Assessment of Potential Public Health Effects from Oil and Gas Operations in Colorado

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Executive Summary

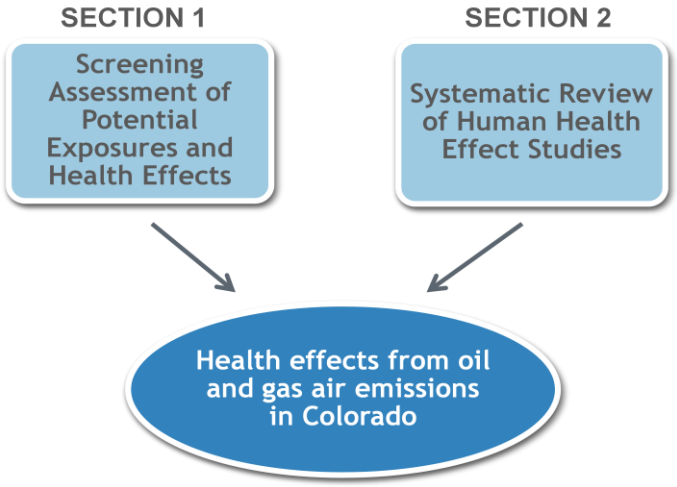
Introduction

Over the last several years, multiple published papers have outlined the potential chemical and non-chemical hazards from oil and gas operations. In addition, studies specifically evaluating the relationship between living near oil and gas operations and the potential for certain adverse health effects have been widely publicized. This information led to heightened public and policy-maker concerns about whether or not harmful health effects occur in people living near oil and gas operations. In 2015, the Colorado Oil and Gas Task Force made several recommendations to the Colorado Department of Public Health and the Environment (CDPHE). Among them was a recommendation to review existing scientific literature and compile a summary of useful findings. That same year, CDPHE established the Oil and Gas Health Information and Response Program to respond to citizen health concerns and conduct evaluations of the exposure and health science related to oil and gas. An evaluation of the potential routes of exposures and types of public concerns reported to the program indicated that the greatest public health priority for evaluation was related to potential health effects from exposures to substances emitted into the air from oil and gas operations. Therefore, the scope of this report was to evaluate existing scientific data to answer the following question:

> Do substances emitted into the air from oil and gas operations result in exposures to Coloradans living near oil and gas operations at levels that may be harmful to their health?

Because each source of scientific information has strengths and weaknesses, an integrated approach used existing information from multiple sources. This report combines two evaluations of scientific information to assess the strength of evidence to answer the main question (Figure 1).

Figure 1. Integration of scientific information to evaluate the potential for health effects in people living near oil and gas operations in Colorado



Section 1: Screening Assessment of Potential Exposures and Health Effects

Sixty-two substances that are likely emitted, though not exclusively, from oil and gas operations were identified as priority substances for analysis. More than 10,000 air samples that measured these substances in regions of Colorado that have substantial oil and gas operations were combined. These data were used to estimate potential air exposures to people living near oil and gas operations (defined as 500 feet or greater from an oil and gas site). These exposures were compared to standard short- and long-term health-based reference values (i.e. "safe" levels) related to cancer and non-cancer effects.

- The screening health risk assessment of these substances found:
    - All measured air concentrations were below short- and long-term "safe" levels of exposure for non-cancer health effects, even for sensitive populations.
    - The concentrations of a small number of substances (benzene, formaldehyde, acetaldehyde) in the air surrounding oil and gas operations were 4-5 times lower than standard short- and long-term health-based reference values for non-cancer effects.
    - The concentrations of the other substances were 5-10,000 times lower than the standard short- and long-term health-based reference values for non-cancer effects.
    - Cancer risks for all substances were within the "acceptable risk" range established by the U.S. EPA.
    - Although well within the acceptable risk range for cancer and non-cancer effects, benzene, acetaldehyde and formaldehyde had the highest estimated risk levels and are high priority for continued monitoring.
    - Overall, available air monitoring data suggest low risk of harmful health effects from combined exposure to all substances.

Section 2: Systematic Review of Human Health Effect Studies

A standard systematic method was used to review all relevant studies that investigated health effects in communities near oil and gas operations. Using this method, the current level of scientific evidence was evaluated for whether or not living near oil and gas operations is related to harmful health effects.

- The review included twelve epidemiological studies with 27 different health effects and the following major conclusions were made:
    - No substantial or moderate evidence for any health effects.
    - Limited evidence for two health effects – self-reported skin symptoms and exacerbation of asthma. Limited evidence means modest scientific findings that support an association, but there are significant limitations.
    - Mixed evidence for 11 health effects, including four different birth outcomes, hematological childhood cancers, hospitalizations for cancer, migraines, self-reported respiratory symptoms and musculoskeletal symptoms, and hospitalizations for neurological, hematological and immune diseases. Mixed evidence means there are

findings that both support and oppose an association between the exposure and the outcome, with neither direction dominating.

- A lack of evidence for three health effects, including respiratory hospitalizations and self-reported psychological symptoms and gastrointestinal symptoms. A lack of evidence means that the outcome has been researched without evidence of an association.
- Insufficient evidence for 11 health effects, including three different birth defects, self-reported neurological symptoms, cardiovascular effects, overall childhood cancer incidence and hospitalizations for psychological, musculoskeletal and gastrointestinal symptoms. Insufficient evidence means that the outcome has not been adequately studied.

Conclusions

- Based on currently available air monitoring data, the risk of harmful health effects is low for residents living near oil and gas operations.
- Studies of populations living near oil and gas operations provide limited evidence of the possibility for harmful health effects. This needs to be confirmed or disputed with higher quality studies.
- At this time, results from exposure and health effect studies do not indicate the need for immediate public health action, but rather indicate the need for more detailed exposure monitoring and systematic analyses of health effects of residents living near oil and gas operations.

Recommendations

- Continued monitoring of exposures to people living near oil and gas including:
  - Continued evaluation of ambient air levels of priority substances in areas with substantial oil and gas operations to assess the potential for community-wide health impacts.
  - Collection of air samples in communities near oil and gas operations using our Colorado Air Mobile Monitoring Laboratory to better characterize short-term exposures for those living in close proximity to oil and gas operations.
- Continued evaluation of health risk using more comprehensive exposure data such as data from the Colorado State University studies that directly measured emissions of substances from oil and gas operations in Garfield County and the north Front Range and data collected by the Colorado Air Mobile Monitoring Laboratory.
- Continued monitoring of health effects in areas with substantial oil and gas operations including:
  - High-quality epidemiological studies with improved characterization of exposures to directly assess the possibility of health effects in communities with substantial oil and gas operations.

- Continued citizen reporting of health concerns to the CDPHE Oil and Gas Health Information and Response Program to monitor for trends in health effects that may be related to exposure.

SECTION 1:

Screening Assessment of Potential Exposures and Health Effects

Introduction

The overall goal of this project was to evaluate the level of evidence from multiple sources of existing scientific information to answer the following question:

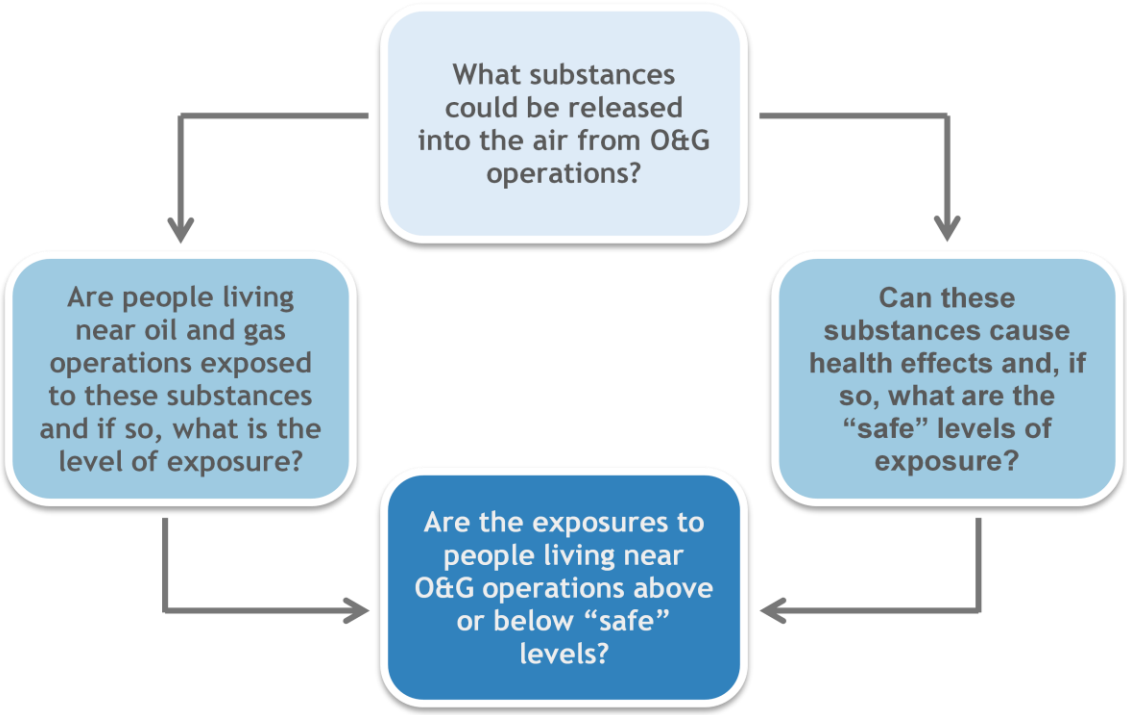
> Do substances emitted into the air from oil and gas operations result in exposures to Coloradans living near oil and gas operations at levels that may be harmful to their health?

The process of oil and gas extraction releases volatile substances (sometimes referred to as volatile organic chemicals or VOCs) into the air. Public health risks from these substances are largely determined by the type and amount of VOCs released into the air that could result in an exposure to someone living near these operations. A person's total exposure to VOCs in the air comes from many different sources at work, in homes, and outdoors. One challenge to evaluating potential public health risks solely from oil and gas operations is that there is a lack of easily accessible information in publicly available literature that directly identifies the types and amounts of substances that are emitted into the air during different phases of oil and gas extraction. There are, however, other sources of information, such as emission databases and air data collected across Colorado in areas of substantial oil and gas operations. These can be used to understand potential oil- and gas-related exposures. Additionally, there are extensive toxicological data on the health effects of VOCs that provide estimates of levels of human exposure that are unlikely to produce harmful non-cancer effects (i.e. "safe" levels) or added cancer risks. Together, these data provide information to estimate the potential for harmful health effects to occur in people who may be exposed to substances emitted into the air from oil and gas operations near their homes (i.e. human health risk assessment).

Process

This assessment was conducted using a screening-level human health risk assessment framework[1]. The following four questions framed the scope of each step in the assessment (Figure 1). Detailed methods and uncertainties for each step are provided in Appendix 1, A-D.

Figure 1. Four questions of the screening health risk assessment



1. **<u>Substance identification</u>: What substances could be released into the air from oil and gas operations?**

   A variety of datasets were evaluated to identify the substances most likely to be released into the air from oil and gas operations in Colorado. Eleven sources of information were located relevant to identifying substances potentially emitted during any phase of oil and gas operations (Appendix 1A). The primary sources were studies that directly measured VOCs from oil and gas operations in Colorado and studies that collected air data in oil and gas areas and used models to estimate percent of oil and gas source contributions to overall measured samples. Ambient air data in areas with substantial oil and gas operations and minimal other industrial activities was used as a secondary source of information. The substances detected at least 50 percent of the time across all datasets were cross-checked with primary source data and any additional substances were added to the list. These were used in the subsequent steps of the assessment. Although substances detected at less than 50 percent may still be potentially emitted from oil and gas operations, the scope of this current assessment was limited to those substances most frequently detected.

2. **Exposure assessment: What are the levels of exposures to these substances?**

Although exceptions may occur, the Colorado Oil and Gas Conservation Commission's established setback distance from residences at is 500 feet or greater from oil and gas operations[2]. Therefore, this exposure analysis only included air samples that were collected at 500 feet or greater from an oil and gas operation. A total of 13 different datasets across 33 locations were combined for the assessment (Appendix 1B). The data represent a range of concentrations across both the Denver-Julesburg and Piceance Basins over eight years (2008-2015) and include more than 10,000 individual air measurements (Appendix 1B, Table 1, Figure 1). The different values from these combined air data were used to represent two different potential exposure scenarios:

A) The maximum air concentration of a substance represents an estimate of an acute (short-term) exposure. An acute exposure is an intermittent, infrequent exposure that could occur for a few hours to a few days. This is what the air might be like from an unanticipated release of emissions during oil and gas activities.

B) The highest average air concentration for a substance across all datasets is used to represent an estimate of a chronic (long-term) exposure. A chronic exposure is a prolonged continuous exposure, generally over the lifetime of an individual. The air data likely indicates what the average outdoor air is like near residences over the life of a normal operating well or wells.

3. **Health effects assessment: What are the "safe" levels of exposure for these substances?**

A consistent, tiered approach was used to identify existing cancer risk estimate values and non-cancer health-based reference values from national and state sources for exposure scenarios A (short-term exposures) and B (long-term exposures) (Appendix 1C, Table 1). These values are generally based on the most sensitive, chemical-induced health effect considered to be relevant to humans. For non-cancer health effects, the health-based reference value is the exposure level below which health effects are not expected to occur, even for potentially sensitive people in the general population (also referred to as a "safe" level in this report). For cancer causing substances, there are no "safe" levels of exposure. Rather, inhalation unit risk (IUR) values are used to assess the incremental increase in cancer risks[3]. Details are provided in Appendix 1C.

4. **Risk Characterization: Are the exposures to people living near oil and gas operations above or below "safe" levels?**

Step 1: This step combines the results of the exposure assessment and the health effects assessment to estimate the level of health risk posed by oil and gas operations.

Non-cancer: The air concentrations of each substance (Step 2) were compared to health-based reference values (Step 3). Details are provided in Appendix 1D.

Individual substances: a hazard quotient (HQ) is determined for each individual substance. This ratio is a risk estimate that indicates the relationship between the exposure level of an individual substance compared to the health-based reference value (i.e. "safe" level). When the HQ is less than or equal to 1.0, harmful effects are not expected, even for sensitive populations. Exposures to substances at levels above a HQ of 1.0 will not necessarily cause harmful health effects and should be further evaluated. For example, a HQ of 2 indicates that the exposure level for a substance was two times higher than the "safe" level but does *not* mean there is a two times increased risk for that effect to occur.

