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Benzene exposure: An overview of monitoring methods and their findings

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ABSTRACT

Benzene has been measured throughout the environment and is commonly emitted in several industrial and transportation settings leading to widespread environmental and occupational exposures. Inhalation is the most common exposure route but benzene rapidly penetrates the skin and can contaminate water and food resulting in dermal and ingestion exposures. While less toxic solvents have been substituted for benzene, it still is a component of petroleum products, including gasoline, and is a trace impurity in industrial products resulting in continued sub to low ppm occupational exposures, though higher exposures exist in small, uncontrolled workshops in developing countries. Emissions from gasoline/petrochemical industry are its main sources to the ambient air, but a person's total inhalation exposure can be elevated from emissions from cigarettes, consumer products and gasoline powered engines/tools stored in garages attached to homes. Air samples are collected in canisters or on adsorbent with subsequent quantification by gas chromatography. Ambient air concentrations vary from sub-ppb range, low ppb, and tens of ppb in rural/suburban, urban, and source impacted areas, respectively. Short-term environmental exposures of ppm occur during vehicle fueling. Indoor air concentrations of tens of ppb occur in microenvironments containing indoor sources. Occupational and environmental exposures have declined where regulations limit benzene in gasoline (<1%) and cigarette smoking has been banned from public and work places. Similar controls should be implemented worldwide to reduce benzene exposure. Biomarkers of benzene used to estimate exposure and risk include: benzene in breath, blood and urine; its urinary metabolites: phenol, *t,t*-muconic acid (*t,t*MA) and *S*-phenylmercapturic acid (SPMA); and blood protein adducts. The biomarker studies suggest benzene environmental exposures are in the sub to low ppb range though non-benzene sources for urinary metabolites, differences in metabolic rates compared to occupational or animal doses, and the presence of polymorphisms need to be considered when evaluating risks from environmental exposures to individuals or potentially susceptible populations.

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1. Introduction

Human exposure characterization is a necessary component of environmental and occupational epidemiological studies, risk characterizations and risk management. Exposure science links emissions of a toxicant with dose and public health [1,2]. Adverse health effects of benzene, in particular blood diseases such as leukemia and aplastic anemia, were initially noted in occupational settings in which the benzene air concentrations were tens to hundreds of ppm [3,4]. That observation, along with toxicological studies of benzene in animals resulted in the establishment of workplace standards in many countries limiting the air concentrations that workers can be exposed to (Table 1). Current epidemiological studies are still investigating what level of benzene exposure leads to blood diseases and other adverse effects in healthy workers, how to extrapolate health effects to environ-

mental exposures and to provide evidence for risk characterization and management of benzene exposure to the public. The assessment of exposure is often the weakest portion of epidemiological studies and improved methods for extrapolation to environmental exposures based on direct inhalation and dermal exposure assessment and biomarker data are needed to be properly ascertain what health outcomes identified in occupational setting are relevant to the general population for current environmental exposures. This manuscript reviews benzene air concentrations and exposures in both occupational and environmental settings along with methodologies for sample collection and analysis. The impact of air concentrations outdoors, indoors and in transit along with activity patterns on personal exposure is discussed. The applicability of different biomarkers of benzene exposure across different magnitude of exposure is also evaluated.

Occupational exposures occur within the petrochemical industry and in manufacturing that require aromatic solvents or glues that contain benzene such as rubber production, shoe manufacturing, and printing [5–8]. Environmental exposures to the general population are predominantly through inhalation due to benzene's

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Table 1
Occupational standards for benzene air concentrations.

