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Critical Review

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New Look at BTEX: Are Ambient Levels a Problem?

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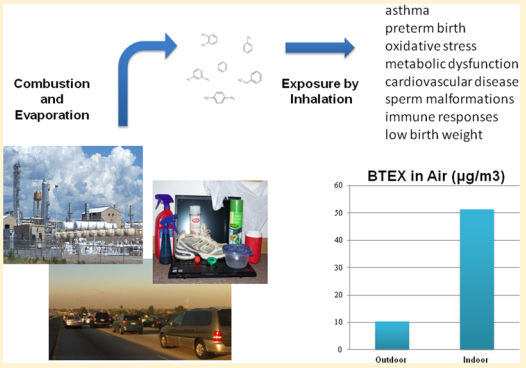
Supporting Information

ABSTRACT: Benzene, toluene, ethylbenzene, and xylene (BTEX) are retrieved during fossil fuel extraction and used as solvents in consumer and industrial products, as gasoline additives, and as intermediates in the synthesis of organic compounds for many consumer products. Emissions from the combustion of gasoline and diesel fuels are the largest contributors to atmospheric BTEX concentrations. However, levels indoors (where people spend greater than 83% of their time) can be many times greater than outdoors. In this review we identified epidemiological studies assessing the noncancer health impacts of ambient level BTEX exposure (i.e., nonoccupational) and discussed how the health conditions may be hormonally mediated. Health effects significantly associated with ambient level exposure included sperm abnormalities, reduced fetal growth, cardiovascular disease, respiratory dysfunction, asthma, sensitization to common antigens, and more. Several hormones including estrogens, androgens, glucocorticoids, insulin, and serotonin may be involved in these health outcomes. This analysis suggests that all four chemicals may have endocrine disrupting properties at exposure levels below reference concentrations (i.e., safe levels) issued by the U.S. Environmental Protection Agency. These data should be considered when evaluating the use of BTEX in consumer and industrial products and indicates a need to change how chemicals present at low concentrations are assessed and regulated.



INTRODUCTION

As the demand for methane increased to meet the world's growing energy needs, so grew the demand for aromatic compounds used as the feedstock for a vast number of materials and products upon which society has become dependent. Along with methane and crude oil, semivolatile gases also surface during fossil fuel extraction. Benzene, toluene, ethylbenzene, and xylene (BTEX; Figure 1) are of particular concern due to their widespread use in gasoline and other consumer products and exposures from vehicular traffic and fossil fuel extraction emissions which are occurring in closer proximity to populated areas.

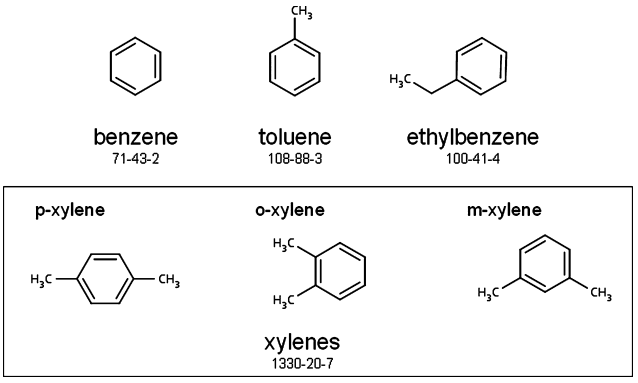


Figure 1. Structures and Chemical Abstracts Service (CAS) Registry numbers of BTEX. Images reprinted from Toxnet, National Institutes of Health, U.S. National Library of Medicine.

Sources and Uses. During the extraction of crude oil and raw natural gas, aromatic compounds, including BTEX are captured at the wellhead as liquids and delivered to refineries. BTEX are then isolated and/or synthesized by catalytic reforming, cracking of naphtha, and other chemical reactions including dealkylation, alkylation, and coal coking. Once isolated, they are used in a variety of products including adhesives, coatings, degreasers, detergents, dyes, explosives, fuels, ink, lacquers, paint, pesticides, polishes, resins, rubber cement, and solvents, which are then utilized in the manufacture of products found in businesses, homes, and schools.[1−6] BTEX are also widely used as intermediates in the synthesis of thousands of other organic compounds by the chemical and pharmaceutical industries and product manufacturers.[3−11] Another common use of BTEX is in fuel formulations.[7] They are combined in specific proportions to make reformates, which are added to motor and aviation fuel to prevent autoignition of the fuels under high temperature and high pressure conditions. According to a 1998 report, BTEX collectively comprised as much as 27.5% of high octane gasoline at the pump.[12]

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Table 1. Range of Mean Exposure to BTEX across Studies Included in Review[a]

aromatic	personal air, $\mu g/m^3$	indoor air, $\mu g/m^3$	outdoor air, $\mu g/m^3$	lowest effect concn, $\mu g/m^3$	RfC,[b] mg/m^3
benzene	1.21−2.8	1.01−24.8	1.5−6.95	1.01[c]	0.03
toluene	14.33	6.95−325.5	7.17−26.9	6.95[c]	5.0
ethylbenzene	2.55	0.8−18.7	0.59−2.06	1.5[d]	1.0
xylenes					0.1
ortho	2.16	0.49−5.9	0.94−4.16	1.5[d]	
meta/para	5.97	1.55−7.23	3.07−13.3	4.1[d]	

[a]The available measure of central tendency (i.e., mean, median, or geometric mean) was used from the studies. [b]Reference concentrations (RfC) were from U.S. EPA Integrated Risk Information System (IRIS) database. [c]Herberth et al.[96] [d]Wallner et al.[119]

Releases to the Environment. BTEX are released to the atmosphere through the combustion of fossil fuels, by evaporation that occurs at service station gas pumps while filling vehicle gas tanks, and during storage tank filling, accidental spillage, and solvent usage.[13−17] BTEX are also released into the atmosphere from oil and gas operations during the processing and storage of crude oil, condensates, and produced water.[18] Current data show the most widespread source of anthropogenic BTEX in outdoor ambient air is through the burning of gasoline and diesel fuels in motor vehicles, stationary engines, and other equipment, as only 5−10% of BTEX emissions in outdoor air come from nonmobile sources.[15,17,19,20]

Indoors BTEX can volatilize from numerous products including household cleaners, fabric and leather treatments, and automotive products.[1,21−23] Further, their use in household cleaning products results in sorption to various indoor surfaces (e.g., carpets, glass, pillows, flooring, and wallcoverings), which contributes to persistent background levels postcleaning.[24] In a recent United States Environmental Protection Agency (U.S. EPA) report ethylbenzene was listed in the top 10 chemicals used in children's products with the highest use in toys, furniture and furnishings, playground and sporting equipment, and plastic and rubber products. Toluene was in the top 10 chemicals in consumer products, primarily fuels, paints, and coatings.[25] In addition, they are present in mainstream[26] and sidestream cigarette smoke.[27,28]

Human Exposure. Across the globe BTEX have been found in cord blood[29] and blood[30−33] of men, children, pregnant women, and those occupationally exposed. Quantifiable levels of BTEX have been detected in personal,[34−39] indoor,[40] and outdoor[41−47] air samples in studies of children, teenagers, and adults in many different countries.[48−52] In Table 1 mean ambient (i.e., nonoccupational) exposure levels are shown for personal, indoor, and outdoor air that were measured in the studies included in this review. Air concentrations are in the low $\mu g/m^3$ range for all compounds, and with the exception of *m*-/*p*-xylene, the highest concentrations were found in indoor air. Further, other studies have shown similar patterns where BTEX concentrations were higher indoors.[48,50]

Endocrine Disruption. Appropriate endocrine signaling is integral to physiological function and maintenance of homeostatic processes that contribute to growth and development, immune responses, reproduction, complex behaviors, metabolism, respiration, cardiovascular function, and aging.

