Reproduction

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

Received 17 April 2024
Accepted 29 July 2024
Available online 29 July 2024
Version of Record published 5 September 2024

REVIEW

IMPACT OF REAL-LIFE ENVIRONMENTAL EXPOSURES ON REPRODUCTION

Evidence for reproductive health effects following exposure to hydraulic fracturing chemical mixtures

Kyle R Siegel[1], Roxanne Bérubé[1], Matthew Day[2], Samantha Heldman[1], Coreen Daley[2], Brooklynn R Murray[1], Rachelle Hecht[1], Élyse Caron-Beaudoin[2] and Christopher D Kassotis[1]

[1]Institute of Environmental Health Sciences and Department of Pharmacology, Wayne State University, Detroit, MI, Michigan
[2]Department of Physical and Environmental Sciences, University of Toronto Scarborough, Toronto, Ontario, Canada

Correspondence should be addressed to C D Kassotis: christopher.kassotis@wayne.edu

This paper forms part of a special series on the Impact of Real-Life Environmental Exposures on Reproduction. The Guest Editors for this special series were Professor Jodi Flaws (University of Illinois, IL, USA) and Professor Vasantha Padmanabhan (University of Michigan, MI, USA).

Abstract

In Brief: Unconventional oil and natural gas (UOG) operations, particularly hydraulic fracturing, have revolutionized oil and gas production, using and containing complex mixtures of chemicals that may impact reproductive health. While there is growing evidence for effects on births in hydraulic fracturing/UOG regions and good mechanistic evidence for potential reproductive toxicity, there is much research still needed to make firm conclusions about these practices and reproductive health.

Abstract: Unconventional oil and natural gas (UOG) operations have emerged over the last four decades to transform oil and gas production in the United States and globally by unlocking previously inaccessible hydrocarbon deposits. UOG development utilizes many compounds associated with conventional oil and gas, as well as some specific to UOG extraction, particularly during hydraulic fracturing (HF). While research is increasing on UOG chemicals and their mixtures, this review discusses the current evidence for reproductive toxicity following exposures to UOG/HF mixtures. These complex chemical mixtures have been demonstrated to interact with numerous mechanisms known to influence reproductive health. A growing number of environmental and controlled laboratory testing studies have reported adverse reproductive health effects in animals exposed to various UOG chemical mixtures. An expanding body of epidemiological literature has assessed adverse birth outcomes, although none has directly examined reproductive measures such as time to pregnancy, semen quality, and other direct measures of fertility. The existing literature provides moderate evidence for decreased birth weights, increased risk of small for gestational age and/or preterm birth, increased congenital abnormalities, and increased infant mortality, though importantly, studies are widely variable in methods used. Most studies utilized distance from UOG operations as an exposure proxy and did not measure actual chemical exposures experienced by those living near these operations. As such, while there is growing evidence for effects on births in these regions and good mechanistic evidence for potential reproductive toxicity, there is much research still needed to make firm conclusions about UOG development and reproductive health.

Published by Bioscientifica Ltd.
https://rep.bioscientifica.com

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

Introduction to UOG development

As conventional oil and gas resources have dwindled (particularly in much of the developed world), unconventional oil and natural gas (UOG) operations have emerged over the last four decades to transform oil and gas production in the United States and abroad by unlocking previously inaccessible hydrocarbon deposits (Choi *et al.* 2023). UOG now accounts for the majority of oil and gas production in the US (US EPA 2015, US EIA 2023). UOG production is defined by its extraction methods, which differ from conventional oil and gas (COG). COG resources are found in discrete pools and reservoirs and are extracted by allowing the oil or gas to flow to the surface, while UOG resources are found in reservoirs with poor permeability and porosity, preventing direct extraction (Ivanova *et al.* 2017). Accessing these resources requires different approaches, such as hydraulic fracturing (HF; high-pressure injection of water, chemicals, and sand to generate fractures in shale and other low-permeability formations), and often results in lower efficiency than COG extraction (Wiseman 2008, Waxman *et al.* 2011, Dubé *et al.* 2022, Jew *et al.* 2022). Oil sand reserves are mixed with sand, clay, and water to extract UOG resources like bitumen (a viscous constituent of petroleum), which then requires dilution with lighter hydrocarbon mixtures for pipeline transportation to achieve refinement or export (Hrudey *et al.* 2012). The resulting diluted bitumen (dilbit) is a complex mixture of heavy and light hydrocarbons, usually with a high sulfur content (Utting *et al.* 2022). UOG extraction also leads to the production of multiple other substances, from heavy oils to natural gas, and includes coal bed methane gas, tight sands gas, shale gas, and oil, heavy and viscous oils, tar sands, and methane hydrates (Ahmed & Meehan 2016), along with considerable wastewater from the producing formation and injected fluids. While these include most of the common types of UOG development, this review will focus specifically on HF chemical mixtures and reproductive toxicity.

HF extraction fluids consist of proppants (e.g. silica, sand, ceramic beads), which prevent the fractures from closing after the injection pressure is released, along with a mixture of other chemical additives (Gallegos *et al.* 2015, US EPA 2015). These added chemicals serve several functions, including bacterial growth prevention, mineral scaling minimization, friction reduction, pH adjustments, corrosion inhibition, iron control, surfactants, clay stabilization, chemical crosslinking, chemical breaking, and gelling or foaming (Stringfellow *et al.* 2014). Commonly used UOG chemicals can be seen in Supplementary Table 1 (see the section on supplementary materials given at the end of this article); however, each UOG operation can employ a different mixture of chemicals with proprietary chemical compositions (Stringfellow *et al.* 2014). This process creates flowback and produced water (FPW) that contains high concentrations of salts and chemicals, some undisclosed, others well-known, such as 1,4-dioxane; organic contaminants; polycyclic aromatic hydrocarbons, or PAHs, such as anthracene and benzo(*a*)pyrene; volatile organic compounds; semi-volatile contaminants; acids; biocides; and surfactants (Colborn *et al.* 2011, Danforth *et al.* 2020). Contamination of local water sources has been demonstrated for some of these compounds, including BTEX (benzene, toluene, ethylbenzene, xylenes) and trace elements (Warner *et al.* 2012, Fontenot et al. 2013, Gross *et al.* 2013, Darrah *et al.* 2014, Llewellyn *et al.* 2015, Kassotis *et al.* 2020).

Overlap in chemicals between UOG/COG

COG operations do not employ HF techniques and therefore do not utilize many of the chemicals found in UOG operations. There is considerable overlap, however, in the chemicals used to facilitate well drilling. When drilling, either water-based drilling muds (WBMs), oil-based drilling muds (OBMs), or synthetic oil-based drilling muds are typically used (Fink 2012, Onojake & Waka 2021). These muds serve several functions including cooling and lubricating the drill bit, removing drill bit cuttings, overcoming the fluid pressure of the formation, ensuring the drilled formation is minimally damaged, stabilizing the shale, controlling viscosity, controlling fluid loss, and reducing corrosion (Fink 2012, Onojake & Waka 2021).

As outlined in Supplementary Table 2, there is also significant overlap in the chemicals used by COG and UOG operations to facilitate oil and gas transportation post-extraction. Additives are used to ease the transportation of natural gas and crude oil by reducing pipeline corrosion, improving flow, and inhibiting the formation of gas hydrates (Fink 2012, Onojake & Waka 2021). Odorizers are always added for olfactory detection in case of leaks, and surfactants are added to remove solids produced during drilling (Fink 2012, Onojake & Waka 2021). Crude oil typically has high wax content and is therefore treated with film-forming chemical inhibitors, which help coat the inside of pipelines, and wax inhibitors to prevent wax buildup (Fink 2012, Onojake & Waka 2021). The types of chemicals used to aid transportation depend on the temperature, the type of target reservoir, the unique chemical composition of the oil or gas, and the individual oil and gas operation (Fink 2012).

Routes of exposure

UOG extractions and processes may lead to the release of chemical mixtures during each stage of development and production (Bolden *et al.* 2018) that can result in exposure through inhalation, ingestion, and dermal absorption routes (Bolden *et al.* 2018, Boogaard 2022, Zhan *et al.* 2023). These substances can be volatile and

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

mobile (e.g. volatile organic compounds (VOCs), BTEX, methane, etc.) or persistent and bioaccumulative (e.g. elements, PAHs, etc.) (Manzetti 2013, Barron *et al.* 2020). Benzene and other VOCs are highly mobile and have been found in the air near UOG operations (Colborn *et al.* 2011, McKenzie *et al.* 2012, Brown *et al.* 2014) as well as in water and groundwater surrounding shale operations (Gross *et al.* 2013, Llewellyn *et al.* 2015). Groundwater and drinking water contamination are also a source of concern in UOG regions. Monitoring studies have reported increasing spill rates for wastewater, crude oil, drilling waters, and/or fracturing fluids in most states examined, with spills often occurring in regions that may impact important drinking water sources (Maloney *et al.* 2017). Supporting concerns over drinking water contamination, several studies have reported UOG-associated chemicals in drinking water sites nearest UOG wells/operations (Osborn *et al.* 2011, Warner *et al.* 2012, Jackson *et al.* 2013, Caron-Beaudoin *et al.* 2022, Gasparyan *et al.* 2024).

The transport of UOG waste and products is mainly achieved by pipelines, breaks of which pose an additional contamination risk to aquatic and terrestrial ecosystems. Studies and remediation processes following large oil spills have demonstrated the persistence of PAHs for years afterward (Environment Canada 2013). UOG wells in the U.S. produce up to an estimated four billion cubic meters of wastewater (inclusive of flowback and produced water) per year (Clark & Veil 2009, Harkness *et al.* 2015). Wastewater is routinely disposed of through injection into deep disposal wells, reused for hydraulic fracturing operations, spread on roads as a de-icing or dust suppressing agent (Tasker *et al.* 2018), and/or pumped into open evaporation pits for disposal (Wiseman 2008, Deutch *et al.* 2011, Lee *et al.* 2011, Lester *et al.* 2015); all additional routes of potential contamination and exposure. Many of the persistent compounds can then bioaccumulate and travel up the food chain to the human diet (Manzetti 2013). As such, animals and humans can be exposed to UOG chemicals from multiple sources. Aquatic animals are exposed through water either by consumption or through their skin and gills, while terrestrial animals, including birds, can be exposed through inhalation, dermal absorption, or ingestion (Ruberg *et al.* 2021).

Evidence of human exposure

Full characterization of health effects associated with exposure to this industry hinges on proper exposure assessments, which are typically based on exposure predictions from models (EPA 2019). Sources of uncertainty in models may lead to exposure misclassification or non-detection of adverse health outcomes (US EPA 2019). While recent scoping and systematic reviews demonstrate a growing body of research reporting significant associations between proximity to UOG and several adverse health outcomes, biomonitoring studies assessing human exposures from UOG development are limited (Werner *et al.* 2015, Bamber *et al.* 2019, Aker *et al.* 2024). Biomonitoring data are useful in assessing human exposure to chemicals by collecting human tissue or specimens such as blood, urine, and hair (NRC 2006). Biomonitoring data becomes particularly useful in environmental health to understand health effects by characterizing exposures when complete exposure data are not available or when exposure to multiple chemicals might have occurred (Arnold *et al.* 2013).

There are limitations to using biomonitoring data. Measuring chemicals in a person's blood or urine does not equate with disease causation (US CDC 2009). Furthermore, there is the potential for intra-individual variability of non-persistent chemicals in the urine (US CDC 2009). While there has been some research measuring specific UOG chemicals in people, including a Canadian cohort (Caron-Beaudoin *et al.* 2018, Caron-Beaudoin *et al.* 2019, Caron-Beaudoin *et al.* 2022, Claustre *et al.* 2023, Gasparyan *et al.* 2024) and small groups in Wyoming (Crowe *et al.* 2016) and Pennsylvania (Marusic 2021), these studies have been largely exploratory and limited in scope with small sample sizes. Further research is urgently needed to better characterize the complex chemical mixtures residents are exposed to near UOG sites.

Evidence for reproductive health effects in animals near UOG operations

Few studies have determined the relationship between UOG and reproductive and developmental outcomes in animal models (Bolden *et al.* 2018). A systematic evaluation of UOG chemicals reported that the majority (76%) did not have any information on reproductive and developmental toxicity. For the chemicals with known information, 65% were possibly associated with adverse reproductive and developmental effects (Elliott *et al.* 2017). This section of the review will report the main reproductive and developmental effects of UOG chemicals on vertebrates and invertebrates. Overall, however, very little research evaluating the reproductive toxicity of UOG mixtures (either observationally or with laboratory animals) has been performed.

Most of the studies on mammals used laboratory mice that were gestationally exposed to a mixture of 23 UOG chemicals through drinking water (Kassotis *et al.* 2015, Kassotis *et al.* 2016*a*, Boule *et al.* 2018, Sapouckey *et al.* 2018). These studies demonstrated that male offspring had a decreased sperm count, increased testis size, and increased serum testosterone (Kassotis *et al.* 2015). Female offspring had modified reproductive organ

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

weights, suppressed pituitary hormone concentrations, and disrupted folliculogenesis (Kassotis *et al.* 2016*a*). Mammary glands collected from these female animals indicated no differences prior to puberty, but they had increased epithelial duct density, hyperplasia, and proliferation-to-apoptosis ratio in early adulthood relative to controls (Sapouckey *et al.* 2018). These laboratory studies using a mixture of UOG chemicals in environmentally relevant concentrations demonstrated that exposure during gestation affects the normal development of reproductive organs and endocrine function in both male and female mice.

Limited field studies on the reproductive effects of UOG chemicals have been conducted in mammals living in proximity to fracking regions. In a case study of dysphagic neonatal foals born at an active UOG operation, exposures occurred through contaminated well water. Males were more affected than females, and foals' dysphagia subsided following environmental management changes (Mullen *et al.* 2020). A study of cow herds living within 1.6 km of a well or battery site (central distribution points that receive crude oil, condensate, and/or produced water from surrounding well sites), or within 8 km of a compressor of a gas plant, was performed to determine reproductive effects from air exposure to sulfur dioxide, hydrogen sulfide, toluene, and benzene. The results suggested no significant associations between chemical exposure, density of oil and gas wells, and pregnancy; though, a 3-day delay in breeding-to-calving was observed in cows with the highest benzene exposures (Waldner & Stryhn 2008). A related study observed calf survival and health in association with air pollution and proximity/density of UOG wells, reporting mortality associated with sulfur dioxide exposures in the first 3 months (Waldner 2008). Related work in a longitudinal cohort of 21 food animals, companion animals, and wildlife reported diverse health issues following UOG fluid exposures, including reproductive health effects. Many of these symptoms improved over time for a subset of animals that were moved away from the source of exposure and did not improve for animals that remained near the presumed exposure site (Bamberger & Oswald 2012, 2015). More comprehensive studies are necessary, specifically focused on the chemical exposures that may underlie reproductive health effects in mammals living near UOG development.

Many UOG toxicity studies have been performed using fish, mainly observing embryonic/larval toxicity. In Canada, fish species during early life stages are particularly vulnerable to UOG waste from pipeline spills, as described in detail previously (Lin *et al.* 2022*a*, Perugini *et al.* 2022). However, reproductive studies are very limited in fish. Endocrine perturbations were observed in cod exposed by ingestion to alkylphenols (20 mg to 80 mg/kg) found in produced water (PW). Male cod had an induction of vitellogenin, while both sexes had decreased serum sex steroids and delayed reproductive organ development (Meier *et al.* 2007). Further research tested lower doses (0.4 mg to 4 mg/kg) of PW samples from Norway on female cod, reporting that low concentrations of alkylphenols induced similar effects on development, while PW samples did not (Meier *et al.* 2011). Juvenile rainbow trout exposed to the water-accommodated fraction from UOG oil exhibited increased expression of androgen and progesterone receptors as well as feminizing and masculinizing effects (De Anna *et al.* 2021). Other research using Nile tilapia reported that a UOG chemical-exposed group with no spirulina in the diet exhibited kidney histological changes, structural gonadal differences, chromosomal defects, cell edema, and decreased weight (Mahmoud *et al.* 2019), whereas spirulina-supplemented groups did not, suggesting potential UOG/diet interactions. A variety of other research has focused on developmental toxicity and cardiometabolic effects, but not specifically on reproductive toxicity (Folkerts *et al.* 2017).

Finally, invertebrate and microbial communities can also be affected by chemicals from UOG operations. *Daphnia magna*, an invertebrate sentinel species, experienced a reduction of 70% in fecundity and delayed first brood after chronic exposure to 0.04% FPW (Blewett *et al.* 2017). While some studies evaluating microbial diversity and UOG operations have determined that exposures to FPW reduced biotic respiration, and modified microbial community structure and functions, resulting in higher species richness and unique functional genes (Amundson *et al.* 2022, Zhong *et al.* 2022), others have reported reduced diversity (Murali Mohan *et al.* 2013, Morono *et al.* 2019). Thus, there is increasing evidence suggesting that exposure to UOG chemicals can affect the reproduction and development of diverse fauna surrounding UOG operations.

Evidence for reproductive health effects in humans near UOG operations

Pre- and post-natal UOG-mediated human health effects are comprehensively reviewed elsewhere (Webb *et al.* 2014, Webb *et al.* 2018, Bamber *et al.* 2019, Deziel *et al.* 2020). We reviewed 17 primary research articles that assessed relationships between UOG well proximity, density, and/or production and adverse birth outcomes with low and moderate confidence. We identified six additional articles that addressed relationships between oil and gas production and adverse birth outcomes, though we were unable to delineate between COG and UOG (McKenzie *et al.* 2014, Janitz *et al.* 2019, McKenzie *et al.* 2019, Schuele *et al.* 2022, Willis *et al.* 2023). We only discuss the former in the text, but all articles are listed in Table 1.

Here, we discuss epidemiological assessments of UOG exposure's effects on five adverse birth

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

Table 1 Summary of human epidemiological studies on reproductive outcomes.