It only means that the potential for harmful effects increases with exposures greater than the health-based reference value.

Combined substances: Evaluating the combined risks to human health from multiple substances is an important component to understanding the potential for health effects to occur from oil and gas emissions. A standard U.S. EPA screening level risk assessment approach was also used to screen for combined short and long term risk potential[4]. A Hazard Index (HI) was derived by summation of all the HQs. This total HI is a very conservative approximation of the total potential non-cancer risk estimate of all substances. The combined risks were also separated based on common (ie. neurological, respiratory). This is a more biologically appropriate method (Appendix 1D, Table 1).

Cancer: To estimate increased cancer risks, the exposure concentration of the substance in the air were multiplied by the inhalation unit risk (IUR) value of the substance (Appendix 1D). For example, a risk level of one in a million ($1x10^{-6}$) implies a likelihood that up to 1 out of one million equally exposed people would contract cancer if exposed continuously (i.e. 24 hours per day) to the specific concentration over a lifetime (i.e. 70 years). This would be in addition to those cancer cases that would normally occur in an unexposed population of one million people[3]. Combined cancer risks were also evaluated for all known cancer causing substances. This approach conservatively assumes that all the substances cause cancer in the body by the same mechanism and therefore, their combined effect is additive. Although this may not be biologically representative of the mechanisms for these substances, this method is consistent with standard U.S. EPA approaches for screening for combined risks.

The cancer and non-cancer health risk estimates are categorized, for individual substances or combined substances, as *elevated, acceptable, or negligible*. These categories were adapted from generally accepted categories used by U.S. EPA and other state agencies to assist in risk management decisions[5] (Table 1).

Table 1. Screening health-risk levels for potential cancer and non-cancer health effects

Screening Health Risk Level	Non-Cancer Risk (HQ/HI)[a]	Cancer Risk Estimate	
Elevated	> 1	≥ $1x10^{-4}$	One in a hundred thousand
Acceptable[c]	0.1 to 1	$1x10^{-6}$ to $1x10^{-4}$ [b]	One in a million to one in a hundred thousand
Negligible	< 0.1	< $1x10^{-6}$	One in a million

[a] HQ= Hazard Quotient; HI=Hazard Index
[b] U.S. EPA's target cancer risk range
[c] "Acceptable" risk levels indicate that harmful non-cancer health effects are not likely to occur below the estimated population threshold level.

Results

- Sixty –two substances were selected as high priority to evaluate in the risk assessment (Table 2).
- More than 10,000 air measurements for all substances were combined.
- Long-term health-based guidelines for approximately 25 percent of the substances were found in the U.S. EPA IRIS database, approximately 50 percent were from Texas Commission on Environmental Quality (TCEQ) and only 5 percent were from other regulatory agencies. Information on similar substances was used to select health-based guidelines for four substances that did not have any published health-based guidelines (Appendix 1D, Table 2).
- For non-cancer health effects, all air concentrations of individual substances were below non-cancer health-based reference values and considered in the "safe" levels of exposure (Figure 2).
    - Benzene, formaldehyde, and acetaldehyde were approximately 4-5 times below standard health-based reference values.
    - Two substances, ethane and methane, do not produce any health effects except at extremely high exposures.
    - Although identified as a high priority substance, acrolein had no air monitoring data to compare with health-based reference values (Appendix 1B, Table 2).
    - All other 56 substances were 5-10,000 times below standard health-based reference values and considered in the negligible risk range.
- For non-cancer health effects of combined air concentrations (Figure 3):
    - For short-term exposures, all substances combined, regardless of the type of health effect, were within "safe" levels (HI = 0.7).
    - For long-term exposures, all substances combined, were slightly elevated above "safe" levels (HI = 1.4) However, this is a very minor finding considering the large number of substances evaluated.
    - Neurological (HI=1.3), upper and lower respiratory (HI=1.3) health effects are the main contributors to the elevated risk estimate, primarily due to the larger number of substances with the potential to cause these effects.
- All four cancer-causing substances (benzene, ethylbenzene, formaldehyde and acetaldehyde) were within acceptable risk range, even for combined exposures (Figure 4).

Table 2. Substances selected for the health risk assessment

Acetaldehyde	Dimethylcyclohexane(trans-13-)	Methane	Propane
Acetone	2,3-Dimethylpentane	Methanol	n-Propylbenzene
Acrolein	2,4-Dimethylpentane	Methylcyclohexane	Propylene
Benzene	Ethane	Methylcyclopentane	Styrene
n-Butane	Ethylbenzene	2-Methylheptane	1,2,3-Trimethylbenzene
2-Butanone	Ethylcyclohexane	3-Methylheptane	1,2,4-Trimethylbenzene
1-Butene	Ethylene	2-Methylhexane	1,3,5-Trimethylbenzene
Butene (cis-2-)	m-Ethyltoluene	3-Methylhexane	2,2,4-Trimethylpentane
Butene (trans-2-)	o-Ethyltoluene	2-Methylpentane	2,3,4-Trimethylpentane
Cyclohexane	p-Ethyltoluene	3-Methylpentane	Toluene
Cyclopentane	Formaldehyde	n-Nonane	n-Undecane
n-Decane	n-Heptane	n-Octane	m-Xylene
p-Diethylbenzene	n-Hexane	n-Pentane	o-Xylene
m-Diethylbenzene	Isobutane	1-Pentene	p-Xylene
Dimethylcyclohexane(cis-13-)	Isopentane	Pentene (cis-2-)	
Dimethylcyclohexane(trans-12-)	Isopropylbenzene	Pentene (trans-2-)	

Figure 2. Short-term and long-term risk estimates (hazard quotients) for each substance for non-cancer effects

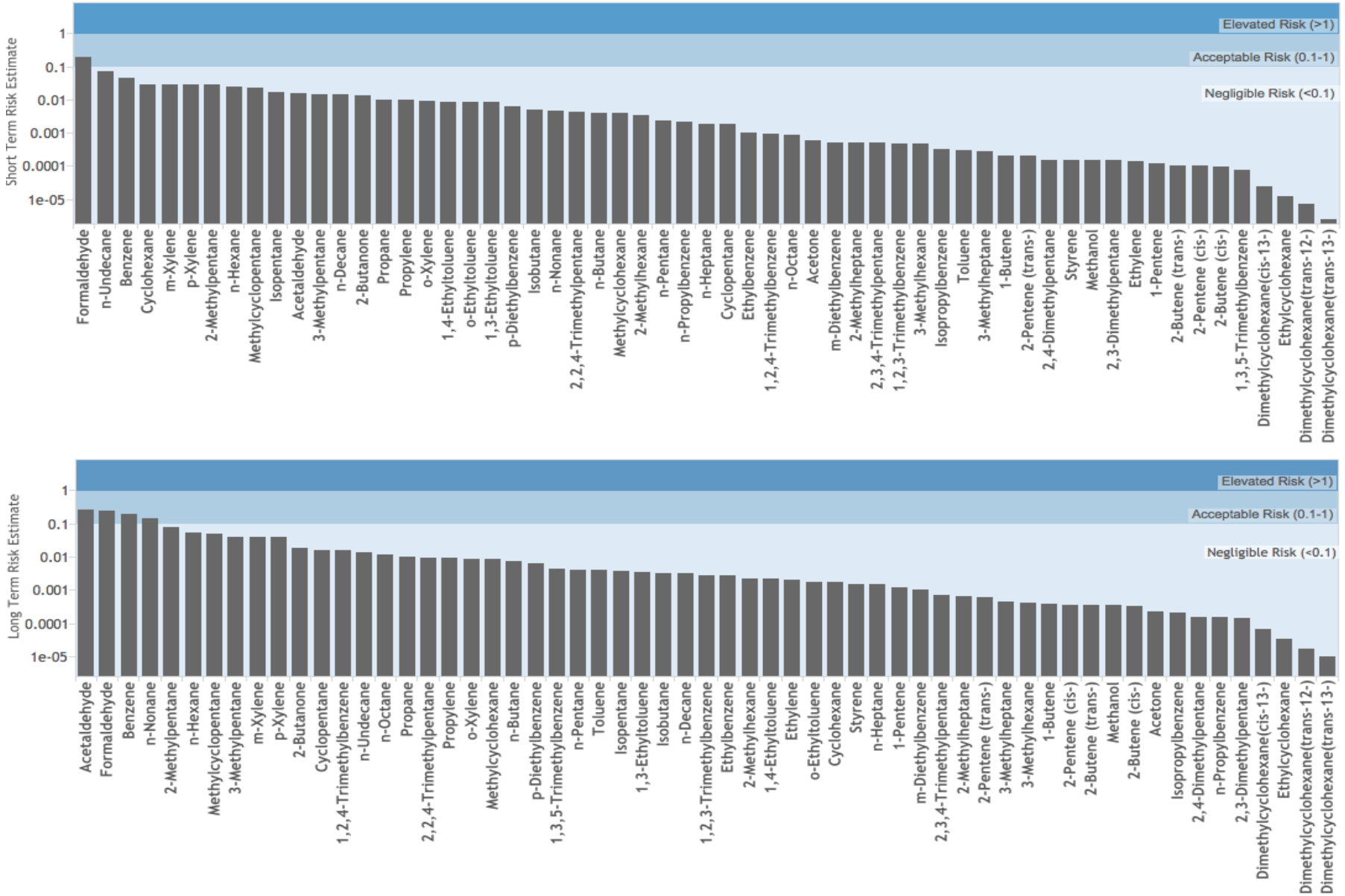


Figure 3. Combined long-term risk estimates (hazard index) by each non-cancer health effect category

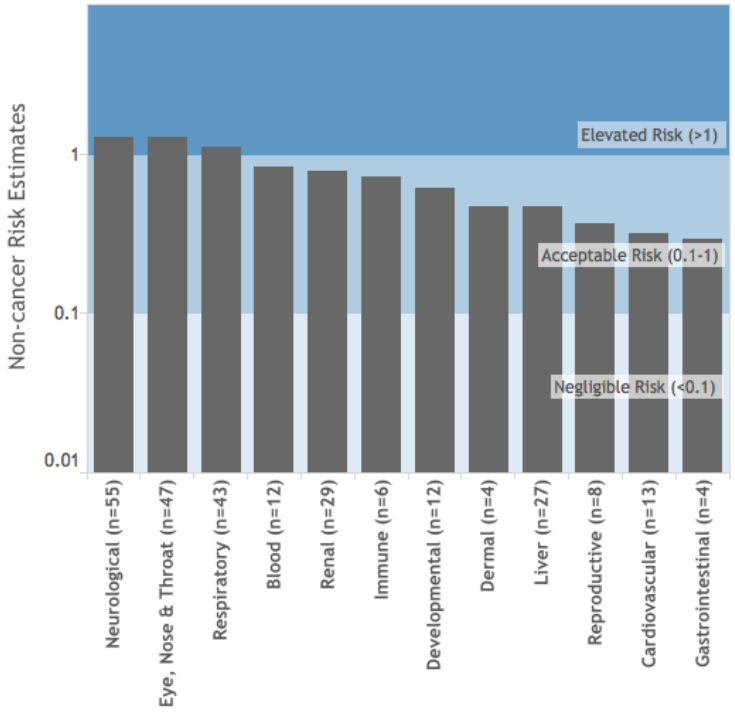
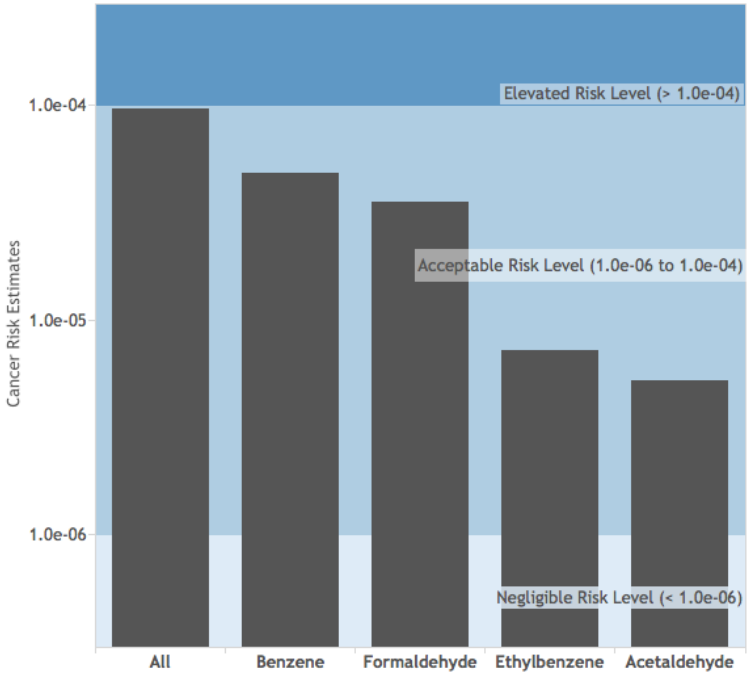


Figure 4. Cancer risk estimates for each type of cancer



Strengths & Limitations

This assessment had the following strengths:

- Multiple sources of reliable information were used to select the high priority substances evaluated in this assessment, resulting in a high level of confidence that the substances represent the majority of the substances emitted from oil and gas operations.
- The air concentration dataset was large including more than 10,000 individual air samples at 33 different locations across two different oil and gas basins.
- Multiple conservative assumptions were used to minimize underestimating any potential health risks:
    - The maximum air concentrations of all the averages and the overall maximum were used to compare against the short- and long-term health-based reference values.
    - A worst-case exposure scenario was used in which a person spends 100 percent of his or her time outdoors residing by the oil and gas operations. A more realistic exposure scenario that includes normal activity patterns, such as time indoors and time away from home, would result in lower exposure values.
    - The lowest of the available health-based reference values for the short-term assessment was used.
    - The combined risk from exposure to all substances combined was evaluated.

This assessment had the following limitations:

- To conduct a screening level assessment, air data collected in regions with substantial oil and gas operations as a substitute for a person's exposure was used. Although these are the best available data, they may not represent individual and community level exposures to people living near oil and gas operations.
- Average and maximum values across all studies are more likely to represent the high end of average long-term exposures, but there is less confidence that these values represent the short-term exposure scenario.
- The air data used represents a person's total outdoor air exposure to both oil and gas and non-oil and gas sources of emissions, such as emissions from vehicles, gas stations, industrial waste landfills or other industries.
- The standard health-based reference values do not account for substance interactions other than additivity. Although a conservative approach was used to assess the potential non-cancer health risks from combined exposures to all substances, this approach may not fully address potential interactions of substances.

