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Review

Biomonitoring of polycyclic aromatic hydrocarbons in human urine

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Abstract

Measurement of polycyclic aromatic hydrocarbons (PAH) metabolites in human urine is the method of choice to determine occupational and/or environmental exposure of an individual to PAH, in particular, when multiple routes of exposure have to be taken into account. Requirements for methods of biomonitoring PAH metabolites in urine are presented. Studies using 1-hydroxypyrene or phenanthrene metabolites including its phenols and dihydrodiols are summarized. The role of these PAH metabolites as established biomarkers and also more recent developments of PAH biomonitoring are discussed.
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1. Introduction

It is well-documented that polycyclic aromatic hydrocarbons (PAH) represent a class of compounds many of which are potent carcinogens for mammals [1–3]. Their significance as environmental and occupational carcinogens [4] has been proven by a series of studies on balancing the carcinogenic potential of various environmental matrices (vehicle exhaust, diesel exhaust extract, tobacco smoke condensate, hard-coal combustion condensate, used motor oil) and fractions thereof [5–12]. At least for these matrices it has been shown that PAH containing more than three aromatic rings account for 70–90% of the total carcinogenic effect. According to the formation of PAH during all kinds of incomplete combustion processes they are widespread in the environment and reach high concentrations at certain workplaces. Hence, they have to be considered as a serious occupational burden. Although no direct experimental evidence is available that PAH are carcinogenic for humans, occupational studies

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strongly indicate that there is a correlation between PAH exposure and cancer incidence for various human tissues such as lung, skin and bladder. As a result of these findings a regular control of the PAH concentrations at various workplaces became mandatory. However, great inter-individual differences of the actual exposure were found for persons working at the same area and even at the same workplace [219,220]. Physiological (breathing behaviour) and working habits (application of breathing masks etc.) were found to be responsible for this variability.

A more realistic parameter for the individual exposure, therefore, may be obtained by measuring the excretion of the incorporated PAH and their metabolites formed by a number of different enzymes, e.g. in the liver, lung and bladder. In the past, 1-hydroxypyrene (1-OHP) has been used as a representative PAH metabolite in occupational studies, and more recently further analytes (phanthrene metabolites, 3-hydroxybenzo[*a*]pyrene) have additionally been brought up [51,81,91,96,100,122,123, 125,161,183,184].

2. Occupational studies

There are various industrial workplaces for which a significant increase of certain cancer diseases has been found that may be attributed to an unusually high exposure to PAH. For instance, PAH exposure is high in coke plants, coal tar and pitch producing and manufacturing industries, aluminium plants, iron and steel foundries, creosote-, rubber-, mineral oil-, soot- and carbon black-producing or manufacturing companies. As highly exposed occupational groups, chimney sweeps, roadmen (pavement-tarring) and roofers (roof-tarring) are also under increased risk.

Significantly increased cancer incidences of the lung and other tissues (scrotum, bladder, kidney and colon) were found for gas and coke plant workers [13–20]. Enhanced rates of skin cancer (scrotum) and neoplasms in other organs have been observed in workers being permanently exposed to coal tar, coal tar pitch or creosote (wood impregnation) [21]. A causal correlation between PAH exposure and cancer incidence is likely in these cases and it should be emphasised that coal tar pitch contains 1–2% benzo[*a*]pyrene and consists of about 50% of polycyclic aromatic hydrocarbons [22].

Elevated cancer risks (lung and other organs) have been stated for aluminium plant (Soederberg technology) and foundry workers [23–27] and increased incidences of skin, scrotum and lung cancer have been observed for workers exposed to mineral oil, in particular cutting oil [28,29] (for review see Ref. [30]). A significantly elevated cancer risk for various organs has also been reported for workers of the soot- and carbon black-manufacturing [31] and increased bladder, stomach, and lung cancer as well as leukaemia rates for workers of the rubber industry [32,33] (for review see Ref. [30]).

It was Sir Percival Pott [34] who verified already more than two centuries ago an unusually high scrotum cancer incidence in chimney-sweeps. More recent studies reported on the enhanced abundance of neoplasms in the respiratory tract, the oesophagus and liver [35–38].

Although no epidemiological studies are available on street pavers it seems that they were under risk at least in the past, since coal tar pitch blended materials had been used in those days [39,40]. Nowadays the application of coal tar pitch-derived materials (carbo-bitumen) has been reduced or completely disappeared so that an occupational risk seems to be unlikely.

Significantly increased lung cancer rates [41] and neoplasms in other organs (larynx, oesophagus, stomach and bladder) indicate, however, an occupational risk for roofers [42].

3. Exposure to PAH

For a basic burden of the general, non-occupationally exposed population, ambient air, water and food may be relevant. Presently, limit values of 1 or 10 ng benzo[*a*]pyrene per m^3 air are recommended or mandatory in various countries (e.g. Italy or Germany). Actually, these concentrations are seldom found or exceeded nowadays in ambient air of rural or even of urban living areas. Elevated concentrations may be expected in areas with dense vehicle traffic, in road tunnels or in areas near to industrial emissions (e.g. coke plants etc.; for review see Ref. [3]).

