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Overview of Chronic Oral Toxicity Values for Chemicals Present in Hydraulic Fracturing Fluids, Flowback, and Produced Waters

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Supporting Information

ABSTRACT: Concerns have been raised about potential public health effects that may arise if hydraulic fracturing-related chemicals were to impact drinking water resources. This study presents an overview of the chronic oral toxicity values—specifically, chronic oral reference values (RfVs) for noncancer effects, and oral slope factors (OSFs) for cancer—that are available for a list of 1173 chemicals that the United States (U.S.) Environmental Protection Agency (EPA) identified as being associated with hydraulic fracturing, including 1076 chemicals used in hydraulic fracturing fluids and 134 chemicals detected in flowback or produced waters from hydraulically fractured wells. The EPA compiled RfVs and OSFs using six governmental and intergovernmental data sources. Ninety (8%) of the 1076 chemicals reported in hydraulic fracturing fluids and 83 (62%) of the 134 chemicals reported in flowback/produced water had a chronic oral RfV or OSF available from one or more of the six sources. Furthermore, of the 36 chemicals reported in hydraulic fracturing fluids in at least 10% of wells nationwide (identified from EPA's analysis of the FracFocus Chemical Disclosure Registry 1.0), 8 chemicals (22%) had an available chronic oral RfV. The lack of chronic oral RfVs and OSFs for the majority of these chemicals highlights the significant knowledge gap that exists to assess the potential human health hazards associated with hydraulic fracturing.

INTRODUCTION

Horizontal drilling and hydraulic fracturing technologies have allowed a significant increase in the production of both natural gas and oil in the United States.[1] Concerns have been raised surrounding the potential public health impacts of this practice,[2−6] however, with much interest and uncertainty centering on the potential for hydraulic fracturing-related chemicals to impact drinking water resources.[1,5−7]

Hydraulic fracturing relies on pumping often millions of gallons of fracturing fluid into wells under high pressure to create fractures in a hydrocarbon formation, with subsequent release and flow of oil and gas to the surface. Fractures are held open by proppants, typically sands, to allow oil and gas to flow from small pores within the rock to the production well. Although fracturing fluid is composed primarily (≥98%) of a carrier (typically water) and proppant, it also contains <2% chemical additives including gelling agents, breakers, acids, biocides, corrosion inhibitors, friction reducers, and surfactants.[5,8−10] Rather than a single chemical formula being used in the fracturing process, the composition of fracturing fluid varies from one geological basin or formation to another and across different hydraulic fracturing companies.[8] Recent studies have raised concern that we lack sufficient data on the chemical composition, toxicity, and environmental fate of hydraulic fracturing fluids, representing a potentially significant data gap for public health decision making.[2,9,11,12] Some of the chemicals used in hydraulic fracturing fluids have been linked to adverse human health outcomes, including reproductive/developmental impacts, neurotoxicity, and carcinogenicity.[5,11−15]

Along with oil and natural gas, large quantities of wastewater are returned to the surface following injection. When pressure on the well is initially released, the water that returns to the surface contains predominantly hydraulic fracturing fluids and is referred to as "flowback". The term "produced water" is used generally to refer to all water that flows from oil and gas wells, including naturally occurring waters from the formation. Produced water will continue to flow to the surface throughout the lifespan of the well. Flowback and produced water may contain chemicals that were injected into the well as part of the hydraulic fracturing fluid formulation as well as chemical substances from the formation that may be mobilized by the water flow. This may include toxic substances such as heavy metals, volatile organic compounds (e.g., BTEX, benzene,

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toluene, ethylbenzene, xylenes), semivolatile organic compounds, and/or radioactive materials, many of which may be found naturally in the rock formation.[16−20]

In an effort to understand whether hydraulic fracturing can impact drinking water sources and to identify driving factors that may affect the severity and frequency of such impacts, the U.S. Environmental Protection Agency (EPA) began conducting research under the *Plan to Study the Potential Impacts of Hydraulic Fracturing on Drinking Water Resources* in 2011.[21] The final report from this study, the *Assessment of the Potential Impacts of Hydraulic Fracturing for Oil and Gas on Drinking Water Resources*, was released as a draft for external peer review in June 2015.[1] For this study, the EPA developed a list of 1173 chemicals that are associated with the hydraulic fracturing industry, including 1076 chemicals with reported use in hydraulic fracturing fluids and 134 chemicals that have been reported in hydraulic fracturing flowback and produced water. Thirty-seven chemicals were reported as used in hydraulic fracturing fluids and detected in flowback/produced water.[1] This chemical list represents a nationwide assessment and reflects the range and variety of chemicals that may be associated with hydraulic fracturing activity.

To support the risk assessment of these chemicals, the EPA compiled toxicity values for noncancer effects and cancer using selected sources of governmental and intergovernmental toxicity assessments. Toxicity values for noncancer effects include chronic oral reference values (RfVs), which estimate the amount of chemical that can be ingested daily by the human population (including sensitive subgroups) that is likely to be without appreciable risk of health effects over a lifetime.[22] The RfV is generally derived based on the most sensitive adverse health effects endpoint identified from the available chemical-specific data, with uncertainty factors applied to reflect limitations of the data used. Toxicity values for cancer include oral slope factors (OSFs), which are the upper bound on increased cancer risk from a lifetime oral exposure to a chemical.[22] The EPA's complete list of hydraulic fracturing-related chemicals as well as all toxicity values obtained for these chemicals is compiled in a publicly available draft database.[23]

Overall, the risk assessment of environmental chemicals depends on a four-step process: (1) hazard identification, (2) dose−response assessment, (3) exposure assessment, and (4) risk characterization.[24] RfVs and OSFs pertain to the first two steps of risk assessment: identifying chemicals that pose health hazards (hazard identification) and characterizing the quantitative relationship between exposure and toxic effect (dose−response assessment). These toxicity values may be used in combination with site-specific chemical exposure information (exposure assessment) in order to evaluate potential public health risks (risk characterization).

Here, we provide an overview of the chronic oral RfVs and OSFs that were identified by the EPA for this list of 1173 chemicals. The goal of this analysis is to evaluate the availability of chronic oral toxicity values for these chemicals and to highlight significant data gaps. We do not, however, make any judgment about the extent to which people may be exposed to these chemicals as a result of hydraulic fracturing activity. Our analysis is focused on identifying values that can be used to assess long-term (chronic) oral exposure to these chemicals in drinking water—the reason being that the EPA's mandate for the hydraulic fracturing study was to focus on the protection of the general population, and acute exposures to these chemicals are more likely to occur for workers. The availability of less-than-chronic toxicity values and toxicity values for other potential routes of exposure (e.g., inhalation, dermal) is not evaluated here.

We summarize the methods used by the EPA to compile the chemical list and to identify toxicity values. We then discuss the extent of the available information, address some of the uncertainties associated with the chemical list, and identify which chemicals appear to be the most toxic. Finally, we present the chronic oral toxicity values that were available for chemicals used in at least 10% of wells nationwide to highlight data availability and potential toxicity of the most commonly used chemicals in hydraulic fracturing fluids.

