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Biological effects of inhaled hydraulic fracturing sand dust. I. Scope of the investigation

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ABSTRACT

Hydraulic fracturing ("fracking") is a process in which subterranean natural gas-laden rock is fractured under pressure to enhance retrieval of gas. Sand (a "proppant") is present in the fracking fluid pumped down the well bore to stabilize the fissures and facilitate gas flow. The manipulation of sand at the well site creates respirable dust (fracking sand dust, FSD) to which workers are exposed. Because workplace exposures to FSD have exceeded exposure limits set by OSHA, a physico-chemical characterization of FSD along with comprehensive investigations of the potential early adverse effects of FSDs on organ function and biomarkers has been conducted using a rat model and related *in vivo* and *in vitro* experiments involving the respiratory, cardiovascular, immune systems, kidney and brain. An undercurrent theme of the overall hazard identification study was, to what degree do the health effects of inhaled FSD resemble those previously observed after crystalline silica dust inhalation? In short-term studies, FSD was found to be less bioactive than MIN-U-SIL® 5 in the lungs. A second theme was, are the biological effects of FSD restricted to the lungs? Bioactivity of FSD was observed in all examined organ systems. Our findings indicate that, in many respects, the physical and chemical properties, and the short-term biological effects, of the FSDs share many similarities as a group but have little in common with crystalline silica dust.

1. Introduction

Retrieval of unconventional natural gas from subterranean rock formations involves horizontal drilling of wells and the technique known as hydraulic fracturing ("fracking") to increase the porosity of the rock, allowing efficient collection of the gas (Goldstein et al., 2014; Lampe and Stolz, 2015). During a complex process that occurs in several stages, fracking fluid is pumped under high pressure into the well bore to create fissures in the rock in order to facilitate diffusion of the gas.

Fracking fluid contains a large number of ingredients, including water, chemical agents, and sand. Depending on the geological characteristics of the rock that is being fractured, the chemicals may include among others: acids that help break down the rock; sand, a "proppant" that enters the fissures to maintain their patency and gas flow (Benson and Wilson, 2015); and surfactants that may prevent the sand from clumping (Stringfellow et al., 2016).

A body of literature exists concerning the potential implications of fracking on public health, particularly on water quality and the environment, and concerns about adverse health effects in organ systems have been expressed (Balise et al., 2016; Bamberger and Oswald, 2015; Fryzek et al., 2013; Korfmacher et al., 2013; Mackie et al., 2013; Shonkoff et al., 2014; Slizovskiy et al., 2015; Werner et al., 2015) or actual effects have been noted (Casey et al., 2016; Rabinowitz et al., 2015; Rasmussen et al., 2016; Tustin et al., 2016).

An additional concern is the health of workers involved in unconventional gas drilling, and interest in work site exposures and the resulting health effects is emerging (Adgate et al., 2014; Chalupka, 2012; Finkel and Hays, 2013; Finkel and Law, 2011; Kovats et al., 2014; Moitra et al., 2015; Zeaman et al., 2015; United States Department of Labor, 2020; United States Department of Labor, n.d). The focus of this interest has been on exposure of workers to airborne dusts during fracking. Esswein and co-workers (Esswein et al., 2013) measured exposures to dusts at gas well drilling sites where the mechanical handling of sand to prepare fracking fluid generates respirable fracking sand dust (FSD). Personal breathing zone samples of dust collected at wells in six geographical areas indicated that exposures to respirable crystalline silica exceeded the full-shift exposure limits set by the Occupational Safety and Health Administration (OSHA), and those recommended by the National Institute for Occupational Safety of Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH); a NIOSH Hazard Alert (NIOSH, 2002) was issued to summarize these findings for workers. Crystalline silica is used in several industries apart from natural gas drilling, and the permissible exposure limit (PEL) set by the OSHA, the NIOSH recommended exposure limit (REL) and the ACGIH threshold limit value (TLV), have been established to prevent the diseases known to be caused by inhalation of silica dust, including silicosis, kidney disease, autoimmune disease, lung cancer and increased susceptibility to tuberculosis (Department of Health and Human Services, 2002; McDonald et al., 2005). In particular, caution has been expressed that hydraulic fracturing might give rise to a new cohort of workers who develop silicosis (Quail, 2017). In addition, concerns also have been voiced about risks to workers associated with the mining and processing of sand for fracking, because air sampling in a preliminary study of fracking sites recorded fine particulate matter (PM2.5) levels

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above the Environmental Protection Agency standard of 12 μg/m^3 (Walters et al., 2015).