In occupational settings, disruptions of endocrine signaling have been associated with exposure to BTEX chemicals individually and combined. Specifically, exposure to benzene has been linked to abnormal sperm production,[53−55] altered menstrual cycles,[56] spontaneous abortion,[57] decreased immune cells[58−61] and antibodies,[58,61,62] and activation of oxidative stress pathways.[61,63] Occupational toluene exposure has been correlated with decreases in luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone,[64] increased risk of spontaneous abortion,[65,66] and decreased fertility in women.[67] Alterations in immune cell numbers,[68] activation of oxidative stress pathways,[69,70] and decreases in liver and kidney function have also been shown.[71] Xylene exposure was correlated with increased risk of oligomenorrehea[72] and ethylbenzene to increases in oxidative stress markers.[73] Exposure to combined BTEX in occupational settings was related to abnormal sperm morphology, reduced number[74] and decreased sperm activity,[75] changes in cytokine expression[76] and natural killer (NK) cell activity with immune challenge,[77] and alterations in antibody isotype concentrations.[78,79] It is clear that BTEX have the ability to disrupt critical endocrine signaling at occupational exposure levels.

Increasingly, research has demonstrated that exposure to ambient concentrations of chemicals, particularly during certain windows of susceptibility (e.g., prenatal and childhood development), can have detrimental impacts on endocrine physiology.[80,81] The ability of current regulatory policies to adequately address these new findings is being debated; thus, it is important to identify chemicals that are of high concern for such an assessment. To our knowledge, neither BTEX as a mixture nor the individual compounds have been tested for regulatory purposes at ambient levels of exposure. Nor have they been tested at ambient levels for their endocrine disrupting properties in *in vivo* controlled laboratory studies.

In this review we identify the available literature on noncancer human health effects of exposure to BTEX, summarize the studies assessing ambient exposure level effects, and identify areas where additional research is needed. To our knowledge, no such review has been conducted to date.

METHODS

Identification of Relevant Studies. A literature search of the health effects of each chemical was conducted in PubMed with no date restrictions through May 2014 using the common systematic or MesH heading (if available) name of each compound in the "Title/Abstract" field. Resulting studies were searched using a list of search terms specific to physiological function in "All Fields" of the search (see the Supporting Information (SI)).

The initial screening of these publications involved scanning titles to remove studies that did not address the physiological impacts of exposure to BTEX and studies that were not in English. Abstracts were then screened to remove reviews and other nonprimary literature. The remaining studies were data extracted, Universal Desktop Ruler (AVPSoft.com) software was used as needed, study findings were cross-checked by two reviewers, and conflicts or disagreements were resolved by

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Table 2. Study Information[a]

Author	Study Design	Method of exposure measurement	Life-stage of exposure	Confounding variables	Exposure assessment	Outcome assessment
Aguilera et al. 2009	prospective	outdoor air sampling	prenatal	++	+	++
Aguilera et al. 2010	prospective	outdoor air sampling	prenatal	++	+	++
Arif and Shah 2007	cross-sectional	personal air sampling	adulthood	++	-	+
Baiz et al. 2011	cross-sectional	personal air sampling	prenatal	++	++	++
Bentayeb et al. 2010	prospective	outdoor air sampling	senescence	++	-	-
Bentayeb et al. 2013	cross-sectional	indoor air sampling	adulthood; senescence	++	-	-
Billionnet et al. 2011	cross-sectional	indoor air sampling	adolescence; adulthood	++	++	-
Buchdahl et al. 2000	prospective	outdoor air sampling	childhood	-	-	++
Choi et al. 2009	case-control	indoor air sampling	childhood; adolescence; adulthood	-	++	++
Choi et al. 2014	cross-sectional	urinary metabolite (t,t-MA) and personal air sampling	senescence	++	++	++
Delfino et al. 2003a	cross-sectional	outdoor air sampling; breath	childhood; adolescence	-	+	-
Delfino et al. 2003b	cross-sectional	outdoor air sampling	childhood; adolescence	-	+	-
Diez et al. 2000	cross-sectional	indoor air sampling	childhood	-	-	-
Ducci et al. 2001	cross-sectional	seminal fluid metabolite (t,t-MA)	adulthood	-	+	++
Dutta et al. 2013	cross-sectional	urinary metabolite (t,t-MA)	adulthood	-	-	++
Erdei et al. 2003	cross-sectional	indoor air sampling	childhood	-	-	++
Estarlich et al. 2011	cross-sectional	outdoor air sampling	prenatal	++	-	++
Ghosh et al. 2012	case-control	outdoor air sampling	prenatal	-	+	++
Gordian et al. 2010	cross-sectional	indoor air sampling	childhood	++	++	-
Herberth et al. 2014	cross-sectional	urinary metabolites (SBMA; SPMA); indoor air sampling	prenatal	-	-	++
Hirsch et al. 1999	cross-sectional	outdoor air sampling	childhood	++	++	-
Hulin et al. 2010	case-control	indoor air sampling	childhood	++	+	-
Junge et al. 2014	cross-sectional	indoor air sampling	prenatal	-	-	++
Lehmann et al. 2001	prospective	indoor air sampling	childhood	-	-	++
Llop et al. 2010	prospective	outdoor air sampling	prenatal	++	+	+
Lupo et al.2011	case-control	outdoor air sampling	prenatal	++	+	++
Martins et al. 2012	prospective	outdoor and indoor air sampling	childhood	++	+	++
Mukherjee et al. 2014	cross-sectional	urinary metabolite (t,t-MA)	adulthood	++	+	++
Nicolai et al. 2003	cross-sectional	outdoor air sampling	childhood	-	+	-
Pelallo-Martinez et al. 2014	cross-sectional	urinary metabolite (t,t-MA; HA)	childhood	-	-	++
Penard-Morand et al. 2010	cross-sectional	outdoor air sampling	childhood	++	+	-
Rive et al. 2013	case-control	urinary metabolite (S-PMA); indoor air sampling	childhood	++	-	-
Rolle-Kampczyk et al. 2002	case-control	urine metabolites (SBMA,SPMA); indoor air sampling	childhood	-	-	-
Rumchev et al. 2004	case-control	indoor air sampling	childhood	++	+	++
Saijo et al. 2004	cross-sectional	indoor air sampling	adulthood	++	++	-
Slama et al. 2009	prospective	personal air sampling	prenatal	++	++	++
Smargiassi et al. 2014	cross-sectional	personal air sampling	childhood	++	+	++
Wallner et al. 2012	cross-sectional	indoor air sampling	childhood	++	++	++
Xu et al. 2009	case-control	blood VOCs	adulthood	++	+	+
Yoon et al. 2010	prospective	outdoor and indoor air sampling	senescence	++	-	++
Zahran et al. 2012	retrospective	outdoor air sampling	prenatal	-	-	++
Zhou et al. 2013	cross-sectional	outdoor air sampling	childhood	++	-	-

[a]VOC, volatile organic compound; *t,t*-MA, *trans,trans*-muconic acid; HA, hippuric acid; SBMA, *S*-benzylmercapturic acid; SPMA and S-PMA, *S*-phenylmercapturic acid; ++, definitely low risk of bias; +, probably low risk of bias; −, probably high risk of bias.

discussion. Specific exclusions included studies of occupational exposure and studies in individuals with multiple chemical sensitivity.

Study Quality Assessment. Study quality was assessed using the Office of Health Assessment and Translation (OHAT) approach.[82] Briefly, the risk of bias (RoB) of the study methodology was evaluated by answering 11 questions (see the SI). Each study was assessed independently by two reviewers, and then discrepancies were resolved through discussion.[82]

RESULTS

Overall Study Quality. Our search identified a total of 42 papers that fit inclusion criteria (Table 2). All studies were assessed for RoB; 13 were rated "high quality" while 30 were rated as "moderate quality." Of the studies rated as moderate quality, 16 did not control for relevant confounders (e.g., smoking or passive smoke exposure), 10 failed to report how many exposure samples had values that were too low to be detected, and 15 used methods to measure the outcome that were not adequately validated (e.g., use of subject self-reported outcomes and questionnaires). See SI Table S1 for a list of confounders used in each study and SI Table S2 for specific RoB questions and ratings for each study. All 42 studies were of sufficient quality (moderate to high) to be included in this review.

