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ORIGINAL ARTICLE

A systematic evaluation of chemicals in hydraulic-fracturing fluids and wastewater for reproductive and developmental toxicity

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Hydraulic-fracturing fluids and wastewater from unconventional oil and natural gas development contain hundreds of substances with the potential to contaminate drinking water. Challenges to conducting well-designed human exposure and health studies include limited information about likely etiologic agents. We systematically evaluated 1021 chemicals identified in hydraulic-fracturing fluids ($n = 925$), wastewater ($n = 132$), or both ($n = 36$) for potential reproductive and developmental toxicity to triage those with potential for human health impact. We searched the REPROTOX database using Chemical Abstract Service registry numbers for chemicals with available data and evaluated the evidence for adverse reproductive and developmental effects. Next, we determined which chemicals linked to reproductive or developmental toxicity had water quality standards or guidelines. Toxicity information was lacking for 781 (76%) chemicals. Of the remaining 240 substances, evidence suggested reproductive toxicity for 103 (43%), developmental toxicity for 95 (40%), and both for 41 (17%). Of these 157 chemicals, 67 had or were proposed for a federal water quality standard or guideline. Our systematic screening approach identified a list of 67 hydraulic fracturing-related candidate analytes based on known or suspected toxicity. Incorporation of data on potency, physicochemical properties, and environmental concentrations could further prioritize these substances for future drinking water exposure assessments or reproductive and developmental health studies.

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INTRODUCTION

Unconventional oil and natural gas development has expanded substantially in the United States in the past decade. Concerns exist about the potential health risks associated with related environmental hazards including exposure to water pollutants.[1,2] Between 2000 and 2013, approximately 8.6 million people were served by a drinking water source located one mile from an unconventional well.[3] Evaluation of relationships between environmental hazards from unconventional natural gas development and risk of adverse human health outcomes is hindered in part by challenges in the exposure assessment. Some of these challenges include incomplete disclosure of the identity and concentrations of chemicals used in unconventional natural gas development,[4,5] the wide range in structures (e.g., organic, inorganic, and radioactive) and physicochemical properties (e.g., log K_{ow}) of chemicals used or produced during development,[6–8] geographic differences in the types of compounds used or produced, the complexity of the dispersion through soil and water, temporal variability in emissions and potential exposures over the life course of a natural gas well,[2] and limited environmental measurements of potentially health-relevant chemicals.[9]

Unconventional natural gas development involves the extraction of gas from previously untapped deposits in deep rock formations using new applications of directional drilling technologies and hydraulic fracturing.[10] After a well is drilled, first vertically and then horizontally into the rock, large quantities of "fracturing fluids", consisting of water, chemicals, and sand (or ceramic beads), are injected under high pressure to create fissures in the rock ("hydraulic fracturing") that release natural gas.[2] Typically, about 15–30 million liters of fluid are used for each well, of which approximately 1–2% consists of chemical additives representing a substantial volume (e.g., 150,000–600,000 liters of chemicals per well over its lifetime).[2] Over 1,000 substances have been identified in fracturing fluids or hydraulic-fracturing wastewater, including solvents, heavy metals, aromatic hydrocarbons, and naturally-occurring radioactive materials, but the exact composition of fracturing fluids remains unknown because chemicals and their concentrations may be classified as confidential business information.[4] Vast amounts of wastewater are generated during unconventional oil and natural gas development. After fracturing, about 30% of injected fluids rapidly return to the surface up through the well as "flowback" (within 1–4 weeks).[11] Over time, "produced" water containing a potentially more harmful mix of the injected fluids along with mobilized naturally-occurring compounds such as heavy metals and radioactive materials slowly resurfaces.[11,12] Flowback and produced wastewater are stored in large open pits (or increasingly commonly in storage tanks) until treatment, reuse, or disposal

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offsite.[11] Possible pathways of potential water contamination due to unconventional natural gas development include faulty or deteriorating well casings, equipment failure, surface spills of fracturing fluids or wastewater on-site or from tanker trucks transporting these liquids, migration of chemicals from fractures to shallow aquifers, leakage from wastewater pits, and unauthorized discharge and release of inadequately treated wastewater into the environment.[1,3,11,13–20] The current evidence suggests that activities at the surface are more likely to contribute to groundwater and surface water contamination; however, the impact of each of these potential pathways on water quality remains difficult to evaluate because of limited data.[3,13,20,21]

Several environmental monitoring studies have suggested that unconventional natural gas development may contaminate ground water[15,19,21,22] and surface water,[23,24] potentially leading to drinking water contamination.[3] These publications have focused primarily on measurements of methane, metals, major cations and anions, and parameters indicative of water quality, such as total dissolved solids, color, or odor.[15,19,23,25] Although these measurements may provide markers of contamination due to hydraulic fracturing, they do not necessarily include measurements of health-relevant chemicals.

Monitoring studies of health-relevant chemicals are emerging.[6,21,26,27] For example, a study commissioned by the West Virginia Department of Environmental Protection examined 13 samples of flowback water and found contamination in excess of drinking water standards with benzene in 10 (77%) samples and with selenium and with toluene each in 3 (23%) samples.[28] In addition, ground and surface water samples collected in a region with intense unconventional natural gas development and known spills in Colorado had greater estrogen and androgen receptor activities based on reporter gene assays in human cell lines, compared with samples from reference areas.[29] More field-based monitoring studies, particularly at residences, are needed to better understand human exposures to chemicals related to unconventional natural gas development.

The biological plausibility for examining the health effects associated with human exposure to hydraulic-fracturing derives mainly from the known or suspected toxic effects of involved chemicals and processes.[29,30] It has been postulated that exposure to known or possible human teratogens from drinking water may occur (e.g., toluene and benzene).[31] McKenzie et al.[32] observed an association between increasing proximity and density of natural gas wells within a 10-mile radius of maternal residence and congenital heart defects.[32] They also observed a decreased risk of pre-term birth and term low birthweight. Further, Stacy et al.[33] observed a decrease in birthweight and an increase in small for gestational age incidence with increasing proximity and density of natural gas wells.[33] As noted by these authors,[32,33] incorporation of environmental sampling or individual exposure measurements and information on migration of potential environmental pollutants could substantially improve upon this non-specific, proximity-based exposure assessment. However, conducting a well-designed sampling campaign is challenging, given the wide variety of potential target pollutants and the limited information available to identify which pollutants have the highest probability of exposure or health impact.