Conclusions

- All measured air concentrations of were below short- and long-term "safe" levels of exposure for non-cancer health effects, even for sensitive populations.
- The concentrations of a small number of substances (benzene, formaldehyde, acetaldehyde) in the air surrounding oil and gas operations were 4-5 times lower than standard short- and long-term health-based reference levels for non-cancer effects.
- The concentrations of the other substances are 5-10,000 times lower than the standard short- and long-term health-based reference values for non-cancer effects.
- Cancer risks for all substances were within the "Acceptable Risk" range established by the U.S. EPA.
- Although well within the range considered "safe" for cancer and non-cancer effects, benzene, acetaldehyde and formaldehyde had the highest estimated risk levels and are high priority for continued monitoring.
- Overall, available air monitoring data suggest low risk of harmful health effects from combined exposure to all substances.

Recommendations

- CDPHE will continue to collect data from citizens who report oil and gas health concerns in order to characterize the types and frequency of symptoms, map locations where symptoms are reported and determine response plans to address the concerns of the communities.
- CDPHE will continue to monitor regional air data in areas with substantial oil and gas operations and evaluate community-specific exposures using our Colorado Air Mobile Monitoring Laboratory that will enable collection of more frequent, real-time air samples over longer periods of time.
- CDPHE currently is supporting a comprehensive risk assessment that will address many of the limitations of this study. The assessment will use recently released data from Colorado State University on the direct emissions of VOC's during each phase of oil and gas extraction. The emission information will generate detailed, realistic exposure scenarios that will estimate potential health risks to people living at various distances from an oil and gas operation.

References

1. U.S. Environmental Protection Agency. (2010). Preliminary Risk-Based Screening Approach for Air Toxics Monitoring Data Sets. Air, Pesticides and Toxics Management Division.
2. Colorado Oil and Gas Conservation Commission. 600 Series Safety Regulations. Regulation 604.a(1). (Published Date: 3/16/2016).
3. U.S. Environmental Protection Agency. Integrated Risk Information System (IRIS). https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system
4. U.S. Environmental Protection Agency. (2003). Framework for Cumulative Risk Assessment. EPA document number EPA/630/P-02/001F.
5. U.S. Environmental Protection Agency Superfund Regional Removal Management Levels https://www.epa.gov/risk

SECTION 2:

Systematic Review of Human Health Effect Studies

Introduction

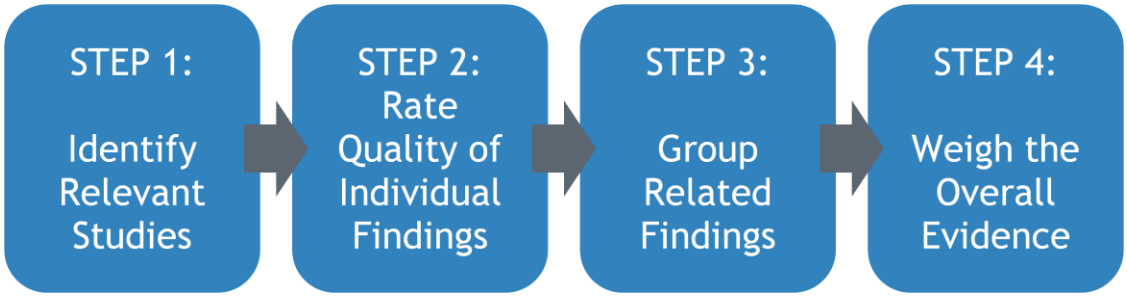
Over the last several years, multiple papers have outlined the potential chemical and non-chemical hazards from oil and gas operations[1-6]. Other studies have evaluated the relationship between living near oil and gas operations and the potential for certain adverse human health effects[9-20]. These studies contribute to the scientific evidence for identifying potential public health concerns that may need further investigation. This section systematically reviews the existing peer-reviewed epidemiology literature and determines the level of scientific evidence for the findings from these studies to answer our main question:

> Do substances emitted into the air from oil and gas operations result in exposures to Coloradans living near oil and gas operations at levels that may be harmful to their health?

Systematic review process

We adapted the various established systematic review frameworks for environmental health assessments, such as GRADE and the Navigation Guide to ensure a standardized and rigorous review[7,8] (Figure 1).

Figure 1. Steps in the review of the epidemiological literature



Twelve studies met our criteria of *an observational human health epidemiologic study evaluating the potential health effects associated with living near oil and gas operations* and were included in this systematic review. The findings within each study were rated as either a low, medium or high quality of evidence based on the strengths and limitations of that study. Each of the findings were grouped into similar health-effect categories and the overall strength of evidence was assessed (Table 1). Details for each step are provided in Appendix 2A. Table 2 provides a summary of the evidence findings for each health effect. Individual study evaluation details, including relevant findings and strengths and limitations, are provided in Appendix 2B.

Table 1. Strength of evidence statements and criteria

Evidence Level	Definition
Substantial	Strong scientific findings that support an association between oil and gas exposure and the outcome, with no credible opposing scientific evidence.
Moderate	Strong scientific findings that support an association between oil and gas exposure and the outcome, but these findings have some limitations.
Limited	Modest scientific findings that support an association between oil and gas exposure and the outcome, but these findings have significant limitations.
Mixed	Both supporting and opposing scientific findings for an association between oil and gas exposure and the outcome, with neither direction dominating.
Failing to show an association	Body of research failing to show an association - indicates that the topic has been researched without evidence of an association; is further classified as a limited, moderate or substantial body of research failing to show an association.
Insufficient	The outcome has not been sufficiently studied.

Strength of evidence findings

Table 2. Summary of overall strength of evidence for epidemiological studies by health effect

Health Effects Categories	Number of studies*	Health Effects	Evidence
Birth outcomes	4	Preterm birth[9,10,11,12]	*Mixed*
		Low APGAR[10,11]	*Mixed*
		Small for gestational age[10,11,12]	*Mixed*
		Birth weight (LBW & mean)[9,10,11,12]	*Mixed*
Birth Defects	1	Congenital heart defects[9]	*Insufficient*
		Oral Clefts[9]	*Insufficient*
		Neural tube defects[9]	*Insufficient*
Respiratory (eye, nose and throat (ENT) and lung)	6	Multiple, self-reported symptoms[13,14,15]	*Mixed*
		Hospitalizations[17,18]	*Failing to show an association*
		Asthma exacerbations[16]	*Limited*
Neurological (migraines, dizziness)	5	Hospitalizations[17,18]	*Mixed*
		Multiple, self-reported[14]	*Insufficient*
		Migraine/severe headache[13,14,15]	*Mixed*
Cancer	4	Overall childhood cancer incidence[19]	*Insufficient*
		Childhood Hematological (Blood) Cancers[19,20]	*Mixed*
		Childhood CNS tumors[19]	*Insufficient*
		Hospitalizations[17,18]	*Mixed*
Skin (irritation, rashes)	2	Multiple, self-reported[14,15]	*Limited*
Psychological (depression, sleep disturbances	4	Multiple, self-reported[13,14,15]	*Failing to show an association*
		Hospitalizations[17]	*Insufficient*
Cardiovascular (heart)	2	Hospitalizations[17]	*Insufficient*
		Multiple, self-reported[14]	*Insufficient*
Gastrointestinal (nausea, stomach pain)	3	Hospitalizations[17]	*Insufficient*
		Multiple, self-reported[14,15]	*Failing to show an association*
Musculoskeletal (joint pain, muscle aches)	2	Hospitalizations[17]	*Insufficient*
		Multiple, self-reported[15]	*Mixed*
Blood/Immune	2	Hospitalizations[17,18]	*Mixed*

** A total of 12 studies were included with some studies evaluating multiple health effects*

Reproductive and developmental effects

Oil and gas operations can emit volatile organic compounds (VOCs) and particulate matter into the air during the extraction process. Some VOCs can cause developmental effects in test animals following high levels of exposure – generally much higher than we have observed for individual VOCs at oil and gas operations. Additionally, systematic reviews of a broad set of data have demonstrated evidence of positive associations between maternal exposures to fine particulate matter in ambient outdoor air pollution in urban areas and adverse birth outcomes[21-23]. However, the ability of specific substances emitted directly from oil and gas operations to cause reproductive and developmental effects has not been proven at residential exposure levels. This review identified four low-quality epidemiological studies that evaluated the relationship between women that lived near oil and gas operations and the likelihood their offspring would have birth defects or other types of adverse effects at birth.

Birth outcomes

There is **MIXED** evidence for whether or not living near oil and gas operations during pregnancy is associated with adverse birth outcomes, such as preterm birth, changes in birth weight, low APGAR scores and small for gestational age, in the infant.

Four studies evaluated various birth outcomes in infants of mothers who lived near well operations9-12. These studies examined commonly used indicators of infant health status such as preterm birth, changes in birth weight, low APGAR scores, small for gestational age and birth weight (see glossary of terms for definitions). Overall, there were conflicting low- to medium-quality findings across the four studies.

Birth defects

There is **INSUFFICIENT** evidence to determine if living near oil and gas operations during pregnancy is associated with birth defects, such as oral clefts, heart defects and neural tube defects in the infant.

Evidence is limited to a single (1) study that evaluated the relationship between maternal residence proximity to O&G operations and the incidence of birth defects in their offspring[9].

Upper (eye, nose and throat) and lower respiratory symptoms

There is **LIMITED** evidence that living near oil and gas operations is associated with exacerbation of existing asthma.

There is **MIXED** evidence for whether or not living near oil and gas operations is associated with self reported upper and lower respiratory symptoms.

There is a limited body of evidence **FAILING TO SHOW AN ASSOCIATION** between living near oil and gas operations and upper and lower respiratory hospitalizations.

Many different substances in the air can cause eye, nose and throat (ENT) irritation or respiratory effects in test animals and humans (see Section 1). Five low-quality and 1 medium- quality study evaluated the relationship between living near oil and gas operations and the occurrence of ENT irritation and respiratory health effects and found conflicting evidence based on the type of the specific health effect evaluated[13-18].

Neurological symptoms

There is **MIXED** evidence for whether or not living near oil and gas operations is associated with migraines or an increased rate of hospitalizations for neurological symptoms.

There is **INSUFFICIENT** evidence to determine if living near oil and gas operations is associated with self reported neurological symptoms.

VOCs can produce neurological effects such as central nervous system damage, headaches, dizziness, visual disorders, loss of coordination, and memory impairment in test animals and humans[24] (see Section 1). Five studies evaluated the relationship between living near oil and gas operations and the occurrence of a variety of different measures for neurological health effects[13-15,17-18]. Overall, the low-quality studies lack clear positive findings for increased occurrence of neurological symptoms in people living in oil and gas areas.

Cancer

There is **INSUFFICIENT** evidence to determine if living near oil and gas operations is associated with increased incidence of overall childhood cancers.

There is **MIXED** evidence to determine whether or not living near oil and gas operations is associated with increased incidence of childhood hematological cancers and rates of adult and child cancer hospitalizations.

Long-term exposure to certain substances that are likely emitted into the air from oil and gas operations, such as benzene, may increase the risk of developing certain types of cancer (see Section 1). However, the development of cancer is complex because many other non-environmental influences, such as genetics and lifestyle behaviors, can also contribute to cancer. Two epidemiological studies evaluated the incidence of childhood cancers in Pennsylvania counties or in rural Colorado[19-20]. Two community level studies examined hospitalization rates in an oil and gas areas compared to an area with no oil and gas[17-18]. Overall, these low quality studies have both supporting and opposing evidence that living near oil and gas operations may be positively associated with cancer.

Dermal Symptoms

There is **LIMITED** evidence that living near oil and gas operations is associated with self-reported dermal symptoms.

Two low-quality studies evaluated dermal outcomes such as rash, irritation, burning, itching, and hair loss in relation to oil and gas activities in Pennsylvania[14,15]. Skin related health effects, however, are unlikely to occur following inhalation exposures to oil and gas related substances in the air (Appendix 1C).

Psychological Effects

There is a limited body of evidence **FAILING TO SHOW AN ASSOCIATION** that living near oil and gas operations is associated with self-reported psychological symptoms (sleep disturbances, fatigue, forgetfulness, anxiety, and depression).

There is **INSUFFICIENT** evidence to determine if living near oil and gas operations is associated with increased rates of psychological hospitalizations.

Measures of mental health, such as reported psychological symptoms, are not necessarily a result of direct exposure to substances emitted from oil and gas but could be indirectly associated with non-chemical environmental stressors such as noise, light or odors. For example, studies have shown associations between living in areas with increased noise and traffic, such as by airports, with increased psychological symptoms[25-28]. Four epidemiological studies evaluated a variety of indicators of psychological well-being, such as depression, anxiety, fatigue, sleep disturbances and forgetfulness specifically in populations living near oil and gas operations [13,14,15,17].

Cardiovascular, Gastrointestinal, Musculoskeletal and Hematological (blood) and Immune Effects

There is **INSUFFICIENT** evidence to determine if living near oil and gas operations is associated with self-reported cardiovascular symptoms and cardiac and gastrointestinal hospitalizations.

There is a limited body of evidence **FAILING TO SHOW AN ASSOCIATION** between living near oil and gas operations and self-reported gastrointestinal symptoms.

There is **MIXED** epidemiologic evidence for whether or not living near oil and gas operations is associated with self-reported musculoskeletal or blood/immune symptoms.

Most of the substances that may be emitted from oil and gas are not known to cause gastrointestinal, cardiovascular or musculoskeletal effects (Appendix 1C). Benzene is the only substance identified in our screening risk assessment that is known to cause harmful blood disorders following repeated or prolonged exposures. Four studies with low quality findings had both supporting and opposing evidence, depending on the health effect, for self-reported symptoms and rates of hospitalizations in people living near oil and gas operations[14,15,17,18].