US NIOSH REL: TWA 0.1 ppm STEL 1 ppm
US OSHA PEL: TWA 1 ppm STEL 5 ppm
EU Commission: TWA 1 ppm
NOHSC Australia: TWA 5 ppm
KOSHA Korea: TWA 1 ppm
NTCHHS China: TWA 2 ppm STEL 15 min 3 ppm

NIOSH—National Institute of Occupational Safety and Health; OSHA—Occupational Safety and Health Administration; NOHSC—National Occupational Health and Safety Commission; KOSHA—Korea Occupational Safety and Health Agency; NTCHSS—National Technological Committee of Health Standards Setting; REL—recommended exposure limit; TWA—time weighted average; STEL—short term exposure limit.

volatility. Benzene is a component of gasoline, thus emissions from mobile sources are major contributors to the benzene air concentrations where gasoline engines are prevalent [9–11]. Benzene is also present in cigarette smoke so smokers and individuals who inhale environmental tobacco smoke (ETS) or second hand smoke (SHS) are exposed to benzene above background ambient air levels. A key to determining exposure is the understanding of activities of workers and populations at risk. The benzene levels in the microenvironment encountered and the activities and behaviors that lead to contact change with time [12,13]. These parameters, combined with biomarker measurements can help define the exposure to dose relationships and lead to approaches that can define how best to reduce benzene exposures.

2. Methodologies for measuring benzene exposure

2.1. Air samples

To determine benzene and other non-polar volatile organic compounds (VOCs) air concentrations, the major pathway for benzene exposure, samples are collected from the air on either an adsorbent or by trapping whole air in a container. Passive vapor monitors or badges which collect VOCs based on diffusion are commonly used in occupational settings to measure ppm concentration levels present within the personal or breathing zone air as they present little burden to the wearer [14,15]. Passive badges have recently been used for environmental measurements where the concentration is typically several orders of magnitude lower by taking precautions to minimize blank contributions from the badge material and when handling of the sample, and from the extraction solvent; by increasing the sampling duration to 24 to 48 h; and by using sensitive analytical techniques [16,17]. Active sampling which employs an air sampling pump to pull air through an adsorbent held in an inert trap can sample greater air volumes providing more sensitivity but require greater field efforts and can be subject to mechanical and electrical failures. Area samples are used to determine microenvironmental levels and can be collected using canisters whose inner surfaces are deactivated to prevent absorption or surface catalyzed reactions from occurring. The sampling duration and flow rate used for active sampling can be set to measure a wide range of air concentrations and to examine peak or integrated exposures. Methodologies for benzene collection and analysis across different media have been recently reviewed [18]. Benzene in air samples is analyzed by gas chromatography (GC) which separates VOCs that are collected simultaneously. The VOCs are transferred from an adsorbent air sample to the GC by extraction with a non-polar solvent or by thermal desorption. Air collected in canisters is passed through a cryotrap to concentrate the VOCs which is subsequently transferred to the GC. The most common detector currently used with a GC is a mass selective detector (mass spectrometer MS) which provides a positive identification of benzene based on its chemical structure, though flame ioniza-

tion and photoionization can be used for quantification. Soil and water can be analyzed in a similar fashion to air samples by purging the benzene from the water or soil and trapping the benzene on an adsorbent to facilitate its transference to a GC. Alternate analytical methods for introducing a sample for GC analysis include headspace and solid phase extraction (SPE) or microextraction (SPME) systems to concentrate the benzene from the sample followed by liquid concentration and injection.

2.2. Real-time monitors

Several on-line, real time or near real time samplers have been developed to provide temporal information of benzene concentrations. Occupational exposures at the ppm levels can be measured using mid-infrared diode laser with Fourier transform infrared (FTIR) single-beam spectrophotometer [19], while ppb have been reported using automated GC systems (concentrate air prior to injection) [20,21], mass spectrometers with atmospheric pressure interfaces [22,23], proton transfer reaction mass spectrometer (PTR-MS) [24], and membrane interface mass spectrometry [25].

2.3. Biomarkers measurements

Biomarkers of benzene exposure include unmetabolized benzene in the blood, breath and urine, urinary benzene metabolites and benzene adducts in DNA, hemoglobin and albumin. Measurements of unmetabolized benzene in blood and urine require an extraction step which is typically followed by GC/MS to separate benzene from other volatile constituents in the sample, and for its identification and quantification. Extraction procedures include purge and trap, head space, SPE and SPME with detection limits in pg/mL or sub-nM range [26,27]. It is essential when measuring benzene blood levels in the general populations to take special care to clean all components, particularly any rubber, such as the tops of vacutainers [28,29]. Since benzene is volatile, losses during collection, storage and analysis are possible.