Study	Location	Period	Study design	Exposure comparisons	Exposure distances	Co-variates included	BW	SGA	PTB	CON-AN	IM	SS
Apergis *et al.* (2019)	OK, USA	1996–2017	RCS	Pre-drilling (1996-2005) vs post-drilling (2006-2017); UOG vs COG	1, 5, 10, and 20 km from maternal address	Yes (maternal race, maternal education, maternal age, children's parity)	↓ (w/in 5 km)	–	–	–	–	Yes (BW)
Busby & Mangano (2017)	PA, USA	1999–2014	RCS	Pre-drilling (2003-2006) vs post-drilling (2007-2010); counties with high UOG activity vs those without	n/a	No	–	–	–	–	↑ (county-wide)	Yes (IM)
Cairncross *et al.* (2022)	AB, CA	2013–2018	RCS	Exposed (maternal residence within 10 km of UOG well) vs unexposed (10+ km from UOG well); well density; term of exposure	10 km from maternal postal code	Yes (parental age, multiple births, infant sex, obstetric comorbidities, area-level socioeconomic status)	–	↑ (preconception, preconception+ pregnancy)	↑ (preconception, preconception+ pregnancy)	↑ (major anomlaies)	↑ (preconception, preconception+ pregnancy)	No
Caron-Beaudoin *et al.* (2021)	BC, CA	2006–2016	RCS	Tertiles for each distance buffer based on UOG well density (lowest exposure to highest exposure)	2.5, 5, and 10 km from maternal postal code	Yes (maternal age, prior poor pregnancy outcomes, pregnancy complications, parity, stillbirth, singleton, multiple birth counts, birth date, infant sex, Apgar score, birthweight, head circumference, gestational age)	↓ (5 km and 10 km buffers)	No change	No change	–	–	No
Casey *et al.* (2016)	PA, USA	2006–2013	RCS	Exposure tertiles		Yes (nenonate sex, gestational age, birth year and season, maternal age, race/ ethnicity, primary care provider status, smoking status during pregnancy, pre-pregnancy body-mass index, parity, antibiotic orders during pregnancy, Medical Assistance receipt)	No change	No change	↑ (highest quartile)	–	–	Yes (PTB)
Currie *et al.* (2017)	PA, USA	2004–2013	RCS	Exposure tertiles; sibling controls	0–3 km for near, 3–15 km for far	Yes (maternal age, maternal marital status, maternal education attainment)	↓ (3 km)	–	–	–	–	Yes (BW)
Cushing *et al.* (2020)	TX, USA	2012–2015	RCS	Number of flaring events	5 km from maternal address	Yes (maternal age, maternal race/ethnicity, maternal educational attainment, pre-pregnancy body mass index, smoking status, primary insurance payer source, parity, high-risk pregnancy, infant sex, prenatal care adequacy, birth year, birth season)	No change	↑ (+10 events)	↑ (+10 events)	–	–	Yes (SGA, PTB)
Erickson *et al.* (2022)	CO, USA	1999–2019	ES	Well density and proximity	County-wide metrics	Some (population, age, gender, race, education, income; all at county level)	MX (den-sity + proximity decreased; increased otherwise)	–	MX (production decreased; density and interaction no effect)	–	––	Yes (PTB)

(Continued)

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

Gaughan *et al.* (2023)	OH, USA	2010–2017	RCS	>= well within 10 km of maternal address at least 1 year prior to birth	10 km from maternal address	Yes (birth year, parity, maternal race, maternal smoking, WIC use, social vulnerability index, ambient PM2.5 concentrations)	–	–	–	↑ (NTDs, spina bifida, limb reduction defects)	–	Yes (any NTDs, limb reductions)
Han *et al.* (2023)	TX, USA	1999–2014	ES	Associations between well number and productivity	n/a	No	–	–	–	↑ (CHDs, microcephaly)	–	Yes (CHDs, microcephaly)
Hill (2018)	PA, USA	2003–2010	DIDS	Pre- and post-drilling; permitted and drilled wells	2.5 km from maternal address	Yes (race, education, age, marital status, WIC status, insurance type, previous risky pregnancy, maternal smoking, birth month, birth year, month/year interaction, child sex)	↓	↑	No change	–	–	NO
Ma *et al.* (2016)	PA, USA	2003–2012	RCS	Counties with UOG wells versus without; pre-drilling versus post-drilling	Zip codes with or without wells	Yes (maternal smoking status, maternal educational attainment, maternal race, maternal age, maternal pre-pregnancy BMI, primary payer for delivery, WIC status, maternal diabetes, maternal hypertension, maternal infection during pregnancy)	–	–	–	↑ (structural and functional)	–	Yes (any, structural, and functional defects)
Stacy *et al.* (2015)	PA, USA	2007–2010	RCS	Well density (tertiles) within 10-mile buffer zone 10 mile buffer zone	10 miles from maternal address	Yes (maternal age, maternal educational attainment, cigarette smoking history, WIC use, gestational diabetes, prenatal visits, pre-pregnancy weight, birth parity, gestational age at birth, infant sex)	↓ (highest tertile)	↑ (highest tertile)	–	–	–	Yes (BW, SGA
Tang *et al.* (2021)	TX, USA	1999–2011	CCS	Exposure tertiles	1, 3, and 7.5 km from maternal address	Yes (maternal smoking status, birth plurality, maternal age, race/ethnicity, maternal education, median household income at maternal address block, 2010 urbanicity, average daily vehicle miles traveled for all trucks in county)	–	–	–	↑ (CHDs, NTDs)	–	Yes (CHDs, NTDs)
Tran *et al.* (2021)	CA, USA	2006–2016	RCS	Maternal address within 1 km of an UOG well (exposed) vs maternal address within 1-10 km of an UOG well (unexposed)	1 and 10 km	Yes (infant sex, conception month, conception year, maternal age, self-reported race/ethnicity, educational attainment, Kotelchuck index of prenatal care, parity, California Air Resources Board designated air basins, urban-rural classifications, modeled annual nitrogen dioxide concentrations, Index of Concentration at the Extremes)	↓ (rural populations)	↑ (rural and urban)	↑ (rural)	–	–	Yes (low BW, SGA)

(Continued)

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

Whitworth *et al.* (2017)	TX, USA	2010–2012	RCS	Exposed (1+ well within 10 mile of maternal residence) vs referant (1 well 10–20 miles from maternal residence)	0.5, 2, and 10 miles	Yes (maternal age, education, parity, smoking during pregnancy, race/ethnicity, pre-pregnancy BMI, infant sex, previous poor pregnancy outcomes, Adequacy of Prenatal Care Utilization Index)	No change	No change	↑ (0.5 and 2 mile)	-	↑ (0.5, 2, and 10 mile)	Yes (PTb)
Whitworth *et al.* (2018)	TX, USA	2010–2012	CCS	Exposure tertiles; exposure trimester	0.5 miles	Yes (maternal education, parity, smoking during pregnancy, pre-pregnancy body mass index, infant sex, previous poor pregnancy outcomes, Kotelchuck Adequacy of Prenatal Care Utilization Index, maternal residential distance to nearest major roadway)	-	-	MX (increased during trimester 2, otherwise non-concentration responsive)	-	-	No

↑increased; ↓decreased; BW, birth weight; CCS, case-control study; CON-AN, congenital abnormalities; DIDA, Difference-in-difference study; ES, ecological study; IM, infant mortality; MX, mixed; PTB, pre-term birth; RCS, retrospective cohort study; SS; statistical significance.

outcomes: low birth weight, small for gestational age (SGA), preterm birth, congenital abnormalities, and infant mortality. Birth weight and SGA are linked to, but distinct from, intrauterine growth restriction during gestation, which is sensitive to air pollution (Stieb *et al.* 2012, Sun *et al.* 2015, Malhotra *et al.* 2019). Preterm birth is affected by environmental, genetic, and sociological factors that present a complex outcome requiring broad covariate control (Goldenberg *et al.* 2008, Simmons *et al.* 2010). Birth defects require temporally specific modulations to modify the fetal body plan. However, determination of teratogenic effects can be difficult, and many defects' etiology is unknown (Dolk 2004, Feldkamp *et al.* 2017). Thus, each birth outcome relies on a complex interplay of factors beyond, but including, environmental exposures that require careful covariate adjustment and study design.

Many of the studies discussed do not directly measure exposure levels. Rather, they use maternal addresses at varying geospatial levels (street address, zip code, county code) and surrounding UOG wells as exposure proxies, although with different comparison designs that can affect confidence in identified associations (Deziel *et al.* 2022). Including only geocoded births for analysis can bias against individuals from medically underserved communities who tend not to be geocoded, but based on one analysis, are more likely to face adverse birth outcomes (Ha *et al.* 2016). The related 'live-birth bias' in observational studies can also underestimate negative associations between exposure/stressors and birth outcomes as one key metric, infant mortality, is intentionally removed (Liew *et al.* 2015). Finally, the application of temporal attributes to exposure, particularly when determining preterm birth rates, can be biased due to fixed effects with cohort start and end dates (Barnett 2011, Strand *et al.* 2011). The limitations produced by each of these biases are excellently discussed elsewhere (Neophytou *et al.* 2021).

Birth weight

Ten of the 17 articles tested for associations between UOG operations and birth weight. Low birth weight was typically defined as < 2500 g per World Health Organization values (Blencowe *et al.* 2019). Over half of the articles reported decreased birth weight, or increased low birth weight risk/odds, in their UOG-proximal populations (Stacy *et al.* 2015, Currie *et al.* 2017, Hill 2018, Apergis *et al.* 2019, Caron-Beaudoin *et al.* 2021, Tran *et al.* 2021). UOG exposure groups with lower birth weights tended to be spatially close to UOG operations, usually within 5 km of maternal residence (Stacy *et al.* 2015, Currie *et al.* 2017, Apergis *et al.* 2019). One article reported complex, non-linear relationships between the proximity and density of UOG and birth weight in Colorado over a two-decade period (Erickson *et al.* 2022). However, this ecological study was conducted at the county level, where aggregate data can obfuscate population/region-specific effects (Morgenstern 1995,

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

Deziel *et al.* 2020). Intricate spatial details are thus necessary to understand the effects of UOG on birth weight. Three studies did not report associations between UOG exposure and birth weight (Casey *et al.* 2016, Whitworth *et al.* 2017, Cushing *et al.* 2020).

Small for gestational age (SGA)

Of the eight papers measuring SGA, five reported the adverse effects of UOG exposure manifested by increased SGA odds or risk (Stacy *et al.* 2015, Hill 2018, Cushing *et al.* 2020, Tran *et al.* 2021, Cairncross *et al.* 2022). Associations were typically observed for the highest UOG exposure group, determined either by exposure tertiles (Stacy *et al.* 2015) or high numbers of UOG-related events (Cushing *et al.* 2020). The remaining three papers did not observe associations between UOG exposure and SGA (Casey *et al.* 2016, Cushing *et al.* 2020, Caron-Beaudoin *et al.* 2021). Two of these three studies focused on individual hospitals within a UOG-productive region, indicating a lack of local UOG effects on SGA but not disqualifying UOG effects on SGA in other regions.

Preterm birth

We identified nine studies that measured preterm birth risks in the context of UOG. Five of these studies observed increased preterm birth risk or odds related to nearby UOG development (Casey *et al.* 2016, Whitworth *et al.* 2017, Cushing *et al.* 2020, Tran *et al.* 2021, Cairncross *et al.* 2022). Three studies reported mixed effects from UOG exposure on preterm birth (Whitworth *et al.* 2017, Caron-Beaudoin *et al.* 2022, Erickson *et al.* 2022). Erickson *et al.* (2022) conducted a county-level ecological study with minimal covariates, potentially losing area-specific effects. Whitworth *et al.* (2018) noted high UOG activity and density during the first and second trimesters were associated with increased preterm birth odds, suggesting temporal specificity in when UOG might influence prematurity. Caron-Beaudoin *et al.* (2021) reported associations with odds of preterm birth that did not follow a monotonic response. One study did not detect associations between UOG exposure and preterm birth (Hill 2018).

Congenital abnormalities

Four of the five studies that measured UOG associations with congenital abnormalities, predominantly structural, noted increased risks (Tang *et al.* 2021, Cairncross *et al.* 2022, Gaughan *et al.* 2023, Han *et al.* 2023). Two independent studies noted increased congenital heart defect (CHD) risks with UOG exposure in Texas cohorts, for the Barnett Shale region and statewide (Tang *et al.* 2021, Han *et al.* 2023). Neural tube defect (NTD) risks were also associated with high UOG exposure for Texas and Ohio cohorts (Tang *et al.* 2021, Gaughan *et al.* 2023). Only one study did not detect significant associations between congenital abnormalities and UOG exposure (Ma *et al.* 2016). However, this study compared retrospective cohorts by zip codes. While a quasi-difference-in-difference design was used, some of the spatiotemporal information used in the study designs for the other four studies was lost, and, perhaps, distinct relationships between abnormality risk and UOG exposure.

Infant mortality

Only three studies directly analyzed the relationship between UOG exposure and infant mortality (Busby & Mangano 2017, Whitworth *et al.* 2017, Cairncross *et al.* 2022). The remaining studies explicitly excluded birth records with infant mortality, potentially engaging in the 'live-birth bias' for perinatal epidemiology (Liew *et al.* 2015). All three studies noted increased infant mortality risk with UOG exposure at varying degrees of confidence. Busby and Mangano (2017) analyzed mortality at the county level without adjusting for covariates that influence infant mortality (Womack *et al.* 2020), while Cairncross (2022) and Whitworth (2017) included relevant spatial and sociodemographic covariates.

Potential mechanisms involved in reproductive health effects

There are numerous mechanistic pathways regulating reproductive health. This review is not intended to comprehensively assess each pathway, which other reviews have thoroughly done (Danzo 1998, Jabbour *et al.* 2009, Balabanic *et al.* 2011, Siebold 2011, Patisaul 2021). This section will focus on a subset of well-reported factors in reproductive health, namely nuclear receptor (NR) function and dysfunction, and discuss known evidence of NR disruption by UOG operation-associated mixtures. It is not within the scope of this review to similarly curate and discuss the bioactivity of individual UOG-associated chemicals, though we will discuss, as available, how environmentally relevant mixtures may significantly alter bioactivities and reproductive toxicity. The role(s) of NRs in vertebrate reproduction, and dysregulation by environmental contaminants, are reviewed elsewhere (Martin & Tremblay 2010, Craig *et al.* 2011, Hughes & Murphy 2021).

Estrogen receptor (ER)

The interactions of estrogens with ERs are crucial for fertility and the development of reproductive organs, secondary sexual characteristics, and sexual behavior (Nilsson & Gustafsson 2002, McCarthy 2008). Exposure to estrogens induces ERα and β to act as transcription factors, homodimerizing and binding to genomic response elements (directly or indirectly) to regulate

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

target genes that control many reproductive processes (Fuentes & Silveyra 2019). Apart from direct ER modulation, xenobiotics can also directly or indirectly disrupt ER signaling by altering the synthesis, transport, distribution, and breakdown of endogenous estrogens or by altering transcription, translation, modification, and degradation of the receptor, as well as proteins upstream and downstream of the signaling pathways (Shanle & Xu 2011, La Merrill *et al.* 2020). Global and tissue-specific knockouts of ERs alter reproductive health (Curtis Hewitt *et al.* 2000, Lee *et al.* 2012). ERα-knockout male and female mice are infertile with immature reproductive organs and mammary glands, disrupted ovulation and sperm maturation, elevated levels of sex steroids, and altered sexual behavior, whereas ERβ knockouts develop normal reproductive organs and sexual behaviors but have some impairments of fertility and ovulation (Couse *et al.* 2000, Lee *et al.* 2012). Similar adverse reproductive effects are seen following exposure to ER antagonists (Branham *et al.* 1996, Buelke-Sam *et al.* 1998, Cho *et al.* 2003, Ali *et al.* 2018) and environmental estrogens (Toppari *et al.* 1996, Paterni *et al.* 2017, Wang *et al.* 2021*b*, Wojnarowski *et al.* 2021).

Many chemicals used in UOG operations are reportedly capable of disrupting ER signaling (Colborn *et al.* 2011, Gordalla *et al.* 2013, Webb *et al.* 2014, Elliott *et al.* 2017, Bolden *et al.* 2018). Surface water (SW) and groundwater (GW) samples collected from UOG regions across the US demonstrated pro- and anti-estrogenic activities, including: North Dakota (Cozzarelli *et al.* 2017, Farag *et al.* 2022); West Virginia (Kassotis *et al.* 2016*b*); Colorado (Kassotis *et al.* 2014, Kassotis *et al.* 2020); Pennsylvania (Bamberger *et al.* 2019); and Wyoming (Kassotis *et al.* 2018*c*), supporting ER disruption by UOG-associated chemicals. In animals, extracts of flowback and produced water (FPW) acted to both activate and inhibit ER activity (He *et al.* 2018b). Additionally, FPW extracts disrupted the gene expression of enzymes responsible for the synthesis of ER activating hormones, ER target genes, and ER itself, in exposed aquatic organisms (He *et al.* 2017, He *et al.* 2018*a*), though this did not always correlate with decreased average brood size and time to brood (Blewett *et al.* 2017). More targeted research demonstrated that an equimolar mixture of 23 diverse HF chemicals displayed putative synergistic anti-estrogenic bioactivity relative to individual component chemical responses (Kassotis *et al.* 2014,Kassotis *et al.* 2016*a*). In animals, prenatal exposure to the 23-mix of HF chemicals (discussed above) at environmentally relevant concentrations resulted in a slew of developmental and reproductive health effects in mice across examined concentrations (Kassotis *et al.* 2016*a*). Male offspring exhibited dose-dependent increases in pubertal testis weight, with concomitant decreased sperm counts and increased serum testosterone (Kassotis *et al.* 2015). Female offspring displayed dose-dependent increases in body weights, modulated pituitary hormone levels, decreased uterine weights, disrupted ovary weights, and disrupted both folliculogenesis and mammary gland development in early adulthood (Kassotis *et al.* 2016*a*, Sapouckey *et al.* 2018). Importantly, these studies did not specifically link these reproductive health outcomes to disruption of ER signaling. UOG-associated chemicals can thus produce complex effects on estrogen signaling and physiology, requiring further studies.

Androgen receptor (AR)

Androgens (testosterone and dihydrotestosterone (DHT)) are male steroidal sex hormones primarily involved in the development and maturation of the male reproductive system as well as the maintenance of secondary sexual characteristics (MacLean *et al.* 1993). Under physiological conditions, both testosterone and DHT are endogenous AR ligands that mediate their actions through the genomic binding of AR (Chang *et al.* 1995). Upon ligand binding, AR undergoes conformational change, nuclear localization, occurs before homodimerization, and binding to androgen response elements (Bevan & Parker 1999, Eder *et al.* 2001). Non-canonical AR signaling can occur through the activation of secondary messenger pathways (Kousteni *et al.* 2001, Estrada *et al.* 2003, Gill *et al.* 2004, Kang *et al.* 2004). AR is widely expressed throughout male reproductive organs (Cooke *et al.* 1991) and plays a role in follicular development (Hillier & Tetsuka 1997, Sen & Hammes 2010). Disruption or dysregulation of AR signaling would therefore be expected to adversely affect both male and female reproductive development. Global knockout of AR alters reproductive health (Yeh *et al.* 2002). AR-knockout male mice have smaller testes and reduced serum testosterone concentrations, with arrested spermatogenesis. AR-knockout female mice have reduced pup counts per litter, supporting negative effects on fertility in each sex (Yeh *et al.* 2002). Similar adverse reproductive effects are seen following exposure to AR antagonists (Gray *et al.* 2006, Wilson *et al.* 2008) and environmental androgens (Gray *et al.* 2006).