Conclusions

- A relatively small number of epidemiological studies (12) have been published that evaluate potential associations between oil and gas emissions and health outcomes.
- There is limited evidence that exacerbation of existing asthma and self-reported dermal symptoms are associated with exposure to substances emitted from oil and gas operations.
- There is a lack of evidence or, in some cases, conflicting evidence concerning the relationship between other health outcomes and oil and gas operations.
- The majority of findings from the studies were ranked as low quality, primarily due to limitations of the study designs that make it difficult to establish clear links between exposures to substances emitted directly from oil and gas and the outcomes evaluated.
- A person's total exposure may reflect multiple substances from both oil and gas and non-oil and gas sources from indoor and outdoor environments. For example, VOCs can be emitted from a variety of sources including oil and gas, other industrial operations, vehicle traffic and everyday consumer products such as nail polish, detergents, sealants, aerosol antiperspirants and deodorants.
- In addition, these epidemiological studies may also reflect the interactions of non-chemical stressors that may or may not be related to oil and gas operations that can contribute to adverse health outcomes in a population.
- Although these observational epidemiology studies alone are not sufficient to determine causality, they provide helpful information to direct further investigation into the public health implications of oil and gas activity near residential areas.
- Studies of populations living near oil and gas operations provide limited evidence of the possibility for harmful health effects. This needs to be confirmed or disputed with higher quality studies.

Recommendations

- Epidemiological studies that include more controlled designs with direct measurements of exposure and determination of health effects are needed to confirm or dispute the associations published in the literature.
- Public health officials should continue to monitor health concerns in areas with substantial oil and gas operations through centralized data collection and analysis.
- Multi-state collaborations should be considered to collect consistent datasets from differing oil and gas basins across the United States in order to more comprehensively evaluate the potential for adverse health effects.

References

1. Adgate JL, Goldstein BD, McKenzie, LM. Potential Public Health Hazards, Exposures and Health Effects from Unconventional Natural Gas Development. Environ. Sci. Technol. 2014; 48(15): 8307-8320
2. Colborn T, Kwiatkowski C, Schultz K, Bachran M. Natural Gas Operations from a Public Health Perspective. Human and Ecological Risk Assessment: An International Journal. 2011; 17(5): 1039-1056.
3. Field RA, Soltis J, Murphy S. Air Quality Concerns of Unconventional Oil and Natural Gas Production. Environ. Sci.: Processes Impacts. 2014; 16: 954-969.
4. Terra Mentis Environmental Consulting. Fort Collins Memorandum 2A Technical Support Document City of Fort Collins. 2015.
5. Goldstein BD, Brooks BW, Cohen SD, Gates AE, Honeycutt ME, Morris JB, Orme-Zavaleta JO, Penning TM, Snawder J. The Role of Toxicological Science in Meeting the Challenges and Opportunities of Hydraulic Fracturing. Toxicological Sciences. 2014. 139(2): 271-283.
6. Werner AK, Vink S, Watt K, Jagals P. Environmental Health Impacts of Unconventional Natural Gas Development: A Review of the Current Strength of Evidence. Science of the Total Environment. 2015; 505: 1127-1141.
7. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. GRADE approach to evaluating the quality of evidence: a pathway. http://training.cochrane.org/path/grade-approach-evaluating-quality-evidence-pathway
8. Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. Systematic Review and Evidence of Integration for Literature-based Environmental Health Science Assessments. Environ Health Perspect. 2014. 122:711-718.
9. 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(4):412-417.
10. Hill E. Shale Gas Development and Infant Health: Evidence from Pennsylvania. Unpublished. The Charles H. Dyson School of Applied Economics and Management, Cornell University, Ithaca, New York. 2013.
11. Casey JA, Savitz DA, Rasmussen SG, Ogburn EL, Pollak J, Mercer DG, Schwartz BS, Unconventional Natural Gas Development and Birth Outcomes in Pennsylvania, USA. Epidemiology. 2016; 27(2): 163-172.
12. Stacy SL, Brink LL, Larkin JC, Sadovsky Y, Goldstein BD, Pitt BR, Talbott EO. Perinatal Outcomes and Unconventional Natural Gas Operations in Southwest Pennsylvania. PLOS ONE. 2015; doi:10.1371/journal.pone.0126425
13. 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; doi: 10.1289/EHP281
14. Rabinowitz PM, Slizovskiy IB, Lamers V, Trufan SJ, Holford TR, Dziura JD, Peduzzi PN, Kane MK, Reif JS, Weiss TR, Stowe MH. Proximity to Natural Gas Wells and Reported Health Status: Results of

a Household Survey in Washington County, Pennsylvania. Environmental Health Perspectives. 2015; 123(1): 21-26.

15. Steinzor N, Subra W, Sumi L. Investigating Links Between Shale Gas Development and Health Impacts Through a Community Survey Project in Pennsylvania. New Solutions. 2013; 23(1): 55-83.
16. Rasmussen SG, Ogburn EL, McCormack M, Casey JA, Bandeen-Roche K, Mercer DG, Schwartz BS. Association Between Unconventional Natural Gas Development in the Marcellus Shale and Asthma Exacerbations. JAMA Intern Med. 2016;doi:10.1001/jamainternmed.2016.2436
17. Jemielita T, Gerton GL, Neidell M, Chillrud S, Yan B, Stute M, Howarth M, Saberi P, Frusti N, Penning TM, Roy J, Propert KJ, Panettieri RA. Unconventional Gas and Oil Drilling is Associated with Increased Hospital Utilization Rates. PLOS ONE. 2015; DOE:10.1371/journal.pone.0131093
18. Werner AK, Watt K, Cameron CM, Vink S, Page A, Jagals P. All-age Hospitalization Rates in Coal Seam Gas Areas in Queensland, Australia, 1995-2011. BMC Public Health. 2016; 16(125).
19. Fryzek J, Pastula S, Jiang X, Garabrant DH. Childhood cancer incidence in Pennsylvania counties in relation to living in counties with hydraulic fracturing sites. JOEM. 2013; 55(7): 796-801.
20. McKenzie LM, Allshouse WB, Byers TE, Bedrick EJ, Serdar B, Adgate JL. Childhood hematologic cancer and residential proximity to oil and gas development. PLoS ONE. 2017; 12(2): e0170423. doi:10.1371/journal.pone.0170423
21. Lamichhane DK, Leem JH, Lee JY, Kim HC. A Meta-Analysis of Exposure to Particulate Matter and Adverse Birth Outcomes. Environ. Health. Toxicol. 2015; doi: 10.5620/eht.e2015011.
22. Sapkota A., Chelikowsky AP, Nachman KE, Cohen AJ, Ritz B. Exposure to Particulate Matter and Adverse Birth Outcomes: A comprehensive review and meta-analysis. Air Qual Atmos Health. 2012; 5: 369. doi:10.1007/s11869-010-0106-3
23. Srám RJ, Binkova B, Dejmek J, Bobak M. Ambient Air Pollution and Pregnancy Outcomes: A Review of the Literature. Environ Health Perspect. 2005; 113(4):375-82.
24. National Institutes of Health. U.S. Department of Health and Human Services. Volatile Organic Compounds (VOCs). ToxTown. 2016. https://toxtown.nlm.nih.gov/text_version/chemicals.php?id=31
25. Morrell S1, Taylor R, Lyle D. A review of health effects of aircraft noise. Aust N Z J Public Health. 1997 Apr;21(2):221-36.
26. Stansfeld S1, Haines M, Brown B. Noise and health in the urban environment. Rev Environ Health. 2000 Jan-Jun;15(1-2):43-82.
27. Recio A, Linares C, Banegas JR, Díaz J. Road traffic noise effects on cardiovascular, respiratory, and metabolic health: An integrative model of biological mechanisms. Environ Res. 2016 Apr;146:359-70
28. Pedersen E. City dweller responses to multiple stressors intruding into their homes: noise, light, odour, and vibration. Int J Environ Res Public Health. 2015 Mar 18;12(3):3246-63.

Glossary of terms and acronyms

Acceptable risk – the level of exposure to a substance or multiple substances that is unlikely to result in adverse health effects, even to the most sensitive populations.

Ambient air – Ambient air refers to the outdoor air surrounding a person through which pollutants can be carried. The ambient concentration of a substance is the concentration estimated in the outdoor environment.

Asthma exacerbation - Short- or long-term episode of worsening asthma symptoms including shortness of breath, wheezing, cough and chest tightness.

Birth weight - Weight of an infant at birth. Studies evaluating the average birth weight of many infants include premature infants, who usually weigh less. Therefore, some studies evaluate 'term birth weight,' which includes only infants who are not premature.

Cancer risk - The probability of contracting cancer over the course of a lifetime, assuming continuous exposure (assumed to be 70 years).

Carcinogen - A substance that can cause cancer.

CDPHE - Colorado Department of Public Health and Environment

CHD - Congenital Heart Defect: An abnormality in the structure of the heart at birth.

CNS tumor - Central nervous system (CNS) tumors are formed in the tissues of the brain or spinal cord.

Elevated risk - The level of exposure to a substance or multiple substances considered to be above a health-based guidance level. An elevated risk level does not necessarily mean that an adverse health effect is expected. Rather, it is a screening level that indicates further in-depth evaluation is warranted for substances that meet this level.

Epidemiologic study - The study and analysis of the patterns, causes, and effects of health and disease conditions in defined populations.

Hazard Index (HI) - The sum of hazard quotients for substances that affect the same target organ or organ system. When different substances can cause similar harmful health effects, it can be appropriate to combine hazard quotients for different substances.

Hazard Quotient (HQ) - A HQ indicates the relationship between the exposure level and the health-based guideline level. When the HQ is less than or equal to 1, harmful effects would not be expected, even for the most sensitive populations. When the hazard quotient is greater than 1, the potential for harmful effects should be examined more closely. For example, a HQ of 2 indicates that the exposure level for a substance was two times higher than the health-based guideline level and an HQ of 0.5 indicates the exposure level for a substance was two times lower than the health-based guideline level

Health-Based Reference Level - For non-cancer health effects, the health based reference value is the exposure level below which health effects are not expected to occur, even for potentially sensitive people in the general population (also referred to as a "safe" level in this report). These health based reference values are developed by federal or state regulatory agencies for use in comparison with exposure levels.

Human health risk assessment – the process to estimate the nature and probability of adverse health effects in humans who may be exposed to substances in the air they breathe or the water they drink, now or in the future.

Inhalation – Breathing. Substances can be inhaled into the nose or lungs and can then be taken into the blood to produce health effects.

LBW - Low birth weight: Infants who weigh less than 5 pounds (2500g) at birth.

Leukemia - A type of cancer affecting white blood cells

Low APGAR score - A newborn is given an APGAR test (appearance, pulse, grimace, activity, respiration) at birth by the delivery physician and scored 1-10. A low APGAR score is below 3.

Negligible risk – the level of exposure to a substance or multiple substances that is highly unlikely to result in adverse health effects, even to the most sensitive populations.

Neoplasm - An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Neoplasms may be benign (not cancer), or malignant (cancer). Also called tumor.

Neoplasm - An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Neoplasms may be benign (not cancer), or malignant (cancer). Also called tumor.

NTD – Neural tube defect. Birth defects of the brain, spine, or spinal cord.

O&G - Oil and gas. Refers to all phases of onshore oil and natural gas exploration and production.

OGHIR – Oil and Gas Health Information and Response Program at the Colorado Department of Public Health and Environment

Oral Cleft - A gap or split in upper lip or roof of mouth caused from incomplete development/fusion during pregnancy.

Premature birth - A birth that takes place before the baby is due (before 37 weeks of pregnancy).

Read-across – an approach that applies the toxicity information and the resulting health-based reference value from one substance to another substance that has similar chemical structure, physical-chemical properties and is anticipated to behave in a similar manner in the body to produce a health effect.

Risk – the likelihood that in a given situation, the conditions or exposure to a substance will be enough to cause an adverse consequence or effect.

SGA - Small for gestational age: babies who are smaller than normal for their gestational age (less than the 10th percentile of weights for their gestational age).

Substance – a manmade or naturally occurring chemical.

Toxicity – the ability of a substance to cause harmful health effects.

US EPA – United States Environmental Protection Agency

Appendix 1A

Substance identification

What substances could be released into the air from oil and gas operations?

Methods

The following sources were used to identify the substances most likely to be released into the air from oil and gas operations in Colorado. These substances were prioritized for evaluation in the risk assessment.

Primary Sources

- Operator emissions inventories submitted to the Air Pollution Control Division (APCD), including gas and liquid analysis documents.
- Two emission characterization studies conducted in Colorado:
    - *Characterizing Air Emissions from Natural Gas Drilling and Well Completion Operations in Garfield County, Colorado*[1]
    - *North Front Range Oil and Gas Air Pollutant Emission and Dispersion Study*[2]
- One source apportionment study conducted in Colorado:
    - *Source Signature of Volatile Organic Compounds from Oil and Natural Gas Operations in Northeastern Colorado*[3]

Secondary Sources

- Colorado ambient air concentration measurements in regions of high oil and gas activity[4].
- Site-specific oil and gas air quality samples or studies in Colorado[567].
- Expert opinion from the CDPHE Air Pollution Control Division and the Colorado Oil and Gas Conservation Commission.

[1] Collett Jr., J. L., J. Ham, A. Hecobian, (2016) Characterizing Emissions from Natural Gas Drilling and Well Completion Operations in Garfield County, Co., Available from: https://www.garfield-county.com/air-quality/documents/CSU-GarCo-Report-Final.pdf (Accessed: February 20, 2017).
[2] Collett Jr., J. L., J. Ham, A. Hecobian, (2016) North Front Range Oil and Gas Air Pollutant Emission and Dispersion Study Report, Available from: http://www.colorado.gov/airquality/tech_doc_repository.aspx?action=open&file=CSU_NFR_Report_Final_20160908.pdf (Accessed: February 20, 2017).
[3] Gilman et al. (2013). Source Signature of Volatile Organic Compounds from Oil and Natural Gas Operations in Northeastern Colorado *Environ. Sci. Technol.* 47 (3), pp 1297–1305
[4] Garfield County Public Health Air Quality Management - Air Monitoring Reports (2008-2015)
[5] Olsson Associates, Inc. Air Quality Sampling Summary Report Production Scenario (2011)
[6] Swarthout RF et al. Volatile Organic Compounds during the NACHTT campaign at the Boulder Atmospheric Observatory: Influence of urban and natural gas sources (2013)
[7] CDPHE Air Emissions Case Study Related to Oil and Gas Development in Erie, Colorado (2012)

A subset of substances was identified as high priority for investigation in this assessment if they were either:

- Identified from a primary source.
- Greater than 50 percent detection frequency across the secondary data sources.

