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# Adverse Reproductive and Developmental Health Outcomes Following Prenatal Exposure to a Hydraulic Fracturing Chemical Mixture in Female C57Bl/6 Mice

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## Abstract

Unconventional oil and gas operations using hydraulic fracturing can contaminate surface and groundwater with endocrine-disrupting chemicals. We have previously shown that 23 of 24 commonly used hydraulic fracturing chemicals can activate or inhibit the estrogen, androgen, glucocorticoid, progesterone, and/or thyroid receptors in a human endometrial cancer cell reporter gene assay and that mixtures can behave synergistically, additively, or antagonistically on these receptors. In the current study, pregnant female C57Bl/6 dams were exposed to a mixture of 23 commonly used unconventional oil and gas chemicals at approximately 3, 30, 300, and 3000 μg/kg·d, flutamide at 50 mg/kg·d, or a 0.2% ethanol control vehicle via their drinking water from gestational day 11 through birth. This prenatal exposure to oil and gas operation chemicals suppressed pituitary hormone concentrations across experimental groups (prolactin, LH, FSH, and others), increased body weights, altered uterine and ovary weights, increased heart weights and collagen deposition, disrupted folliculogenesis, and other adverse health effects. This work suggests potential adverse developmental and reproductive health outcomes in humans and animals exposed to these oil and gas operation chemicals, with adverse outcomes observed even in the lowest dose group tested, equivalent to concentrations reported in drinking water sources. These endpoints suggest potential impacts on fertility, as previously observed in the male siblings, which require careful assessment in future studies.

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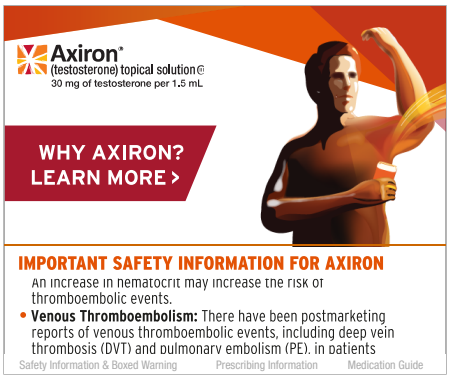




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# Associations between Unconventional Natural Gas Development and Nasal and Sinus, Migraine Headache, and Fatigue Symptoms in Pennsylvania

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# Associations between Unconventional Natural Gas Development and Nasal and Sinus, Migraine Headache, and Fatigue Symptoms in Pennsylvania

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**Running title**: Fracking and sinusitis, migraine, and fatigue

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## ABSTRACT

**Background:** Unconventional natural gas development (UNGD) produces environmental contaminants and psychosocial stressors. Despite these concerns, few studies have evaluated the health effects of UNGD.

**Objectives:** We investigated associations between UNGD activity and symptoms in a cross-sectional study in Pennsylvania.

**Methods:** We mailed a self-administered questionnaire to 23,700 adult patients of the Geisinger Clinic. Using standardized and validated questionnaire items, we identified respondents with chronic rhinosinusitis (CRS), migraine headache, and fatigue symptoms. We created a summary UNGD activity metric that incorporated well phase, location, total depth, daily gas production and inverse distance-squared to patient residences. We used logistic regression, weighted for sampling and response rates, to assess associations between quartiles of UNGD activity and outcomes, both alone and in combination.

**Results:** The response rate was 33%. Of 7,785 study participants, 1,850 (24%) had current CRS symptoms, 1,765 (23%) had migraine headache, and 1,930 (25%) had higher levels of fatigue. Among individuals who met criteria for two or more outcomes, adjusted odds ratios for the highest quartile of UNGD activity compared to the lowest were [OR (95% CI)] 1.49 (0.78, 2.85) for CRS plus migraine, 1.88 (1.08, 3.25) for CRS plus fatigue, 1.95 (1.18, 3.21) for migraine plus fatigue, and 1.84 (1.08, 3.14) for all three outcomes together. Significant associations were also present in some models of single outcomes.

**Conclusions:** This study provides evidence that UNGD is associated with nasal and sinus, migraine headache, and fatigue symptoms in a general population representative sample.

## INTRODUCTION

Unconventional natural gas development (UNGD), which includes the process of hydraulic fracturing, represents an expanding share of energy production worldwide. Shale gas extraction now comprises 40% of U.S. domestic natural gas production (Energy Information Administration 2015). In the past decade particularly rapid increases in UNGD have occurred in Pennsylvania, where more than 8,800 unconventional wells have been drilled.

There are concerns that UNGD could affect the environment via chemical pollutants such as diesel exhaust, volatile organic compounds, combustion products, fugitive emissions, and fracking chemicals (Werner et al. 2015). UNGD has been linked to contamination of air (Macey et al. 2014; Paulik et al. 2015), soil (Maloney and Yoxtheimer 2012), groundwater (Jackson et al. 2013; Drollette et al. 2015), and surface water (Kassotis et al. 2014). UNGD also creates contextual and psychosocial stressors including noise, truck traffic, influxes of non-local workers, and perceived negative impacts on quality of life and the built and social environments (Saberi et al. 2014; Powers et al. 2015; Adgate et al. 2014).

There have been few studies of the health effects of UNGD, despite increasing concern (Mitka 2012; Kovats et al. 2014). Prior studies have been limited by factors including small sample size and imprecise exposure assessment (Adgate et al. 2014). Because expansion of UNGD has outpaced scientific understanding of its potential health impacts, studies of self-reported outcomes have been advocated as a rapid means of generating hypotheses that could influence public policy. Furthermore, some illnesses with plausible links to UNGD, such as pain syndromes and fatigue, are defined solely by symptoms. Yet to date there have been only two epidemiologic studies, each with fewer than 500 participants, of symptoms in relation to UNGD (Steinzor et al. 2013; Rabinowitz et al. 2015).

We used data from a large population-based cross-sectional survey of Pennsylvania adults to identify patients with nasal and sinus symptoms, migraine headache, and higher levels of fatigue. We selected these outcomes because of their high prevalence, large economic costs, and possible links to environmental risk factors through chemical toxicity, irritation, odors, or stress (Hastan et al. 2011; Bhattacharyya 2009; Shashy et al. 2004; Tan et al. 2013; Friedman and De ver Dye 2009; Sjostrand et al. 2010; Bell et al. 1998; Griffith and Zarrouf 2008; Ranjith 2005; Ricci et al. 2007). The purpose of this study was to test the null hypothesis that UNGD is not associated with these three outcomes. To do so, we conducted a case-control analysis in which we compared individuals with one or more of these health outcomes to selected participants with no or minimal evidence of these diseases.



## METHODS

*Study overview*

In early 2014, we performed a cross-sectional survey of primary care patients of the Geisinger Clinic. Information was gathered via a questionnaire designed to study general CRS epidemiology (for questionnaire see Supplemental Material, "Population Study of Nasal and Sinus Symptoms"). The questionnaire did not mention UNGD because that was not its primary purpose. We used residential addresses and information about Pennsylvania unconventional gas wells to create UNGD activity metrics for four time-varying well development phases. We evaluated the associations between UNGD activity and CRS, migraine headache, and fatigue symptoms. The study protocol was approved by the Institutional Review Board (IRB) of the Geisinger Health System with an IRB Authorization Agreement with the Johns Hopkins Bloomberg School of Public Health. Waivers of HIPAA authorization and written informed

consent were approved by the IRB; implied consent was considered to have been provided if the patient returned the mailed questionnaire.

