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Derivation of a dose descriptor for the internal exposure to benzene

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ABSTRACT

In 2022, the Human Biomonitoring (HBM) Commission of the German Environment Agency developed a concept for the risk assessment of carcinogenic substances in HBM studies, focusing on the internal exposure to genotoxic carcinogens. This concept involves deriving a dose descriptor for the internal exposure based on the concentration of specific biomarkers. In this study, the HBM Commission applies this new concept to benzene as a model substance, using urinary S-phenylmercapturic acid (S-PMA) as specific urinary exposure biomarker for benzene in HBM studies. The HBM Commission estimates additional lifetime cancer risks from benzene exposure using S-PMA HBM data from the German Environmental Specimen Bank and the German Environmental Survey (GerES V). Results indicate that there are considerable cancer risks for benzene in the general population for both adults and children. These findings highlight the importance of considering cumulative environmental exposures in public health risk management and demonstrate the applicability of HBM concepts for risk assessment of carcinogenic substances. Future studies should expand this approach to other environmental carcinogens to better inform mitigation strategies.

1. Introduction

While a threshold dose is generally assumed to exist for non-genotoxic carcinogens allowing the derivation of HBM values, a similar assessment approach is not feasible for the exposure assessment of the general population to genotoxic carcinogens in human biological material. To close this gap, the Human Biomonitoring Commission at the German Environment Agency (HBM Commission) in 2022 published a newly developed concept for the assessment of carcinogenic substances in population-based human biomonitoring (Human Biomonitoring Commission of the German Environment Agency, 2022; Wollin et al., 2022).

A key element of this approach is the derivation of a dose descriptor for the internal exposure. In regulatory toxicology, the term *dose descriptor* is used to describe the relationship between a specific effect of a chemical substance and the dose at which it occurs (ECHA, 2012). Dose descriptors of carcinogens are obtained from human and animal studies and can be expressed, for example, as T25 (the dose that is expected to cause 25% additional tumour incidence) or BMD (benchmark dose that leads to a (carcinogenic) effect with a previously defined probability).

By definition (Wollin et al., 2022), the dose descriptor for the

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internal exposure of humans with a genotoxic carcinogen in the context of HBM is based on a unit dose of the external exposure (unit risk, oral slope factor) and represents the calculated internal exposure expressed as the concentration of the biomarker in a body fluid such as blood or urine. While the parameters commonly used in the toxicological-regulatory context for the quantitative description of the additional lifetime cancer risk caused by a substance, such as unit risk or oral slope factor, are referred to in the concept as "quantitative dose descriptors of external exposure", the dose descriptor of the internal exposure (DD_i) refers to the internal exposure to a substance or its specific metabolites relevant for HBM. Thus, the dose descriptor of the internal exposure can be used to calculate corresponding lifetime cancer risks for HBM data in the relevant body fluid. This is a simplified 'Tier 0 approach' that is to be applied exclusively to data aggregated from a defined human population.

The feasibility of the concept for assessing carcinogenic substances in HBM studies was agreed to be tested during a validation phase using selected model substances. The following considerations are made to derive a dose descriptor for the human carcinogen benzene and its urinary exposure biomarker S-phenylmercapturic acid (S-PMA), to evaluate the inherent model assumptions, the uncertainty of necessary parameters and to represent an informed opinion about the new approach. This publication represents the agreed and consolidated opinion of the German HBM Commission.

2. Material, parameters and methods

2.1. Characterization of the compound

Benzene is a highly volatile aromatic hydrocarbon primarily produced through the recovery of petroleum-based sources. It is used as a raw material in the production of numerous chemicals and products, including cleaning agents, paints, and plastics. Benzene enters the environment from both anthropogenic and natural sources, including the combustion of fossil fuels, wood burning (such as forest fires), gasoline vapors, vehicle emissions, and cigarette smoke (ATSDR - Agency for Toxic Substances and Disease Registry, 2007; ATSDR - Agency for Toxic Substances and Disease Registry, 2024; IARC, 2017).

For humans, inhalation is considered the most relevant uptake pathway. After absorption, benzene is rapidly distributed in the body and a high distribution to fatty tissue of various organs due to its high lipophilicity might be expected (ATSDR - Agency for Toxic Substances and Disease Registry, 2007; ATSDR - Agency for Toxic Substances and Disease Registry, 2024). It is not to be expected that benzene accumulates to any significant extent in biota, as shown by experimental results. Benzene is primarily oxidised in the liver to several reactive metabolites that can exert a broad spectrum of toxic effects.

Following acute exposure, benzene has a non-specific (narcotic) effect on the central nervous system (CNS). The chronic effects include bone marrow damage and blood count changes, impairment of the immune system and genotoxic effects (chromosomal aberrations). Benzene is a proven human carcinogen (IARC, 2017). Epidemiological studies show clear associations between occupational exposure to benzene and the occurrence of leukaemia and lymphoma. In animal experiments, benzene also leads to the development of tumours in other tissues and organs (IARC, 2017). Unchanged benzene is largely exhaled via the lungs and to a very limited extent excreted via the kidneys in the urine. The metabolites formed are water-soluble and are excreted in the urine via the kidneys. Urinary benzene and the metabolite S-phenylmercapturic acid (S-PMA) are specific biomarkers for benzene exposure (ATSDR - Agency for Toxic Substances and Disease Registry, 2024). S-PMA is commonly used in occupational and environmental medicine as a well-established, robust and sensitive urinary biomarker for exposure to benzene in the low-exposure range (Schettgen et al., 2008, 2010).