■ METHODS

EPA's List of Hydraulic Fracturing-Related Chemicals and Associated Toxicity Values. The following text summarizes the methods used by the EPA to develop a list of chemicals that are associated with hydraulic fracturing fluids, flowback, or produced water and to identify toxicity values for these chemicals. The complete list of chemicals and toxicity values and data sources was finalized as of June 4, 2015 and is available at the EPA's draft database for this study (http://cfpub.epa.gov/ncea/hfstudy/recordisplay.cfm?deid=308341).[23] In addition to the chronic oral toxicity values, this database also provides inhalation toxicity values, less-than-chronic toxicity values, and physicochemical properties for these chemicals when available. That information is outside the scope of this analysis and not evaluated here.

Identification of Hydraulic Fracturing-Related Chemicals. The EPA identified 10 sources of information (listed in Table SI-1 of the Supporting Information) to use in compiling a list of chemicals associated with hydraulic fracturing operations. Seven of these sources are documents from federal and state government units—including the EPA,[25−28] the United States House of Representatives,[29] the New York State Department of Environmental Conservation (NYSDEC),[20] and the Pennsylvania Department of Environmental Protection (PADEP)[30]—which obtained data directly from industry. Included in this is a list of chemicals provided directly to the EPA by nine major hydraulic fracturing service companies, representing chemicals used in hydraulic fracturing fluids between 2005 and 2010[25] and a list of chemicals detected by these companies in flowback/produced water from 81 wells.[26] The remaining three sources include the following: a technical report prepared by the Gas Technology Institute for the Marcellus Shale Coalition (MSC), which is a drilling industry trade group;[19] a peer-reviewed journal article by Colborn et al.;[5] and the FracFocus Chemical Disclosure Registry 1.0 ("FracFocus 1.0"), which is a national hydraulic fracturing chemical registry developed by the Ground Water Protection Council and the Interstate Oil and Gas Compact Commission.[8] As indicated in Table SI-1, data on chemicals in flowback/produced water was obtained from the MSC technical report, the NYSDEC report, and the data provided to the EPA by the nine service companies. Data on chemicals used in hydraulic fracturing fluids was obtained from the NYSDEC report and the remaining seven sources. The EPA included all of the chemicals identified by these sources. More details on the compilation of the chemical list can be found in Appendix A of the EPA's external review draft of the *Assessment of the Potential Impacts of Hydraulic Fracturing for Oil and Gas on Drinking Water Resources*.[1]

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Identification of Toxicity Values. For the purpose of the hydraulic fracturing study, the EPA developed the following criteria in order to evaluate possible sources of toxicity values.

- The body or organization generating or producing the toxicity value or qualitative assessment must be a governmental or intergovernmental body.
- The data source must include peer-reviewed toxicity values or peer-reviewed qualitative assessments.
- The toxicity values or qualitative assessments must be based on peer-reviewed scientific data.
- The toxicity values or qualitative assessments must be focused on protection of the general public instead of other populations, such as a worker population.
- The body generating the toxicity values or qualitative assessments must be free of conflicts of interest with respect to the chemicals for which it derives toxicity values or qualitative assessments.

More details on these criteria as well as the full list of data sources considered for this study can be found in Appendix G of the EPA's external review draft of the *Assessment of the Potential Impacts of Hydraulic Fracturing for Oil and Gas on Drinking Water Resources.*[1]

After applying these selection criteria, the EPA identified six sources of toxicity values for use in this study (Supporting Information, Table SI-2). Four U.S. governmental sources met the criteria for consideration: the EPA's Integrated Risk Information System (IRIS) database, the EPA's Provisional Peer-reviewed Toxicity Value (PPRTV) database, the EPA's Human Health Benchmarks for Pesticides (HHBP) database, and the Agency for Toxic Substances and Disease Registry (ATSDR). One intergovernmental source, the World Health Organization Concise International Chemical Assessment Documents (CICAD), met the above criteria for consideration. One state source, the California Environmental Protection Agency (CalEPA) Toxicity Criteria Database, met the criteria for consideration.

To identify toxicity values for hydraulic fracturing-related chemicals, the EPA cross-referenced the list of chemicals compiled from the sources in Table SI-1 against the six sources of toxicity values in Table SI-2. The toxicity values identified by the EPA include cancer and noncancer values.

Analysis of Chronic Toxicity Values from EPA's Draft Assessment. For the analysis presented here, we focused on chronic oral toxicity values—specifically, chronic oral RfVs for noncancer effects, and cancer OSFs.

Chronic oral RfVs for noncancer effects include the following.

- Chronic oral reference doses (RfDs) from IRIS, PPRTV, and HHBP databases. An RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.[22] All of these RfDs (IRIS, PPRTV, and HHBP) are derived using the EPA guidance for RfD determination.[31] RfDs can be derived from a no-observed-adverse-effect level, lowest-observed-adverse-effect level, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Chronic oral RfDs reflect daily oral exposure over a lifetime.[22] This estimate is expressed in terms of mg/kg-day.
- Chronic oral minimum risk levels (MRLs) from ATSDR. An MRL is an estimate of daily human exposure to a hazardous substance at or below which the substance is unlikely to pose a measurable risk of harmful (adverse), noncancerous effects. Chronic oral MRLs are calculated based on oral exposure over a duration of 365 days or longer.[32] This estimate is expressed in terms of mg/kg-day.
- Tolerable daily intake (TDI) from CICAD. A TDI is an estimate of a substance, expressed on a body mass basis, to which an individual in a (sub) population may be exposed daily over its lifetime without appreciable health risk.[33] This estimate is expressed in terms of mg/kg-day.
- Oral maximum allowable daily levels (MADLs) from CalEPA. An MADL is the daily oral exposure to a reproductive toxicant at which the chemical would have no observable adverse reproductive effect, assuming exposure at 1000 times that level.[34] This estimate is expressed in terms of μg/day.

Cancer OSFs include the following.

- OSFs from IRIS, PPRTV, and HHBP databases and CalEPA. An OSF is an upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime oral exposure to an agent. This estimate, usually expressed in terms of the proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose−response relationship, that is, for exposures corresponding to risks less than 1 in 100.[22]

Some chemicals had chronic oral RfVs or OSFs available from more than one of the sources in Table SI-2. For these chemicals, we applied the EPA Office of Solid Waste and Emergency Response (OSWER) Directive 9285.7-53 tiered hierarchy of toxicity values to determine which RfV or OSF should be used in our analysis.[35] In this hierarchy, IRIS values are used before any other source, followed by PPRTVs, and then other available values. For the purposes of this analysis, we made one modification to this approach: when considering pesticides, we used HHBP values first, followed by IRIS values, then PPRTVs, and then other values.

Identification of Frequently Used Chemicals from FracFocus 1.0. To identify the chemicals that are used most frequently in hydraulic fracturing fluids, we obtained chemical usage data from the project database of the EPA's *Analysis of Hydraulic Fracturing Fluid Data from the FracFocus Chemical Disclosure Registry 1.0.*[36] This project database contains data that the EPA extracted from FracFocus 1.0 disclosures from January 1, 2011 to February 28, 2013, which included more than 39 000 disclosures from 20 states.[8] As used in this report, "disclosure" refers to all data submitted for a specific oil or gas production well for a specific fracture date. This analysis of FracFocus 1.0 identified 692 unique chemicals that are used in hydraulic fracturing fluids[8] and was one of the 10 sources used by the EPA to identify chemicals as part of the larger hydraulic fracturing study (Table SI-1). These 692 chemicals therefore represent a subset of the total 1076 hydraulic fracturing fluid chemicals identified by the EPA.

