HHS Public Access
Author manuscript
Sci Total Environ. Author manuscript; available in PMC 2019 April 10.

Published in final edited form as:
Sci Total Environ. 2017 January 15; 576: 138–147. doi:10.1016/j.scitotenv.2016.10.072.

Unconventional oil and gas development and risk of childhood leukemia: Assessing the evidence

Elise G. Elliott[a], **Pauline Trinh**[a], **Xiaomei Ma**[a], **Brian P. Leaderer**[a], **Mary H. Ward**[b], and **Nicole C. Deziel**[a]

[a]Yale School of Public Health, Yale University, 60 College St., New Haven, CT 06520, USA

[b]National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, Bethesda, MD 20850, USA

Abstract

The widespread distribution of unconventional oil and gas (UO&G) wells and other facilities in the United States potentially exposes millions of people to air and water pollutants, including known or suspected carcinogens. Childhood leukemia is a particular concern because of the disease severity, vulnerable population, and short disease latency. A comprehensive review of carcinogens and leukemogens associated with UO&G development is not available and could inform future exposure monitoring studies and human health assessments. The objective of this analysis was to assess the evidence of carcinogenicity of water contaminants and air pollutants related to UO&G development. We obtained a list of 1,177 chemicals in hydraulic fracturing fluids and wastewater from the U.S. Environmental Protection Agency and constructed a list of 143 UO&G-related air pollutants through a review of scientific papers published through 2015 using PubMed and ProQuest databases. We assessed carcinogenicity and evidence of increased risk for leukemia/lymphoma of these chemicals using International Agency for Research on Cancer (IARC) monographs. The majority of compounds (>80%) were not evaluated by IARC and therefore could not be reviewed. Of the 111 potential water contaminants and 29 potential air pollutants evaluated by IARC (119 unique compounds), 49 water and 20 air pollutants were known, probable, or possible human carcinogens (55 unique compounds). A total of 17 water and 11 air pollutants (20 unique compounds) had evidence of increased risk for leukemia/lymphoma, including benzene, 1,3-butadiene, cadmium, diesel exhaust, and several polycyclic aromatic hydrocarbons. Though information on the carcinogenicity of compounds associated with UO&G development was limited, our assessment identified 20 known or suspected carcinogens that could be measured in future studies to advance exposure and risk assessments of cancer-causing agents. Our findings support the need for investigation into the relationship between UO&G development and risk of cancer in general and childhood leukemia in particular.

Keywords

air pollution; carcinogens; hydraulic fracturing; shale; wastewater; water contamination

Corresponding author: Nicole C. Deziel, PhD, MHS Yale School of Public Health 60 College St. New Haven, CT 06520 (203) 785-6062, nicole.deziel@yale.edu.

1. INTRODUCTION

Unconventional oil and gas (UO&G) development is a complex, multi-phase process of extracting oil and natural gas from low-permeable rock formations that were inaccessible prior to recent technological advances in hydraulic fracturing and directional drilling. It has expanded rapidly in the past decade and now occurs in as many as 30 states within the United States, with millions of people living within 1 mile of a hydraulically fractured well (US EPA, 2015). Concerns have been raised about the potential exposures to water and air pollutants and related health impacts (Adgate et al., 2014). Chemicals involved in or produced by UO&G development may include reproductive/developmental toxicants (Elliott et al., 2016; Kahrilas et al., 2015; Wattenberg et al., 2015), endocrine disruptors (Kassotis et al., 2014), or known or suspected carcinogenic agents (McKenzie et al., 2012). The limited epidemiologic studies of UO&G development have observed an increase in adverse perinatal outcomes (Casey et al., 2016; McKenzie et al., 2014; Stacy et al., 2015), asthma exacerbations (Rasmussen et al., 2016), dermal irritation (Rabinowitz et al., 2015), hospitalization rates (Jemielita et al., 2015), and nasal, headache, and fatigue symptoms (Tustin et al., 2016).

Childhood leukemia in particular is a public health concern related to UO&G development, and it may be an early indicator of exposure to environmental carcinogens due to the relatively short disease latency and vulnerability of the exposed population (Rothwell et al., 1991; Shy et al., 1994). The age-adjusted incidence rate of leukemia in the United States for children under the age of 15 was 5.3 per 100,000 persons in 2011, the highest among all types of childhood cancer, and the peak age of incidence is 2–5 years (CDC, 2015). The U.S. incidence rates for acute lymphocytic leukemia, the most common subtype of childhood leukemia, increased annually by 1.4% from 2000–2010 (Gittleman et al., 2015). Environmental exposures, such as ionizing radiation, benzene, traffic exhaust, tobacco smoke, and pesticides, have been linked to childhood acute lymphoblastic leukemia, though evidence is generally limited or inconsistent (Bailey et al., 2015a; Bailey et al., 2015b; Tong et al., 2012; Ward et al., 2014; Wiemels, 2012; Zachek et al., 2015). A comprehensive review of the carcinogens and leukemogens associated with UO&G development is not available and could inform future environmental and biological monitoring and human health studies. In this analysis, we aimed to systematically assess the evidence for a possible carcinogenic/leukemogenic role of (1) water contaminants and (2) air pollutants associated with UO&G development.

1.1 Unconventional oil and gas development: description of the process

In oil and gas extraction, a well pad must first be constructed. This involves the use of construction vehicles, heavy equipment, and diesel generators in continuous operation to create roads, clear and set up a well site, and transport materials to the site (Moore et al., 2014). After well pad construction is complete, drilling rigs drill vertically past the deepest freshwater aquifer down to the level of the source formation, such as shale rock, turn and drill horizontally for distances up to 3,000 meters (Laurenzi and Jersey, 2013). After drilling, the well is hydraulically fractured. In this step, large volumes of fracturing fluids consisting of water, chemicals, and proppants (sand or ceramic beads) are forced into wells under high pressure, creating fissures or fractures in the rock along the horizontal section of the wellbore to release oil or gas. Typically, about 15–100 million liters of fluid are used for each well, of which approximately 1–2% are chemical additives, representing a substantial volume of chemicals used per well (estimated as upwards of 114,000 liters) (US DOE, 2013; US EPA, 2012). Chemical additives in fracturing fluids include biocides, surfactants, and anti-corrosive agents (US EPA, 2015). After fracturing, wastewater flows up the wells. Within 1–4 weeks about 30% of injected fracturing fluids rapidly return to the surface through the well as “flowback” water; subsequently, “produced” water returns up the well more slowly. The produced water includes the injected fluids along with mobilized, naturally-occurring compounds (e.g., heavy metals, bromides, radionuclides) (Ferrar et al., 2013; Vidic et al., 2013). Flowback and produced wastewater are stored in large open pits or storage tanks until they can be treated, reused, or disposed of offsite, such as in injection wells. Oil, gas, and produced water flow up the well for years or decades during the production phase of the well (Barbot et al., 2013; Nicot et al., 2014). During production, diesel-power trucks may be used to maintain the wells or transport oil or gas off the well pad. This stage also includes the processing and distribution of the produced oil and gas at other facilities (NYS DEC, 2011).

1.2 Possible pathways of environmental exposure to carcinogenic agents

Possible pathways of water contamination during fracturing and production 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 (Adgate et al., 2014; Brantley et al., 2014; Ferrar et al., 2013; Gross et al., 2013; Jackson et al., 2013b; Osborn et al., 2011; Rozell and Reaven, 2012; Shonkoff et al., 2014; US EPA, 2015; Vengosh et al., 2014; Vengosh et al., 2013; Warner et al., 2012). Surface activities may pose the greater potential threat in the near-term (Drollette et al., 2015), with sub-surface activities potentially presenting a hazard over a longer period of time. Several water quality studies have measured total dissolved solids, isotopes, and other chemicals to characterize a geochemical fingerprint of UO&G development (Jackson et al., 2013a; Vengosh et al., 2013; Warner et al., 2013; Warner et al., 2012); these studies are not necessarily focused on compounds with evidence of toxicity to humans. Studies measuring concentrations of health-relevant chemicals in drinking water sources are emerging (Harkness et al., 2015; Hildenbrand et al., 2015; Llewellyn et al., 2015), but data are limited.

UO&G development activities that could generate air pollution include operation of diesel-powered equipment, use of vehicles to transport materials and waste to and from the site, addition of sand (silica) to the fracturing fluid mixture, volatilization of compounds from wastewater, and processing and distribution of the oil and gas (Moore et al., 2014). Air pollutants, such as diesel exhaust, fine and coarse air particulates, crystalline silica, and polycyclic aromatic hydrocarbons (PAHs), are a few examples commonly cited as being generated as part of the various phases of UO&G development (Burnham et al., 2012; McCawley, 2015; Moore et al., 2014). To our knowledge, no comprehensive list of air pollutants potentially related to UO&G development is available in the published literature or government reports.

1.3 Epidemiologic studies of unconventional oil and gas development

Knowledge of the health risks of UO&G development is sparse, though epidemiologic studies on this topic are emerging. Studies using proximity-based metrics observed associations between UO&G development and congenital heart defects in children (McKenzie et al., 2014), self-reported dermal irritation (Rabinowitz et al., 2015), decreased birth weight and increased incidence of small for gestational age (Stacy et al., 2015), increased preterm birth (Casey et al., 2016), increased in mild, moderate, and severe asthma exacerbations (Rasmussen et al., 2016), and increasesd chronic rhinosinusitis, migraine headache, and fatigue symptoms (Tustin et al., 2016). The number of wells per ZIP code was associated with increased hospitalization rates, particularly in the areas of dermatology, neurology, oncology, and urology (Jemielita et al., 2015).