Uncertainties

It is likely the substances identified do not reflect the full profile of substances emitted from oil and gas operations for these reasons:

- The studies, conducted by Colorado State University that quantified emission rates of 36 VOCs directly from each phase of oil and gas operations, are the only data that were located that identify specific VOCs emitted from oil and gas. These studies, however, did not quantify known constituents in oil and gas or reaction products, such as higher molecular weight volatile hydrocarbons, aldehydes, ketones and alcohols.
- Several additional substances detected in ambient air quality monitoring datasets were not included in this initial screening assessment. The scope of this assessment is limited to substances most frequently detected in air and therefore, of greatest concern for frequent exposures to people living near oil and gas operations.
- Many higher molecular weight hydrocarbons, including some polycyclic aromatic hydrocarbons (PAHs) that are known components of oil and/or natural gas were not analyzed in the majority of studies.
- Pollutants such as particulate matter and ozone were not within the scope of this assessment.
- Although ambient air datasets were selected from high oil and gas activity areas with minimal non-oil and gas activities, many other sources have the potential to emit the same substances as oil and gas operations.

Appendix 1B

Exposure assessment

What are the levels of exposure to these substances?

Data Selection

A thorough search was conducted to locate data containing air concentrations of the substances detected in regions with substantial oil and gas operations in Colorado. Data that met the following criteria were used:

- Original data from a high-quality study or program with clear objectives and methods that identified the location of sampling and any other potential non-oil and gas sources in the area.
- Samples from a region of substantial oil and gas activity that would be representative of residential/community level exposures.
- Samples collected at a distance of 500 feet or greater from a specific oil-and-gas source to reflect general current setback distances established by Colorado Oil and Gas Conservation Commission (COGCC).
- Samples collected in a region that had minimal influence from other potential major sources of air pollution, including roads, industrial activities, or urban areas.
- Samples collected during or after 2008 in order to account for changes and improvements in operational practices and major technological advances including “green completion” technologies that reduce emissions.

Exposure Scenarios

Two different values from these combined air data to represent two different potential exposure scenarios were used:

A) The maximum air concentration of a substance represents an estimate of an acute (short-term) exposure. An acute exposure is an intermittent, infrequent exposure that could occur for a few hours to a few days. This is what the air might be like from an unanticipated release of emissions during oil and gas activities.

B) The highest average air concentration for a substance across all datasets is used to represent an estimate of a chronic (long-term) exposure. A chronic exposure is a prolonged continuous exposure, generally over the lifetime of an individual. The air data likely indicates what the average outdoor air is like near residences over the life of a normal operating well or wells.

Uncertainties

The highest average and the maximum values may not entirely be representative of short- or long-term emissions from oil and gas operations in Colorado due to the following data limitations:

- The data were highly variable across studies including year, location, duration and frequency of sample collection.
- The data could represent air concentrations from oil and gas and non-oil and gas sources and likely do not reflect concentrations of substances solely emitted from oil and gas.
- Ambient air concentrations from these studies were used as surrogates for quantifying potential exposure concentrations to people living near oil and gas operations. There are many assumptions that are made in using this approach:
    - Individual or community level exposures depend on several factors that may not be accounted for in ambient air such as:
        - Frequency and duration of the source emissions.
        - Length of time substance remains in the air (i.e., degradation rates or dispersion).
        - Meteorological conditions.
        - Proximity and geographical location of the resident in relationship to the source of emissions.
        - Length of time the person is in the area where the substance is present.
        - Individual traits (length of time spent indoors vs. outdoors, breathing rate).
        - Air concentrations in the breathing zone of an individual.
- The exposure assumptions are conservative. The daily activity patterns of a person are not accounted for in this assessment. This assessment assumes that a person spends 100 percent of their time outside in the location where samples were collected. This is likely to be a conservative assumption because indoor air concentrations of air pollutants are expected to be the same or lower than the outdoor concentrations (when the indoor concentrations are produced solely by inflow from outside air). Additionally, most people are not at their residences 24 hours a day.
    - The samples represent exposures that would occur at that level over the lifespan of a person (long-term) or would occur for a few hours to a few days (short-term) durations. These assumptions may over- or underestimate the actual concentrations because the data do not account for any short, temporal variations.
- Although acrolein was identified as a substance emitted from oil and gas operations, no air data was located.
- Although methane and ethane were identified as high priority substances, they generally do not produce any health effects except at extremely high exposures.
- The data from the two major oil and gas basins were combined because there were no notable differences in the types or concentrations of substances.

Table 1. Air concentration datasets used in the screening-level health risk assessment

Organization/ Author	County	Basin	Site Location(s)[1]	Site Description	Operation Type or Phase	Year(s)	Season	Total # Samples	Sample Duration	Collection Frequency
Gilman	Weld	Denver-Julesburg	Boulder Atmospheric Observatory	Agricultural region. > 15,000 active oil and gas wells within 100-km radius, 22 well pads within 0.8-km radius. Nearest pad - 300m (984 ft)	Production	2011	Winter	544	5 minutes	Every 30 minutes for one month
Swarthout	Weld	Denver-Julesburg	Boulder Atmospheric Observatory	Agricultural region in area of substantial oil and gas developmen	NA	2011	Winter	550	5 minutes	Every hour for one month
CDPHE	Weld	Denver-Julesburg	Platteville	Agricultural/residential region with multiple wells	NA	2011-2015	All	~2750	3 hours	Daily on an annual basis
CDPHE	Weld	Denver-Julesburg	Erie	Residential neighborhood. 1650' from wellheads and supporting equipment and tanks	Completion	2012	Summer	18	3 hours	One month: every three days (for 17 days) then every day (for 19 days)
CDPHE	Weld	Denver-Julesburg	Erie	Residential neighborhood. 850' from wellheads and supporting equipment and tanks	Completion	2012	Summer	18	3 hours	One month: every three days (for 17 days) then every day (for 19 days)
Thompson	Weld	Denver-Julesburg	7 sites in West Erie, East Erie & Longmont	Residential neighborhoods and rural farmland residences close to wells	Production	2013	Spring	30	5 minutes-24 hours	Four months
FRAPPE [2]	Weld	Denver-Julesburg	16 sites	Rural or residential area in oil and gas region >500 feet away from potential source and multiple wells within 1600 feet of each site	Methane enhancement and wellpads, oil tank, separators, midstream processing plant, pipelines, drilling, compressor, processing, produced water	2014	Summer	18	One minute	One day
Garfield County	Garfield	Piceance	Bell/Melton Ranch	Rural residence with "moderate oil and gas development and heavy natural	Production	2008-2015	All	~3300	24 hours	Every 6 days on an annual basis

[1] Each individual site is represented in Figure 1A.

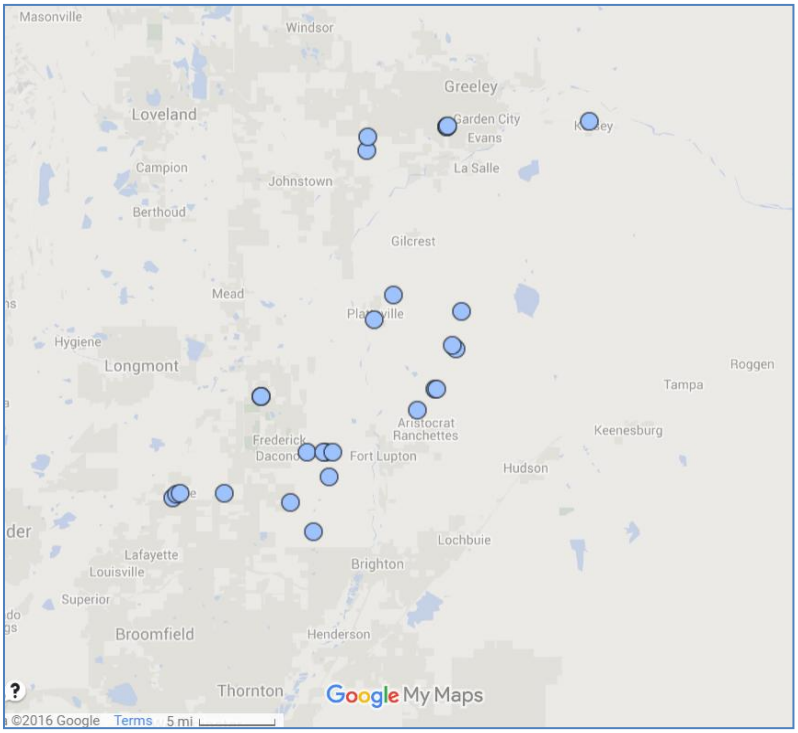
[2]Data provided courtesy of Drs Pfister (CU Boulder), Flocke (CU Boulder) and Crawford (NASA). Data were collected as part of the Front Range Air Pollution and Photochemistry Experiment (FRAPPE), Date received: April, 2016. DOI: 10.5067 https://www-air.larc.nasa.gov/cgi-bin/ArcView/discover-aq.co-2014?C130=1

				gas production"						
Garfield County	Garfield	Piceance	Battlement Mesa	Rural community close to oil and gas	NA	2010-2015	All	~3300	24 hours	Every 6 days on an annual basis
University of Colorado, Boulder[3]	Boulder	Denver-Julesburg	Dawson School	Collected to represent general ambient air in east Boulder with no specific distance from an oil and gas source	NA	2014	Summer	12	3 days	Every 6-10 days for 3 months
University of Colorado, Boulder	Boulder	Denver-Julesburg	Fire Station	Collected to represent general ambient air in east Boulder with no specific distance from an oil and gas source	NA	2014	Summer	12	3 days	Every 6-10 days for 3 months
University of Colorado, Boulder	Boulder	Denver-Julesburg	Stephen Day Park	Collected to represent general ambient air in east Boulder with no specific distance from an oil and gas source	NA	2014	Summer	12	3 days	Every 6-10 days for 3 months
University of Colorado, Boulder	Boulder	Denver-Julesburg	Church	Collected to represent general ambient air in east Boulder with no specific distance from an oil and gas source	NA	2014	Summer	12	3 days	Every 6-10 days for 3 months

[3] Unpublished data courtesy of Dr. Detlev at CU Boulder, Institute of Arctic and Alpine Research (INSTAAR), Date received: Feb 14, 2017.

Figure 1. Maps of sample collection sites

A. Denver-Julesburg Basin



B. Piceance Basin

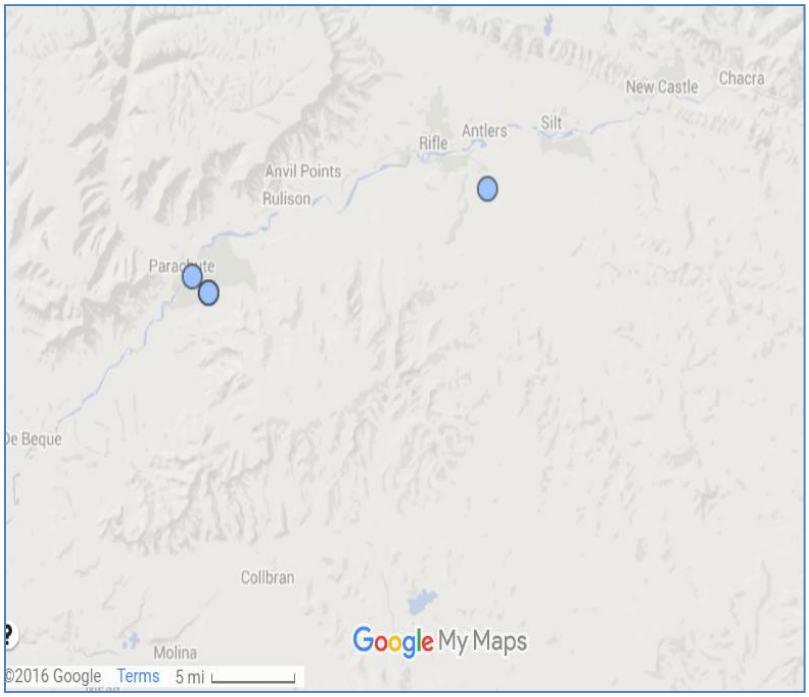


Table 2. Range of average and maximum values of substances across all datasets. The maximum value of the averages was used to represent long-term exposures. The maximum value across all datasets was used to represent the short-term exposure.

Substance	Range of Average Values (ppb)		Maximum Value (ppb)
1,2,3-Trimethylbenzene	0.004	0.035	1.470
1,2,4-Trimethylbenzene	0.018	0.190	2.900
1,3,5-Trimethylbenzene	0.006	0.054	0.244
1-Butene	0.013	0.912	5.920
1-Pentene	0.008	0.680	1.465
2,2,4-Trimethylpentane	0.008	0.711	3.381
2,3,4-Trimethylpentane	0.008	0.053	0.384
2,3-Dimethylpentane	0.031	0.315	1.256
2,4-Dimethylpentane	0.024	0.352	1.344
2-Butanone	0.213	33.100	290.000
2-Methylheptane	0.034	0.260	2.100
2-Methylhexane	0.212	5.000	29.400
2-Methylpentane	0.360	7.462	28.903
3-Methylheptane	0.024	0.179	1.180
3-Methylhexane	0.098	0.905	3.957
3-Methylpentane	0.245	3.986	15.179
Acetaldehyde	0.217	1.327	4.160
Acetone	0.622	2.999	6.702
Acrolein	ND*	ND*	ND*
Benzene	0.186	1.958	8.637
Butene (cis-2-)	0.008	0.232	1.520
Butene (trans-2-)	0.009	0.255	1.670
Cyclohexane	0.143	3.064	30.500
Cyclopentane	0.088	2.002	11.037
Dimethylcyclohexane(cis-13-)	0.027	0.027	0.100
Dimethylcyclohexane(trans-12-)	0.007	0.007	0.030
Dimethylcyclohexane(trans-13-)	0.004	0.004	0.010
Ethane	21.908	207.704	1061.752
Ethylbenzene	0.015	0.669	20.875
Ethylcyclohexane	0.014	0.014	0.050
Ethylene	0.434	11.249	75.000
Formaldehyde	0.511	2.227	8.310
Isobutane	2.100	32.933	172.100
Isopentane	0.016	30.220	139.157

Substance	Range of Average Values (ppb)	Maximum Value (ppb)	Substance
Isopropylbenzene	0.002	0.017	0.175
m-Diethylbenzene	0.004	0.047	0.238
Methane	1.870	3500.000	9127.500
Methanol	4.660	5.400	41.000
Methylcyclohexane	0.143	3.526	16.269
Methylcyclopentane	0.263	3.889	18.331
m-Ethyltoluene	0.010	0.087	2.155
m-Xylene	0.074	0.905	49.875
n-Butane	2.220	74.074	387.500
n-Decane	0.010	0.574	25.800
n-Heptane	0.150	3.360	15.798
n-Hexane	0.507	11.111	44.630
n-Nonane	0.019	5.828	14.868
n-Octane	0.052	0.895	3.732
n-Pentane	1.049	33.696	160.284
n-Propylbenzene	0.004	0.032	1.160
n-Undecane	0.013	0.767	39.800
o-Ethyltoluene	0.003	0.045	2.165
o-Xylene	0.023	0.212	16.500
p-Diethylbenzene	0.008	0.300	2.900
Pentene (cis-2-)	0.007	0.078	0.488
Pentene (trans-2-)	0.008	0.134	0.934
p-Ethyltoluene	0.005	0.056	2.225
Propane	5.210	151.686	723.333
Propylene	0.104	16.143	54.554
p-Xylene	0.074	0.905	49.875
Styrene	0.005	0.363	3.090
Toluene	0.190	5.489	21.000

*ND = no data

Appendix 1C

What are the health-based reference values ("safe" levels) for these substances of potential concern?

