Review

Ellen Webb*, Julie Moon, Larysa Dyrszka, Brian Rodriguez, Caroline Cox, Heather Patisaul, Sheila Bushkin and Eric London

Neurodevelopmental and neurological effects of chemicals associated with unconventional oil and natural gas operations and their potential effects on infants and children

https://doi.org/10.1515/reveh-2017-0008
Received March 7, 2017; accepted July 28, 2017; previously published online October 25, 2017

Abstract: Heavy metals (arsenic and manganese), particulate matter (PM), benzene, toluene, ethylbenzene, xylenes (BTEX), polycyclic aromatic hydrocarbons (PAHs) and endocrine disrupting chemicals (EDCs) have been linked to significant neurodevelopmental health problems in infants, children and young adults. These substances are widely used in, or become byproducts of unconventional oil and natural gas (UOG) development and operations. Every stage of the UOG lifecycle, from well construction to extraction, operations, transportation and distribution can lead to air and water contamination. Residents near UOG operations can suffer from increased exposure to elevated concentrations of air and water pollutants. Here we focus on five air and water pollutants that have been associated with potentially permanent learning and neuropsychological deficits, neurodevelopmental disorders and neurological birth defects. Given the profound sensitivity of the developing brain and central nervous system, it is reasonable to conclude that young children who experience frequent exposure to these pollutants are at particularly high risk for chronic neurological diseases. More research is needed to understand the extent of these concerns in the context of UOG, but since UOG development has expanded rapidly in recent years, the need for public health prevention techniques, well-designed studies and stronger state and national regulatory standards is becoming increasingly apparent.

Keywords: BTEX; children; EDCs; heavy metals; PAHs; particulate matter; UOG.

***Corresponding author: Ellen Webb,** Center for Environmental Health, 2201 Broadway, Suite 302, Oakland, CA 94612, USA, E-mail: webbe02@gmail.com
Julie Moon: Columbia University, New York, NY, USA
Larysa Dyrszka: Physicians for Social Responsibility, Glen Spey, NY, USA
Brian Rodriguez: University of California, Berkeley, Oakland, CA, USA
Caroline Cox: Center for Environmental Health, Oakland, CA, USA
Heather Patisaul: North Carolina State University College of Sciences, Raleigh, NC, USA
Sheila Bushkin: Institute for Health and the Environment, Albany, NY, USA
Eric London: Institute for Basic Research, New York, NY, USA

Introduction

Since the mid-to-late-2000s, unconventional oil and gas (UOG) techniques, including hydraulic fracturing (fracking) have enabled the extraction of fossil fuels from previously inaccessible geological formations such as shale, leading to the rapid spread of UOG development in the US. The scientific and medical communities are beginning to understand that each step of the UOG lifecycle uses and emits significant quantities of chemicals likely to be harmful to environmental and human health (1–10), particularly to infants and developing children (11–15). This paper explores the potential health risks of UOG activity; we are presenting the first literature review to focus explicitly on the effects of the UOG industry on the neurodevelopmental and neurological health of infants and children.

Currently, there are now over 1000 peer-reviewed publications that assess various health hazards and risks of UOG. Some of these studies on UOG development have observed an increase in adverse perinatal outcomes (12–14). Published research focusing on the association between UOG and neurodevelopmental and neurological health in humans is limited and only a few studies to date address this issue, while no studies have focused exclusively on this health topic. Neurological health problems have been reported by residents (16) and observed in companion animals and livestock living in close proximity to UOG development in areas across the US (17). A study by University of Pennsylvania and Columbia University researchers found that UOG in Pennsylvania was associated with an increase in hospitalization rates, including inpatient prevalence rates for neurology among other

health categories (18). Another retrospective study in 2014 of approximately 124,842 births found that there was a potential association between the density of natural gas wells within a 16-km radius of a residence and neural tube defects in infants (12).

Although data is still emerging in this specific health research area, the neurological and neurodevelopmental effects of many UOG chemicals including those we focus on in this review are well known and documented in the scientific literature in many other contexts (Table 1).

This review calls attention to the neurological health impacts of air and water pollution from UOG operations, focusing specifically on five pollutant categories: heavy metals (arsenic and manganese), particulate matter (PM), polycyclic aromatic hydrocarbons (PAHs), BTEX and endocrine-disrupting chemicals (EDCs). The purpose of this paper is to highlight how vulnerable populations, particularly newborns and growing children, may or may not suffer disproportionately from exposure to UOG-related air and water pollutants. We also identify future research needs and present general policy recommendations in light of the identified health risks within these populations.

In our discussion of the health effects of air and water pollution from UOG, we chose these five particular pollutant categories because these pollutant groups have been found in significant concentrations in air and water at or near UOG sites, and are most commonly found in epidemiological studies to be associated with adverse neurological and developmental health outcomes. We do not discuss a number of other pollutants including: methylene chloride, ethylene glycol and other materials from UOG operations that are potentially neurotoxic.

It should be noted that unconventional oil and gas development is a broad and complex term which can refer to modern oil and gas development techniques that may not be covered in this review. UOG generally refers to oil and natural gas produced from atypical sources – including shale/tight formations, oil/tar sands, coal seams and low permeability reservoirs – requiring techniques different from those needed for conventional oil and gas production. For this review, we focus specifically on research pertaining to onshore oil and gas development from shale and tight formations (i.e. low permeability) and do not include studies of coalbed methane, oil sands, or offshore oil and gas development. In a few examples we refer to studies that may also apply to other forms of oil and gas development. While the term hydraulic fracturing ("fracking") is used in the media to refer to UOG activities in general, we use it in this review to refer to its role in oil and gas development from shale and tight formations. This involves the well stimulation technique of injecting pressurized fluid consisting of water, sand and chemicals into a reservoir or low permeability rock formations, in order to mobilize oil or natural gas. Recently, hydraulic fracturing has been combined with other techniques such as directional drilling to increase oil and gas production from unconventional sources.

The neurotoxicity of chemical compounds that are foreign to the body is a serious though understudied public health issue. Ten percentage to 15% or approximately one out of every six children in the US suffers from neurodevelopmental abnormalities, including intellectual disabilities, learning disabilities, autistic disorders, attention deficit disorders and/or emotional disorders (69). Specific epidemiology is further complicated by rapid increases in disorders that are subtle or difficult to diagnose, such as autism and attention deficit disorder (70).

There is ample evidence that environmental toxicants can cause neurodevelopmental problems. Developmental neurotoxicity has been called a "global silent pandemic" – "silent" because the "brain draining" impacts of early life exposure to neurotoxicants are often subtle and subclinical, which can make them hard to detect (71–73). Another aspect of this "silent pandemic" is the lack of safety standards set by regulatory authorities on virtually any of the 85,000+ chemicals that we are exposed to daily, as well as the limited attention clinicians and academic researchers have paid to the "brain drain" caused by neurotoxicity in early life (74). In a 2006 review aimed at drawing attention to how little is known about neurotoxicants, Grandjean and Landrigan (72) identified 201 chemicals neurotoxic to adults and more than 1000 chemicals neurotoxic to animals. In discussing evidence for measurable human consequences, they focused on the neurodevelopmental toxicity of lead, methylmercury, arsenic, polychlorinated biphenyls and toluene. In 2014, the same authors, updated this review and highlighted newly identified developmental neurotoxicants, noting that the list of known neurotoxicants had been growing annually by two substances per year (71).

In this review we discuss the body of scientific and medical literature relevant to the neurodevelopmental health impacts of UOG development and production. We highlight what is currently known and identify data gaps and research limitations.

Methods

For this review, we focus on the scientific literature relevant to the potential neurodevelopmental health effects of

Table 1: Summary of neurodevelopmental and neurological health effects associated with pollutants of concern.

Pollutant groups	Pollutant	Effects			References
		Neurodevelopmental effects	Neurocognitive effects	Neuropsychological effects	
Heavy metals	Arsenic	Interferes with various stages of neurodevelopment, such as by inhibiting neuron growth and induces neural tube defects (NTDs) (19, 20)	Deficits in memory, attention and IQ from early life exposure (21–27)	Impairs self-regulation in newborns (28)	(19–29)
	Manganese	Developmental psychomotor impairment in infants from prenatal exposure (30)	Deficits in IQ and below average performance on tests of verbal/visual/working memory, perceptual reasoning in children with prenatal or drinking water exposure (29, 31–36)	Conduct problems, hyperactivity, and aggressive behavior in children prenatally exposed/exposed via drinking water (37–39)	(29–40)
Polycyclic aromatic hydrocarbons (PAHs)		Neurodevelopmental effects such as SGA, reduced length, reduced birth weight and head circumference from prenatal and early life exposure (41–43) Increased rates of neural tube defects from maternal exposure to PAHs during pregnancy (43)	Reduced verbal and full-scale IQ scores (44–48)	Increased risk of ADHD diagnosis and other childhood psychopathologies like OCD and Tourette's syndrome from impaired self-regulation (49, 50) An increase in symptoms of anxiety, depression and inattention (46, 49–51)	(41–51)
Endocrine disrupting chemicals (EDCs)		Perinatal exposure to EDCs may cause permanent changes in the brain and behavior (52–54)	Compromises learning and memory (55, 56)	Impairs social interaction, increased aggression and anxiety (56) Increases susceptibility to sex- and/or hormonally-differentiated behavioral disorders such as autism spectrum disorder, ADHD and depression (56)	(52–56)
Benzene, toluene, ethylbenzene, and xylene (BTEX)		Neurodevelopmental effects such as small head circumference and growth retardations from prenatal toluene exposure (57, 58) Prenatal toluene exposure can result in language impairment, developmental delays, postnatal growth retardation and cerebellar problems (57–59) Delays development of speech, motor function, and can result in low scores on developmental tests in infants of mothers that abused toluene during pregnancy (60) Neural tube defects from maternal benzene exposure (61)	Benzene and toluene can effect spatial learning and memory (60)	Neurobehavioral effects such as tremors, altered vision, and numbness from xylene exposure (62) Impairs neurobehavioral performance from toluene exposure (63) Increases risk for hyperactivity due to prenatal toluene exposure (57, 58)	(57–63)

Table 1 (continued)

Pollutant groups	Pollutant	Effects			References
		Neurodevelopmental effects	Neurocognitive effects	Neuropsychological effects	
Particulate matter		Neuroinflammation, which in early life can alter neurodevelopment profoundly by modifying cellular processes in the brain and spinal cord, affecting the synaptic connections and plasticity that is required for learning and memory (64)	Problems with memory and executive functions and large deficits in cognition (65) Damage to the nuclei, which are key to basic functions such as auditory processing, balance and autonomic regulation (66)	Development of disorders such as autism, schizophrenia, bipolar disorder and anxiety (67, 68)	(64–68)

Table summarizing health effects and the studies in which the effects were reported. ADHD, Attention deficit hyperactivity disorder.

UOG emissions on children and newborns. This required reviewing three different types of research, including studies of (1) UOG air and water emissions and concentrations; (2) documented neurological health risks and symptoms from exposure to our selected pollutant list; and (3) long-term neurological health outcomes from early life exposure to UOG associated pollutants in other contexts as documented in the literature. We did not include a formal quality assessment of the literature. Additionally, although we primarily focus on human studies, we also refer to experimental animal studies to understand biological mechanisms of neurotoxicity. It should also be noted that in some cases, where literature was limited, we looked at adult and occupational studies. This review draws predominantly from peer-reviewed scientific literature, including animal and human (both in vitro and in vivo) studies, literature reviews on specific pollutants, and book chapters, with an emphasis on more recent publications. However, we included where appropriate, reports and other gray literature.

Our methods are intended to help identify exposure pathways and mechanisms as well as potential neurological health risks and long-term consequences of air and water pollutants associated with UOG. We also intended to promote research to assess the neurotoxicity of air and water pollutants involved with UOG development. We note cases where concentrations exceed relevant air and water quality standards or guidelines and/or levels known to be hazardous to human health (3, 4, 6, 75–80).

This assessment was conducted using a number of search methods, including (1) keyword systematic searches across three science databases (PubMed, Web of Science, ScienceDirect), and (2) searches in existing collections of scientific literature on unconventional oil and natural gas development, such as the PSE Healthy Energy Citation Database on Shale and Tight Gas Development and the Marcellus Shale Initiative Publications Database at Bucknell University. We complemented our search using the Columbia University Library database (CLIO) and Google Scholar, and additionally conducted manual searches of the references included in many of the studies identified.

Results

Sources of air pollution from UOG

UOG operations emit air pollutants linked to adverse neurological effects throughout their lifecycle. In a

study assessing air pollution near natural gas operations in rural Colorado, Colborn et al. (6) identified 35 potential neurotoxins that are associated with the process. Stages of the UOG lifecycle associated with air pollution include the extraction and processing of natural gas, transportation via compressor stations and pipelines, truck transportation of materials to and from well pads, use of vehicular equipment during construction and maintenance, and venting, flaring, production, and leaks from faulty casings (3, 81). These processes release numerous contaminant categories into the air, including our five pollutant categories of concern (1, 3, 4, 6, 12, 77, 79, 80, 82–85).

Sources of water pollution from UOG

Oil and gas development processes release numerous contaminant categories into surrounding water sources, including our pollutant categories of concern (75, 76, 78, 86–90). Water pollution can occur during wastewater disposal, transport, and during and after hydraulic fracturing, processing, production and distribution to the market (7, 91). "Flowback" or "produced" water, the water that travels to the surface following the hydraulic fracturing procedure (typically a mixture of water, gas, oil, metals and fracking fluids), can contaminate groundwater (76). The fracturing fluid used in shale gas development contains organic and inorganic chemicals harmful to human health. Although these chemicals are currently unregulated at the federal or state level, many environmental and public health experts, including the EPA, have reported the presence of fracturing fluids in drinking water (75, 92).

People may be exposed to chemical fluids from UOG development processes in a number of ways, including spills, releases from surface tanks, surface leaks, poor well integrity, accidents during transportation, flowback and produced water during hydraulic fracturing, run-off from storms and blowouts and other events (91). There is often inadequate filtering at treatment facilities which can then lead to harmful chemicals entering the local water supplies and/or being used in agriculture (93). These chemicals are then released into landfills or surface waters. In different areas, this water has been used for other purposes such as irrigation, or for spraying roads to reduce dust or melt ice (94). While surface spills and leaks occurring both during and after well stimulation can lead to water contamination, other oil and gas development processes can also lead to water contamination. In California, for example, researchers are investigating the potential health concerns associated with the reuse of oil field produced water for crop irrigation (95).