Benzene. Thirty-five studies examined relationships between ambient level benzene exposure and health impacts; detailed findings are presented in Table 3. Four studies assessed the effects of ambient exposure during adulthood, 16 in childhood, nine in the prenatal period, three in the elderly, and three in a mixture of adults, children, and adolescents. Average ambient levels ranged from 1.01 to 24.8 $\mu g/m^3$. All of the ambient level exposure studies measured benzene below the reference concentration (RfC) of 0.03 mg/m^3.

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Table 3. Health Effects of Ambient Exposure to Benzene[a]

health outcome	*N*	exposure concn	effect size (OR; 95% CI)[b]	citation
development				
biparietal diameter	81	≥2.6 $\mu g/m^3$	(−1.3; −2.6 to −0.1)[c]	Slama et al.[85]
birth weight	1601703	1.975−4.929 $\mu g/m^3$	(1.82; 1.64−2.02)[c]	Zahran et al.[87]
		<1.4 to ≥2.6 $\mu g/m^3$	(−68; −135 to −1)[c]	Slama et al.[85]
	270	1.6 $\mu g/m^3$	(16.2; −24.6 to 56.9)	Estarlich et al.[86]
	2337	1.1 ppbV	(1.03; 1.00 to 1.05)[d]	Ghosh et al.[88]
low birth weight	354688			
head circumference	85	≥2.6 $\mu g/m^3$	(−3.7; −7.3 to 0.0)[c]	Slama et al.[85]
	2337	1.6 $\mu g/m^3$	(0.04; −0.09 to 0.17)	Estarlich et al.[86]
preterm birth	785	>2.7 $\mu g/m^3$	(6.46; 1.58 to 26.35)[c]	Llop et al.[84]
spina bifida	4531	>2.86−7.44 $\mu g/m^3$	(1.77; 1.04 to 3.00)[c]	Lupo et al.[83]
immune function				
atopy	1629	per 1 $\mu g/m^3$ increase	(0.98; 0.88 to 1.09)	Hirsch et al.[92,g]
	86	6.32−12.59 $\mu g/m^3$	β = 0.32[c]	Choi et al.[93]
alveolar macrophages	321	6.4 mg/L	(1.32; 1.1 to 2.32)[c]	Dutta et al.[95]
CD4+/CD25+ t-cells	56	3.3 $\mu g/m^3$	(−0.92; 1.00 to 1.81)[d]	Baiz et al.[34]
dysplasia	321	6.4 mg/L	(1.71; 1.26 to 4.22)[c]	Dutta et al.[95]
eczema		2.41 $\mu g/m^3$	(1.48; 1.24−1.75)[c]	Zhou et al.[90]
in last year		1.5 to 3.3 $\mu g/m^3$	(1.11; 1.0 to 1.28)[d]	Penard-Morand et al.[91]
eosinophils	321	6.4 mg/L	(1.75; 1.19 to 4.22)[c]	Dutta et al.[95]
IL-3 eosinophil/basophils	40	dnr	r = 0.432[c]	Junge et al.[97]
IL-5 eosinophil/basophils	40	dnr	r = 0.371[c]	Junge et al.[97]
lymphocytes	321	6.4 mg/L	(1.45; 1.21 to 3.44)[c]	Dutta et al.[95]
metaplasia	321	6.4 mg/L	(1.67; 1.22 to 5.45)[c]	Dutta et al.[95]
miR-223	316	1.01 $\mu g/m^3$	(1.17; 1.07 to 1.29)[c]	Herberth et al.[96]
MLH1	140	7.96 mg/L	(1.44; 1.02 to 2.10)[c]	Mukherjee et al.[94]
MSH2	140	7.96 mg/L	(1.64; 1.04 to 2.36)[c]	Mukherjee et al.[94]
neutrophils	321	6.4 mg/L	(1.22; 1.05 to 3.19)[c]	Dutta et al.[95]
sensitization to pollen	4907	1.5−3.3 $\mu g/m^3$	(1.24; 1.0−1.52)[d]	Penard-Morand et al.[91]
WBC count	20	369 μg/(g of Cr)	r = −0.51[c]	Pelallo-Martinez et al.[98]
metabolic function				
HOMA-IR (insulin resistance)	505	0.032 mg/(g of Cr)	(2.00; 1.16−3.46)[c,i]	Choi et al.[113]
reproductive function				
asthenospermic	32	170−430 ng/mL	(nES)[c]	Ducci et al.[89]
normospermic	32	170−430 ng/mL	(nES)[c]	Ducci et al.[89]
oligospermic	32	170−430 ng/mL	(nES)[c]	Ducci et al.[89]
teratospermic	32	170−430 ng/mL	(nES)[c]	Ducci et al.[89]
sperm concn	32	170−430 ng/mL	r= −0.62[c]	Ducci et al.[89]
% normal sperm	32	170−430 ng/mL	r = −0.41[c]	Ducci et al.[89]
% viable sperm	32	170−430 ng/mL	r = −0.89[c]	Ducci et al.[89]
respiratory function				
asthma	192	per 10 $\mu g/m^3$ increase	(2.922; 2.25− 3.795)[c]	Rumchev et al.[99]
		n/a	(4.95; 0.91−27.4)	Rive et al.[105]
	111	0.3−53.5 $\mu g/m^3$	(1.3; 0.4−3.8)	Hulin et al.[106]
in the last year	1012	2.0 $\mu g/m^3$	(1.43; −0.65 to 4.75)	Billionnet et al.[107]
lifetime	4907	1.5−3.3 $\mu g/m^3$	(1.36; 1.0−1.96)[d]	Penard-Morand et al.[91]
	4907	1.5−3.3 $\mu g/m^3$	(1.25; 1.08−1.43)[c]	Penard-Morand et al.[91]
exercise-induced	2104	1.50−6.95 $\mu g/m^3$	(0.72; 0.48−1.07)	Bentayeb et al.[108]
	4907	1.5−3.3 $\mu g/m^3$	(1.32; 1.03−1.82)[c]	Penard-Morand et al.[91]
	1228	3−9 ppb	(1.28; 0.76−2.13)	Gordian et al.[102]
current	1039	>9 ppb	(1.48; 0.81−2.73)	Gordian et al.[102]
current[e]	3233	4.74 to >7.27 $\mu g/m^3$	(2.045; 1.227−3.407)[c]	Nicolai et al.[100]
physician-diagnosed	1255	4.74 to >7.27 $\mu g/m^3$	(2.047; 1.235−4.692)[c]	Nicolai et al.[100]
	550	1.21 $\mu g/m^3$	(1.33; 1.13−1.56)[c]	Arif and Shah[101]
	1228	3−9 ppb	(1.04; 0.67−1.63)	Gordian et al.[102]
	1039	>9 ppb	(1.06; 0.61−1.85)	Gordian et al.[102]
	4209	2.41 $\mu g/m^3$	(0.97; 0.81−1.15)	Zhou et al.[90]
severe asthma	2203	per 1 $\mu g/m^3$ increase	(1.21; 1.01−1.45)[c]	Hirsch et al.[92,g]
	1228	3−9 ppb	(1.34; 0.70−2.54)	Gordian et al.[102]
	1039	>9 ppb	(2.49; 1.22−5.07)[c]	Gordian et al.[102]
symptoms	80	5.67 ng/L	(5.93; 1.64−21.4)[c]	Delfino et al.[103]