Health effects assessment

Methods

A consistent approach was used to identify existing cancer risk estimate values and non-cancer health-based reference values from national and state sources for exposure scenarios A (short-term exposures) and B (long-term exposures) (Table 1). These values are generally based on the most sensitive, chemical-induced health effect considered to be relevant to humans. For non-cancer health effects, the health-based reference value is the exposure level below which health effects are not expected to occur, even for potentially sensitive people in the general population (also referred to as a "safe" level in this report). For cancer causing substances, there are no "safe" levels of exposure.

- Short-Term Exposure Scenario: Short-term health-based reference values can be highly variable across agencies because of multiple factors, including the duration of exposure and type of health effects specific to the agency goals for derivation of these values. The lowest acute values across all sources that were relevant to the exposure scenario of interest for this assessment conservatively used (Table 2).

- Long-Term Exposure Scenario: Chronic values are generally consistent across agencies and represent continuous (24 hour/day), lifetime (70 years) exposure and were selected using a tiered approach. For carcinogenic substances, all inhalation unit risk (IUR) values were chosen from US EPA or California EPA (Table 2).

Table 1. Tiered approach for chronic, non-cancer health limit levels

TIER	SOURCE	DESCRIPTION
Tier I	U.S. Environmental Protection Agency	Acute Exposure Guideline Level (AEGL) Chronic: Reference Concentration (RfC) Cancer: Inhalation Unit Risk (IUR)
Tier II	Center for Disease Control - Agency For Toxic Substances and Disease Registry (ATSDR)	Acute & Chronic: Minimal Risk Level (MRL)
Tier III	U.S. Environmental Protection Agency	Subchronic & Chronic: Provisional Peer Reviewed Toxicity Value (PPRTV)
Tier IV	California EPA	Acute, Subacute and Chronic: Reference Exposure Level (REL)
Tier V	Texas Commission on Environmental Quality (TCEQ)	Short & Long-Term: Air Monitoring Comparison Value (AMCV)
Tier VI	European Chemicals Agency	Short & Long-Term: Derived No Effect

	(ECHA)	Level (DNEL)
Tier VII	Read-Across	Agency established or expert opinion surrogate values

Table 2. Acute and chronic health-based reference values for 62 substances of potential concern emitted from oil and gas operations

CAS #	NAME	Acute (ppb)	Chronic (ppb)	CAS #	NAME	Acute (ppb)	Chronic (ppb)
95-63-6	1,2,4-Trimethylbenzene	3000[1]	12[1]	*1678-91-7*	Ethylcyclohexane	4000[7]	400[7]
526-73-8	1,2,3-Trimethylbenzene	3000[1]	12[1]	*620-14-4*	m-Ethyltoluene	250[2]	25[2]
108-67-8	1,3,5-Trimethylbenzene	3000[1]	12[1]	*611-14-3*	o-Ethyltoluene	250[2]	25[2]
78-93-3	2-Butanone	20000[2]	1,695[1]	*622-96-8*	p-Ethyltoluene	250[2]	25[2]
565-59-3	2,3-Dimethylpentane	8300[7]	2200[7]	*100-41-4*	Formaldehyde	40[3]	8[3]
108-08-7	2,4-Dimethylpentane	8300[2]	2200[2]	*75-28-5*	Isobutane	33000[2]	10000[2]
591-76-4	2-Methylhexane	8300[2]	2200[2]	*78-78-4*	Isopentane	8100[2]	8000[2]
592-27-8	2-Methylheptane	4100[2]	380[2]	*98-82-8*	Isopropylbenzene	510[2]	81[1]
107-83-5	2-Methylpentane	990[2]	90[2]	*74-82-8*	Methane	NA	NA
540-84-1	2,2,4-Trimethylpentane	750[2]	75[2]	*67-56-1*	Methanol	270000[1]	15262[1]
565-75-3	2,3,4-Trimethylpentane	750[2]	75[2]	*108-87-2*	Methylcyclohexane	4000[2]	400[2]
96-14-0	3-Methylpentane	100[2]	100[2]	*96-37-7*	Methylcyclopentane	750[2]	75[2]
589-81-1	3-Methylheptane	4100[2]	380[2]	*106-97-8*	n-Butane	92000[2]	10000[2]
589-34-4	3-Methylhexane	8300[2]	2200[2]	*124-18-5*	n-Decane	1750[2]	175[2]
75-07-0	Acetaldehyde	250[2]	5[1]	*142-82-5*	n-Heptane	8300[2]	2200[2]
67-64-1	Acetone	26000[3]	13000[3]	*110-54-3*	n-Hexane	1700[2]	198[1]
107-02-8	Acrolein	3[3]	0 .01[1]	*111-84-2*	n-Nonane	3000[2]	38[5]
71-43-2	Benzene	180[2]	9.39[1]	*111-65-9*	n-Octane	4100[2]	75[2]
106-98-9	1-Butene	27000[2]	2300[2]	*109-66-0*	n-Pentane	68000[2]	8000[2]
590-19-1	2-Butene (cis)	15000[2]	700[2]	*103-65-1*	n-Propylbenzene	510[2]	203[5]
624-64-6	2-Butene (trans)	15000[2]	700[2]	*1120-21-4*	n-Undecane	550[2]	55[2]
110-82-7	Cyclohexane	1000[2]	1743[1]	*108-38-3*	m-Xylene	1700[3]	23[1]
287-92-3	Cyclopentane	5900[2]	120[2]	*95-47-6*	o-Xylene	1700[3]	23[1]
141-93-5	1,3-Diethylbenzene	460[2]	46[2]	*106-42-3*	p-Xylene	1700[3]	23[1]
105-05-5	1,4-Diethylbenzene	450[2]	46[2]	*109-67-1*	1-Pentene	12000[2]	560[2]
638-04-0	Dimethylcyclohexane (cis-13-)	4000[7]	400[7]	*627-20-3*	Pentene (cis-2-)	12000[2]	560[2]
6876-23-9	Dimethylcyclohexane(trans-12-)	4000[7]	400[7]	*646-04-8*	Pentene (trans-2-)	12000[2]	560[2]
591-21-9	Dimethylcyclohexane(trans-13-)	4000[7]	400[7]	*74-98-6*	Propane	68000[2]	8000[2]
74-84-0	Ethane	NA	NA	*115-07-1*	Propylene	NA	1743[6]
100-41-4	Ethylbenzene	20000[2]	230[1]	*100-42-5*	Styrene	200001	2351
74-85-1	Ethylene	500000[2]	5300[2]	*108-88-3*	Toluene	2000[3]	1327[1]

Sources: [1] EPA [2] TCEQ [3] ATSDR MRL [4] ECHA [5] EPA PPRTV [6] CalEPA [7] Read Across; NA = not applicable - substance is a simple asphyxiant at extremely high exposures with no other toxicological effects.

Uncertainties

- Uncertainties are inherent in the use of toxicity values, which can result in over- or under-estimation of risk. However, these values are generally derived in a way that is intentionally conservative; that is, risk estimates based on these values are more likely to overestimate risk. The general uncertainty for these values comes from a number of sources including uncertainties related to limited toxicity databases, use of animal studies to predict effects in humans, use of dose-response information from levels of exposure to predict adverse health effects at low levels of exposure, use of dose-response information from homogenous animal populations or healthy human populations to predict effects in a diverse general population with a wide range of sensitivities, and the use of models and upper-bound assumptions to estimate cancer risks.
- There is great variability in agency derived acute values mainly due to different exposure durations set by agencies (ie. 1 hour vs 14 day) and health effects used to derive the values. Although the most consistent exposure duration for selection of toxicity values was used, it was not always possible and therefore the most conservative value for the relevant duration of exposure was selected for this assessment.
- No health-based reference values for dimethylcyclohexane (3 isomers) and ethylcyclohexane and propylene were located. We used methylcyclohexane as surrogate for the four substances based on evidence for similar physical-chemical properties and degradation products that will likely result in similar health outcomes.

Appendix 1D

Risk characterization

Are the exposures to people living near oil and gas operations above or below health-based reference values ("safe" levels)?

Methods

Non-Cancer

A screening-level estimate of non-cancer health risks were conducted by comparing the exposure concentration (EC) to the toxicity screening level (SL) – called a Hazard Quotient (HQ) ratio. The cumulative (combined) health risk estimates for substances can be calculated with a Hazard Index (HI). The HI is simply the sum of all HQs. The HI was determined for all substances combined and then segregated by substances that produce similar organ toxicity (Ie. neurological, respiratory) (Table 1). Details of systematic methodology used for selection of these substances into health effect categories available upon request.

$$HQ = \frac{EC}{SL}$$

$$HI = HQ_1 + HQ_2 + HQ_3 \ldots$$

HQ = Hazard Quotient
HI = Hazard Index
EC = Exposure Concentration (mean or maximum ambient air concentrations)
SL = Toxicity Screening Level (varies by agency)

Two different sets of hazard quotients were calculated to represent the two exposure scenarios:

- The maximum air concentration of a substance representing an intermittent, infrequent exposure that could occur for a few hours to a few days was compared to short-term (acute) toxicity values
- The highest average air concentration for a substance across all datasets represents a conservative estimate of long-term, continuous exposures was compared to long-term (chronic) toxicity values

Cancer

To determine the magnitude of potential cancer risk, the exposure concentration of the substance in the air is multiplied by the inhalation unit risk (IUR) value of the substance. All IURs were taken from US EPA's established values.

$$\text{Cancer Risk Estimation} = [EC] \times IUR$$

[EC] = Exposure concentration (maximum average) measured in air
IUR = Inhalation Unit Risk Values

Table 1. Categorization of priority substances by potential to produce health effects in animals and/or humans

ENT		Respiratory		Neurological	
1,2,3-Trimethylbenzene	Acrolein	1,2,3-Trimethylbenzene	Acrolein	1,2,3-Trimethylbenzene	Acrolein
1,2,4-Trimethylbenzene	Benzene	1,2,4-Trimethylbenzene	Benzene	1,2,4-Trimethylbenzene	Benzene
1,2-Dimethylcyclohexane (trans)	Cyclohexane	1,2-Dimethylcyclohexane (trans)	Cyclohexane	1,2-Dimethylcyclohexane (trans)	Cyclohexane
1,3,5-Trimethylbenzene	Ethylbenzene	1,3,5-Trimethylbenzene	Ethanol	1,2-Dimethylcyclohexane (trans)	Ethanol
1,3-Diethylbenzene	Ethylcyclohexane	1,3-Dimethylcyclohexane (cis)	Ethylbenzene	1,3,5-Trimethylbenzene	Ethylbenzene
1,3-Dimethylcyclohexane (cis)	Formaldehyde	1,3-Dimethylcyclohexane (trans)	Ethylcyclohexane	1,3-Diethylbenzene	Ethylcyclohexane
1,3-Dimethylcyclohexane (trans)	Isopropylbenzene	1-Pentene	Formaldehyde	1,3-Dimethylcyclohexane (cis)	Ethylene
1,4-Diethylbenzene	Methanol	2,2,4-Trimethylpentane	Isopropylbenzene	1,3-Dimethylcyclohexane (cis)	Formaldehyde
1-Butene	Methylcyclohexane	2,3,4-Trimethylpentane	Methylcyclohexane	1,3-Dimethylcyclohexane (trans)	Isobutane
2,2,4-Trimethylpentane	Methylcyclopentane	2,3-Dimethylpentane	Methylcyclopentane	1,3-Dimethylcyclohexane (trans)	Isopropylbenzene
2,3,4-Trimethylpentane	m-Ethyltoluene	2,4-Dimethylpentane	m-Ethyltoluene	1,4-Diethylbenzene	Methanol
2,3-Dimethylpentane	m-Xylene	2-Butanone	m-Xylene	1-Pentene	Methylcyclohexane
2,4-Dimethylpentane	n-Heptane	2-Methylheptane	n-Heptane	2,2,4-Trimethylpentane	Methylcyclopentane
2-Butanone	n-Hexane	2-Methylhexane	n-Hexane	2,3,4-Trimethylpentane	m-Ethyltoluene
2-Butene (cis)	n-Nonane	2-Methylpentane	n-Octane	2,3-Dimethylpentane	m-Xylene
2-Butene (trans)	n-Octane	2-Pentene (cis)	o-Ethyltoluene	2,4-Dimethylpentane	n-Decane
2-Methylheptane	o-Ethyltoluene	2-Pentene (trans)	o-Xylene	2-Butanone	n-Heptane
2-Methylhexane	o-Xylene	3-Methylheptane	p-Ethyltoluene	2-Methylheptane	n-Hexane
2-Methylpentane	p-Ethyltoluene	3-Methylhexane	Propylbenzene	2-Methylhexane	n-nonane
3-Methylheptane	Propylbenzene	3-Methylpentane	Propylene	2-Methylpentane	n-Octane
3-Methylhexane	p-Xylene	Acetaldehyde	p-Xylene	2-Pentene (cis)	o-Ethyltoluene
3-Methylpentane	Styrene		Toluene	2-Pentene (trans)	o-Xylene
Acetaldehyde	Toluene			3-Methylheptane	p-Ethyltoluene
	Undecane			3-Methylhexane	Propylbenzene
				3-Methylpentane	p-Xylene
				Acetaldehyde	Toluene
				Acetone	Undecane
				Acetone	

Hematological	
1,2,3-Trimethylbenzene	Ethylene
1,2,4-Trimethylbenzene	Formaldehyde
1,3,5-Trimethylbenzene	m-Xylene
2-Butanone	o-Xylene
Acetaldehyde	p-Xylene
Benzene	

Developmental	
2-Butanone	Methanol
Acetone	m-Xylene
Acrolein	n-Hexane
Benzene	o-Xylene
Ethylbenzene	Propylbenzene
Formaldehyde	p-Xylene

