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Potential hazards of air pollutant emissions from unconventional oil and natural gas operations on the respiratory health of children and infants

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Abstract: Research on air pollutant emissions associated with unconventional oil and gas (UOG) development has grown significantly in recent years. Empirical investigations have focused on the identification and measurement of oil and gas air pollutants [e.g. volatile organic compounds (VOCs), particulate matter (PM), methane] and the influence of UOG on local and regional ambient air quality (e.g. tropospheric ozone). While more studies to better characterize spatial and temporal trends in exposure among children and newborns near UOG sites are needed, existing research suggests that exposure to air pollutants emitted during lifecycle operations can potentially lead to adverse respiratory outcomes in this population. Children are known to be at a greater risk from exposure to air pollutants, which can impair lung function and neurodevelopment, or exacerbate existing conditions, such as asthma, because the respiratory system is particularly vulnerable during development *in utero*, the postnatal period, and early childhood. In this article, we review the literature relevant to respiratory risks of UOG on infants and children. Existing epidemiology studies document the impact of air pollutant exposure on children in other contexts and suggest impacts near UOG. Research is sparse on long-term health risks

associated with frequent acute exposures – especially in children – hence our interpretation of these findings may be conservative. Many data gaps remain, but existing data support precautionary measures to protect the health of infants and children.

Keywords: benzene; formaldehyde; ozone; particulate matter; silica dust; UOG.

Introduction

Hydraulic fracturing (fracking) and other technological advances have enabled the extraction of fossil fuels from previously inaccessible geological formations (e.g. shale), leading to the rapid and extensive spread of unconventional oil and gas (UOG) development in the United States since the mid-to-late 2000s. UOG technologies and practices are now also being considered in a growing number of countries outside of North America. As the shale oil and gas boom continues, policymakers, citizens, and scientists around the world have started to pay more attention to the potential public health impacts of this emerging industry.

The scientific literature on environmental and public health impacts associated with UOG development has grown significantly in recent years. While the rapid growth of this industry was undertaken without substantial public health research, there are now numerous publications clarifying health risks and, increasingly, health outcomes. At the time of this review, there are nearly 700 peer-reviewed publications that assess various environmental and societal impacts of UOG, and of these, more than 80% have been published since the beginning of 2013. In particular, there has been a wave of research on air pollution in areas with high levels of oil and gas activity, such as Texas, Colorado, and Pennsylvania. These investigations have focused mostly on the identification and measurement of air pollutant emissions as well as the influence of UOG on local and regional ambient air quality. Hazardous air pollutants (HAPs) such as

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ground-level ozone precursors (e.g. nitrogen oxides or NO_x), particulate matter (PM), silica, aromatic hydrocarbons, and volatile organic compounds (VOCs), are emitted throughout the lifecycle of UOG development, including well pad construction, drilling, completion, production, midstream processing, storage, and transport. The respiratory health impacts of these pollutants are well known and documented in the scientific literature.

Concurrently, there is interest in the potential impacts of UOG activities on vulnerable populations, such as children and newborns (1–4). A large body of research suggests that children are at a greater risk from exposure to environmental pollution due to various biological and behavioral factors (5–8). A significant number of epidemiological studies have examined health outcomes in children and newborns from exposure to various air pollutants. Some of these pollutants, including ozone, PM, silica dust, benzene, and formaldehyde are associated with UOG activities.

This review considers the potential impacts of air pollution from UOG operations on the respiratory health of children and newborns. We add to the growing body of scientific literature by reviewing recent studies on UOG air pollution as well as the respiratory health outcomes associated with five specific air pollutants associated with UOG development: tropospheric ozone, PM, silica dust, benzene, and formaldehyde. The primary purpose of this review is to highlight how certain vulnerable populations (children and newborns) may suffer disproportionately from health risks from exposure to air pollutant emissions from UOG development. Our intention is to highlight many of the unknown exposure risks and the need for more stringent control of health-protective measures based on the evidence to date about the risks of air pollution to children's respiratory health. In this review, we also identify future research needs and make general policy recommendations in light of the identified hazards and risks to these populations.

Methods

For this review, we focused on the scientific literature relevant to the potential respiratory health impacts of UOG emissions on children and newborns. This required reviewing four different types of research, including studies of 1) UOG air emissions and atmospheric concentrations; 2) the potential respiratory health impacts of air pollutants (ozone, PM, silica dust, benzene, and formaldehyde); 3) health outcomes from childhood exposure to air pollution; and 4) health outcomes associated with UOG. We synthesized the information in a narrative form and did not include a formal quality assessment of

the literature. Additionally, although we primarily focused on infant studies, we also referred to some adult studies when appropriate to understand potential implications for infants and children.

This review is not intended to provide a formal risk assessment that would characterize the exposure levels among children to our pollutants of concern. At present, there is not enough data to understand how much UOG emissions contribute to exposure levels among populations. Instead, we review studies that measure UOG air emissions and atmospheric concentrations of our five pollutants of concern. When provided by the literature, we also note if concentrations exceed relevant air quality standards or guidelines. Our methods are intended to help identify exposure pathways, potential health risks, and to promote research to measure the likelihood and extent of childhood exposure to various air pollutants associated with UOG development.

This review drew from the peer-reviewed scientific literature with a few exceptions. For instance, we cited toxicological data for various air pollutants from several government sources, including the Agency for Toxic Substances and Disease Registry (ATSDR) and the United States Environmental Protection Agency (US EPA). Other government reports were cited where appropriate.

Of note, the term UOG is used in many contexts and may refer to a number of modern oil and gas development techniques, some of which are beyond the scope of this review. UOG generally refers to oil and natural gas produced from atypical reservoir types. UOG development is a broad and complex term. We limited our review to research pertaining to onshore oil and gas development from shale and tight formations (i.e. low permeability) and did not include studies of coalbed methane, oil sands, or offshore oil and gas development. Some of the common technological features of these types of oil and gas development include high volume hydraulic fracturing and directional wells. Hydraulic fracturing is defined as a well stimulation technique where highly pressurized fluid consisting of water, sand, and chemicals is injected into a wellbore to open cracks in low permeability rock formations in order to mobilize oil or natural gas. Higher volumes of fluid are used in the type of hydraulic fracturing employed for shale oil and gas development. Directional wells are defined as those that deviate from the original vertical wellbore at a high angle to target a specific location (e.g. vertically and then laterally into a shale formation) (9).

In our discussion of the health impacts of air pollution, we focused on five particular air pollutants of concern: ozone, PM, silica dust, benzene, and formaldehyde. These five pollutants have received considerable attention in the oil and gas air quality literature. There are numerous studies on atmospheric concentrations of ozone in areas of highly concentrated oil and gas development, such as Wyoming, Utah, Texas, and Colorado (10–14). The Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) have studied respirable crystalline silica in the context of worker safety and hydraulic fracturing operations (15). Numerous studies have measured quantities and types of VOC emissions, and benzene and formaldehyde have often been a particular concern, in part because of their carcinogenic effects on humans and animals. PM is also commonly associated with UOG operations due to diesel emissions from truck traffic and onsite equipment (e.g. generators, pumps, etc.) (16). The potential health outcomes of the five air pollutants included in this review are well known and have been studied in a variety of other contexts (Table 1).

This review employed several search methods, including keyword searches in three science databases (PubMed, Web of Science,

Table 1: Summary of respiratory health effects associated with pollutants of concern,^d and the studies in which the health effect was reported.

| Pollutant | Associated respiratory health outcome | Range of emissions |
|---------------------------------------|--|--|
| Ozone | Systemic, respiratory tract, and lung inflammation (17–19) Reduced lung function as measured by FEV1 (20, 21) Increased susceptibility to infection and decreased immunity (22) Asthma (23) | 67–107 ppbv ^b (24) 57–160 ppbv ^c (12) |
| Particulate matter (2.5 and 10 µm) | Reduced lung function as measured by FEV1 (25) Lung injury via oxidative stress (26) Pulmonary and systemic inflammation (27, 28) Asthma via oxidative stress and inflammation (29) | N/A |
| Benzene | Increased coughing and wheezing (30–32) Asthma (33) Reduced lung function as measured by FEV1 (34, 35) Bronchitis and pulmonary infections (36, 37) | 0–62.7 ppbv (38) 0.3–1.1 ppbv (39) 1–4.9 ppbv ^a (13) 0.075–1.6 ppbv (40) |
| Formaldehyde | Chest discomfort, difficulty breathing, and wheezing (41) Acute respiratory tract illness (42) Reduced pulmonary function (43) Asthma (44–46) | 0–49.6 ppbv (38) 0.3–2.4 ppbv (39) |

This table also summarizes the range of emissions for each pollutant. Studies with an ^a indicate ranges corresponding to a 25th–75th quartile range. Studies with a ^b indicate a range increase in daily max 8-h average concentrations for a 6-day period. Studies with a ^c correspond to a 6-day period between February 28 and March 5, 2011. ^dSilica dust was not included in Table 1 due to limited peer-reviewed literature concerning respiratory effects in children. ppbv, parts per billion by volume.

and ScienceDirect) and in existing collections of scientific literature on this subject, including the PSE Healthy Energy Citation Database on Shale and Tight Gas Development as well as the Marcellus Shale Initiative Publications Database at Bucknell University. Additionally, we complemented our search using the NYU Ehrman Medical Library database and Google Scholar, as well as manual searches of the references included in many of the studies identified.

Results

Sources of air pollution from UOG

UOG operations emit air pollutants linked to adverse respiratory effects throughout their lifecycle (16, 47). Sources of air pollution include emissions from the extraction and processing of natural gas, as well as the transportation via natural gas infrastructure components including compressor stations and pipelines (48–50). Pollutants can be emitted during venting, flaring, production, and leaks from faulty casings (51). In addition, truck transportation of materials to and from well pads and vehicular equipment use during construction and maintenance generate air pollution from particulate matter and diesel exhaust. These processes release numerous contaminants into the air, resulting in elevated concentrations of polycyclic aromatic hydrocarbons (PAHs), methane, ozone, NO_x, and VOCs like benzene, formaldehyde, alkenes, alkanes,

aromatic compounds, and aldehydes (10, 13, 38, 52–58). Many of these pollutant groups have been recognized by the ATSDR, Centers for Disease Control (CDC), EPA, OSHA, and National Institutes of Health (NIH) as hazardous respiratory pollutants.

Health effects of air pollution and childhood vulnerability

Air pollution can cause a range of reactions in the human body, from acute to chronic effects (59). A number of health impacts can result, including respiratory irritation, heart disease, lung disease, and increased susceptibility to acute and chronic infections (59).

The developing respiratory system is vulnerable to air pollution for a number of reasons. First, children's respiratory systems are growing. At the time of birth, the human lung has about 24 million alveoli (60), which represents a fraction of the remaining alveoli needed to develop to allow for a completely functioning respiratory system. It has been estimated that approximately 80% of the alveoli are developed postnatally and continue to develop throughout adolescence (61). The first years of life are considered to be an especially vulnerable period of time (62). From birth to age four, the alveolar count in the human lungs is estimated to increase from roughly 24 million to 257 million (60).