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Table 3. continued

health outcome	N	exposure concn	effect size (OR; 95% CI)[b]	citation
	74	1.82 ppb	(1.23; 1.02−1.48)[c,f]	Delfino et al.[104]
bronchitis	2114	per 1 $\mu g/m^3$ increase	(1.16; 1.04−1.29)[c]	Hirsch et al.[92,g]
obstructive bronchitis	192	>3.6 $\mu g/m^3$	(10; 1.57−63.34)[c]	Rolle-Kampczyk et al.[116]
cough	2211	per 1 $\mu g/m^3$ increase	(1.21; 1.04−1.40)[c]	Hirsch et al.[92]
	3206	4.74 to >7.27 $\mu g/m^3$	(1.423; 1.01−2.005)[c]	Nicolai et al.[100]
	2104	1.50−6.95 $\mu g/m^3$	(0.78; 0.56−1.09)	Bentayeb et al.[108]
EBC pH	51	1.0−10.7 ($\mu g/m^3$)/week[h]	(−0.24; −0.42- −0.06)[c]	Martins et al.[110]
FEV in 1 s	51	1.0−10.7 ($\mu g/m^3$)/week[h]	(−4.33; −7.13 to −1.53)[c]	Martins et al.[110]
	72	2.80 $\mu g/m^3$	(−4.7; −18.8 to 9.5)	Smargiassi et al.[111]
FEV in 1 s, <85% predicted	992	per 1 $\mu g/m^3$ increase	(1.17; 0.81−1.67)	Hirsch et al.[92]
FEF 25−75% of FVC	51	1.0−10.7 ($\mu g/m^3$)/week[h]	(−5.89; −10.16 to −1.62)[c]	Martins et al.[110]
	72	2.80 $\mu g/m^3$	(−3.5; −34.2 to 27.1)	Smargiassi et al.[111]
FEF 25−75%, <70% predicted	981	per 1 $\mu g/m^3$ increase	(1.17; 0.92−1.50)	Hirsch et al.[92]
FEV in 1 s/FVC	51	1.0−10.7 ($\mu g/m^3$)/week[h]	(−1.71; −3.24 to −0.18)[c]	Martins et al.[110]
oxidative stress (8OHdG)	154	0.08 mg/L	β = 8.23[c]	Yoon et al. [112]
pulmonary infections	256	>5.6 $\mu g/m^3$	(2.4; 1.3−4.5)[c]	Diez et al.[109]
wheeze	3192	4.74 to >7.27 $\mu g/m^3$	(1.646; 1.062−2.552)[c]	Nicolai et al.[100]
	2218	per 1 $\mu g/m^3$ increase	(1.08; 0.90−1.29)	Hirsch et al.[92]
	6634	3.57 $\mu g/m^3$	(1.08; 1.02−1.13)[c]	Buchdahl et al.[117]
	4209	2.41 $\mu g/m^3$	(0.99; 0.84−1.15)	Zhou et al.[90]
other physiological effects				
hematocrit	20	369 μg/(g of Cr)	r = −0.64[c]	Pelallo-Martinez et al.[98]
hemoglobin	20	369 μg/(g of Cr)	r = −0.60[c]	Pelallo-Martinez et al.[98]
RBC count	20	369 μg/(g of Cr)	r = −0.42[c]	Pelallo-Martinez et al.[98]

[a]dnr, data not reported; nES, no effect size reported; 8-OHdG, 8-oxo-2′-deoxyguanosine; IL-3, interleukin-3; IL-4, interleukin-4; IL-5, interleukin-5; MIR-223, microRNA-223; MLH1, mutL homologue 1; MSH2, mutS homologue 2; RBC, red blood cell; WBC, white blood cell; HOMA-IR, homeostasis model assessment scores−insulin resistance; EBC, exhaled breath condensate; FEF 25−75%, forced expiratory flow between 25 and 75% of FVC; FEV1, forced expiratory volume in 1 s; FVC, force vital capacity. [b]Except where indicated otherwise. [c]$p < 0.05$. [d]$p = 0.05$. [e]Children exposed to ETS. [f]Lag 0. [g]Exposure at home and school. [h]Mean range across four visits. [i]For second quartile only.

Developmental Effects. There were six studies that evaluated various aspects of development with respect to benzene exposure. One showed that maternal exposure was correlated with increased odds of having offspring with spina bifida.[83] Maternal benzene exposure was also associated with significant alterations in biparietal diameter, preterm birth, and head circumference.[84,85] One study did not find associations between benzene and head circumference.[86] Three studies found benzene exposure to be associated with significant decreases in birth weight,[85,87,88] while one study did not.[86]

Reproductive Effects. A study in men showed that *trans,trans*-muconic acid (*t,t*-MA) levels (a benzene metabolite) were significantly increased in teratospermic (i.e., malformed sperm), oligospermic (i.e., decreased sperm count), and asthenospermic (i.e., decreased sperm motility) individuals. Significant decreases in sperm concentration, normal sperm morphology, and viability were also correlated with increased *t,t*-MA levels.[89]

Immunological Effects. Eleven studies assessed the impact of benzene exposure on several elements of the immune system. In three studies, aspects of allergy including eczema[90,91] and sensitization to pollen[91] were shown to be correlated with benzene exposure. Two studies showed opposing atopy results in subjects exposed to benzene.[92,93] Maternal exposure to benzene was associated with decreases in CD4+CD25+ percentages in newborns.[34] In women, urinary *t,t*-MA was linked to increases in immune cells and decreases in markers of DNA repair in sputum samples which may indicate increased susceptibility to higher rates of spontaneous gene mutations.[94,95] One found that benzene measured in homes was associated with higher concentrations of microRNA-223 (miR-223), which may indicate changes in immune system development.[96] Similarly, in another study exposure *in utero* was correlated to increases in eosinophil/basophil progenitor cells, indicating that benzene may be contributing to immune states that favor the development of later life respiratory diseases.[97] In children, *t,t*-MA was significantly correlated with decreases in white blood cell (WBC) counts.[98]

Effects on Respiratory Function. Thirteen studies assessed the relationship between ambient benzene exposure and asthma, including asthma, asthma in the last year, lifetime asthma, exercise-induced asthma, current asthma, physician-diagnosed asthma, severe asthma, and asthma symptoms. Seven studies that assessed children and one in adults found significantly increased odds of asthma.[91,92,99−104] Four studies showed that benzene was not significantly associated with asthma in children, one found no association in adults and teens, and another no association in adults and elderly.[90,102,105−108] Other ailments associated with asthma include cough and wheeze. Of the three studies that assessed cough, both studies in children showed significantly increased odds associated with benzene[92,100] and one in senescent adults did not find a significant association.[108] Wheeze findings were all studied in children, and the four were evenly split, two finding significantly increased odds[100,117] while the other two did not find an association.[90,92] In children, benzene levels were associated with increased odds of pulmonary infection.[109] Two studies showed increased odds of bronchitis risk and, in wheezy children, loss of lung function (reduced forced expiratory volume and flow), as well as decreases in pH of exhaled breath condensate (EBC), indicative of pulmonary inflammation.[110] In studies not restricted to wheezy children,