Studies have shown that environmental exposures to AR-disrupting UOG chemicals are associated with adverse male developmental and reproductive health outcomes (Webb *et al.* 2014, Balise *et al.* 2016, Bolden *et al.* 2018). SW and air samples near UOG sites have increased levels of AR-disrupting chemicals (Kassotis *et al.* 2016*b*, Bolden *et al.* 2018), most typically producing anti-androgenic effects. *In silico* molecular docking analysis identified five UOG chemicals predicted to directly interact with AR (Tachachartvanich *et al.* 2020). Mechanistic studies have provided evidence that UOG chemicals inhibit AR via a noncompetitive antagonistic mechanism (Tachachartvanich *et al.* 2020). Other research identified 23 of 24 common HF chemicals as anti-androgens, with the mixture of these chemicals acting in an additive manner *in vitro* (Kassotis *et al.* 2015). Murine models gestationally exposed to the 23-mix of HF chemicals at environmentally relevant

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

concentrations exhibited decreased sperm count and reduced serum testosterone (Kassotis *et al.* 2015). A control AR antagonist, flutamide, was included in these experiments and exhibited increased testes weights and a high degree of nipple retention (Kassotis *et al.* 2015). While the 23-mix effects were not shown to operate specifically through AR signaling, the concordance of some effects with those of flutamide provides some evidence for potential AR-mediated effects. Further studies are needed to elucidate adverse developmental and reproductive health outcomes via UOG chemical-mediated AR disruption.

Progesterone receptor

The interaction of intracellular progesterone receptor (PR) isoforms PR-A and PR-B with endogenous progestins is crucial to the establishment and maintenance of pregnancy, initiation of lactation, mammary gland plasticity, and sexual initiation behavior (Conneely & Lydon 2000, Hannan *et al.* 2023). Global and tissue-specific knockouts of PRs in animal models demonstrate that disruptions of these interactions can have adverse effects on reproductive health (Conneely & Lydon 2000). PR null female mice displayed impaired ovulation, implantation, sexual behavior, lactation, and mammary gland development (Lydon *et al.* 1995). PR-A ablation produces infertile females with severely impaired ovulation and uterine morphology and function (Mulac-Jericevic *et al.* 2000), while PR-B null females instead show disrupted mammary gland morphogenesis without ovarian and uterine impairments (Mulac-Jericevic *et al.* 2003). Less is known about the role of PR signaling in male reproductive health (Lydon *et al.* 1995), though PR null male mice have reduced sexual initiation behaviors and response to testosterone (Phelps *et al.* 1998). Clinically, PR antagonists are used to terminate pregnancy (Spitz 2003) and can inhibit ovulation, induce endometrial hyperplasia, and result in irregular menstrual cycling and uterine bleeding (Nallasamy *et al.* 2013, Autry & Wadhwa 2024). Clinical administration of PR agonists is effective for female contraceptives, with the addition of synthetic progestins to androgens resulting in significantly more effective male contraceptives that suppress spermatogenesis (Wang & Swerdloff 2010, Jacobstein & Polis 2014).

The limited toxicological data available for UOG-associated chemicals have identified a small fraction that disrupt PR signaling. Fewer are also reprotoxic (Hamers *et al.* 2006, Bolden *et al.* 2018, Alofe *et al.* 2019). SW and GW samples collected from UOG regions across the US have demonstrated diverse PR bioactivities, including downstream from a UOG wastewater disposal site (Kassotis *et al.* 2016*b*), and from high UOG production regions (Kassotis *et al.* 2018*c*, Bamberger *et al.* 2019). While these studies cannot entirely rule out confounding effects from other sources contributing to these bioactivities, improvements in geochemical fingerprinting and UOG well density/proximity correlation analysis have been able to more strongly associate PR bioactivities with UOG activity (Kassotis *et al.* 2020). Specifically, 'supra-maximal' levels of PR agonism were observed in SW on or directly next to UOG well pads, and moderate PR agonism from SW and GW in areas of medium and high UOG activity in Colorado (Kassotis *et al.* 2020). Proximity to UOG wells was more direct in these samples, with geochemistry linking some of these samples specifically to UOG contamination. More directed testing reported that 12 of 24 tested HF chemicals significantly antagonized PR and 1 acted as a weak agonist. An equimolar mixture of 23 of these HF chemicals displayed additive PR antagonism relative to the individual compounds (Kassotis *et al.* 2016*a*). *In vivo,* mice prenatally exposed to this mixture of 23 HF contaminants experienced decreased uterine weight as well as disrupted folliculogenesis and mammary gland morphogenesis (Kassotis *et al.* 2015, Kassotis *et al.* 2016*a*, Sapouckey *et al.* 2018). Importantly, however, this mixture contains EDCs able to disrupt multiple pathways, so linking these effects to PR or other pathways specifically requires further research.

Thyroid receptor

Thyroid hormones (TH) are steroid-like hormones crucial to vertebrate development and metabolism. Circulating TH predominantly exists as low-activity thyroxine (T_4) until local metabolism to bioactive triiodothyronine (T_3) at target tissues (Bianco *et al.* 2019). Canonical TH signaling occurs through intracellular thyroid receptors (TRs), isoforms α and β (Bianco *et al.* 2019). Unliganded TRs actively repress target genes through interactions with transcriptional co-repressor complexes; only ligand binding facilitates transcriptional activation (Astapova & Hollenberg 2013, Shi 2021). Putative roles for TH signaling in the female reproductive tract have been reviewed elsewhere (Carosa *et al.* 2018). TH signaling through TRs is critical for pregnancy and prenatal development. Maternally, both TR isoforms are expressed in human oocytes and endometrium and are involved in oocyte maturation and uterine physiology (Zhang *et al.* 1997, Aghajanova *et al.* 2011). Clinical studies indicate that maternal thyroid deficiencies during pregnancy alter children's brains and behavior, corroborating pregnancy as a critical window for TH activity, and later-life outcomes, in human neurology (Koopman-Esseboom *et al.* 1994, Haddow *et al.* 1999, Gilbert *et al.* 2012, Medici *et al.* 2013). Prenatally, TH signaling through TRs significantly regulates neurogenesis (Bernal 2007, Barez-Lopez *et al.* 2018, O'Shaughnessy & Gilbert 2020), with isoforms playing distinct, stage-specific roles in neurodevelopment (Bernal & Pekonen 1984, Forrest *et al.* 1991, Wallis *et al.* 2010).

Studies on UOG and TH signaling have focused on interactions between HF chemicals/wastewater and *in vitro* TR bioactivity. Among 24 common HF chemicals

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

tested specifically for effects on TRβ signaling, seven acted as antagonists and two as weak agonists, while an equimolar mix of 23 of these HF contaminants exhibited apparent synergistic effects on TRβ antagonism (Kassotis *et al.* 2015). SW collected downstream of a UOG disposal site antagonized TRβ signaling (Kassotis *et al.* 2016*b*), GW samples from UOG and COG regions minimally, but significantly, activated TRβ, though a UOG wastewater sample from the same area significantly inhibited TRβ (Kassotis *et al.* 2018*b*). While no direct reproductive toxicity related to TR signaling has been reported *in vivo*, a set of directed studies evaluated a causal role for TR antagonism in a mixture of 23 HF chemicals (Robert *et al.* 2018); further research honed this group of chemicals to just the described TR antagonists, demonstrating robust TR-directed effects on amphibian thymocyte differentiation and metamorphosis (Robert *et al.* 2019, McGuire *et al.* 2021, McGuire & Robert 2022).

PPAR disruption, other MDC effects

Peroxisome proliferator-activated receptors (PPAR) are members of the nuclear receptor superfamily involved in metabolite sensing, with gamma, alpha, and beta/delta isoforms expressed broadly throughout the body (Berger & Moller 2002, Boitier *et al.* 2003). Upon ligand binding, PPARs undergo a conformational change allowing for nuclear translocation, heterodimerization with RXRs, and transcriptional responses at target genes (Willson *et al.* 2000, Rogue *et al.* 2010, Rogue *et al.* 2011), primarily regulating glucose and lipid homeostasis (Feige *et al.* 2006, Heikkinen *et al.* 2007). The ligand-binding pocket of PPARs is highly promiscuous relative to other discussed receptors, resulting in diverse ligands both endogenous (e.g. fatty acids and eicosanoid metabolites) and exogenous (e.g. thiazolidinediones, bisphenols, phthalates) (Krey *et al.* 1997, Plutzky 2000, Neschen *et al.* 2007). Natural PPAR ligands show clinical relevance in the treatment of cardiovascular and metabolic diseases (Wu *et al.* 2021), such as type 2 diabetes (thiazolidinediones, PPARγ) and dyslipidemia (fibrates, PPARα) (Nakamura *et al.* 2000, Fruchart *et al.* 2001, Taniguchi *et al.* 2001, Grossman 2003). While the expression of PPARγ is considerably over-expressed in adipose tissue, PPARs are expressed throughout the female reproductive system as well (Vitti *et al.* 2016). A growing number of studies demonstrate potential roles in ovarian function, gestation, and placental communication, with related inhibitory effects on reproductive health and fertility through adverse cardiometabolic outcomes (Vitti *et al.* 2016). Specifically, PPARγ is suggested to have a key role in granulosa cell/oocyte communication, with thiazolidinedione treatment increasing oocyte competence (Minge *et al.* 2008) and decreasing androgenic precursor production in thecal cells (Veldhuis *et al.* 2002). PPARγ also has purported key roles in follicle rupture, implantation, and placental nutrient flow (Fournier *et al.* 2007, Kowalewski *et al.* 2011, Matsuda *et al.* 2013). PPARα is primarily expressed in theca and stroma, positively regulating 17β-hydroxysteroid dehydrogenase and directly influencing the conversion of estradiol to estrone (Lovekamp-Swan *et al.* 2003). Therapeutic PPARα targeting increases oocyte quality in poor responders and aged women (Artini *et al.* 2012), with important roles in follicle development and steroidogenesis (Gatta *et al.* 2013). Despite relatively ubiquitous expression, the role of PPARβ/δ is poorly defined in reproductive tissues.

Limited research has directly evaluated PPAR-disrupting UOG chemicals, and none have assessed links between UOG chemical-mediated PPAR disruption and reproductive outcomes. One study evaluated the PPARγ activity of a mixture of 23 UOG chemicals and several SW samples collected from UOG drilling dense regions (Kassotis *et al.* 2018*a*). This study reported efficacious pro-adipogenic activity by both lab-created and environmental mixtures, with some pro-adipogenic environmental mixtures also exhibiting PPARγ agonism, suggesting a potential causal mechanism (Kassotis *et al.* 2018*a*). Related research also identified a potential role for polyethoxylated alcohols, which are high-use UOG contaminants, in UOG mixture-mediated adipogenesis (Kassotis *et al.* 2018*a*). However, while extremely efficacious in promoting *in vitro* adipogenic activity, neither polyethoxylated alkylphenols nor alcohols interacted with PPARγ, similar to what was seen for the 23 chemical HF mixture (Thurman *et al.* 2014, Getzinger *et al.* 2015, Lester *et al.* 2015, Kassotis *et al.* 2018*b*). *In vivo*, gestational exposure to the same 23 chemical HF mixture increased both male and female mouse body weight (Kassotis *et al.* 2015, Kassotis *et al.* 2016*b*). Both low (Jornayvaz *et al.* 2016) and high birth weight (Hirschler *et al.* 2008) are associated with increased obesity risks later in life, which can contribute to severe adverse health outcomes (e.g. diabetes, cardiovascular disease, hypertension). These data suggest that UOG chemicals have the potential to disrupt metabolic health, which is intimately connected with reproductive health, but the role of PPAR disruption in observed reproductive toxicity has yet to be explored.

Aryl hydrocarbon receptor (AhR)

AhR is a non-NR ligand-activated transcription factor that regulates xenobiotic metabolism, particularly for oil and gas chemicals and dioxin-like compounds (Hahn 2002, Okey 2007, Doering *et al.* 2013, Vogel *et al.* 2020). AhR is involved in diverse physiological processes (Carlson & Perdew 2002, Lin *et al.* 2022*b*). AhR functions and effects have been extensively studied across species (Nebert *et al.* 2004, Head *et al.* 2008, Shankar *et al.* 2020, Xu *et al.* 2021, Lin *et al.* 2022*b*). Related to reproductive health, AhR has roles in ovarian function, the establishment of an optimal environment for fertilization, maintaining pregnancy, and regulation of lifespan and fertility, as well as the ability to affect AR and ER signaling by mediating receptor proteasomal

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

degradation (Hernandez-Ochoa *et al.* 2009, Shaya *et al.* 2019). A growing body of evidence demonstrates that UOG-associated AhR ligands, mainly PAHs and their simple mixtures, can affect AhR signaling and related pathways involved in reproduction, sex-specific receptors, and development of reproductive organs (Pocar *et al.* 2005, Karman *et al.* 2011). AhR can crosstalk with other reproductive pathways in vertebrates (Ohtake *et al.* 2007, Ohtake *et al.* 2009, Shimba & Watabe 2009), though the precise mechanisms underlying impacts on female reproduction have not yet been elucidated (Pocar *et al.* 2005).

No studies have determined a direct relationship between UOG-mediated AhR disruption and reproductive health; however, the detoxification of UOG chemicals and AhR-ligands can produce toxic metabolites (Hawkins *et al.* 2002). These, in turn, can cause the formation of oxidative compounds that damage DNA (Cantrell *et al.* 1996). Studies have demonstrated reduced sperm count and increased apoptosis in mice injected with benzo(*a*)pyrene (Revel *et al.* 2001) and in rats exposed to PAHs by inhalation (Jeng & Yu 2008), an endpoint also observed in men exposed to inhaled hydrocarbons from coke ovens (Hsu *et al.* 2006). Research in rodents demonstrated an AhR-dependent role in these reproductive health effects (Klenov *et al.* 2021). Similar effects were noted in a study with juvenile catfish, where exposures to two AhR agonists (β-naphthoflavone and dimethylbenz(*a*)anthracene, DMBA) increased apoptosis in the ovaries. However, the direct role of AhR was not confirmed (Weber & Janz 2001). As reviewed previously (Bhattacharya & Keating 2011), exposures to DMBA can increase apoptosis, reduce ovarian volume, and decrease follicle number. Finally, a recent study demonstrated AhR-mediated disruption of ovarian steroidogenesis in mice during prepubertal development, indicating that TCDD exposure could affect ovarian function, puberty, and fertility (Devillers *et al.* 2020).

Reactive oxygen species

Reactive oxygen species (ROS) are naturally produced by the human body as a by-product of aerobic respiration. While ROS serve functional roles as signaling molecules in numerous pathways, elevated concentrations of ROS can result in lipid, protein, and DNA damage (Agarwal *et al.* 2005, Kiruthiga *et al.* 2007). In healthy individuals, ROS levels are therefore balanced by the activity of antioxidant enzymes (Sies *et al.* 2022). Elevated ROS is inherent in pregnancy because of normal high placental mitochondrial activity (Pereira & Martel 2014). ROS modify key transcription factors and gene expression patterns, affect embryo growth, and can influence birth outcomes (Dennery 2004). ROS increases are typically matched with antioxidant increases, but abnormally elevated oxidative stress has been shown to reduce antioxidant activity through the consumption of antioxidants, activation of other pathways, including NF-κB or TP53, and the downregulation of the Nrf2 antioxidant pathway (Xiao *et al.* 2003, Myatt & Cui 2004, Faraonio *et al.* 2006, Liu *et al.* 2008). Abnormally elevated oxidative stress has also been linked to several negative pregnancy pathologies and outcomes including preeclampsia, gestational diabetes mellitus, intrauterine growth restriction, recurrent pregnancy loss, spontaneous abortion, reduced birth weight, congenital malformations, and impaired embryo neurodevelopment (Wall *et al.* 2002, Hempstock *et al.* 2003, Takagi *et al.* 2004, Burton *et al.* 2009, Burton *et al.* 2010, Poston *et al.* 2011, Tobola-Wrobel *et al.* 2020). Additionally, elevated oxidative stress has been linked to accelerated oocyte aging and, in males, can result in reduced sperm motility and a lower likelihood of blastocyst formation (Agarwal & Saleh 2002, Virro *et al.* 2004, Wang *et al.* 2021*a*).

Exposure to pollutants, including some linked to UOG and COG, has been shown to increase ROS production and produce a state of oxidative stress (Kiruthiga *et al.* 2007), though limited direct testing has been performed. Increased environmental concentrations of VOCs, PAHs, and trace elements have previously been found to be associated with UOG well proximity in humans (Bolden *et al.* 2018, Caron-Beaudoin *et al.* 2019). Separate studies have found associations between elevated exposure to these compounds and elevated ROS concentrations (Kim *et al.* 2011, Yang *et al.* 2015, Wang *et al.* 2017, Kim *et al.* 2019, Cao *et al.* 2020, Zhang *et al.* 2022, Yan *et al.* 2023). Specifically, urinary concentrations of metals associated with UOG operations were associated with increased oxidative stress markers (Kim *et al.* 2011, Zhang *et al.* 2022). Urinary concentrations of PAHs, BTEX, and other VOCs associated with UOG operations have also been associated with increased oxidative stress biomarkers, DNA damage, and increased gene expression of oxidative stress markers (Kim *et al.* 2011, Yang *et al.* 2015, Wang *et al.* 2017, Kim *et al.* 2019, Cao *et al.* 2020, Zhang *et al.* 2022, Yan *et al.* 2023). Additional research directly investigating changes in oxidative stress in response to UOG proximity will be needed to completely understand the potential reproductive health effects.

Data gaps and recommendations for future research on UOG operations

Environmental exposure to complex mixtures of UOG-associated chemicals clearly can impact endocrine signaling, revealing potential mechanisms through which UOG activity could adversely affect reproductive health. *A priori* determinations of UOG chemicals and/or byproducts' potential roles in reproductive toxicity are difficult to determine through the described assessments on key

Reproduction (2024) **168** e240134
https://doi.org/10.1530/REP-24-0134

reproductive signaling pathways. Reasons include: the unique chemical compositions for each UOG sample (company- and geology-specific changes to the injected mixture); contributions of each regions' unique geochemistry (e.g. inorganic components in a target production region); limited testing for specific receptor bioactivities among UOG chemicals (e.g. PPARγ) and more comprehensively around UOG production sites (e.g. TR, PPARγ, AhR, etc.); limited causal evaluations (receptor bioactivity 'recovery' experiments to assess the specificity of the observed bioactivities); and lack of strong data on extraction efficiencies for UOG compounds in many studies (making it difficult to determine whether the extraction methods utilized resulted in the loss of potentially bioactive compounds) (Kassotis *et al.* 2016*c*). Greater sampling from more UOG sites for endocrine effects is therefore necessary. Additionally, nuclear receptors can be selective in their responses to potential ligands, underscoring the importance of assessing UOG bioactivities on multiple receptor isoforms (Schriks *et al.* 2007), in various tissues (Walker *et al.* 1999, Diel 2002, Shang & Brown 2002, Smith and O'Malley 2004, Giera *et al.* 2011), and across species (Walker *et al.* 1999, Matthews *et al.* 2000, Roberts *et al.* 2011, Bearr *et al.* 2012).