Given a daily breathing volume of 11 m^3, about 15 ng (and definitely less than 110 ng) benzo-[*a*]pyrene are expected to be daily inhaled from ambient air. Based on typical PAH-profiles of ambient air of unpolluted areas [43] the inhaled amount of pyrene and phenanthrene per day can be calculated to be 200 ng and 1000 ng, respectively.

The benzo[*a*]pyrene concentration in drinking water is about 0.1–1 ng/l. Accordingly, a daily intake of at most 2–3 ng benzo[*a*]pyrene and about 10 and 20 times this amount in case of pyrene and phenanthrene may be incorporated from this source.

Food appears to be the main source of PAH intake for humans not occupationally exposed to PAH. Concentrations of benzo[*a*]pyrene in meat and meat products have been restricted to 1 μg/kg in Germany and for food and beverages to 30 ng/kg in Italy. Most of the foodstuffs are less contaminated so that 1 μg/kg rather appears to be a pessimistic value, although occasionally far higher concentrations have been found, especially in marine food (oysters, mussels, smoked fish) and vegetables (green kale). The maximum daily benzo[*a*]pyrene intake from food can be extrapolated to be 1 μg [44], but higher values have also been calculated for the Netherlands [45]. The concentrations of phenanthrene and pyrene very much depend on the kind of foodstuff, but may, however, be estimated to be at least 3–10 times higher.

From the huge number of studies on the PAH exposure at various workplaces a small selection is collated in Table 1 which presents concentration of benzo[*a*]pyrene (B[*a*]P) only. It shows that there are enormous variations even at similar or identical workplaces, but also that significant progress has been made by modernisation of the plants to reduce the emission of PAH. This holds in particular for coke plants for which the limit values have been set to 5 μg B[*a*]P/m^3 for the oven platform and to 2 μg B[*a*]P/m^3 for other workplaces in Germany [46] and 0.15 μg B[*a*]P/m^3 in France for the production of coke electrodes [47].

With regard to biomonitoring it should be noted that the PAH profiles vary not only from one emission source to another, but also within a certain workplace and temporarily even at identical ones, so that extrapolation from the concentration of phenanthrene or pyrene to B[*a*]P cannot generally be made.

4. Metabolism, elimination and excretion of PAH

After incorporation PAH are enzymatically converted primarily to arene-oxides which upon spontaneous isomerisation may give phenols or upon microsomal epoxide hydrolase-mediated addition of water may form *trans*-dihydrodiols. For the first step more or less regio-specifically operating cytochrome P450(CYP)-dependent monooxygenases are responsible, among which predominantly CYP1A1, 1A2, 1B1 and 3A4 are involved in the metabolic activation of PAH. Once formed, dihydrodiols may be further oxidised by CYP enzymes to vicinal dihydrodiol epoxides. If dihydrodiol epoxides are formed as part of a bay- or fjord region of a given PAH, they play a toxicological key role as ultimate carcinogens [185,186] reacting with DNA to form covalent adducts [187,188] — an initial step for the malignant transformation of cells [188,189].

Phenols and dihydrodiols are excreted in the urine in the form of better water-soluble sulfates and glucuronides after conjugation to sulphuric acid catalysed by sulfotransferases or to glucuronic acid catalysed by UDP-glucuronosyltransferases. At least in rodents it could be demonstrated that the conjugation of metabolites to glutathione enzymatically catalysed by glutathione *S*-transferases finally results in the excretion of mercapturic acids (MCA) which are formed from glutathione conjugates by elimination of two amino acid residues (glycine, glutamic acid) and subsequent acetylation of the cysteine moiety. So far, however, it has not been proven that urinary excretion of MCA is relevant in humans. In principal, this excretory pathway cannot be excluded since water-soluble metabolites with molecular mass $<$475 D (mole weights for MCA derived from phenanthrene, pyrene and benzo[*a*]pyrene: 357, 381 and 431 D, respectively) are preferentially excreted in the urine, whereas those with higher molecular masses appear in the faeces [66]. The excretion of other mercapto derivatives such as mercaptoacetic, mercaptolactic and mercaptopyruvic acid in the urine of rodents has also been described [67] but hitherto not found in humans.

It has been demonstrated by animal experiments that PAH are readily transported via lymph and blood from the tissue to which they have been applied

Table 1
Benzo[*a*]pyrene concentration at various workplaces

Workplace	Country	Year	B[*a*]P ($\mu g/m^3$)	Reference
Coke plants				
Oven platform	Poland	1978	20–383	[48]
after modernisation			0–6.8	[48]
Oven platform	Sweden	1982	9.4–13.5	[49]
driver of filling container			4.7–17	[49]
Oven platform	Germany	1983	22.3–33.0	[50]
driver of filling container			4.5	[50]
ramp man			1.33	[50]
various drivers			0.16–0.93	[50]
Oven platform	Germany	1992	10.6–15.8	[51]
driver of filling container			5.8–10.1	[51]
machinist			0.9–4.9	[51]
Aluminium plants (Soederberg technology)				
Various workplaces	Norway	1978	11.3–854	[52]
Copper, brass and zinc foundries	Germany	1983	<0.05–0.1	[53]
Steel foundries			0.38–57.5	
	Canada	1982		[55]
	Germany	1986, 1983, 1988		[53,54,57]
	Finland	1981		[56]
Blast furnace	Germany	1983	0.05–2.75	[53]
Road paving				
using carbo-bitumen	Germany	1989	0.7–22.0	[63]
using petro-bitumen	Germany	1990	0.02	[64]
	Denmark	1989	4.0	[65]
Roofing	Germany	1983	14.0	[53]
	USA	1982	0.4–11.0	[22,58]
Optical industry	Germany	1983	<0.05–19.7	[53]
Tar refinery	Germany	1979	3.6	[59]
Bitumen manufacture	Germany	1983	<0.5	[53]
Brickyard	France	1987	3.4	[60]
Rubber industry	USA	1980	0–32.3	[61]
	Finland	1982	<0.02–0.25	[62]
	Germany	1983	<0.05	[53]