The primary objective of this analysis was to conduct a systematic, screening-level evaluation for potential reproductive and developmental toxicity of chemicals identified in hydraulic-fracturing fluids and wastewater to support prioritization for use in future human exposure studies and health assessments. We used reproductive and developmental toxicity data from a well-recognized source as a first step to triage the vast array of potential environmental contaminants for which information about potential human health effects is otherwise unavailable or insufficient. We focus on reproductive and developmental toxicity because these effects may be early or "signal" indicators of human exposure to environmental hazards due to the relatively short disease latency and vulnerability of the exposed population.[34,35] A secondary objective was to further classify compounds linked to reproductive and developmental toxicity by determining which had current or proposed water quality standards or guidelines as indicators of potential for occurrence in drinking water and current or emerging sampling or removal technologies. Third, we compiled the log octanol–water partition coefficient and the frequency of disclosure of fracturing fluid constituents as additional information that could be used to inform the exposure potential of hydraulic-fracturing chemicals.

METHODS

Classification of Reproductive/Developmental Toxicity

In 2012, the U.S. EPA released a draft progress report on their overall project designed to assess the potential impacts of hydraulic fracturing on drinking water resources using available data and modeling techniques.[4] We obtained the names and Chemical Abstracts Service Registry Numbers (CASRNs) for 1021 chemicals included in the appendix of the report that were used in hydraulic-fracturing fluids ($n = 925$); measured in flowback or produced water ($n = 132$); or both ($n = 36$) across numerous wells and locations.[4] Sources of information included federal and state well permit and construction records, industry-provided data such as the web-based chemical disclosure registry FracFocus,[36] the published literature, and other industry and government reports.

We then searched the REPROTOX information system for reproductive and developmental toxicity data using the CASRNs. REPROTOX is a widely used, publically-available online database of the adverse reproductive and developmental effects of >5000 agents, including medications and environmental chemicals, and is maintained by the Reproductive Toxicology Center (Washington, DC, USA).[37] Results from both animal and human studies from original research articles and toxicity studies reported in drug labeling are cited, reviewed for data quality and strength of the evidence, and summarized in standard formats by subject-matter experts. REPROTOX entries include a succinct statement ("Quick Take") of the direction of animal and human evidence of reproductive or developmental toxicity and a lengthier summary of results from relevant studies.

We designated chemicals as having "no information available" overall if they were either: not present in the database ($N = 644$) or were present but lacked any toxicity data (e.g., only information on chemical properties or product use was available) ($N = 137$). For chemicals with some toxicity information available ($n = 240$), we reviewed the evidence separately based on the toxicity end point (reproductive or developmental) and data source (animal or human) (Figure 1). For each end point and data source, we separately determined whether the evidence supported an association ("possibly associated") or did not support an association ("possibly not associated"). This determination was made by first consulting the Quick Take ($n = 148$). If the Quick Take was absent or did not provide an assessment specific to the data source or end point ($n = 92$), then we assigned the chemical toxicity classification based on the summary. In making these summary-based assignments, we applied exclusionary criteria consistent with the rationale provided in other REPROTOX entries. We excluded results from studies for which methods were unavailable or unclear, studies not following standard toxicity guidelines, studies in which the chemical of interest was evaluated as part of a mixture of other compounds, studies for which only an abstract was available, and those defined as case studies (typically a report of a high exposure incident for <5 individuals). If any studies meeting our criteria reported positive associations, then we classified the chemical as "possibly associated" to create a more inclusive list of candidate analytes.

We then summarized the evidence across animal and human sources for each toxicity end point. Chemicals were considered to be "possibly associated" when either human or animal data suggested an association. We classified chemicals as "possibly not associated" when both evidence from human and animal data did not support an association or when toxicity information from either animal or human studies did not support an association and toxicity could not be assigned based on the other data source. Finally, we evaluated the evidence jointly for both reproductive and developmental toxicity end points, and determined whether chemicals were possibly associated or possibly not associated with either or both endpoints. We calculated frequencies and percentages of

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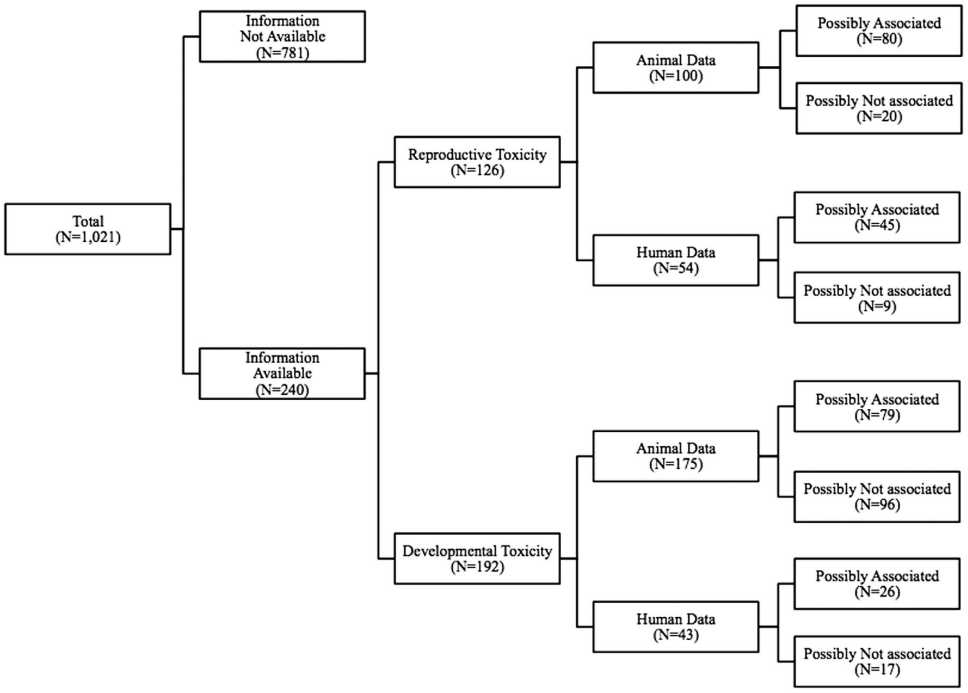