The only epidemiologic analysis of the association between UO&G development and risk of cancer published in the scientific literature reported similar county-level standardized incidence ratios for childhood leukemia before and after drilling of any oil and gas wells in any Pennsylvania counties during 1990–2009 (Fryzek et al., 2013). Also in this analysis, standardized incidence ratios were similar before and after drilling started in counties with unconventional wells, specifically. However, several important shortcomings of this study have been noted. For example, this ecologic study did not account for a latency period between exposure and cancer incidence. In addition, though the study objective was to examine risk associated with hydraulic fracturing, 98% of the wells included in the study were “non-horizontal” wells that likely did not involve the practice of hydraulic fracturing (Goldstein and Malone, 2013). Case-control studies of proximity to other petroleum-based sources provide some evidence of an association with childhood leukemia risk. Two case-control studies in France reported increased odds of childhood leukemia among those living in proximity to the petroleum-based sources of petrol stations and automotive repair garages (Brosselin et al., 2009; Steffen et al., 2004). Another case-control study reported elevated odds of childhood leukemia with proximity to petrol stations, but the relationship was not statistically significant, possibly due to small sample size (Harrison et al., 1999). Another study observed an association with proximity to petrochemical plants and increased odds of leukemia in young adults (20–29 years), but not children ages 0–15 (Yu et al., 2006). Additionally, a human health risk assessment found an increased risk of cancer for residents living ≤0.5 versus >0.5 mile from a well, attributable primarily to benzene, a known human carcinogen associated with leukemia risk (McKenzie et al., 2012). Taken together, these findings support the plausibility of an increased risk of childhood leukemia related to oil and gas development. The current analysis investigates whether there is additional evidence for the plausibility of a carcinogenic risk from air or water contaminants and provides information to improve the specificity of exposure assessments and human health research of the potential adverse effects of UO&G development.

2. METHODS

2.1 Identification of potential water contaminants

We compiled a list of all chemicals used in hydraulic fracturing fluids, detected in hydraulic fracturing wastewater, or both from the U.S. Environmental Protection Agency (US EPA) Appendices A of the progress report "Study of the Potential Impacts of Hydraulic Fracturing on Drinking Water Resources" and draft report "Assessment of the Potential Impacts of Hydraulic Fracturing for Oil and Gas on Drinking Water Resources" (US EPA, 2012; US EPA, 2015). We eliminated duplicate entries and combined the entries for xylene isomers. This yielded a total of 1,177 distinct compounds or groups of compounds (1,043 in fracturing fluids only, 98 in wastewater only, 36 in both). The U.S. EPA developed these chemical lists from federal and state databases of well permits and construction records, industry disclosures and monitoring reports, trade journals, the scientific literature, and governmental and non-governmental reports. The fracturing fluid list contains a greater number of substances because it reflects reported usage and includes disclosed substances used across varying companies, locations, and geological formations. The list of wastewater constituents is shorter because it is based on the limited wastewater measurement data available from industry, government reports, or the published literature.

2.2 Classification of carcinogenicity of potential water contaminants

We searched the International Agency for Research on Cancer (IARC) monographs for evidence of carcinogenicity of the potential water contaminants. IARC is an internationally recognized authority on carcinogenicity of chemicals and other agents (Pearce et al., 2015). The monographs are written by working groups of international experts convened by IARC, and they provide detailed evaluations of the quality and strength of evidence of carcinogenicity of agents. The agents are selected for evaluation based on exposure prevalence and suggestive evidence of likelihood to pose a cancer hazard to humans (Tomatis, 1976). Other organizations evaluate environmental agents for carcinogenicity, such as the U.S. EPA through their Integrated Risk Information System (IRIS) or the National Institutes of Health through their National Toxicology Program (NTP). Their lists of agents evaluated for their carcinogenicity contain much overlap with IARC and are less comprehensive; IARC, IRIS, and NTP have evaluated 1,050, 264, and 243 compounds, respectively (IARC, 2016; IRIS, 2016; NTP, 2014).

Chemicals were designated as "no information available" if they were not evaluated in an IARC monograph. For chemicals that were evaluated, we indicated their IARC carcinogenicity classification: carcinogenic to humans (Group 1), probably carcinogenic to humans (Group 2A), possibly carcinogenic to humans (Group 2B), not classifiable as to their carcinogenicity to humans (Group 3), and probably not carcinogenic to humans (Group 4). We calculated frequencies and percentages of the potential water contaminants in each carcinogenicity classification. For chemicals in Groups 1, 2A, or 2B, we assessed whether these chemicals had evidence linked to leukemia and/or lymphoma specifically, based on the available information on human and animal study data provided in the monograph summary or synthesis.

2.3 Identification of potential air pollutants

We constructed a list of potential air pollutants associated with UO&G development by conducting a comprehensive review of the scientific literature. First, we systematically searched the biomedical and health-oriented PubMed database for papers published through December 31, 2015 using the terms "fracking air", "hydraulic fracturing air", "unconventional gas air", "shale gas air," "unconventional oil air," and "shale oil air," which yielded 136 unique publications. Next, we searched the ProQuest Environmental Science Collection database for papers published in environmental science-oriented journals through December 31, 2015 using the terms "fracking", "hydraulic fracturing", "unconventional gas", "shale gas", "unconventional oil", and "shale oil" with the term "air pollution." This search yielded 42 publications (31 additional, unique publications and 11 previously identified through PubMed). We included three types of studies in this analysis: 1) studies that collected primary air pollutant measurements or presented air pollutant measurements from secondary data sources, such as a state or county dataset ("measurement" studies), 2) studies that modeled air pollutant concentrations using inputs from primary or secondary measurements, emission rates from equipment or UO&G activities, and/or meteorological data ("modeling" studies), and 3) studies with qualitative assessments of potential or expected air pollutants based on review of the scientific literature, government or non-governmental reports, and/or expert judgement about the types of pollutants likely to be generated from UO&G activities ("descriptive" studies). We excluded papers not directly related to environmental air pollution associated with UO&G development (n=86), papers describing generic chemical classes (e.g., volatile organic compounds (VOCs)) but not specific chemical names (e.g., benzene) (n=25), publications that were not peer-reviewed original research or review papers or were corrected and updated after 2015 (n=4), and papers written in foreign languages (n=3). From the 49 publications meeting our criteria, we abstracted chemical names of air pollutants from tables, text, and figures, if explicitly reported as present or predicted to be present at UO&G sites. For example, we abstracted names of target analytes from tables and figures presenting measured or estimated concentrations of pollutants near UO&G sites. This approach is consistent with the U.S. EPA water list construction, which included any compounds reportedly used in hydraulic fracturing fluids or detected in wastewater. We combined individual chemicals into one category if these agents were evaluated as a group by IARC (e.g. xylenes, particulate matter).

2.4 Classification of carcinogenicity of potential air contaminants

We searched the IARC monographs for evidence of carcinogenicity using chemical names of the potential air pollutants. Following the same procedure as for potential water contaminants (Section 2.2), chemicals were designated as "no information available" if they were not present in the IARC monographs; or else were reported as Groups 1, 2A, 2B, 3, or 4. For the compounds in Groups 1, 2A, and 2B, we determined whether the monograph summary or synthesis indicated that there was sufficient evidence of increased risk of leukemia and/or lymphoma specifically, based on human or animal data.

3. RESULTS

3.1 Carcinogenicity of potential water contaminants

Of the 1,177 potential water contaminants assessed, 1,066 compounds (91%) had not been evaluated for carcinogenicity by IARC. The 111 potential water contaminants evaluated included 14 (13%) known human carcinogens (Group 1), 6 (5%) probable human carcinogens (Group 2A), and 29 (26%) possible human carcinogens (Group 2B), and 62 (56%) compounds were not classifiable with respect to their carcinogenicity (Group 3) (Figure 1). None were designated as probably not carcinogenic to humans, though only one compound has ever been assigned this classification. The distribution of compounds among the carcinogenicity classifications was similar between the fracturing fluid compounds and wastewater compounds (Figure 1). Of the 49 potential water contaminants classified as known, probable, or possible human carcinogens (Groups 1, 2A, 2B), 17 had evidence of an increased risk of leukemia and/or lymphoma (Table 1). This included 7 known human carcinogens (1,3-butadiene, benzene, cadmium, ethanol, ethylene oxide, formaldehyde, and quartz), 3 probable carcinogens (dibenz[a,h]anthracene, dichloromethane, tetrachloroethylene), and 7 possible carcinogens (1,2-propylene oxide, benzo[b]fluoranthene, benzo[k]fluoranthene, heptachlor, hydrazine, indeno[1,2,3-cd]pyrene, styrene). This list reflects petroleum-related volatile organic compounds (e.g., benzene), metals (e.g., cadmium), solvents (e.g., dichloromethane, tetrachloroethylene), and PAHs (benzo[b]fluoranthene, dibenz[a,h]anthracene, benzo[k]fluoranthene).

3.2 Identification of potential air pollutants

Our literature review yielded 143 distinct potential air pollutants or groups of pollutants related to UO&G development from 49 studies (Supplemental Table S1, Table 2). Of the 143 compounds, 97 had also been identified in water and 46 were unique to air. A total of 27 studies included measurements, 19 used modeling, and 15 were descriptive in nature; some studies incorporated a combination of these approaches (Table 2). There were 31 studies of gas development, 1 of oil development, and 17 of both. Studies reporting primary measurements or modeled estimates of air pollutants were conducted mainly in Colorado, Pennsylvania, Texas, and Wyoming. Frequently reported air pollutants (reported in ≥5 studies) included benzene, ethylbenzene, hydrogen sulfide, methane, nitrogen oxides, ozone, particulate matter, toluene, and styrene (Supplemental Table S1). Sampling locations included perimeters of UO&G well sites, mobile monitoring stations, and fixed community sites. Sampling durations varied, such as one-time grab samples of 2 to 3 minutes (Macey et al. 2014) and weekly 24-hour integrated samples collected over a period of two years (McKenzie et al. 2012).

