NATIONAL OCCUPATIONAL RESEARCH AGENDA (NORA)

NATIONAL OCCUPATIONAL RESEARCH AGENDA FOR CANCER, REPRODUCTIVE, CARDIOVASCULAR, and OTHER CHRONIC DISEASE PREVENTION (CRC)

November 2017

Developed by the NORA CRC Council

For more information about the National Occupational Research Agenda (NORA), visit the web site: https://www.cdc.gov/niosh/nora/

For monthly updates on NORA, subscribe to NIOSH eNews at www.cdc.gov/niosh/eNews

Disclaimer

This is a product of the National Occupational Research Agenda (NORA) Cancer, Reproductive, Cardiovascular and Other Chronic Disease Prevention (CRC) Council. It does not necessarily represent the views of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services.

INTRODUCTION

What is the National Occupational Research Agenda?

The National Occupational Research Agenda (NORA) is a partnership program to stimulate innovative research and workplace interventions. In combination with other initiatives, the products of this program are expected to reduce the occurrence of injuries and illnesses at work. Unveiled in 1996, NORA has become a research framework for the Nation and National Institute for Occupational Safety and Health (NIOSH). Diverse parties collaborate to identify the most critical issues in workplace safety and health and develop research objectives for addressing those needs.

NORA enters is third decade in 2016 with an enhanced structure. The ten sectors formed for the second decade continue to prioritize occupational safety and health research by major areas of the U.S. economy. In addition, there are seven cross-sectors organized according the major health and safety issues affecting the U.S. working population. While NIOSH is serving as the steward to move this effort forward, it is truly a national effort. NORA is carried out through multi-stakeholder councils, which are developing and implementing research agendas for the occupational safety and health community over the decade (2016-2026). Councils address objectives through information exchange, partnership building, and enhanced dissemination and implementation of evidence-based solutions.

NORA groups health and safety issues into seven cross-sectors. The Cancer, Reproductive, Cardiovascular, and Other Chronic Disease Prevention (CRC) Cross-Sector focuses on occupational safety and health research related to the prevention of cancer, adverse reproductive health outcomes, and cardiovascular disease. Additionally, CRC includes other chronic diseases, such as the evolving areas of occupational neurologic and renal disease. The CRC Council developed strategic objectives for research based on, to the greatest extent possible, basic public health criteria. Such criteria include:

- number/prevalence of workers affected;
- whether the problem is likely to be increasing or decreasing;
- severity;
- economic burden;
- disparity across geographic, age, gender, or racial/ethnic group; and
- availability of effective interventions.

What are NORA Councils?

Participation in NORA Councils is broad, including stakeholders from universities, large and small businesses, professional societies, government agencies, and worker organizations. Councils are co-chaired by one NIOSH representative and another member from outside NIOSH.

Statement of Purpose:

NORA councils are a national venue for individuals and organizations with common interests in occupational safety and health topics to come together. Councils have started the third decade by identifying broad occupational safety and health research objectives for the nation. These research objectives build from advances in knowledge in the last decade, address emerging issues, and are based on council member and public input. Councils will spend the remainder of the decade working together to address the agenda through information exchange, collaboration, and enhanced dissemination and implementation of solutions that work.

Although NIOSH is the steward of NORA, it is just one of many partners that make NORA possible. Councils are not an opportunity to give consensus advice to NIOSH, but instead a way to maximize resources towards improved occupational safety and health nationwide. Councils are platforms that help build close partnerships among members and broader collaborations between councils and other organizations. The resulting information sharing and leveraging efforts promotes widespread adoption of improved workplace practices based on research results.

Councils are diverse and dynamic, and are open to anyone with an interest in occupational safety and health. Members benefit by hearing about cutting-edge research findings, learning about evidence-based ways to improve safety and health efforts in their organization, and forming new partnerships. In turn, members share their knowledge and experiences with others and reciprocate partnerships.