2.2. Consideration of the mechanism of action of carcinogenesis

Due to its genotoxic effects, national and international committees generally classify benzene as a genotoxic carcinogen, for which no safe dose can be derived. Over the last 25 years, they have published various unit risk estimates based on risk-assessment approaches (US EPA, 1998; OEHHA, 2001; Harrison et al., 2010; BAuA, 2012; Health Canada, 2021).

The unit risk factors indicate the expected number of benzene-related cancer cases per unit of the reference system (per liter for drinking water, per cubic meter for air, per kilogram of body weight per day for humans). An inhalation unit risk of 16×10^{-6} $(\mu g/m^3)^{-1}$ denotes, for example that the risk of developing cancer increases by 16×10^{-6} with an average lifetime inhalation of 1 $\mu g/m^3$ benzene.

The relevant assessment and limit values for benzene in Germany are all derived from risk-based assessment approaches. This concerns e.g. the ambient air limit value for the protection of human health (averaged over a calendar year: 5 $\mu g/m^3$, 39. BImSchV, 2010), the drinking water limit value (1 µg/L, TrinkwV, 2023), the trigger value for assessing the soil-groundwater impact pathway (1 µg/L, BBodSchV, 2021), the provisional guidance value for benzene in indoor air (4.5 $\mu g/m^3$, AIR, 2020) as well as the acceptable (0.02 mg/m^3) and tolerable (1.9 mg/m^3) concentrations at the workplace (BAuA, 2012).

2.3. Selection of the quantitative dose descriptor of the external exposure

The data supporting all published unit risk estimates comes from the US Pliofilm cohort study on chronic inhalation exposure to benzene, which involved over 1000 workers from 1940 to 1975 across three factories in the rubber industry (Infante et al., 1977). This cohort was retrospectively evaluated several times with regard to mortality rates and the risk of benzene-induced leukaemia (Rinsky et al., 1981, 1987, 2002; Paxton, 1996; Crump, 1996). The cumulative personal exposure in ppm-years was calculated on the basis of exposure measurements assigned to the individual workers. The second key study is a Chinese workplace investigation conducted on over 70,000 exposed and over 30,000 non-exposed Chinese workers in 672 factories (1949-1987, group analyses) (Hayes et al., 1997).

For the calculation of the internal dose descriptor, we applied the Health Canada assessment published in 2021, in which a unit risk of 16×10^{-6} is used for the determination of 'Toxicological Reference Values' (TRVs) (Health Canada, 2021). The value itself is based on the derivation of the California Environmental Protection Agency (OEHHA, 2001) and is slightly higher than the unit risk values of the US EPA – U.S. Environmental Protection Agency (2005) with $2.2 - 7.8 \times 10^{-6}$, the WHO (Harrison et al., 2010) with 6×10^{-6} or the calculation by the BAuA with 12×10^{-6} (2012), as the approaches differ in some points:

OEHHA (2001) extrapolated from the lower exposure concentrations into the low-dose range, uses the incidence for the endpoint leukaemia with its upper limit of the 95% confidence interval (CI95) and re-assesses the lifetime leukaemia risk for the general population. US EPA – U.S. Environmental Protection Agency (2005), on the other hand, used all exposure data for extrapolation (including the highest exposure group), used mortality instead of morbidity, uses the mean value instead of the CI95 upper limit and does not carry out any further re-assessment of the lifetime leukaemia risk for the general population.

The extrapolation into the low dose range was carried out by the OEHHA (2001) using linear Poisson regression. Model calculations based on relative risks were favoured over those based on absolute risks as relative estimates turned out to be more protective. Furthermore, OEHHA (2001) only considers an exposure duration of 30 years with the assumption that a longer exposure does not contribute to a significantly higher risk of leukaemia.

The unit risk of 16×10^{-6} $(\mu g/m^3)^{-1}$ recommended by Health Canada (2021) refers to the risk for the general population. For this purpose, the authors geometrically averaged the results from the studies

by Rinsky et al. (1981, 1987), Crump (1996) and the Chinese workplace study (Hayes et al., 1997) and then converted the calculated inhalation unit risk to the general population (under the assumptions of a daily breathing volume of 20 m^3 instead of 10 m^3, an exposure duration per year of 365 d instead of 204 d, and an average body weight of 70 kg).

2.4. Toxicokinetics

Benzene is primarily absorbed through inhalation, although oral and dermal exposure can also occur (ATSDR - Agency for Toxic Substances and Disease Registry, 2024). Dermal absorption plays a minor role (<0.2%) (Maibach and Anjo, 1981). The average absorption rate in the lungs is approximately 50% (range: 20-60%) (US EPA – U.S. Environmental Protection Agency, 2002). A so-called steady-state, i.e. a state of equilibrium between absorption and elimination from the blood, is rapidly reached in the blood. After the end of exposure, benzene is eliminated from the blood very quickly. Part of the absorbed benzene is exhaled unchanged (Nomiyama and Nomiyama, 1974). It is reasonable to expect that the lipophilic benzene tends to be distributed in fatty tissues (Low et al., 1989). The elimination of benzene from tissue in animal experiments is biphasic with a shorter half-life of 2.4 - 2.8 h and a longer half-life of 11 - 29 h (Low et al., 1989).

