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Polycyclic aromatic hydrocarbons (PAHs) – Evaluation of EKA and a BAR

Assessment Values in Biological Material – Translation of the German version from 2013

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BAR (2012)

0.3 µg 1-hydroxypyrene (after hydrolysis)/g creatinine[a)]
Sampling time: end of exposure or end of shift; for long-term exposures: at the end of the shift after several previous shifts

EKA (2012)

The following correlation between external and internal exposure was obtained:

Air Benzo[a]pyrene [µg/m³]	Urine 3-Hydroxybenzo[a]pyrene (after hydrolysis) [ng/g creatinine]
0.07	0.7
0.35	2
0.7	3.5
1.0	5
1.5	7

Sampling time: at the beginning of the next shift

MAK value –

Absorption through the skin (2007) H

Carcinogenicity (2007) see Table 1

a) evaluated for non-smokers

Polycyclic aromatic hydrocarbons (PAHs) are formed by incomplete combustion of organic material and their presence in the environment is ubiquitous. Air pollution, barbecued and smoked foods, tobacco smoke and exhaust fumes are sources of exposure to which every human being is exposed. Thus, a background exposure of the general population is measurable. PAHs are found in the environment and at the workplace in the form of mixtures of up to 100 individual components. The relative distribution of an individual PAH in the PAH substance mixture varies markedly depending on the exposure source (IARC 2010).

A series of reviews and monographs have been published on the occurrence, absorption, distribution and toxicity of PAHs (ATSDR 1995; Hartwig 2012; IARC 2010; Jacob and Greim 2004; WHO 1998).

The Commission classifies 17 PAHs as carcinogenic in animal experiments (Category 2). Table 1 shows the classification by the Commission for selected PAHs and their physico-chemical properties (Hartwig 2012). To date, only benzo[a]pyrene as individual substance has been regarded as a human carcinogen (Category 1) by the International Agency for Research on Cancer (IARC) (IARC 2010).

Tab. 1 Classifications and physicochemical data of selected PAHs (according to Hartwig 2012)

Name CAS number	Carcinogen category	Germ cell mutagen category	Formula	Molar mass [g/mol]	Melting point [°C]	Boiling point [°C]	Vapour pressure at 25 °C [Pa]	Log K_{ow}
anthanthrene 191-26-4	2	–	$C_{22}H_{12}$	276.3	264	547	–	–
benzo[*b*]fluoranthene 205-99-2	2	3 B	$C_{20}H_{12}$	252.3	168.3	481	6.7×10^{-5}	6.12
benzo[*a*]anthracene 56-55-3	2	3 A	$C_{18}H_{12}$	228.3	160.7	400	2.8×10^{-5}	5.61
benzo[*j*]fluoranthene 205-82-3	2	3 B	$C_{20}H_{12}$	252.3	165.4	480	2.0×10^{-6}	6.12
benzo[*k*]fluoranthene 207-08-9	2	3 B	$C_{20}H_{12}$	252.3	215.7	480	1.3×10^{-8}	6.84
benzo[*b*]naphtho[2.1-*d*]thiophene 239-35-0	2	3 B	$C_{16}H_{10}S$	234.3	185–188	160–180 (3 Torr)	–	–
benzo[*a*]pyrene 50-32-8	2	2	$C_{20}H_{12}$	252.3	178.1	496	7.3×10^{-7}	6.50
chrysene 218-01-9	2	–	$C_{18}H_{12}$	228.3	253.8	448	8.4×10^{-5}	5.91
cyclopenta[*cd*]pyrene 27208-37-3	2	3 B	$C_{18}H_{10}$	226.3	170	439	–	–
dibenzo[*a,h*]anthracene 53-70-3	2	3 A	$C_{22}H_{14}$	278.4	266.6	524	1.3×10^{-8}	6.50
dibenzo[*a,l*]pyrene 191-30-0	2	3 B	$C_{24}H_{14}$	302.4	162.4	595	–	–
dibenzo[*a,e*]pyrene 192-65-4	2	3 B	$C_{24}H_{14}$	302.4	244.4	592	–	–
dibenzo[*a,h*]pyrene 189-64-0	2	3 B	$C_{24}H_{14}$	302.4	317	596	–	–
dibenzo[*a,i*]pyrene 189-55-9	2	3 B	$C_{24}H_{14}$	302.4	282	594	3.2×10^{-10}	7.3
indeno[1,2,3-*cd*]pyrene 193-39-5	2	–	$C_{22}H_{12}$	276.3	163.6	536	1.3×10^{-8}	6.58

Tab. 1 *(continued)*

Name CAS number	Carcinogen category	Germ cell mutagen category	Formula	Molar mass [g/mol]	Melting point [°C]	Boiling point [°C]	Vapour pressure at 25 °C [Pa]	Log K_{ow}
naphthalene 91-20-3	2	3 B	$C_{10}H_8$	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 2381-21-7	2	–	$C_{17}H_{12}$	216.3	70–71	410	–	–

The IARC classifies the following occupational exposures in Category 1: coal gasification, coke production, coal-tar distillation, aluminium production, chimney sweeping, paving and roofing with coal-tar pitch (IARC 2010). PAH mixtures occurring in pyrolysis products from organic material (such as brown carbon and mineral coal-tar, mineral coal-tar pitch, mineral coal-tar oil and raw coking gas) are also regarded as carcinogenic in humans (Category 1) by the Commission (DFG 2012).

In the present documentation, both a biological reference value (BAR) and exposure equivalents for carcinogenic substances (EKA) are evaluated, in which 1-hydroxypyrene and 3-hydroxybenzo[a]pyrene are applied as parameters in biological materials. For 1-hydroxypyrene as a metabolite of pyrene, comprehensive data are available and the analytical method for its determination is established. On the other hand, 3-hydroxybenzo[a]pyrene, as metabolite of the carcinogenic benzo[a]pyrene, has particular toxicological relevance.

1 Metabolism and Toxicokinetics

1.1 Absorption and distribution

Absorption of PAHs can occur via the lungs, through the skin and by ingestion (WHO 1998).

The PAHs occurring freely or bound to particles, which depends on the boiling point, can be absorbed by inhalation. Depending on the particle diameter, the inhaled particles are deposited in different parts of the airways (Marquardt and Schäfer 2004, p. 89–99). The absorption rate of PAHs in the lungs depends on the PAH type, the size of the particles with which they are absorbed, and the composition of the particles (WHO 1998).

Owing to their lipophilic character, PAHs pass readily through the skin so that, particularly for persons exposed to PAHs occupationally, dermal absorption represents an important route of absorption (Fustinoni et al. 2010; van Rooij et al. 1992, 1993 a, b). After ingestion, absorption is low. Only about 10% of the benzo[a]pyrene ingested with the food is absorbed in the gastrointestinal tract of humans, whereas the greater part passes through without being absorbed. After absorption, higher levels of PAHs are found in the liver, kidneys and adipose tissue than in the blood, CNS and muscle tissue. Within three to four days, redistribution takes place, resulting in increased concentrations in the adipose tissue, adrenal glands, lymph nodes and ovaries. In these organs, PAHs can still be detected months after exposure (Marquardt and Schäfer 2004, p. 592–601).

1.2 Metabolism

The lipophilic character of the PAHs prevents a direct elimination of the absorbed compounds. In a complex metabolism, the PAHs are converted into compounds which are more readily soluble in water and are better elim-

inated. Because of the structural similarities of the PAHs, their biotransformation processes are also very similar (ATSDR 1995).

In the phase I metabolism, the original substance is converted to intermediary epoxides by cytochrome P450 (CYP)-dependent monooxygenases. This reaction represents a bioactivation. Arene oxides can be metabolised to vicinal dihydrodiols by microsomal epoxide hydrolases. A second oxidation of the dihydrodiol by CYP-dependent monooxygenases causes biotransformation to the dihydrodiol epoxide. Bay- and Fjord-region dihydrodiol epoxides are particularly reactive and can react with endogenous macromolecules. They are therefore considered to be the ultimate carcinogens in the PAH metabolism (Hartwig 2012; Marquardt and Schäfer 2004, p. 592–601).

Furthermore, the arene oxides can be converted into less reactive dihydrodiols and phenols and the derivatives of dihydrodiols, i.e. the dihydrodiol epoxides, into tetrols.

In phase II of the biotransformation, these hydroxylated compounds are conjugated by sulfotransferases and UDP glucuronosyl transferases to sulfates and glucuronides, which increases their water solubility. In rodents, an additional conversion of the arene oxides to glutathione conjugates by glutathione S-transferase could be demonstrated, whereby after cleavage of glycine and glutamic acid residues and subsequent acetylation, elimination as mercapturic acids occurs. It remains to be seen whether this route of elimination is also of significance for humans (Hartwig 2012; Jacob and Greim 2004).

Of all PAHs, the metabolism of benzo[a]pyrene has been investigated most extensively. Figure 1 gives a survey of selected biotransformations of benzo[a]pyrene.

In the literature, the metabolites of pyrene and phenanthrene are mainly used to characterise internal exposure of humans to PAHs.

In the metabolism of pyrene, 1-hydroxypyrene represents a major metabolite in mammals (Hansen et al. 2008). In humans, most of the 1-hydroxypyrene reacts to form the corresponding 1-hydroxypyrene glucuronide (Strickland et al. 1994). In the metabolism of pyrene, 1-hydroxypyrene can be further oxidised enzymatically to form 1,6- and 1,8-dihydroxypyrene. These metabolites, which are in a steady state with the corresponding pyrene quinones, could also be detected in human urine (Ruzgyte et al. 2005; Seidel et al. 2008). In the general population, an elimination of 1,8-dihydroxypyrene at the same or higher concentrations than those of 1-hydroxypyrene could be demonstrated. Very high PAH exposures at the workplace shift the pyrene metabolism in favour of 1-hydroxypyrene (Seidel et al. 2008).