The NORA CRC Cross-Sector Council was formed in 2016 as the third decade of NORA was initiated. The CRC Council aims to provide national leadership for the prevention of work-related chronic diseases using a scientific approach to gather and synthesize information, create knowledge, provide recommendations, and deliver products and services to those who can effect prevention. The CRC Council members have intended that the National Occupational Research Agenda for CRC succinctly presents the relevant information toward the overall objectives. The CRC Council recognized the importance of input received from stakeholders through the public comment period on the Agenda. The members of the NORA CRC Council are:

Laura Beane Freeman PhD – Co-Chair
Paul A. Landsbergis, PhD, EdD, MPH – Co-Chair
John D Meyer MD MPH – Co-Chair
Douglas Trout, MD, MHS – Co-Chair
Benjamin C. Amick III, PhD
Paul A. Demers, PhD
Michael L. Eisenberg, MD
Anna Fendley
Erin N. Haynes, DrPH, MS
Jeffery E. Hess, MD, MS
Mika Kivimäki, PhD, MA
Jason Lang, MPH, MS
Tina Lawson, PhD
Jennita Reefhuis, PhD
Emily Smith
Jamie Becker
Kurt Straif, MD, PhD, MPH
John M. Violanti, PhD
Lee Warner, PhD
Teresa Schnorr, PhD
Mary Schubauer-Berigan, PhD

What does the National Occupational Research Agenda for CRC represent?

The National Occupational Research Agenda for CRC is intended to identify the knowledge and actions most urgently needed to identify occupational risk factors to prevent avoidable adverse health outcomes among workers. This Agenda provides a vehicle for all stakeholders to describe the most relevant issues, research gaps, and safety and health needs for the cross-sector. It is meant to be broader than any one agency or organization. It identifies the priorities for the entire country and all of its research and development entities, whether government, higher education, or industry. Because the Agenda is intended to guide national occupational health and safety efforts for CRC, it cannot at the same time be an *inventory* of all issues worthy of attention. The omission of a topic does not mean that topic was viewed as unimportant. Those who developed this Agenda did, however, believe that the number of topics should be small enough so that resources could be focused on a manageable set of objectives, thereby increasing the likelihood of real impact in the workplace.

NIOSH will use the Agendas created by the sector and cross-sector NORA councils as an input into the development of a NIOSH Strategic Plan. Programs will use the burden, need and impact method to write research goals that articulate and operationalize the components of the NORA sector and cross-sector Agendas that NIOSH will take up. NORA Agendas and the NIOSH Strategic Plan are to be separate but linked.

Who are the target audiences?

The National Occupational Research Agenda for CRC provides priorities to guide industry, labor, federal, state, and local governments, as well as to experts in professional associations, academia, and public interest/advocacy groups, in future work intended to reduce adverse health outcomes due to occupational hazards.

The path between the conduct of research and eventual resulting changes in practice can be long and indirect for epidemiologic and laboratory-based studies. Information resulting from a research portfolio addressing the objectives presented below can be used to: (a) guide further work - in both research settings and in the workplace - that will specifically address the objectives and priorities presented; (b) develop appropriate recommendations and guidelines that can be implemented in the workplace; and (c) further research related to these health outcomes in general. The CRC Council supports increasing the integration of occupational safety and health research into “main stream” medical research. Increasing usage, and usability, of electronic health and disability records and other administrative surveillance systems is encouraged

How was the research agenda developed?

This Agenda was developed as a product of a series of meetings of the CRC Council in 2017. The Agenda is based on information from the scientific literature, individual expertise and experience, and discussion within and among the CRC Council members; the Agenda focuses on occupational cancer, adverse reproductive outcomes related to occupation, and CVD among workers. The Agenda currently contains no objectives for neurologic and renal diseases among workers.