3.3 Carcinogenicity of potential air pollutants

Of the 143 potential air pollutants, 114 compounds (80%) had not been evaluated for carcinogenicity by IARC. Of the 29 potential air pollutants evaluated, 7 (24%) were considered carcinogenic to humans (Group 1), 2 (7%) were considered probably carcinogenic to humans (Group 2A), and 11 (38%) were considered possibly carcinogenic to humans (Group 2B) (Figure 1). A total of 9 (31%) compounds were not classifiable with respect to their carcinogenicity (Group 3) (Figure 1). None were designated as probably not carcinogenic to humans (Group 4).

Of the 20 known, probable, or possible carcinogens (Groups 1, 2A, 2B), 11 had evidence of an increased risk of leukemia and/or lymphoma (Table 3). This included 5 known human carcinogens (1,3-butadiene, benzene, ethanol, formaldehyde, diesel engine exhaust), 2 probable human carcinogens (dibenz[a,h]anthracene, tetrachloroethylene), and 4 possible human carcinogens (carbon tetrachloroethylene, chrysene, indeno[1,2,3-cd]pyrene, styrene). This list includes constituents of oil and gas resources (e.g., benzene) and diesel exhaust (e.g., formaldehyde, PAHs, 1,3-butadiene).

4. DISCUSSION

We evaluated the evidence that potential exposures from UO&G development are risk factors for cancer in general and leukemia in particular. Our analysis of 1,177 chemicals in hydraulic fracturing fluids or wastewater and 143 potential air pollutants identified 55 possible, probable, and known carcinogens related to UO&G development activities. However, the vast majority of chemicals (91% of potential water contaminants, 80% of potential air pollutants) were not evaluated for their carcinogenicity by IARC. Of the 55 known, probable, or possible human carcinogens, 20 had some evidence for increased risk of leukemia and/or lymphoma: 1,2-propylene oxide, 1,3-butadiene, benzene, benzo(b)fluoranthene, benzo(k)fluoranthene, cadmium, carbon tetrachloroethylene, chrysene, dibenz(a,h)anthracene, dichloromethane, engine exhaust (diesel), ethanol, ethylene oxide, formaldehyde, heptachlor, hydrazine, indeno(1,2,3-cd)pyrene, quartz, styrene, and tetrachloroethylene. These findings support the hypothesis that exposure to UO&G development could increase the risk of leukemia.

Our findings demonstrate the presence of known and suspected carcinogens surrounding UO&G facilities, but drawing conclusions about cancer or leukemia risk is challenging, due to the varied and limited water and air measurement data. With respect to water, for example, Fontenot et al. (2013) measured metals in private drinking water wells in a community proximate to UO&G activity and observed concentrations of the known carcinogen arsenic in exceedance of U.S. EPA Maximum Contaminant Levels, although possible sources included mobilization of natural constituents and hydrogeochemical changes in addition to UO&G activities. Drollette et al. (2015) detected trace levels of organic compounds, such as the known leukomogen benzene and possible carcinogen ethylbenzene, in private drinking water wells in areas with UO&G development in Pennsylvania, with highest observed concentrations within 1 kilometer of active UO&G operations. Although the observed concentrations were below U.S. EPA Maximum Contaminant Levels, cancer risk is generally assumed not to have a threshold below which there is a safe level of exposure.

With respect to air, our literature review identified six studies measuring hazardous air pollutants associated with childhood leukemia (e.g., benzene, polycyclic aromatic hydrocarbons) near UO&G facilities (Bunch et al., 2014; Macey et al., 2014; McKenzie et al., 2012; Pekney et al., 2014; Rich et al., 2014; Rutter et al., 2015). Differences in location, sampling duration, target agents, and sampling methodology in the air pollution literature hindered our ability to synthesize the air data and place it into context of human health risk. However, some individual studies used the air monitoring data to estimate cancer or health risk. Macey et al. (2014) identified concentrations of benzene, 1,3-butadiene, and formaldehyde in exceedance of EPA IRIS cancer risk levels; however, these were based on grab samples that represented high-exposure scenarios (e.g. ≤20 meters of UO&G separator, compressor station, discharge canal, and well pad). McKenzie et al. (2012) estimated risk to communities based on Colorado measurement data collected over nearly three years from a fixed monitoring station in a rural community. They observed an excess risk of cancer for residents living <0.5 mile from the nearest well, mainly attributable to benzene and 1,3-butadiene. Bunch et al. (2014) used VOC measurements collected over ten years by the Texas Commission on Environmental Quality from seven fixed-site monitors in the Dallas/ Fort Worth area to conduct deterministic and probabilistic risk assessments and found that all but one of the cancer risk estimates were within the acceptable cancer risk range. Pekney et al. (2014) collected mobile measurements of ambient concentrations of pollutants in Pennsylvania and found no exceedances of National Ambient Air Quality Standards for criteria pollutants. These studies indicate that water and air pollution related to UO&G activities may pose a public health and potential cancer risk. More environmental measurements of health-relevant chemicals associated with UO&G development, particularly at residences in close proximity to these facilities, are needed to better characterize human exposures and determine whether confirmed or suspected carcinogens and toxicants are present and at what levels. In particular, studies with longer sampling durations or integrated over longer periods of time would be more relevant to chronic outcomes like cancer.

To our knowledge, our analysis represents the most expansive review of carcinogenicity of hydraulic fracturing-related chemicals in the published literature. Previous studies have examined the carcinogenicity of more selective lists of chemicals. For example, Kahrilas et al. (2015) reviewed the toxicological properties of biocide constituents of fracturing fluids and their degradation and reaction products and found that few had been evaluated by IARC. Compounds identified by Kahrilas et al. included formaldehyde (a known carcinogen associated with an increased risk of leukemia and lymphoma, identified in our analysis), dibromoacetonitrile (a possible carcinogen, identified in our analysis), nitrosamines (includes probable carcinogens, not identified in our analysis), and trihalomethanes (includes possible and probable carcinogens, four identified in our analysis: bromodichloromethane, chloroform, chlorodibromomethane, and bromoform). Stringfellow et al. (2014) assessed 81 common hydraulic fracturing fluid additives and identified five confirmed or suspected carcinogens using the U.S. NTP carcinogenicity evaluations (Stringfellow et al., 2014). Our analysis also identified four of these five chemicals: ethanol (known carcinogen associated with an increased risk of leukemia and lymphoma), acetaldehyde (possible carcinogen), diethanolamine (possible carcinogen), and naphthalene (possible carcinogen). The fifth compound, thiourea, was included in our analysis, but was considered not classifiable with respect to human carcinogenicity by IARC. Colborn et al. (2011) abstracted a list of chemical additives of hydraulic fracturing fluids using information on Material Safety Data Sheets provided by government and natural gas industry sources (Colborn et al., 2011). They found that 25% of the 353 chemicals evaluated could cause cancer and mutations. However, the inclusion criteria for this carcinogenicity evaluation were not provided to make a direct comparison with our findings.

An experimental study on the carcinogenicity of hydraulic fracturing wastewater observed that immortalized human bronchial epithelial cells exposed to flowback water collected from unconventional natural gas drilling of the Marcellus Shale underwent malignant transformation and exhibited altered morphology compared to parental cells (Yao et al., 2015). The flowback water sample contained relatively high concentrations of barium and strontium. However, these metals were not evaluated for carcinogenicity to humans by IARC and therefore were not included in our evaluation. Strontium was not evaluated by the NTP or U.S. EPA IRIS programs; barium was not evaluated by NTP, and it was deemed not classifiable with respect to carcinogenicity by the U.S. EPA.

Looking broadly at UO&G development and cancer risk, other risk factors should also be considered. For example, UO&G development could pose a risk for childhood leukemia through a phenomenon known as population mixing (Belson et al., 2007; Kinlen, 2012). This refers to the migration of new populations into previously contained rural areas, introducing new infectious agents. This could give rise to increasing underlying infections, for which childhood leukemia is a possible complication (Kinlen, 1988; Kinlen, 2012). An alternative hypothesis is that a delayed exposure to infectious agents among individuals who experienced an absence of exposure in very early life could increase the risk of an inappropriate immune response and lead to leukemia (Greaves, 2006; Greaves, 1997). UO&G development is a rapidly expanding industry that creates an influx of specialized, external workers into less populated areas to fill industry jobs (Brasier et al., 2011; Filteau, 2015b; Jacquet, 2014). Additionally, previous examples of resource extraction or energy development have reported population increases up to 80% and worker influx-related impacts on public health and local communities (Ennis and Finlayson, 2015; Filteau, 2015a; Keough, 2015). More research would be needed to demonstrate risk to newly introduced infectious agents. Another possible risk factor for childhood leukemia is parental occupational exposures to agents such as benzene or PAHs from work in the oil and gas industry during the pregnancy period, a critical window of vulnerability for childhood leukemia (Fusion et al., 2001). In addition, parents employed by oil and gas companies could introduce contaminants into the home environment through clothing, shoes, and skin (Newman et al., 2015; Sahmel et al., 2014). Also, the introduction of bromide constituents from hydraulic fracturing wastewater into drinking water sources could increase the subsequent, downstream formation of carcinogenic disinfection byproducts and increase the risk of cancer, such as bladder cancer (Regli et al., 2015). Further, agents released from other components of oil and gas infrastructure, such as petroleum storage tanks (Zusman et al., 2012), petrochemical plants (Yu et al., 2006), and petrol stations (Brosselin et al., 2009; Harrison et al., 1999; Steffen et al., 2004) could pose a leukemia risk.