As metabolites of phenanthrene, 1-, 2-, 3-, 4- and 9-hydroxyphenanthrene have been analysed in human urine (Becker et al. 2003; Heudorf and Angerer 2001 a; Jacob et al. 1999; Martin et al. 1989). In addition, phenanthrene dihydrodiols (Jacob et al. 1999; Seidel et al. 2008) and phenanthrene tetrol (Hecht et al. 2003) could be detected. Whereas the elimination of the monohydroxylated metabolites of the non-carcinogenic phenanthrene represents a detoxification reaction, the formation of phenanthrene tetrol can be regarded as a surrogate for the metabolic activation of PAHs, as the enzyme reactions take place in analogy to those with carcinogenic PAHs such as benzo[a]pyrene (Hartwig 2012; Hecht et al. 2003).

To determine exposure to carcinogenic PAHs, the hydroxylated metabolites of benzo[a]pyrene, benzo[a]anthracene, chrysene and naphthalene were analysed. As a metabolite of benzo[a]pyrene, 3-hydroxybenzo[a]pyrene could be detected in the urine of persons with occupational exposure to PAHs, but also in the general population (Barbeau et al. 2011; Förster et al. 2008; Lafontaine et al. 2004, 2006; Leroyer et al. 2010).

Benzo[a]pyrene tetrols are the metabolic derivatives of the ultimate carcinogen 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene. Using sensitive GC-MS methods, benzo[a]pyrene tetrols were detected in the urine of heavy smokers and persons exposed occupationally to PAHs, but also in the urine of non-smokers (Simpson et al. 2000; Zhong et al. 2011).

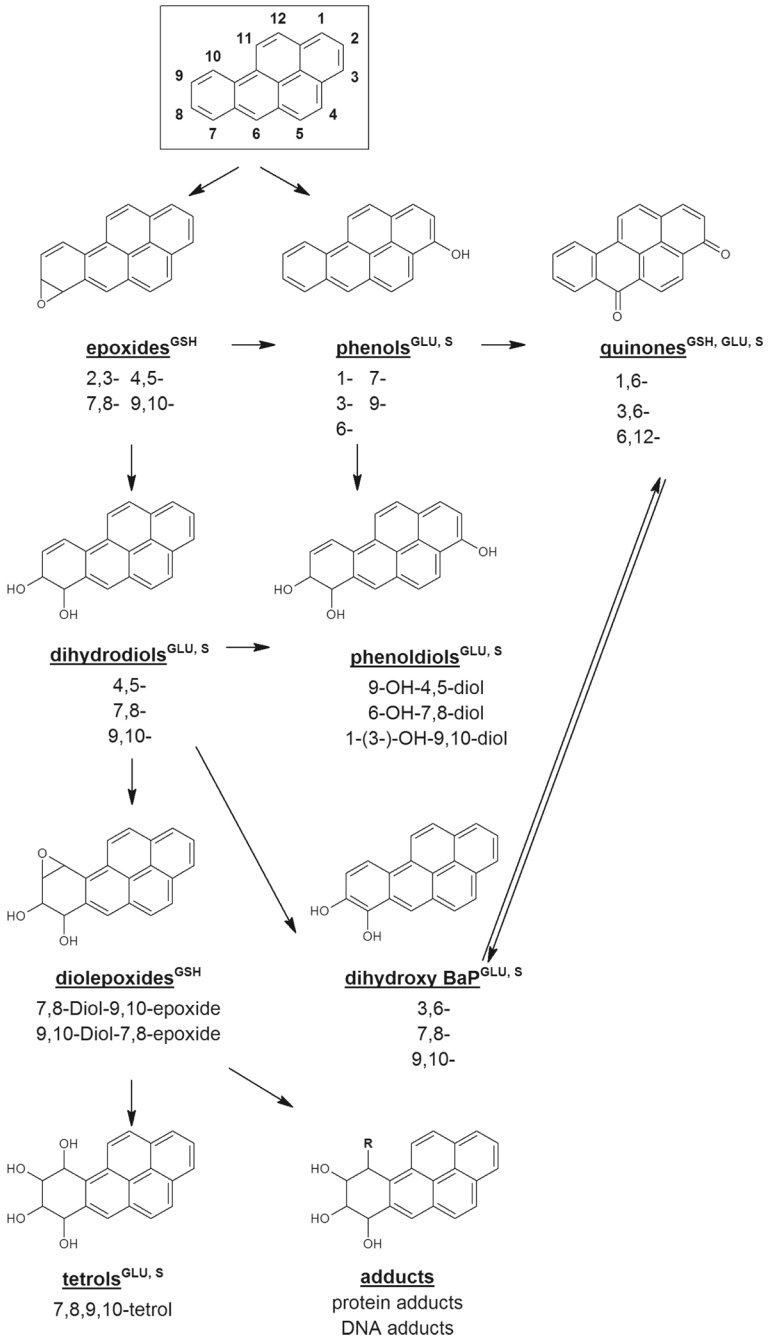

Fig. 1 Reaction paths of benzo[a]pyrene (modified according to ATSDR 1995; Marquardt and Schäfer 2004, p. 592–601; Simpson et al. 2000). Possible conjugation partners: GSH (glutathione), GLU (glucuronic acid), S (sulfate)

Reactive PAH metabolites can bind to proteins such as albumin and haemoglobin as well as to DNA. Different methods for the quantification of these adducts have been published and been discussed in reviews (Jongeneelen 1997; Käfferlein et al. 2010).

1.3 Elimination

In humans, water-soluble metabolites with a molar mass of < 475 g/mol are preferably excreted with the urine, those with higher molar masses preferably with the faeces (Marquardt and Schäfer 1994, p. 49). Correspondingly, the elimination of higher condensed PAHs takes place mainly via the bile through the faeces. Only a small part is excreted with the urine.

In an enterohepatic circulation, in rodents, biliary secreted sulfates, glucuronides and glutathione conjugates of PAH metabolites can be cleaved again in the intestine and then be reabsorbed (Marquardt and Schäfer 2004, p. 89–99; Ramesh et al. 2004; van Schooten et al. 1997). In rats, only low concentrations of absorbed PAHs are excreted in unchanged form, the major part is metabolised and subsequently eliminated via faeces and urine (van Schooten et al. 1997). The individual PAHs have different elimination kinetics. 1-Hydroxypyrene is subject to a biphasic urinary elimination kinetics with an initial half-life of several hours up to two days and a second half-life of 16 days (Jongeneelen et al. 1988). After the uptake of pyrene via the food or skin by test persons, the maximum urinary excretion of 1-hydroxypyrene was determined to be after about 12 hours (Viau and Vyskocil 1995). In persons occupationally exposed to PAHs, the 3-hydroxybenzo[a]pyrene urinary excretion peak was found to occur 10 to 17 hours after 1-hydroxypyrene elimination (Gendre et al. 2002; Lafontaine et al. 2004).

Figure 2 shows the differences in the elimination kinetics of 1-hydroxypyrene and 3-hydroxybenzo[a]pyrene in persons occupationally exposed to PAHs.

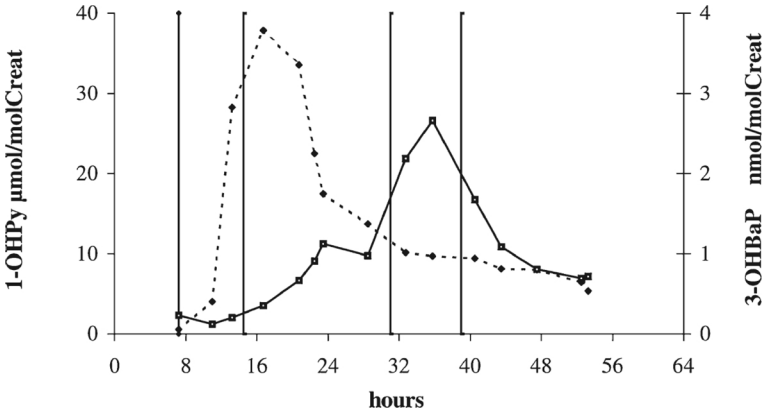

Fig. 2 1-Hydroxypyrene (- -●- -) and 3-hydroxybenzo[a]pyrene (–□–) urinary concentration profiles of a worker at a carbon brake disk plant (Lafontaine et al. 2004, reprinted by permission of Taylor & Francis Ltd, http://www.tandfonline.com)

2 Critical Toxicity

PAHs and substance mixtures containing PAHs have a low acute toxicity (WHO 1998). Carcinogenicity is considered to be the critical end point after occupational exposure to PAHs. Occupational exposure to PAHs is mainly by inhalation and through the skin (Hartwig 2012). Exposed persons have a significantly increased incidence of various types of cancer, primarily in the lungs and skin. The findings indicative of cancer in other organs such as bladder, kidneys, larynx, oesophagus and stomach are less consistent and cannot be clearly evaluated due to possible exposures to a mixture of substances and inadequate data (Boffetta et al. 1997).

More detailed information on the toxicity of PAHs in animal experiments and in humans can be found in the corresponding MAK value documentation (Hartwig 2012).

3 Exposure and Effects

3.1 Relationship between external and internal exposure

With regard to environmental PAH exposures, no or only weak relationships between external and internal PAH exposure from the measurement of PAHs in the air and 1-hydroxypyrene in urine have been determined (Aquilina et al. 2010; Leroyer et al. 2010; Li et al. 2010).