Although direct receptor interaction by single chemicals is somewhat limited, there is even less available information on potential mixture effects, such as those seen from UOG wastewater samples, where dramatically altered (e.g. supra-maximal) bioactivity has been observed (and in some cases, specifically linked to UOG operations) (Paul-Friedman *et al.* 2019, Bérubé *et al.* 2023, Kassotis & Phillips 2023). Therefore, the observed bioactivities in some of these environmental samples may represent only a fraction of their potential. This emphasizes the importance of evaluating complex mixtures associated with UOG activity since the bioactivities of individual UOG-associated chemicals may be insufficient to predict the magnitude of receptor disruption and the potential adverse reproductive effects these complex mixtures may induce in human exposure scenarios. Additionally, while higher concentrations typically have higher bioactivity (and higher overall toxicity), sometimes more concentrated samples may have altogether opposite bioactivities (Kassotis *et al.* 2018*c*). For FPW samples, as well as SW and GW samples, it can also be difficult to separate the confounding effects of salinity and additional sources of environmental pollution from respective sample bioactivities (Kassotis *et al.* 2014, Kassotis *et al.* 2016*b*, He *et al.* 2017, He *et al.* 2018*b*, Kassotis *et al.* 2018*c*, , Bamberger *et al.* 2019). Inclusion of salinity controls (Blewett *et al.* 2017, He *et al.* 2018*a*), as well as improved methods of geochemical fingerprinting and UOG well density/proximity correlation analysis (Cozzarelli *et al.* 2017, Kassotis *et al.* 2020, Farag *et al.* 2022), has been able to better associate receptor bioactivities with UOG activity and spills. Lastly, the FPW, SW, and GW samples evaluated in these studies have undergone diverse extraction methods that could result in the loss of potential bioactive compounds that would be present in an actual exposure scenario. This hypothesized loss is supported by the finding that in the fraction of studies that attempt to quantify target UOG compounds in their samples (Kassotis *et al.* 2014, Cozzarelli *et al.* 2017, He *et al.* 2017, He *et al.* 2018*a*,*b*, Kassotis *et al.* 2018*c*, Bamberger *et al.* 2019, Kassotis *et al.* 2020), those that estimate target compound extraction efficiency showed poor rates of recovery (Kassotis *et al.* 2014, He *et al.* 2018*b*). Therefore, these findings potentially underestimate the ability of environmentally relevant UOG mixtures to disrupt receptor signaling.

There is also diverse evidence for other potential adverse health impacts from UOG operations. Given the epidemiological evidence suggesting adverse neurodevelopmental outcomes from gestational proximity to UOG operations (Webb *et al.* 2018), understanding the role thyroid disruption might play in these pathologies is paramount, as well as expanding the epidemiological (and animal model) research in this area. There is also an interesting base of *in vitro* and lab animal research demonstrating metabolic health impacts of UOG chemicals and mixtures (Kassotis *et al.* 2015, Kassotis *et al.* 2016*a*, 2018*a*,*b*, Kassotis *et al.* 2022, LeFauve *et al.* 2023). While there is a growing body of literature reporting impacted birth weights in relation to UOG, metabolic health more broadly has not yet been assessed in these populations.

As discussed above, exposure to UOG chemicals has been poorly characterized thus far. These chemicals can be released during each stage of development and production (Bolden *et al.* 2018) and can lead to human/animal exposures through inhalation, ingestion, and dermal absorption exposure routes (Bolden *et al.* 2018, Boogaard 2022, Zhan *et al.* 2023). These may include highly mobile chemicals being released into the air; groundwater and surface water contamination via spills, drilling, or contamination via underground injection for disposal and/or hydraulic fracturing; and/or highly persistent chemicals that may accumulate in the environment near UOG operations. Persistent UOG compounds can then bioaccumulate and result in human exposure (Manzetti 2013). As such, animals and humans can be exposed to UOG chemicals from multiple sources. Unfortunately, due to the high complexity of UOG-associated chemicals, there is insufficient data available on bioaccumulation for most of the associated chemicals; the vast majority of these have not been evaluated for persistence, transport, and bioaccumulation near UOG operations. Additionally, despite numerous publications reporting environmental presence of diverse UOG chemicals, there are limited data evaluating human exposure to these chemicals (Caron-Beaudoin *et al.* 2018, 2019, 2022, Claustre *et al.* 2023, Gasparyan *et al.* 2024). These studies have been largely exploratory and limited in scope with

small sample sizes, limiting the ability to draw firm conclusions about risk assessment in populations near UOG operations.

There are inconsistencies among the research evidence because of limitations inherent to epidemiological studies (Liccione 1999). A few reasons why findings in epidemiological studies are at times inconsistent include the exposure metrics used, the population studied, and the presence of confounders (Liccione 1999). For instance, Whitworth *et al.* (2017) and Casey *et al.* (2016) reported no association between the proximity of UOG activity and birth weight, while Hill (2018) reported a positive association. First, different exposure metrics are used by all three studies to describe exposure from nearby UOG developments. Secondly, the populations studied are different, not only in sample size but also in socioeconomic characteristics such as race, income, and education. Typically, very large sample sizes are required to detect slight incidences of adverse health effects (Liccione 1999). The characteristics of the study population in a region may also not be representative of another region (US EPA 2019, Health Canada 2021). Finally, confounders can influence the association between exposure and the health outcome (Cohrssen *et al.* 1987). Covariates such as race, family income, and maternal smoking are examples of well-documented confounders not exclusively measured among epidemiological studies. Confounders are significant when interpreting epidemiological data because, if present they may bias observed associations between exposure and health outcome (Cohrssen *et al.* 1987).

Altogether, we report moderate evidence for the role of UOG operations, utilizing HF, in disrupting nearby human and animal reproductive health. Further research is urgently needed to directly assess reproductive health parameters in these populations more broadly. Despite a lack of broad epidemiological evidence, growing evidence agrees that nearby exposure to UOG development is associated with adverse birth outcomes in humans. While human exposure data are currently limited, animal studies support the role of UOG operations in reproduction, fertility, birth effects, and other reproductive toxicity. *In vitro* data support potential widespread effects on key hormone receptors and signaling pathways central to reproductive health that require further elucidation *in vivo*. Specifically, we call for more research evaluating effects on fertility, time to pregnancy, semen quality, oocyte quality, and other discrete reproductive health parameters, as fertility has been poorly characterized relating to UOG development. Lastly, epidemiological studies will remain limited until more comprehensive exposure assessments are performed in UOG production regions. Existing research has focused on small subsets of chemicals associated with UOG production, instead of the 1500+ known to be used in HF and other phases of UOG development. Considerable research is needed to better evaluate chemical exposures associated with UOG/HF chemical mixture exposures and thus their toxicity.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/REP-24-0134.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

Funding

This work was supported by R00 ES030405 from the National Institute of Environmental Health Sciences (NIEHS) and start-up funds provided by Wayne State University to CDK, as well as by a Catalyst grant from the University of Toronto Data Science Institute and a Discovery Grant from the Natural Sciences and Engineering Research Council of Canada (RGPIN-2023-05253) to ECB.

Author contribution statement

KRS, CDK, and ECB conceived the review outline and organized contributions. All authors contributed to the writing of the text and contributed to the editing of the draft of this manuscript.

References

Agarwal A & Saleh RA 2002 Role of oxidants in male infertility: rationale, significance, and treatment. *Urologic Clinics of North America* **29** 817–827. (https://doi.org/10.1016/s0094-0143(02)00081-2)

Agarwal A, Gupta S & Sharma RK 2005 Role of oxidative stress in female reproduction. *Reproductive Biology and Endocrinology: RB&E* **3** 28. (https://doi.org/10.1186/1477-7827-3-28)

Aghajanova L, Stavreus-Evers A, Lindeberg M, Landgren BM, Sparre LS & Hovatta O 2011 Thyroid-stimulating hormone receptor and thyroid hormone receptors are involved in human endometrial physiology. *Fertility and Sterility* **95** 230–237. (https://doi.org/10.1016/j.fertnstert.2010.06.079)

Ahmed U & Meehan DN 2016 *Unconventional Oil and Gas Resources*. Boca Raton, USA: CRC Press. (https://doi.org/10.1201/b20059)

Aker AM, Friesen M, Ronald LA, Doyle-Waters MM, Takaro TK, Thickson W, Levin K, Meyer U, Caron-Beaudoin E & McGregor MJ 2024 The human health effects of unconventional oil and gas development (UOGD): a scoping review of epidemiologic studies. *Canadian Journal of Public Health* **115** 446–467. (https://doi.org/10.17269/s41997-024-00860-2)

Ali JM, Palandri MT, Kallenbach AT, Chavez E, Ramirez J, Onanong S, Snow DD & Kolok AS 2018 Estrogenic effects following larval exposure to the putative anti-estrogen, fulvestrant, in the fathead minnow (Pimephales promelas). *Comparative Biochemistry and Physiology. Toxicology and Pharmacology* **204** 26–35. (https://doi.org/10.1016/j.cbpc.2017.10.013)

Alofe O, Kisanga E, Inayat-Hussain SH, Fukumura M, Garcia-Milian R, Perera L, Vasiliou V & Whirledge S 2019 Determining the endocrine disruption potential of industrial chemicals using an integrative approach: public databases, in vitro exposure, and modeling receptor interactions. *Environment International* **131** 104969. (https://doi.org/10.1016/j.envint.2019.104969)

Amundson KK, Borton MA, Daly RA, Hoyt DW, Wong A, Eder E, Moore J, Wunch K, Wrighton KC & Wilkins MJ 2022 Microbial colonization and persistence in deep fractured shales is guided by metabolic exchanges and viral predation. *Microbiome* **10** 5. (https://doi.org/10.1186/s40168-021-01194-8)

Apergis N, Hayat T & Saeed T 2019 Fracking and infant mortality: fresh evidence from Oklahoma. *Environmental Science and Pollution Research International* **26** 32360–32367. (https://doi.org/10.1007/s11356-019-06478-z)

Arnold SM, Angerer J, Boogaard PJ, Hughes MF, O'Lone RB, Robison SH & Schnatter AR 2013 The use of biomonitoring data in exposure and human health risk assessment: benzene case study. *Critical Reviews in Toxicology* **43** 119–153. (https://doi.org/10.3109/10408444.2012.756455)

Artini PG, Simi G, Ruggiero M, Pinelli S, Di Berardino OM, Papini F, Papini S, Monteleone P & Cela V 2012 DHEA supplementation improves follicular microenviroment in poor responder patients. *Gynecological Endocrinology* **28** 669–673. (https://doi.org/10.3109/09513590.2012.705386)

Astapova I & Hollenberg AN 2013 The in vivo role of nuclear receptor corepressors in thyroid hormone action. *Biochimica et Biophysica Acta* **1830** 3876–3881. (https://doi.org/10.1016/j.bbagen.2012.07.001)

Autry BM & Wadhwa R 2024 *Mifepristone*. Treasure Island (FL): StatPearls Publishing.

Balabanic D, Rupnik M & Klemencic AK 2011 Negative impact of endocrine-disrupting compounds on human reproductive health. *Reproduction, Fertility, and Development* **23** 403–416. (https://doi.org/10.1071/RD09300)

Balise VD, Meng CX, Cornelius-Green JN, Kassotis CD, Kennedy R & Nagel SC 2016 Systematic review of the association between oil and natural gas extraction processes and human reproduction. *Fertility and Sterility* **106** 795–819. (https://doi.org/10.1016/j.fertnstert.2016.07.1099)

Bamber AM, Hasanali SH, Nair AS, Watkins SM, Vigil DI, Van Dyke M, McMullin TS & Richardson K 2019 A systematic review of the epidemiologic literature assessing health outcomes in populations living near Oil and Natural Gas operations: study quality and future recommendations. *International Journal of Environmental Research and Public Health* **16** 2123. (https://doi.org/10.3390/ijerph16122123)

Bamberger M & Oswald RE 2012 Impacts of gas drilling on human and animal health. *New Solutions* **22** 51–77. (https://doi.org/10.2190/NS.22.1.e)

Bamberger M & Oswald RE 2015 Long-term impacts of unconventional drilling operations on human and animal health. *Journal of Environmental Science and Health. Part A, Toxic/Hazardous Substances and Environmental Engineering* **50** 447–459. (https://doi.org/10.1080/10934529.2015.992655)

Bamberger M, Nell M, Ahmed AH, Santoro R, Ingraffea AR, Kennedy RF, Nagel SC, Helbling DE & Oswald RE 2019 Surface water and groundwater analysis using aryl hydrocarbon and endocrine receptor biological assays and liquid chromatography-high resolution mass spectrometry in Susquehanna County, PA. *Environmental Science. Processes and Impacts* **21** 988–998. (https://doi.org/10.1039/c9em00112c)

Barez-Lopez S, Obregon MJ, Bernal J & Guadano-Ferraz A 2018 Thyroid hormone economy in the perinatal mouse brain: implications for cerebral cortex development. *Cerebral Cortex* **28** 1783–1793. (https://doi.org/10.1093/cercor/bhx088)

Barnett AG 2011 Time-dependent exposures and the fixed-cohort bias. *Environmental Health Perspectives* **119** A422–423. (https://doi.org/10.1289/ehp.1103885)

Barron MG, Vivian DN, Heintz RA & Yim UH 2020 Long-term ecological impacts from oil spills: comparison of Exxon Valdez, Hebei spirit, and deepwater horizon. *Environmental Science and Technology* **54** 6456–6467. (https://doi.org/10.1021/acs.est.9b05020)

Bearr JS, Mitchelmore CL, Roberts SC & Stapleton HM 2012 Species specific differences in the in vitro metabolism of the flame retardant mixture, firemaster(R) BZ-54. *Aquatic Toxicology* **124–125** 41–47. (https://doi.org/10.1016/j.aquatox.2012.06.006)

Berger J & Moller DE 2002 The mechanisms of action of PPARs. *Annual Review of Medicine* **53** 409–435. (https://doi.org/10.1146/annurev.med.53.082901.104018)

Bernal J 2007 Thyroid hormone receptors in brain development and function. *Nature Clinical Practice. Endocrinology and Metabolism* **3** 249–259. (https://doi.org/10.1038/ncpendmet0424)

Bernal J & Pekonen F 1984 Ontogenesis of the nuclear 3,5,3'-triiodothyronine receptor in the human fetal brain. *Endocrinology* **114** 677–679. (https://doi.org/10.1210/endo-114-2-677)

Bérubé R, LeFauve MK, Heldman S, Chiang Y-TT, Birbeck J, Westrick J, Hoffman K & Kassotis CD 2023 Adipogenic and endocrine disrupting mixture effects of organic and inorganic pollutant mixtures. *Science of the Total Environment* **876** 162587. (https://doi.org/10.1016/j.scitotenv.2023.162587)

Bevan C & Parker M 1999 The role of co-activators in steroid hormone action. *Experimental Cell Research* **253** 349–356. (https://doi.org/10.1006/excr.1999.4719)

Bhattacharya P & Keating AF 2011 Ovarian metabolism of xenobiotics. *Experimental Biology and Medicine* **236** 765–771. (https://doi.org/10.1258/ebm.2011.011051)

Bianco AC, Dumitrescu A, Gereben B, Ribeiro MO, Fonseca TL, Fernandes GW & Bocco BMLC 2019 Paradigms of dynamic control of thyroid hormone signaling. *Endocrine Reviews* **40** 1000–1047. (https://doi.org/10.1210/er.2018-00275)

Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, Borghi E, Hayashi C, Estevez D, Cegolon L, *et al.* 2019 National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet. Global Health* **7** e849–e860. (https://doi.org/10.1016/S2214-109X(18)30565-5)

Blewett TA, Delompré PLM, He Y, Folkerts EJ, Flynn SL, Alessi DS & Goss GG 2017 Sublethal and reproductive effects of acute and chronic exposure to flowback and produced water from hydraulic fracturing on the water flea Daphnia magna. *Environmental Science and Technology* **51** 3032–3039. (https://doi.org/10.1021/acs.est.6b05179)

Boitier E, Gautier JC & Roberts R 2003 Advances in understanding the regulation of apoptosis and mitosis by peroxisome-proliferator activated receptors in pre-clinical models: relevance for human health and disease. *Comparative Hepatology* **2** 3. (https://doi.org/10.1186/1476-5926-2-3)

Bolden AL, Schultz K, Pelch KE & Kwiatkowski CF 2018 Exploring the endocrine activity of air pollutants associated with unconventional oil and gas extraction. *Environmental Health: A Global Access Science Source* **17** 26. (https://doi.org/10.1186/s12940-018-0368-z)

Boogaard PJ 2022 Human biomonitoring of low-level benzene exposures. *Critical Reviews in Toxicology* **52** 799–810. (https://doi.org/10.1080/10408444.2023.2175642)

Boule LA, Chapman TJ, Hillman SE, Kassotis CD, O'Dell C, Robert J, Georas SN, Nagel SC & Lawrence BP 2018 Developmental exposure to a mixture of 23 chemicals associated with unconventional oil and gas operations alters the immune system of mice. *Toxicological Sciences* **163** 639–654. (https://doi.org/10.1093/toxsci/kfy066)

Branham WS, Fishman R, Streck RD, Medlock KL, De George JJ & Sheehan DM 1996 ICI 182,780 inhibits endogenous estrogen-dependent rat uterine growth and tamoxifen-induced developmental Toxicity1. *Biology of Reproduction* **54** 160–167. (https://doi.org/10.1095/biolreprod54.1.160)

Brown D, Weinberger B, Lewis C & Bonaparte H 2014 Understanding exposure from natural gas drilling puts current air standards to the test. *Reviews on Environmental Health* **29** 277–292. (https://doi.org/10.1515/reveh-2014-0002)

Buelke-Sam J, Bryant HU & Francis PC 1998 The selective estrogen receptor modulator, raloxifene: an overview of nonclinical pharmacology and reproductive and developmental testing. *Reproductive Toxicology* **12** 217–221. (https://doi.org/10.1016/s0890-6238(98)00003-3)

Burton GJ, Yung HW, Cindrova-Davies T & Charnock-Jones DS 2009 Placental endoplasmic reticulum stress and oxidative stress in the pathophysiology of unexplained intrauterine growth restriction and early onset preeclampsia. *Placenta* **30**(Supplement A) S43–S48. (https://doi.org/10.1016/j.placenta.2008.11.003)

Burton GJ, Jauniaux E & Charnock-Jones DS 2010 The influence of the intrauterine environment on human placental development. *International Journal of Developmental Biology* **54** 303–312. (https://doi.org/10.1387/ijdb.082764gb)