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Table 4. Health Effects of Ambient Exposure to Toluene[a]

health outcome	N	exposure concn	effect size (OR; 95% CI)[b]	ref
development				
low birth weight	354688	3.0 ppbV	(1.02; 1.00−1.05)[d]	Ghosh et al.[88]
immune function				
any symptom	317	325.5 $\mu g/m^3$	(4.17; 1.45−12.0)[c]	Saijo et al.[114]
atopy	86	33.74−41.75 $\mu g/m^3$	β = 0.34[c]	Choi et al.[93]
eczema	39	>30.14 μg/(g of Cr)	(9.00; 1.24−65.1)[c]	Rolle-Kampczyk et al.[116]
elevated IgE	200	13.30 $\mu g/m^3$	(3.3; 1.1−9.8)[c]	Lehmann et al.[115]
miR-223	316	6.95 $\mu g/m^3$	(1.09; 1.02−1.17)[c]	Herberth et al.[96]
senstitzation to egg white	200	13.30 $\mu g/m^3$	(3.3; 1.0−11.1)[d]	Lehmann et al.[115]
sensitization to milk	200	13.30 $\mu g/m^3$	(11.2; 2.1−60.2)[c]	Lehmann et al.[115]
skin symptoms	317	325.5 $\mu g/m^3$	(5.57; 1.38−22.6)[c]	Saijo et al.[114]
respiratory function				
asthma	192	per 10 $\mu g/m^3$ increase	(1.842; 1.405−2.414)[c]	Rumchev et al.[99]
	111	21.3 $\mu g/m^3$	(2.73; 1.28−5.83)[c]	Hulin et al.[106]
	550	14.33 $\mu g/m^3$	(1.21; 0.93−1.58)	Arif and Shah[101]
	1012	11.9 $\mu g/m^3$	(1.42; −0.63 to 4.47)	Billionnet et al.[107]
symptoms	80	26.9 ng/L	(4.96; 1.38−17.8)[c]	Delfino et al.[103]
	74	7.17 ppb	(1.35; 0.99−1.84)	Delfino et al.[104]
breathlessness	144	11.62 $\mu g/m^3$	(3.36; 1.13−9.98)[c]	Bentayeb et al.[118]
FEF 25−75% of FVC	154	0.53 mg/mL	β = −65.00[c]	Yoon et al.[112]
	51	13.4−32.8 ($\mu g/m^3$)/week[e]	(−1.14; −2.49 to 0.29)	Martins et al.[110]
FEV in 1 s	154	0.53 mg/mL	β = −18.23[c]	Yoon et al.[112]
	51	13.4−32.8 ($\mu g/m^3$)/week[e]	(−1.10; −1.97 to −0.23)[c]	Martins et al.[110]
oxidative stress (MDA, 8OHdG)	154	0.53 mg/mL	β = 0.51[c] (MDA) β = 3.92[c] (8OHdG)	Yoon et al.[112]
wheeze	6634	9.26 $\mu g/m^3$	(1.07; 1.01−1.13)[c]	Buchdahl et al.[117]
other physiological effects				
cardiovascular disease	419	0.751 ng/mL	(2.30; 1.2−4.23)[c] (3.49; 1.81−6.73)[c]	Xu et al.[33]

[a]8-OHdG, 8-oxo-2′-deoxyguanosine; MIR-223, microRNA-223; FEF 25−75%, forced expiratory flow between 25 and 75% of FVC; FEV1, forced expiratory volume in 1 s; FVC, force vital capacity; MDA, malondialdehyde; IgE, immunoglobulin E. [b]Except where indicated otherwise. [c]$p < 0.05$. [d]$p = 0.05$. [e]Mean range across four visits.

effects on lung function measured by forced expiratory volume in 1 s (FEV1) and forced expiratory flow between 25 and 75% of FVC (FEF 25−75%) were nonsignificant.[92,111] One study showed that urinary *t,t*-MA was associated with increased inflammation in the lungs of senescent adults.[112]

Metabolic Function. A study in elderly men and women showed that increases in urinary *t,t*-MA were correlated with higher homeostasis model assessment scores (HOMA-IR), indicating insulin resistance.[113]

Other Physiological Effects. In children, *t,t*-MA was significantly correlated with decreases in hemoglobin, hematocrit, and red blood cell (RBC) count.[98]

Toluene. Seventeen studies examined relationships between ambient level exposure to toluene and health impacts (Table 4). Mean ambient levels ranged 11.9−325.50 $\mu g/m^3$ and were below the toluene RfC of 5.0 mg/m^3. Three studies assessed the effects of exposure in adults, six in children, two during the prenatal period, and one in elderly populations, and five assessed a mixture (e.g., adults and adolescents and other combinations).

Developmental Effects. One study showed that gestational toluene exposure was shown to increase the odds of low birth weight.[88]

Immunological Effects. Five studies assessed the effects of toluene exposure on immune function. Toluene was associated with significantly increased odds of "any symptom" and "skin symptoms" in one study of adults.[114] Another study in children showed an association with increased odds of elevated IgE and sensitization to milk and egg white.[115] The chemical was also significantly related to increased odds of bronchitis and eczema in children.[116] Toluene was correlated with atopy in a single study.[93] *In utero* toluene exposure increased odds of miR-223 expression, which may indicate changes in the differentiation of regulatory T cell populations.[96]

Effects on Respiratory Function. Overall 10 studies analyzed the relationship between toluene exposure and respiratory function. Three studies in children showed that toluene was associated with increased odds of asthma or asthma symptoms[99,103,106] while one study did not.[104] Further, two studies in adults and adolescents showed no relationship.[101,107]A single study in children showed that toluene increased odds of wheeze.[117] Two studies, one in wheezy children and another in elderly adults, evaluated the relationship between exposure and lung function and found mixed results. Both showed negative impacts on FEV1; however, FEF 25−75% was significantly decreased in elderly adults but not wheezy children.[110,112] Further, in elderly adults the toluene metabolite hippuric acid (HA) was correlated with significant increases in markers of oxidative stress, indicative of lung inflammation.[112] In one study toluene was associated with increased odds of breathlessness in elderly adults.[118]

Other Physiological Effects. One study in adults found that blood toluene levels were correlated with increased odds of cardiovascular disease (CVD).[33]

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Table 5. Health Effects of Ambient Ethylbenzene Exposure[a]

health outcome	N	exposure concn	effect size (OR; 95% CI)[b]	ref
development				
low birth weight	354688	0.4 ppbV	(1.01; 1.00−1.03)[d]	Ghosh et al.[88]
immune function				
atopy	86	2.01−5.61 $\mu g/m^3$	β = 0.32[c]	Choi et al.[93]
sensitization to milk	200	1.77 $\mu g/m^3$	(5.0; 1.1−21.6)[c]	Lehmann et al.[115]
rhinitis	1012	2.2 $\mu g/m^3$	(1.48; 1.09−2.02)[c]	Billionnet et al.[107]
respiratory function				
asthma	192	per 10 $\mu g/m^3$ increase	(2.541; 1.160−5.567)[c]	Rumchev et al.[99]
	1012	2.2 $\mu g/m^3$	(1.63; −0.11 to 5.20)	Billionnet et al.[107]
	111	2.9 $\mu g/m^3$	(1.9; 0.7−4.9)	Hulin et al.[106]
physician-diagnosed	550	2.55 $\mu g/m^3$	(1.34; 1.01−1.78)[c]	Arif and Shah[101]
symptoms	74	0.59 ppb	(1.38; 1.09−1.75)[c]	Delfino et al.[104]
EBC pH	51	1.7−19.8 ($\mu g/m^3$)/week[e]	(−0.14; −0.23 to −0.04)[c]	Martins et al.[110]
FVC	433	1.5 $\mu g/m^3$	(−4.53; −6.26 to −2.82)[c]	Wallner et al.[119]
FEV in 1 s	433	1.5 $\mu g/m^3$	(−4.49; −6.55 to −2.48)[c]	Wallner et al.[119]
	51	1.7−19.8 $\mu g/m^3$	(−1.79; −3.32 to −0.25)[c]	Martins et al.[110]
	154	0.08 mg/mL	β = −15.10	Yoon et al.[112]
FEF 25−75% of FVC	51	1.7−19.8 $\mu g/m^3$[e]	(−2.48; −4.81 to −0.16)[c]	Martins et al.[110]
	154	0.08 mg/mL	β = −67.67	Yoon et al.[112]
oxidative stress (MDA, 8-OHdG)	154	0.08 mg/mL	β = 2.20[c] (MDA) β = 13.77[c] (8OHdG)	Yoon et al.[112]
wheeze	6634	2.06 $\mu g/m^3$	(1.08; 1.03−1.14)[c]	Buchdahl et al.[117]
other physiological effects				
cardiovascular disease	262	0.135 ng/mL	(3.10; 1.40−6.86)[c]	Xu et al.[33]

[a]8-OHdG, 8-oxo-2′-deoxyguanosine; FEF 25−75%, forced expiratory flow between 25 and 75% of FVC; FEV1, forced expiratory volume in 1 s; FVC, force vital capacity; MDA, malondialdehyde; IL-4, interleukin-4; EBC, exhaled breath condensate. [b]Except where indicated otherwise. [c]$p < 0.05$. [d]$p = 0.05$. [e]Mean range across four visits.