Figure 1. Reproductive and developmental toxicity data available for hydraulic-fracturing chemicals in the REPROTOX information system and possible association with toxicity. Numbers of subcategories under "Information Available" may not add up to the total, as toxicity information may be available for both endpoints, and/or both animal and human data.

hydraulic-fracturing fluid and wastewater chemicals in each of these categories.

Determination of Water Quality Standards

Next, we determined whether the hydraulic-fracturing chemicals linked to reproductive or developmental toxicity based on our REPROTOX evaluation had established drinking water standards or guidelines. First, we assessed which chemicals had a Maximum Contaminant Level (MCL), which is a legally enforceable public water system standard under the National Primary Drinking Water Regulations of the Safe Drinking Water Act. The presence of an MCL indicates that there is a validated sampling methodology, evidence of adverse human health effects, and a reference concentration against which to compare future measurements.[38] Second, we determined whether the substance had either a Maximum Contaminant Level Goal (MCLG) or an EPA oral Reference Dose (RfD). An MCLG is the contaminant concentration in drinking water at or below which no harm would be anticipated to occur. It can serve as a health-based reference concentration. It does not, however, consider sampling techniques or feasibility of removal and is not legally enforceable. An oral RfD is the amount of a compound that can be ingested daily over a lifetime without appreciable risk of harm.[39] It can be converted into a drinking water reference concentration by assuming a 70-kg adult ingests 2 L of water per day and that there are no other sources of exposure, yielding a comparable interpretation as an MCLG. Third, we noted the presence of chemicals on the EPA's Contaminant Candidate Lists (CCLs).[40] CCLs include unregulated contaminants identified for evaluation for future drinking water standards and were published in 1998 (CCL 1), 2005 (CCL2), 2009 (CCL 3), and in a draft form in 2015 (CCL4). The presence on a CCL indicates that a compound has been proposed for regulation due to occurrence or hazard information, but has no enforceable limit because the sampling or measurement methodology is still under development, a feasible removal technique is lacking, a safe level has not been determined, the compound is infrequently present in municipal water systems, or a regulatory decision is in progress.[38,41]

Octanol–Water Coefficient

Information on physicochemical properties could be used to predict the likelihood of chemicals being present in drinking water. Therefore, we estimated the log octanol–water partition coefficient (log K_{ow}) using EPI Suite™, a Windows-based tool developed by the EPA for estimating physicochemical properties of environmental organic compounds.[42] Log K_{ow} is used as a relative indicator of the tendency of an organic compound to adsorb to soil. Log K_{ow} values are generally inversely related to aqueous solubility and directly proportional to molecular weight.[43] Chemicals that are hydrophilic (log $K_{ow} < 0$) tend to be more mobile in water, whereas chemicals that are more hydrophobic (log $K_{ow} > 4$) tend to associate with organic matter and soil. The log K_{ow} also provides some indication of toxicokinetics. Chemicals with a log K_{ow} of 2–4 tend to absorb well through the skin, and those with log K_{ow} of 5–7 tend to bioconcentrate in organisms.[43]

Disclosure Frequency of Fracturing Fluid Chemicals

We identified which fracturing fluid constituents were frequently disclosed based on a short list of frequently reported chemicals provided on the FracFocus website,[36] a voluntary disclosure website of the oil and gas industry. In addition, we indicated which chemicals were listed in at least 10% of all disclosures reported to the FracFocus website, as compiled by the EPA.[3]

RESULTS

Of 1021 identified hydraulic-fracturing chemicals, 781 (76%) lacked reproductive and developmental toxicity information (Figure 1, Table 1). Of the 240 chemicals with available information, 126 chemicals had reproductive toxicity data available, and 192 had developmental toxicity data available (Figure 1, Table 1). The majority of evidence available to determine toxicity came from animal data. For reproductive toxicity, 100 chemicals had animal data compared with 54 chemicals with human data (Figure 1). For developmental toxicity, 175 chemicals had animal data, while 43 had human data available (Figure 1).

Of 126 chemicals with reproductive toxicity data, 103 (82%) chemicals were possibly associated with adverse reproductive effects, while 23 (18%) were classified as possibly not associated (Table 1). Of 192 chemicals with developmental toxicity information, 95 (49%) were possibly associated with developmental toxicity and 97 (51%) were possibly not associated. A total of 41

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Table 1. Reproductive and developmental toxicity of disclosed hydraulic-fracturing chemicals ($n = 1021$).[a]

	Total	*Fracturing fluids*	*Wastewater*
	N (%)	*N (%)*	*N (%)*
Any reproductive and developmental toxicity information	$n = 1021$	$n = 925$	$n = 132$
Toxicity information available	240 (24%)	194 (21%)	73 (55%)
Toxicity information unavailable	781 (76%)	731 (79%)	59 (45%)
Reproductive toxicity information available[b]	$n = 126$	$n = 99$	$n = 43$
Possibly associated[c]	103 (82%)	79 (80%)	39 (91%)
Possibly not associated	23 (18%)	20 (20%)	4 (9%)
Developmental toxicity information available[b]	$n = 192$	$n = 156$	$n = 57$
Possibly associated[c]	95 (49%)	72 (46%)	38 (67%)
Possibly not associated	97 (51%)	84 (54%)	19 (33%)

[a]All chemicals were obtained from the US Environmental Protection Agency hydraulic-fracturing progress report (2012). Only chemicals with available Chemical Abstracts Service Registry Numbers ($n = 1021$) were screened for reproductive and developmental toxicity. [b]Some chemicals have both reproductive and developmental toxicity information available; and therefore, numbers do not add to total with toxicity information available. [c]A total of 41 chemicals were possibly associated with both endpoints; therefore, the total # of chemicals possibly associated with at least one endpoint is $103+95-41=157$.

chemicals were possibly associated with both endpoints. Toxicity information was available for a greater proportion of wastewater constituents (55%) compared with fracturing fluid chemicals (21%) (Table 1). A greater percentage of wastewater chemicals compared with fracturing fluid chemicals with toxicity data were possibly associated with reproductive toxicity (91% compared with 80%) and with developmental toxicity (67% compared with 46%).