Busby C & Mangano JJ 2017 There's a world going on underground – infant mortality and fracking in Pennsylvania. *Journal of Environmental Protection* **8** 381–393. (https://doi.org/10.4236/jep.2017.84028)

Cairncross ZF, Couloigner I, Ryan MC, McMorris C, Muehlenbachs L, Nikolaou N, Wong RCK, Hawkins SM, Bertazzon S, Cabaj J, *et al.* 2022 Association between residential proximity to hydraulic fracturing sites and adverse birth outcomes. *JAMA Pediatrics* **176** 585–592. (https://doi.org/10.1001/jamapediatrics.2022.0306)

Cantrell SM, Lutz LH, Tillitt DE & Hannink M 1996 Embryotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD): theembryonic vasculature is a physiological target for TCDD-induced DNA damage and apoptotic cell death in medaka (Orizias Latipes). *Toxicology and Applied Pharmacology* **141** 23–34. (https://doi.org/10.1006/taap.1996.0256)

Cao L, Zhou Y, Tan A, Shi T, Zhu C, Xiao L, Zhang Z, Yang S, Mu G, Wang X, *et al.* 2020 Oxidative damage mediates the association between polycyclic aromatic hydrocarbon exposure and lung function. *Environmental Health: A Global Access Science Source* **19** 75. (https://doi.org/10.1186/s12940-020-00621-x)

Carlson DB & Perdew GH 2002 A dynamic role for the Ah receptor in cell signaling? Insights from a diverse group of Ah receptor interacting proteins. *Journal of Biochemical and Molecular Toxicology* **16** 317–325. (https://doi.org/10.1002/jbt.10051)

Caron-Beaudoin É, Valter N, Chevrier J, Ayotte P, Frohlich K & Verner MA 2018 Gestational exposure to volatile organic compounds (VOCs) in Northeastern British Columbia, Canada: a pilot study. *Environment International* **110** 131–138. (https://doi.org/10.1016/j.envint.2017.10.022)

Caron-Beaudoin É, Bouchard M, Wendling G, Barroso A, Bouchard MF, Ayotte P, Frohlich KL & Verner MA 2019 Urinary and hair concentrations of trace metals in pregnant women from Northeastern British Columbia, Canada: a pilot study. *Journal of Exposure Science and Environmental Epidemiology* **29** 613–623. (https://doi.org/10.1038/s41370-019-0144-3)

Caron-Beaudoin É, Whitworth KW, Bosson-Rieutort D, Wendling G, Liu S & Verner MA 2021 Density and proximity to hydraulic fracturing wells and birth outcomes in Northeastern British Columbia, Canada. *Journal of Exposure Science and Environmental Epidemiology* **31** 53–61. (https://doi.org/10.1038/s41370-020-0245-z)

Caron-Beaudoin É, Whyte KP, Bouchard MF, Chevrier J, Haddad S, Copes R, Frohlich KL, Dokkie D, Treaty 8 Tribal Association, Juul S, *et al.* 2022 Volatile organic compounds (VOCs) in indoor air and tap water samples in residences of pregnant women living in an area of unconventional natural gas operations: findings from the EXPERIVA study. *Science of the Total Environment* **805** 150242. (https://doi.org/10.1016/j.scitotenv.2021.150242)

Carosa E, Lenzi A & Jannini EA 2018 Thyroid hormone receptors and ligands, tissue distribution and sexual behavior. *Molecular and Cellular Endocrinology* **467** 49–59. (https://doi.org/10.1016/j.mce.2017.11.006)

Casey JA, Savitz DA, Rasmussen SG, Ogburn EL, Pollak J, Mercer DG & Schwartz BS 2016 Unconventional natural gas development and birth outcomes in Pennsylvania, USA. *Epidemiology* **27** 163–172. (https://doi.org/10.1097/EDE.0000000000000387)

Chang C, Saltzman A, Yeh S, Young W, Keller E, Lee HJ, Wang C & Mizokami A 1995 Androgen receptor: an overview. *Critical Reviews in Eukaryotic Gene Expression* **5** 97–125. (https://doi.org/10.1615/critreveukargeneexpr.v5.i2.10)

Cho HW, Nie R, Carnes K, Zhou Q, Sharief NAQ & Hess RA 2003 The antiestrogen ICI 182,780 induces early effects on the adult male mouse reproductive tract and long-term decreased fertility without testicular atrophy. *Reproductive Biology and Endocrinology: RB&E* **1** 57. (https://doi.org/10.1186/1477-7827-1-57)

Choi Y, Kim Y, Woo YC & Hwang I 2023 Water management and produced water treatment in oil sand plant: a review. *Desalination* **567** 116991. (https://doi.org/10.1016/j.desal.2023.116991)

Clark C & Veil J 2009 *Produced Water Volumes and Management Practices in the United States*. Argonne, IL, USA: Argonne National Laboratory (ANL).Available at: https://www.osti.gov/biblio/1007397

Claustre L, Bouchard M, Gasparyan L, Bosson-Rieutort D, Owens-Beek N, West Moberly First Nations Chief and Council, Caron-Beaudoin E, and Verner MA 2023 Assessing gestational exposure to trace elements in an area of unconventional oil and gas activity: comparison with reference populations and evaluation of variability. *Journal of Exposure Science and Environmental Epidemiology* **33** 94–101. (https://doi.org/10.1038/s41370-022-00508-8)

Cohrssen JJ, Draggan S & Morrison RE 1987 *Environmental Impacts on Human Health : the Agenda for Long-Term Research and Development*. New York: Praeger.

Colborn T, Kwiatkowski C, Schultz K & Bachran M 2011 Natural gas operations from a public health perspective. *Human and Ecological Risk Assessment: an International Journal* **17** 1039–1056. (https://doi.org/10.1080/10807039.2011.605662)

Conneely OM & Lydon JP 2000 Progesterone receptors in reproduction: functional impact of the A and B isoforms. *Steroids* **65** 571–577. (https://doi.org/10.1016/s0039-128x(00)00115-x)

Cooke PS, Young P & Cunha GR 1991 Androgen receptor expression in developing male reproductive organs. *Endocrinology* **128** 2867–2873. (https://doi.org/10.1210/endo-128-6-2867)

Couse JF, Hewitt SC & Korach KS 2000 Receptor null mice reveal contrasting roles for estrogen receptor alpha and beta in reproductive tissues. *Journal of Steroid Biochemistry and Molecular Biology* **74** 287–296. (https://doi.org/10.1016/s0960-0760(00)00105-9)

Cozzarelli IM, Skalak KJ, Kent DB, Engle MA, Benthem A, Mumford AC, Haase K, Farag A, Harper D, Nagel SC, *et al.* 2017 Environmental signatures and effects of an oil and gas wastewater spill in the Williston Basin, North Dakota. *Science of the Total Environment* **579** 1781–1793. (https://doi.org/10.1016/j.scitotenv.2016.11.157)

Craig ZR, Wang W & Flaws JA 2011 Endocrine-disrupting chemicals in ovarian function: effects on steroidogenesis, metabolism and nuclear receptor signaling. *Reproduction* **142** 633–646. (https://doi.org/10.1530/REP-11-0136)

Crowe E, Patton S, Thomas D & Thorpe B 2016 When the wind blows - tracking toxic chemicals in gas fields and impacted communities. *Coming Clean* June 2016. Available at: https://comingcleaninc.org/assets/media/documents/When%20the%20Wind%20Blows.pdf

Currie J, Greenstone M & Meckel K 2017 Hydraulic fracturing and infant health: new evidence from Pennsylvania. *Science Advances* **3** e1603021. (https://doi.org/10.1126/sciadv.1603021)

Curtis Hewitt S, Couse JF & Korach KS 2000 Estrogen receptor transcription and transactivation: estrogen receptor knockout mice: what their phenotypes reveal about mechanisms of estrogen action. *Breast Cancer Research* **2** 345–352. (https://doi.org/10.1186/bcr79)

Cushing LJ, Vavra-Musser K, Chau K, Franklin M & Johnston JE 2020 Flaring from unconventional oil and gas development and birth outcomes in the eagle ford shale in South Texas. *Environmental Health Perspectives* **128** 77003. (https://doi.org/10.1289/EHP6394)

Danforth C, Chiu WA, Rusyn I, Schultz K, Bolden A, Kwiatkowski C & Craft E 2020 An integrative method for identification and prioritization of constituents of concern in produced water from onshore oil and gas extraction. *Environment International* **134** 105280. (https://doi.org/10.1016/j.envint.2019.105280)

Danzo BJ 1998 The effects of environmental hormones on reproduction. *Cellular and Molecular Life Sciences* **54** 1249–1264. (https://doi.org/10.1007/s000180050251)

Darrah TH, Vengosh A, Jackson RB, Warner NR & Poreda RJ 2014 Noble gases identify the mechanisms of fugitive gas contamination in drinking-water wells overlying the Marcellus and Barnett Shales. *PNAS* **111** 14076–14081. (https://doi.org/10.1073/pnas.1322107111)

De Anna JS, Castro JM, Darraz LA, Elias FD, Carcamo JG & Luquet CM 2021 Exposure to hydrocarbons and chlorpyrifos alters the expression of nuclear receptors and antioxidant, detoxifying, and immune response proteins in the liver of the rainbow trout, Oncorhynchus mykiss. *Ecotoxicology and Environmental Safety* **208** 111394. (https://doi.org/10.1016/j.ecoenv.2020.111394)

Dennery PA 2004 Role of redox in fetal development and neonatal diseases. *Antioxidants and Redox Signaling* **6** 147–153. (https://doi.org/10.1089/152308604771978453)

Deutch J, Holditch S, Krupp F, McGinty K, Tierney S, Yergin D & Zoback M 2011 *The Secretary of the Energy Board Shale Gas Production Subcommittee Ninety-Day Report, Edn August 11, 2011*. Available at: https://www.energy.gov/sites/prod/files/90day_Report_Second_11.18.11.pdf

Devillers MM, Petit F, Giton F, François CM, Juricek L, Coumoul X, Magre S, Cohen-Tannoudji J & Guigon CJ 2020 Age-dependent vulnerability of the ovary to AhR-mediated TCDD action before puberty: evidence from mouse models. *Chemosphere* **258** 127361. (https://doi.org/10.1016/j.chemosphere.2020.127361)

Deziel NC, Brokovich E, Grotto I, Clark CJ, Barnett-Itzhaki Z, Broday D & Agay-Shay K 2020 Unconventional oil and gas development and health outcomes: a scoping review of the epidemiological research. *Environmental Research* **182** 109124. (https://doi.org/10.1016/j.envres.2020.109124)

Deziel NC, Clark CJ, Casey JA, Bell ML, Plata DL & Saiers JE 2022 Assessing exposure to unconventional oil and gas development: strengths, challenges, and implications for epidemiologic research. *Current Environmental Health Reports* **9** 436–450. (https://doi.org/10.1007/s40572-022-00358-4)

Diel P 2002 Tissue-specific estrogenic response and molecular mechanisms. *Toxicology Letters* **127** 217–224. (https://doi.org/10.1016/s0378-4274(01)00503-3)

Doering JA, Giesy JP, Wiseman S & Hecker M 2013 Predicting the sensitivity of fishes to dioxin-like compounds: possible role of the aryl hydrocarbon receptor (AhR) ligand binding domain. *Environmental Science and Pollution Research International* **20** 1219–1224. (https://doi.org/10.1007/s11356-012-1203-7)

Dolk H 2004 Epidemiologic approaches to identifying environmental causes of birth defects. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* **125C** 4–11. (https://doi.org/10.1002/ajmg.c.30000)

Dubé MG, Dunlop JM, Davidson C, Beausoleil DL, Hazewinkel RRO & Wyatt F 2022 History, overview, and governance of environmental monitoring in the oil sands region of Alberta, Canada. *Integrated Environmental Assessment and Management* **18** 319–332. (https://doi.org/10.1002/ieam.4490)

Eder IE, Culig Z, Putz T, Nessler-Menardi C, Bartsch G & Klocker H 2001 Molecular biology of the androgen receptor: from molecular understanding to the clinic. *European Urology* **40** 241–251. (https://doi.org/10.1159/000049782)

Elliott EG, Ettinger AS, Leaderer BP, Bracken MB & Deziel NC 2017 A systematic evaluation of chemicals in hydraulic-fracturing fluids and wastewater for reproductive and developmental toxicity. *Journal of Exposure Science and Environmental Epidemiology* **27** 90–99. (https://doi.org/10.1038/jes.2015.81)

Environment Canada 2013 Properties, composition and marine Spill behavior, fate and transport of two diluted bitumen products from the Canadian oil sands. In *FaOC Environment Canada* **85**. Natural Resources Canada Ed., p.85. Available at: https://publications.gc.ca/collections/collection_2014/ec/En84-96-2013-eng.pdf

Erickson CL, Barron IG & Zapata I 2022 The effects of hydraulic fracturing activities on birth outcomes are evident in a non-individualized county-wide aggregate data sample from Colorado. *Journal of Public Health Research* **11**. (https://doi.org/10.4081/jphr.2021.2551)

Estrada M, Espinosa A, Muller M & Jaimovich E 2003 Testosterone stimulates intracellular calcium release and mitogen-activated protein kinases via a G protein-coupled receptor in skeletal muscle cells. *Endocrinology* **144** 3586–3597. (https://doi.org/10.1210/en.2002-0164)

Farag AM, Harper DD, Cozzarelli IM, Kent DB, Mumford AC, Akob DM, Schaeffer T & Iwanowicz LR 2022 Using Biological Responses to Monitor Freshwater Post-Spill Conditions over 3 years in Blacktail Creek, North Dakota, USA. *Archives of Environmental Contamination and Toxicology* **83** 253–271. (https://doi.org/10.1007/s00244-022-00943-6)

Faraonio R, Vergara P, Di Marzo D, Pierantoni MG, Napolitano M, Russo T & Cimino F 2006 P53 suppresses the Nrf2-dependent transciption of antioxidant response genes. *Journal of Biological Chemistry* **281** 39776–39784. (https://doi.org/10.1074/jbc.M605707200)

Feige JN, Gelman L, Michalik L, Desvergne B & Wahli W 2006 From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions. *Progress in Lipid Research* **45** 120–159. (https://doi.org/10.1016/j.plipres.2005.12.002)

Feldkamp ML, Carey JC, Byrne JLB, Krikov S & Botto LD 2017 Etiology and clinical presentation of birth defects: population based study. *BMJ* **357** j2249. (https://doi.org/10.1136/bmj.j2249)

Fink J 2012 *Petroleum Engineer's Guide to Oil Field Chemicals and Fluids.* Oxford, UK: Gulf Professional Publishing. Available at: https://www.sciencedirect.com/book/9780123838445/petroleum-engineers-guide-to-oil-field-chemicals-and-fluids#book-description

Folkerts EJ, Blewett TA, He Y & Goss GG 2017 Cardio-respirometry disruption in zebrafish (Danio rerio) embryos exposed to hydraulic fracturing flowback and produced water. *Environmental Pollution* **231** 1477–1487. (https://doi.org/10.1016/j.envpol.2017.09.011)

Fontenot BE, Hunt LR, Hildenbrand ZL, Carlton DD Jr, Oka H, Walton JL, Hopkins D, Osorio A, Bjorndal B, Hu QH, *et al.* 2013 An evaluation of water quality in private drinking water wells near natural gas extraction sites in the Barnett Shale formation. *Environmental Science and Technology* **47** 10032–10040. (https://doi.org/10.1021/es4011724)

Forrest D, Hallbook F, Persson H & Vennstrom B 1991 Distinct functions for thyroid hormone receptors alpha and beta in brain development indicated by differential expression of receptor genes. *EMBO Journal* **10** 269–275. (https://doi.org/10.1002/j.1460-2075.1991.tb07947.x)

Fournier T, Tsatsaris V, Handschuh K & Evain-Brion D 2007 PPARs and the placenta. *Placenta* **28** 65–76. (https://doi.org/10.1016/j.placenta.2006.04.009)

Fruchart JC, Staels B & Duriez P 2001 The role of fibric acids in atherosclerosis. *Current Atherosclerosis Reports* **3** 83–92. (https://doi.org/10.1007/s11883-001-0015-x)

Fuentes N & Silveyra P 2019 Estrogen receptor signaling mechanisms. *Advances in Protein Chemistry and Structural Biology* **116** 135–170. (https://doi.org/10.1016/bs.apcsb.2019.01.001)

Gallegos TJ, Varela BA, Haines SS & Engle MA 2015 Hydraulic fracturing water use variability in the United States and potential environmental

implications. *Water Resources Research* **51** 5839–5845. (https://doi.org/10.1002/2015WR017278)

Gasparyan L, Duc J, Claustre L, Bosson-Rieutort D, Bouchard M, Bouchard MF, Owens-Beek N, West Moberly First Nations Chief And Council, Caron-Beaudoin É & Verner MA 2024 Density and proximity of oil and gas wells and concentrations of trace elements in urine, hair, nails and tap water samples from pregnant individuals living in Northeastern British Columbia. *Environment International* **184** 108398. (https://doi.org/10.1016/j.envint.2023.108398)

Gatta V, Tatone C, Ciriminna R, Vento M, Franchi S, d'Aurora M, Sperduti S, Cela V, Borzi P, Palermo R, *et al.* 2013 Gene expression profiles of cumulus cells obtained from women treated with recombinant human luteinizing hormone + recombinant human follicle-stimulating hormone or highly purified human menopausal gonadotropin versus recombinant human follicle-stimulating hormone alone. *Fertility and Sterility* **99** 2000–8.e1. (https://doi.org/10.1016/j.fertnstert.2013.01.150)

Gaughan C, Sorrentino KM, Liew Z, Johnson NP, Clark CJ, Soriano M, Jr, Plano J, Plata DL, Saiers JE & Deziel NC 2023 Residential proximity to unconventional oil and gas development and birth defects in Ohio. *Environmental Research* **229** 115937. (https://doi.org/10.1016/j.envres.2023.115937)

Getzinger GJ, O'Connor MP, Hoelzer K, Drollette BD, Karatum O, Deshusses MA, Ferguson PL, Elsner M & Plata DL 2015 Natural gas residual fluids: sources, endpoints, and organic chemical composition after centralized waste treatment in Pennsylvania. *Environmental Science and Technology* **49** 8347–8355. (https://doi.org/10.1021/acs.est.5b00471)

Giera S, Bansal R, Ortiz-Toro TM, Taub DG & Zoeller RT 2011 Individual polychlorinated biphenyl (PCB) congeners produce tissue- and gene-specific effects on thyroid hormone signaling during development. *Endocrinology* **152** 2909–2919. (https://doi.org/10.1210/en.2010-1490)