Second, due to their smaller size, children's developing respiratory systems are more exposed to air pollution. Children have a larger lung surface area per kilogram body weight ratio than adults (60). Third, they have narrower airways, which also contributes to their increased susceptibility to irritation by air pollution (63). Fourth, children are shorter and thus inhale a greater concentration of particulate air pollutants and dust (63). Fifth, children have an increased resting respiratory rate compared to adults. Finally, children spend more time outdoors where the concentrations of some air pollutants are highest; and active outdoor play increases ventilation rates, thus increasing exposure to air pollutants relative to adults (60, 64).

Tropospheric ozone

Exposure standards and ozone levels near UOG sites

During the hydraulic fracturing process, diesel-powered trucks haul millions of gallons of water, chemicals, and tons of silica sand to and from the well sites (24, 65, 66). Diesel engines release exhaust containing NOx and VOCs (13, 24). The use of diesel-powered trucks, then, becomes

important because tropospheric or ground level ozone forms when NOx react with VOCs in the presence of sunlight (13, 24). Moreover, the release of NOx and VOCs also occurs with the use of diesel-powered equipment during site preparation, drilling, extraction, transportation via pipelines, at compressor stations (24, 65, 66).

The federal government sets standards, like the National Ambient Air Quality Standards (NAAQS) for criteria pollutants based on levels estimated to pose a health risk. These standards are intended to protect public health. A number of field studies and air quality models have reported ozone levels exceeding the NAAQS of 75 ppb (10, 12–14). For example, Schnell et al. (10) assessed winter-time air quality near a gas field in the Upper Green River Basin, Wyoming (UGRB), and found 8-h ozone average concentrations exceeding 120 ppb. Oltmans et al. (12) also reported winter-time ozone 8-h average concentrations up to 120 ppb. Because high ozone production is considered an urban summer-time phenomenon, the levels reported in these field studies throughout several winters is highly uncharacteristic (12, 13). These winter-time ozone events are likely occurring near other sites with similar topography (12, 13).

Reference exposure levels (RELs) are guidelines and are intended to describe concentrations to which one can

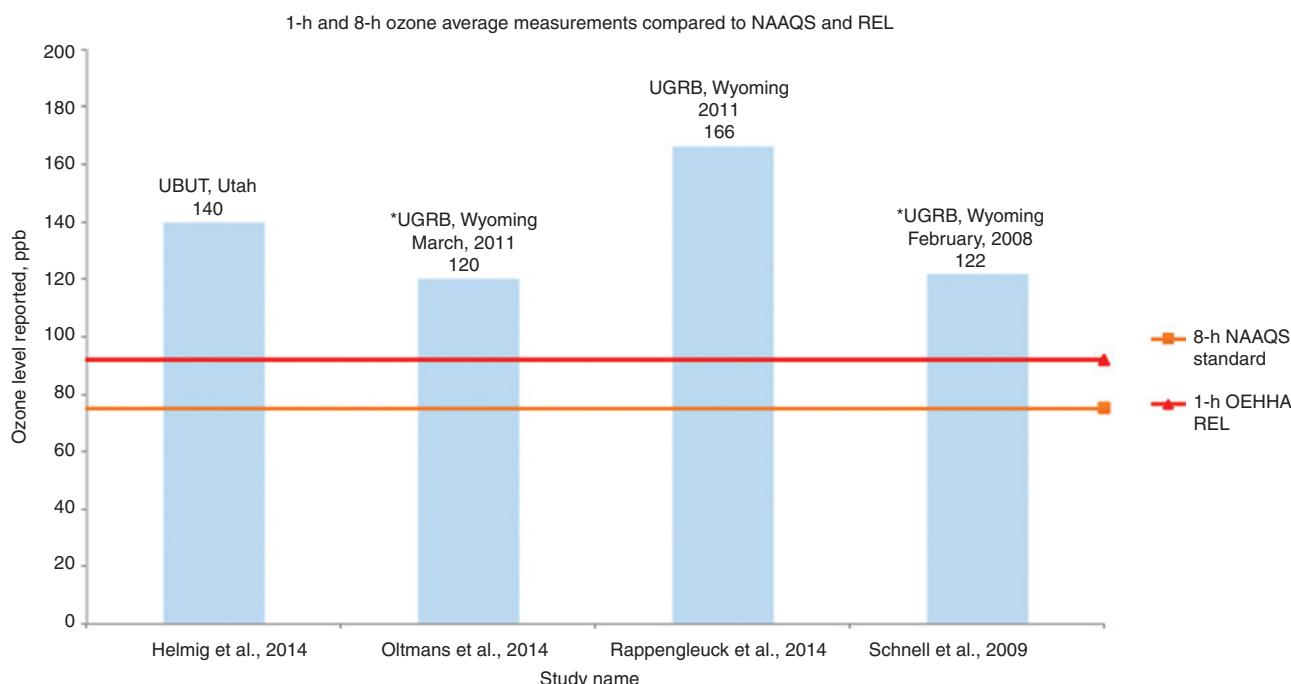


Figure 1: Field study measurements for ozone near UOG development sites.

Locations with * indicate an 8-h average. The red line indicates Office of Environmental Health Hazard Assessment (OEHHA) Acute (1-h) REL. Critical effects above this level include (1) eye irritation and (2) minor changes in lung function tests. The orange line indicates 8-h National Ambient Air Quality Standard (NAAQS) for ozone.

be exposed for an hour without developing adverse health outcomes (Figure 1). Two studies have reported 1-h average ozone concentrations above the California's Office of Environmental Health Hazards Assessment's (OEHHA) acute inhalation REL (13, 14). Modeling studies in the Haynesville and Barnett Shales have also reported increased NO_x and ozone levels in UOG regions (11, 67), and increases have been measured in active production areas in New Mexico (47). In Wyoming and Utah, local ozone emissions resulted from oil and gas production (12).

Acute respiratory symptoms (shortness of breath, wheezing and cough), airway inflammation and pulmonary function

Several studies have focused on the impact of ozone on the respiratory system of infants (68). Changes in respiratory epithelium and hyper-responsiveness due to ozone exposure has been reported (17). Studies have also shown that breathing ozone can lead to the initiation of systemic inflammatory processes (18) and respiratory tract and lung inflammation (19). Although the newly proposed NAAQS for ozone is set to be lowered to 0.70 ppm (70 ppb) in 2017 [currently, it is 0.75 ppm (75 ppb)], exposure concentrations as low as 0.08 ppm (8 ppb) have been reported to result in significant increases in inflammatory markers (i.e. neutrophils, prostaglandins, and inflammatory proteins) (19).

Other studies have implicated ozone exposure during childhood with reductions in lung function. Forced expiratory volume (FEV1) and peak expiratory flow (PEF) have been used to assess the effects on lung mechanics from exposure to ambient ozone and can be used as markers for reduced lung function. Kinney et al. (20) determined that children exposed to ambient ozone experienced decreases in FEV1. A number of other studies have also reported an association between ambient ozone and decreases in lung function particularly in children and adolescents (20, 21, 69).

Immune response and infections

In addition to causing changes to the respiratory system, ozone is believed to affect immune response leading to more lung infections. Studies have reported an association between ozone and an increase in susceptibility to Influenza A infection due to alteration of the pulmonary protease function (22). Specifically, ozone appears to be able to injure the respiratory system and airway epithelial cells resulting in reduced microbial clearance and increasing susceptibility to infection (70, 71). Studies of adults

65 years and older demonstrate an increase in hospitalizations due to pneumonia and exacerbations of chronic obstructive pulmonary disease when environmental ozone levels increase (72); data in children is currently lacking.

Asthma

Some evidence from studies suggests that ozone is implicated in the induction of asthma in children (23). As part of the Children's Health Study (CHS) study, McConnell and colleagues followed 3535 children (9–16 years old) with no previous diagnosis of asthma at baseline from 1993 to 1996 in 12 communities across California and reported that where levels of ambient ozone were in the "maximum" range there were 259 newly reported cases of asthma (23). Other studies have shown that chronic exposure to ozone can cause an increase in respiratory symptoms and exacerbation of pre-existing asthma (73–75). Ground-level ozone concentrations tend to be the highest on warm and sunny days. It is also during these times that children are more likely to be outdoors playing (60).

An association between ozone exposure and hospitalizations for adverse respiratory health effects has been reported (76), particularly for an increase in emergency department (ED) visits and hospitalizations due to asthma (77–81). The Study of Particles and Health in Atlanta (SOPHIA), which was conducted during the time period between 1993 and 2004 in metropolitan Atlanta, Georgia, evaluated more than 90,000 pediatric ED visits for asthma in relation to air pollution (including ozone). After controlling for confounders, ozone was associated with ED visits for asthma during both warm and cold months of the year (80).

School absenteeism

In addition to ED visits and hospitalizations, a significant relationship between high ambient ozone and an increase in school absenteeism has been reported (82). Gilliland et al. (82) investigated the relationship between ozone and school absenteeism in a cohort of fourth grade schoolchildren who lived in 12 communities across southern California. An increase in ozone concentration of 20 ppb was found to be associated with an increase by 62.9% (95% CI, 18.4%–124.1%) in rates for absence due to illness, 82.9% (95% CI, 3.9%–222.0%) for respiratory illnesses, 45.1% (95% CI, 21.3%–73.7%) for upper respiratory illnesses, and 173.9% (95% CI, 91.3%–292.3%) for lower respiratory illnesses and cough in children 9 and 10 years old.

Particulate matter

Exposure standards and PM levels near UOG sites

Ambient particle pollution including PM10 and PM2.5, is commonly released into the surrounding air during UOG operations, especially where there are diesel emissions (16). PM2.5 in particular poses a significant health concern and interacts with airborne VOCs, thus increasing their impact (83). To our knowledge, there is little available field study data about PM levels near UOG sites and further research is needed.

Acute respiratory symptoms (shortness of breath, wheezing and cough), airway inflammation and pulmonary function

PM is a complex mixture of small particle solids, droplets, dust particles, heavy metals, radioactive materials, and/or other organic chemicals that have become suspended in the air and are small enough to be inhaled (27, 59). The most health-damaging particles are those with an aerodynamic diameter of 10 µm or less, (\leq PM¹⁰), because they can penetrate and lodge deep inside the lungs (84). Particles with an aerodynamic diameter of 2.5–10 µm are considered coarse; those with a diameter smaller than or equal to 2.5 µm are considered fine particles. It is important to consider particle size because health impacts are influenced by this factor. For example, particle size determines where particles are deposited in the lung. Coarse particles (2.5–10 µm) are usually deposited in the upper respiratory tract and large airways; fine particles (<2.5 µm) may reach terminal bronchioles and alveoli. Moreover, compared to large particles, fine particles can remain suspended in the atmosphere for longer periods and be transported over longer distances (8).

PM affects more people than any other pollutant and contributes substantially to negative impacts, including respiratory and cardiovascular disease and premature mortality (85). Children are a particularly affected subgroup, especially when they are physically active, as breathing faster increases the particle intake. In addition, children's lungs are still developing, and, they are more likely to get respiratory inflammation and infections infections. These conditions are exacerbated when environmental PM concentrations are high (86).

Particulate pollution is linked to a variety of health effects including onset and exacerbation of asthma (87), irritation of airways, coughing, wheezing, chest tightness, and shortness of breath (88). High concentrations of

particulates are of concern because they absorb airborne chemicals which deposit in the lungs and can lead to local or systemic diseases (83).