Particulate matter (PM)

PM levels near UOG sites

PM is a mixture of solid particles, particle droplets, dust particles, heavy metals, and other organic chemicals that have become suspended in the air, are small enough to be inhaled, and can travel long distances (96–98).

Diesel PM and PM of 10 μm or smaller in diameter are known to be emitted into surrounding air throughout all of the stages of the UOG lifecycle. Such stages include well-site preparation and road construction (which involves trucks and heavy machinery), hydraulic fracturing, production (gas flaring/venting and maintenance), processing and storage (involving compressors), transmission (involving compressor stations), and well abandonment and site rehabilitation (which includes the use of trucks and heavy machinery) (81, 99).

The U.S. Environmental Protection Agency (EPA) National Ambient Air Quality Standards (NAAQS) estimates that levels posing a potential health risk are 35 $\mu g/m^3$ for a 24-h average and 15 $\mu g/m^3$ for an annual average for $PM_{2.5}$ (100). One study reported PM levels exceeding the NAAQs around fracking mining operations. In this study, Walters et al. (79) found $PM_{2.5}$ levels of 5.82–50.8 $\mu g/m^3$ in six 24-h samples around fracksand mines and processing sites in Wisconsin and Minnesota. Five of the six air samples exceeded the EPA standard of 12 $\mu g/m^3$, and researchers pointed out that these may underestimate true levels given that weather conditions can lower $PM_{2.5}$ atmospheric concentration levels (Table 2).

Brown et al. (85) used an air exposure model to determine the concentrations of $PM_{2.5}$ in the air during different 6-h periods over 24 h near three UOG facilities in Pennsylvania. They reported that peak $PM_{2.5}$ exposures occurred 83 times over 14 months of well development with the greatest intensity exposures occurring during well development, drilling, flaring and gas production. Peak exposure levels from compressor stations were reported to take place 118 times and there were 99 peak exposures from a gas processing plant.

Although the EPA has not conducted adequate ambient air quality models of $PM_{2.5}$ near UOG sites, it has emphasized the need for their emission reductions

Table 2: Reported pollutant concentrations and exposure media near UOG sites.

Pollutant groups	Pollutant	Studies for which values were reported	Exposure media and concentrations detected	Standards or guidelines
Heavy metals	Arsenic		Air: No data available	
			Water:	Water:
		Fontenot et al. (75)	**$2200–1.61\times10^{5}$ μg/m³**	EPA MCL: 10,000 μg/m³
		Glenn and Lester (101)	**$1000–5.69\times10^{5}$ μg/m³**	
	Manganese		Air: No data available	
			Water:	Water:
		Boyer et al. (88)	**2.63×10^{6} μg/m³**	EPA Lifetime Health Advisory[a]:
		Alawattegama et al. (78)	**$2.0\times10^{3}–2.63\times10^{6}$ μg/m³**	3×10^{5} μg/m³
Polycyclic aromatic hydrocarbons (PAHs)	Benzo(a) pyrene (BaP)		Air:	Air:
		Colborn et al. (6)[b]	$1.34\times10^{-3}–3.72\times10^{-3}$ μg/m³	NIOSH REL-TWA: 100 μg/m³
		Paulik et al. (102)	<0.16 km from natural gas well: 14×10^{-7} μg/m³	
			0.16–1.6 km from natural gas well: 7.1×10^{-9} μg/m³	
			>1.6 km from natural gas well: 2.9×10^{-9} μg/m³	
			Water: No data available	
	Phenanthrene		Air:	Air:
		Colborn et al. (6)[c]	$1.53\times10^{-3}–4.45\times10^{-3}$ μg/m³	NIOSH REL-TWA: 100 μg/m³
		Paulik et al. (102)	<0.16 km from natural gas well: 2.5×10^{-4} μg/m³	
			0.16–1.6 km from natural gas well: 1.8×10^{-4} μg/m³	
			>1.6 km from natural gas well: 1.7×10^{-4} μg/m³	
			Water: No data available	
	Naphthalene		Air:	Air:
		Colborn et al. (6)[c]	$4.25\times10^{-3}–3.19\times10^{-2}$ μg/m³	NIOSH REL-TWA: 5×10^{4} μg/m³
		Paulik et al. (102)[c]	<0.16 km from natural gas well: 7.4×10^{-3} μg/m³	
			0.16–1.6 km from natural gas well: 8.4×10^{-3} μg/m³	
			>1.6 km from natural gas well: 6.7×10^{-3} μg/m³	
			Water: No data available	
Volatile organic compounds (VOCs)	Benzene		Air:	Air:
		Colborn et al. (6)	0.96–3.51 μg/m³	EPA RfC: 30 μg/m³
		Helmig et al. (4)	**9.9 μg/m³**	ATSDR chronic inhalation MRL:
		McKenzie et al. (12)	**0.096–14 μg/m³**	9.58 μg/m³
		Macey et al. (77)	**5.7–110,00 μg/m³**	
			Water:	Water:
		DiGiulio et al. (86)	Max conc.: **2.47×10^{5} μg/m³**	EPA MCL: 5000 μg/m³
		Gross et al. (76)[d]	Inside excavated area: **1.1×10^{6} μg/m³**	
	Toluene		Air:	Air:
		Colborn et al. (6)	1.51–16.2 μg/m³	EPA RfC: 5000 μg/m³
		McKenzie et al. (12)	0.11–79 μg/m³	ATSDR chronic inhalation MRL:
		Macey et al. (77)	**ND–270,000 μg/m³**	3800 μg/m³
			Water:	Water:
		DiGiulio et al. (86)	Max conc.: 6.77×10^{5} μg/m³	EPA MCL: 1×10^{6} μg/m³
		Gross et al. (76)[d]	Inside excavated area: **1.4×10^{6} μg/m³**	

Table 2 (continued)

Pollutant groups	Pollutant	Studies for which values were reported	Exposure media and concentrations detected	Standards or guidelines
	Ethylbenzene		Air:	Air:
		Colborn et al. (6)[e]	3.04 μg/m³	EPA RfC: 1000 μg/m³
		McKenzie et al. (12)	0.056–8.1 μg/m³	ATSDR chronic inhalation MRL:
		Macey et al. (77)	**ND–1200 μg/m³**	261 μg/m³
			Water:	Water:
		DiGiulio et al. (86)	Max conc.: 1.01×10^{5} μg/m³	EPA MCL: 7.0×10^{5} μg/m³
		Gross et al. (76)[d]	Inside excavated area: 1.2×10^{5} μg/m³	
	Xylenes		Air:	Air:
		Colborn et al. (6)	8.68×10^{-4} to 3.04×10^{-3} μg/m³	EPA RfC: 100 μg/m³
		McKenzie et al. (12)	0.064–3.6 μg/m³	ATSDR chronic inhalation MRL:
		Macey et al. (77)[f]	**ND–4100 μg/m³**	217 μg/m³
			Water:	Water:
		DiGiulio et al. (86)[g]	Max conc.: 2.53×10^{5} μg/m³	EPA MCL: 1×10^{7} μg/m³
		DiGiulio et al. (86)[h]	9.73×10^{5} μg/m³	
		Gross et al. (76)[d]	Inside excavated area: 1.8×10^{6} μg/m³	
Particulate matter	$PM_{2.5}$		Air:	Air:
		Walters et al. (79)	**5.82–50.8 μg/m³**	Primary 1-year average National Air Quality Standard: 12 μg/m³

[a]Lifetime Health Advisories serve as technical guidance for unregulated drinking water contaminants. [b]Colborn et al. (6) reported low PAH air concentrations; however, they may have public health significance. The summed composite of eight PAHs analyzed by Colborn et al. (6) was 15.5 ng/m³. Perera et al. (44, 46) also analyzed these same PAHs and found that a summed concentration >4.16 ng/m³ and >2.26 ng/m³ resulted in lower mental development scores and lower IQ, respectively. [c]Paulik et al. (102) reported an aggregate measure of PAHs (ΣPAH_{62}). Naphthalene contributed an average of 62% to ΣPAH_{62} air concentration measures. [d]Gross et al. (76) reported Kaplan-Meier means for BTEX compounds. [e]Colborn et al. (6) only detected ethylbenzene in one air sample. [f]Macey et al. (77) reported air concentration measurements for mixed xylenes. [g]DiGiulio et al. (86) reported the following max water concentration for o-Xylene. [h]DiGiulio et al. (86) reported the following max water concentration for m-Xylene and p-Xylene. Table summarizing reported exposure media and concentrations for different pollutants found near UOG sites. Regulatory standards and guidelines are listed. Reported concentrations are ranked in ascending order, and those that are in excess of standard or guideline, are shown in bold. EPA, Environmental Protection Agency; MCL, maximum contaminant level; NIOSH, National Institute for Occupational Safety and Health; REL-TWA, reference exposure level time weighted average; RfC, reference concentration.

given adverse health effects identified in the scientific and medical literature and based on their own regulatory analysis of the industry (103).

Exposure pathways and mechanisms

The primary exposure pathway for particulate matter is through inhalation and the particle size influences where the particles travel in the body. Coarse particles (2.5–10 μm in aerodynamic diameter) are usually deposited in the airways and upper respiratory tract, while fine particles (<2.5 μm) may reach terminal bronchioles and alveoli (104). Compared to large particles, fine particles can remain suspended in the air for longer durations of time and travel over longer distances (104). $PM_{2.5}$ (≤2.5 μm) in particular poses a significant health concern, as particles of this size are known to contribute to cardiovascular and respiratory diseases as well as premature death (105, 106).

Experimental studies in both animals and humans have shown that PM can enter the brain through inhalation. In a rodent study, for example, inhalation of particles resulted in translocation of these particles to the brain (107) specifically the brainstem and hippocampus (108). Studies show that high exposure of PM can result in penetration of multiple functional areas of the brain and lead to detrimental effects (109, 110).

Neurological and neurodevelopmental effects

While more research is needed on the mechanisms of particulate matter's toxicity, the effect on the brain is clear (111). There is direct evidence of various types to support the hypothesis exposure to elevated levels of particulate matter can lead to certain brain diseases and functional clinical impairment [for an extensive review, see (112)].

Neuroinflammation, especially in prenatal and early life appears to have a profound effect on brain development, potentially leading to disorders such as autism, schizophrenia, bipolar disorder and anxiety (67). Immune mechanisms of fighting infection is important for proper brain development and functioning (113). Recent evidence suggests that inflammation and its processes can modify cellular processes in the brain and spinal cord, affecting the synaptic connections and plasticity that is required for learning and memory (64).

In a series of studies comparing the effects of air pollution in Mexico City with those of similar cities with significantly lower pollution levels, researchers have consistently encountered neuroinflammation, damage suggestive of oxidative stress, direct neuronal damage, and poor clinical outcome in both animals and humans (66, 109, 110, 114–117).

White matter hyperintensities (WMHs) are extreme vascular lesions routinely found in the elderly, predicting increased risk of dementia and death, signal blood-brain barrier (BBB) disruption and neuroinflammation (118). In one study comparing children from Mexico City with children from less polluted areas, magnetic resonance imaging (MRI) prefrontal white matter hyperintensities (WMHs), were found in 56% of clinically healthy children from Mexico City, compared to 7.6% of children that were from the control site. The children residing in Mexico City in Calderón-Garcidueñas et al.'s (65) study with prefrontal WMHs displayed problems with memory and executive functions, and also had large deficits in cognition (measured by the Weschler Intelligence Test for Children and IQ), compared to children from the control sites where there was less pollution.

The same researchers conducting work on children residing in Mexico City have also found evidence of lesions at several levels of the brain, down to the brainstem. They additionally found damage to the nuclei, which are key to basic functions such as auditory processing, balance and autonomic regulation (119). Early lesions such as these can lead to severe developmental problems, although correlating such issues with the lesions is not clinically feasible in most cases. Therefore, this burden is likely underestimated.

In addition to developmental and degenerative disorders, psychiatric disorders may be associated with particulate matter exposures. Fine particulate matter exposure has been associated with high symptoms of anxiety (68). Although largely unexplored, mechanisms such as inflammatory changes and oxidative stress could explain these findings.

Polycyclic aromatic hydrocarbons (PAHs)

PAH levels near UOG sites

PAHs refer to several hundred chemically-related organic compounds. Benzo[a]pyrene (BaP) is most commonly used as an indicator species of PAH pollution and is one of the PAHs that are found in crude oil. PAHs, found in common crude oil, are known constituents in produced water from UOG but are not being monitored in areas impacted by oil and gas operations. PAH compounds are present in fossil fuels and are also products of their combustion. Fossil fuel combustion is one of the primary sources to ambient PAHs (120).

Some studies have reported PAHs in ambient air samples near UOG operations. Colborn et al. (6) for example, found levels of PAHs (PAH16 ~ 15.5 ng/m^3) near natural gas well pads dangerous to human health. These levels have been associated with significant decreases in IQ and delayed mental development in children exposed in utero (Table 2).

Paulik et al. (102) analyzed for 62 PAHs in rural Ohio where there has been a huge natural gas exploration and production boom and found levels of benzo[a]pyrene, phenanthrene, and other PAH mixtures closest to active natural gas wells to be highest (Table 2).

Exposure pathways and mechanisms

PAHs attach themselves to particles in the air; distribute across air, soil and water and can travel long distances (121). PAHs can enter the body through inhalation, traveling through the lungs into the bloodstream. PAH neurotoxicity is thought to occur indirectly through microglial activation (51). PAHs are thought to cause antiestrogenic effects (122) and DNA damage (123), and can also lead to changes at the cellular level that then affect the exchange of nutrients and oxygen (124). Exposure to PAHs in utero may affect neurological function, immune and metabolic function, and potentially epigenetic programming (44, 121, 125).