We queried the project database to determine the frequency with which each of these chemicals was reported in the FracFocus 1.0 disclosures, including both oil and gas wells and without regard to the concentration of chemical that was used. From this analysis we identified a list of 36 chemicals that were

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reported in at least 10% of disclosures nationwide. A brief background of the project database and detailed information on this query is provided in the Supporting Information.

RESULTS AND DISCUSSION

EPA's List of Hydraulic Fracturing-Related Chemicals. The list of 1173 hydraulic fracturing-related chemicals (1076 used in hydraulic fracturing fluids and 134 detected in flowback/produced water) compiled by the EPA represents a nationwide assessment and reflects the vast range of chemicals that have been reported by the sources in Table SI-1. A single hydraulic fracturing well site will likely have only a small fraction of the chemicals on this list—for instance, the EPA's analysis of FracFocus 1.0 indicated a median of 14 chemicals is used per well for hydraulic fracturing fluid formulation.[8] Likewise, the chemicals present in flowback and produced water have also been demonstrated to vary from site to site and will depend on the chemicals used in fracturing fluid formulation, chemicals that may be present in the supply water used for well injection, as well as site-specific geological and chemical characteristics of the well formation.[18,19]

To our knowledge, the EPA's list of chemicals used in hydraulic fracturing fluids is the most comprehensive compilation of these chemicals to date. Although this list represents the best information available to the EPA at the time of this study, it should not be considered exhaustive. Industry practices are rapidly changing, and it is unclear how many of these 1076 chemicals are currently used; it is possible that a smaller number of chemicals is currently used in abundance, and it is also likely that chemicals are used which are not reported on this list. The prevalence of confidential business information (CBI) is one factor that likely limits the completeness of this chemical list. For instance, companies submitting to FracFocus 1.0 were not required to report the identity of chemicals they claimed as CBI. The EPA's analysis found approximately 11% of chemical records were reported to FracFocus 1.0 as CBI and that more than 70% of FracFocus 1.0 disclosures contained at least one CBI chemical. Of the disclosures containing CBI chemicals, there were an average of five CBI chemicals per disclosure.[8]

In flowback and produced water, some chemicals on the EPA's list are known to be characteristic of hydrocarbon formations and deep formation brines, including a range of volatile organic compounds (e.g., BTEX, napthalene, and related hydrocarbons), semivolatile organic compounds (e.g., acetophenone, methylated phenols), and inorganic constituents (e.g., bromide, chloride, barium, strontium, iron, calcium, radium-226, radium-228). These are not unique to hydraulic fracturing and are similar to chemicals that may be present in produced water from conventional oil and gas wells.[16,18,19] However, some of these chemicals (e.g., BTEX, napthalene, acetophenone) also have reported use in hydraulic fracturing fluids and thus may also be anthropogenic. In total, the EPA's list of chemicals in flowback/produced water includes 37 chemicals that have been reportedly used in hydraulic fracturing fluids; examples include isopropanol, methanol, ethylene glycol, formic acid, 1,4-dioxane, and bis(2-chloroethyl) ether. We were unable to ascertain the origins of these chemicals, because the sources used to compile the flowback/produced water list did not provide information on which chemicals were used in hydraulic fracturing fluids at these wells; however, other studies have demonstrated that chemical additives can persist in flowback/produced water from hydraulically fractured wells.[18,37]

Interestingly, the EPA's list of chemicals in flowback/produced water also included several banned substances, including organochlorine pesticides and Aroclor 1248 [a polychlorinated biphenyl (PCB) commercial mixture]. The sources reporting these chemicals (MSC study and NYSDEC report) expressed uncertainty as to why these banned substances were present and the extent to which they may be detected in flowback/produced water from other hydraulic fracturing sites.[19,20] The MSC study stated that the banned pesticides were detected sporadically and at low concentrations and suggested that they may have originated from laboratory contamination.[19] The NYSDEC report, which referred to the results of the MSC study, suggested that the banned pesticides may have been introduced to the shale or the water during drilling or fracturing operations.[20] It is possible that these chemicals were present in the supply water that was used for well injection or were mobilized from soil or underground.

Although the EPA's list provides valuable information on the chemical composition of flowback/produced water, it is unlikely that the data sources in Table SI-1 were able to capture all of the chemicals present. Chemicals and their metabolites may go undetected in flowback/produced water because they were not targeted in the analytical chemistry methodology or because concentrations were below the analytical limit of detection. Furthermore, due to geographical variation in flowback/produced water composition, it should not be expected that the sources used to build this chemical list are fully representative of flowback/produced waters across all gas and oil fracturing areas of the United States. Such limitations may explain why only a small fraction of the chemicals reported in hydraulic fracturing fluids (37 out of 1076) were also reported in flowback/produced water. It is difficult to draw meaningful conclusions from this observation, however, since the EPA used different sources to identify chemicals in hydraulic fracturing fluids and in flowback/produced water (Table SI-1).

Availability of Chronic Oral Toxicity Values. Toxicity values (if available) for the 1173 hydraulic fracturing-related chemicals, obtained from the sources in Table SI-2, can be found on the EPA's database for this study.[23] Overall, chronic oral RfVs (for noncancer effects) or OSFs (for cancer) were available for 90 (8%) of the 1076 chemicals used in hydraulic fracturing fluids and 83 (62%) of the 134 chemicals reported in flowback or produced water. The availability of data can be broken down as follows.

- For the 1076 chemicals used in hydraulic fracturing fluids, chronic oral RfVs were available for 83 chemicals (8%) and OSFs were available for 23 chemicals (2%). Of these, 16 chemicals (2%) used in hydraulic fracturing fluids had both a chronic oral RfV and OSF available.
- For the 134 chemicals reported in hydraulic fracturing flowback or produced water, chronic oral RfVs were available for 72 chemicals (54%), and OSFs were available for 32 chemicals (24%). Of these, 21 chemicals (16%) in flowback/produced water had both a chronic oral RfV and OSF available.

Taking this information together, 147 (13%) of the total 1173 chemicals used in hydraulic fracturing fluid or found in flowback/produced water had chronic oral RfVs or OSFs available from at least one of the six sources shown in Table SI-

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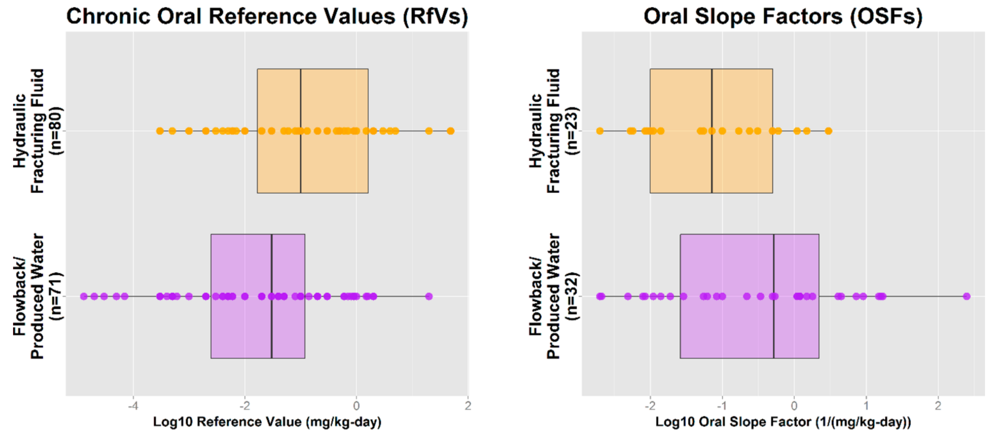