Ring hydrolyzed urinary benzene metabolites: hydroquinone, catechol, and phenol, require extraction from the urine using a solvent, SPE or SPME followed by analysis with GC–FID, GC–MS [30], HPLC/UV or HPLC/MS/MS [31,32]. Some metabolites can be excreted as glucuronide or sulphate conjugates which require hydrolysis by acid or enzymatically to measure the total amount excreted and the proportion bound and unbound excreted [33,34]. Detection limits of 1–5 mg/L are readily obtained and use of isotopically labeled standard improves the precision of the method when a MS is used as the detector for the chromatographic techniques.

The ring opened benzene metabolites *trans*, *trans* muconic acid (*t,t*MA) and *S*-phenyl mercapturic acid (*s*PMA) are at lower concentrations in the urine than the ring hydrolyzed metabolites and require greater volume reductions of the extract solvent and/or more sensitive analytical methodologies. *t,t*MA has been extracted using SPE or SPME followed by analysis by HPLC/UV or HPLC/MS/MS [31,35–40] or if derivatized by GC/MS [41,42]. Detection limits of 5–10 µg/L have been reported. *s*PMA has been analyzed by HPLC/UV and HPLC/MS/MS following extraction with SPE with reported detection limits of <1 µg/L [43–48]. Use of an internal standard is routine to improve precision. Urine excretion rate varies within and between individuals depending on the amount and types of liquid ingested over the course of a day. Collection of complete urine voids over time is difficult. Therefore, some researchers correct urinary concentrations by comparing the metabolite levels to the amount of creatinine excreted or to the specific gravity of the sample, though others have suggested that actual concentration is the better metric to report since creatinine excretion rate is not constant in active people over the course of a day [49].

Table 2

Time weighted average (TWA) air concentrations (ppm) across different industries that have potential benzene exposures.

	GM	Mean	Max	N
Refinery ^a		0.1	7	1400
Marine ^a		0.5	2	140
Service station ^a		0.1	2	350
Coke industry ^a		0.3	7	57
Urban workers ^a		0.007	0.1	670
Petroleum–floatation package ^b	0.77	1.1 ± 0.7	536	
Oil cargo tanks ^c		0.15	0.62	13
Aviation military maintenance ^b		0.8	2	114
Distribution ^b		0.002	0.6	38
BTX process ^d	0.068	0.14 ± 0.15	0.42	
Carboys polymethylene process ^d	0.64	1.1 ± 1.4	5.3	
Methylene di-aniline process ^d	0.099	0.30 ± 0.52	1.9	
Shoe manufacturer ^d	0.062	0.16 ± 0.08	0.16	
Offset printing ^d	0.014	0.017 ± 0.012	0.034	

^a Ref. [8].

^b Ref. [130].

^c Ref. [131].

^d Ref. [132].

2.3.1. Air concentrations

2.3.1.1. Occupational setting. Average work place benzene air concentrations in many industries (Table 2) have declined to <1 ppm in most industrialized developed countries over the previous two decades to meet occupational regulatory standards of between 1 and 5 ppm TWA (Table 1). However, a review of the benzene exposures in the shoemaking industry in China through 2004 still identified concentrations exceeding 100 ppm [6] which appears to continue currently ([50] and as reported elsewhere in this journal for the Shanghai Health Study). The need for regulation and better working conditions in small work shops in China has been suggested [51].

Workers who are part of the transportation industry, such as drivers and service station workers, and individuals in occupation that are near traffic, such as police officers are exposed to levels of tens to hundreds of ppb [52–55]. Peak values for mechanics who are exposed directly to gasoline fumes can approach ppm levels

[56–58]. Working with petroleum derived products, such as oil-based paints and commercial printing, results in a wide range of exposures from <10 ppb up to several hundreds ppb [59,60]. A recent study from Thailand identified that temple workers who continually burn incense are exposed to benzene at 0.01–0.1 ppm as well as other potential carcinogens: 1,3 butadiene and polyaromatic hydrocarbons [61].