Gilbert ME, Rovet J, Chen Z & Koibuchi N 2012 Developmental thyroid hormone disruption: prevalence, environmental contaminants and neurodevelopmental consequences. *Neurotoxicology* **33** 842–852. (https://doi.org/10.1016/j.neuro.2011.11.005)

Gill A, Jamnongjit M & Hammes SR 2004 Androgens promote maturation and signaling in mouse oocytes independent of transcription: a release of inhibition model for mammalian oocyte meiosis. *Molecular Endocrinology* **18** 97–104. (https://doi.org/10.1210/me.2003-0326)

Goldenberg RL, Culhane JF, Iams JD & Romero R 2008 Epidemiology and causes of preterm birth. *Lancet* **371** 75–84. (https://doi.org/10.1016/S0140-6736(08)60074-4)

Gordalla BC, Ewers U & Frimmel FH 2013 Hydraulic fracturing: a toxicological threat for groundwater and drinking-water? *Environmental Earth Sciences* **70** 3875–3893. (https://doi.org/10.1007/s12665-013-2672-9)

Gray LE, Wilson VS, Stoker T, Lambright C, Furr J, Noriega N, Howdeshell K, Ankley GT & Guillette L 2006 Adverse effects of environmental antiandrogens and androgens on reproductive development in mammals. *International Journal of Andrology* **29** 96–105. (https://doi.org/10.1111/j.1365-2605.2005.00636.x)

Gross SA, Avens HJ, Banducci AM, Sahmel J, Panko JM & Tvermoes BE 2013 Analysis of BTEX groundwater concentrations from surface spills associated with hydraulic fracturing operations. *Journal of the Air and Waste Management Association* **63** 424–432. (https://doi.org/10.1080/10962247.2012.759166)

Grossman E 2003 Rosiglitazone reduces blood pressure and urinary albumin excretion in type 2 diabetes: G Bakris et al. *Journal of Human Hypertension* **17** 5–6. (https://doi.org/10.1038/sj.jhh.1001474)

Ha S, Hu H, Mao L, Roussos-Ross D, Roth J & Xu X 2016 Potential selection bias associated with using geocoded birth records for epidemiologic research. *Annals of Epidemiology* **26** 204–211. (https://doi.org/10.1016/j.annepidem.2016.01.002)

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, *et al.* 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *New England Journal of Medicine* **341** 549–555. (https://doi.org/10.1056/NEJM199908193410801)

Hahn ME 2002 Aryl hydrocarbon receptors: diversity and evolution. *Chemico-Biological Interactions* **141** 131–160. (https://doi.org/10.1016/s0009-2797(02)00070-4)

Hamers T, Kamstra JH, Sonneveld E, Murk AJ, Kester MHA, Andersson PL, Legler J & Brouwer A 2006 In vitro profiling of the endocrine-disrupting potency of brominated flame retardants. *Toxicological Sciences* **92** 157–173. (https://doi.org/10.1093/toxsci/kfj187)

Han J, Zhang B, Zhang X, Huang K, Fang V & Xu X 2023 Associations between occurrence of birth defects and hydraulic fracturing activities in Barnett shale region, Texas. *Heliyon* **9** e15213. (https://doi.org/10.1016/j.heliyon.2023.e15213)

Hannan FM, Elajnaf T, Vandenberg LN, Kennedy SH & Thakker RV 2023 Hormonal regulation of mammary gland development and lactation. *Nature Reviews. Endocrinology* **19** 46–61. (https://doi.org/10.1038/s41574-022-00742-y)

Harkness JS, Dwyer GS, Warner NR, Parker KM, Mitch WA & Vengosh A 2015 Iodide, bromide, and ammonium in hydraulic fracturing and oil and gas wastewaters: environmental implications. *Environmental Science and Technology* **49** 1955–1963. (https://doi.org/10.1021/es504654n)

Hawkins SA, Billiard SM, Tabash SP, Brown RS & Hodson PV 2002 Altering cytochrome P4501A activity affects polycyclic aromatic hydrocarbon metabolism and toxicity in rainbow trout (Oncorhynchus mykiss). *Environmental Toxicology and Chemistry* **21** 1845–1853. (https://doi.org/10.1002/etc.5620210912)

He Y, Folkerts EJ, Zhang Y, Martin JW, Alessi DS & Goss GG 2017 Effects on biotransformation, oxidative stress, and endocrine disruption in rainbow trout (Oncorhynchus mykiss) exposed to hydraulic fracturing flowback and produced water. *Environmental Science and Technology* **51** 940–947. (https://doi.org/10.1021/acs.est.6b04695)

He Y, Sun C, Zhang Y, Folkerts EJ, Martin JW & Goss GG 2018*a* Developmental toxicity of the organic fraction from hydraulic fracturing flowback and produced waters to early life stages of zebrafish (Danio rerio). *Environmental Science and Technology* **52** 3820–3830. (https://doi.org/10.1021/acs.est.7b06557)

He Y, Zhang Y, Martin JW, Alessi DS, Giesy JP & Goss GG 2018*b* In vitro assessment of endocrine disrupting potential of organic fractions extracted from hydraulic fracturing flowback and produced water (HF-FPW). *Environment International* **121** 824–831. (https://doi.org/10.1016/j.envint.2018.10.014)

Head JA, Hahn ME & Kennedy SW 2008 Key amino acids in the aryl hydrocarbon receptor predict dioxin sensitivity in avian species. *Environmental Science and Technology* **42** 7535–7541. (https://doi.org/10.1021/es801082a)

Health Canada 2021 *Health Impacts of Air Pollution in Canada: Estimates of Premature Deaths and Nonfata Outcomes*. 2021 Report. Ottawa, ON, USA: Health Canada. Available at: https://publications.gc.ca/site/eng/9.896126/publication.html

Heikkinen S, Auwerx J & Argmann CA 2007 PPARgamma in human and mouse physiology. *Biochimica et Biophysica Acta* **1771** 999–1013. (https://doi.org/10.1016/j.bbalip.2007.03.006)

Hempstock J, Jauniaux E, Greenwold N & Burton GJ 2003 The contribution of placental oxidative stress to early pregnancy failure. *Human Pathology* **34** 1265–1275. (https://doi.org/10.1016/j.humpath.2003.08.006)

Hernandez-Ochoa I, Karman BN & Flaws JA 2009 The role of the aryl hydrocarbon receptor in the female reproductive system. *Biochemical Pharmacology* **77** 547–559. (https://doi.org/10.1016/j.bcp.2008.09.037)

Hill EL 2018 Shale gas development and infant health: evidence from Pennsylvania. *Journal of Health Economics* **61** 134–150. (https://doi.org/10.1016/j.jhealeco.2018.07.004)

Hillier SG & Tetsuka M 1997 Role of androgens in follicle maturation and atresia. *Bailliere's Clinical Obstetrics and Gynaecology* **11** 249–260. (https://doi.org/10.1016/s0950-3552(97)80036-3)

Hirschler V, Bugna J, Roque M, Gilligan T & Gonzalez C 2008 Does low birth weight predict obesity/overweight and metabolic syndrome in elementary school children? *Archives of Medical Research* **39** 796–802. (https://doi.org/10.1016/j.arcmed.2008.08.003)

Hrudey SE, Naeth MA, Therrien R, Van Der Kraak G, Gosselin P, Plourde A & Xu Z 2012 Response to Timoney critique of Royal Society of Canada expert panel on oil sands. *Environmental Science and Technology* **46** 4257–4258. (https://doi.org/10.1021/es300858k)

Hsu PC, Chen IY, Pan CH, Wu KY, Pan MH, Chen JR, Chen CJ, Chang-Chien GP, Hsu CH, Liu CS, *et al.* 2006 Sperm DNA damage correlates with polycyclic aromatic hydrocarbons biomarker in coke-oven workers. *International Archives of Occupational and Environmental Health* **79** 349–356. (https://doi.org/10.1007/s00420-005-0066-3)

Hughes CHK & Murphy BD 2021 Nuclear receptors: key regulators of somatic cell functions in the ovulatory process. *Molecular Aspects of Medicine* **78** 100937. (https://doi.org/10.1016/j.mam.2020.100937)

Ivanova NO, Xu Z, Liu Q & Masliyah JH 2017 Surface forces in unconventional oil processing. *Current Opinion in Colloid and Interface Science* **27** 63–73. (https://doi.org/10.1016/j.cocis.2016.09.013)

Jabbour HN, Sales KJ, Catalano RD & Norman JE 2009 Inflammatory pathways in female reproductive health and disease. *Reproduction* **138** 903–919. (https://doi.org/10.1530/REP-09-0247)

Jackson RB, Vengosh A, Darrah TH, Warner NR, Down A, Poreda RJ, Osborn SG, Zhao K & Karr JD 2013 Increased stray gas abundance in a subset of drinking water wells near Marcellus shale gas extraction. *Proceedings of the National Academy of Sciences of the United States of America* **110** 11250–11255. (https://doi.org/10.1073/pnas.1221635110)

Jacobstein R & Polis CB 2014 Progestin-only contraception: injectables and implants. *Best Practice and Research. Clinical Obstetrics and Gynaecology* **28** 795–806. (https://doi.org/10.1016/j.bpobgyn.2014.05.003)

Janitz AE, Dao HD, Campbell JE, Stoner JA & Peck JD 2019 The association between natural gas well activity and specific congenital anomalies in Oklahoma, 1997–2009. *Environment International* **122** 381–388. (https://doi.org/10.1016/j.envint.2018.12.011)

Jeng HA & Yu L 2008 Alteration of sperm quality and hormone levels by polycyclic aromatic hydrocarbons on airborne particulate particles. *Journal of Environmental Science and Health, Part A, Toxic/Hazardous Substances and Environmental Engineering* **43** 675–681. (https://doi.org/10.1080/10934520801959815)

Jew AD, Druhan JL, Ihme M, Kovscek AR, Battiato I, Kaszuba JP, Bargar JR & Brown GE, Jr 2022 Chemical and reactive transport processes associated with hydraulic fracturing of unconventional oil/gas shales. *Chemical Reviews* **122** 9198–9263. (https://doi.org/10.1021/acs.chemrev.1c00504)

Jornayvaz FR, Vollenweider P, Bochud M, Mooser V, Waeber G & Marques-Vidal P 2016 Low birth weight leads to obesity, diabetes and increased leptin levels in adults: the CoLaus study. *Cardiovascular Diabetology* **15** 73. (https://doi.org/10.1186/s12933-016-0389-2)

Kang HY, Cho CL, Huang KL, Wang JC, Hu YC, Lin HK, Chang C & Huang KE 2004 Nongenomic androgen activation of phosphatidylinositol 3-kinase/Akt signaling pathway in MC3T3-E1 osteoblasts. *Journal of Bone and Mineral Research* **19** 1181–1190. (https://doi.org/10.1359/JBMR.040306)

Karman BN, Hernández-Ochoa I, Ziv-Gal A & Flaws JA 2011 Chapter 31: Involvement of the AHR in development and functioning of the female and male reproductive systems. In *The AH Receptor in Biology and Toxicology*, pp. 437–466. R Pohjanvirta Ed. Hoboken, NJ, USA: John Wiley & Sons, Inc. (https://doi.org/10.1002/9781118140574.ch31)

Kassotis CD & Phillips AL 2023 Complex mixtures and multiple stressors: evaluating combined chemical exposures and cumulative toxicity. *Toxics* **11**. (https://doi.org/10.3390/toxics11060487)

Kassotis CD, Tillitt DE, Davis JW, Hormann AM & Nagel SC 2014 Estrogen and androgen receptor activities of hydraulic fracturing chemicals and surface and ground water in a drilling-dense region. *Endocrinology* **155** 897–907. (https://doi.org/10.1210/en.2013-1697)

Kassotis CD, Klemp KC, Vu DC, Lin CH, Meng CX, Besch-Williford CL, Pinatti L, Zoeller RT, Drobnis EZ, Balise VD, *et al.* 2015 Endocrine-disrupting activity of hydraulic fracturing chemicals and adverse health outcomes after prenatal exposure in male mice. *Endocrinology* **156** 4458–4473. (https://doi.org/10.1210/en.2015-1375)

Kassotis CD, Bromfield JJ, Klemp KC, Meng C-X, Wolfe A, Zoeller RT, Balise VD, Isiguzo CJ, Tillitt DE & Nagel SC 2016*a* Adverse reproductive and developmental health outcomes following prenatal exposure to a hydraulic fracturing chemical mixture in female C57BL/6 mice. *Endocrinology* **157** 3469–3481. (https://doi.org/10.1210/en.2016-1242)

Kassotis CD, Iwanowicz LR, Akob DM, Cozzarelli IM, Mumford AC, Orem WH & Nagel SC 2016*b* Endocrine disrupting activities of surface water associated with a West Virginia oil and gas industry wastewater disposal site. *Science of the Total Environment* **557–558** 901–910. (https://doi.org/10.1016/j.scitotenv.2016.03.113)

Kassotis CD, Tillitt DE, Lin CH, McElroy JA & Nagel SC 2016*c* Endocrine-disrupting chemicals and Oil and Natural Gas operations: potential environmental contamination and recommendations to assess complex environmental mixtures. *Environmental Health Perspectives* **124** 256–264. (https://doi.org/10.1289/ehp.1409535)

Kassotis CD, Kollitz EM, Ferguson PL & Stapleton HM 2018*a* Nonionic ethoxylated surfactants induce adipogenesis in 3T3-L1 cells. *Toxicological Sciences* **162** 124–136. (https://doi.org/10.1093/toxsci/kfx234)

Kassotis CD, Nagel SC & Stapleton HM 2018*b* Unconventional oil and gas chemicals and wastewater-impacted water samples promote adipogenesis via PPARγ-dependent and independent mechanisms in 3T3-L1 cells. *Science of the Total Environment* **640–641** 1601–1610. (https://doi.org/10.1016/j.scitotenv.2018.05.030)

Kassotis CD, Vu DC, Vo PH, Lin C-H, Cornelius-Green JN, Patton S & Nagel SC 2018*c* Endocrine disrupting activities and organic contaminants associated with oil and gas operations in Wyoming groundwater. *Archives of Environmental Contamination and Toxicology* **75** 247–258. (https://doi.org/10.1007/s00244-018-0521-2)

Kassotis CD, Harkness JS, Vo PH, Vu DC, Hoffman K, Cinnamon KM, Cornelius-Green JN, Vengosh A, Lin CH, Tillitt DE, *et al.* 2020 Endocrine disrupting activities and geochemistry of water resources associated with unconventional oil and gas activity. *Science of the Total Environment* **748** 142236. (https://doi.org/10.1016/j.scitotenv.2020.142236)

Kassotis CD, LeFauve MK, Chiang YTT, Knuth MM, Schkoda S & Kullman SW 2022 Nonylphenol polyethoxylates enhance adipose deposition in developmentally exposed zebrafish. *Toxics* **10**. (https://doi.org/10.3390/toxics10020099)

Kim JH, Moon JY, Park EY, Lee KH & Hong YC 2011 Changes in oxidative stress biomarker and gene expression levels in workers exposed to volatile organic compounds. *Industrial Health* **49** 8–14. (https://doi.org/10.2486/indhealth.ms1112)

Kim SS, Meeker JD, Keil AP, Aung MT, Bommarito PA, Cantonwine DE, McElrath TF & Ferguson KK 2019 Exposure to 17 trace metals in pregnancy and associations with urinary oxidative stress biomarkers. *Environmental Research* **179** 108854. (https://doi.org/10.1016/j.envres.2019.108854)

Kiruthiga PV, Shafreen RB, Pandian SK & Devi KP 2007 Silymarin protection against major reactive oxygen species released by environmental toxins: exogenous H2O2 exposure in erythrocytes. *Basic and Clinical Pharmacology and Toxicology* **100** 414–419. (https://doi.org/10.1111/j.1742-7843.2007.00069.x)

Klenov V, Flor S, Ganesan S, Adur M, Eti N, Iqbal K, Soares MJ, Ludewig G, Ross JW, Robertson LW, *et al.* 2021 The aryl hydrocarbon receptor mediates reproductive toxicity of polychlorinated biphenyl congener 126 in rats. *Toxicology and Applied Pharmacology* **426** 115639. (https://doi.org/10.1016/j.taap.2021.115639)

Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, Lutkeschipholt IJ, Van der Paauw CG, Tuinstra LG, Brouwer A & Sauer PJ 1994 Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatric Research* **36** 468–473. (https://doi.org/10.1203/00006450-199410000-00009)

Kousteni S, Bellido T, Plotkin LI, O'Brien CA, Bodenner DL, Han L, Han K, DiGregorio GB, Katzenellenbogen JA, Katzenellenbogen BS, *et al.* 2001 Nongenotropic, sex-nonspecific signaling through the estrogen or androgen receptors: dissociation from transcriptional activity. *Cell* **104** 719–730.