At workplaces with PAH exposure, the exposure of workers can increase far beyond the background exposure. The PAH profiles vary depending on the workplace. Even in a particular branch of industry, clear differences in the internal exposure of the workers can occur in spite of almost identical external exposure to PAHs in the air. As cause, apart from inhalation absorption, dermal absorption has to be considered (Hartwig 2012). The dermal absorption of PAHs can contribute considerably to the total exposure (Fustinoni et al. 2010; Gündel et al. 2000; McClean et al. 2004; Väänänen et al. 2005). For this reason, estimation of PAH exposure in the workplace air alone is insufficient. In human biomonitoring, the PAHs absorbed via different routes (inhalation, through the skin and by ingestion) can be recorded by quantifying specific metabolites in urine. Correlations between the measured PAH concentration in the workplace air and the metabolite concentration in urine are only obtained when persons with dermal exposure are not included in the analysis (Unwin et al. 2006).

A French working group compared 3-hydroxybenzo[a]pyrene concentrations in the urine of persons exposed to PAHs with the benzo[a]pyrene concentrations determined by personal air sampling (Lafontaine et al. 2004). In this study, 38 workers were investigated, who had been active at different workplaces with PAH exposure. Urine samples were collected over a period of more than 48 hours from a time before the shift on the first working day up to a time before the shift on the third working day. The working periods were in a range between 4.4 and 10.4 hours (average value 7.3 hours).

In the investigation of the relationship between external and internal exposure, only those persons were included ($n = 21$) who were mainly exposed to PAHs by inhalation. In these cases, benzo[a]pyrene concentrations in the range between 0.024 and 19.4 µg/m³ were determined in the air. Maxima of 3-hydroxybenzo[a]pyrene excretion in the range of 0.23 to 35 nmol/mol creatinine (0.55 to 83 ng/g creatinine) were found. A close correlation between the concentrations of benzo[a]pyrene in the air and 3-hydroxybenzo[a]pyrene in urine was observed ($n = 21$; $r = 0.95$; $p < 0.0001$).

For the calculation of a function between external and internal exposure at the workplace, benzo[a]pyrene (BaP) concentrations above 5000 ng/m³ were not included and the 3-hydroxybenzo[a]pyrene (3-OH-BaP) concentrations related to an 8-hour exposure. The regression equation was given as

$$c\ (\text{3-OH-BaP}\ [\text{nmol/mol creatinine}]) = 0.001835 \times c\ (\text{BaP}\ [\text{ng/m}^3]) + 0.1729$$

($n = 17$; $r = 0.89$; $p < 0.0001$).

This equation takes into consideration the background exposure resulting from diet, smoking behaviour and exposure during preceding work weeks. The background exposure was given with values of 0.01 to 0.52 nmol/mol creatinine (0.02 to 1.23 ng/g creatinine) (Lafontaine et al. 2004).

Using this equation, the 3-hydroxybenzo[a]pyrene concentrations listed in Table 2 for selected air concentrations during an 8-hour exposure, predominantly by inhalation, are obtained.

Tab. 2 Relationship between benzo[a]pyrene in the air and 3-hydroxybenzo[a]pyrene in urine for an exposure predominantly by inhalation

Air	Urine
Benzo[a]pyrene	3-Hydroxybenzo[a]pyrene (after hydrolysis)
[µg/m³]	[ng/g creatinine]
0.07	0.71
0.35	1.93
0.7	3.46
1.0	4.76
1.5	6.94

Sampling time is at the beginning of the next shift (16 hours after the end of exposure) (Gendre et al. 2002, 2004).

In a further study, in which the concentrations of benzo[a]pyrene in the air and 3-hydroxybenzo[a]pyrene in urine were analysed, no differentiation was made between inhalation and dermal PAH uptake or concerning the wearing of a breathing mask in the investigated workplaces (Förster et al. 2008). No or only weak correlations between the parameters could be found (r = 0.308 to 0.665). Studies in which, in addition to exposure by inhalation, dermal PAH absorption also occurred or breathing masks were worn, are subject to additional uncertainty and therefore less suitable for the derivation of an EKA correlation.

The relationship between benzo[a]pyrene in the air and 1-hydroxypyrene in urine as biomonitoring parameter has been discussed in the literature (ACGIH 2005; Gündel and Angerer 1999; Unwin et al. 2006). The relative distribution of the individual PAHs in the PAH mixture deviates considerably in different industries. Depending on the workplace, the ratio between pyrene and benzo[a]pyrene can vary by factors of 1.1 up to more than 100 (ACGIH 2005; Lafontaine et al. 2004). The American Conference of Governmental Industrial Hygienists (ACGIH) draws attention to this problem and gives a benchmark level of 1 µg 1-hydroxypyrene/l urine, which is defined in a standard pyrene to benzo[a]pyrene ratio of 2.5 (as in coke plants and in mineral carbon pitchblende processing). The determination of the exact ratio between pyrene and carcinogenic PAHs for each exposure source and a calculation of the adapted reference values depending on the pyrene to benzo[a]pyrene ratio is recommended (ACGIH 2005).

Other authors draw attention to the fact that the PAH profiles deviate not only between the individual emission sources, but also time-dependently at specific workplaces, so that an extrapolation of the concentrations for phenanthrene and pyrene on the basis of the measured benzo[a]pyrene concentrations is not generally possible (Jacob and Greim 2004).

Owing to the different compositions of PAHs in substance mixtures at different workplaces and, in addition to this, the frequently occurring dermal uptake of PAHs, it does not seem useful to evaluate an EKA correlation for benzo[a]pyrene in the air and 1-hydroxypyrene in urine.

3.2 Relationship between internal exposure and effects

To date, protein adducts and DNA adducts have mainly been investigated using benzo[a]pyrene as a model substance. A review by Käfferlein et al. (2010) gives an overview of the methods for determining benzo[a]pyrene adducts in human haemoglobin and serum albumin as well as of the results from determinations in persons from the general population and following occupational PAH exposure. DNA adducts of benzo[a]pyrene can be quantified for reactive metabolites such as (+)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide (Pastorelli et al. 2002; Pratt et al. 2011; Rojas et al. 1995).

To characterise the genotoxic effects caused by PAH exposure, the parameters DNA strand breaks and alkali labile side chains are related to PAH metabolites such as 1-hydroxypyrene and hydroxylated phenanthrenes (Cavallo et al. 2006; Marczynski et al. 2007, 2011; Pesch et al. 2007; Qiu et al. 2007; Wilhelm et al. 2007). However, these biological effects are not specific to PAH exposure, so that the effects of additional genotoxic substances or of oxidative stress must also be considered (Angerer et al. 2007).

4 Selection of Indicators

For human biomonitoring following PAH exposure, mainly pyrene- and phenanthrene metabolites are used. The determination of 1-hydroxypyrene as biomarker is widespread (Hansen et al. 2008; Hartwig 2012). Of the phenanthrene metabolites, 1-, 2-, 3-, 4- and 9-hydroxyphenanthrene are mainly used as parameters (Hartwig 2012).

Owing to the low toxicity of the pyrenes and of phenanthrene, however, neither the pyrene nor the phenanthrene metabolites reflect internal exposure to carcinogenic PAHs. From the results obtained for pyrene and phenanthrene metabolites, it is not possible to estimate the concentration of carcinogenic PAH metabolites, as the relative composition of the PAH mixtures show strong fluctuations. For example, the ratio between pyrene and benzo[a]pyrene can vary depending on the workplace by factors between 1.1 and more than 100 (ACGIH 2005; Lafontaine et al. 2004).

Therefore, efforts have been made to use the metabolites of toxicologically more relevant substances such as benzo[a]pyrene, benzo[a]anthracene or chrysene for human biomonitoring. However, higher condensed PAHs are not eliminated preferably via the urine, but via the faeces, resulting in the problematic fact that only extremely low concentrations of metabolites are available in the urine.

Special importance is attributed to 3-hydroxybenzo[a]pyrene as a metabolite of the carcinogen benzo[a]pyrene (Angerer et al. 2007; Barbeau et al. 2011; Gündel et al. 2000; Simon et al. 2000). In addition, methods for the determination of the hydroxylated PAH metabolites of benzo[a]anthracene, benzo[c]phenanthrene, chrysene, fluorene, fluoranthene and naphthalene have been developed (Bouchard et al. 2009; CDC 2005; Onyemauwa et al. 2009; Smith et al. 2002; Xu et al. 2004).

For a biochemical effect monitoring, the protein adducts and DNA adducts of PAHs are determined. For this purpose, different analytical methods are available, especially for the determination of DNA adducts in lymphocytes and lung tissue as well as of haemoglobin and serum albumin adducts of benzo[a]pyrene. However, currently these methods are considered to be not yet sufficiently specific and sensitive for diagnosis (Jacob and Greim 2004; Jongeneelen 1997; Käfferlein et al. 2010).

5 Analytical Methods

The analysis of hydroxylated metabolites of pyrene, phenanthrene and other PAHs is carried out in urine. The methods include enzymatic hydrolysis with subsequent purification in the form of a liquid-liquid extraction (Jacob et al. 2007; Li et al. 2006; Rossella et al. 2009; Serdar et al. 2003), of a solid-phase extraction (Hagedorn et al. 2009; Romanoff et al. 2006; Xu et al. 2004), a solid-phase microextraction (Gmeiner et al. 1998; Smith et al. 2002) or coupled-column techniques (Lintelmann et al. 1994). As sufficiently sensitive analytical separation techniques for quantification, the following methods are used: HPLC (high performance liquid chromatography) with fluorescence 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 et al. 2007; Onyemauwa et al. 2009; Ramsauer et al. 2011; Xu et al. 2004) and gas chromatography with mass spectrometry (GC-MS) after derivatization of the hydroxylated PAH metabolites (Li et al. 2006; Romanoff et al. 2006; Smith et al. 2002).