*Study population*

The Geisinger Clinic provides primary care services to over 400,000 patients, predominantly in central and northeastern Pennsylvania. Our source population consisted of 200,769 adult (age ≥ 18 years) Geisinger primary care patients for whom we had electronic health record (EHR) data and information on race/ethnicity. From this source population we selected 23,700 survey recipients using a stratified sampling design which is described in the following section. We mailed the baseline questionnaire in April 2014. A total of 7,847 (33.1%) individuals returned the questionnaire after three mailings. Questionnaires were returned between April 13 and October 13, 2014. After excluding respondents who lived outside Pennsylvania (n = 62), the study sample consisted of 7,785 participants.

*Rationale and description of the stratified sampling method*

We oversampled racial/ethnic minorities because a primary interest of the parent grant was to understand racial/ethnic differences in CRS epidemiology. Geisinger's catchment area only has approximately 8% racial/ethnic minorities. Oversampling was necessary to ensure a sufficient number of racial/ethnic minorities in the parent study.

Similarly, to ensure an adequate number of CRS patients in the parent CRS study, we oversampled individuals with higher likelihood of having CRS. To do so, we used electronic health record data to identify Geisinger primary care patients with higher, intermediate, and lower likelihood of CRS. These assessments were based on International Classification of

Disease (ICD)-9 codes and Current Procedural Terminology (CPT) codes from the medical record. Patients with a "higher" likelihood of CRS (n = 13,494) had at least two ICD-9 codes for CRS (ICD-9 codes 473.x or 471.x) associated with an outpatient, inpatient, or emergency department encounter; or at least one CPT code for sinus computerized tomography, sinus endoscopy, or sinus surgery. Patients with "intermediate" likelihood of CRS (n = 49,918) had at least one ICD-9 code for asthma (493.x) or allergic rhinitis (477.x); or a single ICD-9 code for CRS associated with an outpatient, inpatient, or emergency department encounter. The 137,357 patients who did not meet criteria for the higher and intermediate likelihood groups were designated as having a "lower" likelihood of CRS.

We divided our source population into six strata based on race/ethnicity and likelihood of CRS. We mailed the baseline CRS survey to a larger percentage of individuals in the strata of interest (see Supplemental Material, Table S1).

*Covariates*

From the EHR we obtained these covariates: sex; current age (years); race/ethnicity (white non-Hispanic, other); smoking status (never, current, former); body mass index (BMI, $kg/m^2$); residential address; and history of receiving Medical Assistance, a means-tested health insurance program that we used as a surrogate for family socioeconomic status (Casey et al. 2013). We used information in the EHR to derive each individual's residential place type (township, borough, or census tract in cities) and Charlson comorbidity index. We computed the Charlson index, which incorporates the number and severity of comorbid illnesses, consistent with previously published criteria (Charlson et al. 1987). We dichotomized race/ethnicity because only 10% of participants were non-white, which is reflective of the general population in

these communities (Casey et al. 2016). Our questionnaire ascertained additional information on educational status, marital status, household income, hay fever, nasal polyps, age at onset of nasal/sinus symptoms (in 5-year categories), history of sinus surgery, and current use of sinusitis medications (antibiotics and oral, inhaled, and nasal corticosteroids). We used United States census data to derive community socioeconomic deprivation (CSD) in townships, boroughs, and cities using a modified version of the Townsend index (Townsend 1987) as previously reported (Liu et al. 2012).

*Outcome ascertainment*

The cardinal symptoms of CRS are nasal congestion/obstruction, nasal discharge (anterior or posterior nasal drip), smell loss, and facial pain or pressure. Our questionnaire ascertained the frequency ("never," "once in a while," "some of the time," "most of the time," or "all the time"), in the past three months, of the aforementioned symptoms (questions 10-15 of the questionnaire, which is included in the Supplemental Material, "Population Study of Nasal and Sinus Symptoms"). Following European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) diagnostic criteria for CRS in epidemiologic studies (Fokkens et al. 2012), we determined participants to have current CRS if they experienced two or more cardinal symptoms (one of which must be nasal congestion/obstruction [question 10] or discharge [question 11 and/or 12]) at least "most of the time" in the past three months.

We ascertained migraine headache via questions from the ID Migraine questionnaire (Lipton et al. 2003) covering the past twelve months. Those with headaches at least "some of the time" (question 80) were asked the frequency ("never," "rarely," "less than half the time," "half the time or more") of headache-associated disability, nausea, and photophobia (questions 81-83).

Using a validated scoring method (Lipton et al. 2003), we dichotomized the three responses. Responses of "never" or "rarely" were scored as no and responses of "less than half the time" or "half the time or more" were scored as yes. Participants who answered yes to at least two of three questions were considered to have migraines.

We ascertained fatigue with eight questions from the PROMIS fatigue short form 8a (Patient-Reported Outcomes Measurement Information System 2015). These items assessed the frequency ("not at all," "a little bit," "somewhat," "quite a bit," "very much") of fatigue and fatigue-related disability in the past week (questions 84-91). We used the instrument's standardized scoring instructions to code responses from 1 ("not at all") to 5 ("very much") and summed the eight values to produce a score ranging from 8 to 40. We excluded individuals who answered fewer than four questions (n = 76). Individuals who answered between 4 and 7 questions were assigned a pro-rated score using this formula: score = (raw sum x 8)/(number of items answered). Fractional scores were rounded up to the nearest integer. Our "higher levels of fatigue" outcome consisted of individuals in the highest quartile (score ≥ 28).

Some respondents met criteria for more than one outcome. In the analysis, we evaluated associations of UNGD with single outcomes (i.e., CRS only; migraine only; or fatigue only) and multiple outcomes (i.e., participants with CRS and migraine; CRS and fatigue; migraine and fatigue; or all three outcomes).



*Reference group*

We performed an unmatched case-control analysis in which we compared individuals with one or more of the three primary outcomes ("cases") to a subset of participants with no or minimal evidence of these outcomes (hereafter referred to as "controls" or the "reference

group"). The reference group comprised study participants who 1) did not meet diagnostic criteria for past or current CRS, 2) reported no migraine headache symptoms, and 3) reported lower levels of fatigue (i.e., first quartile of fatigue score). Individuals with past CRS, intermediate likelihood of migraine, and/or moderate levels of fatigue were excluded from the reference group. These exclusion criteria were intended to produce a reference group free of individuals with a moderate likelihood of having the outcome (in the case of migraine and fatigue) or whose disease had been aggressively managed and treated (in the case of past CRS).