Figure 1. Distribution of chronic oral RfVs and OSFs for chemicals used in hydraulic fracturing fluids (orange) or detected in flowback or produced water (purple), represented as box plots. Box plots show the lower, median, and upper quartile of these distributions, with the RfVs or OSFs of individual chemicals shown as points along the distribution. In these distributions, a single RfV or OSF is indicated for each chemical; if a chemical had values available from multiple sources in Table SI-2, a single value was selected using a modification of the OSWER hierarchy, as described in the text. These distributions only represent chemicals that had chronic oral RfVs or OSFs available from the sources listed in Table SI-2. If a chemical was reported in both hydraulic fracturing fluids and in flowback/produced water, it is shown here in both distributions (n = 24 chronic oral RfVs, n = 9 OSFs). MADLs from CalEPA (n = 3 in fracturing fluid, n = 1 in flowback/produced water) were excluded from the chronic oral RfV distributions due to a difference in units (μg/day versus mg/kg-day), as described in the text.

2. That means 1026 hydraulic fracturing-related chemicals (87%) lack a chronic oral toxicity value from these sources. It is not unusual that more than one-half of chemicals reported in flowback/produced water (62%) have these toxicity values available, compared to the small percentage of chemicals used in hydraulic fracturing fluids (8%) that have these values. Chemicals in flowback/produced water are generally identified through targeted analytical methodologies, which are often aimed at chemicals that are of known toxicological concern and/or which have known associations with oil and gas development. In contrast, the list of chemicals reported in hydraulic fracturing fluids encompasses a wider variety of chemicals, including many that do not have available toxicity values.

There is a continuum with respect to the quality, extent, and reliability of potential toxicity data sources. For the study of hydraulic fracturing-related chemicals, the EPA used only those sources identified as being of the highest quality and reliability (Table SI-2) using criteria developed specifically for the purposes of the study.[1] Thus, if a source of toxicity values was not included here, that only means that it did not meet the criteria for the purposes of the EPA's study. For the six sources that were considered in this study, the number of toxicity values available from each source is summarized in Figure SI-1. U.S. federal sources (IRIS, PPRTV, ATSDR, and HHBP) cumulatively had chronic oral RfVs or OSFs available for 126 chemicals from the EPA's list. The IRIS database had chronic oral RfVs or OSFs available for 89 chemicals on the EPA's list and therefore was the single largest contributor of toxicity values.

Distribution of Chronic Oral Toxicity Values Across All Chemicals. For the chemicals that had chronic oral RfVs or OSFs available, we evaluated the distribution of these values across all chemicals used in hydraulic fracturing fluids and for chemicals reported in flowback or produced water. We excluded CalEPA MADLs from this analysis, due to a difference in units compared to other RfVs (μg/day versus mg/kg-day). This resulted in the exclusion of three chemicals that only had CalEPA MADLs available: ethylene oxide and 2-ethoxyethanol, which were reported in hydraulic fracturing fluids, and lead, which was reported in hydraulic fracturing fluids and flowback/produced water. For the remaining chemicals, the distributions of toxicity values (Figure 1) demonstrate that chronic oral RfVs and OSFs associated with this chemical list span several orders of magnitude.

From these distributions of toxicity values for hydraulic fracturing fluids and for flowback/produced water, we identified the top 10 (or more, in the case of ties) chemicals with the lowest chronic oral RfVs (i.e., the greatest potential toxicity on a mg/kg-day basis; Table 1a and 1b) and the top 10 chemicals with the highest OSFs (i.e., the greatest cancer potency per mg/kg-day of exposure; Table 2a and 2b). Tables 1a and 2a highlight a number of hazardous industrial chemicals that have reported use in hydraulic fracturing fluids. Tables 1b and 2b include several of the aforementioned banned pesticides (heptachlor, heptachlor epoxide, aldrin, dieldrin, lindane, and beta-hexachlorocyclohexane) and one current use pesticide (phorate), which have no reported use in hydraulic fracturing fluids but have been detected in flowback/produced water. Also highlighted are metals/metalloids and polycyclic aromatic hydrocarbons that have been detected in flowback/produced water.

The chemicals in Tables 1 and 2 represent the most toxic chemicals that were observed across a nationwide analysis. However, interpretation of these chronic oral RfVs and OSFs is limited in the absence of environmental concentration data. Although we know that these hazardous chemicals have been used in hydraulic fracturing fluids or reported in flowback/produced water, it is unclear how frequently these chemicals are used or detected. We do not make any judgements about the potential for exposure to these chemicals, as this list is intended to represent the range and variety of chemicals that have been associated with hydraulic fracturing activity. However, this information would need to be taken into account for site-specific risk assessment.

Although there appears to be a trend indicating that chemicals in flowback and produced waters are more toxic than the chemicals used in hydraulic fracturing fluids (Figure 1;

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Table 1. Chemicals with the Lowest Chronic Oral RfVs Used in Hydraulic Fracturing Fluids (a) or Detected in Flowback/Produced Water (b)[a]

CASRN	chemical name	RfV (mg/kg-day)	source of RfV
	(a) hydraulic fracturing fluids		
7440-38-2	*arsenic*	0.0003	*IRIS (RfD)*
7803-51-2	phosphine	0.0003	IRIS (RfD)
107-02-8	*acrolein*	0.0005	*IRIS (RfD)*
123-73-9	(*E*)-crotonaldehyde	0.001	PPRTV (RfD)
75-56-9	1,2-propylene oxide	0.001	HHBP (RfD)
79-06-1	acrylamide	0.002	IRIS (RfD)
100-44-7	benzyl chloride	0.002	PPRTV (RfD)
107-19-7	propargyl alcohol	0.002	IRIS (RfD)
18540-29-9	*chromium(VI)*	0.003	*IRIS (RfD)*
71-43-2	*benzene*	0.004	*IRIS (RfD)*
	(b) flowback or produced water		
1024-57-3	heptachlor epoxide	0.000013	IRIS (RfD)
7723-14-0	phosphorus	0.00002	IRIS (RfD)
309-00-2	aldrin	0.00003	IRIS (RfD)
60-57-1	dieldrin	0.00005	IRIS (RfD)
7440-62-2	vanadium	0.00007	PPRTV (RfD)
7440-38-2	*arsenic*	0.0003	*IRIS (RfD)*
7440-48-4	cobalt	0.0003	PPRTV (RfD)
58-89-9	lindane	0.0003	IRIS (RfD)
7440-36-0	antimony	0.0004	IRIS (RfD)
107-02-8	*acrolein*	0.0005	*IRIS (RfD)*
298-02-2	phorate	0.0005	HHBP (RfD)
7440-43-9	cadmium	0.0005	IRIS (RfD)
76-44-8	heptachlor	0.0005	IRIS (RfD)

[a]Italicized chemicals were reported in both hydraulic fracturing fluids and flowback/produced water.