(gastro-intestinal tract, lung, skin) into other organs [68]. This also may be deduced from the formation of DNA-adducts in the lung following topical application of PAH to the skin of rodents [69–71].

Excretion of orally or intraperitoneally applied PAH is almost complete after 3 days [72–75]. Viau et al. [172] reported the excretion of 57% in the urine and 18% in the faeces of pyrene within 24 h following i.v. injection into rats and Bouchard et al. [173] found half-lives of 5–7 h for 1-OHP. At least for cigarette-smoking humans more than 70% of the PAH inhaled are excreted within 24 h [76]. This is in accordance with a more recent study by Brzeznicki et al. [171] with volunteers exposed to PAH at an aluminium plant reporting a half-life of 9.8 h. Similarly, Viau et al. [174] found a half-life of ~12 h with volunteers exposed to pyrene by ingestion and by dermal application, while Buckley and Lioy reported 4.4 h after dietary exposure to pyrene [121].

5. Biomonitoring of PAH and their metabolites

Initial approaches to utilize the mutagenic potential of urine as a measure for the exposure to PAH led to inconsistent and unsatisfactory results [77–82] which are based on the low sensitivity and the lack of specificity of the method. Actually the parameter measured cannot be unequivocally attributed to PAH or their metabolites.

Accordingly, methods were developed to directly measure the concentration of specific PAH metabolites excreted in urine. The obtained data on urine concentrations of PAH metabolites reflect a more accurate estimation of the quantity of the actual PAH intake of an individual compared to ambient air measurements because it estimates the internal dose from exposure through several routes including both skin absorption and respiratory uptake [199].

For methods of biomonitoring PAH metabolites in urine some requirements have to be met.

1. Analytes (metabolites) should reliably and reproducibly be measurable (no co-elution of analytes).
2. A metabolite concentration of >1–10 ng/l given, the sensitivity of the method should be high enough to be applicable to samples of reasonable size (100–500 ml).
3. The metabolite(s) should be predominantly excreted in the urine rather than in the faeces to minimise the margin of error of the method.
4. As many as possible metabolites (e.g. all phenols and dihydrodiols in case of phenanthrene) of the PAH under study should be measured since the ratio of the various metabolites is not constant but rather varies significantly from one individual to another.
5. The PAH used as indicator should be present as a major constituent of all emissions and more than one PAH and its metabolites should be chosen since the PAH profile differs considerably among emissions.

1-Hydroxypyrene (1-OHP) has been selected as a suitable parameter which at least fulfils the above mentioned preconditions 1, 2 and 5. 1-OHP is the main pyrene metabolite formed in mammals [83–88] although others also have been described, e.g. *trans*-4,5-dihydroxy-4,5-dihydropyrene (K-region dihydrodiol) [83,87], 1,6- and 1,8-pyrene quinone [84], 1,6- and 1,8-dihydroxypyrene [87] as well as two dihydrodiol phenols [87].

Keimig and Morgan [86,89] developed a method to enrich 1-OHP from urine after acidic cleavage of its conjugate by extraction with dichloromethane and subsequent separation by HPLC. This method later was modified by Jongeneelen et al. [90,91] using an enzymatic cleavage of the conjugate with β-glucuronidase/arylsulfatase at pH 5 (1 N HCl and 0.1 mol acetate buffer) at 37°C overnight. Enrichment by SepPak-C_{18} and subsequent HPLC (water–methanol gradient) resulted in recoveries of 78±2% ($n=8$) with a variation coefficient of 2.6% for 60 μg/l 1-OHP using fluorescence detection. These authors further improved their method and reported enhanced recoveries of 83–88±2.9–9.0% for a working range of 8.8/44.0/88 μg/l and a limit of detection of 0.2 μg/l applying a sample volume of 20 μl for the HPLC. They also observed a satisfying long-term stability of 1-OHP for a concentration of 39.6 μg/l over a period of 12 months [92]. Lintelmann and Boos [93,94] developed an automatic HPLC method for the determination of 1-OHP applying a two-column switching technique and adsorption of the analyte on a precolumn with copper phthalocyanine trisulfonic acid immobilised on porous glass. The limit of detection was reported to be 0.01 pmol with a standard deviation of 4.9% ($n=7$) for the reproducibility of an entire analysis within 7 subsequent days.