The International Agency for Research on Cancer (IARC) has recently classified the particulate matter component of outdoor air pollution as a class I carcinogen. Considering the 10–20 year latency period for cancer, it is reasonable to say that childhood exposure to PM plays a role in the later development of cancer (89, 90).

Particulate pollution affects respiratory health, lung development, and lung function in children (as measured by FEV1=forced expiratory volume in 1 second and PEF=peak expiratory flow) (25, 91, 92). As part of CHS, Gauderman et al. (25) studied lung development in children living in 12 southern Californian communities from age 10 to age 18 and correlated the findings with exposures to ambient particulate matter. Exposure was associated with clinically and statistically significant deficits in the FEV1 attained at the age of 18 years. In all 12 communities, a low FEV1 was positively associated with levels of exposure to pollutants including PM10 and PM2.5 (25).

In an experimental study of rat lung tissue, oxidative stress responses to ambient particles from motor vehicles were evaluated, and a significant increase in lipid peroxidation (an indicator of oxidative stress) was seen in lung tissue immediately following 20 h of continuous exposure, but not following a 6-h exposure or intermittent exposures (93). As with ozone, children's higher ventilation rates and increased lung surface area may make them more susceptible to oxidative stress resulting in inflammation, airway injury, and disease (26). Long-term exposure to PM is associated with airway remodeling and chronic inflammation (27, 28).

Immune response and infection

Pulmonary inflammation resulting from PM exposure may trigger systemic inflammation through the action of cytokines and other mediators which enter the general circulation from the lungs (94). Coarse particles deposit in the lung and then subsequently cause the release of cytotoxic and inflammatory markers in plasma (e.g. interleukin-6 and interleukin-8). The bone marrow releases leukocytes and platelets in response to the lung inflammation and is an important component of the systemic inflammatory response (95). In response to lung inflammation, leukocytes and platelets are released from the bone marrow, stimulating further immune responses.

Studies have reported that PM can increase bronchitic symptoms (96) and hospitalization rates for severe

respiratory infections (97, 98). Components of PM2.5 have been associated with hospitalizations for several childhood respiratory diseases including pneumonia, bronchitis, and asthma. PM sources include diesel exhaust, motor vehicle emissions, and fuel combustion processes (97). Positive associations between PM exposure and hospital admissions for respiratory infection are supported by animal toxicological studies. Research demonstrates reduced clearance of bacteria (*Pseudomonas*, *Listeria*) and enhanced pathogenesis of viruses [influenza, respiratory syncytial virus (RSV)] as a result of PM exposure (99).

An increase in hospitalizations due to respiratory infection for children has also been documented (98). Lin et al. (98) examined the association between ambient air pollution and respiratory infections in children under 15 years in Toronto, Canada, between 1998 and 2001. Even at low levels of air pollution (under many standard guidelines), levels in the study were shown to have a significant effect on hospitalization rates due to respiratory infection. Outdoor air pollution could contribute to respiratory infectious disease in infants by causing ongoing inflammation in the lungs. Sheffield et al. (100) looked at several air pollutants, but specifically at fine particulate matter and ozone, which are the pollutants with the strongest evidence linking them to adverse respiratory outcomes and found an association between these pollutants and hospitalization. Their findings support the hypothesis not only that short-term exposure to particulate matter (the one-month average) is associated with more severe bronchiolitis, but also that longer exposure duration – the average over the lifetime of the infant – shows a stronger effect.

Respiratory symptoms and asthma

Both the onset of asthma symptoms and diagnosed asthma have been associated with exposure to ambient particulate matter (101). Peak concentrations of ambient fine particulates have been associated with early increases in bronchodilator use and urinary leukotriene E4 levels among children with persistent asthma (102). A recent systematic review reported that ambient PM2.5 levels have also been found to be associated with an increase in asthma ED visits (103).

Mar et al. (104) studied asthmatic children and adults in Spokane, Washington. Increases in PM were strongly associated with cough (104). When all lower respiratory tract symptoms (wheezing, cough, shortness of breath, sputum production) were grouped together, positive associations in children were reported for each 10 $\mu\text{g}/\text{m}^3$ increase. Sputum production and runny nose

were associated with PM10 and coarse fraction. However, no association was found between increases in PM and the presence of any respiratory symptoms in the adult subjects, suggesting that children are more sensitive than adults to the effects of increased levels of PM air pollution.

In the National Cooperative Inner-City Asthma Study (NCICAS) (105), for the three urban areas with air quality data, each 10 $\mu\text{g}/\text{m}^3$ increase in the mean of the previous 2 days' PM10 value increased the risk for morning asthma symptoms.

Particulate pollution may also play a role in the exacerbation of pre-existing asthma (96). A meta-analysis found that there can be an aggravation of health effects among asthmatics exposed to PM10 (106). An increase in symptoms (cough and phlegm production) and lower pulmonary function among asthmatics has been reported (96, 106–108). In CHS, children with pre-diagnosed asthma had greater lower respiratory tract symptoms (bronchitis and phlegm production) if they resided in communities where there were higher levels of PM10 and PM 2.5 (96). In addition, there was an increased risk for bronchitis symptoms in children with asthma when there was a 19 $\mu\text{g}/\text{m}^3$ increase in PM10. Exposure to an increase in PM10 of 10 $\mu\text{g}/\text{m}^3$ in 1 day reportedly leads to an increase in severity of asthma symptoms and an increase in adverse respiratory function in asthmatic children (109, 110).

Exposure to ambient particle pollution may cause asthma by inducing oxidative stress mechanisms and pulmonary inflammation. Exposure to particulate matter can cause the development of lung injury via oxidative stress mechanisms and pulmonary inflammatory response (27, 29, 111). Specifically, oxidative stress mechanisms cause epithelial cells in the airway to express inflammatory cytokines (29) and chronic inflammation resulting in asthma.

Silica dust

Exposure guidelines and silica dust levels near UOG

In the UOG industry, huge quantities of silica sand are used. Tons of silica sand are added to each UOG well site's fracturing fluid during each 'frack job', which may be repeated at intervals. Silica sand is used in hydraulic fracturing in order to prop open fissures in the shale and facilitate the flow of trapped natural gas (112). Silica occurs in two general forms, crystalline and amorphous. Crystalline silica is generally considered to be more toxic, although health concerns exist for both forms. Silica sand used in fracking is crystalline silica. Transport and use of sand

during fracking emit respirable particles of silica into the air at fracking sites, particles that are small enough to be breathed deep into the lungs (112).

Exposure to fine respirable silica can occur even before the drilling process, when the sand is being mined and extracted, transported in trucks to the distant well pads, or during the process of blending the sand with other hydraulic fracture fluid ingredients (16, 112). Several studies have focused on silica dust dispersion in air and concern for workers near well pads and UOG sites (15, 113–115). Crystalline silica air concentrations have been reported above occupational health standards at oil and gas sites (15, 115). A NIOSH study documented that worker exposure to silica dust used during UOG operations exceeded occupational health standards at every site tested. Some exposures exceeded NIOSH standards by a factor of 10 or more. Esswein and colleagues collected air samples from 11 sites in five states to assess worker exposure levels. More than 50% of the samples collected indicated that silica exposures were higher than OSHA permissible exposure level (PEL) and 68.5% indicated that exposures were higher than the NIOSH REL of 0.05 mg/m³ (15, 116). Furthermore, NIOSH (112) showed that even those workers not working directly with silica were still exposed to respirable silica sand. This is because silica particles become airborne and high concentrations were found in places that were downwind of operations involving silica sand (112).

Given the focus on worker health in relation to silica, very little is known about safe exposure limits for children.

The health risks associated with silica dust

The health risks of silica exposure are related to the ease with which the tiny particles of silica dust are inhaled and are able to reach the deep alveolar recesses of the lungs (15, 112, 117). Respirable silica dust can damage respiratory cells resulting in scarring and subsequent irreversible chronic pulmonary fibrotic disease or silicosis (118). Silica dust can also lead to lung cancer and to an increased susceptibility to tuberculosis (15, 119–122).

Silicosis

Silicosis has only been linked to silica dust particle exposure and not to any other common respiratory irritants or toxins, such as environmental tobacco smoke. Symptoms of silicosis include dry cough, sputum, shortness of breath, and reduced pulmonary function (117). Silicosis

can be categorized into three types: chronic, acute, and accelerated. Chronic silicosis develops over a course of more than 10 years of exposure, while accelerated silicosis develops over 5–10 years of exposure (117). Acute silicosis is less common than the other forms, but develops over the course of a few months or a few years of exposure to very high levels of respirable crystalline silica, and frequently results in death or disability (112). Silicosis is often called a silent killer, because any symptoms associated with it might not be obvious until a thorough medical examination is done (112). There is no known effective treatment for this lung disease (123).

Potential implications for vulnerable populations

Silicosis is often described in the scientific literature as an occupational disease because most existing epidemiological studies have focused on populations of workers employed by industries that mine or use silica. However, there is also concern for potential exposure and similar health outcomes for local residents who live in close proximity to these industrial sites. This includes children whose homes, backyards, and school grounds are located near UOG sites or silica sand transfer stations. Because silica dust particles are easily dispersed in the air (15), vulnerable populations such as children may be easily exposed and are especially at risk. Given the long latency of developing silica-related health problems (10 years or more), it may be years or decades before adverse health effects become apparent.

Interestingly, Kanatani et al. (124) reported that fine desert dust particles can cause asthma exacerbations and an increased risk of hospitalizations for asthma in pediatric populations. They reported that desert dust includes quartz, the most common form of crystalline silica. Future research should focus on enhancing knowledge concerning long-term effects of silica dust on children.

Benzene

Exposure standards and benzene emissions from UOG

VOCs can be released during many stages of the UOG lifecycle (40). Benzene, toluene, ethylene, and xylene (BTEX), a tetrad of VOCs, are commonly found in petroleum products such as gasoline and diesel fuel, and are also found to be associated with UOG operations (125). Oil and natural gas operations also rely heavily on the use of diesel-powered equipment and transportation in each step of the process (16, 40), releasing VOCs.

Table 2: Inhalation MRLs for benzene at different exposure durations.^a

| Benzene inhalation minimum risk levels (MRLs) | | |
|---|----------|-------------------------------|
| Exposure duration | MRL, ppm | MRL, $\mu\text{g}/\text{m}^3$ |
| Acute (<14 days) | 0.009 | 29.3 |
| Intermediate (15–364 days) | 0.006 | 19.6 |
| Chronic (≥ 365 days) | 0.003 | 9.8 |

Benzene conversion factor: 1 ppm=3.26 mg/m³ at 20°C. ^aATSDR's inhalation MRLs provide estimates of daily human exposure to a hazardous substance at or below which that substance is unlikely to pose a measurable risk of harmful (adverse), noncancerous effect. MRLs are guidelines, not standards like PELs or NAAQS. The threshold for developing an adverse health response is significantly less for people experiencing chronic exposures. Individuals residing near UOG sites may more likely experience chronic exposure and be subjected to emissions up to 24 h a day.

Benzene is both a petroleum byproduct as well as an organic compound that occurs naturally in shale rock and other hydrocarbon deposits and is released into the air throughout the UOG development. Benzene emissions

are released from wells, production tanks, compressors, and pipelines (38, 52, 115). A number of UOG studies have identified benzene as a potential health risk (2, 13, 38, 53, 126). Exposure to benzene can occur through inhalation, oral, or dermal exposure, and benzene can volatilize into the air from water and soil (127, 128). Concentrations have been reported near UOG sites that significantly exceeded the minimal risk level (MRL) established by the ATSDR (Table 2) and were associated with health impacts on residents (Figure 2) (38).