Table 2. Chemicals with the Highest OSFs Used in Hydraulic Fracturing Fluids (a) or Detected in Flowback/Produced Water (b)[a]

CASRN	chemical name	OSF (per mg/kg-day)	source of OSF
	(a) hydraulic fracturing fluids		
91-22-5	quinoline	3	IRIS
302-01-2	hydrazine	3	IRIS
7440-38-2	*arsenic*	1.5	*IRIS*
111-44-4	*bis(2-chloroethyl) ether*	1.1	*IRIS*
106-99-0	1,3-butadiene	0.6	CalEPA
79-06-1	acrylamide	0.5	IRIS
18540-29-9	*chromium(VI)*	0.5	*CalEPA*
75-21-8	ethylene oxide	0.31	CalEPA
75-56-9	1,2-propylene oxide	0.24	IRIS
100-44-7	benzyl chloride	0.17	IRIS
	(b) flowback or produced water		
57-97-6	7,12-dimethylbenz(*a*)anthracene	250	CalEPA
309-00-2	aldrin	17	IRIS
60-57-1	dieldrin	16	IRIS
7440-43-9	cadmium	15	CalEPA
1024-57-3	heptachlor epoxide	9.1	IRIS
50-32-8	benzo(*a*)pyrene	7.3	IRIS
76-44-8	heptachlor	4.5	IRIS
53-70-3	dibenz(*a*,*h*)anthracene	4.1	CalEPA
319-85-7	beta-hexachlorocyclohexane	1.8	IRIS
7440-38-2	*arsenic*	1.5	*IRIS*

[a]Italicized chemicals were reported in both hydraulic fracturing fluids and flowback/produced water.

Tables 1 and 2), this may not be the case, given limitations surrounding this data set. These data only represent the fraction of chemicals for which chronic oral toxicity values are available (8% of chemicals reported in hydraulic fracturing fluids and 62% of chemicals reported in flowback/produced water), and therefore, the distributions are likely to change over time as more chemicals are assessed. Furthermore, an individual hydraulic fracturing well site would likely only have a small fraction of the chemicals from this list and could have additional chemicals that were not considered here. Therefore, if we were to consider the range of toxicity values for chemicals present at a specific hydraulic fracturing site, it is likely that it would differ from the nationwide assessment presented here.

Overall, for site-specific risk assessment, the chronic oral RfVs and OSFs compiled by the EPA would need to be coupled with relevant exposure information. This may include information on the frequency of chemical use, volume of chemical use, estimates of potential exposure due to environmental fate and transport processes, potential exposure routes, and data on the ultimate concentrations of these chemicals in the environment.

Chronic Oral Toxicity Values Available for Frequently Used Chemicals. In order to focus our analysis on chemicals that are used most frequently in hydraulic fracturing fluids, we identified a list of 36 chemicals that were reported in at least 10% of disclosures in the EPA's analysis of FracFocus 1.0 (Table 3). For chemicals in Table 3 that had chronic oral RfVs available, we list the critical effect basis for the RfV. The identification of these frequently used chemicals was based strictly on the number of disclosures in which these chemicals were reported. Although it would be useful to know the relative volumes of these chemicals used in hydraulic fracturing fluids, this information is not available from FracFocus 1.0.[8] The information in Table 3 does not reflect the relative concentration of these chemicals in hydraulic fracturing fluid nor should it be considered an approximation of environmental concentration or dose.

Eight (22%) of these frequently used chemicals have chronic oral RfVs available, and none of the chemicals has an OSF (Table 3). All of these RfVs came from federal sources (IRIS, PPRTV, or HHBP), and all were RfDs (in units of mg/kg-day). Critical effects for these chemicals included kidney/renal toxicity, hepatotoxicity, developmental toxicity (extra cervical ribs), reproductive toxicity, and decreased terminal body weight. Chronic oral RfDs ranged from 0.002 mg/kg-day (propargyl alcohol, reported in 33% of disclosures) to 2 mg/kg-day (methanol, reported in 73% of disclosures; ethylene glycol, reported in 47% of disclosures). Propargyl alcohol was also identified among the chemicals with the lowest RfVs in Table 1. Overall, the lack of chronic oral RfVs and OSFs for the majority of these frequently used chemicals suggests that a significant data gap exists with regards to understanding the potential public health implications of hydraulic fracturing.

We note that several of the frequently used chemicals in Table 3 are designated as being "generally recognized as safe" (GRAS) for use in food additives or food contact substances by the U.S. Food and Drug Administration (FDA). This includes quartz-alpha (SiO_2), hydrochloric acid, guar gum, sodium hydroxide, sodium chloride, potassium hydroxide, acetic acid, citric acid, choline chloride, carbonic acid, dipotassium salt, ammonium chloride, and formic acid. GRAS chemicals may be

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Table 3. Chemicals Reported in at Least 10% of Disclosures in EPA's Analysis of FracFocus 1.0 with Chronic Oral RfVs Provided When Available[a]

			RfV		
CASRN	chemical name	percent of disclosures	RfD (mg/kg-day)	source of RfD	critical effect
14808-60-7	quartz-alpha (SiO_2)	86.09%	b	b	b
67-56-1	methanol	73.10%	2	IRIS	extra cervical ribs
64742-47-8	distillates, petroleum, hydrotreated light	67.26%	b	b	b
7647-01-0	hydrochloric acid	65.76%	b	b	b
107-21-1	ethylene glycol	46.82%	2	IRIS	kidney toxicity
67-63-0	isopropanol	46.45%	b	b	b
7727-54-0	diammonium peroxydisulfate	44.09%	b	b	b
9000-30-0	guar gum	39.42%	b	b	b
1310-73-2	sodium hydroxide	39.26%	b	b	b
107-19-7	propargyl alcohol	33.38%	0.002	IRIS	renal and hepatotoxicity
111-30-8	glutaraldehyde	32.97%	b	b	b
7647-14-5	sodium chloride	32.04%	b	b	b
64-17-5	ethanol	30.78%	b	b	b
1310-58-3	potassium hydroxide	30.64%	b	b	b
64-19-7	acetic acid	24.63%	b	b	b
77-92-9	citric acid	23.93%	b	b	b
111-76-2	2-butoxyethanol	23.20%	0.1	IRIS	hemosiderin deposition in the liver
64742-94-5	solvent naphtha, petroleum, heavy arom.	20.89%	b	b	b
91-20-3	naphthalene	18.93%	0.02	IRIS	decreased terminal body weight
10222-01-2	2,2-dibromo-3-nitrilopropionamide	16.46%	b	b	b
67-48-1	choline chloride	14.83%	b	b	b
9003-35-4	phenol-formaldehyde resin	14.46%	b	b	b
584-08-7	carbonic acid, dipotassium salt	13.93%	b	b	b
100-97-0	methenamine	13.72%	b	b	b
68527-49-1	thiourea, polymer with formaldehyde and 1-phenylethanone	13.23%	b	b	b
95-63-6	1,2,4-trimethylbenzene	12.90%	b	b	b
25322-68-3	polyethylene glycol	12.66%	b	b	b
9016-45-9	polyethylene glycol nonylphenyl ether	12.61%	b	b	b
68424-85-1	quaternary ammonium compounds, benzyl-C12−16-alkyldimethyl, chlorides	12.48%	0.44	HHBP	decreased body weight and weight gain
127087-87-0	poly(oxy-1,2-ethanediyl)-nonylphenyl-hydroxy branched	11.87%	b	b	b
12125-02-9	ammonium chloride	11.60%	b	b	b
64-18-6	formic acid	11.44%	0.9	PPRTV	reproductive toxicity
55566-30-8	tetrakis(hydroxymethyl)phosphonium sulfate	11.42%	b	b	b
7758-19-2	sodium chlorite	11.00%	0.03	IRIS	neurodevelopmental effects
68439-51-0	alcohols, C12−14, ethoxylated propoxylated	10.63%	b	b	b
7775-27-1	sodium persulfate	10.30%	b	b	b

[a]OSFs were not available for any of the chemicals in this table. [b]No chronic oral RfV was available.

used by hydraulic fracturing industry operators in an effort to avoid more hazardous chemicals and minimize concern in the public perception.[38] However, GRAS determinations are often specific to certain conditions as expressed in the FDA GRAS Notification Database and therefore do not indicate that the same chemical is safe for use in hydraulic fracturing fluids. For instance, formic acid is considered GRAS for specific use in paper food packaging materials[39] but has a chronic oral RfD of 0.9 mg/kg-day based on reproductive effects from chronic oral exposure.[40] For human health risk assessment in areas of hydraulic fracturing activity, hazard and dose−response relationships for these chemicals need to be assessed in the context of the use and levels that are likely to be encountered in an appropriate exposure scenario.