Ethylbenzene. Twelve studies examined relationships between ambient level exposure to ethylbenzene and health impacts (Table 5). All studies measured levels of ethylbenzene below its RfC of 1.0 mg/m^3. Mean ambient levels among the 13 studies ranged 1.5−19.88 $\mu g/m^3$. Six of the studies assessed the effects of exposure in children, three in adults, one during the prenatal period, one in the elderly, and four in a mixture of age groups.

Developmental Effects. A single study showed that maternal ethylbenzene was associated with increased odds of term low birth weight.[88]

Immunological Effects. Three studies assessed the impact of ethylbenzene exposure on immune function. One study in children showed that ethylbenzene was associated with increased prevalence of sensitization to milk.[115] Another study found that the chemical was associated with increased odds of rhinitis in children and adults.[107] One study showed that ethylbenzene was correlated with atopy.[93]

Effects on Respiratory Function. Two studies in children and one study in senescent adults assessed the relationship between ethylbenzene exposure and lung function. In wheezy children, ethylbenzene exposure was associated with significant decreases in FEV1, FEF 25−75%, and pH changes to EBC, indicative of inflammation of pulmonary tissues.[110] In another study in children the chemical was found to be negatively correlated with FVC and FEV1.[119] The ethylbenzene urinary metabolite mandelic acid was not correlated to changes in lung function in a study of elderly men and women. However, the metabolite was linked to significant increases in oxidative stress markers in the lungs.[112]

Asthma or asthma symptoms were evaluated in five studies, three in children, one in adults, and one in both. The one study in adults found that the chemical was associated with increased odds of physician-diagnosed asthma while in the study with a mixture of age groups no significant relationship was found.[101,107] Two of the three studies in children showed that ethylbenzene exposure was associated with increased odds of asthma or asthma symptoms while one study described no significant relationship.[99,104,106] However, one study found a significant association with increased odds of wheeze in children.[117]

Other Physiological Effects. A single study in adults found ethylbenzene levels in blood were related to increased odds of CVD.[33]

Xylene. Sixteen studies examined ambient level xylene exposure and health impacts (Table 6). Three studies assessed exposure in adults, seven in children, one during the prenatal period, and one in elderly populations, and five assessed a mixture (e.g., adults and adolescents and other combinations). Ambient levels were below the RfC value of 0.1 mg/m^3 and ranged 1.2−26.00 $\mu g/m^3$ (isomers combined).

Developmental Effects. One study found that *in utero* exposures to *m*- + *p*-xylene and *o*-xylene were correlated with significantly increased odds of term low birth weight.[88]

Immunological Effects. Three studies analyzed how xylene exposure affects immune function. One study in children found that all xylene isomers were associated with increased odds of sensitization to milk.[115] Another study found increased odds of "eye symptoms" and "throat and respiratory symptoms" in relation to xylene exposure in adults.[114] One study found *m*- + *p*-xylene and *o*-xylene exposure significantly associated with increased odds of having rhinitis.[107]

Effects on Respiratory Function. Three studies assessed the impact of xylene on respiratory function, two in children and

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Table 6. Health Effects of Ambient Xylene Exposure[a]

health outcome	N	exposure concn	effect size (OR; 95% CI)[b]	ref
development				
low birth weight	354688	1.5 ppbV (*m*- + *p*-X)	(1.03; 1.01−1.06)[c]	Ghosh et al.[88]
		0.5 ppbV (*o*-X)	(1.03; 1.01−1.05)[c]	
immune function				
rhinitis	1012	5.4 $\mu g/m^3$ (*m*- + *p*-X)	(1.46; 1.07−2.00)[c]	Billionnet et al.[107]
		2.2 $\mu g/m^3$ (*o*-X)	(1.43; 1.03−1.99)[c]	
sensitization to milk	200	7.23 $\mu g/m^3$ (*m*- + *p*-X)	(8.0; 1.9−34.2)[c]	Lehmann et al.[115]
		1.56 $\mu g/m^3$ (*o*-X)	(6.0; 1.5−24.2)[c]	
eye symptoms	317	26.0 $\mu g/m^3$	(2.18; 1.03−4.59)[c]	Saijo et al.[114]
throat and respiratory symptoms	317	26.0 $\mu g/m^3$	(2.22; 1.1−4.46)[c]	Saijo et al.[114]
respiratory function				
asthma	1012	5.4 $\mu g/m^3$ (*m*- + *p*-X)	(1.50; −0.41 to 4.71)	Billionnet et al.[107]
		2.2 $\mu g/m^3$ (*o*-X)	(1.65; −0.09 to 5.37)	Billionnet et al.[107]
	192	per 10 $\mu g/m^3$ increase (*p*-X)	(1.485; 0.988−2.231)	Rumchev et al.[99]
		per 10 $\mu g/m^3$ increase (*m*-X)	(1.608; 1.102−2.347)[c]	Rumchev et al.[99]
	112	10.3 $\mu g/m^3$	(1.7; 0.7−4.1)	Hulin et al.[106]
physician-diagnosed	550	5.97 $\mu g/m^3$ (*m*- + *p*-X)	(1.33; 1.08−1.64)[c]	Arif and Shah[101]
	550	2.16 $\mu g/m^3$ (*o*-X)	(1.32; 1.04−1.67)[c]	
symptoms	80	13.3 ng/L (*m*- + *p*-X)	(3.61; 1.13−11.6)[c]	Delfino et al.[103]
	80	4.16 ng/L (*o*-X)	(2.29; 0.89- 5.89)	
	74	3.07 ppb (*m*- + *p*-X)	(1.35; 1.01−1.80)[c]	Delfino et al.[104]
	74	0.94 ppb (*o*-X)	(1.28; 1.00−1.66)[d]	
breathlessness	144	5.18 $\mu g/m^3$ (*m*- + *p*-X)	(1.61; 0.60−4.31)	Bentayeb et al.[118]
	144	2.07 $\mu g/m^3$ (*o*-X)	(2.85; 1.06− 7.68)[c]	
obstructive bronchitis	192	>11.1 $\mu g/m^3$	(10; 1.045− 161.7)[c]	Rolle-Kampczyk et al.[116]
FVC	433	4.1 $\mu g/m^3$ (*m*- + *p*-X)	(−4.88; −6.68 to −3.12)[c]	Wallner et al.[119]
		1.5 $\mu g/m^3$ (*o*-X)	(−4.74; −6.50 to −3.01)[c]	
FEV in 1 s	154	0.10 mg/mL	β = −65.70	Yoon et al.[112]
	433	4.1 $\mu g/m^3$ (*m*- + *p*-X)	(−4.78; −6.91 to −2.48)[c]	Wallner et al.[119]
		1.5 $\mu g/m^3$ (*o*-X)	(−4.64; −6.72 to −2.59)[c]	
	51	6.7−12.9 ($\mu g/m^3$)/week[e]	(−0.25; −1.07 to 0.56)	Martins et al.[110]
FEV in 1 s/FVC	154	0.08 mg/mL	β = −2.44[c]	Yoon et al.[112]
eye symptoms	317	26.0 $\mu g/m^3$	(2.18; 1.03−4.59)[c]	Saijo et al.[114]
oxidative stress (MDA, 8OHdG)	154	0.08 mg/mL	β = 0.84[c] (MDA) β = 8.20[c] (8OHdG)	Yoon et al.[112]
wheeze	6634	5.14 $\mu g/m^3$ (*m*- + *p*-X)	(1.08; 1.03−1.14)[c]	Buchdahl et al.[117]
		2.06 $\mu g/m^3$ (*o*-X)	(1.08; 1.03−1.14)[c]	
other physiological effects				
cardiovascular disease	426	0.478 ng/mL (*m*- + *p*-X)	(2.36; 1.19−4.67)[c]	Xu et al.[33]
cardiovascular disease	199	0.143 ng/mL (*o*-X)	(2.68; 1.14−6.25)[c]	Xu et al.[33]