Kowalewski MP, Meyer A, Hoffmann B, Aslan S & Boos A 2011 Expression and functional implications of peroxisome proliferator-activated receptor gamma (PPARgamma) in canine reproductive tissues during normal pregnancy and parturition and at antiprogestin induced abortion. *Theriogenology* **75** 877–886. (https://doi.org/10.1016/j.theriogenology.2010.10.030)

Krey G, Braissant O, L'Horset F, Kalkhoven E, Perroud M, Parker MG & Wahli W 1997 Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay. *Molecular Endocrinology* **11** 779–791. (https://doi.org/10.1210/mend.11.6.0007)

La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, Patisaul HB, Guyton KZ, Kortenkamp A, Cogliano VJ, Woodruff TJ, *et al.* 2020 Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nature Reviews. Endocrinology* **16** 45–57. (https://doi.org/10.1038/s41574-019-0273-8)

Lee DS, Herman JD, Elsworth D, Kim HT & Lee HS 2011 A critical evaluation of unconventional gas recovery from the Marcellus Shale, Northeastern United States. *KSCE Journal of Civil Engineering* **15** 679–687. (https://doi.org/10.1007/s12205-011-0008-4)

Lee HR, Kim TH & Choi KC 2012 Functions and physiological roles of two types of estrogen receptors, ERα and ERβ, identified by estrogen receptor knockout mouse. *Laboratory Animal Research* **28** 71–76. (https://doi.org/10.5625/lar.2012.28.2.71)

LeFauve MK, Bérubé R, Heldman S, Chiang Y-TT & Kassotis CD 2023 Cetyl alcohol polyethoxylates disrupt metabolic health in developmentally exposed zebrafish. *Metabolites* **13** 359. (https://doi.org/10.3390/metabo13030359)

Lester Y, Ferrer I, Thurman EM, Sitterley KA, Korak JA, Aiken G & Linden KG 2015 Characterization of hydraulic fracturing flowback water in Colorado: implications for water treatment. *Science of the Total Environment* **512–513** 637–644. (https://doi.org/10.1016/j.scitotenv.2015.01.043)

Liccione JJ 1999 Hazard identification of Indoor Air Pollutants. In *Risk Assessment and Indoor Air Quality*, pp. 1–253. RE Albert & EL Anderson Eds. Boca Raton, Fla: Lewis Publisher. (https://doi.org/10.1201/9781420048476.ch3)

Liew Z, Olsen J, Cui X, Ritz B & Arah OA 2015 Bias from conditioning on live birth in pregnancy cohorts: an illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. *International Journal of Epidemiology* **44** 345–354. (https://doi.org/10.1093/ije/dyu249)

Lin F, Alderman SL, Gillis TE & Kennedy CJ 2022*a* Diluted bitumen affects multiple physiological systems in sockeye salmon (*Oncorhynchus nerka*) embryo to juvenile life stages. *Environmental Toxicology and Chemistry* **41** 1937–1949. (https://doi.org/10.1002/etc.5362)

Lin L, Dai Y & Xia Y 2022*b* An overview of aryl hydrocarbon receptor ligands in the last two decades (2002–2022): a medicinal chemistry perspective. *European Journal of Medicinal Chemistry* **244** 114845. (https://doi.org/10.1016/j.ejmech.2022.114845)

Liu G-H, Qu J & Shen X 2008 NF-κB/p65 antagonizes Nrf2-ARE pathway by depriving CBP from Nrf2 and facilitating recruitment of HDAC3 to MafK. *Biochimica et Biophysica Acta* **1783** 713–727. (https://doi.org/10.1016/j.bbamcr.2008.01.002)

Llewellyn GT, Dorman F, Westland JL, Yoxtheimer D, Grieve P, Sowers T, Humston-Fulmer E & Brantley SL 2015 Evaluating a groundwater supply contamination incident attributed to Marcellus Shale gas development. *PNAS* **112** 6325–6330. (https://doi.org/10.1073/pnas.1420279112)

Lovekamp-Swan T, Jetten AM & Davis BJ 2003 Dual activation of PPARalpha and PPARgamma by mono-(2-ethylhexyl) phthalate in rat ovarian granulosa cells. *Molecular and Cellular Endocrinology* **201** 133–141. (https://doi.org/10.1016/s0303-7207(02)00423-9)

Lydon JP, DeMayo FJ, Funk CR, Mani SK, Hughes AR, Montgomery CA, Shyamala G, Conneely OM & O'Malley BW 1995 Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. *Genes and Development* **9** 2266–2278. (https://doi.org/10.1101/gad.9.18.2266)

Ma Z-Q, Sneeringer KC, Liu L & Kuller LH 2016 Time series evaluation of birth defects in areas with and without unconventional natural gas development. *Journal of Epidemiology and Public Health Reviews* **1**. (https://doi.org/10.16966/2471-8211.107)

MacLean HE, Chu S, Warne GL & Zajac JD 1993 Related individuals with different androgen receptor gene deletions. *Journal of Clinical Investigation* **91** 1123–1128. (https://doi.org/10.1172/JCI116271)

Mahmoud MA, Abd El-Rahim AH, Mahrous KF, Abdelsalam M, Abu-Aita NA & Afify M 2019 The impact of several hydraulic fracking chemicals on Nile tilapia and evaluation of the protective effects of Spirulina platensis. *Environmental Science and Pollution Research International* **26** 19453–19467. (https://doi.org/10.1007/s11356-019-05246-3)

Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR & Miller SL 2019 Neonatal morbidities of fetal growth restriction: pathophysiology and impact. *Frontiers in Endocrinology* **10** 55. (https://doi.org/10.3389/fendo.2019.00055)

Maloney KO, Baruch-Mordo S, Patterson LA, Nicot JP, Entrekin SA, Fargione JE, Kiesecker JM, Konschnik KE, Ryan JN, Trainor AM, *et al.* 2017 Unconventional oil and gas spills: materials, volumes, and risks to surface waters in four states of the U.S. *Science of the Total Environment* **581–582** 369–377. (https://doi.org/10.1016/j.scitotenv.2016.12.142)

Manzetti S 2013 Polycyclic aromatic hydrocarbons in the environment: environmental fate and transformation. *Polycyclic Aromatic Compounds* **33** 311–330. (https://doi.org/10.1080/10406638.2013.781042)

Martin LJ & Tremblay JJ 2010 Nuclear receptors in Leydig cell gene expression and function. *Biology of Reproduction* **83** 3–14. (https://doi.org/10.1095/biolreprod.110.083824)

Marusic K 2021 *Fractured: the Body Burden of Living near Fracking, Environmental Health News*. Available at: https://www.ehn.org/fractured-series-on-fracking-pollution-2650624600.html

Matsuda S, Kobayashi M & Kitagishi Y 2013 Expression and function of PPARs in placenta. *PPAR Research* **2013** 256508. (https://doi.org/10.1155/2013/256508)

Matthews J, Celius T, Halgren R & Zacharewski T 2000 Differential estrogen receptor binding of estrogenic substances: a species comparison. *Journal of Steroid Biochemistry and Molecular Biology* **74** 223–234. (https://doi.org/10.1016/s0960-0760(00)00126-6)

McCarthy MM 2008 Estradiol and the developing brain. *Physiological Reviews* **88** 91–124. (https://doi.org/10.1152/physrev.00010.2007)

McGuire CC, Lawrence BP & Robert J 2021 Thyroid disrupting chemicals in mixture perturb thymocyte differentiation in Xenopus laevis tadpoles. *Toxicological Sciences* **181** 262–272. (https://doi.org/10.1093/toxsci/kfab029)

McGuire CC & Robert JR 2022 Developmental exposure to thyroid disrupting chemical mixtures alters metamorphosis and post-metamorphic thymocyte differentiation. *Current Research in Toxicology* **3** 100094. (https://doi.org/10.1016/j.crtox.2022.100094)

McKenzie LM, Witter RZ, Newman LS & Adgate JL 2012 Human health risk assessment of air emissions from development of unconventional natural gas resources. *Science of the Total Environment* **424** 79–87. (https://doi.org/10.1016/j.scitotenv.2012.02.018)

McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS & Adgate JL 2014 Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. *Environmental Health Perspectives* **122** 412–417. (https://doi.org/10.1289/ehp.1306722)

McKenzie LM, Allshouse W & Daniels S 2019 Congenital heart defects and intensity of oil and gas well site activities in early pregnancy. *Environment International* **132** 104949. (https://doi.org/10.1016/j.envint.2019.104949)

Medici M, Timmermans S, Visser W, de Muinck Keizer-Schrama SMPF, Jaddoe VWW, Hofman A, Hooijkaas H, de Rijke YB, Tiemeier H, Bongers-Schokking JJ, *et al.* 2013 Maternal thyroid hormone parameters during early pregnancy and birth weight: the Generation R Study. *Journal of Clinical Endocrinology and Metabolism* **98** 59–66. (https://doi.org/10.1210/jc.2012-2420)

Meier S, Andersen TE, Norberg B, Thorsen A, Taranger GL, Kjesbu OS, Dale R, Morton HC, Klungsoyr J & Svardal A 2007 Effects of alkylphenols on the reproductive system of Atlantic cod (*Gadus morhua*). *Aquatic Toxicology* **81** 207–218. (https://doi.org/10.1016/j.aquatox.2006.12.002)

Meier S, Morton HC, Andersson E, Geffen AJ, Taranger GL, Larsen M, Petersen M, Djurhuus R, Klungsoyr J & Svardal A 2011 Low-dose exposure to alkylphenols adversely affects the sexual development of Atlantic cod (*Gadus morhua*): acceleration of the onset of puberty and delayed seasonal gonad development in mature female cod. *Aquatic Toxicology* **105** 136–150. (https://doi.org/10.1016/j.aquatox.2011.06.003)

Minge CE, Bennett BD, Norman RJ & Robker RL 2008 Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality. *Endocrinology* **149** 2646–2656. (https://doi.org/10.1210/en.2007-1570)

Morgenstern H 1995 Ecologic studies in epidemiology: concepts, principles, and methods. *Annual Review of Public Health* **16** 61–81. (https://doi.org/10.1146/annurev.pu.16.050195.000425)

Morono Y, Wishart JR, Ito M, Ijiri A, Hoshino T, Torres M, Verba C, Terada T, Inagaki F & Colwell FS 2019 Microbial metabolism and community dynamics in hydraulic fracturing fluids recovered from deep hydrocarbon-rich shale. *Frontiers in Microbiology* **10** 376. (https://doi.org/10.3389/fmicb.2019.00376)

Mulac-Jericevic B, Mullinax RA, DeMayo FJ, Lydon JP & Conneely OM 2000 Subgroup of reproductive functions of progesterone mediated by progesterone receptor-B isoform. *Science* **289** 1751–1754. (https://doi.org/10.1126/science.289.5485.1751)

Mulac-Jericevic B, Lydon JP, DeMayo FJ & Conneely OM 2003 Defective mammary gland morphogenesis in mice lacking the progesterone receptor B isoform. *Proceedings of the National Academy of Sciences of the United States of America* **100** 9744–9749. (https://doi.org/10.1073/pnas.1732707100)

Mullen KR, Rivera BN, Tidwell LG, Ivanek R, Anderson KA & Ainsworth DM 2020 Environmental surveillance and adverse neonatal health outcomes in foals born near unconventional natural gas development activity. *Science of the Total Environment* **731** 138497. (https://doi.org/10.1016/j.scitotenv.2020.138497)

Murali Mohan A, Hartsock A, Bibby KJ, Hammack RW, Vidic RD & Gregory KB 2013 Microbial community changes in hydraulic fracturing fluids and produced water from shale gas extraction. *Environmental Science and Technology* **47** 13141–13150. (https://doi.org/10.1021/es402928b)

Myatt L & Cui X 2004 Oxidative stress in the placenta. *Histochemistry and Cell Biology* **122** 369–382. (https://doi.org/10.1007/s00418-004-0677-x)

Nakamura T, Ushiyama C, Shimada N, Hayashi K, Ebihara I & Koide H 2000 Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients. *Journal of Diabetes and its Complications* **14** 250–254. (https://doi.org/10.1016/s1056-8727(00)00124-0)

Nallasamy S, Kim J, Sitruk-Ware R, Bagchi M & Bagchi I 2013 Ulipristal blocks ovulation by inhibiting progesterone receptor-dependent pathways intrinsic to the ovary. *Reproductive Sciences* **20** 371–381. (https://doi.org/10.1177/1933719112459239)

National Research Council (NRC) 2006 Human biomonitoring for environmental chemicals. In *Report by Committee on Human Biomonitoring for Environmental Toxicants*, pp. 1–317. Eds NRC Otn Academics. Division on Earth and Life Studies. Washington, DC, USA: The National Academies Press. The National Academies Press. (https://doi.org/10.17226/11700)

Nebert DW, Dalton TP, Okey AB & Gonzalez FJ 2004 Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. *Journal of Biological Chemistry* **279** 23847–23850. (https://doi.org/10.1074/jbc.R400004200)

Neophytou AM, Kioumourtzoglou MA, Goin DE, Darwin KC & Casey JA 2021 Educational note: addressing special cases of bias that frequently occur in perinatal epidemiology. *International Journal of Epidemiology* **50** 337–345. (https://doi.org/10.1093/ije/dyaa252)

Neschen S, Morino K, Dong J, Wang-Fischer Y, Cline GW, Romanelli AJ, Rossbacher JC, Moore IK, Regittnig W, Munoz DS, *et al.* 2007 n-3 Fatty acids preserve insulin sensitivity in vivo in a peroxisome proliferator-activated receptor-alpha-dependent manner. *Diabetes* **56** 1034–1041. (https://doi.org/10.2337/db06-1206)

Nilsson S & Gustafsson JA 2002 Biological role of estrogen and estrogen receptors. *Critical Reviews in Biochemistry and Molecular Biology* **37** 1–28. (https://doi.org/10.1080/10409230290771438)

Ohtake F, Baba A, Takada I, Okada M, Iwasaki K, Miki H, Takahashi S, Kouzmenko A, Nohara K, Chiba T, *et al.* 2007 Dioxin receptor is a ligand-dependent E3 ubiquitin ligase. *Nature* **446** 562–566. (https://doi.org/10.1038/nature05683)

Ohtake F, Fujii-Kuriyama Y & Kato S 2009 AhR acts as an E3 ubiquitin ligase to modulate steroid receptor functions. *Biochemical Pharmacology* **77** 474–484. (https://doi.org/10.1016/j.bcp.2008.08.034)

Okey AB 2007 An aryl hydrocarbon receptor odyssey to the shores of toxicology: the Deichmann lecture, international congress of toxicology-XI. *Toxicological Sciences* **98** 5–38. (https://doi.org/10.1093/toxsci/kfm096)

Onojake MC & Waka TA 2021 Review of Oilfield Chemicals Used in Oil and Gas Industry. *Asian Journal of Physical and Chemical Sciences* **9** 8–24. (https://doi.org/10.9734/ajopacs/2021/v9i230132)

Osborn SG, Vengosh A, Warner NR & Jackson RB 2011 Methane contamination of drinking water accompanying gas-well drilling and hydraulic fracturing. *Proceedings of the National Academy of Sciences of the United States of America* **108** 8172–8176. (https://doi.org/10.1073/pnas.1100682108)

O'Shaughnessy KL & Gilbert ME 2020 Thyroid disrupting chemicals and developmental neurotoxicity - New tools and approaches to evaluate hormone action. *Molecular and Cellular Endocrinology* **518** 110663. (https://doi.org/10.1016/j.mce.2019.110663)

Paterni I, Granchi C & Minutolo F 2017 Risks and benefits related to alimentary exposure to xenoestrogens. *Critical Reviews in Food Science and Nutrition* **57** 3384–3404. (https://doi.org/10.1080/10408398.2015.1126547)

Patisaul HB 2021 Reproductive toxicology: endocrine disruption and reproductive disorders: impacts on sexually dimorphic neuroendocrine pathways. *Reproduction* **162** F111–F130. (https://doi.org/10.1530/REP-20-0596)

Paul-Friedman K, Martin M, Crofton KM, Hsu CW, Sakamuru S, Zhao J, Xia M, Huang R, Stavreva DA, Soni V, *et al.* 2019 Limited chemical structural diversity found to modulate thyroid hormone receptor in the Tox21 chemical library. *Environmental Health Perspectives* **127** 97009. (https://doi.org/10.1289/EHP5314)

Pereira AC & Martel F 2014 Oxidative stress in pregnancy and fertility pathologies. *Cell Biology and Toxicology* **30** 301–312. (https://doi.org/10.1007/s10565-014-9285-2)

Perugini G, Edgar M, Lin F, Kennedy CJ, Farrell AP, Gillis TE & Alderman SL 2022 Age matters: comparing life-stage responses to diluted bitumen exposure in coho salmon (Oncorhynchus kisutch). *Aquatic Toxicology* **253** 106350. (https://doi.org/10.1016/j.aquatox.2022.106350)

Phelps SM, Lydon JP, O'Malley BW & Crews D 1998 Regulation of male sexual behavior by progesterone receptor, sexual experience, and androgen. *Hormones and Behavior* **34** 294–302. (https://doi.org/10.1006/hbeh.1998.1485)

Plutzky J 2000 Peroxisome proliferator-activated receptors in vascular biology and atherosclerosis: emerging insights for evolving paradigms. *Current Atherosclerosis Reports* **2** 327–335. (https://doi.org/10.1007/s11883-000-0067-3)

Pocar P, Fischer B, Klonisch T & Hombach-Klonisch S 2005 Molecular interactions of the aryl hydrocarbon receptor and its biological and toxicological relevance for reproduction. *Reproduction* **129** 379–389. (https://doi.org/10.1530/rep.1.00294)

Poston L, Igosheva N, Mistry HD, Seed PT, Shennan AH, Rana S, Karumanchi SA & Chappell LC 2011 Role of oxidative stress and antioxidant supplementation in pregnancy disorders. *American Journal of Clinical Nutrition* **94**(Supplement) 1980S–1985S. (https://doi.org/10.3945/ajcn.110.001156)

Revel A, Raanani H, Younglai E, Xu J, Han R, Savouret JF & Casper RF 2001 Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects sperm from DNA damage and apoptosis caused by benzo(a) pyrene. *Reproductive Toxicology* **15** 479–486. (https://doi.org/10.1016/s0890-6238(01)00149-6)

Robert J, McGuire CC, Kim F, Nagel SC, Price SJ, Lawrence BP & De Jesus Andino F 2018 Water contaminants associated with unconventional oil and gas extraction cause immunotoxicity to amphibian tadpoles. *Toxicological Sciences* **166** 39–50. (https://doi.org/10.1093/toxsci/kfy179)

Robert J, McGuire CC, Nagel S, Lawrence BP & Andino FJ 2019 Developmental exposure to chemicals associated with unconventional oil and gas extraction alters immune homeostasis and viral immunity of the amphibian Xenopus. *Science of the Total Environment* **671** 644–654. (https://doi.org/10.1016/j.scitotenv.2019.03.395)

Roberts SC, Noyes PD, Gallagher EP & Stapleton HM 2011 Species-specific differences and structure-activity relationships in the debromination of PBDE congeners in three fish species. *Environmental Science and Technology* **45** 1999–2005. (https://doi.org/10.1021/es103934x)

Rogue A, Spire C, Brun M, Claude N & Guillouzo A 2010 Gene expression changes induced by PPAR gamma agonists in animal and human liver. *PPAR Research* **2010** 325183. (https://doi.org/10.1155/2010/325183)

Rogue A, Lambert C, Josse R, Antherieu S, Spire C, Claude N & Guillouzo A 2011 Comparative gene expression profiles induced by PPARgamma and PPARalpha/gamma agonists in human hepatocytes. *PLoS One* **6** e18816. (https://doi.org/10.1371/journal.pone.0018816)

Ruberg EJ, Elliott JE & Williams TD 2021 Review of petroleum toxicity and identifying common endpoints for future research on diluted bitumen toxicity in marine mammals. *Ecotoxicology* **30** 537–551. (https://doi.org/10.1007/s10646-021-02373-x)

Sapouckey SA, Kassotis CD, Nagel SC & Vandenberg LN 2018 Prenatal exposure to unconventional oil and gas operation chemical mixtures altered mammary gland development in adult female mice. *Endocrinology* **159** 1277–1289. (https://doi.org/10.1210/en.2017-00866)

Schriks M, Roessig JM, Murk AJ & Furlow JD 2007 Thyroid hormone receptor isoform selectivity of thyroid hormone disrupting compounds quantified with an in vitro reporter gene assay. *Environmental Toxicology and Pharmacology* **23** 302–307. (https://doi.org/10.1016/j.etap.2006.11.007)

Schuele H, Baum CF, Landrigan PJ & Hawkins SS 2022 Associations between proximity to gas production activity in counties and birth outcomes across the US. *Preventive Medicine Reports* **30** 102007. (https://doi.org/10.1016/j.pmedr.2022.102007)