We created the reference group as follows. First, we excluded all study participants with one or more of the outcomes of interest. Next, individuals who met criteria for lifetime CRS (i.e., responses of "yes" to at least two cardinal symptoms on questions 1-6, one of which had to be nasal blockage [question 1] or discharge [question 2 and/or 3]) but not current CRS were deemed to have "past CRS" and were excluded from the reference group. We then excluded participants from the reference group if they endorsed any of the three ID Migraine criteria. In other words, members of the reference group either skipped the ID Migraine questions (e.g., because they reported a headache frequency of "never" or "once in a while" on question 80 and were instructed to skip the following three questions) or responded to questions 81-83 with no migraine symptom occurring more frequently than "never" or "rarely." Finally, we excluded individuals from the reference group if their fatigue score was higher than the 25$^{th}$ percentile (i.e., those with fatigue score > 13) or they did not answer at least four of eight PROMIS fatigue items (questions 84-91). No other inclusion or exclusion criteria were applied to the reference group.

*UNGD activity assessment*

We used published descriptions, and our own data, to estimate the duration of each UNGD phase (Gaines 2013; New York State Department of Environmental Conservation 2015; Casey et al. 2016). Pad preparation, which involves the clearing of the well site, lasts approximately 30 days. Drilling of the well then takes 1 to 30 days, proportionate to the total (vertical plus horizontal) depth. After drilling, hydraulic fracturing occurs during a stimulation (fracking) phase that lasts an average of 7 days. Finally, the well produces natural gas during a production phase that lasts months to years.

To capture these complexities of well development, we compiled data on UNGD in Pennsylvania from January 1, 2005 through December 31, 2014, from the Pennsylvania Department of Environmental Protection, the Pennsylvania Department of Conservation and Natural Resources, and SkyTruth (http://skytruth.org). For each well we obtained geographic coordinates; start dates of drilling, stimulation, and production; total depth; and volume of natural gas produced during six- or twelve-month reporting windows.

Using methods described previously (Casey et al. 2016), we created UNGD activity metrics for each phase of well development. Briefly, metrics incorporated all unconventional gas wells in Pennsylvania and were defined as

$$\text{Metric for participant } i = \frac{1}{T}\sum_{t=-1}^{-T}\sum_{j=1}^{n} w_j(t)/\, d_{ij}^2$$

where $T$ was an averaging period in days (in our primary analysis, $T = 90$ because CRS diagnostic criteria require three months of symptoms); $t$ was a temporal summation index whose negative sign represents past dates (e.g., summing from $t = -1$ to -90 indicates that the metric was averaged over 90 consecutive days immediately prior to the survey); $n$ was the number of wells;

$w_j(t)$ was the weight assigned to the $j$th well on day $t$; and $d_{ij}^2$ was the squared distance between well $j$ and the residential address of participant $i$. We set $w_j(t) = 0$ for wells that were inactive in the given phase on day $t$. Active wells were assigned weights during the duration of the relevant phase as follows: for pad preparation and drilling metrics, $w_j(t)$ was 1; for the stimulation metric, $w_j(t)$ was the total depth (a surrogate for hydraulic fracturing chemical volumes and the number of truck trips required to transport stimulation materials); and for the production metric, $w_j(t)$ was the average daily volume of natural gas produced during the corresponding reporting period.

Because the four UNGD phase metrics were highly correlated when averaged over 90 days (Spearman coefficient > 0.90 for each pairwise comparison), we z-transformed the metrics and summed the resulting $z$-scores. For analysis, we divided this continuous composite UNGD activity metric into quartiles for ease of interpretation and because of its skewed distribution.

*Statistical analysis*

We used descriptive statistics to compare characteristics of participants with and without each outcome. To evaluate selection bias with respect to UNGD, we compared distributions of the UNGD activity metric in study participants and questionnaire non-responders. To assess the potential for non-conservative errors due to selection bias with respect to health status, we analyzed distributions of the Charlson comorbidity index in study participants and survey non-responders, stratified by UNGD quartile. Categorical and continuous variables were compared using $\chi^2$ tests and $t$-tests, respectively. For hypothesis testing, $p$-values < 0.05 were considered statistically significant.

We used weighted logistic regression to evaluate associations between UNGD activity and symptoms while adjusting for confounding variables. All models compared individuals with

the outcome(s) of interest ("cases") to the reference group described above ("controls"). The use of sampling weights allowed us to account for the differential patient selection and participation rates in our stratified design, while targeting unbiased measures of association and obtaining robust standard errors. We assigned each participant a sampling weight equal to the inverse probability of inclusion in the study (see Supplemental Material, Table S1). Because the weight in one stratum (150.8) was very substantially larger than the other weights, we truncated this weight by reducing it to the value of the second-highest weight (32.3).

We adjusted all models for these potential confounders that we identified *a priori*: sex, race/ethnicity (non-Hispanic white vs. other), age (linear and quadratic terms; to avoid collinearity we centered the age variable by subtracting its mean [i.e., $A_c = A_i - A_{mean}$]), receipt of Medical Assistance (never vs. ever), and smoking status (never vs. former and current). We tested for additional confounding by adding linear and quadratic terms for BMI and CSD. We retained these covariates in the models if they changed associations between UNGD and the outcome by at least 10%. Analyses were performed in R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata 13.1 (StataCorp, College Station, Texas) using the svy commands.

We reasoned that UNGD might be associated with current CRS only for onset of symptoms after 2006, when UNGD commenced in Pennsylvania. To test the associated hypothesis we stratified the CRS group by date of symptom onset (before/after January 1, 2006) and re-ran models within each stratum. While associations of UNGD activity with our other outcomes could also differ by onset date, our questionnaire did not ascertain the onset date of migraine and fatigue symptoms.

We performed several sensitivity analyses. To explore the impact of sampling weight

choices, we re-ran models with full (i.e., not truncated) weights and again with no weights. To determine whether associations differed by the length of the UNGD assessment period, we compared associations using 7-day, 90-day, and 365-day averaged UNGD metrics that corresponded to the questionnaire's recall windows for the three primary outcomes. To explore spatial differences among groups of participants, we mapped the residential locations of individuals with and without our primary outcomes, stratified by UNGD quartile and case/control status. To assess whether UNGD was associated with symptoms in individuals with past disease or moderate symptoms, we created additional CRS and fatigue models in which we re-classified some previously excluded individuals as "cases" (for details see Supplemental Material, "Models of Past Disease and Moderate Symptoms"). To assess whether unmeasured confounding, including spatial confounding, could be responsible for the observed associations, we created "negative control outcome" models (Lipsitch et al. 2010). These adjusted logistic regression models evaluated associations between UNGD and self-reported outcomes (bad breath, ear pain, and cold/flu symptoms) that we thought were unlikely to be related to UNGD. We expected to find no significant associations between UNGD and these outcomes; the presence of such associations could indicate bias due to unmeasured confounding. In these models, we defined cases as all study participants who reported the symptom at least "most of the time" in the past three months (questions 36, 43, and 48 for bad breath, ear pain, and cold/flu symptoms, respectively). The reference group for each model consisted of all individuals who reported the symptom "never" in the past three months.

## RESULTS

### *Characteristics of the study population*

Questionnaire respondents were 7,785 individuals from 39 counties in central and northeastern Pennsylvania, in regions with and without UNGD (Figure 1). Compared to questionnaire recipients who did not respond, our study population was more likely to be female, white, and older (results not shown). The continuous UNGD activity metric did not differ significantly ($p = 0.26$) between study participants and questionnaire non-responders (Table 1). Study participants were less likely than non-responders to be in the highest UNGD quartile. While the Charlson comorbidity index was higher in responders (mean = 3.43) than in non-responders (mean = 2.52, $p < 0.001$), the mean Charlson values were similar across all UNGD quartiles (Table 1).