Elevated excretion of 1-OHP has been observed in workers occupationally exposed to high PAH concentrations (coke plant, road paving, wood impregnation, aluminium smelting) or in patients treated with tar ointments. A selection of data are collated in Table 2. The excretion of 1-OHP is given in μg/g creatinine and/or μg/l. Occasionally data are also given in μg/24 h urine; in Table 2 these values have been transformed into μg/g creatinine based on the assumption of a daily excretion of 1.2 g creatinine in case of females and of 1.8 g in case of males.

Attempts have been made to use the urinary excretion of 1-OHP as a measure for the occupational lung cancer risk [103] and a value of 2.3 μmol 1-OHP/mol creatinine (4.4 μg/g) has been correlated to a lung cancer risk of 1.3 and proposed to be equal to an ‘‘occupational exposure limit’’ (OEL) of PAH for coke plant workers [103,178]. Similarly, for workers in the primary aluminium industry the value equal to the OEL is 4.9 μmol 1-OHP/mol creatinine (9.4 μg/g) [178]. These values are part of a proposed three-level benchmark guideline concept for urinary 1-OHP as biomarker of occupational exposure to PAH [178] and are based on epidemiological

Table 2
Urinary excretion of 1-hydroxypyrene by non-exposed and occupationally PAH-exposed workers

Workplace	No. of subjects	μg 1-OHP/ g creatinine	μg 1-OHP/l	Reference
Non-exposed				
General population (Germany)	8		0.3	[95]
General population (China)	70	0.8–4.6		[97]
Non-smoker	10	0.03–0.21	9.4–13.5	[96]
	11	<0.10–0.30	4.7–17	[98]
	19	0.04		[175]
Smoker	11	<0.10–0.60	<0.10–0.80	[98]
	9	0.06–0.6		[96]
	22	0.08		[175]
PAH-exposed				
Tar ointment-treated patients	8	0.94–5.81		[98]
	25		7.6	[99]
Electrode paste plant	6	7.1–82.6	9.7–73.5	[98]
	4	18.1–29.6	20.1–50.4	[98]
	14	2.2–125.0	3.2–160.8	[98]
	13	0.58–16.8		[98]
	67	0.2–326		[100]
Pre-shift	34	7.5		[102]
Post-shift	34	19.7		[102]
Graphite oil treatment (glass)	10	0.1–3.8	<0.1–4.2	[98]
Aluminium smelting	37	0.7–126.2	0.2–99.2	[98]
	5	2.3–17		[101]
Steel plant (China)	12	3.5		[97]
Tar impregnation	3	7.1–41.2	12.7–77.1	[98]
	3	1.3–38.5		[90]
	3	1.0–9.1		[103]
	1	80.9–158		[104]
	3	8.2–134.9		[103]
	6	4.8–146.5		[103]
	9	1.2–55.9		[103]
Meat smoking	13	<0.1–1.1	<0.1–1.1	[98]
Waste incinerator	53	<0.1–0.8	<0.1–1.3	[98]
Sleeper plant	14	0.4–8.7		[103]
Coal tar distillation	4	2.3–25.1		[104]
Road paving	31	0.8–16.4		[105]
	4		2.6	[95]
using petro-bitumen (shift)	13		1.0–3.5	[106]
(post shift)	20		0.4–2.4	[106]
using carbo-bitumen				
(pre-shift)	15		0.4–10.9	[106]
(shift)	5		1.3–42.4	[106]
(post shift)	12		5.3–92.1	[106]
Coke plant (China)	15	36.3		[97]
	31	15.9		[97]
(Sweden)		1.9–34.7		[107]
(Germany) oven platform	24	3.3–79.4		[108]
(Germany) oven platform	8		14.1–118.5	[51]
Driver	4		8.2–21.0	[51]
Machinist	4		2.0–6.8	[51]
Automotive repair workers				
Non-smoker	40	0.07		[175]
Smoker	25	0.13		[175]

data correlating B[*a*]P exposure with the cancer incidence. This, however, requires that there is a constant ratio between the pyrene and B[*a*]P concentration which only can be assumed for identical workplaces, but even there large variations have been found [51]. The significance of 1-OHP as biomarker for PAH-exposed aluminium plant workers has also been critically discussed by Vu-Duc and Lafontaine [101].

Based on the finding that 1-hydroxypyrene glucuronide (1-OHPG) is the predominant original metabolite excreted in human urine, Strickland et al. [162,195] developed an analytical method for its determination utilizing immunoaffinity chromatography (IAC) in combination with HPLC. Notably, the authors found a fivefold higher fluorescence yield for 1-OHPG than for the unconjugated 1-OHP, whereas Singh et al. [179] reported 1-OHPG to be threefold more fluorescent than 1-OHP. Nevertheless, the method has been validated and compared to other methods, e.g. simple HPLC [168] and IAC combined with synchronous fluorescence spectroscopy [169], all yielding similar results. In a subsequent study Strickland et al. determined the 1-OHPG concentration from occupationally PAH-exposed workers in comparison to lowly or non-exposed controls (2.16 pmol/ml vs. 0.38 pmol/ml); they also found significantly higher 1-OHPG concentrations in smokers (1.82 pmol/ml) when compared to non-smokers (0.75 pmol/ml) [163,164,167]. This could be confirmed by Hong et al. [170] who also found a positive correlation in smokers between 1-OHPG excretion and GSTT1 (glutathione *S*-transferase) expression as well as GSTM1 deficiency. In addition, Kang et al. [165] studied the inter-individual variation of 1-OHPG excretion after the consumption of charcoal-broiled beef and tried to correlate it with the formation of PAH–DNA adducts in white blood cells by the ELISA assay. Urinary excretion of 1-OHPG reached control levels after 24–75 h. DNA adducts, however, increased markedly only in 40% of the subjects studied. The finding that urinary concentrations of 1-OHPG are elevated in smokers and consumers of roasted or grilled meat was confirmed in a later study [166]; however, even in non-smoking subjects without occupational PAH-exposure, 1-OHPG could be detected.

