A, Lefèbvre E, Jullien A, Chopard-Lallier M, Douki T (2013) The extreme variety of genotoxic response to benzo[a]pyrene in three different human cell lines from three different organs. PLOS One 8(11): e78356

GESTIS (2016) GESTIS database on hazardous substances IFA Institut für Arbeitssicherheit der Deutschen Gesetzlichen Unfallversicherung, Germany. http://limitvalue.ifa.dguv.de/. Accessed 2016.02.09

Gmeiner G, Krassnig C, Schmid E, Tausch H (1998) Fast screening method for the profile analysis of polycyclic aromatic hydrocarbon metabolites in urine using derivatisation-solid-phase microextraction. J Chrom B 705: 132–138

Godschalk RW, Ostertag JU, Moonen EJ, Neumann HA, Kleinjans JC, van Schooten, FJ (1998) Aromatic DNA adducts in human white blood cells and skin after dermal application of coal tar. Cancer Epidemiol. Biomarkers Prev 7: 767–773

Godschalk RW, Ostertag JU, Zandsteeg AM, Van Agen B, Neuman HA, Van Straaten H, Van Schooten FJ (2001) Impact of GSTM1 on aromatic-DNA adducts and p53 accumulation in human skin and lymphocytes. Pharmacogenetics 11: 537–543

Greim H, Angerer J (Hrsg) (1999) PAH-Metabolite (1-Hydroxyphenanthren, 4-Hydroxyphenanthren, 9-Hydroxyphenanthren, 1-Hydroxypyren). Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Band 2: Analysen in biologischem Material, 13. Lieferung, Wiley-VCH, Weinheim

Grimmer G, Dettbarn G, Naujack KW, Jacob J (1991) Excretion of hydroxy derivatives of polycyclic aromatic hydrocarbons of the masses 178, 202, 228 and 252 in the urine of coke and road workers. Int J Environ Anal Chem 43 : 177–186

Grimmer G, Dettbarn G, Jacob J (1993) Biomonitoring of polycyclic aromatic hydrocarbons in highly exposed coke plant workers by measurement of urinary phenanthrene and pyrene metabolites (phenols and dihydrodiols). Int Arch Occup Environ Health 65: 189–199

Gundel, J., Mannschreck, C., Buttner, K., Ewers, U. & Angerer, J. (1996) Urinary levels of 1-hydroxypyrene, 1-, 2-, 3-, and 4-hydroxyphenanthrene in females living in an industrial area of Germany. Arch. environ. Contam. Toxicol., 31, 585–590

Hagedorn HW, Scherer G, Engl J, Riedel K, Cheung F, Errington G, Shepperd J, McEwan M (2009) Urinary excretion of phenolic polycyclic aromatic hydrocarbons (OH-PAH) in nonsmokers and in smokers of cigarettes with different ISO tar yields. J Anal Toxicol 33: 301–309

He S, Baker R (1991) Micronuclei in mouse skin cells following in vivo exposure to benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, chrysene, pyrene and urethane. Environ Mol Mutagen 17: 163–168

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. Int Arch Occup Environ Health 74: 91–101

Heinrich U, Pott F, Mohr U, Fuhst R, König J (1986) Lung tumours in rats and mice after inhalation of PAH-rich emissions. Exp Pathol 29(1): 29-34.

HSE (2011) EH40/2005 Workplace Exposure limits. Containing the list of workplace exposure limits for use with the Control of Substances Hazardous to Health Regilations 2002 (as amended). Published by JSE Books ISBN 9780717664467. http://www.hse.gov.uk/pubns/books/eh40.htm Accessed 2016.06.15

Heinrich U, Roller M, Pott F (1994) Estimation of a lifetime unit lung cancer risk for benzo(a)pyrene based on tumour rates in rats exposed to coal tar/pitch condensation aerosol. Toxicol Lett 72(1-3): 155-161.

HU MHSFA [Ministry of Health, Social and Ministry of Family Affairs] (2000) 25/2000 (IX. 30.) EüM-SzCsM együttes rendelet a munkahelyek kémiai biztonságáról, Hungary [Joint Decree ACGIH TLV]. http://net.jogtar.hu/jr/gen/hjegy_doc.cgi?docid=A0000025.EUM. Accessed 2016.02.09

IARC [International Agency for Research on Cancer] (1983) Polynuclear Aromatic Compounds; Part 1; Chemical, Environmental and Experimental Data. IARC Monogr Eval Carcin Risks Hum 32.

IARC [International Agency for Research on Cancer] (2010) Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Carcin Risks Hum 92:1-852 http://www.iarc.fr

Ingram AJ, Phillips JC (1993) The dermal bioavailability of radiolabelled benzo[a]pyrene from acetone or from oils of differing viscosity, assessed by DNA and protein binding. J Appl Toxicol 13: 25–32

Jacob III P, Wilson M, Benowitz NL (2007) Determination of phenolic metabolites of polycyclic aromatic hydrocarbons in human urine as their pentafluorobenzyl ether

derivatives using liquid chromatography-tandem mass spectrometry. Anal Chem 79: 587–598

IPCS [International Programme on Chemical Safety, WHO] (1998) Selected non-heterocyclic policyclic aromatic hydrocarbons. Environmental Health Criteria 2002, WHO, Geneva.