2.4. Environmental settings

Environmental exposures through inhalation have been measured using personal monitors as well as indoor and/or outdoor air samples in a number of studies. Personnel air concentrations on average exceed indoor air concentrations, which exceed outdoor air concentrations (Table 3). This trend is most evident for the highest personal air concentrations where the outdoor levels serve as a baseline for the levels indoors. Further, proximity to sources and specific activities can add to benzene exposures. Since people spend the majority of their time in indoor microenvironments, contributions to exposures indoors have a larger influence on exposure than time spent outdoors [62–64]. Exposure levels for individuals who are and live with smokers are higher because benzene, along with other VOCs and particulate matter, are emitted from cigarette smoke [65]. Therefore, a number of studies measuring personal and indoor air have recruited populations of non-smokers to better understand non-cigarette sources for these compounds. Typical US personal exposure concentrations and outdoor air levels have declined from a range of 2–10 ppb (includes smokers) and 0.5–7 ppb, respectively [66], in the 1970–1980s to current personal and outdoor levels of 1–2 ppb (only non-smokers) and 0.5–2 ppb, respectively [67,68]. Similar exposures levels have been measured in Europe, though differences across individual cities are noted which may reflect differences in emission controls on petroleum products/automobiles and prevalence of cigarette smoking [62,69]. Levels in urban settings in South Korea and Thailand were 5–10 times higher for outdoors, indoors and personal air [55,70]. Smoking a cigarette directly delivers about 45 µg of benzene to the smokers [71] as well emitting benzene as a constituent of environ-

Table 3

Average and maximum personal, residential indoor and outdoor air concentrations (ppb) for environmental studies.

Location	Personal		Indoor		Outdoor	
	Mean	Max/N	Mean	Max/N	Mean	Max/N
US NJ RIOPA (NS) ^a	0.93 ± 1.4	10/171	0.84 ± 1.3	12/182	0.46 ± 0.52	6.0/182
US TX RIOPA (NS) ^a	1.6 ± 1.6	11/201	1.6 ± 2.0	15/205	0.86 ± 1.78	7.0/205
US CA RIOPA (NS) ^a	1.0 ± 2.2	3.1/171	1.0 ± 1.7	15/177	0.84 ± 0.78	6.7/175
US NY TEACH winter ^b	1.4 ± 1.0	5.0/35	1.8 ± 2.2	13/36		
US NY TEACH summer ^b	1.0 ± 0.7	2.3/31	0.53 ± 0.27	2.1/30		
US CA TEACH winter ^b	2.1 ± 1.1	6.1/				
US CA TEACH fall ^b	1.0 ± 0.6	3.0/				
US Nationwide NHANES ^c	1.7 ± 2.2	70/640				
EU France MACBETH ^d	3.4		2.0		1.3	
EU Helsinki NA EXPOLIS ^e	0.82 ± 0.51	3.1/111	0.62		0.50	2.6/156
EU Helsinki Smk EXPOLIS ^e	1.0 ± 3.3	23/46	1.1	3.7/167	0.50	2.6/156
Birmingham, UK ^f			4.6 ± 4.6	21/64	2.4 ± 2.0	10/64
Australia ^g	1.3	23				
NJ suburban/rural NJ ^h			1.3 ± 2.0	13/100		
Asan, Korea ⁱ			6.8 ± 4.2	/30	7.2 ± 3.9	/30
Seoul, Korea ⁱ			15 ± 22		13 ± 28	/30

NS—non-smoking subjects only.

^a Ref. [67].

^b Refs. [68,133].

^c Ref. [96].

^d Ref. [134].

^e Ref. [135].

^f Ref. [136].

^g Ref. [12].

^h Ref. [79].

ⁱ Ref. [70].

Table 4

Average and maximum non-residential indoor air concentrations (ppb) for environmental studies.

Location	Mean	Max/N
US stores ^a	0.57 (geometric mean)	3.0/
US restaurants ^a	1.0 (geometric mean)	7.6/
Italy gymnasium ^b	7.4 ± 1.9	/4
Italy supermarket ^b	1.4 ± 1.0	5.0/35
Birmingham, offices UK ^c	1.9 ± 0.8	/12
Birmingham, restaurants UK ^c	7.6 ± 1.3	/6
Birmingham, pubs UK ^c	11 ± 11	/6
Birmingham, dept stores UK ^c	3.5 ± 1.9	/8
Birmingham, cinemas UK ^c	6.2 ± 3.0	/6

^a Ref. [86].