In a number of studies phenanthrene metabolites have been utilised for biological monitoring of PAH since this approach meets all five requirements mentioned above. Phenanthrene can be metabolised to five different phenols (1-, 2-, 3-, 4- and 9-hydroxyphenanthrene) and three dihydrodiols (1,2-, 3,4- and 9,10-dihydroxydihydrophenanthrene) which are predominantly excreted in the form of their sulfates and glucuronides [75,110–116] although the excretion of mercapturic, mercaptopyruvic, mercaptolactic and mercaptoacetic acid has also been observed in rodents [67]. Isomeric phenanthrene phenols can be identified and determined following enzymatic hydrolysis either by GC–MS–MS using derivatisation techniques [51,180] or directly by a HPLC method with fluorescence detection [109]. The latter method has some limitations regarding the separation of all five isomeric hydroxyphenanthrenes but allows the simultaneous determination of other PAH phenols such as 1-OHP, 3-hydroxybenz[*a*]anthracene and 3-hydroxybenzo[*a*]pyrene (3-OHBP) [181,182]. However, the HPLC method with fluorescence detection is not sufficient to determine phenanthrene dihydrodiols with the required sensitivity due to limited natural fluorescence of these compounds [181]. However, an indirect method has been successfully developed to determine phenanthrene dihydrodiols in urine of PAH-exposed human individuals [51,96].

Since phenanthrene is oxidised at three different regions and, in contrast to pyrene, also converted into dihydrodiols the urinary metabolite profile can provide information on the balance of the enzymes involved in these processes. Actually, different cytochrome P450 enzymes exhibit also different regiospecificities for the oxidation of phenanthrene [117,118]. Accordingly, induction of single CYP enzymes by xenobiotics or environmental factors may be recognised by analysing the urinary metabolite profile of phenanthrene; e.g. an induction of CYP1A2 has been found in humans after cigarette consumption [96].

While only minor increases of the total phenanthrene metabolites have been found in smokers when compared to non-smokers [96] no elevated concentrations were found in the urine of passive smokers [119,120]. PAH-rich diet resulted in elevated excretion of phenanthrene phenols; an increase of the dietary phenanthrene concentration from 0.5 to

4.4 μg/kg enhanced, however, the excretion only by a factor of 2 (from 0.76 to 1.46 nmol/mmol creatinine) [120]. This agrees with findings of Buckley and Lioy [121] who reported that an increase of dietary PAH (charcoal-grilled meat with a 250-fold higher B[*a*]P concentration) yielded only a 4–12-fold increase of the urinary 1-OHP concentration when compared to controls, although it is not clear whether pyrene is increased to the same extent as benzo-[*a*]pyrene during the grill process.

In Table 3 data on the urinary excretion of phenanthrene metabolites of variously PAH-exposed subjects are compiled.

It has repeatedly been argued that urinary excretion of phenanthrene or pyrene metabolites do not reflect the internal exposure to *carcinogenic* PAH, since these compounds are biologically inactive and cannot be used as surrogates because PAH profiles may differ significantly between various workplaces. As a result, attempts have been made to determine metabolites of other toxicologically more relevant PAH such as benz[*a*]anthracene and benzo[*a*]pyrene. In general these methods all suffer from the fact that metabolites of higher boiling PAH are predominantly excreted in the faeces rather than in the urine (mostly <1%) and that the concentrations to be expected in the urine are extremely low; accordingly, the methodological margin of error is high and results not very reliable.

In an early paper Becher and Bjørseth [122] described a method for the detection of urinary 3-OHBP using reduction by hydrogen iodide and found levels of 0.12 μg/l in the urine of exposed workers. Later Jongeneelen et al. [81] described a HPLC method for the detection of 3-OHBP reporting recoveries of 43% and a detection limit of 1 ng/24 h urine. In a subsequent study a detection limit of 1 μg/l (4 nmol/l) was reported [91]. However, urinary levels of 3-OHBP in workers of a coal tar distillation plant were found to be below the detection limit and the method appears to be less suitable for biomonitoring. Bouchard et al. [161] improved the sensitivity and reproducibility of the HPLC by addition of ascorbic acid to the eluent. More recently, Gündel and Angerer [123] described a HPLC method with fluorescence detection using an enriching precolumn consisting of silica modified with copper phthalocyanine as developed previously by

Table 3
Urinary excretion of phenanthrene metabolites by non-exposed and occupationally PAH-exposed subjects

