A. COVER PAGE

Project Title: Transgenerational work exposures, EDCs and male fertility	
Grant Number: R03OH011540	**Project/Grant Period**: 9/30/2018 – 9/29/2021
Reporting Period: 9/30/2018 – 9/29/2021	**Date Submitted**: 2/14/22
Program Director/ Principal Investigator **John D Meyer MD MPH** **Professor, Dept of Environmental Medicine & Public Health** **ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI** **One Gustave L. Levy Place, Box 1057** **New York, NY 10029** **Phone: (212) 824-7057** **Email: john.meyer@mssm.edu**	**Administrative Official Information** **Jessica Ruth Moise** **Senior Associate Dean for Sponsored Programs** **ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI** **One Gustave L. Levy Place, Box 1075** **New York, NY 10029-6574** **Phone: (212) 824-8300 Fax: (212) 241-3294** **Email: jessica.moise@mssm.edu**
Change of Contact PD/PI:	
Human Subjects: Yes (exempt)	**Vertebrate Animals: No**
hESC: No	**Inventions/Patents: None**

B. ACCOMPLISHMENTS

B.1. What are the major goals of the project?

The goals were to determine the effects of occupational exposures on male fertility indices (primarily sperm concentration) through construction of an intergenerational model of vulnerability. We planned to accomplish this objective through the following specific aims:

1. Analyzing fertility indices (semen parameters) and occupational data collected in 717 working male participants in the Study for Future Families (SFF), to estimate their association with:
    a. Male occupation reported in the SFF
    b. Specific job exposures reported in the SFF
    c. Occupational exposures to endocrine-disrupting (ED) chemicals, through cross-classification of occupation with data from a job-exposure matrix to these chemicals
2. Examining the association of the male partner's fertility indices with parental occupation while in utero:
    a. Assessing associations between male reproductive indices and work, work exposures, and occupational ED exposures of the male-partner's mother and father in 607 SFF participant families
    b. Determining the vulnerability of male fertility indices to a second insult by modeling the effects of male subjects' occupational exposures superimposed on prior parental occupational exposures.

B.2. What did you accomplish under these goals?

Data from 680 male SFF participants with a current occupation and who met abstinence criteria for semen sampling were analyzed. Lower sperm concentration and motility, contrasted with office workers, were seen in some equipment installation, maintenance, and repair occupations. A higher prevalence of exposure to lead (prevalence ratios versus the entire dataset 4.1 (95% CI 2.1-7.9)), and, to a lesser extent, to pesticides/herbicides (PR 1.6 (1.0-2.5)) and to solvents (1.4 (1.1-1.8)) was seen in occupations with lower mean sperm concentrations. Lower sperm concentration was seen in participants who noted work exposure to lead for >3 months contrasted with the unexposed (mean 45.3 x 10^6/mL versus 62.7 x 10^6/mL; p=0.03) a decrement that was increased in those who also had lead exposure outside of work.

In this group of fertile men, we found evidence for associations of reduced sperm quality with several reported occupational exposures, principally lead, and to a lesser extent, pesticides/herbicides and solvents. Depression of semen parameters may be occurring at work even in demonstrably fertile men, particularly in jobs exposed to lead. These results may help to identify occupations where additional consideration of protective measures against exposures with male reproductive toxicity might be warranted.

Additionally, although analyses are not complete, we have found evidence for decreased sperm parameters in men whose mothers worked in jobs considered exposed to EDCs. Total sperm counts were decreased by 76x10^6 in these individuals (contrasted with those born of unexposed mothers; p<0.001) while paternal work with EDCs was associated with only a reduction of 10.9x10^6 (NS). Further analyses are forthcoming on this noteworthy finding.

B.3. Competitive Revisions/Administrative Supplements

None

B.4. What opportunities for training and professional development did the project provide?

The PI, Dr Meyer, gained opportunities to develop additional expertise in reproductive hazards focused on risks to male fertility which complemented his knowledge of occupational risks to pregnancy. Additionally the project served as a demonstration of intergenerational transmission of reproductive risk from mother to her son.

B.5. How did you disseminate the results to communities of interest?

Papers are in current preparation and will be disseminated to the research community. The findings will be of particular interest to practitioners who assess infertility, especially with respect to the hazards of lead exposure, and to those responsible for occupational safety and health in industries noted above, which in many cases have not traditionally been considered at-risk for reproductive hazards. Additionally these will serve as a basis for further consideration of immediate and transgenerational exposure to EDCs and will be expected to be of interest to regulators.

B.6 - What do you plan to do during the next reporting period to accomplish the goals?
Current end of reporting period. However, the results as listed above will be written up and published once completed

C. PRODUCTS

C.1. Publications, conference papers, and presentations
Meyer JD, Swan S, et al *Occupation and semen parameters in a cohort of fertile men*. In preparation for submission

C.2. Website(s) or other Internet site(s) – include URL(s)

C.3. Technologies or techniques

C.4. Inventions, patent applications, and/or licenses

C.5. Other products and resource sharing

D. PARTICIPANTS

D.1. What individuals have worked on the project? Please include calendar, academic, and summer months.

Commons ID	S/K	Name	Degrees(s)	Role	Cal	Aca	Sum	Foreign	Country	SS
jmeyer424		Meyer, John	MD, MPH	PI	1.5					
shannaswan		Swan, Shanna	PhD	Co-I	0.5					

D.2 Personnel updates: **None**

a. Level of Effort:
b. New Senior/Key Personnel:

c. Changes in Other Support:
d. New Other Significant Contributors:

E. IMPACT

E.1 - What is the impact on the development of human resources, if applicable?
Not applicable

E.2 - What is the Public Health Relevance and Impact? The investigator should address how the findings of the project relate beyond the immediate study to improved practices, prevention or intervention techniques, legislation, policy, or use of technology in public health.