Acute respiratory symptoms (shortness of breath, wheezing, and cough), airway inflammation and pulmonary function

The health effects of benzene are well-described in the literature (15, 33, 112, 117, 118, 120, 121) and epidemiological studies have documented the relationship between ambient benzene and respiratory health in children (33). In addition to being a carcinogen (122), benzene is also

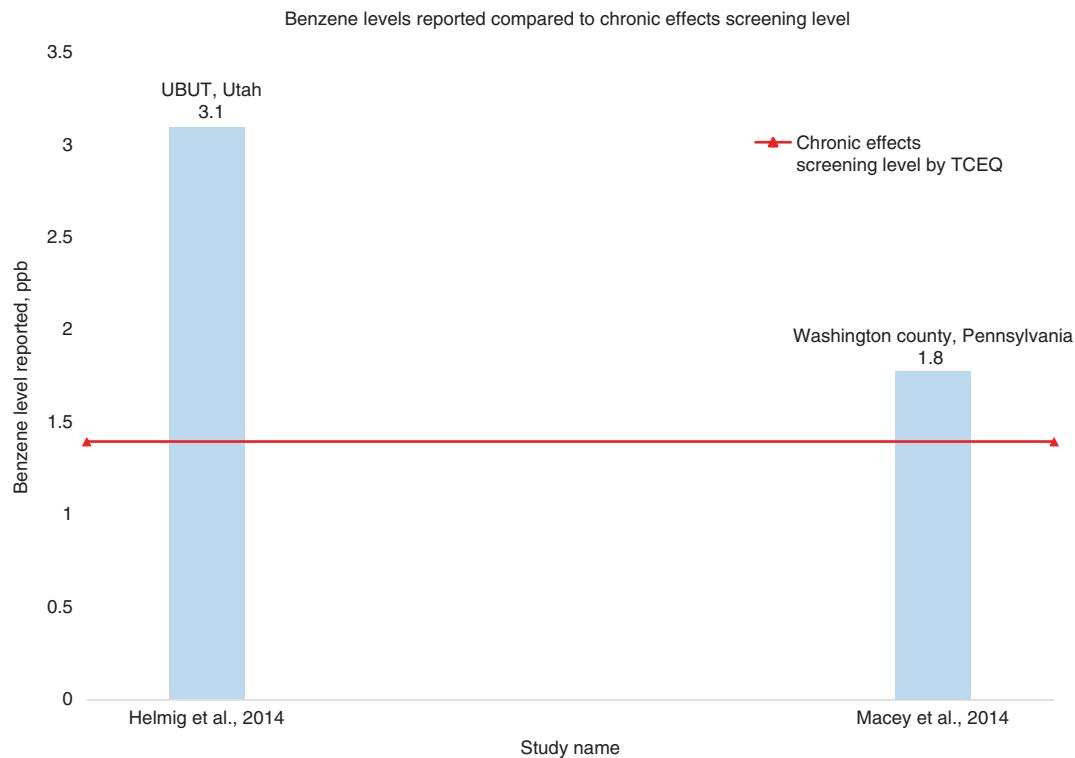


Figure 2: Field study measurements for benzene near UOG development sites.

Helmig et al. reported average benzene levels based on 330 measurements (13). Macey et al. reported one measurement for Washington County, Pennsylvania (38). These values are compared to the chronic effects screening level guidelines set by the Texas Commission on Environmental Quality (1.4 ppb)*.

*Effects screening levels (ESLs) are guidelines and have been used as a reference point in studies (13). They are not enforceable and are established by the Texas Commission on Environmental Quality (TCEQ).

Table 3: Inhalation MRLs for formaldehyde at different exposure durations.^a

| Formaldehyde inhalation minimum risk levels (MRLs) | | |
|--|----------|-------------------------------|
| Exposure duration | MRL, ppm | MRL, $\mu\text{g}/\text{m}^3$ |
| Acute (≤ 14 days) | 0.04 | 49.6 |
| Intermediate (15–364 days) | 0.03 | 37.2 |
| Chronic (≥ 365 days) | 0.008 | 9.9 |

Formaldehyde conversion factor: 1 ppm = 1.24 mg/m³ in air at 25°C.

^aATSDR's inhalation MRLs provide estimates of daily human exposure to a hazardous substance at or below which that substance is unlikely to pose a measurable risk of harmful (adverse), non-cancerous effect. MRLs are guidelines, not standards like PELs or NAAQS. The threshold for developing an adverse health response is significantly less for people experiencing chronic exposures. Individuals residing near UOG sites may more likely experience chronic exposure and be subjected to emissions up to 24 h a day.

a respiratory irritant and can pose serious risks to respiratory health (129, 130). In children, benzene exposure has also been associated with adverse respiratory health outcomes, including increased occurrence of cough and wheezing (30–32), and increased incidence of airway infections and bronchitis (36, 37).

Two studies have also assessed lung function in relation to ambient benzene exposure (34, 35). Martins et al. (35) evaluated the relationship between individual total exposure to air pollution and airway changes in 51 children with wheezing in school settings (classrooms and courtyards) as well in their place of residence. Respiratory effects were assessed four times over a 1-week period. Benzene was associated with a significant decrease in FEV1 (95% CI, -7.13 to -1.53), FEV1/FVC (95% CI, -3.24 to -0.18) and FEF (25%–75%) (95% CI, -10.16 to -1.62) and an increase of Δ FEV1 (95% CI, 0.92–4.65) (35).

VOC mixtures may also be responsible for increased lung inflammation. An inflammatory response and a significant increase in inflammatory markers was observed in a study which assessed indoor exposure to VOCs (25 mg/m³ total hydrocarbon) in men (131).

Immune response and infections

In addition to acute respiratory symptoms, chronic bronchitis and pulmonary infections have been reported to be associated with benzene exposure (36, 37). The Leipzig Allergy High-Risk Children Study (LARS) assessed indoor chemical exposure on the health of infants with a risk for allergic hypersensitivity. The study followed 475 premature infants for 1 year and evaluated associations

between VOC exposures and infections. Twenty-five VOCs were measured in infants' bedrooms using passive air sampling for 4 weeks following birth. Ambient benzene at levels greater than 5.6 $\mu\text{g}/\text{m}^3$ increased the risk of pulmonary infections in babies 6 weeks old (95 % CI, 1.28–4.48) (36).

Respiratory symptoms and asthma

VOC exposures are associated with an increase in respiratory symptoms. Ware and colleagues assessed the relationship between effects of ambient VOC exposures and respiratory symptoms in 8549 children living in Kanawha, West Virginia, a chemical-manufacturing region. The VOCs were found to be associated with an increase in respiratory symptoms in relation to VOC exposure (132).

Asthma is associated with exposure to ambient benzene. (30, 33, 34, 133–135). Several epidemiological studies concerning the relationship between benzene air exposure and respiratory health among children and adolescents found significant associations between benzene exposure and asthma (33). These included both an increase in asthma symptoms (135) and an increased risk of developing of asthma (134).

Formaldehyde

Exposure standards and formaldehyde emissions from UOG

Another volatile compound associated with UOG is formaldehyde. Formaldehyde is produced at numerous points during the UOG lifecycle and is commonly emitted from compressor stations. Formaldehyde can also form from the chemical reaction caused by sunlight interacting with NO_x and VOCs (39). Formaldehyde has been found in air samples in a drilling dense area in Garfield County in rural Western Colorado and near residential sites (39). Concentrations have been reported near UOG sites that significantly exceeded the MRL (Table 3) established by the ATSDR. ATSDR's MRLs are estimated guidelines that describe daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. Macey et al. (38) found formaldehyde levels in three counties that exceeded ATSDR's MRL for chronic inhalation (≥ 365 days) (Figure 3). These levels were associated with health impacts on residents (38).

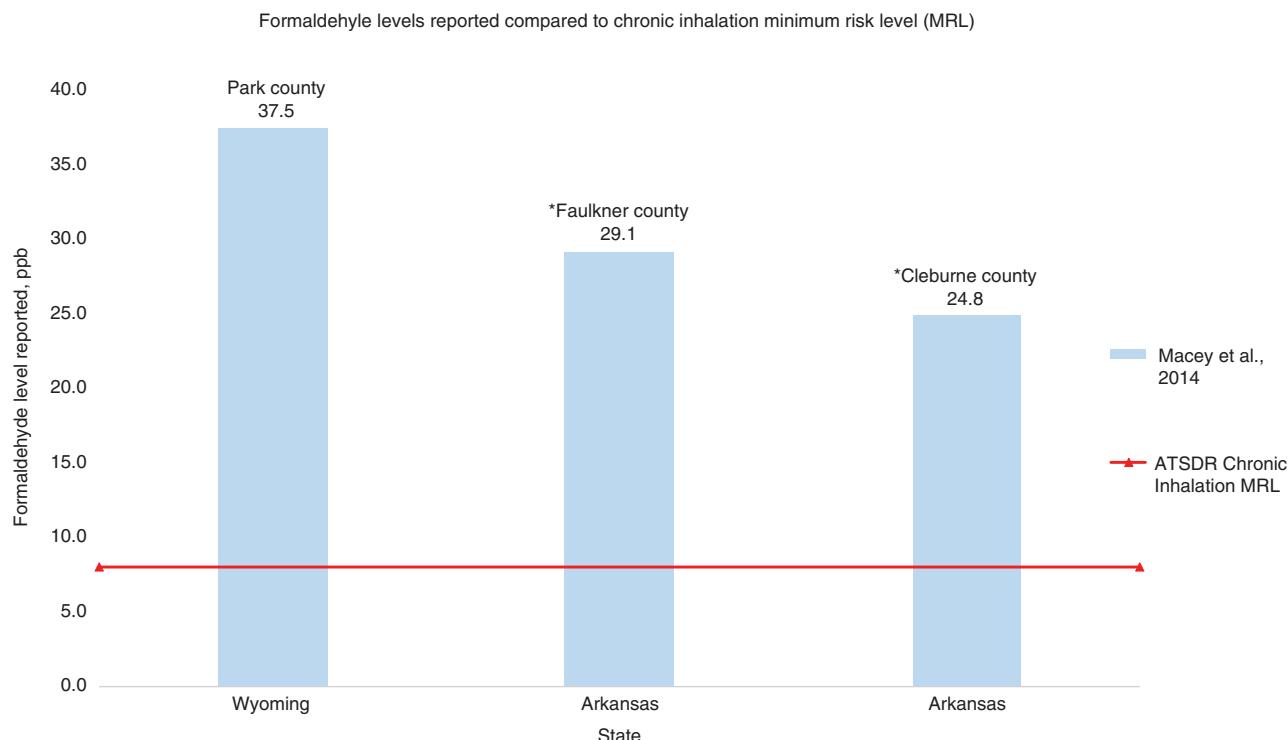


Figure 3: Field study measurement for formaldehyde reported in Macey et al. (38) compared to chronic inhalation (≥ 365 days) MRL of 8 ppb. Values with * indicate levels for which averages were taken. Macey et al. reported a single value for Park County.