^b Ref. [83].

^c Ref. [136].

mental tobacco smoke (ETS). It has been estimated smokers who are not occupationally exposed to benzene on average received 85% of their benzene exposure from smoking and ETS contributes ~23% of the total benzene exposure on average to non-smokers [72]. Environmental tobacco smoke increases indoor benzene levels an average of ~0.8–1.5 ppb with the increase for the 95th home at 4.2 ppb ([73–76]. Therefore avoiding ETS can reduce benzene exposures.

A source of benzene to residences is evaporation of gasoline from the residual in the engine and from the fuel tank in cars parked in garaged attached to homes, particularly since the car is hot after it has been driven. The benzene levels in a garage can be tens to hundreds of ppb but decline with time presenting short term high exposure when the garage is entered. The levels in the home are increased by several ppb with the value being dependent upon the tightness of the seal between the home and the garage and the air exchange between the two [77–80]. The air within and surrounding homes in close proximity (<200 m) to busy roadways or gasoline stations have on average 29–50% higher levels than the background ambient benzene levels at homes in other areas of urban centers [81].

Benzene has been measured in non-residential indoor environments in the US, Europe and Australia (Table 4) [82–86]. One major policy issue that has decreased benzene exposure in public places has been a ban on cigarette smoking in many public spaces and in workplaces. This has resulted in reducing benzene air levels in those locations and an effective decline in general population benzene exposures [65,87,88].

The benzene levels within automobiles and encountered during commuting are higher than in other microenvironments resulting in these activities contributing to a considerable percentage of the total daily benzene exposure [89]. Benzene exposures vary across different modes of transportation, dependent upon the traffic density surrounding and the design of the vehicle driven. Older cars with carburetors released more benzene and were subject to more frequent leaks of small amounts of gasoline into the engine block that could penetrate into the automobile cabin than fuel injection engines [90]. This could still be an issue in developing countries where cars are kept for a longer time and can be maintained by individuals with little formal training on repairs. Concentrations measured in cars, buses and bus depots vary more than order of magnitude from <1 to tens of ppbs across a number of Asian, European and North American cities [91–94]. Exposure during walking or bicycle riding adjacent to or in roadways is 2–3 times background levels [85,95]. Since gasoline emissions affect benzene air concentrations during transportation and in homes with attached garages, reducing the permitted benzene content in fuel has had a direct decline in exposure for the general public. This decline in ambient air concentration should be noted and acted upon in developing

countries where benzene levels in gasoline above 5% are still permitted.

Personal, microenvironmental and ambient air samples for benzene are typically collected over an extended time period, 12 to 48 h, therefore do not identify peak concentrations [96]. Short term excursions in benzene air concentrations and exposures exist around activities close to sources [97]. Refueling of automobiles results in exposure to benzene levels of 20–100 ppb over 2–5 min both to the individuals fueling the car and within the vehicle being fuelled [57,98–100]. However, differences in the emissions occur based upon whether or not control devices are present at the fuel pump. Included are Stage II vapor recovery systems which recycle the fumes from within the gasoline tank and displaced by gasoline to the underground storage tank [101]. Individuals who have hobbies that results in exposure to gasoline, such as fixing automobile engines, can receive elevated short term or long-term benzene exposures. However, if the prevalence of the hobbies is low in the general population few of these individuals would be captured in typical exposure studies so the highest exposures that occur in the general population would be poorly characterized. These activities could possibly be identified within surveys of activities if the appropriate questions are asked. Dermal and ingestion exposure to benzene can also occur in the general public from contact with contaminated water or food. It was estimated that ~7 and ~11 metric tons of benzene were released to surface waters and soil, respectively in 2004 in the US [18].

3. Biomarkers

The measurement of benzene in blood, breath or urine definitively documents a benzene exposure. However, the biological resident time of benzene in the body is minutes to hours [102] so it is difficult to determine the actual and in some cases even the relative exposures across individuals from a single benzene measurement in blood or breath unless details of when the sample was collected relative to the exposure are known.

