



Biomarkers of polycyclic aromatic hydrocarbon exposure in European coke oven workers



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ABSTRACT

Biomonitoring is an excellent method for capturing the results of all exposures, regardless of route. Coke oven workers include certain groups that have the potential for high exposure to polycyclic aromatic hydrocarbons (PAH) and other materials. Biomarkers of exposure to these agents include PAH metabolites as markers of internal dose and carcinogen-DNA adducts as measure of effective dose. The purpose of this study was to determine the levels of these biomarkers in persons with different job duties in a modern coke oven plant. We report that the mean levels of 1-hydroxypyrene (1HP) and carcinogen DNA adducts in the exfoliated urothelial cells of coke oven workers are increased the closer a group of workers is to the ovens and highest in the top oven workers with average 1HP level of 11.6 µg/l and 22 adducts per 10⁹ unadducted nucleotides. Both 1HP and carcinogen DNA adduct levels increased in supervisors, area workers, side oven workers, top and side oven workers, and top oven workers, respectively. These data are the first to demonstrate an increase in target organ genotoxicity in coke oven workers and a relationship with other biomarkers. Future studies will determine the identity of the DNA adducts, their correlation with 1HP levels and the relationship between levels in individual workers.

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1. Introduction

Coke production and associated exposures have been evaluated multiple times by the international agency for research on cancer (IARC) and most recently in 2012 (IARC, 2012). In particular, increased risks for lung cancer were observed for coke production workers and most likely due to the presence of polycyclic aromatic hydrocarbons (PAH) in coke oven mixtures. Overall, IARC concluded that coke oven emissions produce a complex mixture of aromatic DNA adducts and working in coke production is classified as carcinogenic to humans. Most importantly, recent studies also show an excess risk for bladder cancer in PAH-related industries (Rota et al., 2014; Bosetti et al., 2007). In addition, the urinary mutagenic activity in non-smoking

coke oven workers was associated with 1-hydroxypyrene (1HP) in urine (Simioli et al., 2004).

1-Hydroxypyrene (1HP) is the major metabolite of pyrene, a PAH with little or no carcinogenic potency (Collins et al., 1998). Regulatory and advisory bodies are increasingly turning to biomarkers like 1HP as surrogates exposure to the carcinogenic PAH since pyrene is relatively abundant in PAH mixtures, and a sensitive method is available to its determination in urine (ACGIH, 2013; DFG, 2000; ATSDR, 1995). In addition, the excretion of 1HP in urine is well associated with the excretion of 3-hydroxybenzo[a]pyrene in urine, a metabolite of carcinogenic benzo[a]pyrene (Förster et al., 2008; Käfferlein et al., 2012). Finally, several nations have conducted population based screening for 1HP in urine and found that this compound is detectable in almost all samples (ATSDR, 1995). The data from these studies has proven invaluable to understanding the range of exposures in the general population. Nonetheless, linking levels of 1HP or any other PAH metabolite to health outcome has not been possible since the metabolite level is usually a reflection of a very recent exposure and the assumption of a constant exposure based upon a single exposure estimate is tenuous. Subsequently, the advisory 1HP

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levels suggested for exposure have not yet been based on a direct relationship with health outcome, but upon either population background levels (the level above which occupational exposure is assumed) (ACGIH, 2010, 2013) or the current levels in populations where disease has been reported (Jongeneelen, 2004), or as a maximum level of workplace practice (ATSDR, 1995). A novel approach may be to relate the 1HP level of workers with effective dose biomarkers and to determine a specific 1HP level where an increase in the effective dose biomarker becomes evident.

Suitable biomarkers of effective dose of PAH are DNA adducts. Once absorbed, some PAH are metabolized to species capable of binding to DNA and initiating the carcinogenic process (Poirier, 1997). The mode of action of carcinogenic PAH is to covalently bind to DNA and cause a replication error and a subsequent mutation. Individual and specific mutations remain difficult to detect and quantify so most researchers measure the extent of DNA binding or adduct formation to estimate the effective dose to the genome of carcinogen exposure. There is a probabilistic relationship between DNA adduct levels and cancer risk which has been documented directly in prospective studies (Ross et al., 1992) and indirectly through studies of DNA adduct levels in populations with known risk (Rothman et al., 1996; Talaska et al., 1994, 1996, 2002; Vineis et al., 1996). Sensitive methods of analyzing DNA adduct levels have led to applications that allow non-invasive exposure estimates from internal organs (Talaska et al., 1996).

In the current brief report we present initial data on the association between 1HP in urine and the formation of a DNA adduct in exfoliated urothelial cells of coke oven workers. The data sheds some new light on the increased risk of bladder cancers which have been previously reported in PAH-industries.