Acute respiratory symptoms (shortness of breath, wheezing, and cough), airway inflammation and pulmonary function

In children, formaldehyde has been identified as a respiratory tract irritant (119, 136–140). Exposure to formaldehyde can lead to respiratory symptoms (e.g. chest discomfort, difficulty breathing, wheezing, etc.) (41), reduction in pulmonary function (43, 141), acute respiratory tract illness (42), and asthma (44–46).

Formaldehyde initiates inflammation by inducing oxidative stress in lung tissue (142). The pulmonary inflammatory response mechanisms are then responsible for the development of lung diseases and reductions in lung function (45).

Immune response and infection

Formaldehyde also appears to inhibit beneficial immune responses. A significant increase in immune biomarkers in children exposed to high levels of formaldehyde was found in one study (143). Both animal and human studies have indicated that formaldehyde impairs the development of an allergic response in the lungs (142, 144).

Asthma

Studies have suggested a link between inhalation exposure to formaldehyde and the development of asthma (45, 140, 145). Rumchev et al. (140) reported that their case-control study of children residing in Australia indicated that formaldehyde exposure was associated with asthma. McGwin et al. (46) conducted a systematic review and found a positive association between formaldehyde exposure levels and childhood asthma. In a cross-sectional study on indoor formaldehyde exposure in Swedish schools, researchers reported that there were more students with current asthma in schools where there were higher levels of formaldehyde and other VOCs (146).

Discussion

Based on the literature indicating adverse impacts from air pollution on children's health in other contexts, there is potential for adverse respiratory effects in infants and children in the context of UOG. Our review shows that at least five of the pollutant groups used and/or produced by UOG processes have well-known respiratory health effects for infants and children.

Health risks identified

Our review found that these five pollutants are associated with increased respiratory problems in children: asthma prevalence and incidence, chronic and acute respiratory symptoms, adverse lung function and development, and airway inflammation. It is also reasonable to conclude that young children with fragile, developing respiratory systems who experience frequent exposures to these pollutants are at particularly high risk for respiratory tissue injury leading to irreversible pulmonary damage and chronic respiratory diseases.

in close proximity to UOG development. Individuals residing within close proximity (less than or equal to $\frac{1}{2}$ mile) to high-density drilling areas are at greater risk for health effects from exposure to natural gas development than those living greater than $\frac{1}{2}$ mile from wells (53). A recent report documented that approximately 53,000 children residing in Pennsylvania under the age of 10 live within a mile of permitted well sites (150). We recommend that at a minimum, one-mile setbacks should be established between drilling facilities and occupied dwellings such as schools, hospitals, and other dwellings where infants and children might spend a substantial amount of time.

General policy recommendations

Emission reduction standards

In order to ensure public health and safety, especially for infants and children, we recommend federal standards that reduce air pollutant emissions from oil and gas development, including methane, VOCs, PM, and ozone. The EPA's proposed measures to cut methane and VOC emissions from the oil and natural gas industry will not only address climate change, but also reduce the exposure of nearby communities to these pollutants and the subsequent risk of health effects, including respiratory morbidity and mortality. The proposed rule is projected to prevent between 170,000 and 180,000 tons of VOCs and 1900–2500 tons of HAPs from new sources in 2025 (147). At this time, the proposed rule only addresses new and modified sources and further steps will be required to address existing sources. Many practices and technologies to reduce emissions already exist and their implementation is not only feasible, but cost-effective as well.

Increased setbacks from sensitive receptors

Setback distances from UOG development are intended to protect the health and safety of residents (148), including infants and children. Many states establish setback rules with an average distance of 100–1000 feet from a permitted well and sensitive receptors such as schools, hospitals, churches, and other occupied dwellings (149). However, the majority of municipal setback ordinances are not supported by empirical data. Established setback ordinances are typically the result of negotiation between stakeholders (e.g. residents and municipal policymakers) (148). Calls for increased setback distances are due to the potential health risks associated with residing or working

Strengthening standards for tropospheric ozone

Our review found that levels of ozone pollution is a leading contributor to asthma exacerbations and has been linked to a range of other respiratory impacts, and infants and children are disproportionately affected. We know from air monitoring research that ozone levels near UOG sites of oil and gas development can exceed regulatory limits. Both public health professionals and environmental advocates support strong national standards for ground-level ozone.

In 2015, the EPA's Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel recommended lowering the standard to 60 ppb. A health protective level of 60 ppb would begin to address some of the health risks facing children living or attending school near oil and natural gas development. Despite the recommendation put forth by CASAC, in October 2015, the new threshold for ground-level ozone was set at 70 ppb (to go into effect in 2017). This new standard falls short of what many environmentalists and public health experts recommended.

Ozone often triggers asthma attacks, coughing, wheezing, and increases emergency room utilization for severe asthmatic exacerbations. It has been estimated that had the standard been set at 60 ppb this action:

"Would prevent up to 7,900 premature deaths and 1.8 million asthma attacks and 1.9 million school days missed in 2025, for all counties in the U.S. expected to meet the standard that year." (151)

Reducing ozone levels near UOG potentially improves children's health and decreases school absenteeism. In the CHS, the largest long-term study of the health effects of children's chronic exposures to Southern California's air pollution to date, reductions in ambient ozone levels in Southern California between 1990 and 1999 reduced school absences by 2.8 million (152). A more recent

estimate found a reduction of 1 million absences annually if more strict ozone standards were put in place (153).

A stronger ozone standard would also have provided significant public health protections for children and the elderly, those most vulnerable to the ozone's impacts.

OSHA standards for respirable silica dust

Approximately 1.7 million workers in the United States are exposed to respirable silica dust every year (154). In 2013, OSHA proposed new rules for occupational exposure limits to silica dust. The recommended permissible exposure limits was set at 50 $\mu\text{g}/\text{m}^3$ for an 8-h day. OSHA estimates that the proposed rule will save 700 lives and prevent 1600 new cases of silicosis annually (155). New protection standards were announced in March 2016.

We support the finalization and enforcement of these new rules; the protective standards will protect not only workers, but also infants and children living near UOG sites who are often in their house or yard for almost the whole day.

EPA New Source Performance Standards (NSPS) for methane

In August 2015, the US EPA announced new NSPS for methane and VOCs for new and modified sources of release from UOG. These new standards will significantly reduce methane releases by 40%–45% and are estimated to reduce VOC emissions by up to 95%. This will improve air quality and decrease ground-level ozone, which, as shown in the literature, can be a problem for infants and children. We recommend these standards be finalized and that this NSPS be expanded to cover existing UOG facilities.

The health burden and economic impact of childhood asthma

Asthma affects over 7.1 million children in the United States under 18 years and is the third cause of hospitalization among children under 15 years. In 2010, there was an estimated 640,000 emergency room visits due to asthma for children under 15 years. Asthma is one of the leading causes of school absenteeism, and in 2008, asthma was responsible for an estimated 14.4 million lost school days in children (156). The annual direct and indirect cost (i.e. lost days of productivity) for treating asthma in the United States is estimated to be \$56 billion (156). Policies to

reduce the asthma burden created by UOG are an important part of reducing these costs.

Transparency and disclosure: clinical implications

We strongly recommend policies that strengthen disclosure and transparency about chemicals used in UOG. Due to the 2005 Energy Policy Act, a number of chemicals associated with UOG are not reported to the public. Disclosure of chemicals is critical to be able to understand the full scope of respiratory health effects for infants and children. In a 2011 study by Colborn et al. (157), the authors evaluated possible health impacts of chemicals used in UOG and found that over 80% of these chemicals are linked to negative respiratory impacts (n=353). However, the study was limited because of the lack of transparency about the chemical mixtures used in the UOG process.

Precautionary approach

In order to protect the health of children and wellbeing of families, state, federal agencies, and authorities should adopt a precautionary approach when establishing permitting rules and standards for UOG development and production. This also applies to enforcement of standards for air emissions near UOG sites. The federal government sets standards for many air pollutants, based on an estimated risk of health effects at a certain level. Currently, the EPA uses a narrow view of variability and vulnerability in their risk assessment caused by differences in genetic makeup, metabolism, and age of exposures. Therefore, current risk assessment practices provide inadequate protection to the most vulnerable populations, such as infants and children (158). Even when air pollution meets current regulatory levels, adverse respiratory health effects have been reported in children and adverse health effects have been identified at levels once considered safe (159).

Research needs

Improved exposure assessment

While we strongly support a precautionary approach that prevents children's exposure, we recommend that well-designed biomonitoring studies should be undertaken to measure existing exposures to pollutant groups associated with UOG. Currently, only a small number of studies document a causal relationship between pollution created by UOG operations and undesirable health outcomes.

Better population exposure assessment is needed to document these relationships. The most accurate way to obtain information about human exposures from environmental pollution is through well-designed biomonitoring studies.

Air monitoring and modeling

This review documents that air pollution can present significant health threats to infants, children, and others who live near UOG sites. Identification and quantification of air pollutants is an essential part of demonstrating successful risk reduction and ensuring compliance with national standards. There are a number of different methods used to capture air quality data, from community monitoring to remote sensing of regional emission concentrations. UOG companies should fund better real-time monitoring of air pollutants near UOG operations.

Models need to be developed that can account for simultaneous exposures to multiple pollutant groups. Synergistic mechanisms and bioaccumulation of air pollutants are important when assessing respiratory health outcomes.

Review limitations and considerations

This review is not exhaustive in scope. We focus on five particular air pollutants of concern and do not discuss a number of other air pollutants, such as hydrogen sulfide, polycyclic aromatic hydrocarbons, NO_x, and naturally occurring radioactive materials.

The studies we reviewed evaluated exposures in a variety of settings. For example, some of these studies assessed pollutant atmospheric concentrations while others assessed urban- and traffic-related pollution. We also examined exposures from some of these pollutants in both indoor and outdoor settings. The relevance to exposures near UOG sites varies.

Additionally, we were restricted in our assessment by current understanding of some respiratory health effects and their relevance for children living near UOG areas. There remains a dearth of information about UOG impacts on children. Respirable silica is an example where little data about children exists. There is scientific consensus that 1) silica dust causes silicosis and that 2) exposure to quartz dust can lead to an increase in hospitalizations for respiratory illness. But the long-term effects of silica dust on children residing near UOG operations remain to be determined. There is a long latency period for silicosis, lung cancer, and some other respiratory illnesses, so it may be decades before we can document these relationships.

We also did not explore alternative energy sources that may provide a solution to our energy needs without the negative health impacts found with UOG. If we move away from UOG, we need to be cognizant that our energy needs will not go away and that we should support healthier energy choices.

Conclusion

We conclude that exposure to ozone, PM, silica dust, benzene, and formaldehyde is linked to adverse respiratory health effects, particularly in infants and children. However, the scientific literature examining the direct impact of shale gas and oil development on children is just starting to emerge.

In the absence of direct evidence on levels of exposure and adverse health outcomes among infants and children due to UOG air pollution, our focus on key air pollutants and the vulnerability of children serves to identify potential health risks as well as to promote additional research in this area. Research indicates elevated air pollutant emissions and/or atmospheric concentrations in areas with UOG development as well as increased health risks, driven by pollutants such as benzene. Meanwhile, a growing number of epidemiological studies indicate that oil and gas development is associated with adverse health impacts, such as increased birth outcomes, hospitalization rates, and reported health symptoms per person (2, 160, 161). These initial results are consistent with the existing body of epidemiology that observes the impact of air pollutant exposure on children more generally.