This analysis has several limitations. The list of potential water contaminants from fracturing fluids is limited to non-proprietary chemicals that were reported to the U.S. EPA by oil and gas companies and included in the U.S. EPA reports on hydraulic fracturing (US EPA, 2012; US EPA, 2015). Our identification of potential air pollutants was based on information available in the PubMed and ProQuest Environmental Science databases and may not include all potential air pollutants associated with UO&G development. The published literature may be more likely to report air pollutants for which health data are available, which could explain why a greater percentage of chemicals in air were evaluated by IARC compared to chemicals that were potential water pollutants. Additionally, IARC only evaluates chemicals with suspected carcinogenicity. Therefore, the proportion of known, probable, and possible carcinogens among those compounds evaluated may not be representative of the proportion of carcinogens among those not evaluated. Although the IARC monographs are the most comprehensive, systematic carcinogenicity evaluations, a comprehensive literature review of all 1,177 water contaminants and 143 air pollutants could identify additional compounds that pose an increased risk of cancer.

Conducting a well-designed sampling campaign for UO&G development 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. Our list of 143 air pollutants associated with UO&G development (Supplemental Table S1) may serve as a useful resource for researchers designing future studies. Furthermore, our list of known, probable, and possible carcinogens linked to UO&G development can be used as a target analyte list for environmental or biological measurements in future exposure and health studies. Measurements of these compounds in air or water in residences proximate to this activity would provide insights into whether exposures are occurring and at what levels. Additionally, air pollution measurements corresponding to the different phases of UO&G development would provide critical information about the relative contribution of exposures from various aspects of the development activities and priorities for exposure mitigation. Furthermore, geographical and seasonal variations could influence release, concentration, and dispersion of potential air pollutants. Therefore, additional water and air measurement studies are urgently needed to investigate the potential for spatial and temporal variations in exposures.

This analysis could also inform design of exposure metrics for epidemiologic studies. Epidemiologic studies have generally used individual-level, geographic information systems-based inverse-distance weighted metrics to estimate exposure to UO&G development, which characterize UO&G development as a collective process. More specific metrics or measurements could offer improvements to the exposure assessment and potential insights into etiologic agents. Future studies could incorporate environmental and/or biological monitoring of health-relevant chemicals, such as the 55 known, probable, and possible carcinogens in water or air, and examine the relationship between chemical concentrations and proximity and density-based metrics, to determine the extent to which proximity is associated with exposure. Though more measurement data is needed to better understand whether exposures are occurring and at what concentrations, release of any carcinogens from UO&G development should be minimized.

5. CONCLUSIONS

There is a need to better understand the potential risks of UO&G development with carefully designed exposure and epidemiologic studies. We identified 55 known, probable, or possible carcinogens (20 compounds associated with leukemia and/or lymphoma specifically) that are potential water contaminants and/or air pollutants related to UO&G development. Our study provides some support for the hypothesis that exposure to UO&G development could increase the risk of leukemia. Because children are a vulnerable population, research efforts should first be directed towards investigating whether exposure to UO&G development is associated with an increased risk in childhood leukemia. Environmental and biological measurements of the compounds identified in this analysis in communities proximate to UO&G development would be critical for future research on the potential public health impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

Adgate JL, Goldstein BD, McKenzie LM. Potential public health hazards, exposures and health effects from unconventional natural gas development. Environ Sci Technol 2014; 48: 8307–8320. [PubMed: 24564405]

Ahmadi M, John K. Statistical evaluation of the impact of shale gas activities on ozone pollution in North Texas. Sci Total Environ 2015; 536: 457–67. [PubMed: 26232756]

Allen DT. Atmospheric emissions and air quality Impacts from natural gas production and use. Annu Rev Chem Biomol Eng 2014.

Allen DT, Torres VM, Thomas J, Sullivan DW, Harrison M, Hendler A, et al. Measurements of methane emissions at natural gas production sites in the United States. Proc Natl Acad Sci U S A 2013; 110: 17768–73. [PubMed: 24043804]

Bailey HD, Infante-Rivard C, Metayer C, Clavel J, Lightfoot T, Kaatsch P, et al. Home pesticide exposures and risk of childhood leukemia: Findings from the childhood leukemia international consortium. Int J Cancer 2015a; 137: 2644–63. [PubMed: 26061779]

Bailey HD, Metayer C, Milne E, Petridou ET, Infante-Rivard C, Spector LG, et al. Home paint exposures and risk of childhood acute lymphoblastic leukemia: findings from the Childhood Leukemia International Consortium. Cancer Causes Control 2015b; 26: 1257–70. [PubMed: 26134047]

Barbot E, Vidic NS, Gregory KB, Vidic RD. Spatial and temporal correlation of water quality parameters of produced waters from devonian-age shale following hydraulic fracturing. Environ Sci Technol 2013; 47: 2562–9. [PubMed: 23425120]

Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ Health Perspect 2007; 115: 138–45. [PubMed: 17366834]

Brantley SL, Yoxtheimer D, Arjmand S, Grieve P, Vidic R, Pollak J, et al. Water resource impacts during unconventional shale gas development: The Pennsylvania experience. International Journal of Coal Geology 2014; 126: 140–156.

Brasier K, Filteau MR, McLaughlin D, Jacquet J, Stedman R, Kelsey T, et al. Resident's perceptions of community and environmental impacts from development of natural gas in the Marcellus Shale: A comparison of Pennsylvania and New York cases. Journal of Rural Social Sciences 2011; 26: 32–61.

Brosselin P, Rudant J, Orsi L, Leverger G, Baruchel A, Bertrand Y, et al. Acute childhood leukaemia and residence next to petrol stations and automotive repair garages: the ESCALE study (SFCE). Occup Environ Med 2009; 66: 598–606. [PubMed: 19213757]

Brown D, Weinberger B, Lewis C, Bonaparte H. Understanding exposure from natural gas drilling puts current air standards to the test. Rev Environ Health 2014; 29: 277–92. [PubMed: 24690938]

Brown DR, Lewis C, Weinberger BI. Human exposure to unconventional natural gas development: A public health demonstration of periodic high exposure to chemical mixtures in ambient air. J Environ Sci Health A Tox Hazard Subst Environ Eng 2015; 50: 460–72. [PubMed: 25734822]

Bunch AG, Perry CS, Abraham L, Wikoff DS, Tachovsky JA, Hixon JG, et al. Evaluation of impact of shale gas operations in the Barnett Shale region on volatile organic compounds in air and potential human health risks. Sci Total Environ 2014; 468–469: 832–42. [PubMed: 24742557]

Burnham A, Han J, Clark CE, Wang M, Dunn JB, Palou-Rivera I. Life-cycle greenhouse gas emissions of shale gas, natural gas, coal, and petroleum. Environ Sci Technol 2012; 46: 619–27. [PubMed: 22107036]

Carlton AG, Little E, Moeller M, Odoyo S, Shepson PB. The data gap: can a lack of monitors obscure loss of Clean Air Act benefits in fracking areas? Environ Sci Technol 2014; 48: 893–4. [PubMed: 24383715]

Casey JA, Ogburn EL, Rasmussen SG, Irving JK, Pollak J, Locke PA, et al. Predictors of indoor radon concentrations in Pennsylvania, 1989–2013. Environ Health Perspect 2015.

Casey JA, Savitz DA, Rasmussen SG, Ogburn EL, Pollak J, Mercer DG, et al. Unconventional natural gas development and birth outcomes in Pennsylvania, USA. Epidemiology 2016; 27: 163–72. [PubMed: 26426945]

Caulton DR, Shepson PB, Cambaliza MO, McCabe D, Baum E, Stirm BH. Methane destruction efficiency of natural gas flares associated with shale formation wells. Environ Sci Technol 2014; 48: 9548–54. [PubMed: 25051053]

CDC. United States cancer statistics: 1999–2012 Incidence and mortality web-based report. 2016. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, Atlanta: U.S, 2015.

Chang Y, Huang R, Ries RJ, Masanet E. Shale-to-well energy use and air pollutant emissions of shale gas production in China. Applied Energy 2014; 125: 147–157.

Colborn T, Kwiatkowski C, Schultz K, Bachran M. Natural gas operations from a public health perspective. Hum Ecol Risk Assess 2011; 17: 1039–1056.

Drollette BD, Hoelzer K, Warner NR, Darrah TH, Karatum O, O'Connor MP, et al. Elevated levels of diesel range organic compounds in groundwater near Marcellus gas operations are derived from surface activities. Proc Natl Acad Sci U S A 2015; 112: 13184–9. [PubMed: 26460018]

Eapi GR, Sabnis MS, Sattler ML. Mobile measurement of methane and hydrogen sulfide at natural gas production site fence lines in the Texas Barnett Shale. J Air Waste Manag Assoc 2014; 64: 927–44. [PubMed: 25185395]

Edwards PM, Brown SS, Roberts JM, Ahmadov R, Banta RM, deGouw JA, et al. High winter ozone pollution from carbonyl photolysis in an oil and gas basin. Nature 2014; 514: 351–4. [PubMed: 25274311]

Elliott EG, Ettinger AS, Leaderer BP, Bracken MB, Deziel NC. A systematic evaluation of chemicals in hydraulic-fracturing fluids and wastewater for reproductive and developmental toxicity. J Expo Sci Environ Epidemiol 2016.