We identified 738 participants with current CRS and no other primary outcome, 580 with migraine headache only, and 666 with higher levels of fatigue only (Table 2). These conditions were co-occurring in other individuals. There were 268 individuals with CRS and migraine, 347 with CRS and higher levels of fatigue, 420 with migraine and higher levels of fatigue, and 497 with all three outcomes. There were 1,380 participants with no current or past CRS, no migraine headache symptoms, and lower levels of fatigue; these comprised the reference group. Compared to the reference group, individuals with each single outcome were more likely to be younger and current smokers (Table 2). Those with migraine and fatigue were more likely to be female, while those reporting CRS and fatigue were more likely to be white non-Hispanic.

### *Associations of UNGD with symptoms*

The highest quartile of UNGD activity, compared to the lowest, was associated with

significantly increased odds of the following combinations of two or more outcomes: CRS and higher levels of fatigue [odds ratio (OR) = 1.88; 95% confidence interval (CI): 1.08, 3.25]; migraine headache and higher levels of fatigue (OR = 1.95; 95% CI: 1.18, 3.21); and all three outcomes (OR = 1.84; 95% CI: 1.08, 3.14) (Table 3). The second and third quartiles of UNGD were not significantly associated with any of the outcomes. In individuals with only one outcome, the odds ratios for the fourth quartile of UNGD were 1.11 (95% CI: 0.75, 1.65) for current CRS, 1.43 (95% CI: 0.94, 2.18) for migraine headache, and 1.47 (95% CI: 0.996, 2.18) for higher levels of fatigue (Table 3). In general, participants in the fourth quartile of UNGD lived farther north than those in other UNGD quartiles (Figure 2).

When we stratified CRS patients by onset date, the second (OR = 3.27; 95% CI: 1.21, 8.82) and fourth (OR = 3.26; 95% CI: 1.14, 9.36) quartiles of UNGD were associated with significantly increased odds of CRS in those whose symptoms began after 2006 (see Supplemental Material, Table S2). There were no associations in participants with earlier symptom onset.



*Sensitivity analyses*

In participants with multiple outcomes, most inferences were unchanged whether we used the full sampling weights, truncated weights, or no weights (compare Table 3 to Supplemental Material, Table S3). Odds ratios for the fourth quartile of UNGD were consistently higher, and had wider confidence intervals, in fully weighted models than in models with truncated weights. For example, the odds ratio for the association of the fourth quartile of UNGD with the co-existence of migraine and fatigue was 2.89 (95% CI: 1.45, 5.76) in the fully weighted model. In individuals with single outcomes, the fourth quartile of UNGD was significantly associated with

migraine headache (OR = 1.80; 95% CI: 1.02, 3.17) and fatigue (OR = 1.89; 95% CI: 1.10, 3.26) in the models with full weights; significant associations were also present in unweighted models (see Supplemental Material, Table S3).

UNGD activity, when averaged over 7 or 365 days, was highly correlated with the 90-day time-averaged UNGD metric used in the primary analyses (Spearman coefficient = 0.98 for both comparisons). Most inferences and associations were similar when using a 7-day or 365-day averaging period (see Supplemental Material, Table S4). The second quartile of UNGD was associated with past CRS but there were no associations of UNGD with moderate levels of fatigue (see Supplemental Material, Table S5). UNGD was not associated with the negative control outcomes of ear pain, bad breath, or cold/flu symptoms (Table 4).

Because only the highest level of UNGD was associated with our primary outcomes, we compared demographic and socioeconomic characteristics of individuals in the fourth quartile of UNGD to those of participants in other UNGD quartiles (see Supplemental Material, Table S6). Participants in the fourth quartile of UNGD differed on some covariates, several of which were included in the final models. We did not include place type in the final adjusted models because it could be a surrogate for mediators (e.g., individual- or place-level socioeconomic status) of associations between UNGD and symptoms. In a sensitivity analysis that explored the effect of place type, some associations were attenuated slightly when place type was added to the models, but inferences were similar (see Supplemental Material, Table S7).



## DISCUSSION

In our survey of primary care patients in central and northeast Pennsylvania, residential UNGD activity was associated with nasal and sinus symptoms, migraine headache, and higher

levels of fatigue, either alone or in combination. Our findings are suggestive of a threshold in the relationship between UNGD and symptoms, as associations were present only among participants in the fourth quartile of UNGD activity. We found stronger associations in individuals with two or more co-occurring outcomes. In addition, UNGD was associated with CRS in individuals whose nasal and sinus symptoms began after the start of UNGD in Pennsylvania, although these estimates had lower precision due to the small number of subjects with recent CRS onset.

In surveys such as ours, in which selection is based on the outcome, regression models must include sampling weights (or employ another strategy to acknowledge the selection mechanism) to avoid bias. However, extreme sampling weights can significantly increase the model's variance (Potter 1988). To balance bias reduction against variance inflation, several techniques have been developed to truncate large sampling weights. We employed one such technique in our primary analyses. We found associations between UNGD and symptoms in the primary models, and in fully weighted and unweighted models.

There is limited prior evidence linking environmental factors to CRS, migraine headache, and fatigue. Exposure to allergens, toxicants, and secondhand smoke may trigger nasal and sinus symptoms (Fokkens et al. 2012). However, a recent review found insufficient epidemiologic evidence from which to draw conclusions about occupational or environmental risk factors for CRS (Sundaresan et al. 2015). Though migraines have a strong hormonal and genetic component, migraines can also be triggered by noise, odors, and stress (Friedman and De ver Dye 2009; Sjostrand et al. 2010; Sauro and Becker 2009). Similarly, fatigue has multiple risk factors including sleep deprivation, psychosocial stressors, medical disorders, psychiatric factors, occupation, and exposure to low levels of environmental chemicals (Bell et al. 1998; Ranjith

2005; Ricci et al. 2007; Griffith and Zarrouf 2008). Our UNGD activity metrics were designed to capture all potential environmental pathways that could affect these symptoms.

We did not measure participants' exposure to ambient air pollution. We also did not account for conventional oil and gas wells. During our study period the production of conventional gas wells in Pennsylvania was very low compared to that of unconventional wells. Furthermore, Pennsylvania's conventional wells tend to be in the northwest and west, where Geisinger has no patients. The lack of significant geographic overlap with our study population makes confounding of UNGD associations by conventional oil and gas wells unlikely.

Participants in the fourth quartile of UNGD activity lived farther north than those in other quartiles (Figure 2). This spatial separation is due to the location of the Marcellus shale, which constrains UNGD to the northern portion of the Geisinger catchment area. Given the correlation between geography and UNGD, we cannot rule out the possibility that spatial confounding was responsible for the observed associations. However, we note that our models were adjusted for several covariates (such as race/ethnicity and socioeconomic status) that could be associated with both location and outcomes. In addition, the null results in our negative control outcome models did not suggest spatial confounding.