We believe that protecting children's health is a social, scientific, and ethical priority. Large-scale and long-term epidemiological studies are needed but we strongly recommend precautionary measures at this time, in order to protect the health of infants and children.

References

1. Hill EL. Shale gas development and infant health: evidence from Pennsylvania. Charles H Dyson School of Applied Economics and Management, Cornell University, Working Paper Available at [Internet]. 2013 [cited 2015 Jul 13]; Available at: <http://www.ncsu.edu/centrep/worksheets/TREE/documents/Hill.pdf>.
2. McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, et al. Birth Outcomes and Maternal Residential Proximity to Natural Gas Development in Rural Colorado. *Environ Health Perspect* [Internet]. 2014 Jan 28 [cited 2014 Oct 17];122(4). Available at: <http://ehp.niehs.nih.gov/1306722/>.

3. Hays J, de Melo-Martín I. Ethical concerns surrounding unconventional oil and gas development and vulnerable populations. *Rev Environ Health* 2014;29(4):275–6.
4. Webb E, Bushkin-Bedient S, Cheng A, Kassotis CD, Balise V, et al. Developmental and reproductive effects of chemicals associated with unconventional oil and natural gas operations. *Rev Environ Health* 2014;29(4):307–18.
5. Selevan SG, Kimmel CA, Mendola P. Identifying critical windows of exposure for children's health. *Environ Health Perspect* 2000;108(Suppl 3):451–5.
6. Moya J, Bearer CF, Etzel RA. Children's behavior and physiology and how it affects exposure to environmental contaminants. *Pediatrics* 2004;113(4 Suppl):996–1006.
7. Pronczuk-Garbino J, World Health Organization. Children's Health and the Environment [Internet]. 2005. Available at: http://apps.who.int/iris/bitstream/10665/43162/1/9241562927_eng.pdf.
8. World Health Organization. Outdoor Air Pollution: Children's Health and the Environment. WHO training package for the health sector, 2008.
9. EPA. Hydraulic Fracturing Research Study [Internet]. 2010. Available at: <http://www.epa.gov/safewater/uic/pdfs/hfresearchstudyfs.pdf>.
10. Schnell RC, Oltmans SJ, Neely RR, Endres MS, Molenar JV, et al. Rapid photochemical production of ozone at high concentrations in a rural site during winter. *Nature Geosci* 2009;2(2):120–2.
11. Kemball-Cook S, Bar-Ilan A, Grant J, Parker L, Jung J, et al. Ozone impacts of natural gas development in the haynesville shale. *Environ Sci Technol* 2010;44(24):9357–63.
12. Oltmans S, Schnell R, Johnson B, Pétron G, Mefford T, et al. Anatomy of wintertime ozone associated with oil and natural gas extraction activity in Wyoming and Utah. *Elem Sci Anth* 2014;2:000024.
13. Helmig D, Thompson CR, Evans J, Boylan P, Hueber J, et al. Highly elevated atmospheric levels of volatile organic compounds in the Uintah Basin, Utah. *Environ Sci Technol* 2014;48(9):4707–15.
14. Rappenglück B, Ackermann L, Alvarez S, Golovko J, Buhr M, et al. Strong wintertime ozone events in the Upper Green River basin, Wyoming. *Atmos Chem Phys* 2014;14(10):4909–34.
15. Esswein EJ, Breitenstein M, Snawder J, Kiefer M, Sieber WK. Occupational exposures to respirable crystalline silica during hydraulic fracturing. *J Occup Environ Hyg* 2013;10(7):347–56.
16. Moore CW, Zielinska B, Pétron G, Jackson RB. Air impacts of increased natural gas acquisition, processing, and use: a critical review. *Environ Sci Technol* 2014;48(15):8349–59.
17. Devalia JL, Rusznak C, Wang J, Khair OA, Abdelaziz MM, et al. Air pollutants and respiratory hypersensitivity. *Toxicol Lett* 1996;86(2–3):169–76.
18. González-Guevara E, Martínez-Lazcano JC, Custodio V, Hernández-Cerón M, Rubio C, et al. Exposure to ozone induces a systemic inflammatory response: possible source of the neurological alterations induced by this gas. *Inhal Toxicol* 2014;26(8):485–91.
19. Devlin RB, McDonnell WF, Mann R, Becker S, House DE, et al. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. *Am J Respir Cell Mol Biol* 1991;4(1):72–81.
20. Kinney PL, Thurston GD, Raizenne M. The effects of ambient ozone on lung function in children: a reanalysis of six summer camp studies. *Environ Health Perspect* 1996;104(2):170–4.
21. Tager IB, Balmes J, Lurmann F, Ngo L, Alcorn S, et al. Chronic exposure to ambient ozone and lung function in young adults. *Epidemiology* 2005;16(6):751–9.
22. Kesic MJ, Meyer M, Bauer R, Jaspers I. Exposure to ozone modulates human airway protease/antiprotease balance contributing to increased influenza A infection. *PLoS One* 2012;7(4):e35108.
23. McConnell R, Berhane K, Gilliland F, London SJ, Islam T, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002;359(9304):386–91.
24. Edwards PM, Brown SS, Roberts JM, Ahmadov R, Banta RM, et al. High winter ozone pollution from carbonyl photolysis in an oil and gas basin. *Nature* 2014;514(7522):351–4.
25. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351(11):1057–67.
26. Grigg J. Particulate matter exposure in children: relevance to chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2009;6(7):564–9.
27. Anderson JO, Thundiyil JG, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. *J Med Toxicol* 2012;8(2):166–75.
28. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350(26):2645–53.
29. Silbajoris R, Osornio-Vargas AR, Simmons SO, Reed W, Bromberg PA, et al. Ambient particulate matter induces interleukin-8 expression through an alternative NF-κB (nuclear factor-kappa b) mechanism in human airway epithelial cells. *Environ Health Perspect* 2011;119(10):1379–83.
30. Nicolai T, Carr D, Weiland SK, Duhme H, Von Ehrenstein O, et al. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. *Eur Respir J* 2003;21(6):956–63.
31. Hirsch T, Weiland SK, Von Mutius E, Safeca AF, Gräfe H, et al. Inner city air pollution and respiratory health and atopy in children. *Eur Respir J* 1999;14(3):669–77.
32. Buchdahl R, Willems CD, Vander M, Babiker A. Associations between ambient ozone, hydrocarbons, and childhood wheezy episodes: a prospective observational study in south east London. *Occup Environ Med* 2000;57(2):86–93.
33. Ferrero A, Íñiguez C, Esplugues A, Estarlich M, Ballester F. Benzene exposure and respiratory health in children: a systematic review of epidemiologic evidences. *J Pollut Eff Cont* 2014;2(114):2.
34. Delfino RJ, Gong H, Linn WS, Hu Y, Pellizzari ED. Respiratory symptoms and peak expiratory flow in children with asthma in relation to volatile organic compounds in exhaled breath and ambient air. *J Expo Anal Environ Epidemiol* 2003;13(5):348–63.
35. Martins PC, Valente J, Papoila AL, Caires I, Araújo-Martins J, et al. Airways changes related to air pollution exposure in wheezing children. *Eur Respir J* 2012;39(2):246–53.
36. Diez U, Kroessner T, Rehwagen M, Richter M, Wetzig H, et al. Effects of indoor painting and smoking on airway symptoms in atopy risk children in the first year of life results of the LARS-study. *Int J Hyg Environ Health* 2000;203(1):23–8.
37. Rolle-Kampczyk UE, Rehwagen M, Diez U, Richter M, Herbarth O, et al. Passive smoking, excretion of metabolites, and health effects: results of the Leipzig's Allergy Risk Study (LARS). *Arch Environ Health* 2002;57(4):326–31.
38. Macey GP, Breech R, Chernaik M, Cox C, Larson D, et al. Air concentrations of volatile compounds near oil and gas