Workplace	No. of subjects	μg Phenanthrols/g creatinine	μg Phenanthrols/l	Reference
Non-exposed				
General population	8		3.5	[95]
PAH-poor diet	8	1.3		[120]
PAH-rich diet	8	2.5		[120]
Non-smoker	6	1.5		[120]
Non-smoker	10	1.3		[96]
Smoker	9	1.3		[120]
Smoker	6	2.4		[96]
Smoker (lung cancer)	10	1.6		[96]
PAH exposed				
Road pavers	4		34.9	[95]
Pre-shift	4	6.9–25.7		[120]
Post-shift	5	5.1–286		[120]
Wood impregnation plant	1			
Pre-shift	1	44.5		[120]
Post-shift	25	482		[120]
Coke plant	24		70.3	[95]
Coke plant	8	12		[108]
Oven platform	4		103–686	[51]
Driver	4		45–88	[51]
Machinist			7–22	[51]

Lintelmann and Boos [93,94] which allows the simultaneous determination of 3-OHBP and 3-hydroxybenz[*a*]anthracene in human urine with detection limits of 6 and 8 ng/l, respectively. The chromatograms presented, however, evidenced a poor resolution of the analytes and co-elution of interfering compounds. Nevertheless, concentrations of 3–198 ng 3-OHBP/g creatinine and 15–1871 ng 3-hydroxybenz[*a*]anthracene/g creatinine were found for the post-shift urine of workers ($n=19$) of a fire-proof material plant. Selected data on the urinary content of 3-OHBP are presented in Table 4.

A correlation between the amount of B[*a*]P inhaled during 8 working hours and the excretion of its phenols (sum of 3-, 7- and 9-phenol) was found by Grimmer et al. [125]. An inhaled amount of 17.71 μg B[*a*]P corresponded to a urinary excretion of 0.82 μg B[*a*]P phenols. The detection limit for 3-OHBP using HPLC with conventional fluorescence detection is too high to allow its accurate analysis in urine samples from non-exposed persons such as children [181]. Therefore, other more sensitive methods such as HPLC with laser-induced fluorescence detection (LIF) along with an improved sample clean-up or γ-cyclodextrin-modified micellar electrokinetic chromatography with LIF are necessary for low-level (0.5–8 ng/l) measurements of 3-OHBP in urine [183,184]. However, in coke oven workers significantly enhanced 1-OHP levels were measured in urine samples compared to occupationally non-exposed individuals, but in most samples a corresponding increase in 3-OHBP concentrations could not be found [183].

PAH and their metabolites are transported in the organism in the form of covalently bound protein adducts, e.g. derived from hemoglobin or serum albumin, which can be determined by immunological methods including immuno- (IA) and radio-immuno assays (RIA) as well as enzyme linked immunosorbent assay (ELISA) using poly- or monoclonal antibodies [126–134,158,200–202]. Since the life-span of proteins are constant and no enzymatic repair system is involved, measurements of stable PAH protein adducts are thought to allow a more precise estimation of the internal PAH burden of an individual [202]. However, in general it must be considered that serum albumin and hemoglobin adduct measurements are taken as surrogate of determinations of PAH–DNA-adduct levels, but protein adducts have not been demonstrated to be causally involved in the cell transformation process.

Mostly, these immuno assays have been used to determine B[*a*]P and its metabolites, but due to cross reactions with other PAH and their metabolites these assays exhibit minor specificity. Accordingly, concentrations often are given in ng PAH rather than B[*a*]P. Limits of detection for B[*a*]P have been reported to be 0.05–0.4 ng/ml [132,134]. Significantly enhanced concentrations of PAH adducts with serum albumin were found in foundry workers when compared to controls [160]. Measurements of hemoglobin adducts as molecular dosimetry of PAH dihydrodiol epoxide formation have been performed after acidic hydrolysis resulting in PAH tetraol formation by HPLC or by gas chromatography–negative ion chemical ionization with selected ion monitoring (GC/NICI–MS/SIM) [159,203–205].

Since binding of reactive PAH metabolites to DNA is considered to be the initial step of malignant cell transformation [189], it appears reasonable to determine these DNA adducts formed in tissues and body fluids and to correlate their concentration with the individual cancer risk. Different surrogate measurements are in use to assess the genotoxic dose of PAH exposure in target tissues [196]. One readily accessible matrix for adduct measurements is DNA isolated from blood cells. A substantial number of studies have been performed to determine DNA

Table 4
Urinary excretion of 3-hydroxybenzo[*a*]pyrene by non-exposed and occupationally PAH-exposed subjects

Workplace	No. of subjects	ng 3-OH-BP/l	Reference
Non-exposed	48	6	[124]
Coke plant workers	40	280	[124]
Road pavers	10	19	[124]
Fire-proof material plant	19	5–356	[123]

adducts in white blood cells, but also in other target tissues of humans exposed to environmental and dietary PAH recently reviewed by others [176,190,191]. Recently also studies dealing with the intra-individual variation of DNA adduct levels in humans have been reviewed [192].