The MAK Commission's working group "Analyses of Hazardous Substances in Biological Materials" has published a tested analytical method (Lintelmann and Angerer 1999) for the determination of PAH metabolites in urine. Here, the monohydroxylated metabolites of phenanthrene (1-, 4- and 9-hydroxyphenanthrene) and pyrene

(1-hydroxypyrene) are released from their conjugates in the urine by enzymatic hydrolysis, afterwards separated from matrix components by two-dimensional HPLC, and quantified with a fluorescence detector. After further refinement, this method allows the determination of metabolite concentrations of hydroxypyrene and of 1-, 2-, 3-, 4- and 9-hydroxyphenanthrene at a detection limit of 5 ng metabolite/l urine each, so that an application is possible not only for concentration ranges required in occupational medicine, but also for those in environmental medicine (Heudorf and Angerer 2001 a).

For the parameter 3-hydroxybenzo[a]pyrene in urine, analytical methods with detection limits in the low ng/l range have been developed over recent years, which have also been used for determinations in persons in the general population who were not occupationally exposed (Barbeau et al. 2011; Romanoff et al. 2006; Sarkar et al. 2010; Simon et al. 2000). In these methods, the urine is purified after enzymatic hydrolysis using solid phase extraction (Barbeau et al. 2011; Romanoff et al. 2006; Sarkar et al. 2010) or column switching (Simon et al. 2000). The analytical separation and quantification is achieved using HPLC-FD (Barbeau et al. 2011; Simon et al. 2000), gas chromatography coupled with high-resolution mass spectrometry (GC-HRMS) (Romanoff et al. 2006) or LC-MS/MS (Sarkar et al. 2010).

6 Background Exposure

6.1 1-Hydroxypyrene

In the literature, there are many publications available for 1-hydroxypyrene as parameter for the characterization of internal PAH exposure. Various reviews have been published (Hansen et al. 2008; Hartwig 2012; UBA 2005). Table 3 gives an overview of more recent studies with larger numbers of volunteers, in which the urinary 1-hydroxypyrene excretion of the general population was analysed.

Tab. 3 1-Hydroxypyrene levels in the urine of persons not occupationally exposed to PAHs

Analytics	Collective (year of sampling) age, sex	n NS/S	NS		S		References
			Med/P95 (range) [µg/l]	Med/P95 (range) [µg/g creatinine]	Med/P95 (range) [µg/l]	Med/P95 (range) [µg/g creatinine]	
Germany							
HPLC-FD QL 0.012 µg/l	general population (1998) 18–69 years, 289 ♂, 284 ♀	389/184	0.10/0.53 (< QL–1,68)	0.08/0.29 (< QL–0.90)	0.25/1.03 (< QL–4.38)	0.19/0.73 (< QL–1.99)	Becker et al. 2002
HPLC-FD DL 0.005 µg/l	inhabitants of former American Forces housing (1998) 20–64 years, 40% ♂, 60% ♀	288/100		0.08/0.26 (< DL–1.17)		0.15/0.54 (< DL–0.72)	Heudorf and Angerer 2001 b
HPLC-FD DL 0.012 µg/l	housewives (n. d.) 53–58 years, ♀	97/27		0.15/0.46 (0.06–1.56)		0.48/1.45 (0.18–1.50)	Gündel et al. 1996
HPLC-FD DL 0.05 µg/l	general population (1990–1995)	28/21		0.12/0.33 (< 0.04–0.33)		0.23/0.55 (< 0.04–1.31)	Göen et al. 1995
HPLC-FD DL 0.05 µg/l	general population (1990–1995)	49/20		< 0.04/0.38 (< 0.04–0.54)		0.28/0.52 (< 0.04–0.60)	
HPLC-FD DL 0.012 µg/l	general population (1996) 18–70 years, 41 ♂, 28 ♀	42/27	0.16/– (0.05–0.46) µg/24 h		0.35/– (0.11–1.16) µg/24 h		Scherer et al. 2000

Tab. 3 *(continued)*

Analytics	Collective (year of sampling) age, sex	n NS/S	NS		S		References
			Med/P95 (range) [µg/l]	Med/P95 (range) [µg/g creatinine]	Med/P95 (range) [µg/l]	Med/P95 (range) [µg/g creatinine]	
LC-MS/MS QL 0.025 µg/l	general population 22–77 years, 72 ♂, 78 ♀, abstaining from barbecued, smoked and fried foods	50/100	0.05/– (0.02–0.38)		0.15/– (0.03–0.58)		Ramsauer et al. 2011
Italy							
HPLC-FD DL 0.05 µg/l	general population 22–81 years, 183 ♂, 236 ♀	327/92		0.15/0.65 (–)		0.33/1.06 (–)	Roggi et al. 1997
France							
HPLC-FD DL 0.005 µg/l	general population 18–65 years, ♂ 24-h urine	27/27		0.06/– (0.02–0.29)[b]		0.22/– (0.08–1.02)[b]	Lafontaine et al. 2006
HPLC-FD DL 0.020 µg/l	general population 18–65 years, ♂	23/13		0.07/– (0.01–0.32)[b]		0.26/– (0.06–0.64)[b]	Barbeau et al. 2011
USA							
GC-HRMS DL 0.005 µg/l	general population (2003/2004), > 20 years, ♂ + ♀	1477[a]	0.08/0.55 (–)[a]	0.07/0.42 (–)[a]			CDC 2009
GC-HRMS DL 0.003 µg/l	general population (2001/2002), > 20 years, ♂ + ♀	1625[a]	0.05/0.36 (–)[a]	0.04/0.23 (–)[a]			CDC 2005
GC-HRMS DL 0.002 µg/l	general population (1999/2000) > 20 years, ♂ + ♀	1309[a]	0.07/0.80 (–)[a]	0.07/0.54 (–)[a]			
Canada							
HPLC; GC-MS DL n. d.	general population	95/45		0.17/0.62 (–)[a, b] 0.14 (GM NS)		0.23 (GM S)	Viau et al. 1995
UPLC-MS-TOF DL 0.007 µg/l	general population (2005/2006) 16–64 years, 19 ♂, 52 ♀	50[a]		0.08/0.29 (< DL–0.63)[a, b, c]			Bouchard et al. 2009

[a] smoking status not taken into account
[b] calculated from µmol/mol creatinine with 1 µmol/mol creatinine = 1.93 µg/g creatinine
[c] data from sampling on 23 May 2006 (highest median/P95 for the control group of all samplings)
DL = detection limit of the analytical method; GC-HRMS = gas chromatography with high-resolution mass spectrometry; GM = geometric mean; HPLC-FD = high performance liquid chromatography with fluorescence detection; LC-MS/MS = high performance liquid chromatography with tandem mass spectrometric detection; max = maximum; Med = median; n. d. = no details; NS = non-smokers; n = number of study participants; P95 = 95th percentile; QL = quantification limit; S = smokers; UPLC-MS-TOF = ultra performance liquid chromatography with time of flight mass spectrometry

1-Hydroxypyrene excretion levels are significantly affected by the smoking status. Smokers are found to have urinary 1-hydroxypyrene concentrations which are about two to three times as high as those in non-smokers (Barbeau et al. 2011; Heudorf and Angerer 2001 a; Huang et al. 2006; Jacob et al. 1999; Pastorelli et al. 1999; van

Rooij et al. 1994). The level increases with the number of cigarettes smoked (Heudorf and Angerer 2001 b; Pastorelli et al. 1999).

As, in the present documentation, a BAR assessing the exposure of workers in Germany is to be derived, mainly German studies are used for the evaluation. Data given in µmol/mol creatinine were converted into µg/g creatinine for better comparability.

Representative data on the urinary 1-hydroxypyrene excretion in the German general population were presented in the environmental survey of 1998 (Becker et al. 2002). In this study, the PAH metabolites 1-hydroxypyrene and 1-, 2-, 3- and 9-hydroxyphenanthrene were determined in the morning urine of a randomly selected collective of 284 women and 289 men aged between 18 and 69 years. The 1-hydroxypyrene levels in the non-smoking population in Germany were in a range below the detection limit up to 0.90 µg/g creatinine with a median of 0.08 µg/g creatinine (95th percentile: 0.29 µg/g creatinine). With a median of 0.19 µg/g creatinine, the 1-hydroxypyrene concentrations excreted by smokers were about two to three times as high (95th percentile: 0.73 µg/g creatinine). A statistically significantly higher average level of 1-hydroxypyrene in relation to the urine volume was found in men compared with women.

As men excreted more creatinine per volume, there was no difference in the excretion of 1-hydroxypyrene between men and women when related to creatinine. A further factor influencing 1-hydroxypyrene excretion is heating. If the apartment was not heated via a central heating system, higher urinary 1-hydroxypyrene levels were determined (Becker et al. 2002).

In a study involving 1213 children and adults living in houses with a parquet floor containing coal tar parquet glue, high PAH levels were found (Heudorf and Angerer 2001 a). An increase in internal PAH exposure compared with persons from households without parquet glue containing PAHs could not be established. In the case of 289 non-smoking adults with a median of 0.08 µg/g creatinine and a 95th percentile of 0.26 µg/g creatinine, urinary 1-hydroxypyrene excretion levels were similar to those in the environmental survey (Becker et al. 2002). Smokers had levels two times as high as those in non-smokers (Heudorf and Angerer 2001 a).