- production: a community-based exploratory study. *Environ Health* 2014;13:82.
- 39. Colborn T, Schultz K, Herrick L, Kwiatkowski C. An exploratory study of air quality near natural gas operations. *Hum Ecol Risk Assess* 2014;20(1):86–105.
 - 40. Gilman JB, Lerner BM, Kuster WC, de Gouw JA. Source signature of volatile organic compounds from oil and natural gas operations in Northeastern Colorado. *Environ Sci Technol* 2013;47(3):1297–305.
 - 41. Kim K-H, Jahan SA, Lee J-T. Exposure to formaldehyde and its potential human health hazards. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2011;29(4):277–99.
 - 42. Tuthill RW. Woodstoves, formaldehyde, and respiratory disease. *Am J Epidemiol* 1984;120(6):952–5.
 - 43. Franklin P, Dingle P, Stick S. Raised exhaled nitric oxide in healthy children is associated with domestic formaldehyde levels. *Am J Respir Crit Care Med* 2000;161(5):1757–9.
 - 44. Wantke F, Demmer CM, Tappler P, Götz M, Jarisch R. Exposure to gaseous formaldehyde induces IgE-mediated sensitization to formaldehyde in school-children. *Clin Exp Allergy* 1996;26(3):276–80.
 - 45. Thompson CM, Subramaniam RP, Grafström RC. Mechanistic and dose considerations for supporting adverse pulmonary physiology in response to formaldehyde. *Toxicol Appl Pharmacol* 2008;233(3):355–9.
 - 46. McGwin G, Lienert J, Kennedy JI. Formaldehyde exposure and asthma in children: a systematic review. *Environ Health Perspect* 2010;118(3):313–7.
 - 47. Rodriguez MA, Barna MG, Moore T. Regional impacts of oil and gas development on ozone formation in the western United States. *J Air Waste Manag Assoc* 2009;59(9):1111–8.
 - 48. Litovitz A, Curtright A, Abramzon S, Burger N, Samaras C. Estimation of regional air-quality damages from Marcellus Shale natural gas extraction in Pennsylvania. *Environ Res Lett* 2013;8(1):014017.
 - 49. Jackson RB, Down A, Phillips NG, Ackley RC, Cook CW, et al. Natural gas pipeline leaks across Washington, DC. *Environ Sci Technol* 2014;48(3):2051–8.
 - 50. McKain K, Down A, Raciti SM, Budney J, Hutyra LR, et al. Methane emissions from natural gas infrastructure and use in the urban region of Boston, Massachusetts. *Proc Natl Acad Sci USA* 2015;112(7):1941–6.
 - 51. Bar-Ilan Amnon, Grant J, Parikh R, Pollack A, Henderer D, et al. Development of Baseline 2006 Emissions from Oil and Gas Activity in the Piceance Basin [Internet]. 2009. Available at: http://www.wrapair.org/forums/ogwg/documents/2009-01_06_Baseline_Emissions_Piceance_Basin_Technical_Memo_01-20.pdf.
 - 52. Pétron G, Frost G, Miller BR, Hirsch AI, Montzka SA, et al. Hydrocarbon emissions characterization in the Colorado Front Range: a pilot study. *J Geophys Res* 2012;117(D4):D04304.
 - 53. McKenzie LM, Witter RZ, Newman LS, Adgate JL. Human health risk assessment of air emissions from development of unconventional natural gas resources. *Sci Total Environ* 2012;424:79–87.
 - 54. Edwards PM, Young CJ, Aikin K, de Gouw J, Dubé WP, et al. Ozone photochemistry in an oil and natural gas extraction region during winter: simulations of a snow-free season in the Uintah Basin, Utah. *Atmos Chem Phys* 2013;13(17):8955–71.
 - 55. Brown D, Weinberger B, Lewis C, Bonaparte H. Understanding exposure from natural gas drilling puts current air standards to the test. *Rev Environ Health* 2014;29(4):277–92.
 - 56. Roy AA, Adams PJ, Robinson AL. Air pollutant emissions from the development, production, and processing of Marcellus Shale natural gas. *J Air Waste Manage Assoc* 2014;64(1):19–37.
 - 57. Thompson CR, Hueber J, Helmig D. Influence of oil and gas emissions on ambient atmospheric non-methane hydrocarbons in residential areas of Northeastern Colorado. *Elem Sci Anth* 2014;2:000035.
 - 58. Paulik LB, Donald CE, Smith BW, Tidwell LG, Hobbie KA, et al. Impact of natural gas extraction on PAH levels in ambient air. *Environ Sci Technol* 2015;49(8):5203–10.
 - 59. Kampa M, Castanas E. Human health effects of air pollution. *Environ Pollut* 2008;151(2):362–7.
 - 60. Schwartz J. Air pollution and children's health. *Pediatrics* 2004;113(4 Suppl):1037–43.
 - 61. Dietert RR, Etzel RA, Chen D, Halonen M, Holladay SD, et al. Workshop to identify critical windows of exposure for children's health: immune and respiratory systems work group summary. *Environ Health Perspect* 2000;108(Suppl 3):483–90.
 - 62. Bateson TF, Schwartz J. Children's response to air pollutants. *J Toxicol Environ Health Sci, Part A* 2007;71(3):238–43.
 - 63. Landrigan PJ, Kimmel CA, Correa A, Eskenazi B. Children's health and the environment: public health issues and challenges for risk assessment. *Environ Health Perspect* 2004;112(2):257–65.
 - 64. Sly LJ, Carpenter DO. Special vulnerability of children to environmental exposures. *Rev Environ Health* 2012;27(4):151–7.
 - 65. Swarthout RF, Russo RS, Zhou Y, Miller BM, Mitchell B, et al. Impact of Marcellus Shale natural gas development in southwest Pennsylvania on volatile organic compound emissions and regional air quality. *Environ Sci Technol* 2015;49(5):3175–84.
 - 66. Pacsi AP, Kimura Y, McGaughey G, McDonald-Buller EC, Allen DT. Regional ozone impacts of increased natural gas use in the Texas power sector and development in the Eagle Ford shale. *Environ Sci Technol* 2015;49(6):3966–73.
 - 67. Olaguer EP. The potential near-source ozone impacts of upstream oil and gas industry emissions. *J Air Waste Manag Assoc* 2012;62(8):966–77.
 - 68. Triche EW, Gent JF, Holford TR, Belanger K, Bracken MB, et al. Low-level ozone exposure and respiratory symptoms in infants. *Environ Health Perspect* 2006;114(6):911–6.
 - 69. Kinney PL, Ware JH, Spengler JD, Dockery DW, Speizer FE, et al. Short-term pulmonary function change in association with ozone levels. *Am Rev Respir Dis* 1989;139(1):56–61.
 - 70. Stephens RJ, Evans MJ, Sloan MF, Freeman G. A comprehensive ultrastructural study of pulmonary injury and repair in the rat resulting from exposures to less than one PPM ozone. *Chest* 1974;65(Suppl):11S–3S.
 - 71. Foster WM, Costa DL, Langenback EG. Ozone exposure alters tracheobronchial mucociliary function in humans. *J Appl Physiol* 1987;63(3):996–1002.
 - 72. Medina-Ramón M, Zanobetti A, Schwartz J. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol* 2006;163(6):579–88.
 - 73. Gent JF, Triche EW, Holford TR, Belanger K, Bracken MB, et al. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. *J Am Med Assoc* 2003;290(14):1859–67.
 - 74. Thurston GD, Lippmann M, Scott MB, Fine JM. Summertime haze air pollution and children with asthma. *Am J Respir Crit Care Med* 1997;155(2):654–60.

75. Ostro B, Lipsett M, Mann J, Braxton-Owens H, White M. Air pollution and exacerbation of asthma in African-American children in Los Angeles. *Epidemiology* 2001;12(2):200–8.
76. Burnett RT, Smith-Doiron M, Stieb D, Raizenne ME, Brook JR, et al. Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. *Am J Epidemiol* 2001;153(5):444–52.
77. Fauoux B, Sampil M, Quénel P, Lemoulec Y. Ozone: a trigger for hospital pediatric asthma emergency room visits. *Pediatr Pulmonol* 2000;30(1):41–6.
78. Babin SM, Burkhardt HS, Holtry RS, Tabernero NR, Stokes LD, et al. Pediatric patient asthma-related emergency department visits and admissions in Washington, DC, from 2001–2004, and associations with air quality, socio-economic status and age group. *Environ Health* 2007;6:9.
79. Silverman RA, Ito K. Age-related association of fine particles and ozone with severe acute asthma in New York City. *J Allergy Clin Immunol* 2010;125(2):367–73.e5.
80. Strickland MJ, Darrow LA, Klein M, Flanders WD, Sarnat JA, et al. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. *Am J Respir Crit Care Med* 2010;182(3):307–16.
81. Gleason JA, Bielory L, Faglione JA. Associations between ozone, PM2.5, and four pollen types on emergency department pediatric asthma events during the warm season in New Jersey: a case-crossover study. *Environ Res* 2014;132:421–9.
82. Gilliland FD, Berhane K, Rappaport EB, Thomas DC, Avol E, et al. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiology* 2001;12(1):43–54.
83. Southwest Pennsylvania Environmental Health Project (SWPA-EHP). Summary on Compressor Stations and Health Impacts [Internet]. 2015. Available at: <http://www.environmentalhealth-project.org/wp-content/uploads/2012/03/Compressor-station-emissions-and-health-impacts-02.24.2015.pdf>.
84. World Health Organization. Ambient (outdoor) air quality and health: Fact sheet #313 [Internet]. 2014. Available at: <http://www.who.int/mediacentre/factsheets/fs313/en/>.
85. Anenberg SC, Horowitz LW, Tong DQ, West JJ. An estimate of the global burden of anthropogenic ozone and fine particulate matter on premature human mortality using atmospheric modeling. *Environ Health Perspect* 2010;118(9):1189–95.
86. US EPA. Particle Pollution and Your Health [Internet]. 2003. Available at: <http://www3.epa.gov/pm/pdfs/pm-color.pdf>.
87. Gilmour MI, Jaakkola MS, London SJ, Nel AE, Rogers CA. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environ Health Perspect* 2006;114(4):627–33.
88. US EPA. Health | Particulate Matter | Air & Radiation | US EPA [Internet]. 2015 [cited 2015 Aug 4]. Available at: <http://www.epa.gov/airquality/particulatematter/health.html>.
89. Hoek G, Raaschou-Nielsen O. Impact of fine particles in ambient air on lung cancer. *Chin J Cancer* 2014;33(4):197–203.
90. Loomis D, Huang W, Chen G. The International Agency for Research on Cancer (IARC) evaluation of the carcinogenicity of outdoor air pollution: focus on China. *Chin J Cancer* 2014;33(4):189–96.
91. Oftedal B, Brunekreef B, Nystad W, Madsen C, Walker S-E, et al. Residential outdoor air pollution and lung function in schoolchildren. *Epidemiology* 2008;19(1):129–37.
92. Chen C-H, Chan C-C, Chen B-Y, Cheng T-J, Leon Guo Y. Effects of particulate air pollution and ozone on lung function in non-asthmatic children. *Environ Res* 2015;137:40–8.
93. Pereira CEL, Heck TG, Saldiva PHN, Rhoden CR. Ambient particulate air pollution from vehicles promotes lipid peroxidation and inflammatory responses in rat lung. *Braz J Med Biol Res* 2007;40(10):1353–9.
94. US EPA O. Particulate Matter | Air & Radiation | US EPA [Internet]. 2015 [cited 2015 Jul 24]. Available at: <http://www.epa.gov/pm/>.
95. Van Eeden SF, Hogg JC. Systemic inflammatory response induced by particulate matter air pollution: the importance of bone-marrow stimulation. *J Toxicol Environ Health Part A* 2002;65(20):1597–613.
96. McConnell R, Berhane K, Gilliland F, London SJ, Vora H, et al. Air pollution and bronchitic symptoms in Southern California children with asthma. *Environ Health Perspect* 1999;107(9):757–60.
97. Ostro B, Roth L, Malig B, Marty M. The effects of fine particle components on respiratory hospital admissions in children. *Environ Health Perspect* 2009;117(3):475–80.
98. Lin M, Stieb DM, Chen Y. Coarse particulate matter and hospitalization for respiratory infections in children younger than 15 years in Toronto: a case-crossover analysis. *Pediatrics* 2005;116(2):e235–40.
99. US EPA, Sacks J. 2009 Final Report: Integrated Science Assessment for Particulate Matter [Internet]. 2009 [cited 2015 Aug 4]. Available at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546#Download>.
100. Sheffield P, Roy A, Wong K, Trasande L. Fine particulate matter pollution linked to respiratory illness in infants and increased hospital costs. *Health Aff* 2011;30(5):871–8.
101. Islam T, Gauderman WJ, Berhane K, McConnell R, Avol E, et al. Relationship between air pollution, lung function and asthma in adolescents. *Thorax* 2007;62(11):957–63.
102. Rabinovitch N, Strand M, Gelfand EW. Particulate levels are associated with early asthma worsening in children with persistent disease. *Am J Respir Crit Care Med* 2006;173(10):1098–105.
103. Fan J, Li S, Fan C, Bai Z, Yang K. The impact of PM2.5 on asthma emergency department visits: a systematic review and meta-analysis. *Environ Sci Pollut Res Int* 2015.
104. Mar TF, Larson TV, Stier RA, Claiborn C, Koenig JQ. An analysis of the association between respiratory symptoms in subjects with asthma and daily air pollution in Spokane, Washington. *Inhal Toxicol* 2004;16(13):809–15.
105. Mortimer KM, Neas LM, Dockery DW, Redline S, et al. The effect of air pollution on inner-city children with asthma. *Eur Respir J* 2002;19(4):699–705.
106. Weinmayr G, Romeo E, De Sario M, Weiland SK, Forastiere F. Short-term effects of PM10 and NO₂ on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. *Environ Health Perspect* 2010;118(4):449–57.
107. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. *J Allergy Clin Immunol* 2008;121(5):1133–9.e1.
108. McCormack MC, Breysse PN, Matsui EC, Hansel NN, Peng RD, et al. Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma. *Ann Allergy Asthma Immunol* 2011;106(4):308–15.