Sen A & Hammes SR 2010 Granulosa cell-specific androgen receptors are critical regulators of ovarian development and function. *Molecular Endocrinology* **24** 1393–1403. (https://doi.org/10.1210/me.2010-0006)

Shang Y & Brown M 2002 Molecular determinants for the tissue specificity of SERMs. *Science* **295** 2465–2468. (https://doi.org/10.1126/science.1068537)

Shankar P, Dasgupta S, Hahn ME & Tanguay RL 2020 A review of the functional roles of the zebrafish aryl hydrocarbon receptors. *Toxicological Sciences* **178** 215–238. (https://doi.org/10.1093/toxsci/kfaa143)

Shanle EK & Xu W 2011 Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanisms of action. *Chemical Research in Toxicology* **24** 6–19. (https://doi.org/10.1021/tx100231n)

Shaya L, Jones DE & Wilson JY 2019 CYP3C gene regulation by the aryl hydrocarbon and estrogen receptors in zebrafish. *Toxicology and Applied Pharmacology* **362** 77–85. (https://doi.org/10.1016/j.taap.2018.10.021)

Shi YB 2021 Life without thyroid hormone receptor. *Endocrinology* **162**. (https://doi.org/10.1210/endocr/bqab028)

Shimba S & Watabe Y 2009 Crosstalk between the AHR signaling pathway and circadian rhythm. *Biochemical Pharmacology* **77** 560–565. (https://doi.org/10.1016/j.bcp.2008.09.040)

Siebold C 2011 Factors influencing young women's sexual and reproductive health. *Contemporary Nurse* **37** 124–136. (https://doi.org/10.5172/conu.2011.37.2.124)

Sies H, Belousov VV, Chandel NS, Davies MJ, Jones DP, Mann GE, Murphy MP, Yamamoto M & Winterbourn C 2022 Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. *Nature Reviews. Molecular Cell Biology* **23** 499–515. (https://doi.org/10.1038/s41580-022-00456-z)

Simmons LE, Rubens CE, Darmstadt GL & Gravett MG 2010 Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions. *Seminars in Perinatology* **34** 408–415. (https://doi.org/10.1053/j.semperi.2010.09.005)

Smith CL & O'Malley BW 2004 Coregulator function: a key to understanding tissue specificity of selective receptor modulators. *Endocrine Reviews* **25** 45–71. (https://doi.org/10.1210/er.2003-0023)

Spitz IM 2003 Progesterone antagonists and progesterone receptor modulators: an overview. *Steroids* **68** 981–993. (https://doi.org/10.1016/j.steroids.2003.08.007)

Stacy SL, Brink LL, Larkin JC, Sadovsky Y, Goldstein BD, Pitt BR & Talbott EO 2015 Perinatal outcomes and unconventional natural gas operations in southwest pennsylvania. *PLoS One* **10** e0126425. (https://doi.org/10.1371/journal.pone.0126425)

Stieb DM, Chen L, Eshoul M & Judek S 2012 Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environmental Research* **117** 100–111. (https://doi.org/10.1016/j.envres.2012.05.007)

Strand LB, Barnett AG & Tong S 2011 Methodological challenges when estimating the effects of season and seasonal exposures on birth

outcomes. *BMC Medical Research Methodology* **11** 49. (https://doi.org/10.1186/1471-2288-11-49)

Stringfellow, WT, Domen JK, Camarillo MK, Sandelin WL & Borglin S 2014 Physical, chemical, and biological characteristics of compounds used in hydraulic fracturing. *Journal of Hazardous Materials* **275** 37–54. (https://doi.org/10.1016/j.jhazmat.2014.04.040)

Sun X, Luo X, Zhao C, Ng RWC, Lim CED, Zhang B & Liu T 2015 The association between fine particulate matter exposure during pregnancy and preterm birth: a meta-analysis. *BMC Pregnancy and Childbirth* **15** 300. (https://doi.org/10.1186/s12884-015-0738-2)

Tachachartvanich P, Azhagiya Singam ER, Durkin KA, Smith MT & La Merrill MA 2020 Structure-based discovery of the endocrine disrupting effects of hydraulic fracturing chemicals as novel androgen receptor antagonists. *Chemosphere* **257** 127178. (https://doi.org/10.1016/j.chemosphere.2020.127178)

Takagi Y, Nikaido T, Toki T, Kita N, Kanai M, Ashida T, Ohira S & Konishi I 2004 Levels of oxidative stress and redox-related molecules in the placenta in preeclampsia and fetal growth restriction. *Virchows Archiv* **444** 49–55. (https://doi.org/10.1007/s00428-003-0903-2)

Tang IW, Langlois PH & Vieira VM 2021 Birth defects and unconventional natural gas developments in Texas, 1999–2011. *Environmental Research* **194** 110511. (https://doi.org/10.1016/j.envres.2020.110511)

Taniguchi A, Fukushima M, Sakai M, Tokuyama K, Nagata I, Fukunaga A, Kishimoto H, Doi K, Yamashita Y, Matsuura T, *et al.* 2001 Effects of bezafibrate on insulin sensitivity and insulin secretion in non-obese Japanese type 2 diabetic patients. *Metabolism: Clinical and Experimental* **50** 477–480. (https://doi.org/10.1053/meta.2001.21028)

Tasker TL, Burgos WD, Piotrowski P, Castillo-Meza L, Blewett TA, Ganow KB, Stallworth A, Delompre PLM, Goss GG, Fowler LB, *et al.* 2018 Environmental and human health impacts of spreading oil and gas wastewater on roads. *Environmental Science and Technology* **52** 7081–7091. (https://doi.org/10.1021/acs.est.8b00716)

Thurman EM, Ferrer I, Blotevogel J & Borch T 2014 Analysis of hydraulic fracturing flowback and produced waters using accurate mass: identification of ethoxylated surfactants. *Analytical Chemistry* **86** 9653–9661. (https://doi.org/10.1021/ac502163k)

Tobola-Wrobel K, Pietryga M, Dydowicz P, Napierala M, Brazert J & Florek E 2020 Association of oxidative stress on pregnancy. *Oxidative Medicine and Cellular Longevity* **2020** 6398520. (https://doi.org/10.1155/2020/6398520)

Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ, Jr, Jégou B, Jensen TK, Jouannet P, Keiding N, *et al.* 1996 Male reproductive health and environmental xenoestrogens. *Environmental Health Perspectives* **104**(Supplement 4) 741–803. (https://doi.org/10.1289/ehp.96104s4741)

Tran KV, Casey JA, Cushing LJ & Morello-Frosch R 2021 Residential proximity to hydraulically fractured oil and gas wells and adverse birth outcomes in urban and rural communities in California (2006–2015). *Environmental Epidemiology* **5** e172. (https://doi.org/10.1097/EE9.0000000000000172)

US Energy Information Agency (US EIA) 2023 *Annual Energy Outlook 2023*. Available at: https://www.eia.gov/outlooks/aeo/narrative/

US Center for Disease Control and Prevention (US CDC) 2009 *Fourth National Report on Human Exposure to Environmental Chemicals - Volume Two: NHANES 2011–2016 (Updated March 2021)*. Report from Centers for Disease Control and Prevention. Available at: https://stacks.cdc.gov/view/cdc/105344

US Environmental Protection Agency (US EPA) 2015 Assessment of the potential impacts of hydraulic fracturing for oil and gas on drinking water resources. In *OoRa Development (ed.)*. Report #EPA/600/R-15/047 Washington, DC: United States Environmental Protection Agency. Available at: https://cfpub.epa.gov/ncea/hfstudy/recordisplay.cfm?deid=244651

US Environmental Protection Agency (US EPA) 2019 *Guidelines for Human Exposure Assessment* Report # EPA/100/B-19/001, pp. 1–223. Washington, DC: Risk Assessment Forum, US EPA. Available at: https://www.epa.gov/sites/default/files/2020-01/documents/guidelines_for_human_exposure_assessment_final2019.pdf

Utting N, Namsechi B, McMullen C, Brydie J & Ahad JME 2022 Comparing simulated shallow subsurface spills of diluted bitumen and conventional crude oil. *Journal of Contaminant Hydrology* **251** 104099. (https://doi.org/10.1016/j.jconhyd.2022.104099)

Veldhuis JD, Zhang G & Garmey JC 2002 Troglitazone, an insulin-sensitizing thiazolidinedione, represses combined stimulation by LH and insulin of de novo androgen biosynthesis by thecal cells in vitro. *Journal of Clinical Endocrinology and Metabolism* **87** 1129–1133. (https://doi.org/10.1210/jcem.87.3.8308)

Virro MR, Larson-Cook KL & Evenson DP 2004 Sperm chromatin structure assay (SCSA) parameters are related to fertilization, blastocyst development, and ongoing pregnancy in in vitro fertilization and intracytoplasmic sperm injection cycles. *Fertility and Sterility* **81** 1289–1295. (https://doi.org/10.1016/j.fertnstert.2003.09.063)

Vitti M, Di Emidio G, Di Carlo M, Carta G, Antonosante A, Artini PG, Cimini A, Tatone C & Benedetti E 2016 Peroxisome proliferator-activated receptors in female reproduction and fertility. *PPAR Research* **2016** 4612306. (https://doi.org/10.1155/2016/4612306)

Vogel CFA, Van Winkle LS, Esser C & Haarmann-Stemmann T 2020 The aryl hydrocarbon receptor as a target of environmental stressors – implications for pollution mediated stress and inflammatory responses. *Redox Biology* **34** 101530. (https://doi.org/10.1016/j.redox.2020.101530)

Waldner CL 2008 The association between exposure to the oil and gas industry and beef calf mortality in Western Canada. *Archives of Environmental and Occupational Health* **63** 220–240. (https://doi.org/10.3200/aeoh.63.4.220-240)

Waldner CL & Stryhn H 2008 Risk of nonpregnancy, risk of disposal for pregnant cows, and duration of the calving interval in cow-calf herds exposed to the oil and gas industry in Western Canada. *Archives of Environmental and Occupational Health* **63** 241–261. (https://doi.org/10.3200/aeoh.63.4.241-261)

Walker C, Ahmed SA, Brown T, Ho SM, Hodges L, Lucier G, Russo J, Weigel N, Weise T & Vandenbergh J 1999 Species, interindividual, and tissue specificity in endocrine signaling. *Environmental Health Perspectives* **107**(Supplement 4) 619–624. (https://doi.org/10.1289/ehp.99107s4619)

Wall PD, Pressman EK & Woods JR, Jr 2002 Preterm premature rupture of the membranes and antioxidants: the free radical connection. *Journal of Perinatal Medicine* **30** 447–457. (https://doi.org/10.1515/JPM.2002.071)

Wallis K, Dudazy S, van Hogerlinden M, Nordstrom K, Mittag J & Vennstrom B 2010 The thyroid hormone receptor alpha1 protein is expressed in embryonic postmitotic neurons and persists in most adult neurons. *Molecular Endocrinology* **24** 1904–1916. (https://doi.org/10.1210/me.2010-0175)

Wang C & Swerdloff RS 2010 Hormonal approaches to male contraception. *Current Opinion in Urology* **20** 520–524. (https://doi.org/10.1097/MOU.0b013e32833f1b4a)

Wang IJ, Karmaus WJJ & Yang CC 2017 Polycyclic aromatic hydrocarbons exposure, oxidative stress, and asthma in children. *International Archives of Occupational and Environmental Health* **90** 297–303. (https://doi.org/10.1007/s00420-017-1198-y)

Wang L, Tang J, Wang L, Tan F, Song H, Zhou J & Li F 2021*a* Oxidative stress in oocyte aging and female reproduction. *Journal of Cellular Physiology* **236** 7966–7983. (https://doi.org/10.1002/jcp.30468)

Wang LH, Chen LR & Chen KH 2021*b* In vitro and vivo identification, metabolism and action of xenoestrogens: an overview. *International Journal of Molecular Sciences* **22**. (https://doi.org/10.3390/ijms22084013)

Warner NR, Jackson RB, Darrah TH, Osborn SG, Down A, Zhao K, White A & Vengosh A 2012 Geochemical evidence for possible natural migration of Marcellus Formation brine to shallow aquifers in Pennsylvania. *PNAS* **109** 11961–11966. (https://doi.org/10.1073/pnas.1121181109)

Waxman HA, Markey EJ & DeGette D 2011 Chemicals used in hydraulic fracturing. In *Committee of Energy and Commerce (ed.)*. U.S. House of Representatives. Available at: https://www.damascuscitizensforsustainability.org/wp-content/uploads/2012/03/dems.energy.Hydraulic-Fracturing-Report-4.18.11.pdf

Webb E, Bushkin-Bedient S, Cheng A, Kassotis CD, Balise V & Nagel SC 2014 Developmental and reproductive effects of chemicals associated with unconventional oil and natural gas operations. *Reviews on Environmental Health* **29** 307–318. (https://doi.org/10.1515/reveh-2014-0057)

Webb E, Moon J, Dyrszka L, Rodriguez B, Cox C, Patisaul H, Bushkin S & London E 2018 Neurodevelopmental and neurological effects of chemicals associated with unconventional oil and natural gas operations and their potential effects on infants and children. *Reviews on Environmental Health* **33** 3–29. (https://doi.org/10.1515/reveh-2017-0008)

Weber LP & Janz DM 2001 Effect of beta-naphthoflavone and dimethylbenz[a]anthracene on apoptosis and HSP70 expression in juvenile channel catfish (*Ictalurus punctatus*) ovary. *Aquatic Toxicology* **54** 39–50. (https://doi.org/10.1016/s0166-445x(00)00179-x)

Werner AK, Vink S, Watt K & Jagals P 2015 Environmental health impacts of unconventional natural gas development: a review of the current strength of evidence. *Science of the Total Environment* **505** 1127–1141. (https://doi.org/10.1016/j.scitotenv.2014.10.084)

Whitworth KW, Marshall AK & Symanski E 2017 Maternal residential proximity to unconventional gas development and perinatal outcomes among a diverse urban population in Texas. *PLoS One* **12** e0180966. (https://doi.org/10.1371/journal.pone.0180966)

Whitworth KW, Kaye Marshall A & Symanski E 2018 Drilling and production activity related to unconventional gas development and severity of preterm birth. *Environmental Health Perspectives* **126** 037006. (https://doi.org/10.1289/EHP2622)

Willis MD, Carozza SE & Hystad P 2023 Congenital anomalies associated with oil and gas development and resource extraction: a population-based retrospective cohort study in Texas. *Journal of Exposure Science and Environmental Epidemiology* **33** 84–93. (https://doi.org/10.1038/s41370-022-00505-x)

Willson TM, Brown PJ, Sternbach DD & Henke BR 2000 The PPARs: from orphan receptors to drug discovery. *Journal of Medicinal Chemistry* **43** 527–550. (https://doi.org/10.1021/jm990554g)

Wilson VS, Blystone CR, Hotchkiss AK, Rider CV & Gray LE 2008 Diverse mechanisms of anti-androgen action: impact on male rat reproductive tract development. *International Journal of Andrology* **31** 178–187. (https://doi.org/10.1111/j.1365-2605.2007.00861.x)

Wiseman HJ 2008 Untested waters: the rise of hydraulic fracturing in oil and gas production and the need to revisit regulation. *Fordham Environmental Law Review* **20** 115–169.

Wojnarowski K, Podobiński P, Cholewińska P, Smoliński J & Dorobisz K 2021 Impact of estrogens present in environment on health and welfare of animals. *Animals* **11**. (https://doi.org/10.3390/ani11072152)

Womack LS, Rossen LM & Hirai AH 2020 Urban-rural infant mortality disparities by race and ethnicity and cause of death. *American Journal of Preventive Medicine* **58** 254–260. (https://doi.org/10.1016/j.amepre.2019.09.010)

Wu G, Ji Q, Huang H & Zhu X 2021 The efficacy of fish oil in preventing coronary heart disease: a systematic review and meta-analysis. *Medicine* **100** e27253. (https://doi.org/10.1097/MD.0000000000027253)

Xiao GG, Wang M, Li N, Loo JA & Nel AE 2003 Use of proteomics to demonstrate a hierarchical oxidative stress response to diesel exhaust particle chemicals in a macrophage cell line. *Journal of Biological Chemistry* **278** 50781–50790. (https://doi.org/10.1074/jbc.M306423200)

Xu X, Zhang X, Yuan Y, Zhao Y, Fares HM, Yang M, Wen Q, Taha R & Sun L 2021 Species-specific differences in aryl hydrocarbon receptor responses: how and why? *International Journal of Molecular Sciences* **22**. (https://doi.org/10.3390/ijms222413293)

Yan M, Zhu H, Luo H, Zhang T, Sun H & Kannan K 2023 Daily exposure to environmental volatile organic compounds triggers oxidative damage: evidence from a large-scale survey in china. *Environmental Science and Technology* **57** 20501–20509. (https://doi.org/10.1021/acs.est.3c06055)

Yang Q, Qiu X, Li R, Ma J, Li K & Li G 2015 Polycyclic aromatic hydrocarbon (PAH) exposure and oxidative stress for a rural population from the North China Plain. *Environmental Science and Pollution Research International* **22** 1760–1769. (https://doi.org/10.1007/s11356-014-3284-y)

Yeh S, Tsai M-Y, Xu Q, Mu X-M, Lardy H, Huang K-E, Lin H, Yeh S-D, Altuwaijri S, Zhou X, *et al.* 2002 Generation and characterization of androgen receptor knockout (ARKO) mice: an in vivo model for the study of androgen functions in selective tissues. *PNAS* **99** 13498–13503. (https://doi.org/10.1073/pnas.212474399)

Zhan F, Parajulee A, Binnington MJ, Gawor A & Wania F 2023 A multi-pathway exposure assessment for polycyclic aromatic hydrocarbons among residents in the Athabasca oil sands region, Canada. *Environmental Science. Processes and Impacts* **25** 755–766. (https://doi.org/10.1039/d2em00526c)

Zhang SS, Carrillo AJ & Darling DS 1997 Expression of multiple thyroid hormone receptor mRNAs in human oocytes, cumulus cells, and granulosa cells. *Molecular Human Reproduction* **3** 555–562. (https://doi.org/10.1093/molehr/3.7.555)

Zhang M, Liu C, Li WD, Xu XD, Cui FP, Chen PP, Deng YL, Miao Y, Luo Q, Zeng JY, *et al.* 2022 Individual and mixtures of metal exposures in associations with biomarkers of oxidative stress and global DNA methylation among pregnant women. *Chemosphere* **293** 133662. (https://doi.org/10.1016/j.chemosphere.2022.133662)

Zhong C, Nesbo CL, von Gunten K, Zhang Y, Shao X, Jin R, Konhauser KO, Goss GG, Martin JW, He Y, *et al.* 2022 Complex impacts of hydraulic fracturing return fluids on soil microbial community respiration, structure and functional potentials. *Environmental Microbiology* **24** 4108–4123. (https://doi.org/10.1111/1462-2920.16009)