Other German studies determined median levels for 1-hydroxypyrene below the detection limit and 0.15 µg/g creatinine and 95th percentiles of 0.33 and 0.46 µg/g creatinine, respectively. With medians of 0.23 and 0.48 µg/g creatinine, respectively, smokers showed urinary concentrations which were two to three times as high (Göen et al. 1995; Gündel et al. 1996).

In 50 non-smokers, median concentrations (range) of 0.05 µg/l urine (0.02–0.38 µg/l), in smokers 0.15 µg/l (0.03–0.58 µg/l) were measured (Ramsauer et al. 2011). The PAH uptake of the study participants with the diet was, however, reduced due to abstaining from barbecued, smoked and fried foods.

In an Italian study, median levels (95th percentile) of 0.15 µg/g creatinine (0.65 µg/g creatinine) were found in 327 non-smoking test persons (Roggi et al. 1997). On the other hand, the results in two French studies on 23 and 27 non-smokers with medians of 0.07 and 0.06 µg/g creatinine, respectively, (maximum 0.32 and 0.29 µg/g creatinine) were markedly lower. In smokers, the urinary concentrations of 1-hydroxypyrene were approximately three times as high (Barbeau et al. 2011; Lafontaine et al. 2006).

From the USA, comprehensive data on the excretion of the PAH metabolites 1-hydroxypyrene, 1-, 2-, 3- and 4-hydroxyphenanthrene, 2-, 3- and 9-hydroxyfluorene and 1- and 2-hydroxynaphthalene are available. However, no differentiation between smokers and non-smokers was made (CDC 2005, 2009). In the study carried out in 2003/2004 with 1477 test persons, median (95th percentile) 1-hydroxypyrene concentrations of 0.07 (0.42) µg/g creatinine were detected; these values were 0.04 (0.23) µg/g creatinine in 1625 test persons in 2001/2002, and 0.07 (0.54) µg/g creatinine in 1309 test persons in 1999/2000.

In a Canadian study, median levels of 0.08 µg 1-hydroxypyrene/g creatinine (95th percentile: 0.29 µg/g creatinine) were reported with 50 test persons, in which no differentiation between smokers and non-smokers was made

(Bouchard et al. 2009). In another Canadian study, clearly higher median concentrations of 0.17 µg 1-hydroxypyrene/g creatinine (95th percentile: 0.62 µg/g creatinine) were given, in which the geometric mean was 0.14 µg/g creatinine for non-smokers and 0.23 µg/g creatinine for smokers (Viau et al. 1995).

6.2 Hydroxyphenanthrene

The monohydroxylated phenanthrenes 1-, 2-, 3-, 4- and 9-hydroxyphenanthrene are also determined as biomarkers for a PAH exposure. The results are given either for the individual components or in the form of a sum parameter (the sum of hydroxyphenanthrenes). However, a much lower number of studies is available. Table 4 summarises the results on the excretion of these metabolites obtained in more extensive studies.

Tab. 4 Urinary 1-, 2-, 3-, 4- and 9-hydroxyphenanthrene (OH-phen) concentrations in persons not occupationally exposed to PAHs, presented as the sum of hydroxyphenanthrenes

Analytics	Collective (year of sampling) age, sex	n NS/S	NS		S		References
			Med/P95 (range) [µg/l]	Med/P95 (range) [µg/g crea]	Med/P95 (range) [µg/l]	Med/P95 (range) [µg/g crea]	
Germany							
HPLC-FD QL 0.012 µg/l	general population (1998) 18–69 years, 289 ♂, 284 ♀	389/184	0.84/3.11 (max 15.9)	0.67/1.88 (max 4.50)	1.38/3.95 (max 6.70)	1.00/2.51 (max 3.58)	Becker et al. 2002
HPLC-FD DL 0.005 µg/l	inhabitants of former American Forces housing (1998) > 20 years	289/131		0.83/2.56 (n. d.)[a]		1.00/2.62 (n. d.)[a]	Heudorf and Angerer 2001 a
HPLC-FD DL 0.005–0.016 µg/l	housewives (n. d.), 53–58 years, ♀	97/27		1.20/3.86 (0.19–5.70)		1.75/3.97 (0.84–4.41)	Gündel et al. 1996
LC-MS/MS QL 0.025 µg/l	general population 22–77 years, 72 ♂, 78 ♀, abstaining from barbecued, smoked and fried foods	50/100	0.27/– (n. d.)[a]		0.50/– (n. d.)[a]		Ramsauer et al. 2011
USA							
GC-HRMS DL 0.005 µg/l (1-, 2-, 3-, 4-OH-phen)	general population (2003/2004) > 20 years, ♂ + ♀	1424–1476[b]	0.38/1.79 (n. d.)[a), b), c)]	0.32/1.37 (n. d.)[a), b), c)]			CDC 2009
GC-HRMS DL 0.003–0.006 µg/l (1-, 2-, 3-OH-phen)	general population (2001/2002) > 20 years, ♂ + ♀	1621–1622[b]	0.42/2.42 (n. d.)[a), b)]	0.37/1.84 (n. d.)[a, b)]			CDC 2005
GC-HRMS DL 0.011–0.015 µg/l	general population (1999/2000) > 20 years, ♂ + ♀	1238–1297[b]	0.40/2.64 (n. d.)[a), b)]	0.36/2.05 (n. d.)[a), b)]			

[a] values calculated as the sum of medians/95th percentiles of individual analytes

[b] smoking status not taken into account

[c] 9-hydroxyphenanthrene not taken into account

DL = detection limit of the analytical method; GC-HRMS = gas chromatography with high-resolution mass spectrometry; HPLC-FD = high performance liquid chromatography with fluorescence detection; LC-MS/MS = high performance liquid chromatography with tandem mass spectrometric detection; max = maximum; Med = median; n = number of study participants; n. d. = no details; NS = non-smokers; P95 = 95th percentile; QL = quantification limit; S = smokers

Compared with 1-hydroxypyrene, smoking behaviour has less effect on the average hydroxyphenanthrene excretion. It increases slightly in smokers, but is frequently not significant (Becker et al. 2002; Hoepfner et al. 1987; Jacob et al. 1999; Martin et al. 1989).

6.3 3-Hydroxybenzo[a]pyrene

Only in a few studies the parameter 3-hydroxybenzo[a]pyrene has been investigated in persons not occupationally exposed to PAHs (see Table 5).

Tab. 5 Urinary 3-hydroxybenzo[a]pyrene concentrations in persons not occupationally exposed to PAHs

Analysis	Collective (year of sampling) age, sex	n[a] NS/S	n > DL	NS Med/P95 (range) [ng/g creatinine]	S Med/P95 (range) [ng/g creatinine]	References
France						
HPLC-FD DL 0.02 ng/l	general population 18–65 years, 36 ♂ from Grenoble	23/13	5/12	< DL/– (< DL–0.055)[b]	0.055/– (< DL–0.178)[b]	Barbeau et al. 2011
HPLC-FD DL 0.05 ng/l	general population 18–65 years, 54 ♂ from Paris	27/27	5/18	< DL/– (< DL–0.107)[b]	0.055/– (< DL–0.199)	Lafontaine et al. 2006
HPLC-FD DL 0.08 ng/l	general population 20–47 years, 18 ♂, 7 ♀ exposure either to air in industrial area or urban indoor air	25/–	60 of 284/–	< DL/– (< DL–0.225)[b]		Leroyer et al. 2010
USA						
GC-HRMS 10.5 ng/l	general population (2001/2002) > 20 years, ♂ + ♀	1626[c]	n. d.	< DL/186 (n. d.)[c]		CDC 2005

[a] determined several times for the same person at different times

[b] values calculated: 1 nmol/mol creatinine = 2.372 ng/g creatinine

[c] smoking status not taken into account

DL = detection limit of the analytical method; GC-HRMS = gas chromatography with high-resolution mass spectrometry; HPLC-FD = high performance liquid chromatography with fluorescence detection; Med = median; n. d. = no details; n = number of study participants; NS = non-smokers; P95 = 95th percentile; QL = quantification limit; S = smokers

In four studies, median levels below the analytical detection limit were determined for non-smokers (Barbeau et al. 2011; CDC 2005; Lafontaine et al. 2006; Leroyer et al. 2010). In three of the four studies, the maximum values varied in the range between 0.055 and 0.225 ng/g creatinine (Barbeau et al. 2011; Lafontaine et al. 2006; Leroyer et al. 2010). The urinary excretion levels of 3-hydroxybenzo[a]pyrene in smokers in the general population were described as being two times higher than those in non-smokers (Barbeau et al. 2011).

In a study from the USA, a 95th percentile of 186 ng/g creatinine was reported. However, compared with the remaining three studies with detection limits of approximately 0.05 ng/l, these measurements were carried out using a considerably less sensitive analytical method with a detection limit of 10.5 ng/l (CDC 2005). The determined 95th percentile appears comparatively high, as maximum values of 19.5 ng 3-hydroxybenzo[a]pyrene/g creatinine or 83 ng/g creatinine are given in other studies with workers having a high occupational PAH exposure (Förster et al. 2008; Lafontaine et al. 2004).

7 Evaluation

7.1 Evaluation of the biological reference value BAR

7.1.1 1-Hydroxypyrene

The BAR describes the background exposure for a reference population consisting of persons of working age non-occupationally exposed to PAHs. Owing to the marked effect of smoking behaviour on the excretion levels of PAH metabolites, non-smokers and smokers are to be considered separately. For derivation of the BAR only the data of non-smokers are used. In two studies with large subject numbers, 95th percentiles of 0.29 µg/g creatinine and 0.26 µg/g creatinine for non-smokers are given (Becker et al. 2002; Heudorf and Angerer 2001 a). In other German studies, somewhat higher 95th percentiles of 0.33, 0.38 or 0.46 µg/g creatinine were determined for the non-smokers (Göen et al. 1995; Gündel et al. 1996) (see Table 2). In studies from France, no 95th percentiles but maximum values for non-smokers of 0.32 or 0.29 µg/g creatinine were given (Barbeau et al. 2011; Lafontaine et al. 2006). In an Italian study, a higher 1-hydroxypyrene excretion level was determined; the 95th percentile for the 327 non-smokers was 0.65 µg/g creatinine (Roggi et al. 1997).