BACKGROUND

Cancer

Cancer is a leading cause of death in the U.S. [1]. Although cancer is a group of different diseases, it is marked by same feature, the uncontrolled growth and spread of abnormal cells. Many factors play a role in the development of cancer and each type may have its own set of causes. The importance of the factors varies depending on the type of cancer. A person's risk of developing a particular cancer is influenced by a combination of factors that interact in ways that are not fully understood. Some of the factors include non-modifiable factors (e.g. age, sex, race, and family history of cancer) and modifiable factors (e.g. diet, cigarette smoking, and exposure to cancer-causing agents or factors in the workplace).

Less than two percent of chemical or physical agents manufactured or processed in the U.S. have been evaluated by the International Agency for Research on Cancer for carcinogenicity [2]. However, based on well-documented associations between occupational exposures and cancer, researchers have estimated that between 2-8% of all cancers worldwide are caused by exposures to carcinogens in the workplace [3-6]. The range estimates are higher for men (3-14%) than for women (1-2%) [5]. Attributable fractions also vary by type of cancer – for example more than 20% of lung cancer deaths and 7% of bladder cancer deaths have been estimated to be related to occupation [7]. Available estimates are probably underestimates, partly because they do not include a large number of already-identified agents which may be carcinogens (for example those agents listed by IARC as possibly carcinogenic to humans {2B}) and we continue to discover new information about agents in the workplace that may cause cancer [5, 8-10].

Cancers that occur as a result of exposures in the workplace are preventable if exposures to known or suspected carcinogens can be reduced or eliminated [11-13]. To improve the ability to implement effective preventive measures, occupational cancer risks must first be identified and the magnitude of those risks understood. Further research is needed to reduce exposures to carcinogenic agents within and outside the workplace and on which to base authoritative recommendations [14-17].

Adverse Reproductive Health Outcomes

Adverse reproductive outcomes affect both men and women, and effects can manifest at many points throughout the reproductive cycle, including infertility (male and female), menstrual cycle changes, pregnancy loss, pregnancy complications, low birth weight, preterm delivery, developmental abnormalities, and congenital malformations in offspring. Each year, about 24,000 babies are stillborn in the United States and over 350,000 babies are born prematurely [18-22]. Because reproductive outcomes are likely multifactorial, and are often competing outcomes (e.g. a pregnancy that ends in miscarriage cannot result in a birth defect), large studies—often registry- or population-based—are typically required to determine the contribution of workplace factors to adverse reproductive outcomes.

Several chemicals with reported reproductive and developmental effects are still in regular commercial or therapeutic use and thus present potential ongoing exposure to many workers. Examples of these include certain heavy metals, organic solvents, pesticides and herbicides, sterilants, high-level disinfectants, anesthetic gases, and antineoplastic drugs used in healthcare. Many other substances are suspected of producing reproductive or developmental toxicity but sufficient data on their effect are lacking. Progress has been limited in identifying and quantifying the effect of new reproductive hazards, and in separating the contribution of these hazards from other etiologic factors. The pace of laboratory studies to identify hazards and to understand the biologic mechanism of effects in humans has not matched the pace at which new chemicals are introduced into commerce. In addition, there are several non-chemical exposures to consider when evaluating occupational reproductive health; this includes shiftwork, physical demands, heat, and exposure to light at night. A primary goal of occupational reproductive health research is to reduce adverse outcomes, focusing on efforts to: a) understand mechanisms by which workplace toxicants or other factors exert their effects, b) identify populations at risk, and c) evaluate reproductive and developmental hazards to improve public and occupational health.

Cardiovascular Disease

Cardiovascular diseases (CVDs) involve the heart or blood vessels, including cerebrovascular disease (defined to include conditions caused by problems that affect the blood supply to the brain). CVD is the leading cause of death in the United States [23]. Behaviors and other factors that increase the risk of cardiovascular ill health have been characterized [24]. More than half of those with CVD (53%) are less than 60 years old, and CVD is a leading cause of death and permanent disability among workers [25, 26].