[a] *m*-, *p*-, and *o*-X, *m*-, *p*-, and *o*-xylene; 8-OHdG, 8-oxo-2′-deoxyguanosine; FEV1, forced expiratory volume in 1 s; FVC, force vital capacity; MDA, malondialdehyde. [b] Except where indicated otherwise. [c] $p < 0.05$. [d] $p = 0.05$. [e] Mean range across four visits.

Table 7. Health Effects of Ambient BTEX Combined Exposure[a]

health outcome	N	exposure concn	effect size (OR; 95% CI)	ref
development				
biparietal diameter	562	2.27−30.31 $\mu g/m^3$	(−4.82; −9.12 to −0.45)[b]	Aguilera et al.[121]
birth weight	570	14.49 $\mu g/m^3$	(−76.6; −146.3 to −7.0)[b]	Aguilera et al.[120]
respiratory function				
asthma	550	B, 1.21 $\mu g/m^3$; T, 14.33 $\mu g/m^3$; E, 2.55 $\mu g/m^3$; *o*-X, 2.16 $\mu g/m^3$; *m*- + *p*-X, 5.97 $\mu g/m^3$	(1.63; 1.17− 2.27)[b]	Arif and Shah[101]
wheezing attacks	550	B, 1.21 $\mu g/m^3$; T, 14.33 $\mu g/m^3$; E, 2.55 $\mu g/m^3$; *o*-X, 2.16 $\mu g/m^3$; *m*- + *p*-X, 5.97 $\mu g/m^3$	(1.68; 1.08−2.61)[b]	Arif and Shah[101]

[a] B, benzene; T, toluene; E, ethylbenzene; *m*- + *p*-X, *m*- + *p*- xylene; *o*-X, *o*-xylene. [b] $p < 0.05$.

one in senescent adults. In children exposure was linked to decreases in FVC and FEV1, indicating decreased lung function; however, no significant relationship was seen in wheezy children.[110,119] In elderly adults significant changes in metrics used to assess lung function and increases in oxidative stress markers were observed.[112] *o*-Xylene was found to be

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Table 8. Health Outcomes Associated with Exposure to Ambient Concentrations of BTEX and Related Endocrine Factors

health outcome	examples of endocrine factors that may be implicated in the health outcome
asthma and asthma symptoms	adiponectin, ghrelin, leptin[a], estrogens, androgens[b], neuropeptide Y[c], corticotrophin-releasing hormone, cortisol, epinephrine, glucocorticoids[d], insulin, insulin-like growth factor[e],
atopy	estrogens (estradiol), progesterone[f], glucocorticoids[d]
biparietal diameter	glucocorticoids[g], insulin-like growth factor[h]
birth weight	glucocorticoids[g,i], ghrelin, insulin-like growth factor[h], thyroid hormone[j]
bronchitis	estrogens[k]
cardiovascular disease	adiponectin[l,m], arterial natriuretic peptide, brain natriuretic peptide, estrogens, progesterone, relaxin, testosterone[n,o], thyroid hormone[p,w], parathyroid hormone, vitamin D[q], growth hormone[w], insulin-like growth factor[w]
eczema	estrogens (estradiol), progesterone[f], glucocorticoids[d]
elevated IgE	estrogens (estradiol), progesterone[f], epinephrine, glucocorticoids, norepinephine[d]
force vital capacity; forced expiratory flow between 25 and 75% of FVC; forced expiratory volume in 1 s	cortisol, estrogens, progesterone, serotonin, testosterone[r]
oxidative stress	thyroid hormone[s]
preterm birth	relaxin, estrogens (estriol), prostaglandins, corticotrophin-releasing hormone, glucocorticoids[t]
rhinitis	estrogens (estradiol), progesterone[f], glucocorticoids[d]
sensitization to egg white, milk, pollen	estrogens (estradiol), progesterone[f], glucocorticoids[d]
sperm abnormalities (asthenospermic, oligospermic, teratospermic)	activin, estrogens, follicle stimulating hormone, follistatin, glial cell line-dervived neurotrophic factor, inhibin, insulin, insulin-like growth factor, luteinizing hormone, mullerian duct inhibiting substance stem cell factor, somatostatin, testosterone[u]
wheeze	cortisol, epinephrine[d], prostaglandins, leukotrienes[v]

[a]Tsaroucha et al.[182] [b]Carey et al.[130] [c]Groneberg et al..[176] [d]Elenkov.[134] [e]Singh et al.[179] [f]Zierau et al.[131] [g]Khulan and Drake.[128] [h]Gluckman and Pinal.[126] [i]Chrousos.[127] [j]Forhead and Fowden.[184] [k]Gollub et al.[173] [l]Hug and Lodish.[177] [m]Szmitko et al.[181] [n]Bhupathy et al.[170] [o]Clerico et al.[172] [p]Gomberg-Maitland and Frishman.[174] [q]Rostand and Drueke.[178] [r]Behan and Wenninger.[169] [s]Venditti and Meo.[183] [t]Challis et al.[171] [u]Sofikitis et al.[180] [v]Gong.[175] [w]van Zaane et al.[185]

associated with increased odds of breathlessness at night in the elderly adults while *m*- + *p*-xylene were not.[118] *m*-Xylene + *p*-xylene were shown to be associated with increased odds of obstructive bronchitis.[116]

Seven studies evaluated the impact of xylene on asthma. One study in adults showed that all isomers were related to increased odds of physician-diagnosed asthma.[101] However, in the four studies in children the impacts of the isomers varied in their relationship with increased asthma or asthma symptom odds, as seen in Table 6.[99,103,104,106] A study performed in a mixture of age groups showed that xylene was not associated with increased asthma odds.[107] One study found that *o*- and *m* - + *p*-xylene were associated with increased odds of wheeze in children.[117]

Other Physiological Effects. One study found that blood concentrations of *m*- + *p*-xylene and *o*-xylene were associated with increased odds of CVD.[33]

Benzene, Toluene, Ethylbenzene, and Xylene Combined Exposure. Three studies examined relationships between ambient level exposure to combined BTEX and health impacts. The findings, all of which were statistically significant, are presented in Table 7.

Developmental Effects. Birth weight was negatively associated with maternal BTEX exposure in a single study.[120] In a second study fetal brain growth measured as biparietal diameter was negatively associated with maternal BTEX exposure.[121]

Asthma and Associated Symptoms. In one study in adults, odds of physician-diagnosed asthma were significantly higher in those exposed to BTEX whereas those without diagnosed asthma yet exposed to BTEX had significantly increased odds of 1−2 wheezing attacks.[101]

DISCUSSION

Studies in humans show that BTEX exposure is associated with effects on immune, metabolic, respiratory, and reproductive functioning, as well as development. However, it is not well understood *how* BTEX are contributing to the health effects described in this literature review. Several different hormones are involved in the health effects shown in human studies (Table 8). One hypothesis is that BTEX are disrupting endocrine signaling by interfering with the binding, elimination, secretion, synthesis, transport, or action of endogenous hormones. Support for this hypothesis comes from occupational studies of the endocrine disrupting properties of BTEX. Benzene and toluene in particular are associated with endocrine-mediated end points such as abnormal sperm production,[53−55] altered menstrual cycles,[56] and altered concentrations of the reproductive hormones, LH, FSH, and testosterone.[64] The fact that the endocrine system is uniquely susceptible to disruption by low concentrations of environmental chemicals, particularly during development,[122] suggests that endocrine disruption may also ensue from ambient exposure.