Methods applied for the detection of PAH DNA adducts are the ELISA [135,136,196,197], the ultra-sensitive enzymatic radio-immuno assay (USERIA) [137,138], synchronous fluorescence spectrometry (SFS) [139] and ^{32}P-postlabelling (PL) [140,177]. In most cases the limit of detection is in the range of one adduct/10^7–10^8 nucleotides, but methodological improvements have resulted in sensitivities up to one adduct/10^9–10^{10} nucleotides in the meantime [140,177]. As mentioned above, cross reactions with structurally related analytes set limits to the specificity of these assays as well; e.g. in case of the ultimate carcinogen of B[*a*]P, the 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (BPDE) cross reactions were found with the corresponding dihydrodiol epoxides of chrysene and benz[*a*]anthracene [141–144,198]. With these methods significantly enhanced concentrations of PAH–DNA adducts were found for several PAH-exposed workers, selected data of which are presented in Table 5.

In contrast almost no data are available in the literature on the detection of PAH-modified DNA bases in urine which might indicate their low level of appearance. Autrup and Seremet [206] have isolated a urinary guanosine adduct of BPDE following administration of B[*a*]P to rats and this adduct was spectroscopically characterised as a depurinating adduct of BPDE covalently bound to the N7-position of guanosine. However, the excreted amounts of this adduct found in the urine corresponded to less than 0.2% of the administered dose. Recently a study by Roberts et al. [193] reports on the identification and determination of (B[*a*]P-6-yl)-N7-guanosine (BP-6-N7-Gua), another unstable depurinating DNA adduct of B[*a*]P upon one-electron oxidation [194], in human urine by capillary electrophoresis-fluorescence line narrowing (CE-FLN) spectroscopy. With this not easily accessible CE-FLN technique, an absolute detection limit of 2 amol ($\sim 2\times10^{-10}$ M; $S/N\sim3$) is reported for BP-6-N7-Gua and a concentration of 0.9 fmol has been found in urine of individuals exposed to coal-smoke [194]. More recently, Casale et al. [221] have detected both BP-6-N7-Gua and the adenosine analogue BP-6-N7-Ade in the urine of three of seven cigarette smokers (60–340 fmol/mg of creatinine) and three of seven women exposed to coal smoke (0.1–0.6 fmol/mg of creatinine), but not in the urine of control subjects. Interestingly, BP-6-N7-Gua has been detected in the urine of coal smoke-exposed women only, whereas BP-6-N7-Ade has also been found in cigarette smokers. BP-6-N7-Gua has also been identified by the same group previously in the urine and faeces of rats treated with B[*a*]P [207].

As a measure for metabolic activation of B[*a*]P by the BPDE pathway, Simpson et al. [208] have developed a highly sensitive assay to determine urinary levels of B[*a*]P tetraol in humans as permethylated derivative using GC/NICI–MS/SIM technique following an enrichment of the tetraol by reversed-phase and phenyl boronic acid solid-phase extraction with a detection limit of ~1 fmol of the B[*a*]P tetraol derivative ($S/N\sim3$). B[*a*]P tetraol concentrations were in the range of undetectable to 0.2 fmol/μg creatinine for smokers, 0.07–0.92 fmol/μg creatinine for steel workers and 0.7–19 fmol/μg creatinine for psoriasis patients with coal tar ointment [208]. Interestingly, Bowman et al. [209] earlier performed a determination of B[*a*]P tetraol in the same subset of psoriasis patients using immunoaffinity chromatography for analyte enrichment and SFS for quantification developed by Weston et al. [210] and reported a mean value of 150 fmol/ml B[*a*]P tetraol, whereas in the study by Simpson et al. [208] a mean value of 16 fmol/ml urine was observed. The reason for this discrepancy is not clear [208].

For occupationally non-exposed individuals and non-smokers the diet is a major source of the daily amount of PAH uptake [211]. Processing of food and certain cooking methods are known to potentially generate PAH [212–214], but also in uncooked food substantial amounts of PAH can be found reflecting their occurrence in the environment upon incomplete combustion of organic matter [211]. The ingested weekly dose of B[*a*]P from charcoal-broiled and smoked food has been estimated to be in a range of 0.01–4.0 μg/person [44,212]. Although no convincing epidemiological data are available, PAH may

Table 5
PAH–DNA adducts in white blood cells of PAH-exposed workers (in adducts/10^8 nucleotides) [176]