Jarvis IWH, Dreij K, Mattsson Å, Jernström B, Stenius U (Interactions between polycyclic aromatic hydrocarbons in complex nixtures and implications for cancer risk assessment. Toxicology 321: 27-39

Jerina DM, Chadha A, Cheh AM, Schurdak ME, Wood AW, Sayer JM (1991) Covalent bonding of bay-region diol epoxides to nucleic acids. In: Witmer CM, Snyder R, Jollow DJ,

Jongeneelen FJ (1997) Methods for routine biological monitoring of carcinogenic PAH-mixtures. Sci Total Environ 199: 141–149

Jongeneelen FJ (2001) Benchmark guideline for urinary 1-hydroxypyrene as biomarker of occupational exposure to polycyclic aromatic hydrocarbons. Ann occup Hyg 45:3–13

Jongeneelen, FJ, Anzion RBM, Leijdekkers CM, Bos RP, Henderson PT (1985) 1–Hydroxypyrene in human urine after exposure to coal tar and a coal tar derived product. Int Arch Occup Environ Health 57 : 47–55

Kalf GF, Kocsis JJ, Sipes IG (Eds) Biological Reactive Intermediates IV. Molecular and Cellular Effects and Their Impact on Human Health, Plenum Press, New York, NY, 533–553

Kauppinen T, Toikkanen J, Pedersen D, Young R, Ahrens W, Boffetta P, Hansen J, Kromhout H, Maqueda BJ, Mirabelli DD, de la Orden-Rivera V, Pannett B, Plato N, Savela A, Vincent R, Kogevinas M (2000) Occupational exposure to carcinogens in the European Union. Occup environ Med 57:10–18

Klemme JC, Mukhtar H, Elmets CA (1987) Induction of contact hypersensitivity to dimethylbenz[a]anthracene and benzo[a]pyrene in C3H/HeN mice. Cancer Res 47: 6074–6078

Kogevinas M, Hogstedt C, Kauppinen T (2003) Workplace carcinogen and pesticide exposures in Costa Rica. Int J occup environ Health 9: 104–111

Künstler K (1983) Failure to induce tumors by intratracheal instillation of automobile exhaust condensate and fractions thereof in Syrian golden hamsters. Cancer Lett 18(1): 105-108.

Lafontaine M, Chapmartin C, Simon P, Delsaut P, Funck-Brentano C (2006) 3-hydroxybenzo[a]- pyrene in the urine of smokers and non-smokers. Toxicol Lett 162: 181–185

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 KH, Ichiba M, Zhang J, Tomokuni K, Hong YC, Ha M, Kwon HJ, Koh SB, Choi HR, Park CG, Cho SH, Hirvonen A, Strickland PT, Vermeulen R, Hayes RB, Kang D (2003) Multiple biomarkers study in painters in a shipyard in Korea. Mutat Res 540: 89–98

Legraverend C, Harrison DE, Ruscetti FW, Nebert DW (1983) Bone marrow toxicity induced by oral benzo[a]pyrene: protection resides at the level of the intestine and liver.

Toxicol Appl Pharmacol 70: 390–401

Li Z, Romanoff LC, Trinidad DA, Hussain N, Jones RS, Porter EN, Patterson Jr. DG, Sjödin A (2006) Measurement of urinary monohydroxy polycyclic aromatic hydrocarbons using automated liquid-liquid extraction and gas chromatography/isotope dilution high-resolution mass spectrometry. Anal Chem 78: 5744–5751

Lintelmann J, Hellemann C, Kettrup A (1994) Coupled-column high-performance liquid chromatographic method for the determination of four metabolites of polycyclic aromatic hydrocarbons, 1-, 4- and 9-hydroxyphenanthrene and 1-hydroxypyrene, in urine. J Chrom B 660: 67–73

Liu D, Pan L, Yang H, Wang J (2014). A physiologically based toxicokinetic and toxicodynamic model links the tissue distribution of benzo[a]pyrene and toxic effects in the scallop Chlamys farreri. Environ Toxicol Pharmacol 37(2): 493-504

Martin F, Hoepfner I, Scherer G, Adlkofer F, Dettbarn G, Grimmer G (1989) Urinary excretion of hydroxyphenanthrenes after intake of polycyclic aromatic hydrocarbons. Environ Intern 15: 41–47

McClean MD, Rinehart RD, Ngo L, Eisen EA, Kelsey KT, Herrick RF (2004) Inhalation and dermal exposure among asphalt paving workers. Ann Occup Hyg 48: 663–671

Mitchell CE (1982) Distribution and retention of benzo[a]pyrene in rats after inhalation. Toxicol Lett 11: 35–42

Molina E, Pérez-Morales R, Rubio J, Petrosyan P, Cadena LH, Arlt VM, Phillips DH, Gonseblatt ME (2013) The GSTM1null (deletion) and MGMT84rs12917 (phe/phe) haplotype are associated with bulky DNA adducts levels in human leukocytes. Mutation Res 758: 62-68

Montizaan GK, Kramers PGN, Janus JA, Posthumus R (1989) Integrated criteria document PAH, Effects of 10 selected compounds. Bilthoven, The Netherlands: National Institute of Public Health and Environmental Protection, 1989: Re-publication of addendum to Report no. 758474007.