Some PAHs are transplacental carcinogens which can cause phenotypic or genotypic changes in cells in the fetus following carcinogenic exposure. In-utero exposure to transplacental carcinogens can result in the production of tumors in the lung, liver, lymphatic and nervous system in children (126).

In a 2005 study conducted by Environmental Working Group (EWG), 217 chemicals known to be toxic to the brain and nervous system were found in the umbilical cord blood of 10 babies born in US hospitals in 2004. Nine of the 217 chemicals were PAHs (127).

Neurological and neurodevelopmental effects

Fetal growth problems

Gestational and in-vivo PAH exposure in humans has been linked with several adverse neurodevelopmental effects, including small for gestational age (SGA), reduced length, reduced weight and head circumference (41, 42). Choi et al. (41) found that children with high prenatal PAH exposure were more likely to be preterm and/or be SGA (have a fetal growth ratio of <85%).

Researchers believe that these adverse effects during fetal development may be caused by PAHs' ability to change endocrine hormone and receptor levels (128). In one study, researchers found an association between exposure to outdoor airborne PAHs in the urban industrialized state of New Jersey and births that were small for gestational age (SGA) (42). Fifteen thousand four hundred and fifty-one live births were examined in a retrospective cohort study in the Marcellus Shale formation of Southwest Pennsylvania from 2007 to 2010. Results indicated that mothers who lived next to six or more wells per 1.6 km reported lower birth weight and a higher incidence of SGA than mothers who lived near less than 0.87 wells per 1.6 km (13). Two separate but parallel prospective cohort studies found prenatal exposure to airborne PAHs (ranging from 1.80 to 36.47 ng/m^3) to be associated with lower birth weight and head circumference in children of non-smoking African-American and Dominican mothers in inner-city New York and non-smoking Caucasian mothers in Krakow, Poland (129).

Neural tube defects (NTDs)

While several studies have shown that prenatal exposure to PAHs is associated with reduced birth weight and birth head circumference as well as smaller birth size for gestational age, other studies have shown a positive association between maternal exposure to PAHs during pregnancy and increased rates of neural tube defects. Ren et al. (43) reported that higher levels of PAHs in the placenta were associated with a 4.5-fold increase in the risk of NTDs (both anencephaly and spina bifida) relative to controls.

Mental development and cognitive functioning

Neurodevelopmental outcomes such as head circumference and low birth weight can have important implications for future learning; both have been correlated with poorer cognitive functioning and school performance as well as lower IQ (130–132).

Perera et al. (45) performed follow-up assessments of the children with high prenatal exposure to PAH and reported impaired neurodevelopmental health (at 3 years old, the children had lower mental development scores), whereas in children with low prenatal exposure to PAHs there were no such effects. Perera et al. (44, 46) reported reductions in full-scale and verbal IQ scores in children 5 years of age (44), and symptoms of depression, anxiety and problems with attention in children 7 years of age as measured by the Child Behavior Checklist (CBCL) and a slower processing speed index on the Weschler Scale of Intelligence for Children (WISC-IV) (46).

The adverse neurodevelopmental effects of PAHs – such as development of learning disorders or neurocognitive problems – have been reported for a long time (47, 48). In rats, Saunders et al. (133) found a significant correlation between gestational exposure to PAHs and deficits in behavioral and motor effects.

Brain disorders and neuropsychology

Some researchers have followed PAHs' impairment of normal cognitive function and implicated PAH exposure in the etiology of brain disorders. Perera et al. (49) followed children of nonsmoking African-American and Dominican mothers in a prospective cohort study, and assessed the risk of attention deficit hyperactivity disorder (ADHD) diagnosis through the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and found a possible connection between early life exposure to PAHs and childhood ADHD behavior problems.

In this same cohort, Peterson et al. (51) conducted the largest MRI study of the neurological effects of prenatal

exposure to PAHs, following urban youth from gestation to school age. The researchers found a dose-response relationship between prenatal PAH exposure and reductions of white matter in the brain that resulted in high scores for ADHD symptoms and conduct disorder problems. They also found an association between PAH exposure and reduced processing speed during intelligence testing (51). Follow-up assessments of postnatal PAH exposure at 5 years of age found disruption in dorsal prefrontal white matter. Although they could not conclude how these postnatal effects on prefrontal white matter impact cognition or behavior, they predicted further difficulty with processing speed, attention, and impulse control functions supported by the prefrontal cortices. Based on their findings, these researchers hypothesized that PAH could alter levels of monoaminergic neurotransmitters, or their receptors, which regulate early brain development and lateralization (51).

Recently, researchers from Columbia Center for Children's Environmental Health and New York State Psychiatric Institute reported that early life exposure (in utero) to PAH air pollution in 462 children (3–11 years of age) may play a role in the cause of many childhood behavior disorders including ADHD, obsessive-compulsive disorder, Tourette's syndrome and eating disorders (50). PAH was measured by the presence of PAH-DNA adducts in maternal blood at delivery. Children between 3 and 11 years of age, that had been prenatally exposed to PAHs, failed to improve their self-regulation skills, while children of mothers that did not appear to have the presence of PAH-DNA adducts displayed increased capacity for self-regulation (50). In other words, children with prenatal exposure to PAH had persistent problems with self-regulation, as evidenced through a variety of domains such as managing attention, aggression, anxiety/depression, as well as the ability to get along with others. Based on these findings, researchers concluded that childhood exposure PAH significantly heightens the risk for various disorders (50).

Endocrine disrupting chemicals (EDCs)

Levels of EDCs near UOG sites

Of the over 750 chemicals used throughout the process of hydraulic fracturing, more than 100 are known or suspected EDCs, and many others have yet to be assessed due to lack of Chemical Abstract Service numbers and/or proprietary information concerns. This can make searching for health data difficult (1, 134). The 2005 Energy Policy Act, exempted hydraulic fracturing from the Underground Injection Control program and the EPA is prohibited from regulating fracking under the Safe Drinking Water Act (1974) (7). Due to these actions, fracturing fluids are excluded from federal disclosure rules and a number of chemicals associated with UOG are not reported to the public.

A mounting number of studies have reported EDC activity in surface and/or groundwater near UOG operations (89, 90, 135). Kassotis et al. (89) found greater EDC activity in surface and ground water from fracturing fluid spill sites in areas where more intensive natural gas development, compared with reference sites with limited UOG activity.

In another study, the same researchers, assessed EDC activity of fracturing chemicals in surface water at a West Virginia injection well disposal site accepting wastewater partly from UOG operations (90). The researchers reported antagonist activities for most of the chemicals that were analyzed. Given that currently in this country, over 95% of end disposal of hydraulic fracturing wastewater from UOG operations occurs via injection wells (with over 140,000 such wells in operation), these environmental impacts and health consequences on surrounding organisms can be thought to be widespread (90).

Exposure pathways and mechanisms

The Endocrine Society defines EDCs as "exogenous chemical(s), or mixtures of chemicals, that interfere with any aspect of hormone action" (52, 55). Once EDCs are absorbed into the body, they act via a range of mechanisms to alter hormone action, thereby causing a spectrum of adverse effects such as hormone-dependent cancers, infertility, miscarriage and birth defects (55, 136–138). These mechanisms can include direct agonism or antagonism of hormone receptors, disruption of steroidogenic enzymes, and impairment of steroid receptor expression among others (56).

Commonly used UOG chemicals have been shown to be able to act as antagonistic EDCs in animal studies. In one animal study, prenatal exposure (via maternal ingestion) to concentrations equal to and less than those found in three oil and gas wastewater samples (first, from a ruptured pipeline actively leaking; second, an open storage tank, and third, a closed storage tank in Colorado) resulted in adverse male reproductive outcomes in mice. Specifically, there was an increase in weight of testis, body and heart and a decrease in sperm counts (135). Kassotis et al. (139) found that pregnant mice that were prenatally exposed to drinking water contaminated with UOG chemicals from

gestational day through birth displayed a host of fertility and endocrine-related adverse health effects including suppressed pituitary hormone concentrations across experimental groups (prolactin, luteinzing hormone (LH), follicle stimulating hormone (FSH), etc.), increased body weights, changes in uterine and ovary weights, disrupted folliculogenesis, among other reported effects. Exposure to EDCs during the perinatal period has been shown to cause permanent changes in the brain and behavior (52–54).

Neuroendocrine systems coordinate virtually all homeostatic processes and functions, including growth, stress, energy balance, stress, lactation and reproduction. Importantly, the neuroendocrine system coordinates an organism's response to the environment including chemical exposures. Although still lacking a formal definition, the term "neuroendocrine disruptors (nEDCs)" has been used to describe chemical impacts on endocrine-related brain development and function including the function of the nervous system (140, 141). Importantly, neuroendocrine disruption is different than neurotoxicity, which defines processes resulting in neuronal cell death and related to up or downstream consequences (e.g. oxidative stress or inhibition of neurotransmission) including peripheral neuropathies. The neuroendocrine system, like other neural systems, is not fully mature at birth and can be extremely sensitive to hormones and nEDCs at many points in the life span, most notably the prenatal window and the pubertal transition (142). It is also, in many aspects, sexually dimorphic, thus resulting in sex-specific vulnerabilities (143).

Cognition, behavior and learning

Although beyond the scope of the present review, numerous prior analyses have linked nEDCs with adverse neural and behavioral outcomes in a variety of animal models, including impaired social interaction/activity, compromised learning and memory, increased anxiety and aggression, modified brain sex differences, altered hippocampal spine density and advanced puberty (55, 56). Other endocrine disruptors (including those not apparently associated with UOG development) such as BPA appear to affect social and maternal behavior and reproductive functions. Low dose oral BPA exposure have been observed on oxytocin and related pathways. Oxytocin is a peptide hormone critical for mediating social and maternal behaviors, such as licking-grooming in animals (56, 144). Developmental exposure to bisphenol A (BPA) has been shown to alter the sexual differentiation of neural circuits involved in the control of reproductive functions and behavior including ovulation and sexual receptivity (143, 145).

Brain disorders and neuropsychology

Exposure to nEDCs that disrupt hormone function during critical periods of prenatal development may enhance susceptibility to sex- and/or hormonally-differentiated behavioral disorders. This is an outcome which has been interpreted to indicate that EDC exposure might contribute to the etiology of disorders with sex-biased prevalence rates such as autism spectrum disorders, ADHD and depression (56). These potential linkages should be viewed with caution, however, because although it is widely postulated that EDCs are contributing to clinical neural and behavioral disorders, specific evidence for such a relationship is sparse, even for well-studied EDCs like BPA. That said, detrimental effects on aspects of cognitive function and reasoning, including IQ, have clearly been shown in both animal models and humans for EDCs such as the PBDEs and PCBs. Effects are particularly evident in arctic populations where exposure is especially high and chronic. These effects can be exacerbated by co-exposure to other contaminants, including heavy metals, emphasizing their significance within a complex exposure paradigm. While difficult to quantify, the economic costs of EDC exposure on neurobehavioral deficits and diseases have been estimated to be in the range of 150 billion euros for the EU (146). These estimates contextualize the real "costs" of EDC exposures even if they cannot be specifically attributed to a clinically diagnosable cognitive or other neural disorder. Currently, the research on specific UOG chemicals that are nEDCs is sparse, but due to what is emerging about well-studied EDCs like BPA, more research exploring the potential link between UOG EDC exposures and disruptions during prenatal neurodevelopment is apparently needed.

Arsenic and manganese

Levels of heavy metals near UOG sites

Arsenic has been found in both flowback wastewater and produced water (water that is found in gas formations underground and comes to the surface over the lifetime of the well) from hydraulic fracturing sites on the Marcellus Shale (87). Studies have also confirmed arsenic contamination of ground/drinking water from flowback and

produced water being treated and then released back into the environment. For example, Fontenot et al. (75) found higher levels of arsenic in the private wells of homeowners living within 3 km of sites of natural gas extraction in the Barnett Shale region in Texas. These levels exceeded EPA's maximum contaminant limit for drinking water of 10 μg/L (Table 2) (21, 87). Glenn and Lester (101) found that contamination by arsenic and various other heavy metals of groundwater exceeded maximum contaminant levels and health risk limits in the Gulf Coast aquifer of Texas, a region inhabited by more than 7.5 million people and in the proximity of at least 86,000 facilities (oil, gas and storage wells) This number is most likely an underestimate because certain well types were excluded from analysis (Table 2).

The heavy metal manganese has also been found in flowback water from fracking operations, and in drinking water near UOG sites at levels known to be hazardous to human health (78). Manganese can contaminate groundwater as acids in fracking fluids will cause metal dissolution (147).

Boyer et al. (88) found that after hydraulic fracturing, within 3000 feet of shale gas wells in rural Pennsylvania, there was an increase in concentrations of manganese in drinking water wells. The concentrations spanned from near or below the drinking water standard (0.05 mg/L) to above safety levels after drilling occurred (Table 2) (88). A 2015 report on well water contamination in a rural community within 4 km of unconventional shale gas extraction similarly reported concentrations of manganese found in well water (78). Twenty-five of the reporting households documented levels exceeding the maximum contaminant level (SMCL) of 0.05 mg/L (the highest was 2.627 mg/L) (Table 2) (78). Manganese water contamination has also been reported in other regions across the US such as Pennsylvania (148). Notably, two fracking lawsuits have involved plaintiffs reporting neurological symptoms from exposure to test-verified manganese groundwater contamination in Pennsylvania and West Virginia (149).

Exposure pathways and mechanisms

Arsenic ranks as number one in the Agency for Toxic Substances and Disease Registry (ATSDR)'s list of 275 environmental substances that pose the most significant threat to human health (150). In addition to gastrointestinal, respiratory, cardiovascular, and other diseases, acute and chronic arsenic exposure is associated with neurotoxicity, nerve inflammation (neuritis) and neuropathy, with possible long-lasting effects (151, 152).

Consuming contaminated drinking water is generally the main route of human exposure to arsenic, in addition to consuming food that is irrigated with contaminated water or from food prepared with contaminated groundwater (21). Infants are more vulnerable to exposure because of their greater consumption than adults on a body-weight basis. After ingestion, 60–90% of organic and inorganic arsenic is absorbed into the bloodstream (153). Mechanisms of arsenic neurotoxicity include interference with neurotransmitter release and metabolism, and induction of oxidative stress (21).