CRS, migraine headache, and fatigue are highly prevalent and produce significant societal costs. CRS affects 2-16% of U.S. adults and results in emergency department visits, antibiotic prescriptions, sinus surgeries, and direct healthcare costs (Hastan et al. 2011; Bhattacharyya 2009; Shashy et al. 2004; Tan et al. 2013). Migraines have a prevalence of 11-14% and cause substantial temporary disability, emergency department visits, outpatient clinic visits, and analgesic use (Lipton et al. 2007; Burch et al. 2015). Fatigue prevalence, defined in various ways across studies, is estimated at 7-45%, and fatigue costs U.S. employers over $100

billion per year in lost productive work time (Ricci et al. 2007). From a public health and economic perspective it is vital to understand modifiable risk factors for these illnesses.

Recent reviews have noted the lack of high-quality evidence regarding the health effects of UNGD (Adgate et al. 2014; Werner et al. 2015). Our study of 7,785 Pennsylvania residents is the largest survey of symptoms with respect to UNGD and has several strengths when compared to prior studies. We selected a population-based adult sample with no exclusion criteria. Reporting bias was minimized by the fact that UNGD was not identified as a study aim, and response rates did not differ by proximity to UNGD. Our time-varying UNGD activity metric incorporated well phase and intensity measures such as total depth and gas production. We used standardized and validated instruments to assess fatigue and migraine, respectively, and we used consensus epidemiologic guidelines to assess CRS.

This study had several limitations. In general, cross-sectional surveys such as ours cannot assess temporal relations between exposures and outcomes, and we did not ascertain the onset dates of some symptoms. We note, however, that our UNGD activity metrics could theoretically be used to establish temporality, as they can be computed for any date prior to symptom onset. Our ascertainment of self-reported outcomes was susceptible to various types of information bias. For example, despite the fact that our questionnaire did not mention UNGD, individuals residing near UNGD may have over-reported symptoms. There was some evidence of selection bias, as survey participants had poorer health (measured by the Charlson comorbidity index) than non-responders. However, differences in health status were similar across levels of UNGD activity. Another limitation is that our estimates of well development phase durations, although based on published average values, may have been incorrect for individual wells. Further exposure misclassification could have occurred because our UNGD activity metric was based on

residential addresses. Participants' exposure to UNGD activity could have been affected by unmeasured factors such as occupation, travel, and time spent outdoors. Additionally, our UNGD activity metric did not allow identification of specific exposures or exposure pathways.

## CONCLUSIONS

UNGD was associated with CRS, migraine headache, and fatigue symptoms in a large population-based survey. Associations were stronger in patients with two or more outcomes. Our work has several advantages over previous studies, making it an important addition to the growing body of evidence that UNGD is associated with adverse health effects. Further research, including more sophisticated exposure and outcome measurements, is necessary to evaluate whether these associations are causal and to elucidate the mechanisms for these findings.

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## TABLES

**Table 1**. Comparison of selected characteristics in survey responders and non-responders.

| | Responders (n = 7,785) | Non-responders (n = 15,525) | *p*-value |
|---|---|---|---|
| Continuous composite UNGD activity metric, mean (sd) | -0.02 (1.80) | 0.01 (2.78) | 0.26[a] |
| UNGD activity, n (%) | | | |
| Quartile 1 | 2052 (26.4) | 3775 (24.3) | < 0.001[b] |
| Quartile 2 | 1828 (23.5) | 3996 (25.7) | |
| Quartile 3 | 2017 (25.9) | 3814 (24.6) | |
| Quartile 4 | 1888 (24.3) | 3940 (25.4) | |
| Charlson index, mean (sd) | 3.43 (2.76) | 2.52 (2.65) | < 0.001[a] |
| Charlson index stratified by quartiles of UNGD activity, mean (sd) | | | |
| Quartile 1 | 3.27 (2.61) | 2.46 (2.46) | |
| Quartile 2 | 3.37 (2.71) | 2.48 (2.57) | NA |
| Quartile 3 | 3.61 (2.83) | 2.68 (2.85) | |
| Quartile 4 | 3.47 (2.86) | 2.48 (2.70) | |
| | $p < 0.001$[c] | $p < 0.001$[c] | |

Abbreviations: UNGD, unconventional natural gas development; sd, standard deviation; NA, not applicable.
Patients who lived outside Pennsylvania were excluded (n = 390). UNGD activity was averaged over 90 days prior to the survey.
[a] *p*-value computed with *t*-test.
[b] *p*-value computed with chi-square test.
[c] Within responders and non-responders separately, *p*-values were computed with one-way analysis of variance (ANOVA) to compare mean Charlson index across quartiles of UNGD.

Table 2: Characteristics of study population by self-reported outcome(s).