3.1. Benzene in blood and urine

Routine exposures to benzene can increase the background body burden so differences in benzene levels in blood, breath and urine can help distinguish between exposed and non-exposed populations particularly for occupational exposures and for smokers vs. non-smokers. For example, benzene blood concentrations distinguished three groups of occupationally exposed workers in Mexico: service station attendants (median 0.1 ppm), street vendors (0.02 ppm) and office workers (0.013 ppm), with non-smokers having lower benzene blood levels than smokers [29]. Individual benzene blood levels were not highly matched to the paired air concentration as the latter were average values over time while the blood concentrations were reflective of the exposure during the last minutes prior to the blood collection. Thus, if short term excursions or valleys of durations of a few minutes exist in the exposure just prior to the blood collection, the air sample and blood sample would represent different exposure concentrations. Benzene blood levels measured as part of the National Health and Nutritional Examination Survey (NHANES) [103,104], have been compared to benzene air concentrations to determine their applicability as a biomarker and have been used to try to distinguish between benzene exposed and non-exposed workers on a population basis. A larger difference was identified in both the geometric mean and 75th percentile benzene blood concentration of smokers compared to non-smokers (factor of 3) than across the range of air concentrations for these two groups. For the NHANES data the adjusted R^2 and β were stronger for smokers than non-smokers and the overall association in a generalized linear regression model

Table 5

Biomarker levels with occupational exposures and/or smoking status.

GM (max)	Blood benzene (nM)	Urine benzene (nM)
Benzene exposed worker pre ^a	1.4 (3.0)	6.9 (28)
Benzene exposed worker post ^a	12 (38)	27 (330)
Reference workers pre ^a	0.9 (1.0)	1.8 (10)
Reference workers post ^a	0.7 (1.0)	0.7 (2.0)
Smoker worker ^b	6.5 (15)	2.8 (69)
Nonsmoker worker ^b	4.8 (170)	5.3 (67)
Smoker ^c		0.40 (3.2)
Nonsmoker ^c		20 (2.2)
Smoker worker in traffic ^d		2.1 (24)
Nonsmoker worker in traffic ^d		2.4 (10)
	urinary <i>t,t</i> MA mg/g creatinine	Urinary <i>s</i> PMA mg/g creatinine
Exposure level <0.1 ppm ^e	0.92 ± 0.54	
Exposure level 0.1–1 ppm ^e	1.2 ± 0.5	
Exposure level >1 ppm ^e	1.4 ± 0.8	
Exposure level <7 ppm pre/post-shift ^f	1.2 ± 1.2/2.8 ± 3.1	
Exposure level 7–20 ppm pre/post-shift ^f	4.9 ± 3.4/10. ± 4.6	
Exposure level >20 ppm pre/post-shift ^f	11. ± 7.0/17. ± 6.7	
Exposure level <0.1 ppm ^g	0.59 ± 0.22	0.0041 ± 0.0052
Exposure level >1 ppm ^g	10 ± 15	0.029 ± 0.043
Smoker non-occupational exposure ^h	0.093 ± 0.088 0.59(max) (N = 111)	
Nonsmoker non-occupational exposure ^h	0.055 ± 0.065 0.140(max) (N = 264)	
Traffic police-control/refinery worker-control ⁱ	0.75–0.05/0.19–0.010	
Press-control/fisherman-control ⁱ	560–80/0.18–0.020	
Gas station attendant-control/mechanic-control ⁱ	4.0–0.120/0.28–0.12	
Smoking taxi drivers pre/post-shift ^j	0.131 ± 62/0.154 ± 70	0.0028 ± 1.9/0.0038 ± 1.5
Nonsmoking taxi drivers pre/post-shift ^j	0.105 ± 67/0.122 ± 70	0.0022 ± 1.7/0.0021 ± 1.9

^a Ref. [130].^b Ref. [112].^c Ref. [137].^d Ref. [54].^e Refs. [54,132].^f Ref. [36].^g Ref. [124].^h Ref. [138].ⁱ Ref. [113].^j Ref. [53].