Male infertility and subfertility accounts for roughly half of the 10-15% prevalence of overall failure to conceive a child. An accumulated body of evidence across the past two decades suggests fetal origins of adult male reproductive dysfunction. Male reproductive dysfunction could proceed intergenerationally, with parental work contributing to male subfertility in the next generation, and increased vulnerability to second insult in the adult male exposed in utero or via parental occupation. This work is one of the first to examine the role of occupational exposures sustained by parents of male subjects in reduced fertility or susceptibility to insult from occupational exposures in the subsequent generation. The richness of this dataset, combined with the linkage of male fertility parameters with parental occupational data, is an opportunity to test a novel hypothesis on intergenerational transmission of male subfecundity, the results of which are so far indicative of an association. The findings of this proposed study lay the groundwork for efforts to reduce potentially hazardous occupational exposures in both fertile men and women across generations. This proposal addresses the CDC/NISOH/NORA cross-sector program in Cancer, Reproductive and Cardiovascular Diseases which aims to better identify and control reproductive toxicant exposures, and is relevant to the health of workers in the Healthcare, Manufacturing, and Construction NORA sectors. Since the overall contribution of occupational exposures to male and female infertility remains unknown; this effort makes a significant contribution toward a research agenda on male and intergenerational workplace exposures and fertility. The work supports NIOSH r2p initiatives in providing detailed information on adverse reproductive exposures in the workplace, and their mitigation, as well as increasing protection of workers who may be at greater risk from prior parental exposures.

F. CHANGES

F.1 – Changes in approach and reasons for change, including changes that have a significant impact on expenditures
None

F.2 - Actual or anticipated challenges or delays and actions or plans to resolve them
Work on the project was significantly delayed by the response to the COVID19 pandemic occurring in the late winter and early spring of 2020 to the present time, with particular disruption to research work in New York City, and which necessitated redeployment and assumption of other clinical duties by the PI, a medical doctor. Additionally, the pandemic response entailed disruptions in normal work, working space, and information technology, and projected activities involving the statistical analyses of the work were not possible during much of the period from March through the present. These will be continued across the next year as the pandemic response permits

F.3 - Significant changes to human subjects, vertebrate animals, biohazards, and/or select agents
None

G. Special Reporting Requirements

G.1 Special Notice of Award Terms and Funding Opportunities Announcement Reporting Requirements
N/A

G.2 Responsible Conduct of Research
N/A

G.3 Mentor's Research Report or Sponsor Comments
N/A

G.4 Human Subjects

G.4.a Does the project involve human subjects? **Yes (Exemption 4: use of previously recorded data that was nonidentifiable).**

G.4.b Inclusion Enrollment Data **N/A**

G.4.c ClinicalTrials.gov **N/A**

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA? **No**

G.5 Human Subject Education Requirement
Are there personnel on this project who are newly involved in the design or conduct of human subject's research?
No

G.6 Human Embryonic Stem Cells (HESCS)
Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?
No

G.7 Vertebrate Animals
Does this project involve vertebrate animals?
No

G.8 Project/Performance Sites

Offices of PI in Dept of Environmental Medicine & Public Health; Icahn School of Medicine at Mount Sinai; New York, NY

G.9 Foreign Component

None

G.10 Estimated Unobligated Balance

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

Not applicable

G.11 Program Income

Is program income anticipated during the next budget period? **No**

G.12 F&A Costs

Is there a change in performance sites that will affect F&A costs? **No**

I. OUTCOMES

I. Provide a concise summary of the outcomes or findings of the award, written for the general public in clear and comprehensible language, without including any proprietary, confidential information or trade secrets
Note: project outcome information will be made public in NIH RePORTER

Male infertility and subfertility accounts for roughly half of the 10-15% prevalence of overall failure to conceive a child. This work is one of the first to examine the role of occupational exposures sustained by parents of male subjects in reduced fertility or susceptibility to insult from occupational exposures in the subsequent generation. Using a unique dataset of male reproductive parameters and male-maternal questionnaire data, we modeled effects of work exposures of two generations on men's semen and hormonal parameters.

Lower sperm concentration and motility, contrasted with office workers, were seen in some equipment installation, maintenance, and repair occupations. A higher prevalence of exposure to lead, and, to a lesser extent, to pesticides/herbicides and to solvents was seen in occupations with lower mean sperm concentrations. Lower sperm concentration was seen in participants who noted work exposure to lead that went on for 3 months or longer compared with those not exposed, This decrement in semen quality was increased further in those who also had lead exposure outside of work. Depression of semen quality may be occurring at work even in demonstrably fertile men, particularly in jobs exposed to lead. These results may help to identify occupations where additional consideration of protective measures against exposures with male reproductive toxicity might be warranted.

Additionally, we have found preliminary evidence for decreased sperm quality in men whose mothers worked in jobs that likely exposed them to endocrine-disrupting chemicals (EDCs). Total sperm counts were decreased in men whose mothers were probably exposed at work contrasted with those born of unexposed mothers, while probable paternal work with EDCs did not lead to a similar reduction. Further analyses are forthcoming on this finding. The findings of this study will help inform efforts to reduce work hazards and exposures in both fertile men and women and cross-generationally.