Arsenic impairs the developing brain by inhibiting neuron growth both in the central and peripheral nervous system. It additionally interferes with various stages of neurodevelopment including synapse formation and neuronal migration (19). Arsenic has been shown to cross the placenta and may also cross the BBB and directly affect the central nervous system (21). One study reported that in-vitro arsenic exposure can induce disturbances in neuronal development and apoptosis of neuronal cells in human fetal brain explants (154).

Manganese, like arsenic, is a known neurotoxin that can produce cognitive, neuropsychological and motor deficits in both humans and animals. Chronic exposure has been linked to Parkinson's disease (155, 156). According to a recent review of the literature, potential mechanisms include dysregulation of the dopaminergic system and alteration of the working memory network due to impacts on the striatum, frontal and parietal cortex (the region integral to sensory information and working memory performance) (155). Notably, both animal and human studies have shown that concurrent exposure to arsenic and manganese can have additive effects on newborns intellectual functioning. In one study, 11–13 year olds with exposure to both arsenic and manganese showed greater deficits in intellectual functioning (29). More research is needed on both the mechanisms by which manganese induces cognitive impairment and on the psychiatric effects of chronic manganese exposure.

Neurological and neurodevelopmental effects

Cognition, motor and intellect

Developmental deficits, including cognitive deficits due to arsenic neurotoxicity, were first reported in 1955 in Japan after arsenic was found in a dried milk product used for bottle-feeding infants. There were more than 12,000 cases of poisoning and more than 100 deaths (157). Researchers

Dakeishi et al. (157) conducted follow-up studies 14 years later on the infants who had survived, finding that the participants had higher rates of mental retardation and epilepsy, and lower IQ, with 10 times the rate of IQs below 85 compared to unaffected controls.

Since then, various longitudinal studies have reported impairments to children's intellectual function due to short-term arsenic exposure, both in utero and/or during childhood. These studies are complemented by animal research showing that learning rates are affected by arsenic exposure during the prenatal period up to 4 months of age (158).

According to a recent review of epidemiological studies on the developmental neurotoxicity of arsenic, 15 out of 17 studies focusing on cognitive outcomes found that early life exposure is associated with deficits in intelligence and memory. The researchers warn that these effects may occur at even low levels of exposure (below current safety guidelines) and that some neurocognitive consequences may manifest only later in life (21). In another systematic review of 41 articles on pre- or postnatal exposure in children up to 16 years of age to heavy metals (including arsenic and manganese), researchers Rodriguez-Barraco et al. (22), suggests that a 50% increase in arsenic levels in urine and manganese levels in hair would be associated with a 0.39 and 0.7 point decrease in the IQ of children age 5–15 and 6–13 years, respectively. Decreased IQ was demonstrated in verbal performance and full-scale tests. In 13 of the 15 studies that Rodriguez-Barraco examined, exposure to arsenic in urine and drinking water was correlated with significant negative neurodevelopmental effects on children, as measured by decreased performance on a variety of tests. These tests included the IQ test (verbal, performance and full-scale), and working memory, vocabulary, object assembly and picture completion tests (22).

Varying levels of exposure to arsenic-contaminated water has been linked with neurodevelopmental impairments in memory, attention and intelligence testing in children in Taiwan, Mexico, India and Bangladesh (23–26). In a study of children in Taiwan, the high arsenic exposure (184.99 ± 225.29 μg/L) group demonstrated significant deficits in pattern memory and switching attention as compared to the low arsenic exposure group (131.19 ± 343.70 μg/L) over a long-term period of 11.28 ± 2.58 and 8.10 ± 6.07 years, respectively (23). In a study of children in India, arsenic exposure was found to be significantly associated with decreased performances in vocabulary development, object assembly, and picture completion tests (25). In a cross-sectional study in Mexico, children exposed to high levels of arsenic had lower scores on the verbal intelligence (IQ) and long-term memory and linguistic abstraction factors of the Wechsler Intelligence Scale when compared to children exposed to lower levels of arsenic (62.9 ± 0.03 μg As/g creatinine, 40.2 ± 0.03 μg As/g creatinine urine) (27).

Similar neurodevelopmental impairments have been reported in children exposed to manganese. Many studies have reported below average performance by children with prenatal or drinking water exposure to manganese in tests of verbal and visual memory, perceptual reasoning and working memory (31, 32). Psychomotor impairment has been found in infants with prenatal exposure to manganese at as early as 6 months (30). Such findings corroborate those of occupational studies (i.e. of welders) (159) and non-human primate studies showing deficits in non-spatial and spatial memory (160). Studies have also reported below average performance on tests of intellectual function in school-age children that had been exposed to manganese (29, 33–35, 40). For example, studies in Bangladesh have linked exposure to manganese-contaminated drinking water with decreased IQ and mathematical performance (34, 36).

Neuropsychology and behavior

Studies have reported a significant association between early life exposure to arsenic and adverse neuropsychological effects. A birth study of 100 mothers in Nepal, for example, found a significant inverse association between in-utero exposure to arsenic and newborns' self-regulation, an indicator on the Brazelton neuro-behavioral assessment of newborns considered to be integral to children's normal neuropsychological development (28).

In young children, it has been reported that high manganese exposure can affect learning, memory, lower cognition, motor function deficits, and lead to behavioral problems (37–39). One study found more problems with impulsive, aggressive and hyperactive behavior among first to third graders who had prenatal exposure to high levels of manganese (37). Bouchard et al. (38) found a significant association between high levels of manganese in hair and an increase in hyperactivity and behavioral problems in children exposed to manganese via tap water in Quebec, Canada. Importantly, the mean level of manganese in water in this study did not even reach 0.1 mg/L in comparison to the health risk standard of 1 L daily as reported by the U.S. Department of Health and Human Services' Toxicological Profile of Manganese (161). In another study using 0.2 mg/L of manganese as a median exposure level in utero, manganese exposure was associated with

increased risk of conduct problems in children at 5 and 10 years of age. Stratifying by gender, exposure was associated with low prosocial scores for girls and an increased risk of emotional problems for boys (39).

Neural tube defects (NTDs)

The prevalence of NTD in the US is 5.3 per 10,000 live births, depending on a range of factors including genetic susceptibility, nutritional status and the presence of environmental toxicants (20). Very early developmental anomalies can have devastating and lasting effects on the brain. Arsenic has been shown to induce neural tube defects in several experimental animals – including mice, rats, hamsters and chicks – after crossing the placenta and accumulating in the neuroepithelium of the developing embryos of these animals (20). Mazumdar et al. (20) produced the first study in humans demonstrating that environmental exposure to arsenic influences risk of neural tube defects (NTDs). NTDs, including spina bifida, anencephaly, and encephalocele occur when the neural tube does not close by the 28th day of gestation. Infants with anencephaly are born without the cranial vault, and the cerebellum is often absent. Additionally, the brainstem can be hypoplastic, and many fetuses are aborted or stillborn. Infants with spina bifida often have many other medical issues including learning difficulties and hydrocephalus (the excessive accumulation of cerebrospinal fluid in the brain, creating potentially harmful pressure on brain tissue) (43).

Although not as overt as anencephaly or spina bifida, developmental changes occurring at the time of neural tube closure can cause severe cognitive and behavioral symptoms. In a study of 86 thalidomide survivors, 15 of their mothers had taken thalidomide between days 20 and 24 of neural development (162). Of the children of these 15 mothers, 4 were diagnosed with autism. There were no autism cases in the cohort who had taken thalidomide later in pregnancy. There was additional evidence of brainstem injury, leading to the hypothesis that the interruption of development during this time frame can have multiple impacts ranging from the physical effects noted in NTD as well as the harder to diagnose and characterize defects as seen in autism (163). Similarly, mothers who take the anticonvulsant valproic acid during pregnancy have a three-fold increase in major anomalies including NTD. More recently it has been noted that there is also a significant increase in the rate of developmental problems, including decreased verbal intelligence, communications problems, and the diagnosis of autism spectrum disorders (164). These finding highlight the fact that arsenic's association with NTD should be an indication to study the effects of neurocognitive development in the exposed population.

Benzene, toluene, ethylbenzene and xylene (BTEX)

BTEX levels near UOG sites

BTEX – benzene, toluene, ethylbenzene and xylene – are a tetrad of volatile organic compounds and have routinely been found near UOG sites (165). These compounds are emitted in every stage of the UOG lifecycle – from machinery used in well site preparation; well drilling, fracking, and well completion processes; flowback or produced water; gas flaring/venting and maintenance during production; separators, condensate tanks, and compressors used in processing and storage; pipelines, compressor stations and gas venting used in transmission; and finally, from machinery used in well abandonment and site rehabilitation (7, 77, 82–84).

A number of studies have found elevated BTEX concentrations in ambient air samples and water samples near UOG sites that exceed regulatory standards and/or minimum health risk levels established by the Agency for Toxic Substances and Disease Registry (ATSDR), Center for Disease Control and Prevention (CDC), and the Environmental Protection Agency (EPA) (Table 2) (3, 4, 76, 77, 80, 166).

Researchers Rich and Orimoloye (80) reported elevated concentrations of ambient BTEX compounds in residential areas at different distances from a natural gas facility in six counties in Texas. Concentrations of benzene were elevated when compared to the U.S. EPA's Urban Air Toxics Monitoring Program. Twenty-four hour benzene concentrations ranged from 0.6 parts per billion by volume (ppbv) to 592 ppbv. One hour benzene concentrations ranged from 2.94 ppbv to 2900.20 ppbv (Table 2) (80).

McKenzie et al. (3) measured hydrocarbons near drilling sites in Colorado and found benzene levels in the air to be as high as 22 ppbv, many magnitudes higher than the 0.4 ppb concentration in ambient air that the EPA has estimated could put 1 in every 100,000 exposed people at an increased risk of cancer (Table 2) (3, 12). All four BTEX compound concentrations increased with proximity to the well site.

Macey et al. (77) found similarly elevated concentrations in air samples collected near UOG operations in

five states, including Arkansas, Colorado, Ohio, Pennsylvania, Wyoming. The air samples contained varying National Ambient Air Quality Standards (NAAQS), including benzene concentrations exceeding health risk levels by several orders of magnitude at up to 885 feet, and toluene and xylene samples exceeding ATSDR risk levels (Table 2). Elevated concentration levels of BTEX chemicals (including benzene) have also been found in groundwater near UOG sites (86). Gross et al. (76), for example, reported in 90% of the groundwater samples contaminated by surface spills from UOG wells in Colorado, benzene measurements exceeded the US EPA National Drinking Water maximum contaminant level of 5 ppb (Table 2).

Exposure pathways and mechanisms

Exposure to BTEX can occur through inhalation, dermal contact, transplacental or oral exposure from drinking water (167). While several studies have established the interactive effect of BTEX neurotoxicity, more research is needed on its mechanisms. Proposed mechanisms include oxidative DNA damage, apoptosis and fragmentation resulting in changes in signaling pathways, and cellular homeostasis (62, 168). Being highly lipophilic, these substances have easy access to the CNS.

Neurological and neurodevelopmental effects

Analyzing the neurotoxic and developmental effects of these compounds is challenging, especially in humans. Frequently, exposures are not specific, and exposure to one or more BTEX compounds might also accompany exposures to other neurotoxic compounds such as formaldehyde. Most of the human studies have employed occupational settings [which are generally airborne concentrations averaged over a period, either a long-term exposure limit (8 h time weighted average) or a short-term exposure limit (15 min period) and inhalant abusers (episodic binge exposures to high concentrations] (169, 170).

Low to moderate concentrations of toluene have been linked with impaired cognitive, auditory and neuromuscular functions. Studies in experimental animals have found that exposure to both benzene and toluene can affect spatial learning and memory, even at levels considered subtoxic (60). Toluene exposure has been shown to cause intellectual, psychomotor, and neuromuscular impairment at moderate concentrations (80–150 ppm) (60). Infants of mothers that abused toluene during pregnancy showed delayed development of speech, motor function and had low scores on developmental tests. At high levels of exposure (1000–20,000 ppm), humans experience severe CNS dysfunction and in some cases can lead to permanent damage and death (60). In occupational settings "clinical neurobehavioral deficits" may be absent or low level, however when tested neurobehavioral performance is impaired (63). These performance tests give a continuous dimensional reading to the exposure and may be used to identify the beginnings of pathology not yet apparent (171). Some of these dimensions include motor performance, audiometry or tests of color vision. These dimensions were reflected in a study on young healthy volunteers given a single exposure to 200 ppm of toluene (172). A robust decline in a perceptual learning task was found amongst the study participants when a "distractor" was also present, a result that was not seen without the distractor (172). This illustrates the fact that relatively sophisticated testing must be conducted to document the subclinical effects of these toxicants (172).

Occupational exposure to xylene at the level of 14 ppm has been shown to cause anxiety, forgetfulness, difficulty with concentration, and other neurologic dysfunction (173). At more extreme (accidental) levels of exposure such as 10,000 ppm, amnesia, brain hemorrhage, unconsciousness and seizures have been reported (173). According to a 2015 review of approximately 150 peer-reviewed animal and human studies relevant to xylene toxicity, neurological effects include delayed nerve signaling, while neurobehavioral effects include tremors, altered vision, and numbness (62).

Xylene and toluene have also been associated with impaired neurodevelopment. Children exposed to toluene in utero have been reported to be born with small head circumference, serious facial deformations, and general growth retardations. A follow-up study at 3 years of age showed that these same children had hyperactivity, language impairment, developmental delays, postnatal growth retardation and cerebellar problems (57, 58). In another study of these same children, a high incidence of postnatal microcephaly and developmental delay was reported (59). It should be noted that these studies were primarily examining inhalant abusers and it is likely that the dosing was very high. Similar effects have been reported for xylene exposure (62).

Ethylbenzene's neurotoxicity has been reported in animal and human studies. Neurologic effects associated with inhalation exposure to ethylbenzene has included hearing loss, with worsening of auditory response and changes to cochlear anatomy (174). Notably, these effects occurred even when exposed levels of ethylbenzene were

lower than health standards established by OSHA and National Institute for Occupational Safety and Health (NIOSH) (174).

