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Urinary elimination kinetics of 3-hydroxybenzo(*a*)pyrene and 1-hydroxypyrene of workers in a prebake aluminum electrode production plant: Evaluation of diuresis correction methods for routine biological monitoring

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous carcinogenic pollutants emitted in complex mixtures in the ambient air and contribute to the incidence of human cancers. Taking into account all absorption routes, biomonitoring is more relevant than atmospheric measurements to health risk assessment, but knowledge about how to use biomarkers is essential. In this work, urinary elimination kinetic of 1-hydroxypyrene (1-OHP) and 3-hydroxybenzo(*a*)pyrene (3-OHBaP) were studied in six electrometallurgy workers after PAHs exposure. Spot samples were collected on pre- and post-shift of the last workday then the whole urinations were separately sampled during the weekend. Non-linear mixed effects models were built to study inter- and intra-individual variability of both urinary metabolites toxicokinetic and investigate diuresis correction ways. Comparison of models confirmed the diuresis correction requirement to perform urinary biomonitoring of pyrene and BaP exposure. Urinary creatinine was found as a better way than specific gravity to normalize urinary concentrations of 1-OHP and as a good compromise for 3-OHBaP. Maximum observed levels were 1.0 μmol/mol creatinine and 0.8 nmol/mol creatinine for 1-OHP and 3-OHBaP, respectively. Urinary 1-OHP concentrations on post-shift were higher than pre-shift for each subject, while 3-OHBaP levels were steady or decreased, and maximum urinary excretion rates of 3-OHBaP was delayed compared to 1-OHP. These results were consistent with the sampling time previously proposed for 3-OHBaP analysis, the next morning after exposure. Apparent urinary half-life of 1-OHP and 3-OHBaP ranged from 12.0 h to 18.2 h and from 4.8 h to 49.5 h, respectively. Finally, inter-individual variability of 1-OHP half-life seemed linked with the cutaneous absorption extent during exposure, while calculation of 3-OHBaP half-life required the awareness of individual urinary background level. The toxicokinetic modeling described here is an efficient tool which could be used to describe elimination kinetic and determine diuresis correction way for any other urinary biomarkers of chemicals or metals exposure.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous pollutants emitted during incomplete combustion of organic matter and distillation of coal or petroleum. They are found in the atmosphere as complex gaseous and particulate mixtures, whose composition varies according to the emission sources. Within this chemical family, benzo(*a*)pyrene (BaP) is classified as a proven human carcinogen while several other PAHs are classified as possible or probable human carcinogens (IARC, 2010). By contrast, pyrene is a non-carcinogenic PAH, extensively studied due to its abundance in mixtures. Environmental exposure occurs by tobacco consumption, diet, and atmospheric pollution. In addition, high occupational exposure levels are reported in some industries using products derived from coal (Unwin et al., 2006). In France,

Abbreviations: PAHs, Polycyclic Aromatic Hydrocarbons; 3-OHBaP, 3-hydroxybenzo(*a*)pyrene; 1-OHP, 1-hydroxypyrene; SG, Urinary specific gravity

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1.6 million workers are exposed to PAHs with 93,000 worked in the metallurgy industry (Guignon and Sandret, 2005) including carbon electrode manufacturing, which is classified as probably carcinogenic to humans (IARC, 2010). In this sector, the mean levels reported for BaP and pyrene were 4.9 μg/m^3 and 11.2 μg/m^3, respectively (Forster et al., 2008). These levels were largely higher than the French recommended value for BaP, equal to 150 ng/m^3. However, atmospheric measurement cannot assess human exposure: wearing respiratory mask can generate an over-estimation of exposure and dermal uptake, which is the main absorption way of PAHs for numerous tasks, can lead to an under-estimation of exposure (Elovaara et al., 1995; VanRooij et al., 1993).

For assessing health risk, biomonitoring is more relevant than air monitoring because it allows the evaluation of the internal dose of chemicals. Urinary analyses are widely used, because exposure biomarkers accumulate in the bladder between two urinations and it is very easy to collect urine samples. To take into account the variation of diuresis, urinary concentrations stated in mass per volume unit need to be corrected. Normalization by urinary creatinine is mainly used although age, sex, ethnicity and muscular mass influence its excretion and can change the interpretation of urinary biomarkers levels (Truchon et al., 2014). Furthermore, this correction is valuable only if metabolites undergo the same excretion mechanisms than the creatinine, *ie* via glomerular filtration (Boeniger et al., 1993). To overcome these difficulties, normalization by specific gravity (SG) has been proposed to take into account fluctuations in urine dilution (Sauvéet al., 2015). Nowadays, research on the optimal approach to adjustment of urinary concentrations in spot urine samples, in order to perform biomonitoring, is still an important challenge (Weaver et al., 2015).