Benzene is predominantly oxidised in the liver to form the highly reactive benzene epoxide. The main metabolite phenol can be formed from this benzene epoxide by spontaneous tautomerization, which is excreted in the urine after conjugation with glucuronic acid or sulphate. The conjugation of the epoxide with glutathione and the subsequent degradation of the glutathione adduct leads to the formation of S-phenylmercapturic acid (S-PMA). The opening of the epoxide via epoxide hydrolase leads via the formation of a dihydrodiol and o-quinone and subsequent ring-opening to the formation of the intermediate metabolite trans-, trans-muconaldehyde, which is finally excreted in urine as trans, trans-muconic acid (t,t-Muc) (Arnold et al., 2013). Induction of the liver enzymes (CYP2E1) leads to accelerated biotransformation (Sato et al., 1981). Fig. 1 shows a simplified overview of the biotransformation of benzene and the metabolites described here.

The half-lives for urinary excretion of the metabolites determined in an occupational health study on workers exposed to benzene were 5.0 ± 2.3 h for t,t-Muc and 9.1 ± 3.7 h for the metabolite S-PMA (Boogaard and van Sittert, 1995).

2.5. Selection of the biomarker and considerations on F_{ue}

The measurement of unmetabolized benzene in blood is a highly specific biomarker that, besides occupational applications, is also used in environmental exposure assessment (Fustinoni et al., 1995; Vaughan Watson et al., 2021; Karthikeyan et al., 2024). However, due to the short half-life of benzene in blood, urinary biomarkers better reflect integrated exposure over a longer time window and are therefore more suitable for estimating daily exposure. Moreover, urine collection is more feasible for large-scale environmental studies than blood sampling, which might also be prone to external contamination and/or analyte losses during storage. Among the urinary metabolites of benzene mentioned above, S-PMA is a highly specific biomarker of exposure (ATSDR - Agency for Toxic Substances and Disease Registry, 2024; Schettgen et al., 2008). Recently, Bowman et al. (2023) also proposed the urinary precursor of S-PMA, 6-hydroxy-2,4-cyclohexadienyl mercapturic acid (pre-PhMA, pre-SPMA) as a novel and specific urinary biomarker for assessing benzene exposure, but stability issues as well as a lack of consistency in the interlaboratory data do currently not allow this biomarker to be used for human biomonitoring. Although phenol is one of the main metabolites of benzene in urine, it is not suitable for human biomonitoring because it is physiologically produced and excreted in relatively high amounts. t,t-Muc excreted in urine could, in principle, serve as a suitable biomarker of benzene exposure in an occupational health context (Boogaard and van Sittert, 1995). However, as t,t-Muc can also be formed metabolically from the food additive sorbic acid, this metabolite is not suitable for the monitoring of environmental exposures to benzene. In contrast, no relevant interfering factors are known for urinary S-PMA excretion. Therefore, S-PMA is considered the most specific biomarker for benzene exposure. Moreover, S-PMA has been applied in several large-scale human biomonitoring studies, allowing international comparability (Kenwood et al., 2026; Park et al., 2026).

In occupational health studies on workers exposed to benzene, the urinary excretion fraction (F_{ue}) of S-PMA was measured as a function of the inhaled benzene dose using personal air measurements and data on the excretion of S-PMA in spot urine at the end of the shift during several

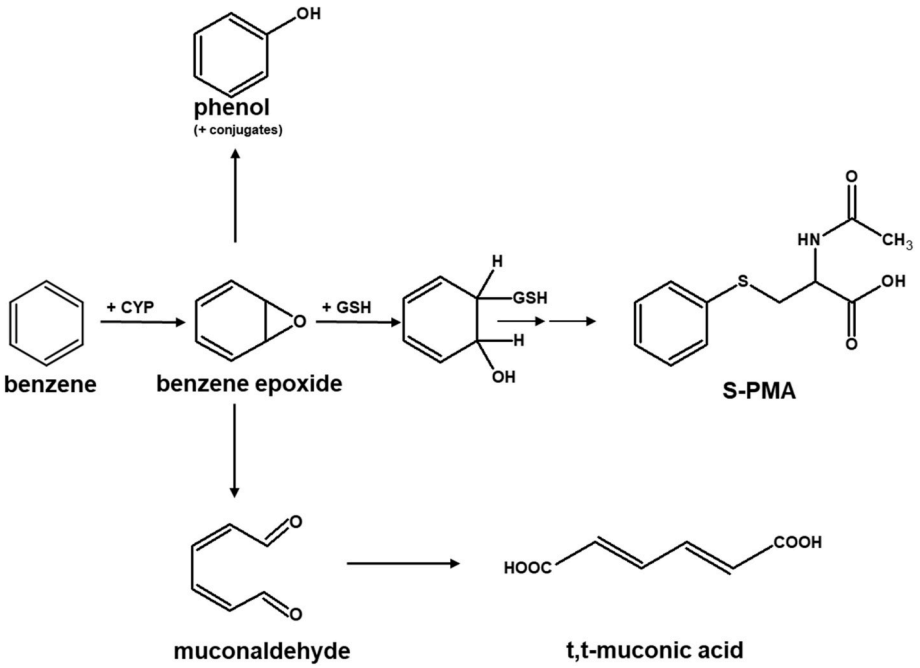


Fig. 1. Simplified illustration of the biotransformation of benzene.

consecutive days. The average F_{ue} reported was 0.11% (range 0.05 - 0.26%, n = 14) (Boogaard and van Sittert, 1995).