Neural tube defects (NTDs)

Studies have linked maternal benzene exposure to neural tube defects in both experimental animals and human infants. In Texas, a state that has very high ambient benzene levels, mothers living in areas with high benzene levels were reported to more likely have children with spina bifida than women living in areas with lower levels (61). In Sweden, women exposed to benzene and other organic solvents in biomedical research laboratories were found to be at an elevated risk for neural crest (cells which migrate through the embryo and engender several cell populations, including the peripheral nervous system) malformations during pregnancy (175). At a Marine Corps Base Camp in North Carolina, maternal exposure to benzene and trichloroethylene-contaminated drinking water was associated with NTDs (176). In a retrospective study of 124,842 births between 1996 and 2009 in rural Colorado, McKenzie et al. (12) found that the prevalence of NTDs were possibly associated with the highest exposure of mothers to natural gas development (based on density and proximity of natural gas wells within a 16-km radius of residence).

Discussion

Based on the literature indicating adverse impacts from air and water pollution on children's health in other contexts, there is potential for adverse neurological and developmental effects in infants and children in the context of UOG. Our review shows that at least five of the pollutant groups used and produced by UOG processes have well-known neurological and developmental health effects on infants and children.

Health risks identified

Our review found that five pollutant categories are associated with increased neurological and neurodevelopmental problems in developing children: heavy metals (arsenic and manganese), particulate matter, BTEX, PAHs and EDCs. We found that these five pollutant groups are associated with neurotoxicity, neuroinflammation, psychomotor effects and neuromuscular effects. Some of these pollutant categories are also linked with neural tube defects and neurodevelopmental effects such as impaired memory, intellectual function, learning and cognitive function. Finally, we also found that some of these pollutants are associated with brain disorders, adverse neuropsychological effects, and behavioral effects including impulsivity, aggression, hyperactivity and ADHD (Table 1).

Given the profound sensitivity of the developing brain and central nervous system, it is reasonable to conclude that young children who experience frequent exposure to these pollutants are at particularly high risk for chronic neurological diseases.

Susceptibility during prenatal, postnatal and reproductive years

The entire nervous system, consisting of the brain, spinal cord and peripheral nerves, is highly vulnerable to environmental toxicants especially during development (74, 177, 178). During critical stages of cellular growth, migration and synaptic organization, even subtle disruptions can have profound and reorganizational effects on neurodevelopment and can result in permanent brain damage or neural impairments (74, 177, 178). Numerous studies have repeatedly shown that chemical exposures that produce little to no perceptible adverse effects in an adult brain can significantly impact neurodevelopment (71, 178). The human brain undergoes substantial growth and development during the prenatal period. Beginning with the formation of the neural tube at 2 weeks of life and continuing through until birth, the development of the central nervous system involves the formation of 100 billion neurons and more than 100 trillion synaptic connections (179). It is therefore not surprising that the prenatal window is considered one of the periods of the greatest vulnerability to neurotoxicants, neuroendocrine disruptors and other environmental insults (179, 180), receptivity (143). Although the developing fetus was once thought fully protected from exogenous exposures, it is now clear that the placenta and fetus are unable to block the passage of many of the environmental toxicants to which the mother is exposed. Within the developing brain, billions of cells must be precisely located, interconnected and specialized. To achieve this, neurons need to develop and migrate along precise pathways. The ability to repair any anomaly is unlikely, if at all possible, which can lead to permanent deficits (72, 73, 181, 182).

There are many mechanisms by which typical development can be interrupted. Mounting research has

detected more than 200 such chemicals in umbilical cord blood, showing that babies are being born "pre-polluted" with a host of chemicals, some of which are neurotoxic (71). Routes of fetal exposure include transplacental transmission, wherein compounds pass through the placental barrier and reach the embryo and/or fetus by mimicking or binding to essential compounds (183), through ingestion of amniotic fluid and via transdermal exposure (184, 185). At least some of these compounds reach the fetal brain. The BBB which imparts some protection from toxicant exposure, is not fully formed until approximately 6 months after birth, leaving the developing brain particularly susceptible to exposure during prenatal and neonatal life (72).

The period after birth is also considered an enhanced window of vulnerability, though for different reasons. First, the brain is still remodeling and organizing, which it will continue to do long into early adulthood. It is thus still susceptible to developmental disruption, but via potentially different mechanisms and in distinct regions (186). Second, exposure pathways for neurotoxicants are heightened during infancy and childhood compared to later in life. Children experience greater internal exposures to toxicants than adults because they eat, drink and breathe more toxicants per pound of body weight than adults (187). This is the result of having greater interaction with chemical toxicants (from spending more time on the floor and putting objects in mouths), and having different morphometry compared to adults (187). Children are often not able to detoxify, metabolize or excrete toxicants as efficiently as adults can due to their underdeveloped metabolic systems (187). Even as children grow into adolescents, their developing central nervous system remains vulnerable to environmental toxicants. This is because synaptic remodeling, myelination and additional developmental processes continue in cortical regions as well as other areas of the brain fundamental to cognitive reasoning, executive function, impulse control and other high-level behaviors (188). Chronic exposures, even at low levels, are particularly concerning for children because they are still developing and have years of life remaining over which to be exposed. Thus, there is heightened risk of developing chronic diseases later in life (189).

In our discussion of neurotoxicity, it is important to keep in mind that the factors of dose, duration, and frequency of exposure to neurotoxicants interplay to influence their ultimate effect in the developing brain (190). One reason why the pandemic of neurotoxicity was first called "silent" is that some neurotoxin effects are subtle and thus discerned only through special testing rather than standard examination, which is designed to detect clinical neural disorders.

Finally, it is important to understand the distinction between neurotoxicity (which results in cell death) and neurodevelopmental impact (which can constitute organizational and other changes within the CNS without obvious pathology). Although the specific mechanisms by which chemicals alter brain organization and function remain largely unresolved, subclinical effects may reflect a dose-dependent continuum of toxic effects, wherein low doses may cause surprisingly large functional decrements (72). The rapidly growing body of literature on the neurodevelopmental consequences of neurotoxicant exposures in early life emphasizes their likely role in the etiology of neurodevelopmental as well as neurodegenerative disorders later in life (71, 179, 191).

When provided by the literature, we discuss in this review the biological mechanisms of neurotoxicity and neurodevelopmental disorders (oxidative stress, DNA damage, apoptosis, etc.). Measurements of cognitive and neurobehavioral deficits in the literature include the IQ test, the Wechsler Scale of Intelligence for Children (WISC-IV), and the Child Behavior Checklist (CBCL), a widely used method for identifying "problem" behavior in children, such as aggressiveness (192).

The significant impact of pollutants on neurodevelopment

The Collaborative on Health and the Environment's 2008 Consensus Statement on Environmental Agents also examined the role of environmental agents on neurodevelopmental disorders (193). They concluded that the existing animal and human studies suggest a greater proportion of development is environmentally influenced than has been generally believed and note the serious implications for families, schools, local communities and society at large (193). Additionally, in another paper Bellinger (194) assessed the risk of different factors on neurodevelopment and full-scale IQ, and determined that environmental chemical exposures had a greater impact on the brain than pediatric conditions like traumatic brain tumors, brain injury and congenital heart disease.

Any discussion on the topic of environmental effects of pollutants on neurodevelopment must carefully address the developmental status of the fetus or young child and the effects of exposure on certain stages of brain development, the variation in exposure routes between children and adults, the endpoints used to measure effects, the

time frame used to measure effects factoring in the "downstream" effect of exposures on the developing organism, and various other issues (178). Unfortunately, regulatory standards have not been developed to sufficiently account for these questions.

The significant impact of neurotoxicants on IQ is attributed not to the magnitude of the effect on the individuals, but rather to the prevalence of exposure across the population (194, 195). Small decrements in IQ could go unnoticed, depending on the specific study method. Since some disorders such as diabetes, depression, and hypertension can be clearly defined using "cutoff values of continuously distributed measurements", some researchers argue that it is not always a question of whether an individual has a disorder but the extent to which the disorder is evident (194, 195). Neurodevelopmental disorders fit into this "continuously distributed dimensional category". IQ is easily measured and has been studied for a long time, but other more complex disorders can be harder to quantitate (194, 195). Some of these are more common than easily measured and recognized disorders. Disorders that are more difficult to measure include social awareness and sensory integration. In an effort to strengthen the diagnostic practices of more subtle disorders, the National Institute of Mental Health has advocated for changes in the field of nosology, or the classification of diseases, and has termed the effort the Research Domain Criteria (RDoC) (196). This will focus on intrinsic biologically based symptoms and is likely to be independent of clinically defined disorders (197). Current epidemiology has been largely based on correlating risk factors with disorders, thus grossly underestimating the effects of many risks on the many aspects of brain development that are likely to be the building blocks of disorders (196).

General policy recommendations

Increased setback distances from UOG development

As we discussed previously (15), setback distances from UOG development are intended to protect the health and safety of residents (198), including infants and children. Many states establish setback rules with an average distance ranging between 100 and 1000 feet from the wellbore to the sensitive receptor such as schools, hospitals, churches and other occupied dwellings (199). Established setback ordinances are typically the result of negotiation between stakeholders (e.g. residents and municipal policymakers) (198, 200). Calls for increased setback distances are due to the potential health risks associated with residing or working in close proximity to UOG development. Individuals residing within a close distance (≤0.8 km) to high-density drilling areas are at greater risk for health effects from exposure to natural gas development than those living >0.8 km mile from wells (3).

Definitive conclusions based on comprehensive measurement and analysis of exposure levels is still to be determined, but based on a Delphi survey conducted by the SWPA-Environmental Health Project, it was found that 89% of the scientists, public health and medical professionals participating in the study favored a setback of at least 0.4 km and 50% of participants favored a 1.6–2 km (201). Haley et al. (200) found that existing setback distances are likely not adequate to protect the public. Our results suggest that setbacks may not be sufficient to reduce potential threats to human health in areas where UOG development occurs. It is more likely that a combination of reasonable setbacks with controls for other sources of pollution associated with the process will be required.

We recommend that at a minimum, 1.6 km setbacks, preferably greater, should be established between drilling facility lines and the property line of occupied dwellings such as schools, hospitals and other spaces where infants and children might spend a substantial amount of time. (3, 198).

The health burden, economic and social effects of adverse neurodevelopmental health

Neurodevelopmental brain disorders, which affect 10–15% of all births in the US (71), include learning disabilities, ADHD, dyslexia, sensory deficits, mental retardation and autism spectrum disorders. Given that the list of human neurotoxicants is growing annually (in 2006, Grandjean and Landrigan found an increase of two substances per year from 202 to 214 in 2006–2014), it is reasonable to assume that the risk of neurodevelopmental and neurodegenerative disorders is also increasing (71). It is also important to consider the health consequences of mixed exposures since most populations are exposed to more than one contaminant at a time (71).

Studies assessing adverse neurodevelopmental exposures (e.g. lead and methyl mercury) have found that if policy interventions were put in place to prevent or minimize environmental exposures, large economic costs could be avoided (202, 203). Given what has been seen with other environmental exposures and neurodevelopmental outcomes, without adequate preventive measures and political action, economic losses and health

consequences will be seen for years to come. A report produced by the European Brain Council estimated that brain disorders cost Europe almost 800 billion pounds ($1 trillion) a year, more than cancer, cardiovascular disease and diabetes put together (204).

i. IQ loss and estimated costs:
In a report on the Clean Air Act by the EPA, the net effect of IQ on expected lifetime income was estimated to be $3000 more per additional IQ point (205). More recently, Grandjean and Landrigan, and separately, Elise Gould, have all estimated a loss of lifetime earnings capacity of about $18,000 with each lost IQ point (206). Given that the list of human neurotoxicants is growing annually, it is reasonable to predict that the estimated economic effect in dollars is much greater today. Policies to reduce the potential social and economic burden of IQ loss created by UOG will likely become an important part of reducing these costs in future years.
ii. ADHD and estimated costs:
Children with ADHD are at greater risk not only for poor academic performance but also for risk-taking behaviors and lower-earnings in adulthood. In the US, ADHD imposes a cost of between $36 and $52 billion annually, or $12,005–$17,458 per person (49).
iii. EDCs and estimated costs:
Bellanger et al. (146) has estimated the potential health care costs for EDC exposure-induced neurobehavioral deficits and disorders in the EU to exceed 150 billion euros.
iv. Small for gestational age (SGA) and estimated costs:
There is greater likelihood of health problems later in life for SGA infants, including metabolic syndrome, obesity, glucose intolerance and type II diabetes (41, 207), all of which pose costs to the individual as well as society. The American Diabetes Association reported total costs of diagnosed diabetes to have risen to $245 billion in 2012 from $174 billion in 2007 (208). Given the length of time since this report was released, we can anticipate that the costs are now higher.

Accounting for low-level and chronic exposures

In many of these studies, chemical concentrations were below federal exposure limits, but above the concentrations found to have health effects; that is because government standards do not take into account low-level, chronic exposure experienced by the increasing numbers of people in close proximity to oil and gas operations (6).

Precautionary approach

To protect the health of children and well-being of families, state and federal agencies and authorities should adopt a precautionary approach when establishing permitting rules and standards for UOG development and production. This also applies to enforcement of standards for air and water quality near UOG sites. The federal government sets standards for many air and water pollutants, based on an estimated risk of health effects at a certain level. Currently, the EPA uses a narrow view of variability and vulnerability in their risk assessment caused by differences in genetic makeup, metabolism, and age of exposures. Therefore, current risk assessment practices provide inadequate protection to the most vulnerable populations, such as infants and children (209).

Mandatory testing and international clearinghouse

Controlling the developmental neurotoxicity pandemic is very difficult since a lot of data is needed for regulation by government authorities. In 2014, Grandjean and Landrigan proposed mandatory testing of industrial chemicals and the development of an international "clearinghouse" on neurotoxicity, an agency that would "promote optimum brain health, not just avoidance of neurological disease, by inspiring, facilitating and coordinating research and public policies that aim to protect brain development during the most sensitive life stages" from exposure to neurotoxic, industrial chemicals (71).