Approximately 160,000 workers (August 2020) are employed in the oil and gas sector in the United States [U.S. Department of Labor(a)], including all occupations related to this industry, such as workers involved in drilling, extraction, and support (U.S. Energy Information Administration, 2020). Typically, workers who service the gas wells are itinerant, moving from one site to another after having spent a few weeks at each well during the fracking stage. As such, there is no registry from which the prevalence of lung diseases in workers due to FSD inhalation can be deduced, and whether inhalation of FSD is associated with clinical symptoms of silica-induced diseases is currently unknown (HEI-Energy Research Committee, 2019a, 2019b). In contrast, emerging epidemiological studies have been performed to track the public health effects of hydraulic fracturing (see above). Thus, an investigation of the possible toxic effects of inhaled FSD on workers is critically needed. Many dust-unrelated risks and exposures confront workers in the oil and gas development sector, and recent comprehensive analyses have identified these as well as called for controlled epidemiological investigations, engineering controls to limit dust exposures (Esswein et al., 2019), and exposure and risk assessment studies related to the myriad possible exposures occurring in unconventional oil and gas drilling (HEI-Energy Research Committee, 2019a, 2019b).

Because crystalline silica in the form of α-quartz is a major component of FSD, workers exposed to FSD are at concentrations exceeding occupational exposure limits are at increased risk for malignant and non-malignant lung diseases. The International Agency for Research on Cancer has determined that crystalline silica in the form of quartz is carcinogenic in humans (International Agency for Research on Cancer, 2012). In addition, the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health have reviewed the numerous additional health risks associated with silica exposure (NIOSH, 2002; OSHA, 2012). Especially concerning is the observation that current occupational exposure limits may not be sufficient to entirely control the risk of silicosis, a progressive restrictive lung disease associated with inhalation of crystalline silica (NIOSH, 2002; Leung et al., 2012; OSHA, 2010). The most common form of silicosis, chronic silicosis, is caused by exposure to dusts containing crystalline silica and is associated with many years of exposure to relatively low concentrations of dusts containing crystalline silica (NIOSH, 2002). Silicosis is caused by exposure to many different types of dusts that contain crystalline silica, as confirmed by many studies and risk assessments (NIOSH, 2002; OSHA, 2010). Months of exposure are recommended to produce the equivalent silica lung burden in a rat on a mass basis (mg/g) to that received by a worker during a 45-yr working lifetime exposed at the silica PEL (Hubbs et al., 2005). Since those risk assessments have been established, the current studies were not designed to address risk for chronic silicosis or cancer after FSD exposure.

However, additional malignant and non-malignant diseases of the respiratory tract are also associated with exposures to silica-containing dusts in multiple industries (NIOSH, 2002; OSHA, 2010). In particular, silica-exposed workers without silicosis can still have impaired lung function (OSHA, 2010). Bronchitis and airflow limitation as well as a spectrum of extrapulmonary conditions are among the many risks in those exposed to crystalline silica (American Thoracic Society, 1997). The lung burdens (mg/g) produced in these studies were consistently less than a worker would receive in a few years working in sites where exposures are poorly controlled.

The sand used during hydraulic fracturing is comprised primarily of α-quartz, and it is reasonable to suspect that the effects of inhaled FSD could mimic the well-known toxic effects of crystalline silica occurring in humans and modeled in the literature. However, the toxicities of respirable FSD have not been established, either in humans or in animal models.