Workplace	No. of subjects	Method[a]	Positive samples (%)	Mean	Range	Reference
Aluminium plant	30	SFS	3.3		n.d.–216.7	[139]
	25	PL		1.48	0.3–4.1	[145]
	21	PL		3.08	0.4–7.1	[145]
	29	PL		1.3	0.2–2.4	[145]
Coke plant	41	SFS	75.6			[137]
		USERIA	66.7		n.d.–1143.3	[137]
	38	SFS	10.5			[146]
		USERIA	34.2	56.7	n.d.–73.3	[146]
	13	HPLC	23.1		n.d.–>456.7	[147]
	51	SFS	47.1	5.2		[148]
(controls)	44	ELISA	29.5	2.8	n.d.–51.3	[148]
	31	ELISA		15.3	n.d.–22.3	[149]
(local controls)	15	ELISA		13.0		[149]
(rural controls)	13	ELISA		2.3		[149]
	63	ELISA		24.5		[149]
	62	PL		11.6		[149]
(local controls)	19	PL		21.1		[149]
(local controls)	18	PL		10.2		[149]
(rural controls)	15	PL		8.2		[149]
(rural controls)	14	PL		4.4		[149]
	68	PL		13.0		[150]
(controls)	13	USERIA		10.7		[150]
	68	USERIA		1.67		[150]
(controls)	13	PL		1.54		[150]
Roofers	28	PL	25.0			[138]
(controls)	9	USERIA	22.2			[138]
	12	USERIA	83.3		n.d.–66.7	[151]
(controls)	12	PL	16.7		n.d.–31.3	[151]
Foundry	20	PL	35.0		n.d.–9.6	[138]
(controls)	9	USERIA	22.2		n.d.–0.3	[138]
	18	USERIA	72.2	8.0	n.d.–13.3	[152]
	13	ELISA	100	20.7	n.d.–31.1	[152]
	4	ELISA	100	50.0	n.d.–28.7	[152]
		ELISA			3.3–66.7	
					26.7–93.3	
(controls)	10	ELISA	20.0	2.2	n.d.–10.0	[152]
	16	PL	17.6	0.06	n.d.–0.6	[153]
	6	PL	77.8	1.2	n.d.–3.0	[153]
	2	PL	66.7	3.5	n.d.–10	[153]
(controls)	9	PL	11.1	0.2	n.d.–1.9	[153]
	53	PL		9.2–26		[154]
	61	PL		0.7–2.4		[155]
(controls)	19	PL		0.2		[155]
Firemen	43	ELISA	34.9	62.3		[156]
(controls)	38	ELISA	34.2	38.3		[156]
	9	PL		2.6		[157]

[a] ELISA, enzyme linked immunosorbent assay; SFS, synchronous fluorescence spectrometry; PL, ^{32}P-postlabelling; USERIA, ultra-sensitive enzymatic radio-immunoassay; HPLC/SFS, high-performance liquid chromatography/synchronous fluorescence spectrometry.

play a role in the etiology of human colorectal cancer. This idea is supported by the demonstration of Alexandrov et al. [215] that colon mucosa is capable of activating B[*a*]P to the DNA-reactive metabolite BPDE, as analysed by B[*a*]P tetraol formation using a HPLC method with fluorescence detection. With this fluorimetric assay these authors also detected BPDE DNA adduct levels in colon mucosa samples of smokers and non-smokers in the range of 0.2–1 adduct/10^8 nucleotides [215].

An experimental protocol using accelerated mass spectrometry (AMS), an ultra-sensitive method to determine isotope ratios [216], has recently been set up that could be applied to determine PAH–DNA adducts [217]. Advantages and limitations for DNA adduct analysis have recently been discussed [216]. This method is based on a postlabelling of the adducts with [^{14}C]acetic anhydride with quantification of ^{14}C by AMS and allow determination of DNA adducts with a 1000-fold increased sensitivity compared to ^{32}P-postlabelling. The method to determine BPDE-N^2-desoxyguanosine, the major DNA adduct formed among the set of stable DNA adducts of B[*a*]P, as the pentakis(acetyl) derivative by AMS after postlabelling with [^{14}C]acetic anhydride has now been optimised and validated [216] for use in human samples including urine. In another study 5 μg ^{14}C-labelled B[*a*]P was given to patients undergoing breast surgery [218]. At surgery, DNA adduct levels of 6.61–208.38 adducts/10^{12} nucleotides were measured by AMS. Given the increased detection limit for DNA adduct measurements, application of AMS technology in the near future has clearly the potential to clarify the role of low level DNA adduct formation by dietary carcinogens such as PAH in the etiology of human malignancies.

6. Conclusions

Measurement of PAH metabolites in human urine is the method of choice to determine recent exposure of an individual to PAH, in particular, when multiple routes of exposure have to be taken into account. 1-OHP excreted in urine is a sensitive biomarker for and significantly correlates with PAH exposure, although a wide interindividual variation occurs frequently. Despite the fact that this interindividual variation in urinary 1-OHP concentration also among similar exposed subjects reflects major individual differences in absorption, metabolism and/or excretion, quantitation of 1-OHP in urine is presently and will also be in the future the principal method applied in industrial health practise to monitor PAH exposure. In addition, several studies clearly demonstrate that expanded biomonitoring of the urinary phenanthrene metabolite profile consisting of five isomeric phenols and three isomeric dihydrodiols could be advantageous. This profile depends on the degree of PAH exposure and yields information on an individual's balance of PAH-metabolizing enzymes like cytochrome P450 and epoxide hydrolase. Since biomonitoring of both pyrene and phenanthrene metabolites are not reflecting the internal exposure to carcinogenic PAH, there is an obvious need for methods to allow determination of effect markers of carcinogenic PAH like B[*a*]P. Recent strategies adopted to determine urinary tetraol metabolites of B[*a*]P, although excreted in low concentrations, but related to its bioactivation pathway, may point to the right direction of future biomonitoring, but appears at present to be too laborious for routine analysis. Methods to determine purine base adducts of B[*a*]P at low concentrations in urine such as capillary electrophoresis with laser induced fluorescence detection or AMS technology are certainly suitable for studies with small sample size, but do not have the potential to allow future routine measurements in environmental and occupational medicine.

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