Information about the 157 chemicals associated with at least one toxicity end point is presented in Table 2. Of these, 95 were constituents of fracturing fluids, 38 were detected in wastewater, and 24 in both. A total of 67 had a current federal water quality standard (MCL: $n = 23$), or had a reference value that could be used as a water quality guideline (MCLG: $n = 23$, RfD: $n = 48$), or were proposed for a federal water quality standard (CCL: $n = 24$). Several chemicals had more than one of these indicators. For example, the 23 chemicals with MCLGs all had MCLs. Examples of fracturing fluid constituents associated with reproductive or developmental effects with a water quality standard or guideline included: 1,2-propanediol, acrolein, bisphenol-A, and chlorine dioxide. Examples of chemicals in the wastewater linked to adverse reproductive or developmental effects with a water quality standard or guideline included: metals (e.g., arsenic, cadmium, lead, and mercury); polycyclic aromatic hydrocarbons (e.g., benzo(a)pyrene); volatile organic compounds (e.g., benzene and toluene); and other organics (e.g., di(2-ethylhexyl) phthalate and dibutyl phthalate). Reproductive or developmental outcomes were the basis for 3 out of 23 chemicals with an MCLG/MCL: benzo (a)pyrene, chlorine dioxide, and di(2-ethylhexyl) phthalate. A reproductive or developmental outcome was the basis for 9 of 48 chemicals with an oral reference dose, though four of these were structurally related: acrylic acid, borax, boric acid, boron, boron sodium oxide, carbon disulfide, chlorine, methyl ethyl ketone, and phenol.

The 157 chemicals possibly associated with reproductive or developmental toxicity included a wide variety of inorganic and organic structures (Table 2). The 94 chemicals with log K_{ow} values had estimates ranging from −13.17 (ethylenediaminetetraacetic acid tetrasodium salt) to 8.39 (di(2-ethylhexyl) phthalate). A total of 40 had $\log K_{ow} < 0$, indicating high mobility in water, 16 chemicals had a log K_{ow} in the 2–4 range, indicating tendency for dermal absorption, and 6 had log K_{ow} of 5–7, indicating ability to bioconcentrate. There were 119 fracturing fluid constituents possibly associated with reproductive and/or developmental toxicity (Table 2). Of these, 18 were reported to be frequently disclosed.

DISCUSSION

Based on our systematic evaluation of 1021 chemicals in hydraulic-fracturing fluids or wastewater, the substances and processes used in unconventional natural gas development indicate the potential for reproductive and developmental health risks. However, the majority of chemicals (76%) had undetermined toxicity due to insufficient information. Thus, we were able to evaluate reproductive and/or developmental toxicity for only 24% of chemicals. Of 240 chemicals with sufficient information available, 157 (65%) were possibly associated with reproductive and/or developmental toxicity. The 67 chemicals found to be possibly associated with reproductive or developmental toxicity and with a current drinking water standard, health-based guideline, or proposed for a drinking water standard included a range of compounds, such as metals, solvents, pesticides, polycyclic aromatic hydrocarbons, and volatile organic compounds. These 67 compounds could represent a starting point for consideration in future drinking water exposure assessments or reproductive or developmental health studies of unconventional oil and natural gas development. Effect levels, concentrations in environmental media, and physicochemical properties of the compounds could be incorporated to further prioritize this list for future health studies.

Because of the large number of known and potentially unknown chemicals used and produced in unconventional oil and natural gas development, a major challenge to conduct efficient and well-designed human exposure assessments is the lack of a clear target list of chemicals. The health effects of unconventional natural gas development have yet to be elucidated; thus, putative etiologic agents are not known. Therefore, biological and environmental measurements of health-relevant chemicals are limited, and a way to select priority chemicals for sampling is needed. Ideally, selection of target analytes would be based on a combination of human toxicity and exposure levels. However, in light of the paucity of data on environmental concentrations of hydraulic fracturing-related compounds, we prioritized chemicals based primarily on toxicologic potential for one related set of outcomes. This systematic and transparent approach could be updated to incorporate tap water sampling data as it becomes available. In addition, incorporation of environmental fate and transport parameters of these compounds would help predict the likelihood of these compounds entering drinking water sources.

Some previously published studies have characterized toxicological properties of chemicals used in unconventional oil and natural gas development with a focus on the fracturing fluid constituents. Stringfellow et al.[8] compiled inhalation and oral

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Table 2. Characteristics of hydraulic-fracturing chemicals possibly associated with reproductive and/or developmental toxicity ($n = 157$).