The use of creatinine-related values is recommended for 1-hydroxypyrene excretion (Viau et al. 2004).

Because of possible differences in air exposure, heating and dietary habits, especially the results from German studies are used for the derivation of a BAR for 1-hydroxypyrene in urine. Based on the data of the environmental survey (Becker et al. 2002) and the study by Heudorf and Angerer (2001 a), for non-smoking adults in the general population

a BAR of 0.3 µg 1-hydroxypyrene (after hydrolysis)/g creatinine

is established.

Sampling time is at the end of exposure or the end of a shift, for long-term exposures after several shifts.

In the case of smokers, a doubling to tripling of 1-hydroxypyrene excretion is to be expected.

7.1.2 Hydroxyphenanthrene

As the determination of monohydroxylated phenanthrene metabolites has not yet become fully recognised as a standard parameter for characterizing PAH exposure, and phenanthrene has only a low toxicity, the derivation of a BAR is not considered necessary at present.

7.1.3 3-Hydroxybenzo[a]pyrene

To estimate the health risk of workers, metabolites of the carcinogenic PAHs have greater importance than the less toxic PAHs such as pyrene and phenanthrene. For 3-hydroxybenzo[a]pyrene, a metabolite of the carcinogen benzo[a]pyrene, only a few studies are available in which the urinary concentrations of persons not occupationally exposed to PAHs were determined using a sufficiently sensitive analytical method. For adult non-smokers, median levels below the given detection limits of 0.08 ng/l, 0.05 ng/l and 0.02 ng/l and peak values of 0.055 up to 0.225 ng/g creatinine were determined (Barbeau et al. 2011; Lafontaine et al. 2006; Leroyer et al. 2010). As no 95th percentile was given in any of the relevant studies, the maximum value would have to be used for the derivation. This would provide, for 3-hydroxybenzo[a]pyrene, a reference value of 0.2 ng 3-hydroxybenzo[a]pyrene (after hydrolysis)/g creatinine for non-smoking adults. As, however, in the studies examining 3-hydroxybenzo[a]pyrene in persons without occupational PAH exposure, only non-representative collectives of the general population were analysed, no BAR for 3-hydroxybenzo[a]pyrene has been established.

7.2 Evaluation of EKA

A study in 38 workers exposed to PAHs in different workplaces revealed a relationship between the airborne benzo[a]pyrene exposure and the urinary concentration of the metabolite 3-hydroxybenzo[a]pyrene (Lafontaine et al. 2004). Using the given relationship between external and internal exposure the following EKA are obtained for an 8-hour PAH uptake, mainly by inhalation:

Air Benzo[a]pyrene [µg/m³]	Urine 3-Hydroxybenzo[a]pyrene (after hydrolysis) [ng/g creatinine]
0.07	0.7
0.35	2
0.7	3.5
1.0	5
1.5	7

Sampling time is at the beginning of the next shift (16 hours after the end of exposure) (Gendre et al. 2002, 2004).

In the EKA correlation, benzo[a]pyrene was used as parameter, although this describes the total exposure to PAHs only insufficiently. Apart from benzo[a]pyrene, further carcinogenic compounds in PAH substance mixtures are present; taking them into account in form of effect equivalents would be desirable.

8 Interpretation

When interpreting the analytical data, in addition to smoking behaviour, further personal confounders have to be taken into account. As causes of BAR excursions – apart from active and passive tobacco smoking – atmospheric exposures from open hearths or small heating units using fossil fuels, the consumption of barbecued and smoked foods, the use of tar-containing medication or living in areas with high industrial PAH emissions have, for example, also to be taken into consideration (Becker et al. 2002; Strickland et al. 1996; van Maanen et al. 1994; WHO 1998; Wilhelm et al. 2007).

The BAR relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3 g/l. In addition to this, the Commission considers it useful, for further improving the validity of the analyses, to select a narrower target range of 0.5–2.5 g/l for urine samples. As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated test persons is recommended (Bader et al. 2016).

The EKA correlation applies only at workplaces where PAH exposure is mainly by inhalation. Additional dermal PAH absorption can cause a clear increase in internal exposure. Considering the elimination kinetics of 3-hydroxybenzo[a]pyrene, sampling has to take place at the beginning of the next shift (see Section 1.3).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

References

ACGIH (American Conference of Governmental Industrial Hygienists) (2005) Polycyclic aromatic hydrocarbons (PAHs). In: Documentation of the Threshold Limit Values and Biological Exposure Indices, ACGIH, Cincinnati, OH

Angerer J, Ewers U, Wilhelm M (2007) Human biomonitoring: state of the art. Int J Hyg Environ Health 210(3-4): 201–228. DOI: 10.1016/j.ijheh.2007.01.024

Aquilina NJ, Delgado-Saborit JM, Meddings C, Baker S, Harrison RM, Jacob P III, Wilson M, Yu L, Duan M, Benowitz NL (2010) Environmental and biological monitoring of exposures to PAHs and ETS in the general population. Environ Int 36(7): 763–771. DOI: 10.1016/j.envint.2010.05.015

ATSDR (Agency for Toxic Substances and Disease Registry) (1995) Toxicological profile for polycyclic aromatic hydrocarbons. ATSDR, Atlanta, GA. https://www.atsdr.cdc.gov/toxprofiles/tp69.pdf, accessed 16 Nov 2020

Bader M, Ochsmann E, Drexler H, Hartwig A, MAK Commission (2016) Addendum to creatinine as reference parameter for the concentration of substances in urine. BAT Value Documentation, 2010. MAK Collect Occup Health Saf 1(1): 266–268. DOI: 10.1002/3527600418.bbgeneral05e1715

Barbeau D, Maître A, Marques M (2011) Highly sensitive routine method for urinary 3-hydroxybenzo[a]pyrene quantitation using liquid chromatography-fluorescence detection and automated off-line solid phase extraction. Analyst 136(6): 1183–1191. DOI: 10.1039/c0an00428f

Becker K, Kaus S, Krause C, Lepom P, Schulz C, Seiwert M, Seifert B (2002) Umwelt-Survey 1998, Band III: Human-Biomonitoring. Stoffgehalte in Blut und Urin der Bevölkerung in Deutschland. WaBoLu-Hefte 1/02. Umweltbundesamt, Berlin. https://www.umweltbundesamt.de/sites/default/files/medien/publikation/long/2104.pdf, accessed 30 Sep 2020

Becker K, Schulz C, Kaus S, Seiwert M, Seifert B (2003) German Environmental Survey 1998 (GerES III): environmental pollutants in the urine of the German population. Int J Hyg Environ Health 206(1): 15–24. DOI: 10.1078/1438-4639-00188

Boffetta P, Jourenkova N, Gustavsson P (1997) Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control 8(3): 444–472. DOI: 10.1023/a:1018465507029

Bouchard M, Normandin L, Gagnon F, Viau C, Dumas P, Gaudreau É, Tremblay C (2009) Repeated measures of validated and novel biomarkers of exposure to polycyclic aromatic hydrocarbons in individuals living near an aluminum plant in Quebec, Canada. J Toxicol Environ Health A 72(23): 1534–1549. DOI: 10.1080/15287390903129481

Cavallo D, Ursini CL, Bavazzano P, Cassinelli C, Frattini A, Perniconi B, Di Francesco A, Ciervo A, Rondinone B, Iavicoli S (2006) Sister chromatid exchange and oxidative DNA damage in paving workers exposed to PAHs. Ann Occup Hyg 50(3): 211–218. DOI: 10.1093/annhyg/mei072

CDC (Centers for Disease Control and Prevention) (2005) Third national report on human exposure to environmental chemicals. NCEH 05-0570. CDC, Atlanta, GA. https://clu-in.org/download/contaminantfocus/pcb/third-report.pdf, accessed 16 Nov 2020

CDC (Centers for Disease Control and Prevention) (2009) Fourth national report on human exposure to environmental chemicals. CDC, Atlanta, GA. https://www.cdc.gov/exposurereport/pdf/fourthreport.pdf, accessed 16 Nov 2020

DFG (Deutsche Forschungsgemeinschaft) (ed) (2012) List of MAK and BAT Values 2012. Maximum Concentrations and Biological Tolerance Values at the Workplace. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, report 48. Wiley-VCH, Weinheim. DOI: 10.1002/9783527666034

Förster K, Preuss R, Angerer J, Roßbach B, Brüning T, Simon P (2008) 3-Hydroxybenzo[a]pyrene in the urine of workers with occupational exposure to polycyclic aromatic hydrocarbons in different industries. Occup Environ Med 65(4): 224–229. DOI: 10.1136/oem.2006.030809

Fustinoni S, Campo L, Cirla PS, Martinotti I, Buratti M, Longhi O, Foà V, Bertazzi P (2010) Dermal exposure to polycyclic aromatic hydrocarbons in asphalt workers. Occup Environ Med 67(7): 456–463. DOI: 10.1136/oem.2009.050344

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. Polycycl Aromat Compd 22(3-4): 761–769. DOI: 10.1080/10406630290103915

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. Polycycl Aromat Compd 24(4-5): 433–439. DOI: 10.1080/10406630490468766