| Characteristic | Overall study population | Individuals with no primary outcome | | Individuals with one or more primary outcomes | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Reference group[a] | Individuals who were neither cases nor controls[b] | Current CRS only | Migraine headache only | Higher levels of fatigue only | Current CRS and migraine | Current CRS and higher levels of fatigue | Migraine and higher levels of fatigue | Current CRS, migraine headache, and higher levels of fatigue |
| Total number, n | 7785 | 1380 | 2889 | 738 | 580 | 666 | 268 | 347 | 420 | 497 |
| Sex, n (%) | | | | | | | | | | |
| Male | 2909 (37.4) | 656 (47.5) | 1242 (43.0) | 335 (45.4) | 113 (19.5) | 233 (35.0) | 50 (18.7) | 126 (36.3) | 63 (15.0) | 91 (18.3) |
| Female | 4876 (62.6) | 724 (52.5) | 1647 (57.0) | 403 (54.6) | 467 (80.5) | 433 (65.0) | 218 (81.3) | 221 (63.7) | 357 (85.0) | 406 (81.7) |
| Race/ethnicity, n (%) | | | | | | | | | | |
| White non-Hispanic | 7043 (90.5) | 1183 (85.7) | 2653 (91.8) | 707 (95.8) | 508 (87.6) | 598 (89.8) | 257 (95.9) | 333 (96.0) | 357 (85.0) | 447 (89.9) |
| Other | 742 (9.5) | 197 (14.3) | 236 (8.2) | 31 (4.2) | 72 (12.4) | 68 (10.2) | 11 (4.1) | 14 (4.0) | 63 (15.0) | 50 (10.1) |
| Age in years, mean (sd) | 55.3 (16.1) | 58.8 (17.0) | 57.6 (15.9) | 57.1 (14.9) | 46.1 (14.3) | 57.3 (15.1) | 48.5 (13.2) | 56.1 (14.7) | 46.5 (13.6) | 47.8 (13.1) |
| Smoking status, n (%) | | | | | | | | | | |
| Never | 4268 (54.8) | 805 (58.3) | 1615 (55.9) | 404 (54.7) | 340 (58.6) | 334 (50.2) | 141 (52.6) | 178 (51.3) | 220 (52.4) | 231 (46.5) |
| Current | 1130 (14.5) | 134 (9.7) | 353 (12.2) | 100 (13.6) | 96 (16.6) | 113 (17.0) | 57 (21.3) | 61 (17.6) | 86 (20.5) | 130 (26.2) |
| Former | 2387 (30.7) | 441 (32.0) | 921 (31.9) | 234 (31.7) | 144 (24.8) | 219 (32.9) | 70 (26.1) | 108 (31.1) | 114 (27.1) | 136 (27.4) |
| History of receiving Medical Assistance, n (%) | | | | | | | | | | |
| Never | 6876 (88.3) | 1286 (93.2) | 2690 (93.1) | 694 (94.0) | 467 (80.5) | 588 (88.3) | 216 (80.6) | 293 (84.4) | 302 (71.9) | 340 (68.4) |
| Ever | 909 (11.7) | 94 (6.8) | 199 (6.9) | 44 (6.0) | 113 (19.5) | 78 (11.7) | 52 (19.4) | 54 (15.6) | 118 (28.1) | 157 (31.6) |
| Body mass index ($kg/m^2$), mean (sd) | 30.2 (7.0) | 29.0 (6.3) | 29.9 (6.5) | 30.4 (7.0) | 29.7 (7.3) | 31.7 (7.9) | 29.8 (7.3) | 31.3 (7.4) | 31.7 (7.7) | 31.2 (8.1) |
| Place type, n (%) | | | | | | | | | | |
| Township | 4949 (63.6) | 907 (65.7) | 1900 (65.8) | 476 (64.5) | 332 (57.2) | 417 (62.6) | 170 (63.4) | 213 (61.4) | 242 (57.6) | 292 (58.8) |
| Borough | 2135 (27.4) | 371 (26.9) | 762 (26.4) | 188 (25.5) | 183 (31.6) | 192 (28.8) | 72 (26.9) | 101 (29.1) | 122 (29.0) | 144 (29.0) |
| Census tract in city | 701 (9.0) | 102 (7.4) | 227 (7.9) | 74 (10.0) | 65 (11.2) | 57 (8.6) | 26 (9.7) | 33 (9.5) | 56 (13.3) | 61 (12.3) |
| Community socioeconomic deprivation, mean (sd) | 0.0 (3.6) | -0.3 (3.6) | -0.1 (3.6) | -0.1 (3.5) | 0.3 (3.7) | 0.1 (3.6) | 0.2 (3.5) | 0.1 (3.7) | 0.6 (3.7) | 0.6 (3.8) |
| UNGD activity metric, n (%)[c] | | | | | | | | | | |
| Quartile 1 [-0.61 to -0.47] | 1946 (25.0) | 358 (25.9) | 745 (25.8) | 181 (24.5) | 140 (24.1) | 155 (23.3) | 63 (23.5) | 91 (26.2) | 101 (24.0) | 112 (22.5) |
| Quartile 2 [-0.47 to -0.39] | 1946 (25.0) | 345 (25.0) | 731 (25.3) | 187 (25.3) | 145 (25.0) | 174 (26.1) | 65 (24.3) | 83 (23.9) | 92 (21.9) | 124 (24.9) |
| Quartile 3 [-0.39 to -0.16] | 1946 (25.0) | 373 (27.0) | 733 (25.4) | 188 (25.5) | 131 (22.6) | 172 (25.8) | 70 (26.1) | 73 (21.0) | 98 (23.3) | 108 (21.7) |
| Quartile 4 [> -0.16] | 1947 (25.0) | 304 (22.0) | 680 (23.5) | 182 (24.7) | 164 (28.3) | 165 (24.8) | 70 (26.1) | 100 (28.8) | 129 (30.7) | 153 (30.8) |

Abbreviations: CRS, chronic rhinosinusitis; UNGD, unconventional natural gas development; sd, standard deviation. Percentages may not total 100 due to rounding.

[a] Individuals in the reference group reported no past or current CRS; no headache-related nausea, photophobia, or disability; and lower levels ($\leq 25^{th}$ percentile) of fatigue.

[b] These individuals did not meet criteria for any primary outcome and were excluded from the reference group because of past CRS, intermediate probability of migraine headache, and/or moderate levels of fatigue.
[c] UNGD activity was averaged over the 90 days prior to the survey.

**Table 3**. Associations of UNGD with symptoms in individuals with one or more primary outcomes, compared to a reference group.

| | Current CRS only (n = 736)[a] | Migraine headache only (n = 580) | Higher levels of fatigue only (n = 666) | Current CRS and migraine (n = 266)[a] | Current CRS and higher levels of fatigue (n = 347)[a] | Migraine and higher levels of fatigue (n = 420) | All three outcomes (n = 496)[a] |
|---|---|---|---|---|---|---|---|
| UNGD quartile | Adjusted odds ratios (95% confidence intervals) | | | | | | |
| 1 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 2 | 1.17 (0.80, 1.72) | 1.14 (0.74, 1.75) | 1.48 (1.01, 2.17) | 0.82 (0.43, 1.57) | 1.06 (0.62, 1.80) | 1.06 (0.63, 1.78) | 1.05 (0.63, 1.78) |
| 3 | 0.76 (0.52, 1.12) | 0.89 (0.58, 1.36) | 1.22 (0.84, 1.77) | 0.74 (0.38, 1.47) | 0.94 (0.53, 1.66) | 0.80 (0.49, 1.31) | 0.73 (0.42, 1.27) |
| 4 | 1.11 (0.75, 1.65) | 1.43 (0.94, 2.18) | 1.47 (0.996, 2.18) | 1.49 (0.78, 2.85) | 1.88 (1.08, 3.25) | 1.95 (1.18, 3.21) | 1.84 (1.08, 3.14) |

Abbreviations: UNGD, unconventional natural gas development; CRS, chronic rhinosinusitis.

For all models, the reference group consisted of individuals with no current or past CRS, no migraine headache symptoms, and the lowest quartile of fatigue score. All models included sampling weights, with the highest weight truncated to the value of second-highest weight. Models included these covariates: sex, race/ethnicity (white non-Hispanic vs. other), centered age (linear and quadratic terms), Medical Assistance (never vs. ever), and smoking status (never vs. current and former). UNGD activity was averaged over the 90 days prior to the survey.

[a] These models included centered body mass index as an additional covariate. Because individuals with unknown body mass index were excluded, these case counts are slightly lower than those reported in the text.

**Table 4**. Associations of UNGD with negative control outcomes.

| | Ear pain yes (n = 422) vs. no (n = 3917) | Bad breath yes (n = 846) vs. no (n = 2628) | Cold/flu symptoms yes (n = 307) vs. no (n = 2442) |
|---|---|---|---|
| | Adjusted odds ratios (95% confidence intervals) | | |
| UNGD quartile | | | |
| 1 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 2 | 0.92 (0.58, 1.44) | 0.87 (0.61, 1.22) | 1.04 (0.58, 1.84) |
| 3 | 0.53 (0.32, 0.87) | 1.12 (0.80, 1.57) | 1.15 (0.66, 2.00) |
| 4 | 1.16 (0.74, 1.83) | 0.95 (0.67, 1.35) | 1.14 (0.64, 2.01) |

Abbreviations: UNGD, unconventional natural gas development; CRS, chronic rhinosinusitis.

Individuals with the symptom at least "most of the time" in the past three months were compared to those with the symptom "never" in the past three months. All models included sampling and response weights, and the highest weight was truncated to the value of the second-highest weight. Models included these covariates: sex, race/ethnicity (white non-Hispanic vs. other), centered age (linear and quadratic terms), Medical Assistance (never vs. ever), and smoking status (never vs. current and former). UNGD activity was averaged over the 90 days prior to the survey.