Urinary 1-hydroxypyrene (1-OHP), the main metabolite of pyrene, was proposed as the first biomarker of PAHs exposure by Jongeneelen in 1985 (Jongeneelen et al., 1985). It is the most commonly used biomarker to perform PAH biomonitoring (Strickland et al., 1996) and many exposure data are available (Hansen et al., 2008). 1-OHP was correlated with genotoxic effect in some studies (Siwińska et al., 2004; Talaska et al., 2014), but not systematically (Marczynski et al., 2011), probably due to the high variability of the BaP/pyrene ratio according to industrial sectors and activities of workers (Barbeau et al., 2015; Lafontaine et al., 2004). Thus, 1-OHP might be not the most appropriate biomarker to assess carcinogenic PAHs exposure. Urinary 3-hydroxybenzo(*a*)pyrene (3-OHBaP) is more appropriate to evaluate carcinogenic exposure because it is an urinary metabolite of BaP (Boogaard, 2008). Due to a complex BaP metabolism with production of many metabolites (Gelboin, 1980) and elimination predominantly via the feces, urinary 3-OHBaP represented only 0.21% of BaP dose injected in rats (Marie et al., 2010). A high sensitive and reliable analytical method has recently been developed to use urinary 3-OHBaP as biomarker for occupational biomonitoring (Barbeau et al., 2011). The maximum urinary 3-OHBaP concentration of workers involved in an electrode manufacturing plant was found at 5.27 nmol/mol creatinine, while maximum of 1-OHP was higher by three orders of magnitude, reaching 6.99 μmol/mol creatinine (Barbeau et al., 2014).

In order to set the best sampling time representing the exposure and being convenient to implement, biomonitoring requires knowledge about elimination kinetic and related influencing factors. The different absorption routes affect considerably the urinary elimination rate of 1-OHP. In human, the maximum urinary excretion took place between 2.2 h and 9.7 h after a dietary exposure (Buckley and Lioy, 1992; Chien and Yeh, 2010; Li et al., 2012), while this maximum appeared 1–2 h after the post-shift for a respiratory absorption (Lafontaine et al., 2002) and 10–15 h for a dermal uptake (Viau and Vyskocil, 1995). In the same way, the urinary half-life of 1-OHP ranged from 3.0 to 5.7 h (Li et al., 2012), from 3.7 to 9.9 h (St Helen et al., 2012) and from 11.5 to 15 h (Viau and Vyskocil, 1995) after oral, inhalation and dermal absorption, respectively. Thus, in addition to individual characteristics, differences of exposure conditions in workplaces, especially the cutaneous absorption extent, could explain the important variability of apparent 1-OHP half-lives observed in occupational studies, as well in different industrial sectors (Lafontaine et al., 2004), as in the same sector for several tasks (Buchet et al., 1992; Sobus et al., 2009). Pre-shift urine sample collected at the end of the workweek is considered as the best sampling time to analyse 1-OHP when the main route of exposure is skin uptake, while post-shift sample collected at the end of the workweek remains the best if inhalation is the main way of absorption (Bouchard and Viau, 1999). However, there is still no consensus and ACGIH recommends only post-shift at end of workweek as sampling time for 1-OHP (ACGIH, 2015). For 3-OHBaP, maximum urinary excretion appeared between 10 and 17 h after the post-shift (Gendre et al., 2002) and the only apparent urinary half-life calculated in humans for this metabolite was 8.8 h (Lafontaine et al., 2004). But urinary 3-OHBaP concentrations measured in the urine collected at the post-shift of the penultimate workday were not statistically different than those found at the pre-shift of the last workday, when the exposure is relatively constant over the workweek (Barbeau et al., 2014). Conversely, when occupational exposure is variable during the workweek, 60% of the maximum urinary 3-OHBaP concentrations were found on pre-shift, versus 17% on post-shift of the last workday (Barbeau et al., 2015). Currently, pre-shifts of the first and of the last workdays remain the proposed urine sampling times to analyse this metabolite (Gendre et al., 2004).

The aim of this study was to fill the lack of data about the toxicokinetic of urinary 3-OHBaP and make a comparison with 1-OHP, the common PAH exposure biomarker. Furthermore, the usefulness of different kinds of diuresis correction was studied for these urinary metabolites. The maximum urinary excretion rate, the influence of inter-individual variability and the appropriate normalization technique of urinary concentrations were studied using non-linear mixed effects models in a group of electrometallurgy workers.

2. Materials and methods

2.1. Study population

The subjects were 6 non-smoking, healthy, male volunteers between 30 and 60 years old, working in a prebaked electrodes production plant. A questionnaire was completed by each worker in order to inform them about the study and obtain their consent. No special instruction concerning diet was given. Urinary analyses were prescribed by the occupational physician of the plant as part of PAHs exposure monitoring. During the last day of the workweek, one worker (W1) stored the cooled electrode after its extrusion, three workers (W2, W3, W4) loaded raw materials (carbon and pitch coke), one (W5) was in charge of administrative tasks in an office and the last one (W6) performed electrode extrusion and cleaning installations. All workers carried P3 masks and handling gloves, except workers 5 and 6.

2.2. Urine collection

Urine samples were collected at the beginning and at the post-shift on the last workday of the week in 50 ml propylene bottles. From this post-shift, subjects collected separately all urinations in their entirety in 500 ml propylene bottles during the weekend. Urine volume was measured at the laboratory before storage at