Cardiovascular	
1-Pentene	Cyclopentane
2-Methylheptane	Isobutane
2-Pentene (cis)	m-Xylene
2-Pentene (trans)	o-Xylene
3-Methylheptane	p-Xylene
Acrolein	Toluene
Benzene	

Dermal	
1,3-Diethylbenzene	Acetaldehyde
1,4-Diethylbenzene	Benzene

Reproductive	
2-Butanone	m-Xylene
Acrolein	n-Hexane
Benzene	o-Xylene
Cyclohexane	p-Xylene

Immune	
Acetaldehyde	Ethylbenzene
Acrolein	Formaldehyde
Benzene	Toluene

Gastrointestinal	
Benzene	o-Xylene
m-Xylene	p-Xylene

Cancer	
1-Butene	Ethylbenzene
2-Butene (cis)	Formaldehyde
2-Butene (trans)	Methanol
2-Methylpentane	Methylcyclopentane
3-Methylpentane	m-Xylene
Acetaldehyde	n-hexane
Acrolein	o-Xylene
Benzene	p-Xylene
Ethanol	Undecane

Renal	
1,2-Dimethylcyclohexane (trans)	Ethylcyclohexane
1,3-Diethylbenzene	Isopropylbenzene
1,3-Dimethylcyclohexane (cis)	Methylcyclohexane
1,3-Dimethylcyclohexane (trans)	Methylcyclopentane
1,4-Diethylbenzene	m-Ethyltoluene
2,2,4-Trimethylpentane	m-Xylene
2,3,4-Trimethylpentane	n-Hexane
2-Butanone	n-Nonane
2-Methylpentane	n-Octane
3-Methylpentane	o-Ethyltoluene
Acetaldehyde	o-Xylene
Acetone	p-Ethyltoluene
Acrolein	Propylbenzene
Ethylbenzene	p-Xylene
	Toluene

Hepatic	
1,2,3-Trimethylbenzene	Ethylene
1,2,4-Trimethylbenzene	Isopropylbenzene
1,2-Dimethylcyclohexane (trans)	Methanol
1,3,5-Trimethylbenzene	Methylcyclohexane
1,3-Diethylbenzene	Methylcyclopentane
1,3-Dimethylcyclohexane (cis)	m-Ethyltoluene
1,3-Dimethylcyclohexane (trans)	m-Xylene
1,4-Diethylbenzene	o-Ethyltoluene
2-Butanone	o-Xylene
Acetaldehyde	p-Ethyltoluene
Cyclohexane	Propylbenzene
Ethanol	p-Xylene
Ethylbenzene	Toluene
Ethylcyclohexane	

Uncertainties

- In accordance with the U.S. EPA guidance, both carcinogenic and non-carcinogenic risks for multiple contaminants are assumed to be additive. This assumption is associated with several limitations, and could result in under- or over-estimation of risk. For example, the assumption of additivity of risk does not account for synergistic or antagonistic chemical interactions.

Appendix 2A

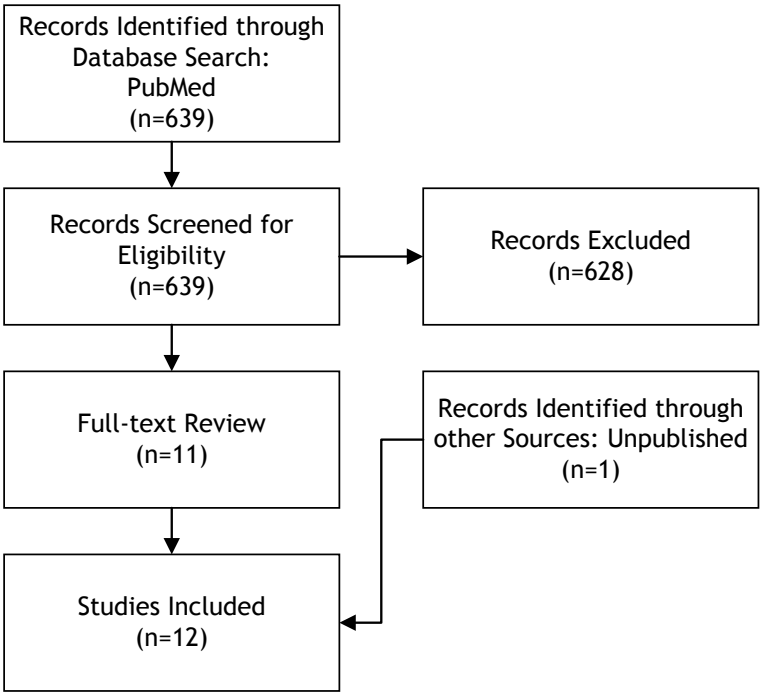
Systematic Review Methodology

Literature search

A thorough search was conducted with the objective of *identifying observational human health studies evaluating the potential health effects associated with living near oil and gas operations*. PubMed was the primary research database used to obtain articles. Review articles and risk assessments were screened for references to identify any additional original sources of data.

The following PubMed search term was used to identify relevant records: **(("Oil and Gas Industry"[Mesh] OR "Natural Gas"[Mesh]) AND (epidemiolog* or symptom*)) OR ((oil OR natural gas) AND (epidemiolog* OR health OR symptom*) AND (unconventional OR drilling OR shale OR coal OR production OR development) NOT ("Occupational Health"[Mesh] OR "Animal Experimentation"[Mesh]) AND ("2016/01/01"[Date - Publication] : "3000"[Date - Publication]))**

Figure 1. Systematic literature search process



Studies were excluded if one or more of the following criteria were met:

- Exposure to oil and gas chemicals was not measured in, or estimated for, the study subjects.
- Failed to quantify associations between exposures and a specific outcome (i.e., did not measure odds ratio values, relative risk).
- Did not include original data or observations (i.e., literature review, health impact or risk assessment).

- Did not define oil and gas operations to include all or any processes associated with the development and production of shale or coal-seam gas resources using conventional and unconventional methods (including hydraulic fracturing).
- Not representative of the United States regulatory and operational environment.
- Study population not representative of the general population in the United States.

Quality assessment

Each health outcome in a study was rated as high, medium, or low quality based on a modified GRADE system[11]. The GRADE system is a well-established framework for conducting a transparent and objective assessment of the quality of the literature as part of a systematic literature review. The findings were rated by individual health outcomes; therefore, it was possible for a single study to have multiple findings of differing quality. Observational studies and their findings start as "low" quality and are upgraded according to the strengths and limitations of the study. The body of evidence is downgraded or upgraded according to strengths and limitations in the broad areas of study design, study quality, consistency of findings and directness of effect.

The primary considerations for strengths and limitations in the above areas include:

- Population
    - Methods of selecting exposed and control groups.
    - Relevance of study population to the population of interest.
- Exposure characterization
    - Method for defining exposure.
    - Method for measuring exposure (self-report or other method).
    - Adequacy of exposure group size.
- Health outcome
    - Relevance of outcome studied to outcomes of interest.
    - Method for measurement of outcome (validated tools, etc.).
    - Adequacy of outcome group sizes.
    - Full vs. selective outcome reporting.
    - Effect size and width of confidence intervals.
    - Temporal and dose-response effect.
- Confounders
    - Adequate control for confounders (ie. smoking, education level, etc.).

[11] Balshem H et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011: 64(4):401-6

Study quality was defined as the following:

> **High-quality:** We are confident the true effect is close to that of the estimate of the effect outlined in the study. High quality findings originate from well-designed and well-controlled studies with few limitations. In the context of observational epidemiology studies, high quality does not necessary imply causation. High quality implies that an observed association persists between an exposure and effect in an appropriately-sized study population after adjusting for appropriate confounders.
>
> **Medium- quality**: We are moderately confident of the effect estimate outlined in the study. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Moderate-quality findings originate from studies that may be well-designed, but have significant limitations that affect the interpretation of the results. In the context of observational epidemiology studies, moderate quality implies the finding of an observed association with an interpretation that may be limited by a small study population or insufficient adjustment for important confounders.
>
> **Low-quality**: Our confidence in the effect estimate outlined in the study is limited. The true effect may be substantially different from the estimate of the effect. Low quality findings originate from studies with significant methodological limitations that affect the interpretation of the results. In the context of observational epidemiology studies, low quality implies the finding of an observed association with an interpretation that is significantly restricted by major study limitations.

Health outcome categories and level-of-evidence conclusions

For each health outcome, relevant findings from individual studies were grouped and evaluated to derive level-of-evidence statements based on the following criteria:

Substantial evidence refers to either:

A. Robust scientific findings that support the outcome with no credible opposing scientific evidence. This was defined as any of the following:
   - At least one high-quality positive finding, plus supporting findings at least one of which is medium-quality, with no opposing findings (must include studies of at least two cohorts).
   - At least three medium-quality positive findings from studies of at least two cohorts, with no opposing findings.
   - Many high- and medium-quality positive findings from studies of at least two cohorts that heavily outweigh opposing findings.

B. A robust body of scientific literature that has examined the outcome and failed to demonstrate a positive finding. This was defined as any of the following:
   - At least one high-quality study lacking a positive finding, plus at least one medium- quality supporting study, and no opposing findings (must include studies of at least two cohorts).
   - At least three medium-quality studies lacking a positive finding from studies of at least two cohorts, and no opposing findings.
   - Many high- and medium-quality studies lacking a positive finding that heavily outweigh opposing findings.

Moderate evidence refers to:

A. Strong scientific findings that support the outcome, but these findings have some limitations. This was defined as any of the following:
   - A single high-quality positive finding, with no opposing findings.
   - At least one medium quality positive finding, plus supporting findings with no opposing findings; supporting findings can include animal studies.
   - Many medium- and low-quality positive findings from studies of at least two cohorts that heavily outweigh opposing findings.

B. A strong body of scientific literature that has examined the outcome and failed to demonstrate a positive finding. This was defined as any of the following:
   - A single high-quality study lacking a positive finding, and no opposing findings
   - At least one medium-quality study lacking a positive finding, plus supporting findings, and no opposing findings.
   - Many medium and low-quality studies lacking positive findings from studies of at least two cohorts that heavily outweigh opposing findings.

Limited evidence refers to:

A. Modest scientific findings that support the outcome, but these findings have significant limitations. This was defined as any of the following:
   - A single medium-quality positive finding.
   - Two or more low-quality positive findings from studies of at least two cohorts.
   - Many low-quality positive findings from studies of at least two cohorts that outweigh opposing findings.

B. Modest scientific findings that have examined the outcome and failed to demonstrate a positive finding. This was defined as any of the following:
   - A single medium-quality study lacking a positive finding.
   - Two or more low-quality studies lacking positive findings from studies of at least two cohorts.
   - One low-quality study lacking a positive finding supported by animal studies.
   - Many low-quality studies lacking positive findings from studies of at least two cohorts that outweigh opposing findings.

Mixed evidence refers to:

Both supporting and opposing scientific findings for the outcome with neither direction dominating. This was defined as the following:
- Mixed findings, with neither direction dominating.

Insufficient evidence refers to:

The outcome has not been sufficiently studied. This was defined as any of the following:
- A single low-quality positive finding or less.
- We found no studies examining the outcome or relevant parameters.

Appendix 2B

Summary of Human Health Effect Studies

Author	Year	Title	Publication	State	Study Type	Population	Health Outcome	Quality Rating
McKenzie[9]	2014	Birth Outcomes and Maternal Residential Proximity to Natural Gas Development in Rural Colorado	Environmental Health Perspectives	Colorado	Retrospective cohort	Mothers living within various densities of a well site	Birth defects	*Low*
Hill[10]	2013	Unconventional Natural Gas Development and Infant Health: Evidence from Pennsylvania	Unpublished	Pennsylvania	Cross-sectional	Mothers living near a completed gas sites versus a future gas site	Birth outcomes	*Low*
Casey[11]	2016	Unconventional Natural Gas Development and Birth Outcomes in Pennsylvania, USA	Epidemiology	Pennsylvania	Retrospective cohort	Mothers living within various proximities of a gas development site	Birth outcomes	*Medium*
Stacy[12]	2015	Perinatal Outcomes and Unconventional Natural Gas Operations in Southwest Pennsylvania	PLOS ONE	Pennsylvania	Retrospective cohort	Mothers living within various densities of a well site	Birth outcomes	*Low*
Tustin[13]	2016	Associations between Unconventional Natural Gas Development and Nasal and Sinus, Migraine Headache, and Fatigue Symptoms in Pennsylvania	Environmental Health Perspectives	Pennsylvania	Cross-sectional	Survey of residents in Pennsylvania	Upper respiratory and neurological	*Low*
Rabinowitz[14]	2015	Proximity to Natural Gas Wells and Reported Health Status: Results of a Household Survey in Washington County, Pennsylvania	Environmental Health Perspectives	Pennsylvania	Cross-sectional	Survey of residents in Pennsylvania	Self reported symptoms	*Low*
Steinzor[15]	2013	Investigating Links Between Shale Gas Development and Health Impacts Through a Community Survey Project in Pennsylvania	New Solutions	Pennsylvania	Cross-sectional	Survey of residents in Pennsylvania	Self reported symptoms	*Low*
Rasmussen[16]	2016	Association Between Unconventional Natural Gas Development in the Marcellus Shale and Asthma Exacerbations	JAMA Intern Med.	Pennsylvania	Nested case-control	Asthma patients living within various metrics of oil and gas operation	Respiratory	*Medium*
Jemielita[17]	2015	Unconventional Gas and Oil Drilling is Associated with Increased Hospital Utilization Rates	PLOS ONE	Pennsylvania	Ecological	Patients in relation to active oil/gas wells	Hospitalization Rates	*Low*
Werner[18]	2016	All-age hospitalization rates in coal seam gas areas in Queensland, Australia, 1995-2011	BMC Public Health	Australia	Ecological	Coal seam gas population in Australia	Hospitalization Rates	*Low*
Fryzek[19]	2013	Childhood Cancer Incidence in Pennsylvania Counties in Relation to Living in Counties with Hydraulic Fracturing Sites	Journal of Environmental Medicine	Pennsylvania	Ecological	Children with cancer before and after oil/gas drilling	Childhood cancer	*Low*
McKenzie[20]	2017	Childhood Hematologic Cancer and Residential Proximity to Oil and Gas Development.	PLOS ONE	Colorado	Case-control	Children living within various densities of oil and gas	Childhood cancer	*Low*