109. Yu O, Sheppard L, Lumley T, Koenig JQ, Shapiro GG. Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study. *Environ Health Perspect* 2000;108(12):1209–14.
110. Slaughter JC, Lumley T, Sheppard L, Koenig JQ, Shapiro GG. Effects of ambient air pollution on symptom severity and medication use in children with asthma. *Ann Allergy Asthma Immunol* 2003;91(4):346–53.
111. Møller P, Folkmann JK, Forchhammer L, Bräuner EV, Danielsen PH, et al. Air pollution, oxidative damage to DNA, and carcinogenesis. *Cancer Lett* 2008;266(1):84–97.
112. National Institute for Occupational Safety and Health (NIOSH). Hazard Alert: Worker Exposure to Silica during Hydraulic Fracturing [Internet]. 2012. Available at: https://www.osha.gov/dts/hazardalerts/hydraulic_frac_hazard_alert.html.
113. Coussens C, Martinez RM, others. Health Impact Assessment of Shale Gas Extraction: Workshop Summary [Internet]. National Academies Press; 2013 [cited 2015 Jul 21]. Available at: https://books.google.com/books?hl=en&lr=&id=aVqfAwAAQBAJ&oi=fnd&pg=PT10&dq=Health+impact+assessment+of+shale+gas+extraction:+workshop+summary.+Washington&ots=30xCaHDGfm&sig=_MUOqz1wv0GHKBg3Hky9CoN6HRI.
114. Korfmacher KS, Jones WA, Malone SL, Vinci LF. Public health and high volume hydraulic fracturing. *New Solut* 2013;23(1):13–31.
115. Witter RZ, Tenney L, Clark S, Newman LS. Occupational exposures in the oil and gas extraction industry: state of the science and research recommendations. *Am J Ind Med* 2014;57(7):847–56.
116. Shonkoff SB, Hays J, Finkel ML. Environmental public health dimensions of Shale and tight gas development. *Environ Health Perspect* [Internet]. 2014 Apr 16 [cited 2015 Aug 4]. Available at: <http://ehp.niehs.nih.gov/1307866>.
117. United States Environmental Protection Agency (EPA). Ambient Levels and Noncancer Health Effects of Inhaled Crystalline and Amorphous Silica: Health Issue Assessment, 1996.
118. CDC – NIOSH Publications and Products – Health Effects of Occupational Exposure to Respirable Crystalline Silica (2002-129) [Internet]. [cited 2015 Jul 24]. Available at: <http://www.cdc.gov/niosh/docs/2002-129/>.
119. Steenland K, Ward E. Silica: a lung carcinogen. *CA Cancer J Clin* 2014;64(1):63–9.
120. Madl AK, Donovan EP, Gaffney SH, McKinley MA, Moody EC, et al. State-of-the-science review of the occupational health hazards of crystalline silica in abrasive blasting operations and related requirements for respiratory protection. *J Toxicol Environ Health B Crit Rev* 2008;11(7):548–608.
121. Thomas CR, Kelley TR. A brief review of silicosis in the United States. *Environ Health Insights* 2010;4:21–6.
122. International Agency for Research on Cancer (IARC). A review of human carcinogens: chemical agents and related occupations. *IARC Monographs* 2012;100F.
123. Bang KM, Mazurek JM. Silicosis mortality, prevention, and control—United States, 1968–2002 (Reprinted from MMWR, vol 54, pg 401–405, 2005). *AMER MEDICAL ASSOC* 515 N STATE ST, CHICAGO, IL 60610 USA; 2005. 2585–2586 p.
124. Kanatani KT, Ito I, Al-Delaimy WK, Adachi Y, Mathews WC, et al. Desert dust exposure is associated with increased risk of asthma hospitalization in children. *Am J Respir Crit Care Med* 2010;182(12):1475–81.
125. US EPA. Waste and Cleanup Risk Assessment Glossary [Internet]. 2010 [cited 2015 Aug 3]. Available at: <http://www.epa.gov/oswer/riskassessment/glossary.htm>.
126. Pétron G, Karion A, Sweeney C, Miller BR, Montzka SA, et al. A new look at methane and nonmethane hydrocarbon emissions from oil and natural gas operations in the Colorado Denver-Julesburg Basin. *J Geophys Res Atmos* 2014;119(11):2013JD021272.
127. ATSDR. Toxicological Profile: Benzene [Internet]. 2007 [cited 2015 Apr 1]. Available at: <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14>.
128. US EPA. Benzene TEACH Chemical Summary [Internet]. 2007 [cited 2015 Apr 1]. Available at: http://www.epa.gov/teach/chem_summ/BENZ_summary.pdf.
129. Agency for Toxic Substances & Disease Registry (ATSDR). ATSDR – Toxicological Profile: Benzene [Internet]. 2007 [cited 2015 Aug 3]. Available at: <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14>.
130. US EPA O. Benzene | Technology Transfer Network Air Toxics Web site | US EPA [Internet]. 2012 [cited 2015 Aug 3]. Available at: <http://www.epa.gov/airtoxics/htlthe/benzene.html>.
131. Koren HS, Graham DE, Devlin RB. Exposure of humans to a volatile organic mixture. III. Inflammatory response. *Arch Environ Health* 1992;47(1):39–44.
132. Ware JH, Spengler JD, Neas LM, Samet JM, Wagner GR, et al. Respiratory and irritant health effects of ambient volatile organic compounds. The Kanawha County Health Study. *Am J Epidemiol* 1993;137(12):1287–301.
133. Heinrich J. Influence of indoor factors in dwellings on the development of childhood asthma. *Int J Hyg Environ Health* 2011;214(1):1–25.
134. Rumchev K, Spickett J, Bulsara M, Phillips M, Stick S. Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax* 2004;59(9):746–51.
135. Rive S, Hulin M, Baiz N, Hassani Y, Kignnlman H, et al. Urinary S-PMA related to indoor benzene and asthma in children. *Inhal Toxicol* 2013;25(7):373–82.
136. Smedje G, Norbäck D. Incidence of asthma diagnosis and self-reported allergy in relation to the school environment—a four-year follow-up study in schoolchildren. *Int J Tuberc Lung Dis* 2001;5(11):1059–66.
137. U.S. EPA Toxicity and Exposure Assessment for Children's Health. Formaldehyde: TEACH Chemical Summary, 2007.
138. Krzyzanowski M, Quackenboss JJ, Lebowitz MD. Chronic respiratory effects of indoor formaldehyde exposure. *Environ Res* 1990;52(2):117–25.
139. Olsen JH, Døssing M. Formaldehyde induced symptoms in day care centers. *Am Ind Hyg Assoc J* 1982;43(5):366–70.
140. Rumchev KB, Spickett JT, Bulsara MK, Phillips MR, Stick SM. Domestic exposure to formaldehyde significantly increases the risk of asthma in young children. *Eur Respir J* 2002;20(2):403–8.
141. Committee on the Assessment of Asthma and Indoor Air. Clearing the Air: Asthma and Indoor Air Exposures [Internet]. Institute of Medicine (IOM); 2000. Available at: <http://aspe.hhs.gov/sp/asthma/appxh.pdf>.
142. Lino dos Santos Franco A, Domingos HV, Damazo AS, Breithaupt-Faloppa AC, de Oliveira APL, et al. Reduced allergic lung inflammation in rats following formaldehyde exposure: long-term effects on multiple effector systems. *Toxicology* 2009;256(3):157–63.

143. Erdei E, Bobvos J, Brózik M, Páldy A, Farkas I, et al. Indoor air pollutants and immune biomarkers among Hungarian asthmatic children. *Arch Environ Health* 2003;58(6):337–47.
144. Ezratty V, Bonay M, Neukirch C, Orset-Guillossou G, Dehoux M, et al. Effect of formaldehyde on asthmatic response to inhaled allergen challenge. *Environ Health Perspect* 2007;115(2):210–4.
145. Daisey JM, Angell WJ, Apte MG. Indoor air quality, ventilation and health symptoms in schools: an analysis of existing information. *Indoor Air* 2003;13(1):53–64.
146. Smedje G, Norbäck D, Edling C. Asthma among secondary schoolchildren in relation to the school environment. *Clin Exp Allergy* 1997;27(11):1270–8.
147. US EPA. Regulatory Impact Analysis of the Proposed Emission Standards for New and Modified Sources in the Oil and Natural Gas Sector [Internet]. 2015. Available at: http://www3.epa.gov/airquality/oilandgas/pdfs/og_prop_ria_081815.pdf.
148. Fry M. Urban gas drilling and distance ordinances in the Texas Barnett Shale. *Energy Policy* 2013;62:79–89.
149. Richardson N, Gottlieb M, Krupnick A, Wiseman H. The State of State Shale Gas Regulation [Internet]. 2013. Available at: http://www.rff.org/files/sharepoint/WorkImages/Download/RFF-Rpt-StateofStateRegs_Report.pdf.
150. Ridlington, Dutzik T, Van Heeke T, Garber A, Masur D. Dangerous and Close: Fracking Near Pennsylvania's Most Vulnerable Residents. 2015. PennEnvironment Research & Policy Center, Frontier Group 2015.
151. US EPA, Office of Air and Radiation, Office of Air Quality Planning and Standards. Regulatory Impact Analysis of the Proposed Revisions to the National Ambient Air Quality Standards for Ground-Level Ozone [Internet]. 2014. Available at: <http://www.epa.gov/glo/pdfs/20141125ria.pdf>.
152. Hall JV, Brajer V, Lurmann FW. Economic valuation of ozone-related school absences in the South Coast Air Basin of California. *Contemp Econ Policy* 2003;21(4):407–17.
153. Berman JD, Fann N, Hollingsworth JW, Pinkerton KE, Rom WN, et al. Health benefits from large-scale ozone reduction in the United States. *Environ Health Perspect* 2012;120(10):1404–10.
154. NIOSH. CDC – Silica, General Publications – NIOSH Workplace Safety and Health Topic [Internet]. 2015 [cited 2015 Jul 30]. Available at: <http://www.cdc.gov/niosh/topics/silica/>.
155. Occupational Safety & Health Administration (OSHA). Crystalline Silica Rulemaking [Internet]. 2014. Available at: <https://www.osha.gov/silica/index.html>.
156. American Lung Association. Asthma & Children Fact Sheet [Internet]. American Lung Association. 2014 [cited 2015 Jul 30]. Available at: <http://www.lung.org/lung-disease/asthma/resources/facts-and-figures/asthma-children-fact-sheet.html>.
157. Colborn T, Kwiatkowski C, Schultz K, Bachran M. Natural Gas Operations from a Public Health Perspective. *Hum Ecol Risk Assess* 2011;17(5):1039–56.
158. Janssen S, Sass J, Schettler T, Solomon G. Strengthening Toxic Chemical Risk Assessments to Protect Human Health [Internet]. 2014. Available at: <http://www.nrdc.org/health/files/strengthening-toxic-chemical-risk-assessments-report.pdf>.
159. Kim JJ, American Academy of Pediatrics Committee on Environmental Health. Ambient air pollution: health hazards to children. *Pediatrics* 2004;114(6):1699–707.
160. Rabinowitz PM, Slizovskiy IB, Lamers V, Trufan SJ, Holford TR, et al. Proximity to Natural Gas Wells and Reported Health Status: Results of a Household Survey in Washington County, Pennsylvania. *Environ Health Perspect* [Internet]. 2014 Sep 10 [cited 2015 Jun 4]; Available at: <http://ehp.niehs.nih.gov/1307732>.
161. Jemielita T, Gerton GL, Neidell M, Chillrud S, Yan B, et al. Unconventional gas and oil drilling is associated with increased hospital utilization rates. *PLoS One* 2015;10(7):e0131093.