Occupational exposures associated with heart disease have been a topic of interest for a number of years. Some of the more well-characterized exposures of concern are specific chemical agents [27] —arsenic, carbon disulfide, carbon monoxide, methylene chloride, industrial solvents, and lead. Non-chemical workplace factors of concern include physical exertion and physical inactivity, excessive heat or cold, noise, shift work, long work hours and psychosocial factors such as job strain (high demand-low control work) and other job stressors. Reviews and meta-analyses of shift work and CVD outcomes have been published recently [28, 29]. A recent comprehensive review found moderately strong evidence for a relationship between coronary heart disease and job strain and low job decision latitude. More limited evidence was found for iso-strain, job demands, effort-reward imbalance, low support, lack of organizational justice, lack of skill discretion, insecure employment, night work, long work weeks and noise [30]. The Sixth International Conference on Work Environment and Cardiovascular Diseases adopted a

statement in 2013 that "10%–20% of all causes of CVD deaths among working age populations….are work-related" [31]. While some specific physical and chemical exposures are better controlled currently than in the past, further research is needed to better understand: the mechanisms by which occupational factors increase risk; the proportion of CVD due to occupational factors; and the effectiveness of various interventions to reduce CVD among workers. Since CVD is the leading cause of death in the US, a priority needs to be given to such research.

THE OBJECTIVES

The following objectives in this agenda are intended to assist in guiding researchers and other occupational safety and health professionals to further investigate workplace agents or workplace factors which may be associated with the health effects addressed by the CRC, and to minimize occupational exposure to such agents, with the ultimate goal of reducing morbidity and mortality. For all the objectives below, increased data are needed related to diverse and vulnerable populations, which may include for example ageing workers, young workers, and female workers [9, 32]. Additionally, effective communication of study results to all stakeholders is critical. Ideally, scientific knowledge should be rapidly shared and translated into public health programs and evidence-based practices. Where there are key uncertainties, employers and employees should be equipped with resources to help them make informed, evidence-based decisions that acknowledge both what is known and what is unknown. Educational programs should be developed and conducted with stakeholders to: (1) expand awareness of health outcomes among workers, employers, and other stakeholders; and (2) promote implementation of preventive measures to reduce risk in the workplace.

CANCER

Objective 1: Improve the ability to assess the burden associated with occupational cancer.

A number of surveillance activities can be used to estimate exposure levels and the number of workers exposed to known and potential carcinogens across the entire U.S. workforce. However, all have limitations. A nationally representative occupational exposure survey — to gather and provide data needed to describe potential exposures agents in workplaces in the U.S. – would be beneficial for all types of occupational health research including research focused on occupational cancer.

While data from current cancer registries are crucial in enabling public health professionals to understand and address the burden of cancer (https://www.cdc.gov/cancer/npcr/index.htm), incomplete occupational information makes documentation and the study of cancer to address occupational factors difficult. All states now have cancer registries, but accessing the data currently requires application to and approval from each state, which can make large-scale multi-site studies a challenge. Further development of the occupational data collection with the registries, and more streamlined approaches to accessing population-based cancer registries, would make occupational information accessible for research and surveillance purposes on a national basis [33].

Additionally, other surveillance methods should be promoted to identify potential workplace carcinogens and emerging occupational hazards [34]. For example, improvements in the development and maintenance of large registries, and subsequent linkage of registry data with other relevant data sources, would promote occupational cancer surveillance and etiologic cancer research [35].

Lastly, the study of the economic burden of occupational cancer, a subset of broader studies [36], is an underdeveloped area and could be important in increasing awareness of the need for occupational cancer research.

Objective 2: Assess the magnitude and characteristics of worker exposures and associated control technologies.

Research is needed to develop and evaluate industrial hygiene sampling and analytical methods (including biomonitoring and other methods) for the determination of carcinogen exposures.; Research should be conducted to develop exposure profiles of carcinogens using currently available industrial hygiene methods along with new methods as they are developed – such work should include intervention-effectiveness research [10, 33]. Occupational environments in which cancer may be attributable to multiple exposures should be addressed where feasible. These multiple exposures may include conditions and factors such as chemicals, biologic agents, and physical and psychosocial factors [9].