The EPA's FracFocus 1.0 project database provides valuable insight into chemicals that are used frequently in hydraulic fracturing fluids but does not represent a complete record of chemical usage. As stated previously, FracFocus 1.0 does not provide information on chemicals that were claimed as CBI, and therefore, CBI chemicals were excluded from this analysis. Furthermore, the EPA was unable to analyze FracFocus 1.0 ingredient records that were not able to be assigned standardized chemical names, which resulted in approximately 35% of FracFocus 1.0 ingredient records being excluded from the project database.[8] There may also be a regional bias to the frequency of use estimates, as over 78% of FracFocus 1.0 disclosures came from five states (Texas, Colorado, Pennsylvania, North Dakota, and Oklahoma), and 47% of disclosures were from Texas alone.[8] Since chemical usage is expected to vary by region,[8] there may be chemicals used frequently in some regions of the United States that were not identified or were underrepresented by this analysis. Therefore, although we know that the chemicals in Table 3 are used frequently in hydraulic fracturing fluids, there may be other frequently used chemicals that were not identified by this analysis.

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Implications for Risk Assessment. Our analysis demonstrates that we lack chronic oral RfVs and OSFs for the majority of chemicals that are associated with hydraulic fracturing operations, including those known to be frequently used in hydraulic fracturing fluids. This finding, along with other studies that have identified gaps in toxicity information for hydraulic fracturing chemicals,[5,9,11,12,15] suggests a significant knowledge gap exists with respect to the scientific community's understanding of the potential public health impacts that these chemicals may have on drinking water resources. With the limited availability of toxicity values, risk assessment is difficult and potential impacts on drinking water resources and human health may not be assessed adequately. This lack of toxicity values is not unique to the hydraulic fracturing industry; in fact, there are estimated to be tens of thousands of chemicals in industrial use that have not undergone significant toxicological evaluation. A principal reason for this data gap is the high cost and time needed to perform guideline animal studies and develop comprehensive, peer-reviewed assessments of chemical toxicity.[41]

The lack of chronic oral RfVs and OSFs for the majority of these chemicals means that risk assessors, researchers, and the public may need to turn toward other toxicity values or alternative data sources in order to assess the potential toxicity of these chemicals. For instance, in situations where chronic toxicity values are not available, it may be useful to employ less-than-chronic toxicity values in order to estimate potential hazards. We note that 93 chemicals from the EPA's list (56 reported in hydraulic fracturing fluids, 57 reported in flowback/produced water, and 20 reported in both) have less-than-chronic oral RfVs available from the sources in Table SI-2, including subchronic oral RfDs from the PPRTV database and acute and intermediate oral MRLs from ATSDR.[23] Of these 93 chemicals, 85 (91%) also had a chronic oral RfV available from the sources in Table SI-2, while eight chemicals (9%) only had the less-than-chronic value. Less-than-chronic values should be used with caution, as chronic oral RfVs are more relevant for the assessment of long-term chemical exposure via drinking water. Furthermore, chronic oral RfVs should also be protective of acute effects and therefore are more relevant for the protection of public health.

Alternate sources of toxicity values, including cancer and noncancer-related information, could include values from state, national, international, private, and academic organizations that did not meet the criteria for inclusion in this study but could be high-quality and reliable sources. There is also an abundance of chemical toxicity information which has not been formalized into an assessment and may be found in the scientific literature and databases [e.g., EPA's Aggregated Computational Toxicology Resource (ACToR) database, http://actor.epa.gov/dashboard/], including results from guideline tests, high-throughput screening assays, alternative assays, and quantitative structure−activity (QSAR) models. The relevance, quality, and availability of information from potential alternative data sources is not evaluated here. However, several recent studies have compiled and assessed the availability of various types of acute and chronic toxicity data and other relevant information (e.g., physiochemical properties) for subsets of chemicals that are associated with the hydraulic fracturing industry.[5,9,11,12,15] When available, these data may be useful for identifying chemicals that may pose public health hazards and prioritizing these chemicals for further research and assessment. Similar to our findings for RfVs and OSFs, however, these studies found that toxicity data was often not available for these chemicals.

Hazard identification is further complicated by the likelihood that any given exposure will be to a mixture of chemicals of chemicals at varying concentrations, with potential for additive or nonadditive (e.g., synergistic or antagonistic) interactions. Such interactions make hazard and dose−response relationships more difficult to predict and have been cited as a potentially significant challenge toward understanding the potential public health impacts of hydraulic fracturing.[2,13] To better understand these interactions, it would be useful to conduct toxicity studies using environmentally realistic mixtures of these chemicals.

In addition to the need for more toxicity studies and assessments, well-informed risk management decisions would also benefit from a better understanding of the identity of the chemicals that are associated with hydraulic fracturing. Industry use of CBI represents an obstacle to risk assessment, as it obscures the chemicals that are used at particular sites. Information on chemical formulations would allow the toxicity of these fluids to be more thoroughly assessed and also help to inform exposure assessment near hydraulic fracturing sites. As researchers have recently noted, it can be difficult to determine whether water contamination issues or community health effects are attributable to hydraulic fracturing activity, since chemical formulations and water quality data are often not publically released due to confidentiality agreements.[5,42,43]

Finally, exposure assessment studies are needed to better characterize the frequency and severity of the impacts of hydraulic fracturing-related chemicals on public health. Potential pathways by which hydraulic fracturing activities may impact water resources have been described by the EPA and in the peer-reviewed literature.[1,6,7,44] For instance, the EPA has documented incidents in which water has been contaminated by accidental spills of hydraulic fracturing fluids or flowback/produced water.[45] There have also been a limited number of high-profile incidents, such as a hydraulic fracturing well blowout near Killdeer, ND, that was linked to the contamination of a drinking water aquifer with brine and hydraulic fracturing-related chemicals.[46] However, the number of studies and documented impacts on water resources remains small. Thus, there is still limited understanding of the potential for the public to be exposed to hydraulic fracturing-related chemicals and mixtures of chemicals through drinking water.