Of the 42 studies included in this review, 11 assessed prenatal exposure and 20 assessed childhood exposures. Many of the health conditions, such as decreased fetal growth, altered immune system development, increased susceptibility to allergies, and asthma are thought to have roots in early development.[123−125] Hormones such as insulin-like growth factor,[126] thyroid hormone,[127] cortisol,[128] estrogens, and androgens[129] play roles in the regulation and programming of growth patterns and the development of immunity. Further, endocrine signaling (e.g., glucocorticoid, estrogen, and progestrone) modulates immune function throughout life and has been shown to play important roles in inflammatory responses in allergic conditions and asthma.[130−135] For example, evidence suggests that benzene and its metabolites

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interact with immune cells in complex and even opposing manners, specifically modulating the Th2 response, which is one way benzene acts to contribute to immune dysregulation.[136,137] Altered fetal growth is also important given the growing body of literature that shows associations between low birth weight and reduced growth rates during gestation and childhood, and chronic endocrine-mediated health conditions.[124,138−145] This indicates that disruptions during development can result in lifelong susceptibility to disease.

Clearly many of the conditions that are linked to BTEX may result from changes in endocrine signaling. The use of *in vitro* and *in vivo* models using concentrations of BTEX relevant to human exposure would contribute to our understanding of the roles BTEX play in the endocrine aspects of these conditions. Such studies would also clarify which conditions can be causally attributed to ambient BTEX exposure.

Limitations of the Research. Findings that appear inconsistent in the presented studies can result from several known sources of heterogeneity. These include age group assessed, geographic location, how the health effect was measured, time of year, how exposure was measured, inherent differences between subjects, and other differences in how the studies were performed. Our study quality analysis revealed that control for confounding variables was not consistently performed. Of particular concern is the failure of some studies to control for confounders such as smoking, a known source of BTEX. A common limitation in epidemiological research is the lack of control for exposure to other air pollutants, which could lead to misrepresentation of effect sizes in either direction. No studies in this review consistently controlled for other relevant exposures. Further, it is clear that exposures indoors and outdoors differ as well as the amount of time spent in these environments. Fifteen studies estimated exposure by using air monitoring that occurred outdoors (Table 2) which may underestimate true exposure levels because on average people spend greater than 83% of their time indoors[110,120,146] and indoor levels can be many times greater than outdoor levels. Martins et al.[110] showed that average toluene concentrations were about 16 times greater inside schools (38.0 $\mu g/m^3$) compared to outside in the school courtyard (2.3 $\mu g/m^3$). This trend continued with ethylbenzene and xylene where concentrations inside were up to 19 times greater when compared to levels outdoors. These findings suggest that indoor exposure may have a greater influence on health outcomes than outdoor exposure. The use of personal monitors (e.g., backpacks, hip holsters, and clips) or models that measure both indoor and outdoor air concentrations and take into account time spent in each environment are likely to provide better estimates of exposure. In addition there were five studies that measured metabolites in urine or seminal fluid. The use of metabolites such as *t,t*-MA as biomarkers of ambient exposure could be difficult to attribute only to exposure to benzene because *t,t*-MA is also a metabolite of sorbic acid, which was not controlled for in three of the five studies assessed.[147] Further, it is difficult to accurately determine ambient air exposures from metabolite levels. Another limitation is the use of nonstandardized and nonvalidated surveys. There were 15 studies that used this method to determine the health effect in question, which may have resulted in individuals incorrectly answering questions, and self-misdiagnosis.

While our literature search for this review was very thorough, there are a few limitations. One is the *a priori* exclusion of non-English studies. The epidemiological studies identified were observational and therefore are not direct indicators of a causal link between BTEX and health effects. Further, the number of studies evaluating a given health impact were limited, in many cases only 1−2 studies were identified, indicating that there are research gaps that prohibit a meta-analysis for the majority of end points. One exception is respiratory effects for which a meta-analysis would be useful in clarifying mixed findings.

Summary. BTEX are common constituents of outdoor air, and evidence suggests that they are in much higher concentrations in indoor air. Further, health effects were observed at exposure concentrations that were in many cases orders of magnitude below the U.S. EPA reference concentrations (i.e., safe daily exposure level). As described earlier, occupational exposure studies demonstrate that BTEX have endocrine disruptive activity. This review suggests that BTEX may also have endocrine disrupting properties at low concentrations, presenting an important line of inquiry for future research.

BTEX are used globally in consumer products, and are released from motor vehicles and oil and natural gas operations that are increasingly in close proximity to homes, schools, and other places of human activity. In addition to the health effects demonstrated in this review, BTEX are also precursors to other air pollutants such as tropospheric ozone, polycyclic aromatic hydrocarbons, particulate matter, and ultrafine particles[16,148,149] which have been connected to myriad health effects, many of which are endocrine related.[150−167] Tremendous efforts have led to the development of successful regulations focused on controlling greenhouse gases in an attempt to reduce global temperatures. Similar efforts need to be directed toward compounds that cause poor air quality both indoors and outdoors. Although vehicular emissions are the largest outdoor source of BTEX, converting to alternative energy sources will not reduce demand for infrastructure materials and consumer products. Consequently, BTEX-containing products and manufactured goods used indoors will persist, continuing to expose people to concentrations that may be contributing to chronic health conditions. While benzene has received some regulatory attention that has resulted in the use of "safer" alternatives,[168] benzene alternatives such as toluene and xylene may not be safe in chronic low level exposure scenarios. Innovative ideas for truly safer alternatives will allow us to minimize the use of potentially harmful substances. In addition, improvements in how chemicals with human health impacts at low concentrations are assessed and regulated are urgently needed in order to protect public health by reducing BTEX exposure.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text giving the search logic and study quality assessment details, tables listing reported study confounders (Table S1), and RoB analysis results (Table S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS AND DEFINITIONS:

8-OHdG	8-oxo-2′-deoxyguanosine
BTEX	benzene, toluene, ethylbenzene, and xylene
CVD	cardiovascular disease
DNR	data not reported
ΔFEV1	improvement of forced expiratory volume in 1 s
EBC	exhaled breath condensate
FEF 25−75%	forced expiratory flow between 25 and 75% of FVC
FEV1	forced expiratory volume in 1 s
FSH	follicle stimulating hormone
FVC	force vital capacity
HA	hippuric acid
HOMA-IR	homeostasis model assessment scores− insulin resistance
IgE	immunoglobulin E
IL-3	interleukin-3
IL-4	interleukin-4
IL-5	interleukin-5
IL-12	interleukin-12
IFN-γ	interferon-γ
LH	luteinizing hormone
MDA	malondialdehyde
MHA	methylhippuric acid
MIR-223	microRNA-223
MLH1	mutL homologue 1
MSH2	mutS homologue 2
NES	no effect size reported
NHANES	National Health and Nutrition Examination Survey (United States)
NK	natural killer
NO_2	nitrogen dioxide
OHAT	Office of Health Assessment and Translation
OR	odds ratio
RBC	red blood cell
RfC	reference concentration
RoB	risk of bias
t,t-MA	*trans,trans*-muconic acid
U.S.	United States
U.S. EPA	United States Environmental Protection Agency
VOCs	volatile organic compounds
WBC	white blood cell

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