Ennis G, Finlayson M. Alcohol, violence, and a fast growing male population: Exploring a risky-mix in "boomtown" Darwin. Social Work in Public Health 2015; 30: 51–63. [PubMed: 25375394]

Evans RB, Prezant D, Huang YC. Hydraulic fracturing (fracking) and the Clean Air Act. Chest 2015; 148: 298–300. [PubMed: 26238825]

Ferrar KJ, Michanowicz DR, Christen CL, Mulcahy N, Malone SL, Sharma RK. Assessment of effluent contaminants from three facilities discharging Marcellus Shale wastewater to surface waters in Pennsylvania. Environ Sci Technol 2013; 47: 3472–81. [PubMed: 23458378]

Field RA, Soltis J, Murphy S. Air quality concerns of unconventional oil and natural gas production. Environ Sci Process Impacts 2014; 16: 954–69. [PubMed: 24699994]

Filteau MR. Go back to Texas, gas bastards! How a newcomer population of itinerant energy workers manage dirty work stigma in the Marcellus Shale region. Society & Natural Resources 2015a; 28: 1153–1167.

Filteau MR. A localized masculine crisis: Local men's subordination within the Marcellus Shale region's masculine structure. Rural Sociology 2015b; 80: 431–455.

Fryzek J, Pastula S, Jiang X, Garabrant DH. Childhood cancer incidence in Pennsylvania counties in relation to living in counties with hydraulic fracturing sites. J Occup Environ Med 2013; 55: 796–801. [PubMed: 23836020]

Fusion MLLG, Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer Res 2001; 2542–2546. [PubMed: 11289128]

Gittleman HR, Ostrom QT, Rouse CD, Dowling JA, de Blank PM, Kruchko CA, et al. Trends in central nervous system tumor incidence relative to other common cancers in adults, adolescents, and children in the United States, 2000 to 2010. Cancer 2015; 121: 102–12. [PubMed: 25155924]

Goetz JD, Floerchinger C, Fortner EC, Wormhoudt J, Massoli P, Knighton WB, et al. Atmospheric emission characterization of Marcellus shale natural gas development sites. Environ Sci Technol 2015; 49: 7012–7020. [PubMed: 25897974]

Goldstein BD, Malone S. Obfuscation does not provide comfort: response to the article by Fryzek et al on hydraulic fracturing and childhood cancer. J Occup Environ Med 2013; 55: 1376–8. [PubMed: 24202245]

Greaves M The causation of childhood leukemia: a paradox of progress? Discov Med 2006; 6: 24–8. [PubMed: 17234124]

Greaves MF. Aetiology of acute leukaemia. Lancet 1997; 349: 344–9. [PubMed: 9024390]

Gross SA, Avens HJ, Banducci AM, Sahmel J, Panko JM, Tvermoes BE. Analysis of BTEX groundwater concentrations from surface spills associated with hydraulic fracturing operations. J Air Waste Manag Assoc 2013; 63: 424–32. [PubMed: 23687727]

Harkness JS, Dwyer GS, Warner NR, Parker KM, Mitch WA, Vengosh A. Iodide, bromide, and ammonium in hydraulic fracturing and oil and gas wastewaters: environmental implications. Environ Sci Technol 2015; 49: 1955–63. [PubMed: 25587644]

Harrison RM, Leung PL, Somervaille L, Smith R, Gilman E. Analysis of incidence of childhood cancer in the West Midlands of the United Kingdom in relation to proximity to main roads and petrol stations. Occup Environ Med 1999; 56: 774–80. [PubMed: 10658564]

Hildenbrand ZL, Carlton DD Jr., Fontenot BE, Meik JM, Walton JL, Taylor JT, et al. A comprehensive analysis of groundwater quality in the Barnett Shale region. Environ Sci Technol 2015; 49: 8254–62. [PubMed: 26079990]

IARC. IARC monographs on the evaluation of carcinogenic risks to humans, 2016 Available online at: http://monographs.iarc.fr/. (Accessed July 2016).

IRIS. IRIS Assessments, 2016 Available online at: https://www.epa.gov/iris. (Accessed May 2016).

Jackson RB, Vengosh A, Carey JW, Davies RJ, Darrah TH, O'Sullivan F, et al. The environmental costs and benefits of fracking. Annual Review of Environment and Resources 39, 2014, pp. 327–362.

Jackson RB, Vengosh A, Darrah TH, Warner NR, Down A, Poreda RJ, et al. Increased stray gas abundance in a subset of drinking water wells near Marcellus shale gas extraction. Proc Natl Acad Sci U S A 2013a; 110: 11250–5. [PubMed: 23798404]

Jackson RE, Gorody AW, Mayer B, Roy JW, Ryan MC, Van Stempvoort DR. Groundwater protection and unconventional gas extraction: the critical need for field-based hydrogeological research. Ground Water 2013b; 51: 488–510. [PubMed: 23745972]

Jacquet JB. Review of risks to communities from shale energy development. Environ Sci Technol 2014; 48: 8321–33. [PubMed: 24624971]

Jemielita T, Gerton GL, Neidell M, Chillrud S, Yan B, Stute M, et al. Unconventional gas and oil drilling is associated with increased hospital utilization rates. PLoS One 2015; 10: e0131093. [PubMed: 26176544]

Kahrilas GA, Blotevogel J, Stewart PS, Borch T. Biocides in hydraulic fracturing fluids: a critical review of their usage, mobility, degradation, and toxicity. Environ Sci Technol 2015; 49: 16–32. [PubMed: 25427278]

Karion A, Sweeney C, Kort EA, Shepson PB, Brewer A, Cambaliza M, et al. Aircraft-based estimate of total methane emissions from the Barnett Shale region. Environ Sci Technol 2015; 49: 8124–8131. [PubMed: 26148550]

Kassotis CD, Tillitt DE, Davis JW, Hormann AM, Nagel SC. Estrogen and androgen receptor activities of hydraulic fracturing chemicals and surface and ground water in a drilling-dense region. Endocrinology 2014; 155: 897–907. [PubMed: 24424034]

Kemball-Cook S, Bar-Ilan A, Grant J, Parker L, Jung J, Santamaria W, et al. Ozone impacts of natural gas development in the Haynesville Shale. Environ Sci Technol 2010; 44: 9357–63. [PubMed: 21086985]

Keough SB. Planning for growth in a natural resource boomtown: challenges for urban planners in Fort McMurray, Alberta. Urban Geography 2015; 36: 1169–1196.

Kinlen LJ. Evidence for infective cause of childhood leukemia. The Lancet 1988.

Kinlen LJ. An examination, with a meta-analysis, of studies of childhood leukaemia in relation to population mixing. Br J Cancer 2012; 107: 1163–8. [PubMed: 22955857]

Lampe DJ, Stolz JF. Current perspectives on unconventional shale gas extraction in the Appalachian Basin. J Environ Sci Health A Tox Hazard Subst Environ Eng 2015; 50: 434–46. [PubMed: 25734820]

Lan X, Talbot R, Laine P, Torres A. Characterizing fugitive methane emissions in the Barnett Shale area using a mobile laboratory. Environ Sci Technol 2015; 49: 8139–8146. [PubMed: 26148552]

Laurenzi IJ, Jersey GR. Life cycle greenhouse gas emissions and freshwater consumption of Marcellus shale gas. Environ Sci Technol 2013; 47: 4896–903. [PubMed: 23548112]

Lavoie TN, Shepson PB, Cambaliza MO, Stirm BH, Karion A, Sweeney C, et al. Aircraft-based measurements of point source methane emissions in the Barnett Shale Basin. Environ Sci Technol 2015; 49: 7904–7913. [PubMed: 26148549]

Llewellyn GT, Dorman F, Westland JL, Yoxtheimer D, Grieve P, Sowers T, et al. Evaluating a groundwater supply contamination incident attributed to Marcellus Shale gas development. Proc Natl Acad Sci U S A 2015; 112: 6325–30. [PubMed: 25941400]

Lyon DR, Zavala-Araiza D, Alvarez RA, Harriss R, Palacios V, Lan X, et al. Constructing a spatially resolved methane emission inventory for the Barnett Shale region. Environ Sci Technol 2015; 49: 8147–8157. [PubMed: 26148553]

Macey GP, Breech R, Chernaik M, Cox C, Larson D, Thomas D, et al. Air concentrations of volatile compounds near oil and gas production: a community-based exploratory study. Environ Health 2014; 13: 82. [PubMed: 25355625]

McCawley M Air contaminants associated with potential respiratory effects from unconventional resource development activities. Semin Respir Crit Care Med 2015; 36: 379–87. [PubMed: 26024346]

McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, Adgate JL. Birth outcomes and maternal residential proximity to natural gas development in rural colorado. Environ Health Perspect 2014; 122: 412–7. [PubMed: 24474681]

McKenzie LM, Witter RZ, Newman LS, Adgate JL. Human health risk assessment of air emissions from development of unconventional natural gas resources. Sci Total Environ 2012; 424: 79–87. [PubMed: 22444058]

Melikoglu M Shale gas: Analysis of its role in the global energy market. Renewable & Sustainable Energy Reviews 2014; 37: 460–468.

Moore CW, Zielinska B, Petron G, Jackson RB. Air impacts of increased natural gas acquisition, processing, and use: a critical review. Environ Sci Technol 2014; 48: 8349–59. [PubMed: 24588259]

Nathan BJ, Golston LM, O'Brien AS, Ross K, Harrison WA, Tao L, et al. Near-field characterization of methane emission variability from a compressor station using a model aircraft. Environ Sci Technol 2015; 49: 7896–7903. [PubMed: 26011292]

Nduagu EI, Gates ID. Unconventional heavy oil growth and global greenhouse gas emissions. Environ Sci Technol 2015; 49: 8824–8832. [PubMed: 26114481]

Newell RG, Raimi D. Implications of shale gas development for climate change. Environ Sci Technol 2014; 48: 8360–8. [PubMed: 24754840]

Newman N, Jones C, Page E, Ceballos D, Oza A. Investigation of childhood lead poisoning from parental take-home exposure from an electronic scrap recycling facility - Ohio, 2012. MMWR Morb Mortal Wkly Rep 2015; 64: 743–5. [PubMed: 26182192]

Nicot JP, Scanlon BR, Reedy RC, Costley RA. Source and fate of hydraulic fracturing water in the barnett shale: a historical perspective. Environ Sci Technol 2014; 48: 2464–71. [PubMed: 24467212]

NTP. 13th Report on carcinogens, 2014 Available online at: http://ntp.niehs.nih.gov/go/roc. (Accessed April 2016).