Nelson G, Ross J, Prusiewicz CM, Sangaiah R, Gold A (2002) Identification of stereochemical configurations of cyclopenta[cd]pyrene DNA adducts in strain A/J mouse lung and C3H10T1/2CL8 cells. Polycyclic Aromat Compd 22: 923–931

Nesnow S, Davis C, Nelson G, Ross JA, Allison J, Adams L, King LC (1997) Comparison of the morphological transforming activities of dibenzo[a,l]pyrene and benzo[a]pyrene in C3H10T1/2CL8 cells and characterization of the dibenzo[a,l]pyrene-DNA adducts. Carcinogenesis 18: 1973–1978

Nesnow S, Davis C, Nelson GB, Lambert G, Padgett W, Pimentel M, Tennant AH, Kligerman AD, Ross JA (2002) Comparison of the genotoxic activities of the K-region dihydrodiol of benzo[a]pyrene with benzo[a]pyrene in mammalian cells: morphological cell transformation, DNA damage, and stable covalent DNA adducts. Mutat Res 521: 91–102

Nesnow S, Ross J, Beck S, Lasley J, Nelson G, Lamberg G, Platt KL, Agarwal SC (1994) Morphological transformation and DNA adduct formation by dibenz[a,h]anthracene and its metabolites in C3H10T1/2Cl8 cells. Carcinogenesis 15: 2225–2231

NIOSH [National Institute for Occupational Safety and Health] (1994) Polynuclear aromatic hydrocarbons by GC Method 5515 NIOSH Manual of Analytical Methods (NMAM), Fourth Edition http://www.cdc.gov/niosh/docs/2003-154/pdfs/5515.pdf Accessed 2016.02.11

NIOSH [National Institute for Occupational Safety and Health] (1998a) Polynuclear aromatic hydrocarbons by HPLC Method 5506. NIOSH Manual of Analytical Methods (NMAM), Fourth Edition http://www.cdc.gov/niosh/docs/2003-154/pdfs/5506.pdf Accessed 2016.02.11

NIOSH [National Institute for Occupational Safety and Health] (1998b) Method 5800. Polycyclic Aromatic Compounds, Total (PACs). NIOSH Manual of Analytical Methods (NMAM), Fourth Edition http://www.cdc.gov/niosh/docs/2003-154/pdfs/5800.pdf Accessed 2016.02.11

NIOSH [National Institute for Occupational Safety and Health] (2011) Pocket guide to chemical Hazards Coal tar pitch volatiles. CAS number 65996-93-2. http://www.cdc.gov/niosh/npg/npgd0145.html. Accessed 2016.02.09

NIOSH [National Institute for Occupational Safety and Health] (2016). Benzo[a]pyrene and Poly aromatic compounds, total (PACS). NIOSH Manual of Analytical Methods (NMAM), Fourth Edition. http://www.cdc.gov/niosh/docs/2003-154/method-p.html Accessed 2016.02.11

Nishikawa T, Nakamura T, Fukushima A, Takagi Y (2005) Further evaluation of the skin nucleus test: results obtained using 10 polycyclic aromatic hydrocarbons. Mutat Res 588: 58–63

NL SZW [Het ministerie van Sociale Zaken en Werkgelegenheid/The Ministry of Social Affairs and Employment] (2008) Publication 2006/01OSH. http://www.ser.nl/nl/grenswaarden/benzo%20a%20pyreen.aspx. Accessed 2016.02.10

Nousiainen U, Törrönen R, Hänninen O (1984) Differential induction of various carboxylesterases by certain polycyclic aromatic hydrocarbons in the rat. Toxicology 32: 243–251

NRC [National Research Council] (1972) Polycyclic organic matter. Washington: National Academy of Sciences; 1972.

NRC [National Research Council] (1983) Polycyclic aromatic hydrocarbons. Evaluation of sources and effects. Washington: National Academy Press; 1983.

NTP (National Toxicology Program) (2000) Toxicology and carcinogenesis studies of naphthalene in F 344/N rats (inhalation studies), US Department of Health and Human Services, TR 500, Public Health Services, Bethesda, MD

Old LJ, Benacerraf B, Carswell E (1963) Contact reactivity to carcinogenic polycyclic hydrocarbons. Nature 198: 1215–1216

Onyemauwa F, Rappaport SM, Sobus JR, Gajdošová D, Wu R, Waidyanatha S (2009) Using liquid chromatography-tandem mass spectrometry to quantify monohydroxylated metabolites of polycyclic aromatic hydrocarbons in urine. J Chrom B 877: 1117–1125

OSHA [Occupational Safety and Health Administration] Coal Tar Pitch Volatiles (CTPV) Coke Oven Emissions (COE) Selected Polynuclear Aromatic Hydrocarbons (PAHs). Method number 58. https://www.osha.gov/dts/sltc/methods/organic/org058/org058.html. Accessed 2016.02.10

Paleologo M, van Schooten FJ, Pavanello S, Kriek E, Zordan M, Clonfero E, Bezze C, Levis AG (1992) Detection of benzo[a]pyrene-diol-epoxide–DNA adducts in white blood cells of psoriatic patients treated with coal tar. Mutat Res 281: 11–16

Partanen T, Chaves J, Wesseling C, Chaverri F, Monge P, Ruepert C, Aragon A, Van Rooij, JGM, Bodelier-Bade MM, Jongeneelen FJ (1993) Estimation of individual dermal and respiratory uptake of polycyclic aromatic hydrocarbons in 12 coke oven workers. Br J. ind Med 50: 623–63

Pavanello S, Levis AG (1994) Human peripheral blood lymphocytes as a cell model to evaluate the genotoxic effect of coal tar treatment. Environ. Health Perspect 102 (Suppl. 9): 95–99

Pavanello S, Favretto D, Brugnone F, Mastrangelo G, Dal Pra G, Clonfero E (1999) HPLC/fluorescence determination of anti-BPDE–DNA adducts in mononuclear white blood cells from PAH-exposed humans. Carcinogenesis 20: 431–435

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: 639–648

Popp W, Vahrenholz C, Schell C, Grimmer G, Dettbarn G, Kraus R, Brauksiepe A, Schmeling B, Gutzeit T, von Bülow J, Norpoth K (1997) DNA single strand breakage, DNA adducts, and sister chromatid exchange in lymphocytes and phenanthrene and pyrene metabolites in urine of coke oven workers. Occup Environ Med 54 : 176–183

Pott F, Stöber W (1983) Carcinogenicity of airborne combustion products observed in subcutaneous tissue and lungs of laboratory rodents. Environ Health Perspect 47: 293-303.