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 Chromatogr B Biomed Sci Appl 705(1): 132–138. DOI: 10.1016/s0378-4347(97)00526-4

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 exposures to PAH. Sci Tot Environ 163(1-3): 195–201. DOI: 10.1016/0048-9697(95)04484-i

Gündel J, Angerer J (1999) Elimination of 1-hydroxypyrene in the urine of workers from different workplaces as an indicator of occupational PAH exposure. Polycycl Aromat Compd 17(1-4): 157–169. DOI: 10.1080/10406639908020611

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(4): 585–590. DOI: 10.1007/BF00212444

Gündel J, Schaller KH, Angerer J (2000) Occupational exposure to polycyclic aromatic hydrocarbons in a fireproof stone producing plant: biological monitoring of 1-hydroxypyrene, 1-, 2-, 3- and 4-hydroxyphenanthrene, 3-hydroxybenz(a)anthracene and 3-hydroxybenzo(a)pyrene. Int Arch Occup Environ Health 73(4): 270–274. DOI: 10.1007/s004200050427

Hagedorn H-W, 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(6): 301–309. DOI: 10.1093/jat/33.6.301

Hansen ÅM, Mathiesen L, Pedersen M, Knudsen LE (2008) Urinary 1-hydroxypyrene (1-HP) in environmental and occupational studies – a review. Int J Hyg Environ Health 211(5-6): 471–503. DOI: 10.1016/j.ijheh.2007.09.012

Hartwig A (ed) (2012) Polycyclic aromatic hydrocarbons (PAH). MAK Value Documentation, 2008. In: The MAK-Collection for Occupational Health and Safety. Part I: MAK Value Documentations, vol 27. Wiley-VCH, Weinheim, 1–216. Also available from DOI: 10.1002/3527600418.mb0223orge0027a

Hecht SS, Chen M, Yagi H, Jerina DM, Carmella SG (2003) r-1,t-2,3,c-4-Tetrahydroxy-1,2,3,4-tetrahydrophenanthrene in human urine: a potential biomarker for assessing polycyclic aromatic hydrocarbon metabolic activation. Cancer Epidemiol Biomarkers Prev 12(12): 1501–1508

Heudorf U, Angerer J (2001 a) 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(2): 91–101. DOI: 10.1007/s004200000214

Heudorf U, Angerer J (2001 b) Urinary monohydroxylated phenanthrenes and hydroxypyrene – the effects of smoking habits and changes induced by smoking on monooxygenase-mediated metabolism. Int Arch Occup Environ Health 74(3): 177–183. DOI: 10.1007/s004200000215

Hoepfner I, Dettbarn G, Scherer G, Grimmer G, Adlkofer F (1987) Hydroxy-phenanthrenes in the urine of non-smokers and smokers. Toxicol Lett 35(1): 67–71. DOI: 10.1016/0378-4274(87)90087-7

Huang W, Caudill SP, Grainger J, Needham LL, Patterson DG Jr (2006) Levels of 1-hydroxypyrene and other monohydroxy polycyclic aromatic hydrocarbons in children: a study based on U.S. reference range values. Toxicol Lett 163(1): 10–19. DOI: 10.1016/j.toxlet.2005.08.003

IARC (International Agency for Research of Cancer) (2010) Benzo[a]pyrene. In: Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC monographs on the evaluation of carcinogenic risks of chemicals to humans, vol 92. IARC, Lyon, 394–422. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono92.pdf, accessed 16 Oct 2020

Jacob J, Greim H (eds) (2004) Polycyclische aromatische Kohlenwasserstoffe. Forschungsbericht. Wiley-VCH, Weinheim

Jacob J, Grimmer G, Dettbarn G (1999) Profile of urinary phenanthrene metabolites in smokers and non-smokers. Biomarkers 4(5): 319–327. DOI: 10.1080/135475099230705

Jacob P 3rd, Wilson M, Benowitz ML (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(2): 587–598. DOI: 10.1021/ac060920l

Jongeneelen FJ (1997) Methods for routine biological monitoring of carcinogenic PAH-mixtures. Sci Total Environ 199(1-2): 141–149. DOI: 10.1016/s0048-9697(97)00064-8

Jongeneelen FJ, Anzion RBM, Scheepers PTJ, Bos RP, Henderson PT, Nijenhuis EH, Veenstra SJ, Brouns RME, Winkes A (1988) 1-Hydroxypyrene in urine as a biological indicator of exposure to polycyclic aromatic hydrocarbons in several work environments. Ann Occup Hyg 32(1): 35–43. DOI: 10.1093/annhyg/32.1.35

Käfferlein HU, Marczynski B, Mensing T, Brüning T (2010) Albumin and hemoglobin adducts of benzo[a]pyrene in humans – analytical methods, exposure assessment and recommendations for future directions. Crit Rev Toxicol 40(2): 126–150. DOI: 10.3109/10408440903283633

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. Polycycl Aromat Compd 24(4-5): 441–450. DOI: 10.1080/10406630490471447

Lafontaine M, Champmartin C, Simon P, Delsaut P, Funck-Brentano C (2006) 3-Hydroxybenzo[a]pyrene in the urine of smokers and non-smokers. Toxicol Lett 162(2-3): 181–185. DOI: 10.1016/j.toxlet.2005.09.019

Leroyer A, Jeandel F, Maitre A, Howsam M, Deplanque D, Mazzuca M, Nisse C (2010) 1-Hydroxypyrene and 3-hydroxybenzo[a]pyrene as biomarkers of exposure to PAH in various environmental exposure situations. Sci Total Environ 408(5): 1166–1173. DOI: 10.1016/j.scitotenv.2009.10.073

Li Z, Romanoff LC, Trinidad DA, Hussain N, Jones RS, Porter EN, Patterson DG Jr, 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(16): 5744–5751. DOI: 10.1021/ac0606094

Li Z, Mulholland JA, Romanoff LC, Pittman EN, Trinidad DA, Lewin MD, Sjödin A (2010) Assessment of non-occupational exposure to polycyclic aromatic hydrocarbons through personal air sampling and urinary biomonitoring. J Environ Monit 12(5): 1110–1118. DOI: 10.1039/c000689k

Lintelmann J, Angerer J (1999) PAH metabolites (1-hydroxyphenanthrene, 4-hydroxyphenanthrene, 9-hydroxyphenanthrene, 1-hydroxypyrene) Biomonitoring Method, 1999. In: Angerer J, Schaller KH, Greim H (eds) Analyses of Hazardous Substances in Biological Materials, vol 6. Wiley-VCH, Weinheim, 163–187. Also available from DOI: 10.1002/3527600418.bi0pahmete0006

Lintelmann J, Hellemann C, Ketrup A (1994) Coupled-column high-performance liquid chromatographic method for the determination of four metabotites of polycyclic aromatic hydrocarbons, 1-, 4- and 9-hydroxyphenanthrene and 1-hydroxypyrene, in urine. J Chromatogr B Biomed Appl 660(1): 67–73. DOI: 10.1016/0378-4347(94)00267-3

van Maanen JMS, Moonen EJC, Maas LM, Kleinjans JCS, van Schooten FJ (1994) Formation of aromatic DNA adducts in white blood cells in relation to urinary excretion of 1-hydroxypyrene during consumption of grilled meat. Carcinogenesis 15(10): 2263–2268. DOI: 10.1093/carcin/15.10.2263

Marczynski B, Raulf-Heimsoth M, Spickenheuer A, Mensing T, Welge P, Förster K, Angerer J, Pesch B, Bramer R, Käfferlein HU, Breuer D, Hahn JU, Brüning T (2007) Ambient and biological monitoring of exposure and genotoxic effects in mastic asphalt workers exposed to fumes of bitumen. J Occup Environ Hyg 4(Suppl 1): 127–136. DOI: 10.1080/15459620701296617

Marczynski B, Raulf-Heimsoth M, Spickenheuer A, Pesch B, Kendzia B, Mensing T, Engelhardt B, Lee EH, Schindler BK, Heinze E, Welge P, Bramer R, Angerer J, Breuer D, Käfferlein HU, Brüning T (2011) DNA adducts and strand breaks in workers exposed to vapours and aerosols of bitumen: associations between exposure and effect. Arch Toxicol 85(Suppl 1): S53–S64. DOI: 10.1007/s00204-011-0682-5

Marquardt H, Schäfer SG (eds) (1994) Lehrbuch der Toxikologie. Wissenschaftsverlag, Mannheim

Marquardt H, Schäfer SG (eds) (2004) Lehrbuch der Toxikologie, 2nd ed. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart

Martin F, Hoepfner I, Scherer G, Adlkofer F, Dettbarn G, Grimmer G (1989) Urinary excretion of hydroxy-phenanthrenes after intake of polycyclic aromatic hydrocarbons. Environ Int 15(1-6): 41–47. DOI: 10.1016/0160-4120(89)90008-1

McClean MD, Rinehart RD, Ngo L, Eisen EA, Kelsey KT, Wiencke JK, Herrick RF (2004) Urinary 1-hydroxypyrene and polycyclic aromatic hydrocarbon exposure among asphalt paving workers. Ann Occup Hyg 48(6): 565–578. DOI: 10.1093/annhyg/meh044

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 Chromatogr B Analyt Technol Biomed Life Sci 877(11-12): 1117–1125. DOI: 10.1016/j.jchromb.2009.02.067

Pastorelli R, Guanci M, Restano J, Berri A, Micoli G, Minoia C, Alcini D, Carrer P, Negri E, La Vecchia C, Fanelli R, Airoldi L (1999) Seasonal effect on airborne pyrene, urinary 1-hydroxypyrene, and benzo(a)pyrene diol epoxide-hemoglobin adducts in the general population. Cancer Epidemiol Biomarkers Prev 8(6): 561–565