## FIGURE LEGENDS

**Figure 1**. Map of study area. Thick black outlines designate Pennsylvania counties with at least one participant (from U.S. Census Bureau TIGER/line files). Numbers within the borders of each county indicate the total number of participants (T) and the number with chronic rhinosinusitis symptoms (NS), migraine headache (H), and higher levels of fatigue (F) (data from the Geisinger Clinic). Gray circles show locations of drilled unconventional natural gas wells as of December 2014 (from Pennsylvania Department of Environmental Protection). Black stars represent Geisinger hospitals and clinics. Map was made with ArcGIS Desktop (release 10, Esri, Redlands, CA).

**Figure 2**. Locations of study participants in the fourth quartile of UNGD activity (**A**) and all other UNGD quartiles (**B**). Blue crosses: participants with at least one primary outcome (current CRS, migraine headache, and/or higher levels of fatigue). Black circles: reference group participants with no current or past CRS, no migraine headache symptoms, and lower levels of fatigue. Yellow circles: locations of all drilled unconventional natural gas wells in Pennsylvania as of December 31, 2014. Patient residential locations were from the Geisinger Clinic; county boundaries from the U.S. Census Bureau TIGER/line files; and UNGD wells from the Pennsylvania Department of Environmental Protection. Maps were made with ArcGIS Desktop (release 10, Esri, Redlands, CA).

Figure 1.

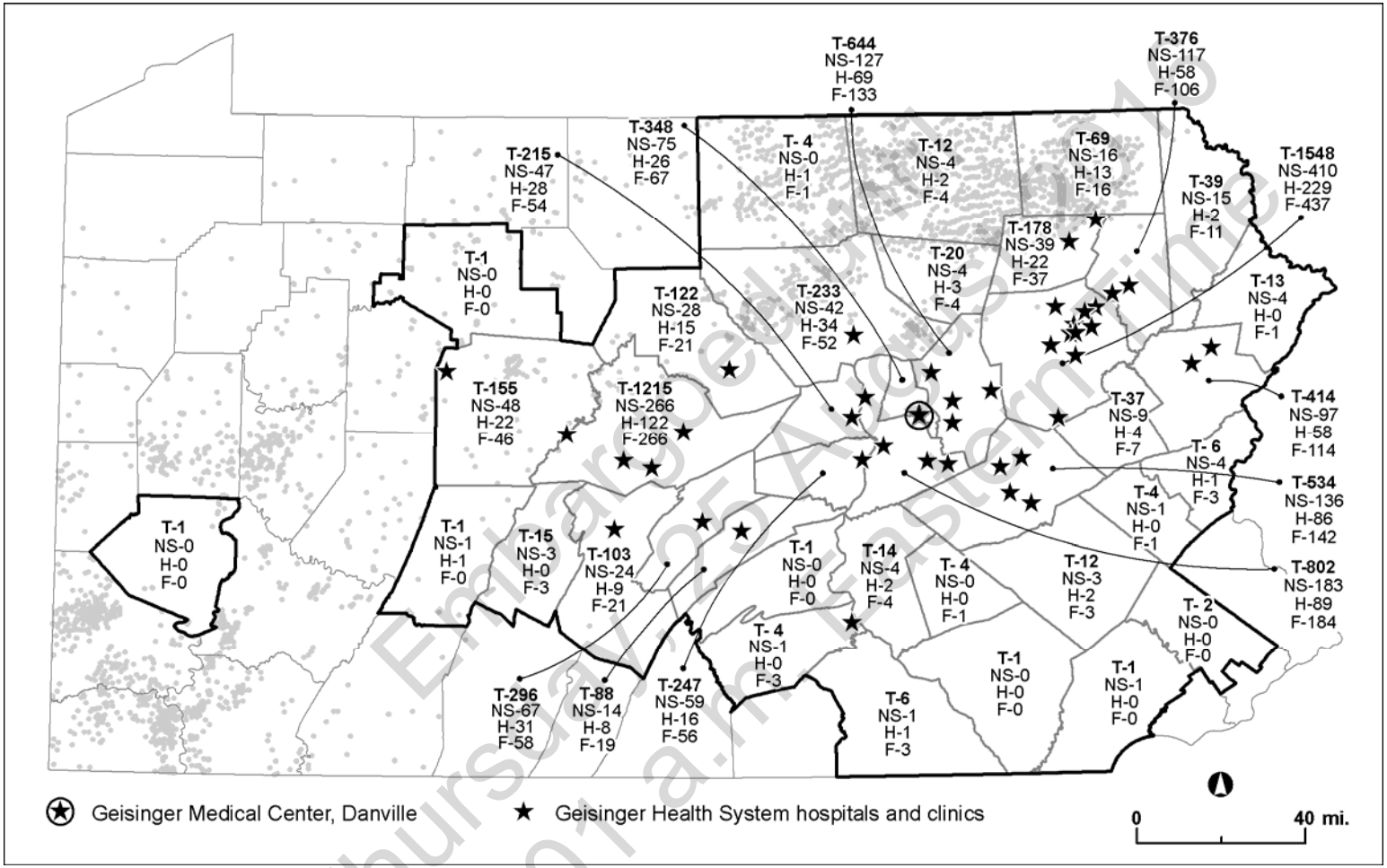
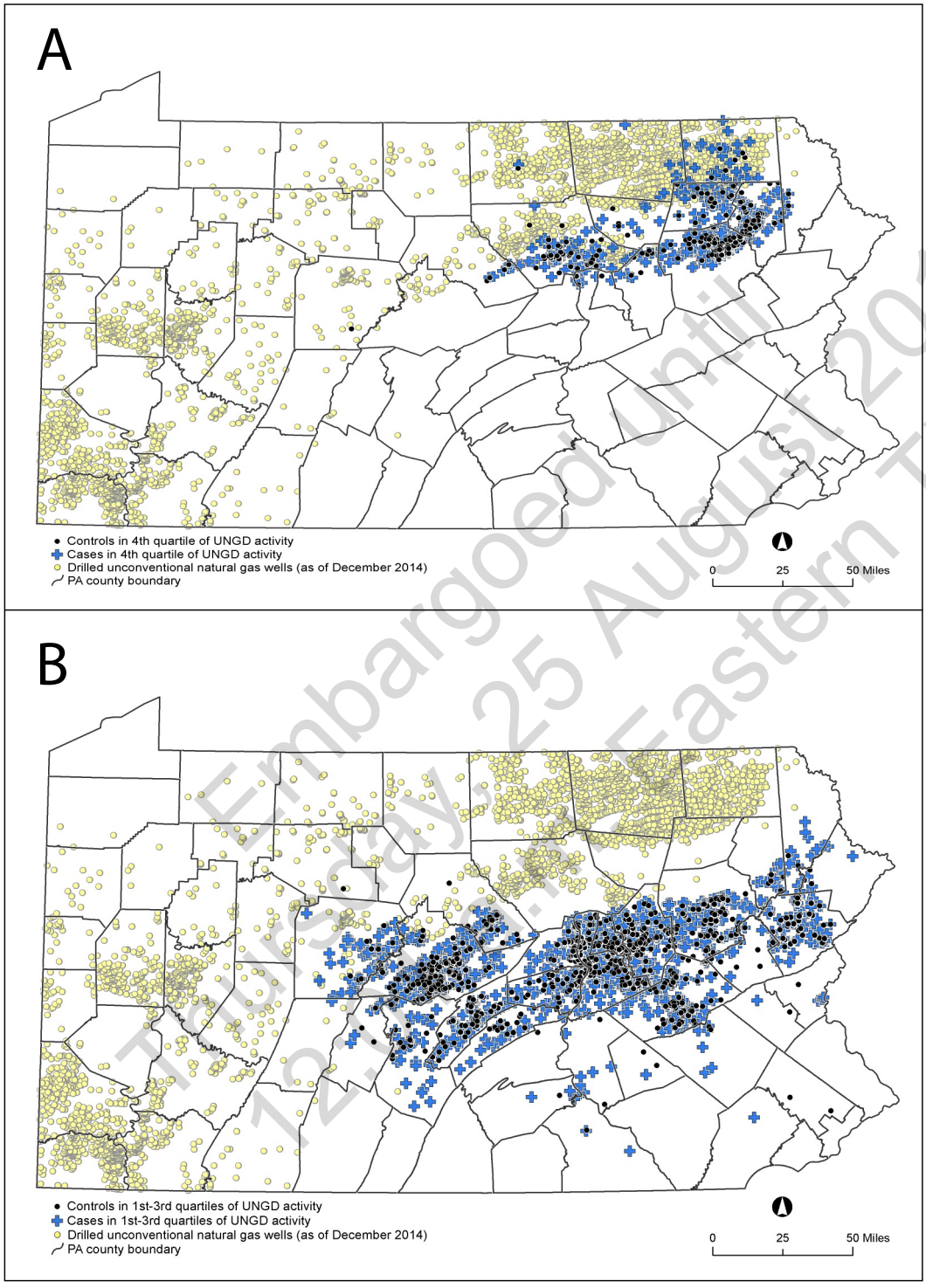