In another study, the F_{ue} was determined using data from a human biomonitoring study with non-smoking study participants from the general population (Göen and Zethner, 2019; Göen et al., 2020; individual data according to personal communication) in the neighbourhood of hydrocarbon conveying plants in Lower Saxony and outside these plants. The age of the participants ranged from 18 to 78 years. Data on the excretion of S-PMA in 24-h urine were averaged from 4 measurements over an exposure period of two weeks and were compared with the amount of inhaled benzene as determined by personal passive sampling in each case (assuming a daily breathing volume of 20 m^3 (ECHA, 2012)). These calculations resulted in a median Fue of 0.22% (median 0.0022, range 0.00033 – 0.102, n = 163) for this collective with low exposures to benzene. In this case, the median and not the mean value was selected for this environmental HBM study, as the median is more robust against outliers. Under consideration of the huge difference in exposure levels in both studies (over three orders of magnitude), the difference is surprisingly low and thus supports the urinary excretion fraction published by Boogaard and van Sittert (1995), which was derived for employees with comparatively high exposure to benzene.

The HBM Commission is aware of the different exposure levels of the general population and workers in both studies, but nevertheless chose to use the already published F_{ue} of 0.11% (Boogaard and van Sittert, 1995) as the conservative estimate for further derivation.

3. Results

3.1. Derivation of the dose descriptor of the internal exposure to benzene – the model

Based on the procedure described before (Wollin et al., 2022), first, the unit risk corresponding to a benzene concentration of 1 µg/m^3 in air is back-calculated to determine the daily intake. We use in the following the unit risk of 16 x 10^{-6} (µg/m^3)$^{-1}$ for the general population from Health Canada (2021) because it has been derived transparently based on a well-established data basis.

Intake per day and kg body weight (bw) = air concentration
× breathing volume per day ÷ body weight

i.e. for a "unit concentration" of 1 µg/m^3, a daily intake of

$$1\ \frac{\mu g}{m^3} \times 20\ m^3 \Big/ day \div 70\ kg = 0.286\ \frac{\mu g}{kg\ bw\ x\ day}$$

can be calculated.

From this inhalation unit risk dose for benzene, the molar mass ratio of the metabolite S-PMA (measured in urine) and benzene, and toxicokinetic data on the excretion fraction of the metabolite (F_{ue}), the dose descriptor of the internal exposure can now be calculated in analogy to the calculation of HBM values. According to the EFSA Guidance on default values (EFSA Scientific Committee, 2012), a body weight of 70 kg should be used as default for the European adult population for consumer dietary risk assessment (over 18 years old).

The calculated external dose is first converted into the corresponding amount of the specific metabolite S-PMA excreted in the urine as follows:

concentration in urine = Intake of benzene per kg bw and day ÷ excreted urine volume per kg bw and day
× excreted proportion of SPMA in urine in amount of administered substance(F_{ue}) × $\frac{molar\ mass_{metabolite\ S-PMA}}{molar\ mass_{benzene}}$

The daily urine volume is assumed to be 0.03 L/kg bw/d for children and men and 0.035 L/kg bw/d for women, which is used in the derivation of the HBM values since 2025 based on recent data from the German Environmental Specimen Bank (Human Biomonitoring Commission of the German Environment Agency, 2025). The molar mass of benzene is 78.1 g/mol and for S-PMA 239.3 g/mol. As described above, the mean F_{ue} value of 0.0011 was used for the excreted proportion of the metabolite in the urine.

This means that the previously calculated intake quantity in relation to the unit concentration of benzene in the air corresponds for children and men to a numerically urine concentration of S-PMA of:

$$0.286\ \frac{\mu g}{kg\ bw\ x\ day} \div 0.03\ \frac{L}{kg\ bw\ x\ day} \times \frac{239.3}{78.1}\ \frac{g/mol}{g/mol} \times 0.0011 = 0.032\ \frac{\mu g}{L}$$

The corresponding value for women is: 0.0275 µg/L.

These calculated S-PMA concentrations in urine correspond to an intake of 1 µg/m^3 benzene and thus, using Health Canada's unit risk (2021), to an excess lifetime cancer (leukaemia) risk of 16 x 10^{-6}.

The HBM Commission recommends not using creatinine-normalised data, as the physiological creatinine formation is associated with age, sex, physical activity and also meat consumption (Carrieri et al., 2001; Human Biomonitoring Commission, 2005; Sallsten and Barregard, 2021; Abraham et al., 2023).

The further conversion of the above calculated S-PMA concentrations to a unit risk concentration for S-PMA in urine, i.e. for 1 µg/L, results for children and men in a unit risk of 500 x 10^{-6} per 1 µg/L S-PMA and for women in a unit risk of 582 x 10^{-6} per 1 µg/L S-PMA and corresponds to the dose descriptor of the internal exposure.

Dose descriptor of the internal benzene exposure ***(DD_i)***

$$\textbf{\textit{for children and men}} = \mathbf{500\ x\ 10^{-6}}\ \textit{per}\ 1\ \frac{\mu g}{L}\ S-PMA\ in\ urine$$

Dose descriptor of the internal benzene exposure ***(DD_i)***

$$\textbf{\textit{for women}} = \mathbf{582\ x\ 10^{-6}}\ \textit{per}\ 1\ \frac{\mu g}{L}\ S-PMA\ in\ urine$$

It should be noted that, in addition to individual enzyme polymorphisms of benzene metabolism (Kim et al., 2007), extrapolation into the low-dose range is also associated with considerable uncertainties. The application of the concept is therefore only recommended as a risk characterisation instrument for large, population-based studies (see 4.).