Appendix 2C

Individual study evaluations

Health Effects Categories	Total number of studies	Health Effects	Number of studies per quality rating						Evidence
			No Association			Positive Association			
			Low	Med	High	Low	Med	High	
Birth defects	1	Congenital heart defects[9]				1			*Insufficient*
		Oral clefts[9]	*1*						*Insufficient*
		Neural tube defects[9]				*1*			*Insufficient*
Birth outcomes	4	Preterm birth[9,10,11,12]	*3*				*1*		*Mixed*
		Low APGAR[10,11]		*1*		*1*			*Mixed*
		Small for gestational age[10,11,12]		*1*		*2*			*Mixed*
		Birth weight[9,10,11,12]	*1*	*1*		*2*			*Mixed*
Eye, Nose & Throat and Respiratory	6	Multiple, self-reported symptoms[13,14,15]	*3*			*2*			*Mixed*
		Hospitalizations[17,18]	*2*						*Failing to show an association*
		Asthma exacerbation[16]					*1*		*Limited*
Skin (irritation, rashes)	2	Multiple,self-reported[14,15]				*2*			*Limited*
Neurological (migraines, dizziness)	5	Hospitalization rates[17,18]	*1*			*1*			*Mixed*
		Multiple, self-reported[14]	*1*						*Insufficient*
		Migraine/severe headache[13,14,15]	*2*			*1*			*Mixed*
Cancer	4	Overall childhood cancer incidence[19]	*1*						*Insufficient*
		Childhood Hematological Cancers[19,20]	*2*			*1*			*Mixed*
		Childhood CNS tumors[19]				*1*			*Insufficient*
		Hospitalization[17,18]	*1*			*1*			*Mixed*
Psychological (depression, sleep disturbances	4	Multiple, self-reported[13,14,15]	*3*						*Failing to show an association*
		Hospitalization[17]	*1*						*Insufficient*
Cardiovascular (heart)	2	Hospitalization rates[17]				*1*			*Insufficient*
		Multiple, self-reported[14]	*1*						*Insufficient*
Gastrointestinal nausea, stomach pain)	3	Hospitalization rates[17]	*1*						*Insufficient*
		Multiple, self-reported[14,15]	*2*						*Failing to show an association*
Musculoskeletal (joint pain, muscle aches)	2	Hospitalization rates[17]	*1*						*Insufficient*
		Multiple, self-reported[15]	*1*			*1*			*Mixed*
Blood	2	Hospitalization rates[17,18]	*1*			*1*			*Mixed*

REFERENCE NUMBER: 9	
McKenzie L *et al*. **Birth Outcomes and Maternal Residential Proximity to Natural Gas Development in Rural Colorado.**	
Quality: *Low-quality evidence based on the strengths and limitations*	
Findings: ✓ Positive association with **congenital heart defects** and **neural tube defects**. ✓ No associations with oral clefts, preterm birth, or reduced fetal growth.	
Strengths: • Exposure and outcome data obtained from valid sources • Exposure metric was weighted by well distance for every well within 10 miles of maternal residence and included 4 exposure groups • CHD, oral cleft, birth weight, preterm birth outcomes adjusted for maternal and infant covariates: maternal age, ethnicity, smoking, alcohol use, education, elevation, infant parity, sex and gestational age	Limitations: • Exposure metric did not account for phases and production levels • Assumes mother lived at same residence through entire pregnancy • Focused only on Caucasian births • Does not consider stillbirths • Indirect exposure measurement • Incorrect methodology for assessing cancer clusters • Did not adjust for other environmental covariates • Preterm birth continuous variable would have been better than dichotomous • Mean difference in birth weight of 24g may not be clinically significant • NTD adjustment does not include main covariates

REFERENCE NUMBER: 10	
Hill E. **Shale Gas Development and Infant Health: Evidence from Pennsylvania (working paper).**	
Quality: *Low-quality evidence based on the strengths and limitations*	
Findings: ✓ Positive associations with **lower birth weights, APGAR scores** and **small for gestational age** ✓ No associations with premature birth outcome	
Strengths: • Exposure and outcome data obtained from valid sources • Study population is large and representative of a general population • Adjusted for main confounders: Race, education, mothers age, smoking, WIC, insurance, marital status, gender	**Limitations:** • Incomplete vital statistic records are not considered • Measures of exposure are lacking and does not quantify multiple wells, well density, well activity, or phases of production • Indirect exposure measurement • Methodology overly complicated

REFERENCE NUMBER: 11	
Casey, J.A. *et al*. **Unconventional Natural Gas Development and Birth Outcomes in Pennsylvania, USA.**	
Quality: *Medium-quality evidence based on the strengths and limitations*	
Findings: ✓ Positive association with **preterm birth**. ✓ No associations with APGAR score, small for gestational age birth, or term birth weight.	
Strengths: • Study population is large and representative of a general population • Exposure and outcome data obtained from valid sources • Measure of exposure is cumulative estimate using inverse distance squared method including distance, duration, phases and production volume • Adjusted for clinical, demographic and environmental confounders: neonate sex, gestational age, season and year of birth, maternal age, race/ethnicity, PCP status, smoking status during pregnancy, pre-pregnancy body mass index, parity, antibiotic orders during pregnancy, receipt of medical assistance (socioeconomics), distance to major road, community socioeconomic deprivation, residential greenness • Dose-response evident for preterm birth	**Limitations:** • Assumes 2013 addresses were the same as during pregnancy • Dichotomous measure of preterm birth, without clear information on the actual number of weeks or days difference between groups • Significant findings for preterm birth were not seen in unadjusted analysis, only after adjustment • Indirect exposure measurement

REFERENCE NUMBER: 12	
Stacy SL *et al*. **Perinatal Outcomes and Unconventional Natural Gas Operations in Southwest Pennsylvania.**	
Quality: *Low-quality evidence based on the strengths and limitations*	
Findings: ✓ Positive association with **decreased birth weight** and **small for gestational age** ✓ No association with premature birth	
Strengths: • Exposure and outcome data obtained from valid sources • Only singleton births, with complete records • Population was limited to births with at least one well within 10 miles to eliminate possible unidentified confounders • Inverse distance weighted approach to quantify exposure • Each exposure group had over 3,000 subjects • Adjusted for main confounders: gender, mother's age, mother's education, pre-pregnancy weight, race, WIC, prenatal care, gestational diabetes, cigarette smoking during pregnancy, parity. • Birth weight evaluated as a continuous variable • Apparent dose response for small for gestational age	**Limitations:** • Population included only three counties (18% of total wells) • Incomplete exposure metrics did not account for phases, durations, production amounts • No adjustment done for exposure covariates • No control group in premature birth analysis • Indirect exposure measurement • Birth weight higher in second and third quartiles than referent group, and only lower in fourth quartile

REFERENCE NUMBER: 13	
Tustin AW *et al*. **Associations between Unconventional Natural Gas Development and Nasal and Sinus, Migraine Headache, and Fatigue Symptoms in Pennsylvania.**	
Quality: Low-quality evidence based on the strengths and limitations	
Findings: ✓ No associations with **CRS**, **fatigue** and **migraine** when evaluated individually.	
Strengths: • Study population is large and representative of a general population • Exposure data obtained from valid source • Exposure metrics estimate distance, number of wells, duration of phases, depth and volume of gas produced (surrogate for chemical volumes and truck traffic) • Adjusted for main confounders: sex, race/ethnicity, age, medical assistance, smoking status, BMI, CSD • Measurements of migraine and CRS defined outcome • Low likelihood of bias demonstrated by comparison of responders vs. non responders	**Limitations**: • Self reported health outcomes • Individual outcomes were non-significant making the importance of the findings for two or more outcomes unclear • Prorated fatigue analysis methods may magnify response bias • Low response rate (33%) • Significant findings confidence intervals were close to null • For 6 of the 7 outcomes, the third quartile has lower odds ratios than reference group (lack of dose response) • Indirect exposure measurement

REFERENCE NUMBER: 14	
Rabinowitz PM *et al*. **Proximity to Natural Gas Wells and Reported Health Status: Results of a Household Survey in Washington County, Pennsylvania.**	
Quality: *Low quality evidence based on the strengths and limitations*	
Findings: ✓ Positive associations with **self reported skin conditions** and **upper respiratory symptoms** ✓ No associations seen with lower respiratory, cardiac, gastrointestinal, or neurologic self reported symptoms	
Strengths: • Hypothesis-generating survey study with random selection • Study population is large • Adjusts for main confounders: age, sex, smokers in household, presence of animals, education level, work type, awareness of environmental risk • Exposure data obtained from valid source	Limitations: • Measure of exposure does not include phases of operation or well density • Indirect exposure measurement • Measures self-reported symptoms with unblended exposure

REFERENCE NUMBER: 15	
Steinzor N *et al*. **Investigating Links Between Shale Gas Development and Health Impacts Through a Community Survey Project in Pennsylvania.**	
Quality: *Low-quality evidence based on the strengths and limitations*	
Findings: ✓ Positive associations with **self reported upper and lower respiratory, dermal, musculoskeletal, neurological and psychological self-reported symptoms** (throat irritation, sinus problems, nasal irritation, eye burning, severe headache, skin rashes, loss of sense of smell, persistent cough, frequent nose bleeds, swollen painful joints) ✓ No associations seen with lower respiratory, neurological, gastrointestinal, musculoskeletal, psychological self-reported symptoms (joint pain, shortness of breath, sleep disorders, forgetfulness, feeling weak and tired, increased fatigue, lumbar pain, muscle aches, diarrhea)	
Strengths: • Hypothesis generating health symptom survey	**Limitations**: • Population is not generalizable to a broader population • Exposure does not include control group • Self reported measures of exposure and outcomes • Unclear methodology • No standardization or metrics of symptoms • No confounding variables used in analysis

REFERENCE NUMBER: 16	
Rasmussen SG *et al*. **Associations Between Unconventional Natural Gas Development in the Marcellus Shale and Asthma Exacerbations.**	
Quality: *Medium quality evidence based on the strengths and limitations*	
Findings: ✓ Positive associations with **asthma exacerbations**	
Strengths: • Nested case-control study • Study population is large and representative of a general population • Exposure and outcome data obtained from valid sources • Measure of exposure is comprehensive and includes estimated activity metrics for 4 different phases using density/proximity (inverse distance squared method), well characteristics, and dates/durations of phases, total depth and volume metrics (surrogates for truck traffic and fugitive emissions/ compressor engine activity) • Adjusted for time-varying covariates (age, season, smoking status, overweight/obesity status, medical assistance, type-2 diabetes) and non-time-varying covariates (sex, race/ethnicity)	**Limitations:** • Only patients most recent address were used • Only events that occurred at Geisinger facilities are represented • Indirect exposure measurement

REFERENCE NUMBER: 17	
Jemielita T *et al*. **Unconventional Gas and Oil Drilling is Associated with Increased Hospital Utilization Rates.**	
Quality: *Low-quality evidence based on the strengths and limitations*	
Findings: ✓ Positive associations with **cardiology** and **neurology** inpatient hospitalization rates. ✓ No associations with oncology, dermatology and urology.	
Strengths: • Study population is large, distributed and representative of a typical population by zip code • Exposure and outcome data obtained from valid sources • Exposure metric included well density • A dose response is evident for cardiology inpatient prevalence	**Limitations:** • Ecological study at ZIP code level • Neurology outcome only significantly associated with wells per km^2 and not wells per zip code • Measures of exposures are lacking • Well density (number of wells per km2) is at a ZIP code level and may not accurately reflect individual exposure • No specific confounders were evaluated (relied on poisson regression to correct for possible confounders) • Health outcomes were only at a broad category level and specific health effects in the various medical categories were not identified

REFERENCE NUMBER: 18	
Werner AK *et al*. All-age hospitalization rates in coal seam gas areas in Queensland, Australia, 1995-2011.	
Quality: *Low quality evidence based on the strengths and limitations*	
Findings: ✓ Positive associations with **neoplasms** and **blood/immune** hospitalization rates ✓ No associations seen with nervous system and eye hospitalization rates	
Strengths: • Study population is large, distributed and representative of three areas of Queensland, Australia • Outcome data obtained from valid sources • Adjusted for age, sex, proportion indigenous, proportion Australian-born, proportion employed full-time, proportion white collar, median household income, mean household size	**Limitations:** • Ecological study • Measures of exposure is limited to area with/without coal seam gas • Confidence intervals are close to null with no adjustment for multiple comparisons • Associations are seen only when compared to rural reference population • Neoplasm hospitalizations can include either cancerous or non-cancerous effects and cannot conclusively be linked to a cancer outcome

REFERENCE NUMBER: 19	
Fryzek J, *et al*. **Childhood cancer incidence in Pennsylvania counties in relation to living in counties with hydraulic fracturing sites.**	
Quality: *Low quality evidence based on the strengths and limitations*	
Findings: ✓ Positive association **CNS tumor** incidences. ✓ No association with all childhood cancers and childhood leukemia.	
Strengths: • Study population is large and representative of a general population at a county level • Exposure and outcome data obtained from valid sources • Adjusted for age, sex and race	**Limitations:** • Ecological study at a county level • CNS tumors significant finding is only seen in counties with the fewest number of wells • Subjects are divided relative to first well drilled per county (before or after drilling) • Despite an estimated CNS tumor SIR of 1.13, the 95% confidence interval is close to null (1.02) • Does not consider exposure covariates • Indirect exposure measurement

REFERENCE NUMBER: 20	
McKenzie LM, *et al*. **Childhood Hematologic Cancer and Residential Proximity to Oil and Gas Development.**	
Quality: *Low quality evidence based on the strengths and limitations*	
Findings: ✓ Positive association **childhood acute lymphocytic leukemia**. ✓ No association with non-Hodgkin's lymphoma.	
Strengths: • Exposure and outcome data obtained from valid sources • Exposure metric used inverse distance weighted method and included a latency period • Adjusted for main confounders: age, race, gender, elevation , socio-economic status, year of diagnosis	**Limitations:** • Indirect exposure measurement for cases and controls • Limited number of cases (ALL n=15) • Did not account for resident mobility or full address history during exposure time period • Reported analysis did not include an adjustment for maternal smoking and specific results that did include smoking were not provided • High percentage excluded (27%) due to missing address or lat/long • Despite an estimated ALL odds ratio of 4.3, the 95% confidence interval is close to null (1.1) • Age 20-24 introduces different measures of exposure in grouped analysis • Did not evaluate overall hematological cancers including acute myeloid leukemia, which is more closely associated with the chemicals of concern as specified in this study