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(1): 54-66.

Ramsauer B, Sterz K, Hagedorn HW, Engl J, Scherer G, McEwan M, Errington G, Shepperd J, Cheung F (2011) A liquid chromatography/tandem mass spectrometry (LC-MS/MS) method for the determination of phenolic polycyclic aromatic hydrocarbons (OH-PAH) in urine of non-smokers and smokers. Anal Bioanal Chem 399: 877–889

Reznik-Schüller H, Mohr U (1977) Pulmonary tumorigenesis in Syrian golden hamsters after intratracheal instillations with automobile exhaust condensate. Cancer 40(1): 203-210.

Rigdon RH, Neal J (1966) Gastric carcinomas and pulmonary adenomas in mice fed benzo[a]pyrene. Tex Rep Biol Med 24: 195–207

Rihs HP, Pesch B, Kappler M, Rabstein S, Roßbach B, Angerer J, Scherenberg M, Adams A, Wilhelm M, Seidel A, Brüning T (2005) Occupational exposure to polycyclic aromatic hydrocarbons in German industries: Association between exogenous exposure and urinary metabolites and its modulation by enzyme polymorphisms. Toxicol Lett 157: 241–255

Romanoff LC, Li Z, Young KJ, Blakely NC, Patterson DG Jr., Sandau CD (2006) Automated solid-phase extraction method for measuring urinary polycyclic aromatic hydrocarbon metabolites in human biomonitoring using isotope-dilution gas chromatography high-resolution mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 835: 47–54

Romundstad P, Haldorsen T, Andersen A (2000) Cancer incidence and cause specific mortality among workers in two Norwegian aluminum reduction plants. Am J Ind Med 37(2): 175-183.

Rossella F, Campo L, Pavanello S, Kapka L, Siwinska E, Fustinoni S (2009) Urinary polycyclic aromatic hydrocarbons and monohydroxy metabolites as biomarkers of exposure in coke oven workers. Occup Environ Med 66: 509–516

Sanderson E, Kelly P, Farant JP (2005) Effect of Søderberg smelting technology, anode paste composition, and work shift on the relationship between benzo[a]pyrene and individual polycyclic aromatic hydrocarbons. J Occup Environ 2(2): 65-72.

Santella RM, Perera FP, Young TL, Zhang YJ, Chiamprasert S, Tang D, Wang LW, Beachman A, Lin JH, DeLeo VA (1995) Polycyclic aromatic hydrocarbon–DNA and protein adducts in coal tar treated patients and controls and their relationship to glutathione S-transferase genotype. Mutat Res 334: 117–124

Sarkar M, Liu J, Koval T, Wang J, Feng S, Serafin R, Jin Y, Xie Y, Newland K, Roethig HJ (2010) Evaluation of biomarkers of exposure in adult cigarette smokers using Marlboro snus. Nicotine Tob Res 12: 105–116

Sartorelli P, Cenni A, Matteucci G, Montomoli L, Novelli MT, Palmi S (1999) Dermal exposure assessment of polycyclic aromatic hydrocarbons: in vitro percutaneous penetration from lubricating oil. Int Arch Occup Environ Health 72: 528–532

Sax NI, Lewis JR Sr. (1984) Dangerous properties of industrial materials, 7th ed, Van Nostrand Reinhold Co, New York, 2451–2452

Schoket B, Hewer A, Grover PL, Phillips DH (1988) 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: 1253–1258

Schulte A, Ernst H, Peters L, Heinrich U (1994) Induction of squamous cell carcinomas in the mouse lung after long-term inhalation of polycyclic aromatic hydrocarbon-rich exhausts. Exp Toxicol Pathol 45(7): 415-421

Scicchitano DA (2005) Transcription past DNA adducts derived from polycyclic aromatic hydrocarbons. Mutat Res 577: 146–154

Serdar B, Waidyanatha S, Zheng Y, Rappaport SM (2003) Simultaneous determination of urinary 1-and 2- naphthols, 3- and 9-phenanthrols and 1-pyrenol in coke oven workers. Biomarkers 8: 93–109

Simon P, Morele Y, Delsaut P, Nicot T (1999) Automated column-switching high-performance liquid chromatography method for the determination of 1-hydroxypyrene in human urine. J Chrom B 732: 91–101

Simon P, Lafontaine M, Delsaut P, Morele Y, Nicot T (2000) Trace determination of urinary 3- hydroxybenzo[a]pyrene by automated column-switching high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 748: 337–348

Simpson CD, Wu MT, Christiani DC, Santella RM, Carmella SG, Hecht S (2000) Determination of r-7,t-8,9,c-10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene in human urine by gas chromatography/negative ion chemical ionization/mass pectrometry. Chem Res Toxicol 13: 271–280

Smith WE (1956) Sebaceous gland activity as a measure of the relative carcinogenicity of certain oils and tars. New York Pathological Society 32: 77–78

Smith CJ, Walcott CJ, Huang W, Maggio V, Grainger J, Patterson Jr DG (2002) Determination of selected monohydroxy metabolites of 2-, 3- and 4-ring polycyclic aromatic hydrocarbons in urine by solid-phase microextraction and isotope dilution gas chromatography-mass spectrometry. J Chrom B 778: 157–164

Strickland, P., Kang, D. & Sithisarankul, P. (1996) Polycyclic aromatic hydrocarbon metabolites in urine as biomarkers of exposure and effect. Environ. Health Perspect., 104, 927–932