Of note, using other unit risks (e.g. US EPA, WHO or BAuA, see 2.3.) as well as a different assumption for the F_{ue} can result in an up to 14.5 fold lower DD_i than calculated by us.

3.2. Application scenarios for the calculation of additional lifetime cancer risks

The dose descriptor of internal exposure (DDi) can be used to estimate cancer risks based on HBM data obtained in population-based studies. Additional cancer risks can be calculated for both time-limited, variable exposures and long-term constant average exposures, provided that an appropriate model for cumulative exposure is available. The calculation of exposure-based additional lifetime cancer risks

is of particular interest for risk assessment as well as risk management.

It must be considered that susceptibility to carcinogenic substances is not constant over lifespan. The US and California Environmental Protection Agencies compared the sensitivity to genotoxic carcinogens in adult and pre-adult life stages in a large number of animal studies and found that when exposed in early life stages (pre- and postnatal to adolescence) animals exhibited cancer incidences that were one to two orders of magnitude higher than those observed in adult animals. In the absence of meaningful studies for earlier life stages, both US authorities therefore consider the assumption of increased susceptibility in this phase to be scientifically justified and recommend that the increased vulnerability of unborn babies, infants, children and adolescents to genotoxic carcinogenic substances be taken into account in the assessment and thus in the calculation of cancer risks by using appropriate adjustment factors (US EPA, 2005; CalEPA – California Environmental Protection Agency, 2009). The HBM Commission also considers that the risks for pregnant women with regard to genotoxic carcinogens are not fully mapped.

CalEPA – California Environmental Protection Agency (2009) derived an overall factor of 2.2 for the calculation of lifetime risks (70 years of exposure) on the basis of its life-stage-specific adjustment factors and the data of the 50th percentile with additional consideration of prenatal exposure, while the US EPA derived an overall factor of 1.7. A comparison of the different approaches can be found in CalEPA – California Environmental Protection Agency (2009).

As long as no age-specific studies, especially for the sensitive childhood and adolescent years, are available for the respective carcinogenic compound, the HBM Commission uses a child factor of 2 when calculating additional lifetime cancer risks for carcinogenic substances according to the new concept based on the US EPA and CalEPA.

3.2.1. Calculation of additional lifetime cancer risks using urinary S-PMA data from the German Environmental Specimen Bank

Using S-PMA levels in urine samples from the German Environmental Specimen Bank, the additional lifetime cancer risk was calculated for adults aged 20-30 years.

An analysis of 60 human samples from the Environmental Specimen Bank (30 male and 30 female subjects) from 2021 shows for men a median 24-h-urine concentration of 0.11 µg/L and a 95th percentile of 0.20 µg/L for the benzene metabolite S-PMA in urine. The respective values for women are a median of 0.08 µg/L and a 95th percentile of 0.199 µg/L (Pluym et al., 2026; internal data from the German Environment Agency).

The additional cancer risk should be calculated on the assumption of lifelong exposure, i.e. also during early developmental phases. Since in the case of benzene the unit risk derivations, and thus also the calculated dose descriptor of internal exposure, are based on workplace studies, this does not yet take into account the assumed higher sensitivity of children. The previously described child factor 2 is applied here:

$$\boldsymbol{ALCR} = DD_i \; x \; urine\; concentration\; of\; S-PMA \times child\; factor$$

ALCR = Additional lifetime cancer risk, DDi = Dose Descriptor of internal exposure, S-PMA = benzene metabolite S-phenylmercapturic acid.

For the calculated dose descriptor of 500 x 10^{-6} per 1 µg/L S-PMA, a urine concentration of 0.11 µg/L for men (median) and a child factor of 2, the additional lifetime risk for men is as follows:

$$500 \times 10^{-6} \frac{L}{\mu g} \times 0.11 \times 2 = \mathbf{110 \times 10^{-6} = 11 \times 10^{-5}}$$

Analogue results for the 95th percentile for men (0.20 µg/L) are: $200 \times 10^{-6} = 2 \times 10^{-4}$

For the calculated dose descriptor of 582 x 10^{-6} per 1 µg/L S-PMA, a urine concentration of 0.08 µg/L for women (median) and a child factor of 2, the additional lifetime risk for women is as follows:

$$582 \times 10^{-6} \frac{L}{\mu g} \times 0.08 \times 2 = \mathbf{93.1 \times 10^{-6} = 9.31 \times 10^{-5}}$$

Analogue results for the 95th percentile for women (0.199 µg/L) are: $232 \times 10^{-6} = 2.32 \times 10^{-4}$

When calculating risks in this way, it is important to be aware that these are population-based lifetime risks, not individual cancer risks, as each person has a different risk due to their individual physical constitution (e.g. genetic susceptibility, previous illnesses, pregnancy, gender) and their specific exposure history (e.g. through habits, workplace, place of residence). The unit risk is also only an estimate of a mean expected value (with an upper and lower confidence interval).

