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A guidance value of 1-hydroxypyrene in urine in view of acceptable occupational exposure to polycyclic aromatic hydrocarbons

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HIGHLIGHTS

- The recommended state-of-the-art limit level guidance of 1-hydroxypyrene in urine is 1.0 μmol/mol creatinine.
- It is valid for coke oven workers with a typical pyrene/BaP ratio of 2.5.
- For work environments with a deviating PAH-profile an adjustment procedure with the pyrene/BaP ratio is suggested.

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ABSTRACT

Occupational exposure limits for carcinogens are increasingly based on excess lifetime risks of cancer. Acceptable limits in some countries in Europe are set at 4/1000 (=highest tolerable risk level) and 4/100,000 (=acceptable risk level) based on 40 year working exposure for the occupational population. When an exposure metric is used that is fairly new, epidemiology does not offer dose–response data that is needed for the derivation of a science based limit value. The urinary concentration of 1-hydroxypyrene is a fairly new bioindicator of exposure to polycyclic aromatic hydrocarbons (PAH). Nowadays, measurements of 1-hydroxypyrene in urine are routinely applied to control industrial exposure to PAH as present in coke ovens and primary aluminium production and to control exposure of professionals when handling coal tar derived products. Due to lacking dose–response data from epidemiological studies, a cancer risk based limit of 1-hydroxypyrene in urine cannot be derived. An alternative derivation procedure is proposed for the limit value that can be used as guidance for the intermediate period. For the period in-between, it is suggested to take the 'no observed genotoxic effect level' (=NOGEL) in PAH-exposed workers as the point-of-departure for setting the limit value. The genotoxic endpoints are genotoxic effects in white blood cells of PAH-exposed workers (chromosomal aberrations, sister chromatid exchanges, micronuclei, comet assay, DNA adducts).

In order to assess the point-of-departure for limit setting, cross-sectional studies were searched for that report on the response of early genotoxic effects in white blood cells of workers that could be related to the degree of PAH-exposure (expressed as 1-hydroxypyrene in urine). Nine cross-sectional studies were traced that met these requirements. From each study, the concentration of 1-hydroxypyrene in end-of-shift urine samples was determined, at which no genotoxic effects was found. From 4 out of 9 studies a no-observed genotoxic effect level could be derived, the lowest level was 1.0 μmol/mol creatinine. This limit level is recommended as a state-of-the-art guidance, valid when the PAH-profile in the work environment is similar to that of coke oven with a typical pyrene/BaP ratio of 2.5. For work environments with a deviating PAH-profile an adjustment procedure with the pyrene/BaP ratio is suggested.

1. Introduction

Polycyclic aromatic hydrocarbons (PAH) are compounds consisting of carbon and hydrogen with at least two conjugated aromatic rings. In the subgroup of PAH with 4 and more rings the carcinogenic PAH are found. Benzo(*a*)pyrene (BaP), a 5-ring PAH, is recognised as a potent carcinogenic PAH. This subgroup is low-volatile and can be inhaled, mainly as compounds in

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particulate matter. After uptake in the body the PAH are metabolised to intermediates. Some of these metabolites are responsible for the ultimate mutagenic and carcinogenic effects. After some time, the major part of the metabolites of low weight PAH is excreted in urine. A smaller proportion leaves the body with the faeces, whereas for high weight PAH the faecal route is the main elimination route.

The level of PAH metabolites in urine can be used as a biological indicator of exposure to PAH. Studies are especially available on the excretion of 1-hydroxypyrene in the urine. The method was introduced in 1985 (Jongeneelen et al., 1985, 1987) and is now applied worldwide in industry with PAH-emissions and PAH-exposures (especially coke ovens, primary aluminium industry and coal tar distillation). The first workshop on 1-hydroxypyrene showed that this metabolite can easily been measured in human urine, including of those who are not occupationally exposed (Levin, 1995). Many papers were published since then and several reviews of this method of monitoring of PAH were compiled in the period after introduction (Buchet et al., 1992; Levin, 1995; Dor et al., 1999; Bouchard and Viau, 1999; Unwin et al., 2006; Hansen et al., 2008).

In studies with additional personal air sampling, there was not always a correlation to the PAH-concentration in the ambient air. Most probably, this is primarily due to the fact that pyrene and other PAH are not only absorbed by inhalation, but also through the skin (Greim, 2008). The 1-hydroxypyrene concentration in the urine might also depend on the metabolic activity at the point of entry into the organism (primarily the skin and the respiratory tract) and its distribution in the human body. In a study with 170 workers exposed to PAH, genetic polymorphism of the enzymes was largely excluded as the most substantial explanation for the inter-individual differences in 1-hydroxypyrene excretion. Only three of the 11 polymorphisms tested had any influence on excretion. But with factors of 1.4–1.6, these differences were very small (Rihs et al., 2005).