Figure 2.



# Fracking Linked to Cancer-Causing Chemicals, New YSPH Study Funds

October 24, 2016

**Fracking and Disease**

*Photo credit: Dreamstime*

An expansive new analysis by Yale School of Public Health researchers confirms that numerous carcinogens involved in the controversial practice of hydraulic fracturing have the potential to contaminate air and water in nearby communities.

Fracking is now common in the United States, currently occurring in 30 states, and with millions of people living within one mile of a fracking site. The study suggests that the presence of carcinogens involved in or released by hydraulic fracturing operations has the potential to increase the risk of childhood leukemia. The presence of chemicals alone does not confirm exposure or risk of exposure to carcinogens and future studies are needed to evaluate cancer risk.

“Because children are a particularly vulnerable population, research efforts should first be directed toward investigating whether exposure to hydraulic fracturing is associated with an increased risk,” said lead author Nicole Deziel, Ph.D., assistant professor. Childhood leukemia is a particular concern because of the severity and short latency period of the disease.

The study is published in the journal *Science of the Total Environment*.

The team examined an extensive list of more than 1,000 chemicals that may be released into air or water as a result of fracking. “Previous studies have examined the carcinogenicity of more selective lists of chemicals,” said Deziel. “To our knowledge, our analysis represents the most expansive review of carcinogenicity of hydraulic fracturing-related chemicals in the published literature.”

> “To our knowledge, our analysis represents the most expansive review of carcinogenicity of hydraulic fracturing-related chemicals in the published literature."
>
> — NICOLE DEZIEL

According to the findings, the majority of chemicals (>80 percent) lacked sufficient data on cancer-causing potential, highlighting an important knowledge gap. Of the 119 compounds with sufficient data, 44 percent of the water pollutants and 60 percent of air pollutants were either confirmed or possible carcinogens. Because some chemicals could be released to both air and water, the study revealed a total of 55 unique compounds with carcinogenic potential. Furthermore, 20 chemicals had evidence of increased risk for leukemia or lymphoma specifically. This analysis creates a priority list of carcinogens to target for future exposure and health studies.

Fracking, also known as unconventional oil and gas development, has increased dramatically in recent years, and the practice is expected to grow in the future. The process involves drilling deep, as far as two miles, into the earth and releasing a high-pressure mixture of water, sand and chemicals that fracture the rock and release the gas or oil trapped inside. While fracking increases the production of domestic oil and natural gas and decreases prices, it is controversial because of the significant amounts of water that must be used as well as transported to fracking sites, as well as the release of carcinogens.

The team has begun been testing air and water samples for some of these known and suspected carcinogens in a community with particularly intense exposure to fracking to evaluate whether people there are exposed to these compounds, and if so, at what concentrations.

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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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**Keywords:** developmental toxicity; hydraulic fracturing; reproductive toxicity; shale; unconventional natural gas; wastewater

## 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

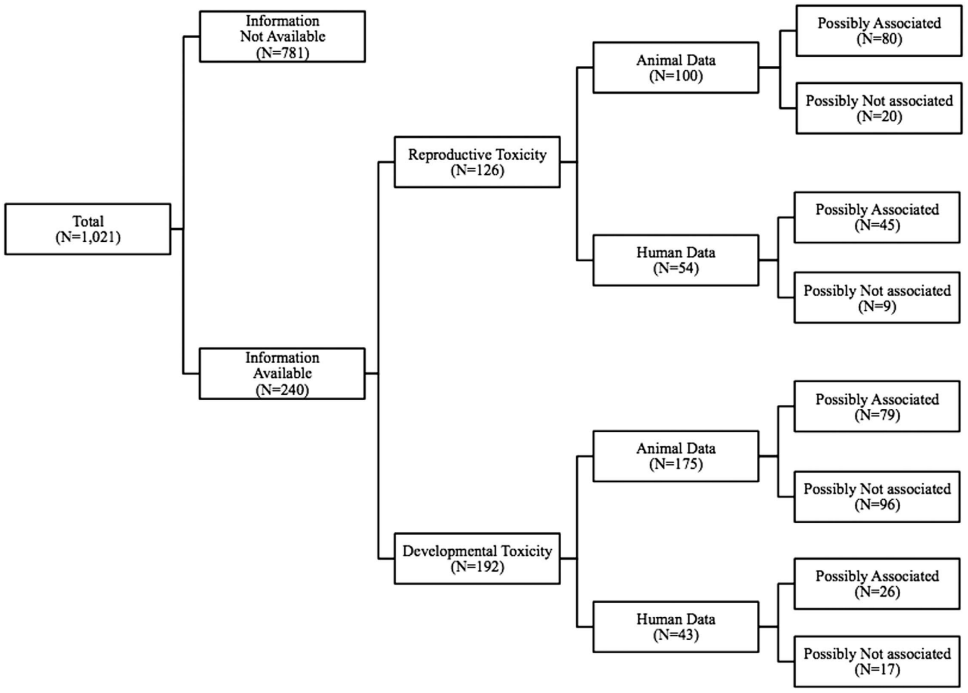


**Figure 1.** Reproductive and developmental toxicity data available for hydraulic-fracturing chemicals in the REPROTOX information system and possible association with toxicity. Numbers of subcategories under "Information Available" may not add up to the total, as toxicity information may be available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

**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

**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 |

**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 |

**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 |

**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.

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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