CASRNs	Chemical name	Source	Evidence for toxicity (animal/human)		MCLG/MCL (mg/l)	Contaminant candidate list[a]	Oral reference dose (mg/kg/day)	Estimated log K_{ow}[b]
			Reproductive toxicity[c]	Developmental toxicity[d]				
Existing or proposed water quality standard or health guideline (n = 67)								
71-36-3	1-Butanol	FF	+/o	+/o	—	CCL 3	0.10	0.84
111-76-2	2-Butoxyethanol[e]	FF	+/o	o/o	—	—	0.1	0.57
109-86-4	2-Methoxyethanol	FF	+/o	+/o	—	CCL 3	—	−0.91
95-48-7	2-Methylphenol	WW	+/o	o/o	—	CCL 1, 2	0.05	2.06
108-39-4	3-Methylphenol	WW	+/o	o/o	—	—	0.05	2.06
75-07-0	Acetaldehyde[e]	FF	o/o	+/+	—	CCL 3	—	−0.17
67-64-1	Acetone	FF, WW	+/o	−/o	—	—	0.9	−0.24
98-86-2	Acetophenone	FF, WW	+/o	o/o	—	—	0.1	1.67
107-02-8	Acrolein	FF, WW	o/o	+/o	—	CCL 3	0.0005	0.19
79-06-1	Acrylamide	FF	+/+	−/o	0/TT	—	0.002	−0.81
79-10-7	Acrylic acid	FF	+/o	−/o	—	—	0.5[f]	0.44
309-00-2	Aldrin	WW	o/o	+/o	—	CCL 1	0.003	6.75
7429-90-5	Aluminum	FF, WW	o/o	+/o	—	CCL 1, 2	—	NA
62-53-3	Aniline	FF	o/o	+/o	—	CCL 3	—	1.08
7440-36-0	Antimony	WW	+/o	−/o	0.006/0.006	—	0.0004	NA
7440-38-2	Arsenic	FF, WW	+/+	o/o	0/0.010	—	0.0003	NA
71-43-2	Benzene	FF, WW	+/+	−/+	0/0.005	—	0.004	1.99
50-32-8	Benzo(a)pyrene	WW	o/o	+/o	0/0.0002[g]	—	—	6.11
80-05-7	Bisphenol A	FF	+/+	+/+	—	—	0.05	3.64
1303-96-4	Borax[e]	FF	+/+	+/o	—	—	0.2[f]	NA
10043-35-3	Boric acid[e]	FF	+/+	+/o	—	—	0.2[f]	NA
7440-42-8	Boron	WW	+/+	o/o	—	CCL 1, 2	0.2[f]	NA
1330-43-4	Boron sodium oxide[e]	FF	+/+	+/o	—	—	0.2[f]	NA
7440-43-9	Cadmium	WW	+/+	o/o	0.005/0.005	—	0.0005/0.001	NA
75-15-0	Carbon disulfide	WW	o/o	+/o	—	—	0.1[f]	1.94
7782-50-5	Chlorine	FF, WW	+/+	+/+	—	—	0.1[f]	NA
10049-04-4	Chlorine dioxide[h]	FF	+/+	+/+	0.8/0.8[g]	—	0.03	NA
67-66-3	Chloroform	WW	+/+	−/o	0.07/0.070	—	0.1	1.52
74-87-3	Chloromethane	WW	+/o	−/o	—	CCL 3	—	1.09
7440-47-3	Chromium[i]	WW	+/o	+/o	0.1/0.1	—	0.003	NA
7440-48-4	Cobalt	WW	o/o	+/o	—	CCL 3	—	NA
7440-50-8	Copper	FF, WW	+/+	+/o	1.3/1.3	—	—	NA
98-82-8	Cumene	FF, WW	+/o	o/o	—	—	0.1	3.45
57-12-5	Cyanide, free	WW	o/o	+/o	0.2/0.2	—	—	−0.69
117-81-7	Di(2-ethylhexyl) phthalate	FF, WW	+/−	+/−	0/0.006[g]	—	0.02	8.39
84-74-2	Dibutyl phthalate	WW	+/+	+/+	—	—	0.1	4.61
75-09-2	Dichloromethane	WW	o/+	−/o	0/0.005	—	0.006	1.34
60-57-1	Dieldrin	WW	o/o	+/o	—	CCL 1	0.00005	5.45
84-66-2	Diethyl phthalate	WW	−/o	+/o	—	—	0.8	2.65
106-89-8	Epichlorohydrin	FF	+/o	−/o	0/TT	—	—	0.63
100-41-4	Ethylbenzene	FF, WW	o/o	+/o	0.7/0.7	—	0.1	3.03
107-21-1	Ethylene glycol[e]	FF, WW	+/o	+/o	—	CCL 3	2	−1.20
75-21-8	Ethylene oxide	FF	+/+	+/o	—	CCL 3	—	−0.05
50-00-0	Formaldehyde	FF	+/+	−/+	—	CCL 3	0.2	0.35
7439-92-1	Lead	FF, WW	o/+	o/+	0/TT	—	—	NA
58-89-9	Lindane	WW	+/o	−/−	0.0002/0.0002	—	0.0003	4.26
7439-96-5	Manganese	WW	o/o	+/o	—	CCL 1	0.14	NA
7439-97-6	Mercury (inorganic)	WW	o/o	o/+	0.002/0.002	—	—	NA
67-56-1	Methanol[e]	FF, WW	o/o	+/o	—	CCL 3	2	−0.63
78-93-3	Methyl ethyl ketone	WW	+/o	+/o	—	—	0.6[f]	0.26

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Table 2. (Continued).