The concern being considered in this series of investigations is that exposures to FSD could have adverse effects even after short-term exposures at concentrations that may occur in poorly controlled fracking sites. The reports that follow this introduction describe *in vivo* and *in vitro* experiments that were performed in a rat model to fill this critical knowledge gap. The airborne particles that were collected from fracking sites were subjected to physical and chemical characterizations. In order to investigate the potential early toxicity of FSDs, the effects of treatment with FSDs on function of lung and several extrapulmonary organ systems and associated biomarkers were examined following i.t. instillation or inhalation of 10 or 30 mg/m^3 FSD for 6 h/d for 4 d. The organ systems investigated during this study (Table 1) included the respiratory, cardiovascular and immune systems, as well as kidney and brain. Additionally, cytotoxicity, inflammatory and molecular mechanisms were investigated. The methods and approaches taken in the seven studies in this series (Table 1) were as follows:

- *Study II. Particle characterization and pulmonary effects following intratracheal instillation* (Fedan et al., 2020). The following topics were addressed: Dust endotoxin levels; particle characterization with scanning electron microscope, dynamic light scattering, X-ray diffraction, energy dispersive, mineral, and electron paramagnetic resonance spectroscopy analyses; inflammatory response after i.t. instillation, *i.e.*, bronchoalveolar lavage markers and lung histopathology.
- *Study III. Cytotoxicity and pro-inflammatory responses in murine macrophages* (Olgun et al., 2020). The following topics were addressed: Analysis of bacterial growth; macrophage cell viability; •OH radicals and reactive oxygen species; DNA damage; cytokine production; dark-field study of macrophages.
- *Study IV. Pulmonary ventilatory and non-ventilatory effects* (Russ et al., 2020). The following topics were addressed: Description of inhalation chamber and respirable particle size characterization; lung burden and lung clearance; tracheal particle deposition; lung mechanics; airway reactivity to methacholine *in vivo* and *in vitro*; neural regulation of airways; vascular permeability; epithelial ion transport; lactate dehydrogenase (LDH) and cytokine release in cultured airway epithelial cells; inflammatory markers in bronchoalveolar lavage; lung histopathology; gene expression.
- *Study V. Pulmonary inflammatory, cytotoxic and oxidant effects* (Sager et al., 2020). The following topics were addressed: FSD particles in alveolar macrophages; inflammatory mediators and cells in bronchoalveolar lavage; lung histopathology; gene expression profiling.
- *Study VI. Cardiovascular effects* (Krajnak et al., 2020). The following topics were addressed: Microvessel reactivity to phenylephrine and acetylcholine; reactive oxygen species in heart and kidney; cardiac function; protein and transcript levels in heart and kidney.
- *Study VII. Neuroinflammation and altered synaptic protein expression* (Sriram et al., 2020). The following topics were addressed:

Table 1
Tandem papers describing the overall investigation of the biological effects of FSD.

Topic	Authors (See references)	Paper
Introduction to investigation	Fedan et al., (2020) (this paper)	I
FSD physical and chemical characterization and preliminary pulmonary effects	Fedan et al. (2020)	II
Cytotoxicity	Olgun et al. (2020)	III
Pulmonary effects: functional effects	Russ et al. (2020)	IV
Pulmonary: inflammatory, cytotoxic and oxidant effects	Sager et al. (2020)	V
Cardiovascular and kidney effects	Krajnak et al. (2020)	VI
Neuroinflammatory effects	Sriram et al. (2020)	VII
Immunotoxicity	Anderson et al. (2020)	VIII
Summary and significance	Investigative Team (2020)	IX

Neuroinflammation; blood-brain barrier; biogenic amine neurotransmitter levels; neuronal synaptic protein expression; astroglial activation; myelin basic protein.

- *Study VIII. Immunotoxicity* (Anderson et al., 2020). The following topics were addressed: Immunophenotyping; natural killer cells; hematology and serum chemistries; IgM response to sheep red blood cells.

An underlying theme of the overall study is, to what degree do the short-term health effects of inhaled FSDs resemble those observed after crystalline silica dust is inhaled? Our findings indicate that crystalline silica and FSDs differ in their physico-chemical properties. Where direct comparisons could be made, FSDs caused weaker biological effects than crystalline silica but also effects on many organ systems after short-term inhalation exposure of rats.

2. Disclaimer

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

Declaration of Competing Interest

The author declares that there are no conflicts of interest in relation to this publication.

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