Research needs

Improved exposure assessment

While we strongly support a precautionary approach that prevents children's exposure, we recommend that well-designed biomonitoring studies should be undertaken to measure existing exposures to pollutant groups associated with UOG. Currently, only a small number of studies document a causal relationship between pollution created by UOG operations and undesirable health outcomes. Better population exposure assessment is needed to document these relationships. The most accurate way to obtain information about human exposures from environmental pollution is through well-designed biomonitoring studies.

Mental health monitoring before and after UOG development

There should be the requirement by legislation or executive mandate that states monitor the mental health impacts of UOG development and operations, with an appointed external advisory panel of health experts, and paid for by a dedicated commonwealth revenue source such as a severance tax on UOG. Research should be integrated with the creation of an Unconventional Natural Gas and Oil Development Health Registry. The procedural guidelines should specify not only that children be included in all health studies, but as a vulnerable population they should be given specific attention as President Clinton directed in his Executive Order 13045 to reduce environmental health risks and safety risks to children.

Lack of transparency and research barriers

The 2005 Energy Policy Act, exempted hydraulic fracturing from the Underground Injection Control program and the EPA is prohibited from regulating fracking under the Safe Drinking Water Act (1974) (7). Due to these actions, a number of chemicals associated with UOG are not reported to the public. Disclosure of chemicals is critical in understanding the full scope of neurological health effects for infants and children. In a 2011 review about the human health effects of the 353 chemicals used in natural gas operations (as identified by Chemical Abstract Service numbers), Colborn et al. (1) determined that approximately 40–50% of the chemicals used could affect the brain and nervous system. However, the study was limited because of the lack of transparency about chemical mixtures used in the UOG process. The nondisclosure of these chemicals creates barriers to efficient research practices and contributes to the lack of knowledge concerning UOG and its potential health effects (7). Since a number of chemicals associated with UOG are not disclosed to the public, there exists uncertainty about the chemical makeup of UOG fluids. In many states, companies are not required to disclose information about the concentrations or what chemicals are used in the process because of trade secret protections.

Maximum contaminant levels

Researchers have reported that it is difficult to measure health risks from many of the compounds used in oil and gas development because many of them lack scientifically based maximum contaminant levels (7).

Review limitations considerations

This review is not exhaustive in scope. To make the review manageable, we focus on five particular pollutant groups of concern and do not discuss a number of other air and water pollutants that are known to cause neurodevelopmental harm, such as cadmium and methylene chloride, among others. Thus, the review is not comprehensive, but rather representative of a major issue.

The studies we reviewed evaluated exposures in a variety of settings. For example, some of these studies assessed atmospheric and water concentrations from UOG operations while others assessed emissions from oil and gas refineries as well as urban traffic. We also examined exposures from some of these pollutants in both indoor and outdoor settings. In some cases, where literature is lacking, we examined studies focusing on both conventional and unconventional sources of oil and gas development. The relevance to exposures near UOG sites varies.

This review is not intended to provide a formal risk assessment that would characterize the exposure levels among children to our pollutants of concern. Instead, we review studies that measure UOG air emissions and atmospheric concentrations of our five pollutants categories of concern.

Additionally, UOG is a recent development, and the most effective epidemiological studies will take a long time to complete. Further, there is still much that is unknown about neurological health effects and their relevance for children living near UOG areas. Though there is far more research than there was 5 years ago, there are still only a number of epidemiological studies that explore the associations between risk factors and health outcomes in people living close to UOG development.

Conclusion

We reviewed the body of evidence of whether UOG has the potential to increase air and water pollution in the surrounding communities where it takes place and result in neurological and developmental harm. We conclude that exposure to heavy metals (arsenic and manganese), particulate matter, BTEX, EDCs and PAHs is linked to adverse neurological and developmental health effects, particularly in infants and children. However, the scientific literature examining the direct impact of UOG development on children is just starting to emerge.

Studies indicate that the chemicals that are used in or are byproducts of UOG operations have been linked to serious neurodevelopmental health problems in infants,

children, and young adults. Early life exposure to these air and water pollutants has been shown to be associated with learning and neuropsychological deficits, neurodevelopmental disorders, and neurological birth defects, with potentially permanent consequences to brain health. More research is needed to understand the extent of these concerns in the context of UOG, but since UOG development has expanded rapidly in recent years, the need for public health prevention techniques, well-designed studies, and stronger state and national regulatory standards is becoming increasingly apparent.

Acknowledgment: Authors are grateful to Sophia Ptacek and Elaine Hill for their assistance. We also wish to thank the Center for Environmental Health (CEH), and the Institute of Health and the Environment for their support and guidance.

Author Statement

Research funding: The authors have no relevant financial relationships. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent is not applicable. Ethical approval: The conducted research is not related to either human or animal use.

References

1. Colborn T, Kwiatkowski C, Schultz K, Bachran M. Natural gas operations from a public health perspective. Hum Ecol Risk Assess 2011;17(5):1039–56.
2. Goldstein BD, Kriesky J, Pavliakova B. Missing from the table: role of the environmental public health community in governmental advisory commissions related to Marcellus Shale drilling. Environ Health Perspect 2012;120(4):483.
3. McKenzie LM, Witter RZ, Newman LS, Adgate JL. Human health risk assessment of air emissions from development of unconventional natural gas resources. Sci Total Environ 2012;424:79–87.
4. Helmig D, Thompson CR, Evans J, Boylan P, Hueber J, et al. Highly elevated atmospheric levels of volatile organic compounds in the Uintah Basin, Utah. Environ Sci Technol 2014;48(9):4707–15.
5. Saberi P. Navigating medical issues in shale territory. New Solut 2013;23(1):209–21.
6. Colborn T, Schultz K, Herrick L, Kwiatkowski C. An exploratory study of air quality near natural gas operations. Hum Ecol Risk Assess 2014;20(1):86–105.
7. Shonkoff SB, Hays J, Finkel ML. Environmental public health dimensions of shale and tight gas development. Environ Health Perspect 2014;122(8):787–95.
8. Finkel M, Hays J, Law A. The shale gas boom and the need for rational policy. Am J Public Health 2013;103(7):1161–3.
9. Witter RZ, McKenzie L, Stinson KE, Scott K, Newman LS, et al. The use of health impact assessment for a community undergoing natural gas development. Am J Public Health 2013;103(6):1002–10.
10. Hays J, Shonkoff SB. Toward an understanding of the environmental and public health impacts of unconventional natural gas development: a categorical assessment of the peer-reviewed scientific literature, 2009–2015. PLoS One 2016;11(4):e0154164.
11. Hays J, de Melo-Martín I. Ethical concerns surrounding unconventional oil and gas development and vulnerable populations. Rev Environ Health 2014;29(4):275–6.
12. McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, et al. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environ Health Perspect (Online) 2014;122(4):412.
13. Stacy SL, Brink LL, Larkin JC, Sadovsky Y, Goldstein BD, et al. Perinatal outcomes and unconventional natural gas operations in Southwest Pennsylvania. PLoS One 2015;10(6):e0126425.
14. Casey JA, Savitz DA, Rasmussen SG, Ogburn EL, Pollak J, et al. Unconventional natural gas development and birth outcomes in Pennsylvania, USA. Epidemiology (Cambridge, Mass.) 2016;27(2):163.
15. Webb E, Hays J, Dyrszka L, Rodriguez B, Cox C, et al. Potential hazards of air pollutant emissions from unconventional oil and natural gas operations on the respiratory health of children and infants. Rev Environ Health 2016;31(2):225–43.
16. Subra W. Community health survey results. Pavilion: WY Residents, 2010.
17. Bamberger M, Oswald RE. Impacts of gas drilling on human and animal health. New Solut 2012;22(1):51–77.
18. Jemielita T, Gerton GL, Neidell M, Chillrud S, Yan B, et al. Unconventional gas and oil drilling is associated with increased hospital utilization rates. PLoS One 2015;10(7):e0131093.
19. Vahidnia A, van der Voet GB, de Wolff FA. Arsenic neurotoxicity – a review. Hum Exp Toxicol 2007;26(10):823–32.
20. Mazumdar M, Ibne Hasan MO, Hamid R, Valeri L, Paul L, et al. Arsenic is associated with reduced effect of folic acid in myelomeningocele prevention: a case control study in Bangladesh. Environ Health 2015;14:34.
21. Tolins M, Ruchirawat M, Landrigan P. The developmental neurotoxicity of arsenic: cognitive and behavioral consequences of early life exposure. Ann Glob Health 2014;80(4):303–14.
22. Rodriguez-Barranco M, Lacasaña M, Aguilar-Garduño C, Alguacil J, Gil F, et al. Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: a systematic review and meta-analysis. Sci Total Environ 2013;454–455:562–77.
23. Tsai SY, Chou HY, The HW, Chen CM, Chen CJ. The effects of chronic arsenic exposure from drinking water on the neurobehavioral development in adolescence. Neurotoxicology 2003;24(4–5):747–53.
24. Rosado JL, Ronquillo D, Kordas K, Rojas O, Alatorre J, et al. Arsenic exposure and cognitive performance in Mexican schoolchildren. Environ Health Perspect 2007;115(9):1371–5.
25. von Ehrenstein OS, Poddar S, Yuan Y, Mazumder DG, Eskenazi B, et al. Children's intellectual function in relation to arsenic exposure. Epidemiology 2007;18(1):44–51.
26. Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, et al. Water arsenic exposure and intellectual function in 6-year-old children in Araihazar, Bangladesh. Environ Health Perspect 2007;115(2):285–9.

27. Calderon J, Navarro ME, Jimenez-Capdeville ME, Santos-Diaz MA, Golden A, et al. Exposure to arsenic and lead and neuropsychological development in Mexican children. Environ Res 2001;85(2):69–76.
28. Parajuli RP, Fujiwara T, Umezaki M, Watanabe C. Association of cord blood levels of lead, arsenic, and zinc with neurodevelopmental indicators in newborns: a birth cohort study in Chitwan Valley, Nepal. Environ Res 2013;121:45–51.
29. Wright RO, Amarasiriwardena C, Woolf AD, Jim R, Bellinger DC. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. Neurotoxicology 2006;27(2):210–6.
30. Su F-C, Liao H-F, Hwang Y-H, Hsieh W-S, Wu H-C, et al. In utero exposure to manganese and psychomotor development at the age of six months. J Occup Saf Health 2007;15(3):204–17.
31. Woolf A, Wright R, Amarasiriwardena C, Bellinger D. A child with chronic manganese exposure from drinking water. Environ Health Perspect 2002;110(6):613–6.
32. Wasserman GA, Liu X, Parvez F, Factor-Litvak P, Ahsan H, et al. Arsenic and manganese exposure and children's intellectual function. Neurotoxicology 2011;32(4):450–7.
33. Bouchard MF, Sauvé S, Barbeau B, Legrand M, Brodeur MÈ, et al. Intellectual impairment in school-age children exposed to manganese from drinking water. Environ Health Perspect 2011;119(1):138–43.
34. Wasserman GA, Liu X, Parvez F, Ahsan H, Levy D, et al. Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect 2006;114:124–9.
35. Riojas-Rodriguez H, Solís-Vivanco R, Schilmann A, Montes S, Rodríguez S, et al. Intellectual function in Mexican children living in a mining area and environmentally exposed to manganese. Environ Health Perspect 2010;118(10):1465–70.
36. Khan K, Wasserman GA, Liu X, Ahmed E, Parvez F, et al. Manganese exposure from drinking water and children's academic achievement. Neurotoxicology 2012;33(1):91–7.
37. Ericson JE, Crinella FM, Clarke-Stewart KA, Allhusen VD, Chan T, et al. Prenatal manganese levels linked to childhood behavioral disinhibition. Neurotoxicol Teratol 2007;29(2):181–7.
38. Bouchard M, Laforest F, Vandelac L, Bellinger D, Mergler D. Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. Environ Health Perspect 2007;115(1):122–7.
39. Rahman SM, Kippler M, Tofail F, Bölte S, Hamadani JD, et al. Manganese in drinking water and cognitive abilities and behavior at 10 years of age: a prospective cohort study. Environ Health Perspect 2017;125(5):057003.
40. Claus Henn B, Ettinger AS, Schwartz J, Téllez-Rojo MM, Lamadrid-Figueroa H, et al. Early postnatal blood manganese levels and children's neurodevelopment. Epidemiology 2010;21(4):433–9.
41. Choi H, Rauh V, Garfinkel R, Tu Y, Perera FP. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction. Environ Health Perspect 2008;116(5):658–65.
42. Vassilev ZP, Robson MG, Klotz JB. Associations of polycyclic organic matter in outdoor air with decreased birth weight: a pilot cross-sectional analysis. J Toxicol Environ Health A 2001;64(8):595–605.
43. Ren A, Qiu X, Jin L, Ma J, Li Z, et al. Association of selected persistent organic pollutants in the placenta with the risk of neural tube defects. Proc Natl Acad Sci USA 2011;108(31):12770–5.
44. Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, et al. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics 2009;124(2):e195–202.
45. Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, et al. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect 2006;114:1287–92.
46. Perera FP, Tang D, Wang S, Vishnevetsky J, Zhang B, et al. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6–7 years. Environ Health Perspect 2012;120(6):921.
47. Otto D, Skalik I, Bahboh R, Hudnell K, Šrám R. Neurobehavioral performance of Czech school children born in years of maximal air pollution. Neurotoxicology 1997;18:903.
48. Wormley DD, Ramesh A, Hood DB. Environmental contaminant-mixture effects on CNS development, plasticity, and behavior. Toxicol Appl Pharmacol 2004;197(1):49–65.
49. Perera FP, Chang HW, Tang D, Roen EL, Herbstman J, et al. Early-life exposure to polycyclic aromatic hydrocarbons and ADHD behavior problems. PLoS One 2014;9(11):e111670.
50. Margolis AE, Herbstman JB, Davis KS, Thomas VK, Tang D, et al. Longitudinal effects of prenatal exposure to air pollutants on self-regulatory capacities and social competence. J Child Psychol Psychiatry 2016;57(7):851–60.
51. Peterson BS, Rauh VA, Bansal R, Hao X, Toth Z, et al. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. JAMA Psychiatry 2015;72(6):531–40.
52. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, et al. Endocrine-disrupting chemicals: an endocrine society scientific statement. Endocr Rev 2009;30(4):293–342.
53. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs Jr DR, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev 2012;33(3):378–455.
54. Vandenberg LN. Low-dose effects of hormones and endocrine disruptors. Vitam Horm 2014;94:129–65.
55. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, et al. EDC-2: the endocrine society's second scientific statement on endocrine-disrupting chemicals. Endocr Rev 2015;36(6):E1–150.
56. Frye CA, Bo E, Calamandrei G, Calza L, Dessì-Fulgheri F, et al. Endocrine disrupters: a review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems. J Neuroendocrinol 2012;24(1):144–59.
57. Arnold GL, Kirby RS, Langendoerfer S, Wilkins-Haug L. Toluene embryopathy: clinical delineation and developmental follow-up. Pediatrics 1994;93(2):216–20.
58. Bowen SE, Hannigan JH. Binge toluene exposure in pregnancy and pre-weaning developmental consequences in rats. Neurotoxicol Teratol 2013;38:29–35.
59. Pearson MA, Rimsza ME, Hoyme HE, Seaver LH. Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. Pediatrics 1994;93(2):211–5.
60. Walker B Jr. Neurotoxicity in human beings. J Lab Clin Med 2000;136(3):168–80.
61. Lupo PJ, Symanski E, Waller DK, Chan W, Langlois PH, et al. Maternal exposure to ambient levels of benzene and neural tube defects among offspring: Texas, 1999–2004. Environ Health Perspect 2011;119(3):397.