CASRNs	Chemical name	Source	Evidence for toxicity (animal/human)		MCLG/MCL (mg/l)	Contaminant candidate list[a]	Oral reference dose (mg/kg/day)	Estimated log K_{ow}[b]
			Reproductive toxicity[c]	Developmental toxicity[d]				
7439-98-7	Molybdenum	WW	+/+	−/o	—	CCL 3	—	NA
872-50-4	N-Methyl-2-pyrrolidone	FF	+/o	o/o	—	CCL 3	—	−0.11
91-20-3	Naphthalene[e]	FF, WW	o/o	+/o	—	CCL 1	0.02	3.17
7440-02-0	Nickel	WW	o/+	+/o	—	—	0.02	NA
72-55-9	p,p'-DDE	WW	+/+	+/+	—	CCL 1, 2	—	6.00
108-95-2	Phenol	FF, WW	+/o	−/o	—	—	0.3[f]	1.51
85-44-9	Phthalic anhydride	FF	+/o	+/o	—	—	2	2.07
91-22-5	Quinoline	FF	o/o	+/o	—	CCL 3	—	2.14
7782-49-2	Selenium	WW	o/o	+/o	0.05/0.05	—	0.005	NA
7440-24-6	Strontium	WW	o/+	o/+	—	CCL 3	—	NA
100-42-5	Styrene	FF	o/+	+/−	0.1/0.1	—	0.2	2.89
127-18-4	Tetrachloroethylene	WW	o/+	−/−	0/0.005	—	0.006	2.97
108-88-3	Toluene	FF, WW	o/o	o/+	1/1	—	0.08	2.54
7440-62-2	Vanadium	WW	+/o	o/o	—	CCL 1, 2, 3	—	NA
1330-20-7	Xylenes	FF, WW	+/o	−/o	10/10	—	0.2	3.09
7440-66-6	Zinc	FF, WW	o/+	o/o	—	—	0.3	NA
7646-85-7	Zinc chloride	FF	+/−	+/−	—	—	0.3	NA
No existing or proposed water quality standard or health guideline (n = *90*)								
71-23-8	1-Propanol	FF	o/o	+/o	—	—	—	0.35
57-55-6	1,2-Propanediol	FF, WW	−/−	+/+	—	—	—	−0.78
111-90-0	2-(2-Ethoxyethoxy)ethanol	FF	+/o	o/o	—	—	—	−0.69
110-80-5	2-Ethoxyethanol	FF	+/o	+/o	—	—	—	−0.42
2682-20-4	2-Methyl-3(2H)-isothiazolone	FF	+/o	−/o	—	—	—	−0.83
106-44-5	4-Methylphenol	WW	+/o	o/o	—	—	—	2.06
26172-55-4	5-Chloro-2-methyl-3(2H)-isothiazolone	FF	+/o	−/o	—	—	—	−0.34
57-97-6	7,12-Dimethylbenz(a)anthracene	WW	o/o	+/o	—	—	—	6.62
107-13-1	Acrylonitrile	WW	o/o	+/o	—	—	—	0.21
7446-70-0	Aluminum chloride	FF	+/o	o/o	—	—	—	NA
12125-02-9	Ammonium chloride[e]	FF	o/o	+/−	—	—	—	NA
10025-91-9	Antimony trichloride	FF	+/o	−/o	—	—	—	NA
1309-64-4	Antimony trioxide	FF	+/o	o/o	—	—	—	NA
68131-74-8	Ashes, residues	FF	o/+	+/o	—	—	—	NA
80-08-0	Benzamine, 4,4'-sulfonylbis-	FF	o/o	o/+	—	—	—	0.77
100-51-6	Benzyl alcohol	WW	o/o	o/+	—	—	—	1.08
7440-70-2	Calcium	WW	+/+	+/−	—	—	—	NA
1305-62-0	Calcium hydroxide	FF	o/o	o/+	—	—	—	−0.87
1333-86-4	Carbon black	FF	+/o	o/o	—	—	—	NA
124-38-9	Carbon dioxide	FF, WW	o/o	+/o	—	—	—	0.83
471-34-1	Carbonic acid calcium salt (1:1)	FF	o/o	+/−	—	—	—	−2.12
1066-30-4	Chromium(III) acetate	FF	+/o	+/o	—	—	—	−0.98
7758-98-7	Copper sulfate	FF	o/o	+/o	—	—	—	NA
7447-39-4	Copper(II) chloride	FF	+/+	+/o	—	—	—	NA
91-64-5	Coumarin	FF	o/o	o/+	—	—	—	1.51
50-99-7	D-Glucose	FF	o/o	+/+	—	—	—	−2.89
3252-43-5	Dibromoacetonitrile	FF	o/o	+/o	—	—	—	0.47
7173-51-5	Didecyldimethylammonium chloride[e]	FF	+/o	−/o	—	—	—	4.66
111-42-2	Diethanolamine	FF	+/o	o/o	—	—	—	−1.71
111-46-6	Diethylene glycol	FF	+/o	−/o	—	—	—	−1.47
111-77-3	Diethylene glycol monomethyl ether	FF	+/o	o/o	—	—	—	−1.18
627-93-0	Dimethyl adipate	FF	o/o	+/o	—	—	—	1.39

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Table 2. (Continued).