NYS DEC. Well permit issuance for horizontal drilling and high-volume hydraulic fracturing to develop the Marcellus Shale and other low-permeability gas reservoirs, 2011 Available online at: http://www.dec.ny.gov/data/dmn/rdsgeisfull0911.pdf. (Accessed May 2016).

Olaguer EP. The potential near-source ozone impacts of upstream oil and gas industry emissions. J Air Waste Manag Assoc 2012; 62: 966–77. [PubMed: 22916444]

Osborn SG, Vengosh A, Warner NR, Jackson RB. Methane contamination of drinking water accompanying gas-well drilling and hydraulic fracturing. Proc Natl Acad Sci U S A 2011; 108: 8172–6. [PubMed: 21555547]

O'Sullivan F, Paltsev S. Shale gas production: potential versus actual greenhouse gas emissions. Environmental Research Letters 2012; 7: 1–6.

Pacsi AP, Kimura Y, McGaughey G, McDonald-Buller EC, Allen DT. Regional ozone impacts of increased natural gas use in the Texas power sector and development in the Eagle Ford shale. Environ Sci Technol 2015; 49: 3966–73. [PubMed: 25723953]

Pearce N, Blair A, Vineis P, Ahrens W, Andersen A, Anto JM, et al. IARC monographs: 40 Years of evaluating carcinogenic hazards to humans. Environ Health Perspect 2015; 123: 507–14. [PubMed: 25712798]

Pekney NJ, Veloski G, Reeder M, Tamilia J, Rupp E, Wetzel A. Measurement of atmospheric pollutants associated with oil and natural gas exploration and production activity in Pennsylvania's Allegheny National Forest. J Air Waste Manag Assoc 2014; 64: 1062–1072. [PubMed: 25283004]

Rabinowitz PM, Slizovskiy IB, Lamers V, Trufan SJ, Holford TR, Dziura JD, et al. Proximity to natural gas wells and reported health status: results of a household survey in Washington County, Pennsylvania. Environ Health Perspect 2015; 123: 21–6. [PubMed: 25204871]

Rasmussen SG, Ogburn EL, McCormack M, Casey JA, Bandeen-Roche K, Mercer DG, et al. Association between unconventional natural gas development in the Marcellus Shale and asthma exacerbations. JAMA Intern Med 2016.

Regli S, Chen J, Messner M, Elovitz MS, Letkiewicz FJ, Pegram RA, et al. Estimating potential increased bladder cancer risk due to increased bromide concentrations in sources of disinfected drinking waters. Environ Sci Technol 2015; 49: 13094–102. [PubMed: 26489011]

Rella CW, Tsai TR, Botkin CG, Crosson ER, Steele D. Measuring emissions from oil and natural gas well pads using the mobile flux plane technique. Environ Sci Technol 2015; 49: 4742–4748. [PubMed: 25806837]

Rich AL, Crosby EC. Analysis of reserve pit sludge from unconventional natural gas hydraulic fracturing and drilling operations for the presence of technologically enhanced naturally occurring radioactive material (TENORM). New Solut 2013; 23: 117–35. [PubMed: 23552651]

Rothwell CJ, Hamilton CB, Leaverton PE. Identification of sentinel health events as indicators of environmental contamination. Environ Health Perspect 1991; 94: 261–3. [PubMed: 1683284]

Roy AA, Adams PJ, Robinson AL. Air pollutant emissions from the development, production, and processing of Marcellus Shale natural gas. J Air Waste Manag Assoc 2014; 64: 19–37. [PubMed: 24620400]

Rozell DJ, Reaven SJ. Water pollution risk associated with natural gas extraction from the Marcellus Shale. Risk Anal 2012; 32: 1382–93. [PubMed: 22211399]

Rutter AP, Griffin RJ, Cevik BK, Shakya KM, Gong L, Kim S, et al. Sources of air pollution in a region of oil and gas exploration downwind of a large city. Atmospheric Environment 2015; 120: 89–99.

Sahmel J, Barlow CA, Simmons B, Gaffney SH, Avens HJ, Madl AK, et al. Evaluation of take-home exposure and risk associated with the handling of clothing contaminated with chrysotile asbestos. Risk Anal 2014; 34: 1448–68. [PubMed: 24517168]

Shonkoff SB, Hays J, Finkel ML. Environmental public health dimensions of shale and tight gas development. Environ Health Perspect 2014; 122: 787–95. [PubMed: 24736097]

Shy C, Greenberg R, Winn D. Sentinel health events of environmental contamination: a consensus statement. Environ Health Perspect 1994; 102: 316–7. [PubMed: 8033875]

Stacy SL, Brink LL, Larkin JC, Sadovsky Y, Goldstein BD, Pitt BR, et al. Perinatal outcomes and unconventional natural gas operations in Southwest Pennsylvania. PLoS One 2015; 10: e0126425. [PubMed: 26039051]

Steffen C, Auclerc MF, Auvrignon A, Baruchel A, Kebaili K, Lambilliotte A, et al. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. Occup Environ Med 2004; 61: 773–8. [PubMed: 15317919]

Stringfellow WT, Domen JK, Camarillo MK, Sandelin WL, Borglin S. Physical, chemical, and biological characteristics of compounds used in hydraulic fracturing. J Hazard Mater 2014; 275: 37–54. [PubMed: 24853136]

Swarthout RF, Russo RS, Zhou Y, Miller BM, Mitchell B, Horsman E, et al. Impact of Marcellus Shale natural gas development in southwest Pennsylvania on volatile organic compound emissions and regional air quality. Environ Sci Technol 2015; 49: 3175–84. [PubMed: 25594231]

Ternes ME. Regulatory programs governing shale gas development. Chemical Engineering Progress 2012; 108: 60–64.

Tomatis L The IARC program on the evaluation of the carcinogenic risk of chemicals to man. Ann N Y Acad Sci 1976; 271: 396–409. [PubMed: 1069530]

Tong J, Qin L, Cao Y, Li J, Zhang J, Nie J, et al. Environmental radon exposure and childhood leukemia. J Toxicol Environ Health B Crit Rev 2012; 15: 332–47. [PubMed: 22852813]

Townsend-Small A, Marrero JE, Lyon DR, Simpson IJ, Meinardi S, Blake DR. Integrating source apportionment tracers into a bottom-up inventory of methane emissions in the Barnett Shale hydraulic fracturing region. Environ Sci Technol 2015; 49: 8175–8182. [PubMed: 26148556]

Tustin AW, Hirsch AG, Rasmussen SG, Casey JA, Bandeen-Roche K, Schwartz BS. Associations between unconventional natural gas development and nasal and sinus, migraine headache, and fatigue symptoms in Pennsylvania. Environ Health Perspect 2016; [Epub ahead of print].

US DOE. Modern shale gas development in the United States: An update, 2013 Available online at: https://www.netl.doe.gov/File%20Library/Research/Oil-Gas/shale-gas-primer-update-2013.pdf. (Accessed May 2016).

US EPA. Study of the potential impacts of hydraulic fracturing on drinking water resources: Progress report. EPA 601/R-12/011, 2012 Available online at: www.epa.gov/hfstudy. (Accessed May 2016).

US EPA. Assessment of the potential impacts of hydraulic fracturing for oil and gas on drinking water resources. EPA/600/R-15/047, 2015 Available online at: www.epa.gov/hfstudy. (Accessed May 2016).

Vengosh A, Jackson RB, Warner N, Darrah TH, Kondash A. A critical review of the risks to water resources from unconventional shale gas development and hydraulic fracturing in the United States. Environ Sci Technol 2014; 48: 8334–8348. [PubMed: 24606408]

Vengosh A, Warner N, Jackson R, Darrah T. The effects of shale gas exploration and hydraulic fracturing on the quality of water resources in the United States. Procedia Earth and Planetary Science 2013; 7: 863–866.

Vidic RD, Brantley SL, Vandenbossche JM, Yoxtheimer D, Abad JD. Impact of shale gas development on regional water quality. Science 2013; 340: 1235009. [PubMed: 23687049]

Vinciguerra T, Yao S, Dadzie J, Chittams A, Deskins T, Ehrman S, et al. Regional air quality impacts of hydraulic fracturing and shale natural gas activity: Evidence from ambient VOC observations. Atmos Environ 2015; 110: 144–150.

Walters K, Jacobson J, Kroening Z, Pierce C. PM 2.5 airborne particulates near frac sand operations. J Environ Health 2015; 78: 8–12.