Pastorelli R, Cerri A, Mezzetti M, Consonni E, Airoldi L (2002) Effect of DNA repair gene polymorphisms on BPDE-DNA adducts in human lymphocytes. Int J Cancer 100(1): 9–13. DOI: 10.1002/ijc.10463

Pesch B, Kappler M, Straif K, Marczynski B, Preuss R, Roßbach B, Rihs HP, Weiss T, Rabstein S, Pierl C, Scherenberg M, Adams A, Käfferlein HU, Angerer J, Wilhelm M, Seidel A, Brüning T (2007) Dose-response modeling of occupational exposure to polycyclic aromatic hydrocarbons with biomarkers of exposure and effect. Cancer Epidemiol Biomarkers Prev 16(9): 1863–1873. DOI: 10.1158/1055-9965.EPI-07-0033

Pratt MM, John K, MacLean AB, Afework S, Phillips DH, Poirier MC (2011) Polycyclic aromatic hydrocarbon (PAH) exposure and DNA adduct semi-quantitation in archived human tissues. Int J Environ Res Public Health 8(7): 2675–2691. DOI: 10.3390/ijerph8072675

Qiu L, Leng S, Wang Z, Dai Y, Zheng Y, Wang Z (2007) Path analysis of biomarkers of exposure and early biological effects among coke-oven workers exposed to polycyclic aromatic hydrocarbons. Cancer Epidemiol Biomarkers Prev 16(6): 1193–1199. DOI: 10.1158/1055-9965.EPI-07-0001

Ramesh A, Walker SA, Hood DB, Guillén MD, Schneider K, Weyand EH (2004) Bioavailability and risk assessment of orally ingested polycyclic aromatic hydrocarbons. Int J Toxicol 23(5): 301–333. DOI: 10.1080/10915810490517063

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(2): 877–889. DOI: 10.1007/s00216-010-4355-7

Roggi C, Minoia C, Sciarra GF, Apostoli P, Maccarini L, Magnaghi S, Cenni A, Fonte A, Nidasio GF, Micoli G (1997) Urinary 1-hydroxypyrene as a marker of exposure to pyrene: an epidemiological survey on a general population group. Sci Total Environ 199(3): 247–254. DOI: 10.1016/s0048-9697(97)05458-2

Rojas M, Alexandrov K, Auburtin G, Wastiaux-Denamur A, Mayer L, Mahieu B, Sebastien P, Bartsch H (1995) Anti-benzo[a]pyrene diolepoxide–DNA adduct levels in peripheral mononuclear cells from coke oven workers and the enhancing effect of smoking. Carcinogenesis 16(6): 1373–1376. DOI: 10.1093/carcin/16.6.1373

Romanoff LC, Li Z, Young KJ, Blakely NC III, 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(1-2): 47–54. DOI: 10.1016/j.jchromb.2006.03.004

van Rooij JGM, Bodelier-Bade MM, De Looff AJA, Dijkmans APG, Jongeneelen FJ (1992) Dermal exposure to polycyclic aromatic hydrocarbons among primary aluminium workers. Med Lav 83(5): 519–529

van Rooij JGM, Bodelier-Bade MM, Jongeneelen FJ (1993 a) Estimation of individual dermal and respiratory uptake of polycyclic aromatic hydrocarbons in 12 coke oven workers. Br J Ind Med 50(7): 623–632. DOI: 10.1136/oem.50.7.623

van Rooij JGM, van Lieshout EMA, Bodelier-Bade MM, Joogeneelen FJ (1993 b) The effect of the reduction of dermal PAH contamination on the internal dose of creosote workers. Abstracts and poster presentations of the NVT annual meeting, 14 Jan 1993. Hum Exp Toxicol 12(4): 353

van Rooij JGM, Veeger MMS, Bodelier-Bade MM, Scheepers PTJ, Jongeneelen FJ (1994) Smoking and dietary intake of polycyclic aromatic hydrocarbons as sources of interindividual variability in the baseline excretion of 1-hydroxypyrene in urine. Int Arch Occup Environ Health 66(1): 55–65. DOI: 10.1007/BF00386580

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(8): 509–516. DOI: 10.1136/oem.2008.042796

Ruzgyte A, Bouchard M, Viau C (2005) Development of a high-performance liquid chromatographic method for the simultaneous determination of pyrene-1,6- and 1,8-dione in animal and human urine. J Anal Toxicol 29(6): 533–538. DOI: 10.1093/jat/29.6.533

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(2): 105–116. DOI: 10.1093/ntr/ntp183

Scherer G, Frank S, Riedel K, Meger-Kossien I, Renner T (2000) Biomonitoring of exposure to polycyclic aromatic hydrocarbons of nonoccupationally exposed persons. Cancer Epidemiol Biomarkers Prev 9(4): 373–380

van Schooten FJ, Moonen EJC, van der Wal L, Levels P, Kleinjans JCS (1997) Determination of polycyclic aromatic hydrocarbons (PAH) and their metabolites in blood, feces, and urine of rats orally exposed to PAH contaminated soils. Arch Environ Contam Toxicol 33(3): 317–322. DOI: 10.1007/s002449900259

Seidel A, Spickenheuer A, Straif K, Rihs H-P, Marczynski B, Scherenberg M, Dettbarn G, Angerer J, Wilhelm M, Brüning T, Jacob J, Pesch B (2008) New biomarkers of occupational exposure to polycyclic aromatic hydrocarbons. J Toxicol Environ Health A 71(11-12): 734–745. DOI: 10.1080/15287390801985265

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(2): 93–109. DOI: 10.1080/1354750021000046570

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 Chromatogr B Biomed Sci Appl 732(1): 91–101. DOI: 10.1016/s0378-4347(99)00270-4

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(2): 337–348. DOI: 10.1016/s0378-4347(00)00350-9

Simpson CD, Wu MT, Christiani DC, Santella RM, Carmella SG, Hecht SS (2000) Determination of r-7,t-8,9,c-10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[α]pyrene in human urine by gas chromatography/negative ion chemical ionization/mass spectrometry. Chem Res Toxicol 13(4): 271–280. DOI: 10.1021/tx990202c

Smith CJ, Walcott CJ, Huang W, Maggio V, Grainger J, Patterson DG Jr (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 Chromatogr B Analyt Technol Biomed Life Sci 778(1-2): 157–164. DOI: 10.1016/s0378-4347(01)00456-x

Strickland PT, Kang D, Bowman ED, Fitzwilliam A, Downing TE, Rothman N, Groopman JD, Weston A (1994) Identification of 1-hydroxypyrene glucuronide as a major pyrene metabolite in human urine by synchronous fluorescence spectroscopy and gas chromatography–mass spectrometry. Carcinogenesis 15(3): 483–487. DOI: 10.1093/carcin/15.3.483

Strickland P, Kang D, Sithisarankul P (1996) Polycyclic aromatic hydrocarbon metabolites in urine as biomarkers of exposure and effect. Environ Health Perspect 104(Suppl 5): 927–932. DOI: 10.1289/ehp.96104s5927

UBA (Umweltbundesamt) (2005) 1-Hydroxypyren im Urin als Indikator einer inneren Belastung mit polyzyklischen aromatischen Kohlenwasserstoffen (PAK) – Referenzwert für 1-Hydroxypyren im Urin. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 48(10): 1194–1206. DOI: 10.1007/s00103-005-1160-0

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. DOI: 10.1093/annhyg/mel010

Väänänen V, Hämeilä M, Kalliokoski P, Nykyri E, Heikkilä P (2005) Dermal exposure to polycyclic aromatic hydrocarbons among road pavers. Ann Occup Hyg 49(2): 167–178. DOI: 10.1093/annhyg/meh094

Viau C, Vyskočil A (1995) Patterns of 1-hydroxypyrene excretion in volunteers exposed to pyrene by the dermal route. Sci Total Environ 163(1-3): 187–190. DOI: 10.1016/0048-9697(95)04495-m

Viau C, Vyskočil A, Martel L (1995) Background urinary 1-hydroxypyrene levels in non-occupationally exposed individuals in the Province of Québec, Canada, and comparison with its excretion in workers exposed to PAH mixtures. Sci Total Environ 163(1-3): 191–194. DOI: 10.1016/0048-9697(95)04496-n

Viau C, Lafontaine M, Payan JP (2004) Creatinine normalization in biological monitoring revisited: the case of 1-hydroxypyrene. Int Arch Occup Environ Health 77(3): 177–185. DOI: 10.1007/s00420-003-0495-9

WHO (World Health Organisation) (1998) Selected non-heterocyclic polycyclic aromatic hydrocarbons. Environmental Health Criteria, 202. WHO, Geneva. https://wedocs.unep.org/bitstream/handle/20.500.11822/29533/EHC202PAH.pdf?sequence=1&isAllowed=y, accessed 16 Nov 2020

Wilhelm M, Eberwein G, Hölzer J, Gladtke D, Angerer J, Marczynski B, Behrendt H, Ring J, Sugiri D, Ranft U (2007) Influence of industrial sources on children's health – hot spot studies in North Rhine Westphalia, Germany. Int J Hyg Environ Health 210(5): 591–599. DOI: 10.1016/j.ijheh.2007.02.007

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(19): 2299–2308. DOI: 10.1002/rcm.1625

Zhong Y, Carmella SG, Hochalter JB, Balbo S, Hecht SS (2011) Analysis of r-7,t-8,9,c-10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene in human urine: a biomarker for directly assessing carcinogenic polycyclic aromatic hydrocarbon exposure plus metabolic activation. Chem Res Toxicol 24(1): 73–80. DOI: 10.1021/tx100287n