Objective 3: Conduct analytic epidemiology and toxicology studies of prioritized populations and exposures to identify (or rule out) potential occupational carcinogens.

Prioritization of individual agents as well as occupation/industries or workplace factors should be based on available literature and findings of authoritative groups. The National Institute of Environmental Health Science's National Toxicology Program [37] and the World Health Organization's International Agency for Research on Cancer [10, 34, 38] provide reviews of chemicals/agents and identify those lacking key epidemiologic or toxicologic data that would allow for more definitive classification.

Additional and parallel efforts should be undertaken to identify related and emerging issues in occupational cancer. This may include research to:

- identify and characterize agents or workplace factors for which there are limited data (e.g., epidemiologic or toxicologic) related to occupational carcinogenicity;
- identify and characterize important interactions of potential or known occupational carcinogens with other exposures (both occupational and non-occupational), workplace factors, or markers of genetic susceptibility [9, 33, 39];
- investigate occupational factors which may affect the clinical course of cancer among workers, including such factors as return to work [40-42];
- where possible, include quantitative exposure assessments to increase the usefulness of those studies in assessing the exposure response relationship [32];
- facilitate the development of risk-based recommendations aimed at reducing exposures to known carcinogens (e.g., ionizing radiation) for which the quantitative risk at occupationally relevant levels is uncertain;
- encourage the use of collaborative research studies to expand the power of available data in the assessment of occupational carcinogens [43].

Objective 4: Develop laboratory-based research.

Laboratory-based research is needed to support surveillance and research efforts aimed at preventing occupational cancer. Laboratory-based research includes a wide range of activities, including study of pre-clinical markers of exposure and effect (to assist in the identification of carcinogens by providing measures of effect or exposure) and study of key mechanistic pathways for high priority chemical and physical agents [44].

Objective 5: Perform research to investigate the effectiveness of workplace screening for early detection of occupational cancers.

Medical screening remains an important component of occupational health practice in many instances. Research is needed to improve currently available screening methods for occupational cancer. One important area of study

involves international collaboration to assess the effect (efficacy) of low-dose computed tomography screening among workers exposed workers to lung carcinogens [45- 47].

Objective 6: Develop new methods for and conduct quantitative cancer risk assessments in support of authoritative recommendations for preventing occupational cancers.

Quantitative risk assessment models may be the basis of authoritative recommendations aimed at prevention. New methods of quantitative risk assessment will be important to inform and advance the prioritization of study of potential carcinogens as new information concerning occupational agents of concern is made available. This may be particularly relevant for carcinogens or potential carcinogens whose quantitative risk at occupationally relevant levels is uncertain.

ADVERSE REPRODUCTIVE HEALTH OUTCOMES

Objective 7: Improve understanding of mechanisms by which hazardous agents and workplace factors are related to adverse reproductive outcomes.

Improving understanding of mechanisms (and mode(s) of action) is important for a variety of reasons: improving our ability to identify potential reproductive hazards, supporting the biologic plausibility of associations between exposures and adverse effects, and predicting possible reproductive and developmental effects of new or untested chemicals in the workplace.

New chemicals, materials, and processes are introduced into commerce at rates which exceed the ability and availability of toxicologic testing. As a result, sufficient data on the reproductive toxicity of these are lacking. Laboratory-based studies that can identify the mutagenicity, teratogenicity, and other hazards to the reproductive systems of both men and women, as well as the developing fetus, should be expanded. Chemicals identified as having high potential for reproductive toxicity, or which demonstrate evidence of toxicity and are in frequent use, should be made priority targets for epidemiologic and population-based investigations to determine their health effects in humans. New efforts to prioritize chemicals for evaluation, or develop improved toxicologic testing protocols, should try to complement existing efforts (such as the European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)) where possible.