62. Niaz K, Bahadar H, Maqbool F, Abdollahi M. A review of environmental and occupational exposure to xylene and its health concerns. EXCLI J 2015;14:1167–86.
63. Foo S, Jeyaratnam J, Koh D. Chronic neurobehavioural effects of toluene. Br J Ind Med 1990;47(7):480–4.
64. Wu Y, Dissing-Olesen L, MacVicar BA, Stevens B. Microglia: dynamic mediators of synapse development and plasticity. Trends Immunol 2015;36(10):605–13.
65. Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, Gómez-Garza G, Barragán-Mejía G, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain Cogn 2008;68(2):117–27.
66. Calderón-Garcidueñas L, Engle R, Mora-Tiscareño A, Styner M, Gómez-Garza G, et al. Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. Brain Cogn 2011;77(3):345–55.
67. Meyer U, Feldon J, Dammann O. Schizophrenia and autism: both shared and disorder-specific pathogenesis via perinatal inflammation? Pediatr Res 2011;69(5 Pt 2):26R–33R.
68. Power MC, Kioumourtzoglou MA, Hart JE, Okereke OI, Laden F, et al. The relation between past exposure to fine particulate air pollution and prevalent anxiety: observational cohort study. Br Med J 2015;350:h1111.
69. Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2009. Vital Health Stat 2010;(247):1–82.
70. Bellinger DC. Interpreting epidemiologic studies of developmental neurotoxicity: conceptual and analytic issues. Neurotoxicol Teratol 2009;31(5):267–74.
71. Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. Lancet Neurol 2014;13(3):330–8.
72. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. Lancet 2006;368(9553):2167–78.
73. Kraft AD, Aschner M, Cory-Slechta DA, Bilbo SD, Caudle WM, et al. Unmasking silent neurotoxicity following developmental exposure to environmental toxicants. Neurotoxicol Teratol 2016;55:38–44.
74. Grandjean P. Only one chance: how environmental pollution impairs brain development – and how to protect the brains of the next generation. New York: Oxford University Press, 2013.
75. Fontenot BE, Hunt LR, Hildenbrand ZL, Carlton Jr DD, Oka H, et al. An evaluation of water quality in private drinking water wells near natural gas extraction sites in the Barnett Shale formation. Environ Sci Technol 2013;47(17):10032–40.
76. Gross SA, Avens HJ, Banducci AM, Sahmel J, Panko JM, et al. Analysis of BTEX groundwater concentrations from surface spills associated with hydraulic fracturing operations. J Air Waste Manag Assoc 2013;63(4):424–32.
77. Macey GP, Breech R, Chernaik M, Cox C, Larson D, et al. Air concentrations of volatile compounds near oil and gas production: a community-based exploratory study. Environ Health 2014;13:82.
78. Alawattegama SK, Kondratyuk T, Krynock R, Bricker M, Rutter JK, et al. Well water contamination in a rural community in southwestern Pennsylvania near unconventional shale gas extraction. J Environ Sci Health A Tox Hazard Subst Environ Eng 2015;50(5):516–28.
79. Walters K, Jacobson J, Kroening Z. PM 2.5 airborne particulates near frac sand operations. J Environ Health 2015;78(4):8–12.
80. Rich AL, Orimoloye HT. Elevated atmospheric levels of benzene and benzene-related compounds from unconventional shale extraction and processing: human health concern for residential communities. Environ Health Insights 2016;10:75.
81. Srebotnjak T, Rotkin-Ellman M. Fracking fumes: air pollution from hydraulic fracturing threatens public health and communities. Natural Resources Defense Council, 2014.
82. Pétron G, Frost G, Miller BR, Hirsch AI, Montzka SA, et al. Hydrocarbon emissions characterization in the Colorado front range: a pilot study. J Geophys Res 2012;117(D4):1–19.
83. Moore CW, Zielinska B, Petron G, Jackson RB. Air impacts of increased natural gas acquisition, processing, and use: a critical review. Environ Sci Technol 2014;48(15):8349–59.
84. Pétron G, Karion A, Sweeney C, Miller BR, Montzka SA, et al. A new look at methane and nonmethane hydrocarbon emissions from oil and natural gas operations in the Colorado Denver–Julesburg Basin. J Geophys Res 2014;119(11):6836–52.
85. Brown DR, Lewis C, Weinberger BI. Human exposure to unconventional natural gas development: a public health demonstration of periodic high exposure to chemical mixtures in ambient air. J Environ Sci Health Part A 2015;50(5):460–72.
86. DiGiulio D, Wilkin RT, Miller C, Oberley G. Investigation of groundwater contamination near Pavillion, Wyoming. US Env. Protection Agency draft report. 2011, US EPA. Available from: http://www.epa.gov/region8/superfund/wy/pavillion/EPA_ReportOnPavillion_Dec-8-2011.pdf.
87. Balaba RS, Smart RB. Total arsenic and selenium analysis in Marcellus Shale, high-salinity water, and hydrofracture flowback wastewater. Chemosphere 2012;89(11):1437–42.
88. Boyer E, Sumstock BR, Clark J, Madden M, Rizzo DE. The impact of Marcellus gas on rural drinking water systems. 2012.
89. Kassotis CD, Tillitt DE, Davis JW, Hormann AM, Nagel SC. Estrogen and androgen receptor activities of hydraulic fracturing chemicals and surface and ground water in a drilling-dense region. Endocrinology 2014;155(3):897–907.
90. Kassotis CD, Iwanowicz LR, Akob DM, Cozzarelli IM, Mumford AC, et al. Endocrine disrupting activities of surface water associated with a West Virginia oil and gas industry wastewater disposal site. Sci Total Environ 2016;557–558:901–10.
91. Rozell DJ, Reaven SJ. Water pollution risk associated with natural gas extraction from the Marcellus Shale. Risk Anal 2012;32(8):1382–93.
92. Llewellyn GT, Dorman F, Westland JL, Yoxtheimer D, Grieve P, et al. Evaluating a groundwater supply contamination incident attributed to Marcellus Shale gas development. Proc Natl Acad Sci 2015;112(20):6325–30.
93. Lutz BD, Lewis AN, Doyle MW. Generation, transport, and disposal of wastewater associated with Marcellus Shale gas development. Water Resour Res 2013;49(2):647–56.
94. Vidic RD, Brantley SL, Vandenbossche JM, Yoxtheimer D, Abad JD. Impact of shale gas development on regional water quality. Science 2013;340(6134):1235009.
95. Shonkoff SB. Hazard assessment of chemical additives used in oil fields that reuse produced water for agricultural irrigation. Livestock watering, and groundwater recharge in the San Joaquin valley of California: Preliminary results. Oakland, CA: PSE Healthy Energy Inc., 2016.
96. Organization WH. Implementing the WHO stop TB strategy: a handbook for national TB control programmes. Geneva, Switzerland: World Health Organization, 2008.

97. Anderson JO, Thundiyil JG, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. J Med Toxicol 2012;8(2):166–75.
98. Kampa M, Castanas E. Human health effects of air pollution. Environ Pollut 2008;151(2):362–7.
99. Litovitz A, Curtright A, Abramzon S, Burger N, Samaras C. Estimation of regional air-quality damages from Marcellus Shale natural gas extraction in Pennsylvania. Environ Res Lett 2013;8(1):014017.
100. Davidson CI, Phalen RF, Solomon PA. Airborne particulate matter and human health: a review. Aerosol Sci Technol 2005;39(8):737–49.
101. Glenn SM, Lester LJ. An analysis of the relationship between land use and arsenic, vanadium, nitrate and boron contamination in the Gulf Coast aquifer of Texas. J Hydrol 2010;389(1):214–26.
102. Paulik LB, Donald CE, Smith BW, Tidwell LG, Hobbie KA, et al. Emissions of polycyclic aromatic hydrocarbons from natural gas extraction into air. Environ Sci Technol 2016;50(14):7921–9.
103. Regulatory Impact Analysis Final New Source Performance Standards and Amendments to the National Emissions Standards for Hazardous Air Pollutants for the Oil and Natural Gas Industry 2012 April 2012; Available from: https://www3.epa.gov/ttn/ecas/regdata/RIAs/oil_natural_gas_final_neshap_nsps_ria.pdf.
104. Outdoor Air Pollution: Children's Health and the Environment. WHO training package for the health sector. World Health Organization, 2008 [cited 2017 February 21].
105. Tran HT, Alvarado A, Garcia C, Motallebi N, Miyasato L. Methodology for estimating premature deaths associated with long-term exposure to fine airborne particulate matter in California. Sacramento, CA: California Environmental Protection Agency, Air Resources Board, 2008.
106. Anenberg SC, Horowitz LW, Tong DQ, West JJ. An estimate of the global burden of anthropogenic ozone and fine particulate matter on premature human mortality using atmospheric modeling. Environ Health Perspect 2010;118(9):1189.
107. Allen JL, Liu X, Pelkowski S, Palmer B, Conrad K, et al. Early postnatal exposure to ultrafine particulate matter air pollution: persistent ventriculomegaly, neurochemical disruption, and glial activation preferentially in male mice. Environ Health Perspect 2014;122(9):939–45.
108. Wang B, Feng WY, Wang M, Shi JW, Zhang F, et al. Transport of intranasally instilled fine Fe_2O_3 particles into the brain: microdistribution, chemical states, and histopathological observation. Biol Trace Elem Res 2007;118(3):233–43.
109. Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β-42 and α-synuclein in children and young adults. Toxicol Pathol 2008;36(2):289–310.
110. Calderon-Garciduenas L, Torres-Jardón R, Kulesza RJ, Park SB, D'Angiulli A. Air pollution and detrimental effects on children's brain. The need for a multidisciplinary approach to the issue complexity and challenges. Front Hum Neurosci 2014;8:613.
111. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci 2009;32(9):506–16.
112. Xu X, Ha SU, Basnet R. A review of epidemiological research on adverse neurological effects of exposure to ambient air pollution. Front Public Health 2016;4:157.
113. Boulanger LM. Immune proteins in brain development and synaptic plasticity. Neuron 2009;64(1):93–109.
114. Calderon-Garciduenas L, Mora-Tiscareño A, Styner M, Gómez-Garza G, Zhu H, et al. White matter hyperintensities, systemic inflammation, brain growth, and cognitive functions in children exposed to air pollution. J Alzheimers Dis 2012;31(1):183–91.
115. Calderon-Garciduenas L, Torres-Jardon R. Air pollution, socioeconomic status, and children's cognition in megacities: the Mexico city scenario. Front Psychol 2012;3:217.
116. Calderon-Garciduenas L, Franco-Lira M, Mora-Tiscareño A, Medina-Cortina H, Torres-Jardón R, et al. Early Alzheimer's and Parkinson's disease pathology in urban children: friend versus Foe responses – it is time to face the evidence. Biomed Res Int 2013;2013:161687.
117. Calderon-Garciduenas L, Serrano-Sierra A, Torres-Jardón R, Zhu H, Yuan Y, et al. The impact of environmental metals in young urbanites' brains. Exp Toxicol Pathol 2013;65(5):503–11.
118. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. Br Med J 2010;341:c3666.
119. Calderón-Garcidueñas L, D'Angiulli A, Kulesza RJ, Torres-Jardón R, Osnaya N, et al. Air pollution is associated with brainstem auditory nuclei pathology and delayed brainstem auditory evoked potentials. Int J Dev Neurosci 2011;29(4):365–75.
120. Boström C-E, Gerde P, Hanberg A, Jernström B, Johansson C, et al. Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. Environ Health Perspect 2002;110(Suppl 3):451.
121. Kim K-H, Jahan SA, Kabir E, Brown RJ. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. Environ Int 2013;60:71–80.
122. Santodonato J. Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. Chemosphere 1997;34(4):835–48.
123. Perera F, Tang D, Whyatt R, Lederman SA, Jedrychowski W. DNA damage from polycyclic aromatic hydrocarbons measured by benzo [a] pyrene-DNA adducts in mothers and newborns from Northern Manhattan, the World Trade Center Area, Poland, and China. Cancer Epidemiol Prev Biomarkers 2005;14(3):709–14.
124. Dejmek J, Solanský I, Benes I, Lenícek J, Srám RJ. The impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome. Environ Health Perspect 2000;108(12):1159.
125. Urso P, Gengozian N. Subnormal expression of cell-mediated and humoral immune responses in progeny disposed toward a high incidence of tumors after in utero exposure to benzo [a] pyrene. J Toxicol Environ Health A Curr Issues 1984;14(4):569–84.
126. Tang D, Li TY, Liu JJ, Chen YH, Qu L, et al. PAH-DNA adducts in cord blood and fetal and child development in a Chinese cohort. Environ Health Perspect 2006;114(8):1297–300.
127. Houlihan J, Kropp T, Wiles R, Gray S, Campbell C. Body burden. the pollution in newborns: a benchmark investigation of industrial chemicals, pollutants, and pesticides in human umbilical cord blood. Washington, DC: Environmental Working Group, 2005.
128. Fertuck K, Kumar S, Sikka HC, Matthews JB, Zacharewski TR. Interaction of PAH-related compounds with the α and β isoforms of the estrogen receptor. Toxicol Lett 2001;121(3):167–77.