CASRNs	Chemical name	Source	Evidence for toxicity (animal/human)		MCLG/MCL (mg/l)	Contaminant candidate list[a]	Oral reference dose (mg/kg/day)	Estimated log K_{ow}[b]
			Reproductive toxicity[c]	Developmental toxicity[d]				
1119-40-0	Dimethyl glutarate	FF	+/o	o/o	—	—	—	0.90
63148-62-9	Dimethyl polysiloxane	FF	+/o	−/o	—	—	—	8.16
64-17-5	Ethanol[e]	FF	o/+	o/+	—	—	—	−0.14
141-43-5	Ethanolamine	FF	+/o	−/o	—	—	—	−1.61
60-00-4	Ethylenediaminetetraacetic acid	FF	o/o	+/o	—	—	—	−3.86
64-02-8	Ethylenediaminetetraacetic acid tetrasodium salt[e]	FF	o/o	+/o	—	—	—	−13.17
139-33-3	Ethylenediaminetetraacetic acid, disodium salt	FF	o/o	+/o	—	—	—	−11.70
10028-22-5	Ferric sulfate	FF	o/+	o/o	—	—	—	NA
75-12-7	Formamide	FF	o/o	+/o	—	—	—	−1.61
79-14-1	Glycolic acid	FF	+/o	+/o	—	—	—	−1.07
5470-11-1	Hydroxylamine hydrochloride	FF	o/o	+/o	—	—	—	NA
7439-89-6	Iron	FF, WW	o/+	o/o	—	—	—	NA
7720-78-7	Iron(II) sulfate	FF	o/+	o/o	—	—	—	NA
67-63-0	Isopropanol[e]	FF, WW	o/o	+/o	—	—	—	0.28
7439-93-2	Lithium	WW	o/+	o/+	—	—	—	NA
7439-95-4	Magnesium	WW	o/+	o/o	—	—	—	NA
7786-30-3	Magnesium chloride	FF	o/+	o/o	—	—	—	NA
7791-18-6	Magnesium chloride hexahydrate	FF	o/+	o/o	—	—	—	NA
1309-42-8	Magnesium hydroxide	FF	o/+	o/o	—	—	—	NA
1309-48-4	Magnesium oxide[e]	FF	o/+	o/o	—	—	—	NA
119-36-8	Methyl salicylate	FF	+/o	+/o	—	—	—	2.60
110-91-8	Morpholine	FF	o/o	+/o	—	—	—	−0.56
68-12-2	N,N-Dimethylformamide[e]	FF	o/o	+/o	—	—	—	−0.93
110-26-9	N,N'-Methylenebisacrylamide	FF	+/o	o/o	—	—	—	−1.52
7786-81-4	Nickel sulfate	FF	o/+	+/o	—	—	—	NA
25154-52-3	Nonylphenol (mixed)	FF	o/o	+/o	—	—	—	5.99
10028-15-6	Ozone	FF	+/o	+/+	—	—	—	NA
79-21-0	Peracetic acid	FF	+/o	o/o	—	—	—	−1.07
7447-40-7	Potassium chloride	FF	+/+	o/−	—	—	—	NA
7778-50-9	Potassium dichromate	FF	+/o	+/o	—	—	—	NA
7681-11-0	Potassium iodide	FF	o/o	o/+	—	—	—	NA
14808-60-7	Quartz	FF	+/o	o/o	—	—	—	NA
81-88-9	Rhodamine B	FF	o/o	+/o	—	—	—	1.85
7631-86-9	Silica	FF, WW	+/o	o/o	—	—	—	NA
2492-26-4	Sodium 2-mercaptobenzothiolate	FF	+/o	−/o	—	—	—	−0.48
532-32-1	Sodium benzoate	FF	o/o	+/o	—	—	—	−2.27
7647-15-6	Sodium bromide	FF	+/o	−/−	—	—	—	NA
151-21-3	Sodium dodecyl sulfate[e]	FF	o/o	+/o	—	—	—	1.69
7681-52-9	Sodium hypochlorite	FF	+/+	+/+	—	—	—	NA
7681-82-5	Sodium iodide	FF	o/o	o/+	—	—	—	NA
7631-99-4	Sodium nitrate	FF	+/o	o/o	—	—	—	NA
7632-00-0	Sodium nitrite	FF	+/o	o/o	—	—	—	NA
11138-47-9	Sodium perborate	FF	+/−	o/o	—	—	—	NA
54-21-7	Sodium salicylate	FF	o/+	+/o	—	—	—	−1.49
10476-85-4	Strontium chloride	FF	o/+	o/+	—	—	—	NA
7440-28-0	Thallium and compounds	WW	o/+	o/+	—	—	—	NA
68-11-1	Thioglycolic acid[e]	FF	+/o	−/o	—	—	—	0.03
62-56-6	Thiourea	FF	o/o	+/o	—	—	—	−1.31
7440-31-5	Tin	WW	o/o	+/o	—	—	—	NA

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Table 2. (Continued).

CASRNs	Chemical name	Source	Evidence for toxicity (animal/human)		MCLG/MCL (mg/l)	Contaminant candidate list[a]	Oral reference dose (mg/kg/day)	Estimated log K_{ow}[b]
			Reproductive toxicity[c]	Developmental toxicity[d]				
7772-99-8	Tin(II) chloride	FF	o/o	+/o	—	—	—	NA
7440-32-6	Titanium	WW	+/o	o/o	—	—	—	NA
13463-67-7	Titanium dioxide	FF	+/o	o/o	—	—	—	NA
126-73-8	Tributyl phosphate	FF	+/o	+/o	—	—	—	3.82
112-27-6	Triethylene glycol	FF	+/o	−/o	—	—	—	−1.75
112-24-3	Triethylenetetramine	FF	o/o	+/o	—	—	—	−2.65
150-38-9	Trisodium ethylenediaminetetraacetate	FF	o/o	+/o	—	—	—	−13.15
57-13-6	Urea	FF	o/o	+/o	—	—	—	−1.56
7732-18-5	Water[e]	FF	o/+	o/o	—	—	—	NA

Abbreviations: CASRNs, Chemical Abstract Service Registry Numbers; CCL, Contaminant Candidate List; FF, fracturing fluid; MCL, Maximum Contaminant Level; MCLG, Maximum Contaminant Level Goal; NA, not applicable; WW, wastewater. [a]CCLs are lists of unregulated contaminants prioritized for evaluation for future drinking water standards and were published in 1998 (CCL 1), 2005 (CCL2), 2009 (CCL 3), and in a draft form in 2015 (CCL4). [b]Estimated log K_{ow} values were obtained from EPI Suite.[42] Log K_{ow} values for most inorganic compounds are not applicable (NA). [c]+, evidence supports a positive association between chemical and reproductive toxicity; −, evidence supports an inverse association between chemical and reproductive toxicity; o, evidence does not support an association. [d]+, evidence supports a positive association between chemical and developmental toxicity; −, evidence supports an inverse association between chemical and developmental toxicity; o, evidence does not support an association. [e]Chemicals in fracturing fluids disclosed in >10% of oil or gas wells, according to FracFocus and/or EPA, 2015 for 18 out of 119 chemicals detected in fracturing fluids (FF). [f]The critical endpoint was a reproductive or developmental outcome for 9 chemicals, out of 48 chemicals with an oral reference dose. [g]Potential long-term health effects of exposure above MCL was associated with reproductive or developmental outcomes for 3 out of 23 chemicals with an MCLG/MCL. [h]Maximum Residual Disinfectant Level Goal (MRDLG) and Maximum Residual Disinfectant Level for chlorine dioxide. [i]Oral reference dose for chromium applies to chromium (VI).