Objective 8: Improve the efficiency and effectiveness of systems to identify adverse reproductive outcomes, potential workplace risk factors and workers at risk.

Improved data systems and surveillance methods to collect occupational information and information on the reproductive health of workers (potentially retrospectively and/or prospectively) are needed to better identify and link adverse reproductive outcomes and potential workplace risk factors.

8A. *Develop rapid screening methods for reproductive outcomes*

The largest need is to develop new, more rapid methods to screen large numbers of chemicals and to identify those that are potential reproductive hazards. This would allow researchers to prioritize the chemicals and workplace factors with potentially greater severity and broader workplace exposure.

8B. *Improve tools to collect and code occupation and industry from vital records, surveillance systems, and surveys.*

Currently, the U.S. standard certificates of live birth, fetal death, and infant death do not include parents' occupation. Although many state birth registries collect parental occupational data, national data linkage efforts,

and state and regional comparisons are limited by this lack of inclusion. Parental occupation is also not collected in many surveillance registries for congenital anomalies, childhood cancer, stillbirth, and developmental disorders. Investment in improved surveillance systems that can collect quality occupational data is needed to improve our ability to identify worker subpopulations or workplace exposures that are associated with excess risk. Population-based surveys could also be developed, or existing systems could be expanded, to support the measuring and monitoring of the prevalence and incidence of adverse reproductive outcomes related to occupational exposures and hazards.

In the past, the major argument for excluding occupation from vital records, surveillance systems, and population-based surveys was the complexity and cost of coding occupational data to a format that could be reliably and reproducibly analyzed. However, in recent years autocoding systems have become available that can simplify this task. For example, the NIOSH Industry & Occupation Computerized Coding System (NIOCCS) is a web-based system that translates free text into standardized Census occupational codes. Continuing efforts towards developing and improving autocoding systems for use with vital records, surveillance systems, and surveys is critical for supporting the inclusion of parental occupational data in these systems. Coding systems should be able to account for work patterns over time (e.g. as employees leave one job to begin another) and holding multiple jobs at the same time.

8C. *Develop standard definitions for occupational factors (including work organization, schedule, stress, and physical demands); as well as valid and reliable methods for estimating occupational exposures (such as job-exposure matrices and autocoding algorithms).*

The quality and completeness of occupational data affect the ability of this information to be autocoded. Developing detailed guidance on how to collect occupational data would likely improve the quality and utility of data. Higher quality data would make it possible to conduct large-scale epidemiologic surveys required to identify associations of workplace exposures with adverse reproductive outcomes. Likewise, developing standard definitions for occupational factors and exposures would provide uniform measures for use in public health and clinical practice, and these standard definitions could improve the synthesis of information. Standard definitions involve standards for classification of exposures obtained from individuals in surveys, or development of reliable job-exposure matrices (JEMs) that provide accurate estimates of exposures sustained in the course of work (e.g. chemical and metal exposures, physical job strain, shiftwork, job stressors). Additionally, reliable estimates of exposure can expedite the efficient study of large populations and help determine the risks of occupational exposure above those seen in baseline studies.

Objective 9: Conduct and communicate studies of exposure and outcome; identify and quantify risk of adverse reproductive health outcomes associated with the workplace.

9A. *Conduct studies of high priority reproductive hazards.*

Studies of high priority reproductive hazards need to be carried out to assess their effect on adverse reproductive outcomes, including infertility (male and female), menstrual cycle changes, pregnancy loss, pregnancy complications, low birth weight, preterm delivery, developmental abnormalities, and congenital malformations or later childhood outcomes in offspring. Exposure assessment is needed to understand the scope of exposure to reproductive hazards in the workplace. Exposure assessment studies should be prioritized based on toxicologic studies combined with human exposure information, where applicable and available. Field studies should include an assessment of types of exposures, dose and frequency of use, and use of personal protective equipment (PPE) and engineering controls to reduce or eliminate exposures.