To our knowledge, the EPA's list of 1173 chemicals is currently the most comprehensive attempt to identify chemicals that have been used as hydraulic fracturing fluids or detected in flowback/produced water in the United States. The chronic oral RfVs and OSFs compiled by the EPA are high-quality, peer-reviewed toxicity values that can be applied for the protection of public health. Although other recent studies have examined the toxicity of hydraulic fracturing-related chemicals, they have generally done so for a more limited number of chemicals and on an endpoint-specific basis. Thus, the EPA's databases provide a broad-based and relevant starting point for risk assessment. Toxicity is just one component of risk assessment, with cumulative exposure being the other. For the risk assessment of hydraulic fracturing chemicals, we emphasize that the RfVs and OSFs compiled by EPA are best used on a site-specific basis. Knowledge of the chemicals being used at a particular well site, the environmental fate and transport of these chemicals, the likelihood of spills and other unintentional releases, and other such factors should be taken

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into account when considering the risk associated with hydraulic fracturing-related chemicals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.5b04645.

Sources used to compile EPA's list of hydraulic fracturing-related chemicals, sources used to identify toxicity values, relative contribution of toxicity values from each of these sources, and details on the query used to identify frequently used chemicals from EPA's analysis of FracFocus 1.0 (PDF)

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Notes

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REFERENCES

(1) *Assessment of the Potential Impacts of Hydraulic Fracturing for Oil and Gas on Drinking Water Resources (External Review Draft)*; EPA/600/R-15/047; U.S. Environmental Protection Agency, Office of Research and Development: Washington, DC, 2015. http://cfpub.epa.gov/ncea/hfstudy/recordisplay.cfm?deid=244651.

(2) Goldstein, B. D.; Brooks, B. W.; Cohen, S. D.; Gates, A. E.; Honeycutt, M. E.; Morris, J. B.; Orme-Zavaleta, J.; Penning, T. M.; Snawder, J. The role of toxicological science in meeting the challenges and opportunities of hydraulic fracturing. *Toxicol. Sci.* **2014**, *139* (2), 271−283.

(3) Finkel, M.; Hays, J.; Law, A. The Shale Gas Boom and the Need for Rational Policy. *Am. J. Public Health* **2013**, *103* (7), 1161−1163.

(4) Korfmacher, K. S.; Jones, W. A.; Malone, S. L.; Vinci, L. F. Public health and high volume hydraulic fracturing. *New Solut.* **2013**, *23* (1), 13−31.

(5) Colborn, T.; Kwiatkowski, C.; Schultz, K.; Bachran, M. Natural Gas Operations from a Public Health Perspective. *Hum. Ecol. Risk Assess.* **2011**, *17* (5), 1039−1056.

(6) Shonkoff, S. B. C.; Hays, J.; Finkel, M. L. Environmental Public Health Dimensions of Shale and Tight Gas Development. *Environ. Health Perspect.* **2014**, *122* (8), 787−795.

(7) Vengosh, A.; Jackson, R. B.; Warner, N.; Darrah, T. H.; Kondash, A. A Critical Review of the Risks to Water Resources from Unconventional Shale Gas Development and Hydraulic Fracturing in the United States. *Environ. Sci. Technol.* **2014**, *48* (15), 8334−8348.

(8) *Analysis of Hydraulic Fracturing Fluid Data from the FracFocus Chemical Disclosure Registry 1.0*; EPA/601/R-14/003; Office of Research and Development, U.S. Environmental Protection Agency: Washington, DC, 2015; http://www2.epa.gov/hfstudy/analysis-hydraulic-fracturing-fluid-data-fracfocus-chemical-disclosure-registry-1-pdf.

(9) Stringfellow, W. T.; Domen, J. K.; Camarillo, M. K.; Sandelin, W. L.; Borglin, S. Physical, chemical, and biological characteristics of compounds used in hydraulic fracturing. *J. Hazard. Mater.* **2014**, *275*, 37−54.

(10) Barati, R.; Liang, J.-T. A Review of Fracturing Fluid Systems Used For Hydraulic Fracturing of Oil and Gas Wells. *J. Appl. Polym. Sci.* **2014**, *131*, 16.

(11) Wattenberg, E. V.; Bielicki, J. M.; Suchomel, A. E.; Sweet, J. T.; Vold, E. M.; Ramachandran, G. Assessment of the Acute and Chronic Health Hazards of Hydraulic Fracturing Fluids. *J. Occup. Environ. Hyg.* **2015**, *12* (9), 611−624.

(12) Kahrilas, G. A.; Blotevogel, J.; Stewart, P. S.; Borch, T. Biocides in Hydraulic Fracturing Fluids: A Critical Review of Their Usage, Mobility, Degradation, and Toxicity. *Environ. Sci. Technol.* **2015**, *49* (1), 16−32.

(13) Kassotis, C. D.; Klemp, K. C.; Vu, D. C.; Lin, C.-H.; Meng, C.-X.; Besch-Williford, C. L.; Pinatti, L.; Zoeller, R. T.; Drobnis, E. Z.; Balise, V. D.; Isiguzo, C. J.; Williams, M. A.; Tillitt, D. E.; Nagel, S. C. Endocrine-Disrupting Activity of Hydraulic Fracturing Chemicals and Adverse Health Outcomes After Prenatal Exposure in Male Mice. *Endocrinology* **2015**, *156* (12), 4458−73.

(14) Webb, E.; Bushkin-Bedient, S.; Cheng, A.; Kassotis, C. D.; Balise, V.; Nagel, S. C. Developmental and reproductive effects of chemicals associated with unconventional oil and natural gas operations. *Rev. Environ. Health* **2014**, *29* (4), 307−318.

(15) Elliott, E. G.; Ettinger, A. S.; Leaderer, B. P.; Bracken, M. B.; Deziel, N. C. A systematic evaluation of chemicals in hydraulic-fracturing fluids and wastewater for reproductive and developmental toxicity. *J. Exposure Sci. Environ. Epidemiol.* **2016**, 1−10.

(16) Haluszczak, L. O.; Rose, A. W.; Kump, L. R. Geochemical evaluation of flowback brine from Marcellus gas wells in Pennsylvania, USA. *Appl. Geochem.* **2013**, *28*, 55−61.

(17) Abualfaraj, N.; Gurian, P. L.; Olson, M. S. Characterization of Marcellus Shale Flowback Water. *Environ. Eng. Sci.* **2014**, *31* (9), 514−524.

(18) Orem, W.; Tatu, C.; Varonka, M.; Lerch, H.; Bates, A.; Engle, M.; Crosby, L.; McIntosh, J. Organic substances in produced and formation water from unconventional natural gas extraction in coal and shale. *Int. J. Coal Geol.* **2014**, *126*, 20−31.

(19) Hayes, T. *Sampling and analysis of water streams associated with the development of Marcellus shale gas*; Marcellus Shale Coalition: Des Plaines, IL, 2009; http://eidmarcellus.org/wp-content/uploads/2012/11/MSCommission-Report.pdf.

(20) *Revised draft supplemental generic environmental impact statement (SGEIS) on the oil, gas and solution mining regulatory program: Well permit issuance for horizontal drilling and high-volume hydraulic fracturing to develop the Marcellus shale and other low-permeability gas reservoirs*; New York State Department of Environmental Conservation (NYSDEC): Albany, NY, 2011; http://www.dec.ny.gov/energy/75370.html.

DOI: 10.1021/acs.est.5b04645
Environ. Sci. Technol. 2016, 50, 4788−4797

(21) *Plan to study the potential impacts of hydraulic fracturing on drinking water resources*; EPA/600/R-11/122; U.S. Environmental Protection Agency, Office of Research and Development: Washington, DC, 2011; http://www2.epa.gov/hfstudy/plan-study-potential-impacts-hydraulic-fracturing-drinking-water-resources-epa600r-11122.