3.2.2. Calculation of additional lifetime cancer risks using urinary S-PMA data from the German Environmental Survey GerES V (2014-2017)

A further application example uses HBM data from the German Environmental Survey (GerES), which provides representative information on the body burden of environmental substances in the German population. In the GerES V study, S-PMA concentrations were determined in morning urine for the period January 2015 - June 2017 to assess the benzene exposure of children and adolescents (Schwedler et al., 2021; German Environment Agency, 2023). In analogy to the previous section, these concentrations can be used to calculate additional lifetime cancer risks separately by sex and other factors (see Tables 1 and 2). The data allow an assessment of the association between benzene air pollution, corresponding risk and S-PMA excretion. Potential associations between benzene intake via food and drinking water were not assessed.

An interesting finding here is that adolescents aged 12-17 who smoke also have an increased lifetime cancer risk due to higher benzene exposure if they were exposed to similar benzene concentrations throughout their lives. This difference disappears when the median exposure is considered instead of the 95th percentile for both groups, as it is due to the higher cigarette consumption of a few individuals at the right-hand, higher end of the exposure distribution.

The statistical meaning of the HBM results used for the calculation should always be taken into account when interpreting and using the calculated lifetime cancer risks.

4. Evaluation of uncertainties and discussion

Uncertainties in exposure and risk assessment are generally discussed under three categories: scenario, model and parameter uncertainties with both qualitative and quantitative descriptions. These should support a transparent evaluation of inherent uncertainty to enable its full consideration in risk assessments (BfR, 2022; WHO/IPCS, 2008). They should differentiate between knowledge gaps, inherent statistical uncertainty (population heterogeneity) and the subjectivity of choice of model parameters.

This study was conducted to verify the applicability of the previously published concept to derive a risk-related dose descriptor of inner exposure for genotoxic carcinogens (Wollin et al., 2022). The term “dose descriptor” is used to designate the exposure level (dose or concentration) that corresponds to a quantified level of risk of health effects in a specific study. It uses standard mathematical models and mainly standard defaults for the physiological parameters. Hereby the results reflect only a low tier estimate. In this situation, each exposure scenario is defined by the study design of the underlying HBM study (sample size and target population: distributions of age, gender, body weight, breathing volumes as well as influential variables like activity levels, drinking and nutritional behaviour, smoking and environmental benzene exposure).

Using the unit risk approach for the calculation of a prognostic dose descriptor of the internal exposure requires the back-calculation of the benzene dose from the measured S-PMA concentration in urine. By this,

Table 1
Calculation of comparative additional lifetime cancer risks (ALCR) based on HBM data (median) for the benzene metabolite S-PMA in the urine of children and adolescents in Germany (GerES V, 2014-2017) as a function of age, sex and smoking habits (German Environment Agency, 2023; Schwedler et al., 2021).

Age group In years	Sex	Number N-S	N-S + S	DD_i per 1 µg/l	S-PMA P50 (N-S) µg/L	S-PMA P50 (N-S + S) µg/L	ALCR (N-S)	ALCR (N-S + S)
3-11	Male	669	669	500 x 10^{-6}	0.09	0.09	**90 x 10^{-6}**	**90 x 10^{-6}**
3-11	Female	655	658	582 x 10^{-6}	0.09	0.09	**105 x 10^{-6}**	**105 x 10^{-6}**
12-17	Male	409	447	500 x 10^{-6}	0.09	0.09	**90 x 10^{-6}**	**90 x 10^{-6}**
12-17	Female	454	485	582 x 10^{-6}	0.09	0.1	**105 x 10^{-6}**	**116 x 10^{-6}**

DDi = Dose-Descriptor of the internal exposure to S-PMA in urine, N-S = Non-smoker, S = Smoker, ALCR = Additional lifetime cancer risk.

Table 2
Calculation of comparative additional lifetime cancer risks (ALCR) based on HBM data (95th percentile) for the benzene metabolite S-PMA in the urine of children and adolescents in Germany (GerES V, 2014-2017) depending on age, sex and smoking habits (German Environment Agency, 2023; Schwedler et al., 2021).

Age group In years	Sex	Number N-S	N-S + S	DDi per 1 µg/L	S-PMA P95 (N-S) µg/L	S-PMA P95 (N-S + S) µg/L	ALCR (N-S)	ALCR (N-S + S)
3-11	Male	669	669	500 x 10-6	0.32	0.32	320 x 10-6	320 x 10-6
3-11	Female	655	658	582 x 10-6	0.35	0.36	407 x 10-6	419 x 10-6
12-17	Male	409	447	500 x 10-6	0.29	0.99	290 x 10-6	990 x 10-6
12-17	Female	454	485	582 x 10-6	0.38	0.75	442 x 10-6	873 x 10-6

DDi = Dose-Descriptor of the internal exposure to S-PMA in urine, N-S = Non-smoker, S = Smoker, ALCR = Additional lifetime cancer risk.

an uncertainty analysis should include the model assumptions as well as all measured or estimated model parameters. Within the concept, the benzene uptake and the benzene metabolism are linked to the measurements of S-PMA. We assume that the S-PMA concentration is an adequate indicator of the benzene body burden (internal exposure), resulting from mainly the aggregated benzene exposure over the decisive time before urine sampling (cf. urinary half-life of 9.1 h, Boogaard and van Sittert, 1995). The possible contribution of benzene contamination in food and drinking water was ignored due to an assumed low impact and lacking data. The S-PMA measurement is, thus, an indicator linked to the risks due to the overall benzene exposure within a defined study population. Extrapolation from only single morning urine, spot urine or even 24-h-urine individual S-PMA values to lifetime risks, ignoring intra- and inter-individual variances as well as changing individual conditions over the lifetime overstresses the appropriateness of the resulting estimates. The results should therefore be interpreted as aggregated risk descriptors reflecting the population-level risk at the time of the study. Restrictions due to parameter uncertainties are discussed below.