129. Choi H, Jedrychowski W, Spengler J, Camann DE, Whyatt RM, et al. International studies of prenatal exposure to polycyclic aromatic hydrocarbons and fetal growth. Environ Health Perspect 2006;114(11):1744–50.
130. Chaikind S, Corman H. The impact of low birthweight on special education costs. J Health Econ 1991;10(3):291–311.
131. Hack M, Breslau N, Weissman B, Aram D, Klein N, et al. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. N Engl J Med 1991;325(4):231–7.
132. Hack M, Lucas A, Knobloch H. Effect of very low birth weight on cognitive abilities at school age. N Engl J Med 1992;1992(326):202–3.
133. Saunders CR, Das SK, Ramesh A, Shockley DC, Mukherjee S. Benzo(a)pyrene-induced acute neurotoxicity in the F-344 rat: role of oxidative stress. J Appl Toxicol 2006;26(5):427–38.
134. Waxman HA, Markey EJ, DeGette D. Chemicals used in hydraulic fracturing. United States House of Representatives Committee on Energy and Commerce Minority Staff, 2011.
135. Kassotis CD, Klemp KC, Vu DC, Lin CH, Meng CX, et al. Endocrine-disrupting activity of hydraulic fracturing chemicals and adverse health outcomes after prenatal exposure in male mice. Endocrinology 2015;156(12):4458–73.
136. Tyler CR, Jobling S, Sumpter JP. Endocrine disruption in wildlife: a critical review of the evidence. Crit Rev Toxicol 1998;28(4):319–61.
137. Akingbemi BT, Hardy MP. Oestrogenic and antiandrogenic chemicals in the environment: effects on male reproductive health. Ann Med 2001;33(6):391–403.
138. Baskin LS, Himes K, Colborn T. Hypospadias and endocrine disruption: is there a connection? Environ Health Perspect 2001;109(11):1175.
139. Kassotis CD, Bromfield JJ, Klemp KC, Meng CX, Wolfe A, et al. Adverse reproductive and developmental health outcomes following prenatal exposure to a hydraulic fracturing chemical mixture in female C57Bl/6 mice. Endocrinology 2016;157(9):3469–81.
140. Gore AC, Patisaul HB. Neuroendocrine disruption: historical roots, current progress, questions for the future. Front Neuroendocrinol 2010;31(4):395–9.
141. Waye A, Trudeau VL. Neuroendocrine disruption: more than hormones are upset. J Toxicol Environ Health B Crit Rev 2011;14(5–7):270–91.
142. Patisaul HB, Adewale HB. Long-term effects of environmental endocrine disruptors on reproductive physiology and behavior. Front Behav Neurosci 2009;3:10.
143. Rebuli ME, Patisaul HB. Assessment of sex specific endocrine disrupting effects in the prenatal and pre-pubertal rodent brain. J Steroid Biochem Mol Biol 2016;160:148–59.
144. Sullivan AW, Beach EC, Stetzik LA, PerryA, D'addezio AS, et al. A novel model for neuroendocrine toxicology: neurobehavioral effects of BPA exposure in a prosocial species, the prairie vole (Microtus ochrogaster). Endocrinology 2014;155(10):3867–81.
145. Wolstenholme JT, Rissman EF, Connelly JJ. The role of Bisphenol A in shaping the brain, epigenome and behavior. Horm Behav 2011;59(3):296–305.
146. Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L. Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. J Clin Endocrinol Metab 2015;100(4):1256–66.
147. Lester Y, Ferrer I, Thurman EM, Sitterley KA, Korak JA, et al. Characterization of hydraulic fracturing flowback water in Colorado: implications for water treatment. Sci Total Environ 2015;512–513:637–44.
148. Glauser W. New legitimacy to concerns about fracking and health. Can Med Assoc J 2014;186(8):E245–6.
149. Nicholson B, Blanson K. Tracking fracking case law: hydraulic fracturing litigation. Nat Resour Environ 2011;26:25.
150. Mitchell VL. Health risks associated with chronic exposures to arsenic in the environment. Rev Mineral Geochem 2014;79(1):435–49.
151. Luo J, Shu W. Arsenic-induced developmental neurotoxicity. Handb Arsenic Toxicol 2014;363.
152. Tyler CR, Allan AM. The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. Curr Environ Health Rep 2014;1:132–47.
153. Hall AH. Chronic arsenic poisoning. Toxicol Lett 2002;128(1):69–72.
154. Chattopadhyay S, Bhaumik S, Purkayastha M, Basu S, Chaudhuri AN, et al. Apoptosis and necrosis in developing brain cells due to arsenic toxicity and protection with antioxidants. Toxicol Lett 2002;136(1):65–76.
155. Guilarte TR. Manganese neurotoxicity: new perspectives from behavioral, neuroimaging, and neuropathological studies in humans and non-human primates. Front Aging Neurosci 2013;5:23.
156. Aschner M, Erikson KM, Hernández EH, Tjalkens R. Manganese and its role in Parkinson's disease: from transport to neuropathology. Neuromolecular Med 2009;11(4):252–66.
157. Dakeishi M, Murata K, Grandjean P. Long-term consequences of arsenic poisoning during infancy due to contaminated milk powder. Environ Health 2006;5:31.
158. Rodriguez VM, Carrizales L, Mendoza MS, Fajardo OR, Giordano M. Effects of sodium arsenite exposure on development and behavior in the rat. Neurotoxicol Teratol 2002;24(6):743–50.
159. Chang Y, Woo ST, Lee JJ, Song HJ, Lee HJ, et al. Neurochemical changes in welders revealed by proton magnetic resonance spectroscopy. Neurotoxicology 2009;30(6):950–7.
160. Schneider JS, Decamp E, Koser AJ, Fritz S, Gonczi H, et al. Effects of chronic manganese exposure on cognitive and motor functioning in non-human primates. Brain Res 2006;1118(1):222–31.
161. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for manganese. Atlanta, GA: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, 2008. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=102&tid=23.
162. Stromland K, Nordin V, Miller M, Akerström B, Gillberg C. Autism in thalidomide embryopathy: a population study. Dev Med Child Neurol 1994;36(4):351–6.
163. Arndt TL, Stodgell CJ, Rodier PM. The teratology of autism. Int J Dev Neurosci 2005;23(2–3):189–99.
164. Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? Reprod Toxicol 2009;28(1):1–10.
165. Waste and Cleanup Risk Assessment Glossary. United States Environmental Protection Agency, 2010. Available from: http://www.epa.gov/oswer/riskassessment/glossary.htm

166. McCawley M. Air, noise, and light monitoring results for assessing environmental impacts of horizontal gas well drilling operations. Prepared for the Department of Environmental Protection, Division of Air Quality, 2013.
167. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for benzene. Atlanta, GA: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, 2007. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14.
168. Huang L, Fang S, Chen C. Effect of benzene, toluene, xylene occupational exposure on DNA damage of peripheral blood cells in female jewel processing workers. Mod Prev Med 2010;37(13):2410–1.
169. Topping M. Occupational exposure limits for chemicals. Occup Environ Med 2001;58(2):138–44.
170. Bowen SE, Batis JC, Paez-Martinez N, Cruz SL. The last decade of solvent research in animal models of abuse: mechanistic and behavioral studies. Neurotoxicol Teratol 2006;28(6):636–47.
171. Iregren A, Gamberale F. Human behavioral toxicology: central nervous effects of low-dose exposure to neurotoxic substances in the work environment. Scand J Work Environ Health 1990;16(suppl 1):17–25.
172. Kobald SO, Wascher E, Blaszkewicz M, Golka K, van Thriel C. Neurobehavioral and neurophysiological effects after acute exposure to a single peak of 200 ppm toluene in healthy volunteers. Neurotoxicology 2015;48:50–9.
173. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for xylene. Atlanta, GA: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, 2007.
174. Zhang M, Wang Y, Wang Q, Yang D, Zhang J, et al. Ethylbenzene-induced hearing loss, neurobehavioral function, and neurotransmitter alterations in petrochemical workers. J Occup Environ Med 2013;55(9):1001–6.
175. Wennborg H, Magnusson LL, Bonde JP, Olsen J. Congenital malformations related to maternal exposure to specific agents in biomedical research laboratories. J Occup Environ Med 2005;47(1):11–9.
176. Ruckart PZ, Bove FJ, Maslia M. Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: a case-control study. Environ Health 2013;12(1):104.
177. Rice D, Barone S, Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect 2000;108(suppl 3):511–33.
178. Rauh VA, Margolis AE. Research review: environmental exposures, neurodevelopment, and child mental health – new paradigms for the study of brain and behavioral effects. J Child Psychol Psychiatry 2016;57(7):775–93.
179. Miodovnik A. Environmental neurotoxicants and developing brain. Mt Sinai J Med 2011;78(1):58–77.
180. Rodier PM. Environmental causes of central nervous system maldevelopment. Pediatrics 2004;113(4 Suppl):1076–83.
181. Gore AC, Martien KM, Gagnidze K, Pfaff D. Implications of prenatal steroid perturbations for neurodevelopment, behavior, and autism. Endocr Rev 2014;35(6):961–91.
182. Gore AC, Walker DM, Zama AM, Armenti AE, Uzumcu M. Early life exposure to endocrine-disrupting chemicals causes lifelong molecular reprogramming of the hypothalamus and premature reproductive aging. Mol Endocrinol 2011;25(12):2157–68.
183. Leith Sly J, Carpenter DO. Special vulnerability of children to environmental exposures. Rev Environ Health 2012;27(4):151–7.
184. Murphy VE, Smith R, Giles WB, Clifton VL. Endocrine regulation of human fetal growth: the role of the mother, placenta, and fetus. Endocr Rev 2006;27(2):141–69.
185. Myren M, Mose T, Mathiesen L, Knudsen LE. The human placenta – an alternative for studying foetal exposure. Toxicol In Vitro 2007;21(7):1332–40.
186. Sisk CL. Hormone-dependent adolescent organization of socio-sexual behaviors in mammals. Curr Opin Neurobiol 2016;38:63–8.
187. Moya J, Bearer CF, Etzel RA. Children's behavior and physiology and how it affects exposure to environmental contaminants. Pediatrics 2004;113(Supplement 3):996–1006.
188. Arain M, Haque M, Johal L, Mathur P, Nel W. Maturation of the adolescent brain. Neuropsychiatr Dis Treat 2013;9:449.
189. Haugen AC, Schug TT, Collman G, Heindel JJ. Evolution of DOHaD: the impact of environmental health sciences. J Dev Orig Health Dis 2015;6(2):55–64.
190. Bellinger DC, Herbert MR, Landrigan PJ, Lanphear BP, Pessah I. Scientific consensus statement on environmental agents associated with neurodevelopmental disorders. Collaborative on Health and the Environment's Learning and Developmental Disabilities Initiative (LDDI), 2008.
191. Landrigan PJ. What causes autism? Exploring the environmental contribution. Curr Opin Pediatr 2010;22(2):219–25.
192. Kaufman AS, Raiford SE, Coalson DL. Intelligent testing with the WISC-V. Hoboken, New Jersey: John Wiley & Sons, 2015.
193. Gilbert SG, Miller E, Martin J, Abulafia L. Scientific and policy statements on environmental agents associated with neurodevelopmental disorders. J Intellect Dev Disabil 2010;35(2):121–8.
194. Bellinger DC. A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. Environ Health Perspect 2012;120(4):501–7.
195. Rose G. Mental disorder and the strategies of prevention. Psychol Med 1993;23(3):553–5.
196. NIMH Research Domain Criteria (RDoC). NIMH Research Domain Criteria (RDoC) 2017 [February 21, 2017]. Available from: https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml.
197. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med 2013;11:126.
198. Fry M. Urban gas drilling and distance ordinances in the Texas Barnett Shale. Energy Pol 2013;62:79–89.
199. Richardson N, Gottlieb M, Krupnick A, Wiseman H. The state of state shale gas regulation. Washington, DC: Resources for the Future, 2013.
200. Haley M, McCawley M, Epstein AC, Arrington B, Bjerke EF. Adequacy of current state setbacks for directional high-volume hydraulic fracturing in the Marcellus, Barnett, and Niobrara Shale plays. Environ Health Perspect 2016;124(9):1323–33.
201. The Problem of Setback Distance for Unconventional Oil & Gas Development: an analysis of expert opinions. Southwest Pennsylvania Environmental Health Project (EHP) 2016 [cited Issue 2]. Available from: http://www.environmentalhealthproject.org/dl/26.
202. Attina TM, Trasande L. Economic costs of childhood lead exposure in low- and middle-income countries. Environ Health Perspect 2013;121(9):1097–102.

203. Trasande L, Landrigan PJ, Schechter C. Public health and economic consequences of methyl mercury toxicity to the developing brain. Environ Health Perspect 2005;113(5): 590–6.
204. Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21(10):718–79.
205. Agency EP. The benefits and costs of the Clean Air Act 1970–1990. United States Environmental Protection Agency, 1997.
206. Sibara J. Disability studies and the environmental humanities. Lincoln, Nebraska: University of Nebraska Press, 2017.
207. Boney CM, Verma A, Tucker R, Vohr BR. Fetal programming and risk of metabolic syndrome: prevention efforts for high-risk populations: in reply. Pediatrics 2005;116(2):519–20.
208. Economic Costs of Diabetes in the U.S. in 2012. The American Diabetes Association 2013. Available from: http://www.diabetes.org/advocacy/news-events/cost-of-diabetes.html – sthash.2sqUUmD3.dpuf.
209. Janssen S, Sass J, Schettler T, Solomon G. Strengthening toxic chemical risk assessments to protect human health. Nat Resour 2012. Available from: https://www.nrdc.org/sites/default/files/strengthening-toxic-chemical-risk-assessments-report.pdf.