Ward MH, Colt JS, Deziel NC, Whitehead TP, Reynolds P, Gunier RB, et al. Residential levels of polybrominated diphenyl ethers and risk of childhood acute lymphoblastic leukemia in California. Environ Health Perspect 2014; 122: 1110–6. [PubMed: 24911217]

Warner NR, Christie CA, Jackson RB, Vengosh A. Impacts of shale gas wastewater disposal on water quality in western Pennsylvania. Environ Sci Technol 2013; 47: 11849–57. [PubMed: 24087919]

Warner NR, Jackson RB, Darrah TH, Osborn SG, Down A, Zhao K, et al. Geochemical evidence for possible natural migration of Marcellus Formation brine to shallow aquifers in Pennsylvania. Proc Natl Acad Sci U S A 2012; 109: 11961–6. [PubMed: 22778445]

Wattenberg EV, Bielicki JM, Suchomel AE, Sweet JT, Vold EM, Ramachandran G. Assessment of the acute and chronic health hazards of hydraulic fracturing fluids. J Occup Environ Hyg 2015; 12: 611–624. [PubMed: 25894916]

Wiemels J Perspectives on the causes of childhood leukemia. Chem Biol Interact 2012; 196: 59–67. [PubMed: 22326931]

Yacovitch TI, Herndon SC, Petron G, Kofler J, Lyon D, Zahniser MS, et al. Mobile laboratory observations of methane emissions in the Barnett Shale region. Environ Sci Technol 2015; 49: 7889–7895. [PubMed: 25751617]

Yao Y, Chen T, Shen SS, Niu Y, DesMarais TL, Linn R, et al. Malignant human cell transformation of Marcellus Shale gas drilling flow back water. Toxicol Appl Pharmacol 2015; 288: 121–30. [PubMed: 26210350]

Yu CL, Wang SF, Pan PC, Wu MT, Ho CK, Smith TJ, et al. Residential exposure to petrochemicals and the risk of leukemia: using geographic information system tools to estimate individual-level residential exposure. Am J Epidemiol 2006; 164: 200–7. [PubMed: 16754633]

Zachek CM, Miller MD, Hsu C, Schiffman JD, Sallan S, Metayer C, et al. Children's cancer and environmental exposures: Professional attitudes and practices. J Pediatr Hematol Oncol 2015; 37: 491–7. [PubMed: 26334434]

Zavala-Araiza D, Lyon D, Alvarez RA, Palacios V, Harriss R, Lan X, et al. Toward a functional definition of methane super-emitters: Application to natural gas production sites. Environ Sci Technol 2015; 49: 8167–8174. [PubMed: 26148555]

Zielinska B, Campbell D, Samburova V. Impact of emissions from natural gas production facilities on ambient air quality in the Barnett Shale area: a pilot study. J Air Waste Manag Assoc 2014; 64: 1369–83. [PubMed: 25562933]

Zusman M, Dubnov J, Barchana M, Portnov BA. Residential proximity to petroleum storage tanks and associated cancer risks: Double Kernel Density approach vs. zonal estimates. Sci Total Environ 2012; 441: 265–76. [PubMed: 23147397]

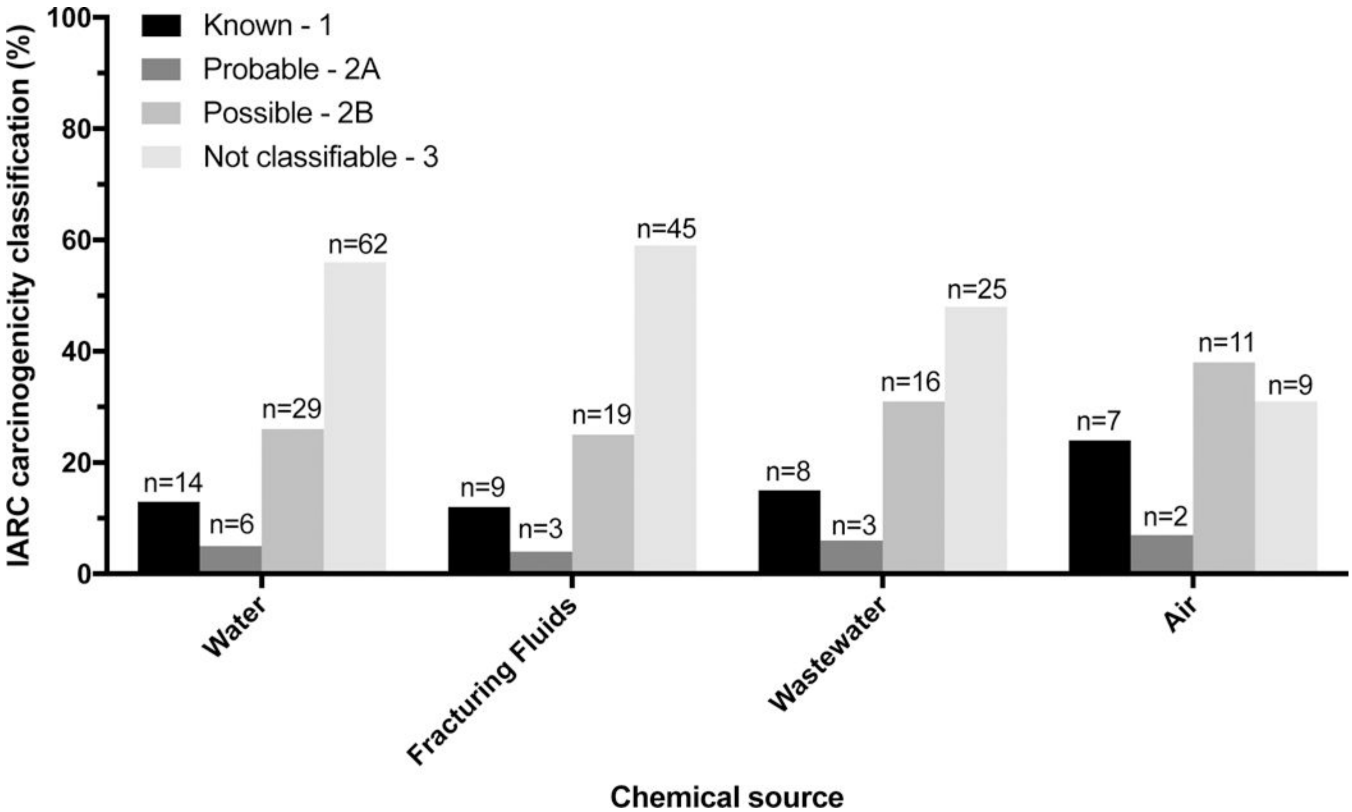

Figure 1.

International Agency for Research on Cancer carcinogenicity classification of chemicals in water (n=111), hydraulic fracturing fluids (n=76), hydraulic fracturing wastewater (n=52), and in air (n=29) related to unconventional oil and gas development.[1,2]

Table 1.

Potential water contaminants related to unconventional oil and gas development with evidence of carcinogenicity (n=49).[1]

CASRNs	Chemical Name	Associated with Leukemia/Lymphoma[2]	Water source	IARC Monograph Publication Year	IARC Monograph Volume #
Group 1: Carcinogenic to humans					
106–99-0	1,3-Butadiene	Leukemia, Lymphoma	FF	2012	Sup 7, 54, 71, 97, 100F
7440–38-2	Arsenic	-	FF, WW	2012	23, Sup 7, 100C
71–43-2	Benzene	Leukemia, Lymphoma	FF, WW	2012	29, Sup 7, 100F
50–32-8	Benzo(a)pyrene	-	WW	2012	Sup 7, 92, 100F
7440–41-7	Beryllium	-	WW	2012	Sup 7, 58, 100C
7440–43-9	Cadmium	Leukemia, Lymphoma	WW	2012	58, 100C
18540–29-9	Chromium (VI)	-	FF, WW	2012	Sup 7, 49, 100C
64–17-5	Ethanol[3]	Leukemia, Lymphoma	FF	2012	96, 100E
75–21-8	Ethylene oxide	Leukemia, Lymphoma	FF	2012	97, 100F
50–00-0	Formaldehyde	Leukemia, Lymphoma	FF	2012	Sup 7, 62, 88, 100F
14808–60-7	Quartz	Lymphoma	FF	2012	Sup 7, 68, 100C
13982–63-3	Radium 226	-	WW	2012	78, 100D
15262–20-1	Radium 228	-	WW	2012	78, 100D
7664–93-9	Sulfuric acid	-	FF	2012	54, 100F
Group 2A: Probably carcinogenic to humans					
79–06-1	Acrylamide	-	FF	1994	60
100–44-7	Benzyl chloride	-	FF	1999	29, Sup 7, 71
53–70-3	Dibenz(a,h)anthracene	Lymphoma	WW	2010	Sup 7, 92
75–09-2	Dichloromethane	Lymphoma	WW	in prep	Sup 7, 71, 110
106–89-8	Epichlorohydrin	-	FF	1999	11, Sup 7, 71
127–18-4	Tetrachloroethylene	Leukemia, Lymphoma	WW	2014	Sup 7, 63, 106
Group 2B: Possibly carcinogenic to humans					
75–56-9	1,2-Propylene oxide	Leukemia, Lymphoma	FF	1994	60
542–75-6	1,3-Dichloropropene	-	FF	1999	41, Sup 7, 71
123–91-1	1,4-Dioxane	-	FF, WW	1999	11, Sup 7, 71

CASRNs	Chemical Name	Associated with Leukemia/Lymphoma[2]	Water source	IARC Monograph Publication Year	IARC Monograph Volume #
108–10-1	4-Methyl-2-pentanone	-	FF	2013	101
75–07-0	Acetaldehyde[3]	-	FF	1999	36, Sup 7, 71
107–13-1	Acrylonitrile	-	WW	1999	71
1309–64-4	Antimony trioxide	-	FF	1989	47
205–99-2	Benzo(b)fluoranthene	Lymphoma	WW	2010	92
207–08-9	Benzo(k)fluoranthene	Lymphoma	WW	2010	92
75–27-4	Bromodichloromethane	-	WW	1999	52, 71
1333–86-4	Carbon black	-	FF	2010	65, 93
67–66-3	Chloroform	-	WW	1999	Sup 7, 73
68603–42-9	Coconut oil acid/Diethanolamine condensate (2:1)	-	FF	2013	101
7440–48-4	Cobalt	-	WW	1991	52
98–82-8	Cumene	-	FF, WW	2013	101
117–81-7	Di(2-ethylhexyl) phthalate	-	FF, WW	2013	77, 101
3252–43-5	Dibromoacetonitrile	-	FF	2013	52, 71, 101
111–42-2	Diethanolamine	-	FF	2013	77, 101
100–41-4	Ethylbenzene	-	FF, WW	2000	77
76–44-8	Heptachlor	Lymphoma	WW	2001	Sup 7, 53, 79
302–01-2	Hydrazine	Leukemia	FF	1999	4, Sup 7, 71
193–39-5	Indeno(1,2,3-cd)pyrene	Lymphoma	WW	2010	Sup 7, 92
7439–92-1	Lead	-	FF, WW	1987, 2006	23, Sup 7, 87
91–20-3	Naphthalene[3]	-	FF, WW	2002	82
7440–02-0	Nickel	-	WW	1990	Sup 7, 49
139–13-9	Nitrilotriacetic acid	-	FF	1999	48, 73
94–59-7	Safrole	-	WW	1987	10, Sup 7
100–42-5	Styrene	Leukemia	FF	2002	60, 82
13463–67-7	Titanium dioxide	-	FF	2010	47, 93

[1] All chemicals were obtained from the U.S. Environmental Protection Agency Appendices A of the progress report “Study of the Potential Impacts of Hydraulic Fracturing on Drinking Water Resources” (2012) and draft report “Assessment of the Potential Impacts of Hydraulic Fracturing for Oil and Gas on Drinking Water Resources” (2015).