2. Materials and methods

2.1. Study subjects

The study collective consisted of 32 coke oven workers including 3 supervisors, 7 top oven workers, 10 side oven workers, 2 top and side oven workers, and 10 side product area workers. All workers were male with a median age of 49 years (range 32–53 years). 16 persons were smokers. The working tasks included coal filling (e.g., top-side workers) and coke pushing and transfer (e.g., side oven workers). Top and side oven workers were employees with mixed working tasks. The supervisors were involved in keeping the coking process running. Side product workers were working on the area of the coke plant (e.g., in the ammonium sulphate plant, locksmith, etc.) but were not directly involved in the coke oven work. Median time of employment was 15 years (range 2–35 years). Complete personal protective measures including breathing masks (e.g., P2 dust masks) and leather gloves were supplied by the company and workers were encouraged (but not forced) to use them on a voluntary basis. The gloves were worn for a prolonged period of time by all workers in the plant with a median time of 5 h/shift (range 1–7 h/shift). Because PAH can be taken up by multiple routes including inhalation, dermal and even oral absorption (open mouth, hand mouth contact) and cause systemic effects the focus was on biomarkers of internal and effective dose (Marczynski et al., 2009).

In order to evaluate internal and effective dose during similar work tasks individual results were pooled for analyses as follows: those whose primary work task was to work directly on the ovens (side oven workers, top and side oven workers and top oven workers) were pooled as oven workers and those whose primary

work area was not on the the ovens themselves, supervisors and side product area workers, were also pooled.

2.2. Biological monitoring

Preshift urine samples were used in order to estimate better the chronic exposure of the participants since 1HP has a triphasic elimination pattern with half lives of 5.5 h, 23 h, and 384 h. Preshift samples, therefore, emphasize the contribution of the longer lived compartments (ACGIH, 2013). All urine samples were collected mid-week. Urine samples were treated with glycerin (10%, v/v 9/1), frozen and shipped on dry ice to the University of Cincinnati where they were kept frozen until analysis. Samples were thawed, then filtered as described earlier (Talaska et al., 1993), the supernatant was used for the analysis of 1HP and the cells captured on the filters were used for isolation of DNA and carcinogen-DNA adduct analysis. 1HP levels and DNA adduct levels were determined as described earlier (Peters et al., 2008) using the methods of Jongeneelen et al. (1985) for 1HP and Reddy and Randerath (1986) as modified (Rothman et al., 1996) for DNA adduct levels in exfoliated urothelial cells. The limit of quantification for 1HP was 0.03 µg/l and for DNA adducts 0.5 adducts per 10⁹ unadducted nucleotides. Urinary creatinine was measured in urine according to Jaffé and to verify the functional status of the workers' kidneys. All workers showed creatinine levels between 0.3 and 3.0 g/l; thus, within the range of being acceptable for biomonitoring analyses (WHO 1996; ACGIH 2013; UBA 2005).

3. Results and discussion

Sufficient DNA was obtained from all samples to provide a limit of quantitation of 0.5 adducts per 10⁹ unadducted nucleotides (relative adduct labeling (RAL)). Only one adduct (adduct 4) out of 6 adducts identified in the study was significantly correlated with 1HP levels in coke oven workers (correlation coefficient 0.69, $p < 0.001$). The median 1HP level and DNA adduct level in all workers was 1.9 µg/l and 3.6 adducts per 10⁹ unadducted nucleotides. Fig. 1 shows the mean levels of 1HP (and standard error of the mean (SEM) in subgroups of coke oven workers including supervisors (supers), side product area workers (area), side oven workers (side oven), workers of both the top and side of the ovens (top and side oven) and top oven workers (top oven). Fig. 2 displays the mean and SEM. All oven workers (top, top and side, and side oven workers) had the highest levels of both 1HP and adduct 4 compared to the side product workers and the supervisors. Since there were no significant differences between workers who worked away from the ovens (supervisors and side product area workers) and those who did (top, top and side, and side oven workers) we also pooled these groups together to compare the difference between oven and non-oven work. Figs. 3 and 4 display the 1HP and adduct 4 data (respectively) of the comparison of workers who worked away from the ovens (mean 1HP: 2.5 µg/l; mean adduct 4: 3.2 adducts/10⁹ nucleotides) and oven workers (mean 1HP: 7.4 µg/l; mean adduct 4: 17.4 adducts/10⁹ nucleotides). In each case the difference between the two groups was statistically significant at $p < 0.02$. Sixteen of 32 workers reported current cigarette smoking. However, overall smokers did not have higher levels of either 1HP or DNA adducts than non-smokers. The effect of smoking appeared to be greater in workers who did not work directly near the ovens (supervisors and side product area workers). In this group the correlation between the numbers of cigarettes smoked were 0.63 (with 1HP) and 0.7 (with adduct 4), but this was not statistically significant due to the small sample size.

There have been many recommendations made as to the level of 1HP that may be used as a workplace standard for exposure. The

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