The model described in Chapter 3 comprises three sub-models: (1) the benzene exposure to HBM metabolite prediction, (2) the back-calculation model from S-PMA urinary concentration to benzene air concentration, and (3) the unit risk-based risk description. As a Tier 0 approach (WHO/IPCS, 2008), the calculation relies on simplifying assumptions and default values for most parameters. The model formula describes a multiplicative combination of the selected parameter values, resulting in a single value (point estimate). The models include the parameters described in Table 3. The uncertainty of each parameter influences the result directly: The prediction of the S-PMA concentration in urine depends on the nominator parameters for benzene air concentration, breathing volume and the proportion of the metabolite in urine (F_{ue}). Any parameter value overestimate in the nominator would result in an overestimate of the benzene intake and the expected S-PMA urine concentration. An overestimate of the urine excretion (denominator) would result in an underestimate of the risk. The daily breathing volume as well as the excreted urine volume (Human Biomonitoring Commission of the German Environment Agency, 2025) are associated to the body weight (depending on age), justifying the use of body weight related defaults for the breathing volume and the urine volumes.

The choice for the F_{ue} was made in the narrow window of $F_{ue} = 0.11 – 0.22\%$ from a literature review. The chosen value of $F_{ue} = 0.11\%$ was based on the established procedure of the HBM Commission to select conservative defaults, i.e. using a more protective approach. The benzene air exposure at the workplace in this study with concentrations in the lower mg/m^3 range was clearly higher than the benzene levels for the general population (Göen and Zethner, 2019; Göen et al., 2020), which ranged from 0.4 to 15 µg/m^3.

A qualitative description of the parameters is given above together with a short discussion of inherent uncertainties due to the state of knowledge. The population variability with respect to polymorphisms in benzene metabolism is ignored due to a lack of sufficient knowledge. The influence of age and gender is estimated by corresponding stratification.

To assign a numerical factor of uncertainty to each of the model parameters, a uniform measure (e.g., dispersion, coefficient of variance) and a suitable data basis for an estimation would be required, which is not available for the examples given.

Table 3 gives an overview over the set of inherent parameters, indicating the complexity of risk descriptor estimation. Parameter uncertainties depend strongly on the quality of the data. Using default values for a tier 0 estimate causes an abdication of population variance. A simple consideration of uncertainty influence was conducted by a stepwise inclusion of lower- and upper-bound values or by multiplication by an estimated uncertainty factor. The estimated uncertainty factors depend on the HBM studies and the population structure, by this, subjective numerical estimates (expert judgements) are reported. In Table 3 we give a proposal for an uncertainty indicator that takes into account the variability (the statistical uncertainty) for all model parameters in a standardized scale. By this it gives an impression of the sensitivity of the resulting risk estimate on the choice between average to an upper bound estimates.

The selection or estimation of parameters, extrapolating from sampling and measurements that may not be representative and defaults to an entire lifetime risk involves parameter as well as methodological uncertainties. Deliberately omitting intra-individual exposure variance over life-time and inter-individual variance leads to a description of risk, which is valid only for the time of the S-PMA measurement. The selection of estimated parameters strongly influences the estimation. Uncertainty arises here from knowledge gaps, difference in expert opinions, and the possible lack of representativeness of the data. The averaging method carries risks because information from outliers and variance in the dataset are suppressed. The expected variance and the inherent

Table 3
Description of parameter uncertainty.

Parameter	Quality	Scenarios	Uncertainties	Uncertainty factor	Description of the Population	Source	Overall influence of parameter to results
S-PMA concentration in urine	Measurement	Students: German Environmental Specimen Bank Göen et al. (2020)	Unknown frequency of polymorphism differences, Ignoring data variance due to aggregation $Factor_{Q95\%/\ Median}$ Males ~ 5 and females ~4	$Factor_{Q95\%/\ Median}$ Males ~5 females ~ 4 Non-smoker ~4 smoker ~5	Described above	GerES V: (Schulz et al., 2021; Schwedler et al., 2021) Göen et al. (2020)	Low/ medium
Benzene air concentration [µg/m^3]	Measurement		Timing of measurement, Ignoring variance due to aggregation	$Factor_{Q95\%/\ Median}$ ~3.5	Adolescents, right skewed distribution (gM = 1.23, aM = 1.66, gSD = 2.0, Q95% = 3.3 [µg/ m^3],	GerES IV Göen et al. (2020)	Low/ medium
F_{ue}	Estimate	0.11 – 0.22, occupational settings and selected individual measurements (adults)	Ignoring variance, Expert judgement based on literature data	UC-Factor = 2.0 due to lack of empirical data	Occupationally exposed workers	Literature review, Fue = 0.11 as an expert judgement	Medium
Body weight [kg]	Using default values for a 95th quantile estimate	All: 70 kg body weight average over life time	Ignoring population variance, development over life-time, using outdated data, no age and gender association to breathing rates	Adults $Factor_{Q95\%/\ Median}$ Males ~ 1.3 and females ~ 1.4 with higher deviation in younger ages < 15 years due to variance in development	Children, adolescents, adults Male adults Female adults	Literature review	High
Breathing volume [m^3/ day]	Default for the mean, insufficient information about the population exposure scenario and activity		Ignoring population variance, parameter is correlated with age, gender, activity level and body weight	$Factor_{Q95\%/\ Median}$ ~1.3	Age stratified descriptions for the general population	(ECHA, 2012), AUH (1995), U.S.EPA (2009,2011 Chapter 6)	Medium/ high
Body weight standardized excreted urine volume per day	Calculation as default or measurement		Ignoring variance due to defaults for body weight, correlation to body weight	$Factor_{Q95\%/\ Median}$ Males ~ 1.6 females ~ 1.65		HBM-K (2025)	Medium
Unit risk	Choice of a Standard for comparative evaluation		Selection of UR = 16* 10^{-6} (Health Canada) by expert judgement	Literature indicates to different values by a factor of 7.3, due to different data, study populations: UR ranges from 2.2* 10^{-6} (US EPA 1998) up to 16* 10^{-6} (Health Canada)	Occupational settings	Literature review	High
Molar masses	Standard		-	none			None