Suntzeff VA, Cowdry EV, Croninger A (1955) Microscopic visualization of the degeneration of sebaceous glands caused by carcinogens. Cancer Res 15: 637–640

SWE SWEA [The Swedish Work Environment Authority] (2011) The Swedish Work Environment Authority's provisions and general recommendations on occupational exposure limit values, Sweden. http://www.av.se/dokument/inenglish/legislations/eng1118.pdf

Thyssen J Althoff J, Kimmerle G, Mohr U (1980) Investigation of the carcinogenic burden of air pollution in man. XIX. Effect of inhaled benzo[a]pyrene in Syrian golden hamsters: A pilot study. Zentralbl Bakteriol Hyg I Abt Orig B 171: 441–444

Tremblay C, Armstrong B, Theriault 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(3): 335-348.

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(4): 395-403.

USA ACGIH [American Conference of Governmental Industrial Hygienists] (2012) TLVs and BEIs. Threshold limit values for chemical substances and physical agents and biological exposure indices. Appendix B. Cincinnati, OH, USA

USA NIOSH [National Institute for Occupational Safety and Health] (2007) Pocket guide to chemical hazards department of health and human services. Coal tar pitch volatiles. Centers for Disease Control and Prevention, USA. http://www.cdc.gov/niosh/npg/npgd0145.html. Accessed 2016.02.10

USA OSHA [Occupational Safety and Health Administration] (2006) Annotated PELS; Table Z1. Air Contaminants, USA. Coal tar pitch volatiles. https://www.osha.gov/dsg/annotated-pels/tablez-1.html. Accessed 2016.02.10

USEPA [US Environmental Protection Agency] (1989) Mouse oral subchronic toxicity of pyrene. Study No. 042-010, Washington, DC
Van der Bijl P, Gareis A, Lee H, van Eyk AD, Stander IA, Cilliers J (2002) Effects of two barrier creams on the diffusion of benzo[a]pyrene across human skin. J South African Dental Assoc 57: 49–52

Van Rooij JGM, Bodelier-Bade MM, Jongeneelen FJ (1993a) Estimation of individual dermal and respiratory uptake of polycyclic aromatic hydrocarbons in 12 coke oven workers. Br J ind Med 50: 623–632

Van Rooij JGM, van Lieshout EMA, Bodelier-Bade MM, Jongeneelen FJ (1993b) 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: 200–207

Verma N, Pink M, Rettenmeier AW, Schmitz-Spanke S (2012) Review on proteomic analyses of benzo[a]pyrene toxicity. Proteomics 12: 1731-1755

Wenzel-Hartung (1992) Teilvorhaben Kanzerogenitätsprüfung von umwelt- und arbeitsplatzrelevanten PAH nach intrapulmonaler Applikation bei Ratten. [Sub-project:

Carcinogenicity assessment of PAH of environmental and workplace relevance after intrapulmonary administration in rats]. Government Reports Announcements & Index 92: 172; as referenced by DFG (2012)

Wenzel-Hartung R, Brune H, Grimmer G, Germann P, Timm J, Wosniok W (1990) Evaluation of the carcinogenic potency of four environmental polycyclic aromatic compounds following intrapulmonary application in rats. Exp Pathol 40: 221–227

Weyand EH, Chen YC, Wu Y, Koganti A, Dunsford HA, Rodriguez LV (1995) Differences in the tumorigenic activity of a pure hydrocarbon and a complex mixture following ingestion: benzo[a]pyrene vs manufactured gas plant residue. Chem Res Toxicol 8(7): 949-954.

Wheeler LA, Saperstein MD, Lowe NJ (1981) Mutagenicity of urine from psoriatic patients undergoing treatment with coal tar and ultraviolet light. J. invest. Dermatol. 77: 181–185

White J, White A (1939) Inhibition of growth of the rat by oral administration of methylcholanthrene, benzpyrene, or pyrene and the effect of various dietary supplements. J Biol Chem 131: 149–161

Wolff RK, Griffith WC, Henderson RF, Hahn FF, Harkema JR, Rebar AH, Eidson AF, McClellan RO (1989) Effects of repeated inhalation exposures to 1-nitropyrene, benzo[a]pyrene, Ga_2O_3 particles, and SO_2 alone and in combination of particle clearance, bronchoalveolar lavage fluid composition, and histopathology. J Toxicol Environ Health 27: 123–138

Wu MT, Simpson CD, Christiani DC, Hecht SS (2002) Relationship of exposure to coke-oven emissions and urinary metabolites of benzo[a]pyrene and pyrene in coke-oven workers. Cancer Epidemiol Biomarkers Prev 11: 311–314

Xu X, Zhang J, Zhang L, Liu W, Weisel CP (2004) Selective detection of monohydroxy metabolites of polycyclic aromatic hydrocarbons in urine using liquid chromatography/triple quadrupole tandem mass spectrometry. Rapid Commun Mass Spectrom 18: 2299–2308

Yadav JS, Seth N (1998) Effect of polycyclic aromatic hydrocarbons on somatic chromosomes of coal tar workers. Cytobios 93. 165–173

Yamagiwa K, Ichikawa K (1915) Über die künstliche Erzeugung von Papilloma. Verh Jap Path Ges 5: 142–148

ANNEX 1: 1-Hydroxypyrene as a biomarker for PAH exposure

Annex Table 1: Urinary excretion of 1-hydroxypyrene (median or range) in control persons [compilation of DFG (2012)]