acute toxicity values (i.e., lethal dose-50) for 81 hydraulic-fracturing chemical additives and found that 13 (16%) chemicals exhibited low or moderate toxicity; 25 (31%) lacked mammalian toxicity data, and the remainder ($n = 43$, 53%) were considered as non-toxic.[8] Wattenberg et al.[44] characterized the acute and chronic toxicity for 168 constituents of hydraulic-fracturing fluids commonly used in North Dakota, and found that 24 of the 168 (14%) constituents were associated with reproductive and developmental toxicity.[44] This is similar to our observation that 119 (12%) of all 961 constituents of fracturing fluids reviewed were associated with either reproductive or developmental toxicity. They also reported sparse data for commonly used fracturing chemicals with 59% and 35%, respectively, lacking chronic and acute toxicity information.[44] Kahrilis et al.[45] specifically examined the toxic effects of biocides used in fracturing fluids and identified five chemicals that exhibited reproductive or developmental toxicity.[45] We also identified two of these five substances (chlorine dioxide and didecyldimethylammonium chloride) as being possibly associated with reproductive or developmental toxicity; we did not evaluate the other three (bronopol, dazomet, and tributyltetradecylphosphonium) because they were not present in the REPROTOX database, possibly because of limited available data. Based on publically-available toxicity databases, material safety datasheets, and scientific publications, Colborn et al.[30] identified 353 chemicals used during natural gas operations with more than 75% linked to at least 1 of 12 health endpoints (e.g., respiratory effects and cancer).[30] In addition, a US House of Representatives report[46] found that 9 of 750 chemicals used in oil and gas hydraulic fracturing in 2005–2009 had MCLs which they applied as a proxy for toxicity.[46]

An improved understanding of the fate and transport of chemicals used or produced in unconventional natural gas development could help predict the exposure potential. We included the log K_{ow} as one physicochemical property predictive of mobility in the environment. Other investigators have compiled more detailed physicochemical properties on a subset of fracturing fluids to predict fate and transport.[8,45] For example, Rogers et al.[47] developed a screening framework for prioritizing 659 constituents of fracturing fluids likely to be present in groundwater using mobility and persistence characteristics and frequency of disclosure, and identified 15 chemicals of interest.[47] Three of these chemicals had a health-based standard and were also identified as candidate analytes using our toxicity-based framework: acrylamide, ethylbenzene, and xylenes. Combining our toxicity-based approach with a chemistry-based framework could inform the design of future studies.

Our analysis includes a systematic and transparent review of more than >1000 chemicals found in both fracturing fluids and wastewater. Gaps in our knowledge of the toxicities of chemicals related to hydraulic fracturing highlight the need to improve our understanding of the potential adverse health effects associated with these compounds. Although a single oil or natural gas well will not be associated with >1000 compounds, each well could yield a complex mixture of tens or hundreds of substances[44] that may lead to enhanced toxicity compared with the evaluation of single chemical compounds in isolation. Our observation that a greater proportion of chemicals in wastewater were linked to reproductive and developmental toxicity compared with fracturing fluids was consistent with previous findings suggesting wastewater produced by unconventional oil and natural gas activities may be more toxic than the fracturing fluids themselves. This may be in part because a greater proportion of wastewater chemicals had available toxicity information, and null toxicology studies may be more likely to remain unreported. Nevertheless, additional focus may be needed to study not only what chemicals go into the well, but also what chemicals and by-products are generated during natural gas operations.

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Given the wide range of potential compounds associated with unconventional natural gas development and the paucity of exposure measurement data, we applied a screening-level evaluation of reproductive and developmental toxicity of these chemicals to narrow the list to those chemicals with a higher potential for public health impact. Several uncertainties were present in our analysis. Fracturing fluid chemicals classified as confidential business information under the Toxic Substances Control Act could not be included.[4] In addition, the list of >1000 substances was obtained by the EPA several years ago and different formulations may be in use over time. We relied on one publicly available database to classify the 1021 chemicals for reproductive and developmental toxicity and did not perform a comprehensive literature review for each chemical. Therefore, the absence of a listing in REPROTOX does not necessarily mean an absence of health hazard information. The REPROTOX® database is updated on an agent-by-agent basis, and the literature summaries may not include the most current information on specific chemicals. Also, publication bias may occur, in which null or negative findings are not published. However, comparisons of REPROTOX against other public reproductive toxicity databases have revealed that REPROTOX has a high consistency with other sources.[48] We erred on the side of being more inclusive with our list, to avoid eliminating a potentially health-relevant compound. We included compounds possibly associated with reproductive or developmental toxicity and did not conduct a traditional risk assessment approach that considered the dose at which the compounds elicited an effect. We used frequency of disclosure based on the FracFocus website as an indicator of prevalence or potential exposure. However, this information source only applies to compounds in fracturing fluids, the list is not complete, reporting is voluntary, and does not provide any information on naturally-occurring compounds mobilized from the gas extraction process that may be present in wastewater.

We used current and proposed water quality standards as indicators of occurrence, toxicity, and sampling and removal methodologies. One paradox worth noting is that hydraulic fracturing chemicals were exempted from complying with the EPA Safe Drinking Water Act under the Energy Policy Act of 2005.[49]

Although drinking water contamination has been identified as an important potential source of exposure associated with hydraulic fracturing, other public health concerns in relation to unconventional natural gas development include air pollution, greenhouse gas emissions, noise pollution, seismic activities and social stressors.[1,50] Quantification of these potential exposures remains vital for evaluation of the public health impact of unconventional oil and natural gas extraction.

CONCLUSION

Though data are limited, numerous constituents of fracturing fluids and wastewater have been linked to reproductive and/or developmental toxicity. Therefore, carefully designed, rigorous exposure, and epidemiologic studies are urgently needed to investigate public health uncertainties and form a scientific basis for appropriate evidence-based policies. The 67 chemicals we identified as possibly associated with either reproductive or developmental toxicity with a current or proposed federal drinking water standard or health-based guideline represent a feasible starting point for evaluation in future drinking water exposure studies or human health studies particularly with respect to these outcomes. Further prioritization could be achieved with the inclusion of environmental measurements from specific geographic regions of interest, as those data become available, in addition to information on physicochemical properties and toxicologic potency.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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