Abbreviations: SD: standard deviation, aM: arithmetic mean, CV coefficient of variation, gCV: geometric coefficient off variation, gM: geometric mean, gSD: geometric standard deviation, $Q_{95\%}$: 95th quantile, LOQ: level of quantification.

uncertainty are not reflected. The influence of each parameter uncertainty on the target variable uncertainty can be assessed by stepwise multiplying (nominator parameters) or dividing (denominator parameters). This indicates, for example, that the body weight has only low influence, but that the estimated breathed air volume and the environmental benzene concentration are more influential.

The analytical accuracy in the low concentration range of S-PMA measurements also contributes to the uncertainty. At the same time, a high proportion of values below the LOQ was determined. Thus, highly sensitive and reliable methods for the quantification of S-PMA are required in order to apply the current approach and allow comparability across studies. Undocumented factors such as polymorphism of benzene metabolism as well as individual activity levels and methodological differences in the determination of S-PMA might also contribute to this uncertainty.

The uncertainty analysis for all selected or estimated parameters (esp. F_{ue}) and the assumptions made (extrapolation of aggregated single S-PMA data to a lifetime risk, ignoring of intra- and inter-individual variance, comparatively higher uncertainty of benzene and S-PMA measurements in the low concentration range) suggest that the dose descriptor derived here should above all be used for comparative statements about expected population risks, as stated before. The authors see a need to improve the data quality of these parameters by further research. Nevertheless, the approach presented here is an innovative and a valuable tool for the risk assessment of benzene in the general population and gives strong indication that the resulting risks are considerable.

On an individual level, a precautionary lifestyle (non-smoking, living environment, diet etc.) may also result in a lower carcinogenic risk. The approach described here aims solely at comparing substance risks under similar conditions, e.g. to establish a comprehensible and well-founded basis for an informed and targeted reduction of exposures (and associated risks). Communicating the results, it should be mentioned that the result is an upper bound estimate, due to the conservative parameter

selection. It should additionally be noted, that the approach does not intend to quantify the incidence risk for adverse non-cancer effects (like immunological or haematological diseases).

5. Conclusion

This publication presents the application of the German HBM Commission's concept for evaluating carcinogenic substances in population-based human biomonitoring (Wollin et al., 2022), focusing on the carcinogen benzene and using the urinary excretion of S-PMA as a specific biomarker. The model and its assumptions are carefully described and drawbacks and uncertainties are comprehensively addressed, while choosing a conservative approach for risk estimation. This novel human biomonitoring approach is based on the absorbed internal exposure and thus enables the estimation and comparison of population-based carcinogenic risks across all sources of exposure. Using data from the German environmental specimen bank (24-h urine samples), the calculated additional lifetime cancer risks from exposure to benzene range from 9.3 x 10^{-5} (median) – 2.3 x 10^{-4} (95th percentile) for non-smoking adults. For children, the calculated additional lifetime cancer risk ranges from 9 x 10^{-5} (median) – 4.4 x 10^{-4} (95th percentile) according to data from the German Environmental Survey GerES V.

These data show that population cancer risks for benzene are considerable under unfavourable conditions. As benzene is generated both from natural and anthropogenic sources, further measures for exposure and risk reduction on the general population level – at least for the anthropogenic sources - should be taken into consideration. These are in parts easily preventable like (passive) smoking, but also other known influence factors like industrial or traffic emissions should be taken into account (Schwedler et al., 2021). Future applications of the human biomonitoring concept to more environmental carcinogens will be useful to further complement the picture on carcinogenic risks from environmental exposures in order to support risk management and mitigation strategies, prioritize measures and evaluate their success.

CRediT authorship contribution statement

T. Schettgen: Writing – review & editing, Writing – original draft, Conceptualization. **K.-M. Wollin:** Writing – review & editing, Writing – original draft, Conceptualization. **M. Schümann:** Writing – review & editing, Writing – original draft, Conceptualization. **T. Göen:** Writing – review & editing, Writing – original draft, Conceptualization. **Y. Chovolou:** Writing – review & editing, Writing – original draft, Conceptualization. **P. Apel:** Writing – review & editing, Writing – original draft, Conceptualization. **M. Kolossa-Gehring:** Writing – review & editing, Writing – original draft, Conceptualization. **H.M. Koch:** Writing – review & editing, Writing – original draft, Conceptualization. **C. Röhl:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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