Persons exposed	Number	Country	1-Hydroxypyrene		References
			(µg/g creatinine)	(µg/l urine)	
general population	2747	United States	0.044	0.047	CDC 2005
women	1399		0.042	0.043	2001–2002
men	1348		0.046	0.055	2001–2002
general population	2312	United States	0.073	0.078	CDC 2003
women	1206		0.077	0.071	1999–2000
men	1106		0.070	0.085	1999–2000
general population					
non-smokers	389	Germany	0.08	0.10	UBA 1998
– West Germany	182			0.09	
– East Germany	45			0.11	
smokers	184		0.19	0.25	
general population	140	Canada	0.17		Viau et al. 1995 b
non-smokers	95		0.14		
smokers	45		0.23		
general population					UBA 1990
non-smokers		Germany			
– West Germany	75			0.12	
– East Germany	75			0.30	
general population	139	Germany	<0.04–0.13		Göen et al. 1995
non-smokers	80		<0.04–0.054		
smokers	59		<0.04–0.13		
general population	70	People's Republic of China	0.8–4.6		Zhao et al. 1990
general population		France			Lafontaine et al. 2006
non-smokers	27		0.06 (0.02–0.29)		
smokers	27		0.22 (0.08–1.02)		
general population	8	Germany		0.3	Grimmer et al. 1991 b
non-smokers	10	Germany	0.54±0.34[a]		Jacob et al. 1999 a
smokers	9		0.41±0.18[a]		
non-smokers	11	Germany	<0.1–0.3	<0.1–0.3	Angerer et al. 1992
smokers	11		<0.1–0.8	<0.1–0.8	
non-smokers	97	Germany	0.06–1.56		Gündel et al. 1996
smokers	27			0.18–1.50	

Annex Table 1 (continued)

Persons exposed	Number	Country	1-Hydroxypyrene		References
			(µg/g creatinine)	(µg/l urine)	
general population		Italy			Granella and Clonfero 1993
non-smokers	19		0.04		
smokers	20		0.08		
patients treated with tar ointment	8	Germany	0.94–5.81		Angerer et al. 1992
	25	Italy		7.60	Clonfero et al. 1989

[a] mean

Annex Table 2: Urinary excretion of 1-hydroxypyrene (median or range) in ocuupationally exposed persons [compilation of DFG (2012)]

Persons exposed	Number	Country	1-Hydroxypyrene		References
			(µg/g creatinine)	(µg/l urine)	
industrial plant	43		<0.l–0.8		Göen et al. 1995
meat smokehouse	13	Germany	<0.1–1.1	<0.1–1.1	Göen et al. 1995; Angerer et al. 1992
railway sleeper plants	14	Netherlands	0.4–8.7		Jongeneelen 1992
fire fighting (fire brigade)	43	Canada	<0.1–6.9		Caux et al. 2002
car repair shops		Italy			
non-smokers	40		0.07		Granella and
smokers	25		0.13		Clonfero 1993

Annex Table 2 (continued)

Persons exposed	Number	Country	1-Hydroxypyrene		References
			(µg/g creatinine)	(µg/l urine)	
different industries (total)	237	Germany	5.38 (0.12–279.63)		BGFA 2005; Jacob and Seidel 2002; Rossbach and Angerer 2002
production of graphite electrodes and special carbon products	71		8.65 (0.36–90.84)		
production of fireproof materials	68		11.27 (0.31–279.63)		
coking plant	47		4.30 (0.51–34.82)		
production of fireproof materials	24		4.98 (0.28–27.14)		
tar distillation	18		1.51 (0.31–5.08)		
fire damage restoration	5		0.46 (0.13–2.09)		
hydraulic engineering and corrosion protection	4		1.98 (0.83–7.88)		
production of graphite electrodes	34	Norway	19.7		Bentsen-Farmen et al. 1999
	67	Germany	8.7		Angerer et al. 1997 b
	67	Germany	0.2–326		Mannschreck et al. 1996
	23	Germany	7.1–125.0		Göen et al. 1995
	6	Germany	7.1–82.0	9.7–73.5	Angerer et al. 1992
	4		18.1–129.6	20.1–50.4	
	14		2.2–125.0	3.2–160.8	
	13		0.58–16.8		
coal-tar impregnation plants	3	Netherlands	1.3–38.5		Jongeneelen 1992
	1		80.9–158		
	3		8.2–134.9		
	6		4.8–146.5		
	9		1.2–55.9		
	3	Germany	7.1–41.2	12.7–77.1	Angerer et al. 1992

Annex Table 2 (continued)

Persons exposed	Number	Country	1-Hydroxypyrene		References
			(µg/g creatinine)	(µg/l urine)	
	3	Netherlands	1.0–9.1		Jongeneelen et al. 1986
creosote workers		Canada	3.14 (0.35–20.19)		Viau et al. 1995 b
coal tar distillation	4	Netherlands	2.3–25.1		Jongeneelen et al. 1986
coking plant	15	People's Republic of China	36.3		Zhao et al. 1990
	31	Sweden	15.9		Levin et al. 1995 a
	10		1.9–34.7		
oven topside area	24	Germany	3.3–79.4		Strunk et al. 2002
	8	Germany		14.1–118.5	Grimmer et al. 1993 b
charging-car driver	4	Germany		8.2–21.0	Grimmer et al.
machine operator	4			2.0–6.9	1993 b
aluminium smelter	5	Netherlands	2.3–17		Vu-Duc and Lafontaine 1996
	25	Germany	0.1–126.2		Göen et al. 1995
	37	Germany	0.7–126.2	0.2–99.2	Angerer et al. 1992
steelworks	12	People's Republic of China		3.5	Zhao et al. 1990
graphite oil treatment of glass forms	10	Germany	0.85 (0.1–3.8)	<0.1–4.2	Göen et al. 1995; Angerer et al. 1992
road construction					
road construction (in general)	49	Germany	0.22	0.18	Marczynski et al. 2006
	4	Germany		2.6	Grimmer 1993 c
	31	Netherlands	0.8–16.4		Jongeneelen et al. 1988
hot bitumen processing	66	Germany	0.44	0.30	Marczynski et al. 2006
petro bitumen processing	20	Germany		0.4–2.4	Knecht and Woitowitz 1989
coal-tar bitumen processing	12			5.3–92.1	
waste incineration					
municipal plant	53	Germany	<0.l–0.8	<0.1–1.3	Göen et al. 1995; Angerer et al. 1992