Recently, Yamano et al. (2013) studied personal exposure of coke oven workers by measuring 15 airborne PAHs and calculated the carcinogenic potency of the exposure and concluded that urinary 1-hydroxypyrene, among 10 other urinary hydroxylated PAH-metabolites, was the most comprehensive carcinogenic biomarker of exposure to PAHs (Yamano et al., 2013). Käfferlein et al. (2012) showed, based on studies with DNA damage in workers exposed to BaP, that 1-hydroxypyrene is the preferred parameter to assess exposure of PAH at the workplace among a series of urinary PAH-metabolites.

Up to now two proposals for setting a limit value of 1-hydroxypyrene in urine have been published:

(1). The British Health & Safety Executive (HSE) has set a hygiene based Biological Monitoring Guidance Value (BMGV) for 1-hydroxypyrene at 4.0 μmol/mol creatinine in post-shift samples (HSE EH40, 2011; Unwin et al., 2006). The value is derived from the 90-percentile of measurements in British companies in various industries with good industrial hygiene practice. The BMGV is not a health-based limit. HSE says that BMGVs are non-statutory and any biological monitoring undertaken in association with a guidance value needs to be conducted on a voluntary basis. BMGVs are intended to be used as tools in meeting the employer's primary duty to ensure adequate control. Where a BMGV is exceeded, it does not necessarily mean that any corresponding airborne standard has been exceeded, nor that ill health will occur. It is intended that where they are exceeded, this will give an indication that investigation into current occupational hygiene measures and work practices is necessary.

(2). The American Conference of Governmental Industrial Hygienists (ACGIH) has also prepared a guideline for biological monitoring of PAH (ACGIH, 2010). ACGIH concluded that data were not sufficient to justify a numerical Biological Exposure Index (BEI) scientifically, based on health outcome or based upon correlation with an airborne exposure as the TLV. Therefore, the "Nq" notation (=nonquantitative) was recommended due to insufficient data to support a numerical BEI. However, the BEI Committee of the ACGIH stated that presence of 1-hydroxypyrene in urine above a benchmark level of about 1 μg/L (=0.5 μmol/mol) is evidence of occupational exposure to PAH, since very few non-occupationally exposed persons, smokers or nonsmokers, will excrete this amount of 1-hydroxypyrene. ACGIH recommends a benchmark value of 1.0 μg 1-hydroxypyrene/L (=0.5 μmol/mol) in urine to be considered as a post-shift level indicating occupational exposure to PAH. The BEI Committee could not determine whether this level is an indication of a health risk or an overexposure.

Occupational exposure limits for carcinogens are nowadays often based on a specified excess risk rate of cancer. Acceptable cancer risks values are set at certain excess mortality rates (in Germany and The Netherlands: 4/1000 as the highest tolerable risk level and 4/100,000 as the acceptable target risk level, based on 40 year working exposure for the occupational population). In Germany, the exposure–risk relationship for BaP led to a limit concentration of BaP of 700 ng/m^3 at the tolerable risk level, whereas a concentration BaP of 7 ng/m^3 was proposed to meet the acceptable risk level (BAUA, 2011). The Netherlands Health Council did a similar exercise and recommended a little lower cancer risk-based Occupational Exposure Limit (OEL) for benzo(*a*)pyrene (BaP) of 5.7 ng BaP/m^3 at the acceptable target risk level, respectively, 550 ng BaP/m^3 at the highest tolerable risk level, valid for and PAH-exposure from coal-derived sources (Health Council of Netherlands, 2006).

However, a risk-based limit level of the bioindicator 1-hydroxypyrene in urine has not been recommended, nor considered. In The Netherlands several industrial companies with PAH-exposure apply regular biological monitoring programmes and unions support this approach. The companies involved apply routine measurements of urinary 1-hydroxypyrene as a tool to control occupational hygiene. They are willing to continue the biological monitoring of PAH and are seeking for a guidance value for the interpretation of urinary 1-hydroxypyrene measurements that is equivalent to the risk based airborne Occupational Exposure Limit (OEL) of BaP. Because results of epidemiological studies and/or animal studies with dose–response data of cancer are lacking, the derivation of an excess cancer mortality risk based limit of 1-hydroxypyrene in urine is not yet possible. In this paper the key challenge is to propose an acceptable limit value of 1-hydroxypyrene in urine that can be used as a guidance value for the intermediate period. The composition of PAH-mixtures varies considerably across different occupational settings in various industries. This means that a single indicator cannot apply to all workplaces (Bouchard & Viau, 1999). The additional challenge is to propose an adjustment procedure by which 1-hydroxypyrene in urine can be the surrogate bioindicator for variable PAH mixtures.

2. Methods

2.1. Genotoxic response as biological endpoint

Benzo(*a*)pyrene and most PAH are genotoxic carcinogens. There are neither epidemiological studies nor animal studies of the relationship between exposure to PAH, measured as 1-hydroxypyrene in urine and the risk of developing cancer. A risk-based derivation

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