between benzene blood and benzene air concentration was influenced by smoking, exposure-smoking interactions, gender, age and body mass index (BMI) [105]. Smoking workers who are exposed to low occupational benzene exposures also have higher blood benzene levels than non-smokers in the same industry, though urinary benzene levels of smokers were not consistently higher than non-smokers (Table 5). Benzene blood levels are higher after work shifts compared to before work shifts while no differences were noted in pre- and post-shift samples for a reference group not exposed to benzene. Urinary benzene levels were linearly related to work shift air concentrations ($N = 139$, 4 samples per worker) over an exposure range of <0.2–100 ppm indicating that urinary benzene provides a biomarker of exposure over the previous 24 h, though the 95th confidence interval around the data extends over an order of magnitude [106–108]. Individual paired urinary benzene concentration pre- and post-shift samples do not always show increases in the post-shift samples which may reflect benzene exposure that occurred during the previous work shift and from the environment. Blood and breath benzene levels have biological half lives of seconds to minutes while urinary benzene levels reflect exposures since the previous one to two voids for single exposure. Individuals who are routinely exposed to benzene will have elevated background benzene in these biological fluids compared to a non-exposed population, though their peak benzene levels will be within minutes of the end of the exposure.

3.2. Urinary metabolites

Urinary ring hydrolyzed benzene metabolites, phenol, catechol and hydroquinone have been related to occupational exposures at

high levels, exceeding 10 ppm but have not been related to exposures <1 ppm (Table 5) [109,110]. Thus, while these metabolites have been used as biomarkers in early occupational studies when the exposures exceeded 10 ppm their background urinary levels preclude their use as a biomarker for exposures at lower occupational or environmental exposures.

Urinary *t,t*MA has been shown to increase with benzene exposures from <0.1 to 20 ppm across a variety of occupational settings as well as between smokers and non-smokers. Urinary metabolite levels represent exposures of the previous several hours for brief exposures though can be elevated for days for routinely exposed individuals after the exposure has stopped. These results suggest that it is a valid biomarker for sub-ppm exposures (Table 5). However, level of urinary *t,t*MA have not always been related to air concentrations of benzene [111]. One possible reason is *t,t*MA is also a metabolite of sorbic acid a common food additive resulting in increases in urinary *t,t*MA in the absence of benzene exposure [39,112]. The population mean *t,t*MA urinary levels across a number of occupations with benzene exposures from 10 to several hundreds of ppbs (traffic policeman, oil refinery worker, press worker, fishermen, gas station attendants, mechanics) were 2–33 times higher than levels in controls in a number of studies [113]. Urinary *s*PMA has been proposed as a better biomarker than *t,t*MA for benzene exposure below 1 ppm [114]. Urinary *s*PMA has been shown to increase with benzene exposure at sub-ppm levels and has no other known sources besides benzene exposures (Table 5). One study though, did not find either *t,t*MA or *s*PMA related to benzene exposure ranging from 10 ppb to ppm levels while urinary benzene was and observed that smoking status was a key factor influencing urinary benzene levels [115]. Smoking status in the general popula-

tion and by workers exposed to occupational benzene levels below a few tenths of a ppm can contribute more to urinary *t,t*MA and/or *s*PMA than received from environmental or occupational sources [138,139].

3.3. Benzene adducts

Benzene adducts have been proposed as biomarkers of longer term benzene exposure since several benzene metabolites include reactive electrophiles: benzene oxides, 1,2 and 1,4 benzoquinone, muconaldehydes and benzene diepoxide, which have the potential to form adducts. Hemoglobin adducts have biological half lives approximate four months, the average lifespan of red blood cell, while DNA adducts can have longer residence time dependant upon how long cells containing the DNA remain in the body. Protein adducts in serum were higher in exposed workers compared to controls (0.2–55 ppm vs. <0.01–0.5 ppm) [116,117]. Hemoglobin adducts of benzene oxide have been measured in dried blood spots of neonates and adults and suggested to be linked to benzene exposure [118]. While benzene adducts hold promise of being a valid biomarker of exposure most laboratories do not have the analytical capability to measure them with the necessary sensitivity.