References to Annex 1 Tables

Angerer J, Schaller K-H, Lehnert G (1992) Bio-Monitoring von beruflichen Belastungen gegenüber polycyclischen aromatischen Kohlenwasserstoffen – Hochdruckflüssigkeitschromatographische Bestimmung des Metaboliten 1-Hydroxypyren im Harn, 4th International Colloquium Strasbourg, Oct. 22–23 1992; as referenced by DFG (2012)

Angerer J, Mannschreck C, Gündel J (1997 b) Biological monitoring and biochemical effect monitoring of exposure to polycyclic aromatic hydrocarbons. Int Arch Occup Environ Health 70: 365–377

Bentsen-Farmen RK, Botnen IV, Notø H, Jacob J, Vrebø S (1999) Detection of polycyclic aromatic hydrocarbon metabolites by high-pressure liquid chromatography after purification on immunoaffinity columns in urine from occupationally exposed workers. Int Arch Occup Environ Health 72: 161–168

BGFA [Berufsgenossenschaftliches Forschungsinstitut für Arbeitsmedizin] (2005) Abschlussbericht zum Forschungsvorhaben des HVBG: PAK-Belastung amArbeitsplatz – Reduzierung hoher innerer Belastung durch betriebliche Maßnahmen anhand von biochemischem Effekt-Monitoring. BGFA, Bochum; as referenced by DFG (2012)

CDC [Centers for Disease Control and Prevention] (2003) Second National Report on Human Exposure to Environmental Chemicals, National Center for Environmental Health, Atlanta, GA, USA, NCEH Pub. No 02–0716

CDC (2005) Third National Report on Human Exposure to Environmental Chemicals, National Center for Environmental Health, Atlanta, GA, USA, NCEH Pub. No 05–0570

Clonfero E, Zordan M, Venier P, Paleologo M, Levis AG, Cottica D, Pozzoli L, Jongeneelen FJ, Bos RP, Anzion RBM (1989) Biological monitoring of human exposure to coal tar. Urinary excretion of total PAH, 1-hydroxypyrene and mutagens in psoriatic patients. Int Arch Occup Environ Health 61: 363–369

Caux C, O'Brien C, Viau C (2002) Determination of firefighter exposure to polycyclic aromatic hydrocarbons and benzene during fire fighting using measurement of biological indicators. Appl Occup Environ Hyg 17: 379–386

Göen T, Gündel J, Schaller K-H, Angerer J (1995) The elimination of 1-hydroxypyrene in the urine of the general population and workers with different occupational exposure to PAH. Sci Total Environ 163: 195–201

Granella M, Clonfero E (1993) Urinary excretion of 1-pyrenol in automotive repair workers. Int Arch Occup Environ Health 65: 241–245

Grimmer G, Brune H, Dettbarn G, Jacob J, Mohtashamipur E, Norpoth K, Wenzel-Hartung R (1991 b) Urinary and faecal excretion of phenanthrene and phenanthrols by rats following oral, intraperitoneal, or intrapulmonary application. Polycyclic Aromat Compd 2: 39–47

Grimmer G, Dettbarn G, Jacob J (1993 b) Biomonitoring of polycyclic aromatic hydrocarbons in highly exposed coke plant workers by measurement of urinary phenanthrene and pyrene metabolites (phenols and dihydrodiols). Int Arch Occup Environ Health 65: 189–199

Grimmer G (1993 c) Relevance of polycyclic aromatic hydrocarbons as environmental carcinogens. In: Garrigues P, Lamotte M (Eds) Polycyclic Aromatic Compounds – Synthesis, Properties, Analytical Measurements, Occurrence and Biological Effects, Verlag Gordon & Breach, Yverdon, Schweiz, 31–41

Gündel J, Mannschreck C, Büttner K, Ewers U, Angerer J (1996) Urinary levels of 1–hydroxypyrene, 1-, 2-, 3-, and 4-hydroxyphenanthrene in females living in an industrial area of Germany. Arch Environ Contam Toxicol 31: 585–590

Jacob J, Grimmer G, Dettbarn G (1999 a) Profile of urinary phenanthrene metabolites in smokers and non-smokers. Biomarkers 4: 319–327

Jacob J, Seidel A (2002) Zwischenbericht zum Verbundvorhaben des HVBG: PAH-Belastung am Arbeitsplatz – Reduzierung hoher innerer Belastung durch betriebliche Maßnahmen anhand von Ambient und Biological Monitoring. Teilprojekt B: Bestimmung mehrfach-hydroxylierter PAH-

Metaboliten und der individuellen Suszeptibilität; as referenced by DFG (2012)

Jongeneelen FJ, Bos RP, Anzion RBM, Theuws JLG, Henderson PT (1986) Biological monitoring of polycyclic aromatic hydrocarbons: metabolites in urine. Scand J Work Environ Health 12: 137–143