[2] We abstracted leukemia/lymphoma association information from the IARC monographs report of an association with an increased risk of leukemia and/or lymphoma. If the association with leukemia and/or lymphoma was not reported in the monographs due to no/insufficient evidence of an association with an increased risk of leukemia and/or lymphoma, or if there was a null association, we determined the chemical not to be associated with leukemia and/or lymphoma (“-”).

CASRNs, Chemical Abstract Service Registry Numbers; FF, fracturing fluid; IARC, International Agency for Research on Cancer; WW, wastewater.

Table 2.

Studies evaluating air pollutants related to unconventional oil and national gas development (n=49).

Author	Measurements (n=27)	Modeling (n=19)	Descriptive (n=15)	Unconventional Fuel Type	Author	Measurements (n=27)	Modeling (n=19)	Descriptive (n=15)	Unconventional Fuel Type
Adgate et al. (2014)	.	.	x	Gas	McCawley (2015)	x	.	x	Gas
Ahmadi & John (2015)	x	.	.	Gas	McKenzie et al. (2012)	x	.	.	Gas
Allen et al. (2013)	.	.	x	Gas	Melikoglu (2014)	.	.	x	Gas
Allen (2014)	x	.	.	Gas	Moore et al. (2014)	.	.	x	Gas
Brown et al. (2014)	x	x	x	Gas	Nathan et al. (2015)	x	x	.	Gas
Brown et al. (2015)	.	x	.	Gas	Nduagu et al. (2015)	.	x	.	Oil
Bunch et al. (2014)	x	.	.	Gas	Newell et al. (2014)	.	.	x	Gas
Burnham et al. (2012)	.	x	.	Gas/Oil	Olaguer (2012)	.	x	.	Gas/Oil
Carlton et al. (2014)	.	.	x	Gas	O'Sullivan & Paltsev (2012)	.	x	.	Gas
Casey et al. (2015)	x	.	.	Gas/Oil	Pacsi et al. (2015)	.	x	.	Gas
Caulton et al. (2014)	x	.	.	Gas	Pekney et al. (2014)	x	.	.	Gas/Oil
Chang et al. (2014)	.	x	.	Gas	Rella et al. (2015)	x	.	.	Gas/Oil
Eapi et al. (2014)	x	.	.	Gas	Rich et al. (2014)	x	.	.	Gas
Edwards et al. (2014)	x	x	.	Gas/Oil	Roy et al. (2014)	.	x	.	Gas
Evans et al. (2015)	.	.	x	Gas/Oil	Rutter et al. (2015)	x	.	.	Gas/Oil
Field et al. (2014)	.	.	x	Gas/Oil	Shonkoff et al. (2014)	.	.	x	Gas
Goetz et al. (2015)	x	x	.	Gas	Swarthout et al. (2015)	x	.	.	Gas
Jackson et al. (2014)	x	x	x	Gas/Oil	Ternes (2012)	.	.	x	Gas/Oil
Karion et al. (2015)	x	x	.	Gas/Oil	Townsend-Small et al. (2015)	x	.	.	Gas
Kemball-Cook et al. (2010)	.	x	.	Gas	Vinciguerra et al. (2015)	x	.	.	Gas
Lampe & Stolz (2015)	.	.	x	Gas	Walters et al. (2015)	x	.	x	Gas/Oil
Lan et al. (2015)	x	x	.	Gas/Oil	Yacovitch et al. (2015)	x	x	.	Gas/Oil
Lavoie et al. (2015)	x	.	.	Gas	Zavala-Araiza et al. (2015)	.	x	.	Gas
Lyon et al. (2015)	.	x	.	Gas/Oil	Zielinska et al. (2014)	x	.	.	Gas
Macey et al. (2014)	x	.	.	Gas/Oil					

Table 3.

Potential air pollutants related to unconventional oil and natural gas development with evidence of carcinogenicity (n=20).[1]

CASRNs	Chemical Name	Associated with Leukemia/Lymphoma[2]	Reference	IARC Monograph Publication Year	IARC Monograph Volume #
Group 1: Carcinogenic to humans					
106–99-0	1,3-Butadiene	Leukemia, Lymphoma	Brown et al. (2015), Macey et al. (2014), McKenzie et al. (2012), Olaguer (2012)	2012	Sup 7, 54, 71, 97, 100F
71–43-2	Benzene	Leukemia, Lymphoma	Brown et al. (2015), Bunch et al. (2014), Field et al. (2014), Jackson et al. (2014), Lampe & Stolz (2015), Macey et al. (2014), McCawley (2015), McKenzie et al. (2012), Moore et al. (2014), Pekney et al. (2014), Rich et al. (2014), Rutter et al. (2015), Shonkoff et al. (2014), Ternes (2012)	2012	29, Sup 7, 100F
	Engine exhaust (diesel)	Leukemia, Lymphoma	Adgate et al. (2014), Lampe & Stolz (2015), McCawley (2015), Shonkoff et al. (2014)	2013	46, 105
64–17-5	Ethanol	Leukemia, Lymphoma	McCawley (2015)	2012	96, 100E
50–00-0	Formaldehyde	Leukemia, Lymphoma	Brown et al. (2015), Field et al. (2014), Jackson et al. (2014), Macey et al. (2014), McCawley (2015), Olaguer (2012), Shonkoff et al. (2014), Ternes (2012)	2012	Sup 7, 62, 88, 100F
	Particulate matter	-	Adgate et al. (2014), Brown et al. (2015), Brown et al. (2014), Evans et al. (2015), Field et al. (2014), Goetz et al. (2015), Jackson et al. (2014), Macey et al. (2014), Moore et al. (2014), Pacsi et al. (2013), Pekney et al. (2014), Roy et al. (2014), Song et al. (2015), Ternes (2012), Vinciguerra et al. (2015), Walters et al. (2015)	2015	109
	Radon	-	Casey et al. (2015), Evans et al. (2015), Shonkoff et al. (2014)	2012	43, 78, 100D
Group 2A: Probably carcinogenic to humans					
53–70-3	Dibenz(a,h)anthracene	Lymphoma	McCawley (2015)	2010	Sup 7, 92
127–18-4	Tetrachloroethylene	Leukemia, Lymphoma	Brown et al. (2015)	2014	Sup 7, 63, 106
Group 2B: Possibly carcinogenic to humans					
75–07-0	Acetaldehyde	-	Brown et al. (2015), McCawley (2015), Ternes (2012)	1999	36, Sup 7, 71
107–13-1	Acrylonitrile	-	Shonkoff et al. (2014)	1999	71
	Carbon tetrachloride	Lymphoma	Brown et al. (2015)	1999	20, Sup 7, 71
	Chrysene	Lymphoma	McCawley (2015)	2010	92
98–82-8	Cumene	-	McCawley (2015), McKenzie et al. (2012)	2013	101
100–41-4	Ethylbenzene	-	Brown et al. (2015), Bunch et al. (2014), Field et al. (2014), Jackson et al. (2014), Lampe & Stolz (2015), Macey et al.	2000	77

CASRNs	Chemical Name	Associated with Leukemia/Lymphoma[2]	Reference	IARC Monograph Publication Year	IARC Monograph Volume #
			(2014), McCawley (2015), McKenzie et al. (2012), Moore et al. (2014), Pekney et al. (2014), Rich et al. (2014), Shonkoff et al. (2014), Ternes (2012)		
193–39-5	Indeno(1,2,3-cd)pyrene	Lymphoma	McCawley (2015)	2010	Sup 7, 92
	Isoprene	-	McCawley (2015), McKenzie et al. (2012), Olaguer (2012), Rutter et al. (2015)	1999	60, 71
7439–92-1	Lead	-	Brown et al. (2015), Ternes (2012)	1987, 2006	23, Sup 7, 87
91–20-3	Naphthalene	-	Brown et al. (2015), McCawley (2015)	2002	82
100–42-5	Styrene	Leukemia	McCawley (2015), McKenzie et al. (2012), Pekney et al. (2014), Rutter et al. (2015)	2002	60, 82

[1] All compounds were abstracted from the scientific literature through systematic review of studies (n=49) including measurement, modeling, or descriptive summary of air pollutants potentially associated with unconventional oil and gas development.

[2] If an association with leukemia and/or lymphoma was not reported in the IARC monographs due to no/insufficient evidence, or if there was a null association, we determined the chemical not to be associated with leukemia and/or lymphoma (“-”).

CASRNs, Chemical Abstract Service Registry Numbers; IARC, International Agency for Research on Cancer.