3.4. Variability in benzene metabolism

The internal dose of benzene and the percentage of benzene that is metabolized to each metabolite vary with exposure level. A greater percentage of the benzene is absorbed at lower exposures based on Henry's Law which governs the air-blood equilibrium [102]. The percentage of benzene excreted as *t,t*MA and hydroquinone was higher at lower exposure while the percentage of phenol and catechol excreted was higher at exposures below 1 ppm than in individuals exposed to 10's to 100's of ppm or to animals dosed at high levels [34,50,119,120]. Rappaport et al. [50] suggest that two pathways are responsible for benzene metabolism at different doses. In addition, genetic difference could also alter metabolism efficiencies of benzene across different pathways, with a number of different polymorphism suggested to be important, including: *GSTT1*, *CYP2E1*, *NADPH*, and *NQO1* [112,121–129]. These variations could alter the risk extrapolation from high to low exposures and need to be considered when evaluating the potential health impact of low occupational and environmental exposures.

4. Discussion

Benzene exposures still commonly occur within both occupational and environmental settings, though they have been declining over the last several decades. Occupational exposures are now typically below the regulatory standard of 1 ppm and often below 0.1 ppm. However, identifying higher exposures, exceeding 10's of ppm exist in small, unregulated workplaces is an important data gap. Environmental exposures among the general population are much lower than occupational exposures, ranging from <1 to 10 ppb with the primary environmental benzene sources being mobile emissions and cigarette smoke (both for smokers and environmental tobacco smoke). A comparison of the ranges of benzene exposures is presented in Fig. 1. Exposures to the general population from these sources have been reduced significantly outdoors and indoors by lowering the benzene content in gasoline and prohibiting smoking in many public places. Personal habits and microenvironments visited control the variations in an individual's exposure. Data gaps for identifying exposures potentially leading to health risks to the general population are identifying the highest non-occupationally exposed populations globally and peak environmental exposures that occur for the general population. Several biomarkers, urinary benzene, *t,t*MA and *s*PMA along with

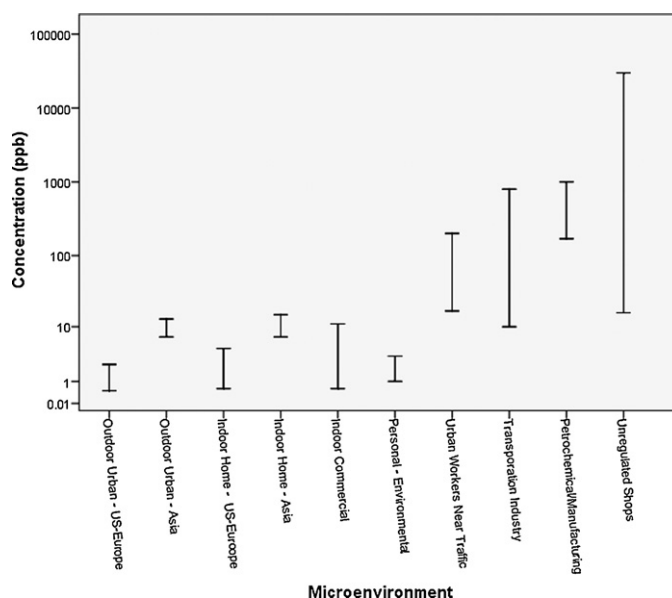


Fig. 1. Ranges of Reported benzene air concentrations in different microenvironments.

benzene adducts are potentially valid at occupational and environmental exposures below 0.1 ppm, though disagreements still exist in the literature as to contributions to these metabolites from non-benzene sources at the lowest exposure range. Further, the percent of the benzene dose that is excreted as each metabolite appears to vary going from 10 ppb exposures to 10 ppm exposures and may be altered by polymorphisms in various genes controlling benzene metabolism. The importance of such variations in benzene metabolism on an extrapolation of health risk from occupational exposures of tens to hundreds of ppm to exposures of tens of ppb is not known. The key to understanding and determining how to best reduce exposure will be a combination of valid biomarker measurements and an exposure analysis of important contacts to elucidate the sources of benzene exposure.

Conflicts of interest

None declared.

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