Jongeneelen FJ, Scheepers PTJ, Groenedijk A, van Aerts LAGJM, Anzion RBM, Bos RP, Veenstra SJ (1988) Airborne concentrations, skin contamination, urinary metabolite excretion of polycyclic aromatic hydrocarbons among paving workers exposed to coal tar-derived road tars. Am Ind Hyg Assoc J 49: 600–607

Jongeneelen FJ (1992) Biological exposure limit for occupational exposure to coal tar pitch volatiles at coke ovens. Int Arch Occup Environ Health 63: 511–516

Knecht U, Woitowitz HJ (1989) Risk of cancer from the use of tar bitumen in road works. Br J Ind Med 46: 24–30

Lafontaine M, Chapmartin C, Simon P, Delsaut P, Funck-Brentano C (2006) 3-hydroxybenzo[a]-pyrene in the urine of smokers and non-smokers. Toxicol Lett 162: 181–185

Levin JO, Rhén M, Sikström E (1995 a) Occupational PAH exposure: urinary 1-hydroxypyrene levels of coke oven workers, aluminium smelter pot-room workers, road pavers, and occupationally non-exposed persons in Sweden. Sci Total Environ 163: 169–177

Mannschreck C, Gündel J, Angerer J (1996) Occupational exposure to PAHs – Biological monitoring of hydroxylated metabolites. Polycyclic Aromat Compd 11: 11–18

Marczynski B, Raulf-Heimsoth M, Preuss R, Kappler M, Schott K, Pesch B, Zoubek G, Hahn JU, Mensing T, Angerer J, Käfferlein HU, Brüning T (2006) Assessment of DNA damage in WBCs of workers occupationally exposed to fumes and aerosols of bitumen. Cancer Epidemiol Biomarkers Prev 15: 645–651

Rossbach B, Angerer J (2002) PAK-Belastung am Arbeitsplatz – Reduzierung hoher innerer Belastung durch betriebliche Maßnahmen anhand von Ambient und Biological Monitoring. Report of the results for the period from January 1999 to September 2001, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine of University of Erlangen-Nuremberg; as referenced by DFG (2012)

Strunk P, Ortlepp K, Heinz H, Rossbach B, Angerer J (2002) Ambient and biological monitoring of coke plant workers – determination of exposure to polycyclic aromatic hydrocarbons. Int Arch Occup Environ Health 75: 354–358

UBA [Umweltbundesamt] (1990) Umweltsurvey 1990/92. Data online under http://www.uba.de/

UBA [Umweltbundesamt] (1998) Umweltsurvey 1998. Data online under http://www.uba.de/

Viau C, Vyskocil A, Martel L (1995 b) Background urinary 1-hydroxypyrene levels in non-occupationally exposed individuals in the Province of Quebec, Canada, and comparison with its excretion in workers exposed to PAH mixtures. Sci Total Environ 163: 191–194

Vu-Duc TM, Lafontaine M (1996) 1-Hydroxypyrene in human urines as biomarker of exposure to PAH in work related processes in an aluminium production plant. Polycyclic Aromatic Compd 11: 1–9

Wagner M, Bolm-Audorff U, Hegewald J, Fishta A, Schlattmann P, Schmitt J, Seidler A (2015) Occupational polycyclic aromatic hydrocarbon exposure and risk of larynx cancer: a systematic review and meta-analysis. Occup Environ Med.;72(3):226-33.

Zhao ZH, Quan WY, Tian DH (1990) Urinary 1-hydroxypyrene as an indicator of human exposure to ambient polycyclic aromatic hydrocarbons in coal-burning environment. Sci Total Environ 92: 145–154

ANNEX 2: Cancer risk assessment derived from the study of Armstrong et al

Table 1: URR („Unit Relative Risks", calculated woth the log-linear model) for lung cancer in various industrial sectors or occupations with PAH exposure (Armstrong et al 2003, 2004; table taken from AGS (2011) as presented)

Group	Number of studies	Average URR* (95 % C. I.)	Test for heterogeneity (p-het)
All cohorts	39	**1.20 (1.11 – 1.29)**	0.007
According to sector / PAH source /occupation			
Coking plant	10	1.17 (1.12 – 1.22)	
Gasworks	4	1.15 (1.11 – 1.20)	
Aluminium production	8	1.16 (1.05 – 1.28)	
Summary of the three above sectors	22	**1.17 (1.12 – 1.22)**	> 0.20
Coal anodes	4	4.30 (0.81 – 22.79)	
Asphalt[2]	3	17.50 (4.21 – 72.78)	
Tar distillation	3	12.28 (0.48 – 314.4)	
Chimney sweeps	2	16.24 (1.64 – 160.7)	
Power plant	3	< 1000 (0 - > 1000)	
Carbon black production	2	0 (0 – 1000)	
Quantitative exposure data in the original study			
BaP	10	1.29 (1.11 – 1.49)	
Proxy[a]	6	1.16 (1.11 – 1.21)	
None	23	1.17 (1.03 – 1.33)	
Exclusion of less accurate estimates			
only URR with SE[b] < 10	31	1.20 (1.11 – 1.30)	0.002
only URR with SE < 1	19	1.18 (1.12 – 1.23)	0.19
Smoking behaviour			
adjusted	35	1.16 (1.11 – 1.21)	
non-adjusted	4	1.31 (1.16 – 1.48)	

*: URR = Relative risk in relation to a cumulative exposure of 100 µg BaP· (m^3 · years)$^{-1}$; data from Armstrong et al. (2003, 2004).

a: Calculated BaP concentration derived from concentration data for PAH, carbon black or BSM;

b: SE: Standard error

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