(22) *U.S. Environmental Protection Agency Terminology Services: Vocabulary catalog-Integrated Risk Information System (IRIS) Glossary*; http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary.

(23) *Compilation of Physicochemical and Toxicological Information About Hydraulic Fracturing-Related Chemicals (Draft Database)*; EPA/600/R-15/134; U.S. Environmental Protection Agency: Washington, DC, 2015; http://cfpub.epa.gov/ncea/hfstudy/recordisplay.cfm?deid=308341.

(24) National Research Council. *Risk Assessment in the Federal Government: Managing the Process*; National Academy Press: Washington, DC, 1983.

(25) *Data received from oil and gas exploration and production companies, including hydraulic fracturing service companies 2011 to 2013*; Nonconfidential business information source documents are located in Federal Docket ID: EPA-HQ-ORD2010−0674; http://www.regulations.gov/#!docketDetail;rpp=100;so=DESC;sb=docId;po=0;D=EPA-HQ-ORD-2010-0674.

(26) *Sampling data for flowback and produced water provided to EPA by nine oil and gas well operators (non-confidential business information)*; http://www.regulations.gov/#!docketDetail;rpp=100;so=DESC;sb=docId;po=0;D=EPA-HQ-ORD-2010-0674.

(27) *Evaluation of impacts to underground sources of drinking water by hydraulic fracturing of coalbed methane reservoirs*; EPA/816/R-04/003; U.S. Environmental Protection Agency, Office of Solid Waste: Washington, DC, 2004.

(28) Material Safety Data Sheets: (a) Encana/Halliburton Energy Services, Inc.: Duncan, OK. Provided by Halliburton Energy Services during an onsite visit by the EPA on May 10, 2010. (b) Encana Oil and Gas (USA), Inc.: Denver, CO. Provided to US EPA Region 8.

(29) *Chemicals used in hydraulic fracturing*; U.S. House of Representatives, Committee on Energy and Commerce, Minority Staff: Washington, D.C., 2011; http://democrats.energycommerce.house.gov/sites/default/files/documents/Hydraulic-Fracturing-Chemicals-2011-4-18.pdf.

(30) *Chemicals used by hydraulic fracturing companies in Pennsylvania for surface and hydraulic fracturing activities*; Pennsylvania Department of Environmental Protection (PADEP): Harrisburg, PA, 2010; http://files.dep.state.pa.us/OilGas/BOGM/BOGMPortalFiles/MarcellusShale/Frac%20list%206-30-2010.pdf.

(31) *A review of the reference dose and reference concentration processes*; EPA/630/P-02/002F; U.S. Environmental Protection Agency, Risk Assessment Forum: Washington, DC, 2002; http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=51717.

(32) Agency for Toxic Substances and Diesease Registry (ATSDR) Glossary of Terms; http://www.atsdr.cdc.gov/glossary.html.

(33) World Health Organization (WHO) International Programme on Chemical Safety Concise International Chemical Assessment Documents; http://www.who.int/ipcs/publications/cicad/en/.

(34) Title 27, California Code of Regulations Article 8. No Observable Effect Levels; http://www.oehha.ca.gov/prop65/law/pdf_zip/RegsArt8.pdf.

(35) *Human Health Toxicity Values in Superfund Risk Assessments (OSWER Directive 9285.7-53)*; U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response: Washington, DC, 2003; http://www.epa.gov/oswer/riskassessment/pdf/hhmemo.pdf.

(36) *Analysis of Hydraulic Fracturing Fluid Data from the FracFocus Chemical Disclosure Registry 1.0: Project database*; EPA/601/R-14/003; U.S. Environmental Protection Agency, Office of Research and Development: Washington, DC, 2015; http://www2.epa.gov/hfstudy/epa-project-database-developed-fracfocus-1-disclosures.

(37) Lester, Y.; Ferrer, I.; Thurman, E. M.; Sitterley, K. A.; Korak, J. A.; Aiken, G.; Linden, K. G. Characterization of hydraulic fracturing flowback water in Colorado: Implications for water treatment. *Sci. Total Environ.* **2015**, *512-513*, 637−644.

(38) Loveless, D.; Holtsclaw, J.; Saini, R.; Harris, P.; Fleming, J. Fracturing Fluid Comprised of Components Sourced Solely from the Food Industry Provides Superior Proppant Transport. Presented at the Society of Petroleum Engineers (SPE) Annual Technical Conference and Exhibition, Denver, CO, Oct 31−Nov 2, 2011; http://www.baroididp.com/premium/tech_papers/source_files/pe/H08755_SPE147206.pdf.

(39) U.S. Food and Drug Administration Select Committee on GRAS Substances (SCOGS) Opinion: Ethyl formate, Sodium formate, Formic acid. 21 CFR 186.1316; http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS/ucm261288.htm.

(40) *Provisional Peer-Reviewed Toxicity Values for Formic Acid (CASRN 64-18-6)*; U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Superfund Health Risk Technical Support Center: Cincinnati, OH;http://hhpprtv.ornl.gov/issue_papers/FormicAcid.pdf.

(41) Judson, R.; Richard, A.; Dix, D. J.; Houck, K.; Martin, M.; Kavlock, R.; Dellarco, V.; Henry, T.; Holderman, T.; Sayre, P.; Tan, S.; Carpenter, T.; Smith, E. The toxicity data landscape for environmental chemicals. *Environ. Health Perspect.* **2009**, *117* (5), 685−695.

(42) Llewellyn, G. T.; Dorman, F.; Westland, J. L.; Yoxtheimer, D.; Grieve, P.; Sowers, T.; Humston-Fulmer, E.; Brantley, S. L. Evaluating a groundwater supply contamination incident attributed to Marcellus Shale gas development. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112* (20), 6325−6330.

(43) Brantley, S. L.; Yoxtheimer, D.; Arjmand, S.; Grieve, P.; Vidic, R.; Pollak, J.; Llewellyn, G. T.; Abad, J.; Simon, C. Water resource impacts during unconventional shale gas development: The Pennsylvania experience. *Int. J. Coal Geol.* **2014**, *126*, 140−156.

(44) Burton, G. A., Jr.; Basu, N.; Ellis, B. R.; Kapo, K. E.; Entrekin, S.; Nadelhoffer, K. Hydraulic "Fracking": Are Surface Water Impacts An Ecological Concern? *Environ. Toxicol. Chem.* **2014**, *33* (8), 1679−1689.

(45) *Review of state and industry spill data: characterization of hydraulic fracturing-related spills*; EPA/601/R-14/001; Office of Research and Development, U.S. Environmental Protection Agency: Washington, DC, 2015; http://www2.epa.gov/hfstudy/review-state-and-industry-spill-data-characterization-hydraulic-fracturing-related-spills-1.

(46) *Retrospective case study in Killdeer, North Dakota: study of the potential impacts of hydraulic fracturing on drinking water resources*; EPA 600/R-14/103; Office of Research and Development, U.S. Environmental Protection Agency: Washington, DC, 2015; http://www2.epa.gov/hfstudy/retrospective-case-study-killdeer-north-dakota.

DOI: 10.1021/acs.est.5b04645
Environ. Sci. Technol. 2016, 50, 4788−4797