When practical, future studies should identify and act on opportunities to use common study protocols, analytic methods, and quality control procedures to minimize extraneous inter-study differences. Studies should seek to identify and include vulnerable subpopulations, such as workers experiencing social, racial, or gender disparity,

for whom the combined effect of work and environmental factors may accentuate the risk of reproductive outcomes, and who may need more global occupational and public health interventions.

In addition, there is a dearth of studies of male reproductive health in the workplace; studies are needed to identify workplace toxicants that affect male reproductive health directly, or could be carried home to expose family members. For example, occupational exposures among male nurses is a growing concern, as the percentage of men in the nursing field continues to rise, from 2.7% in 1970 to 9.6% in 2011 [48]. Antineoplastic drugs can cause infertility in men when used at therapeutic doses, and male cancer patients who are treated with antineoplastic drugs are advised to bank their sperm before treatment due to these known infertility risks. Yet, it remains unknown if chronic low-dose occupational exposure to antineoplastic drugs also affects male fertility or could expose female sexual partners via seminal transmission. Evidence regarding safety of high-level disinfectants used in healthcare settings on male reproduction is also scant.

There is also a strong need to evaluate the effectiveness of preventive efforts, such as use of PPE, engineering controls, workplace pregnancy policies, or temporary reassignment to reduce risks to workers during sensitive reproductive periods, such as while attempting to conceive, during pregnancy, and while breastfeeding. Enhanced protection programs often rely on an employee disclosing their (or their partner's) pregnancy or intention to become pregnant. These are sensitive and often private topics, however, and some hazards pose the greatest risks during the first few weeks of pregnancy, when a woman may not realize she is pregnant. Therefore it is unclear whether these temporary enhanced protection programs are effective at reducing hazards in practice. Research is also needed to clarify whether changes in a pregnant worker's body shape, weight, and respiratory system might require different PPE as the pregnancy progresses.

9C. *Include the study of individual medical and public health implications beyond initial reproductive outcomes.*

Adverse reproductive exposures are increasingly recognized as having implications for health and disease across the lifespan, for both parents and children. For parents, disorders of reproduction can reflect the influence of underlying disease processes and predict future disease risk. For example, infertility is a reported risk factor for both ovarian and testicular cancers. Poor birth outcomes can be a result of past socioeconomic factors, stress, abuse, and poor maternal health; they can also predict future adverse health consequences, including diabetes, cardiovascular disease, and reproduction dysfunction into the next generation. Children born too soon, too small, or with congenital anomalies are more likely to suffer other health outcomes throughout life, beyond those directly associated with the adverse birth outcome. For example, children with congenital anomalies, and some exposures such as radiation *in utero,* are more likely to have childhood and adult cancers. Preterm infants are more likely to develop diabetes, cardiovascular disease, asthma, and cognitive or psychosocial disorders.

Researchers are increasingly examining the role of *in utero* exposure on later health outcomes, even among individuals who had otherwise unremarkable gestations and births. The *fetal origins* hypothesis posits that many childhood and adult diseases have roots in disruptions in fetal development. The exposure-response relationship is recognized to differ across life stages, such that *in utero*, peripubertal, and adult exposures to the same chemical might lead to substantially different risks. Reproductive cohorts, with parental occupational information, could be leveraged to follow-up children's health related to prenatal occupational exposures.

CARDIOVASCULAR DISEASE

Objective 10: Understand underlying mechanisms for CVD among workers.

Surveillance and research are needed to better understand the mechanisms by which occupational factors may be associated with initiating CVD or contributing to its progression. Work is needed in the design and conduct of studies, using laboratory-based, biomonitoring, ambulatory monitoring, toxicological, epidemiological or other

methods, to improve understanding of potential mechanisms by which occupational agents or factors may lead to CVD. In studying these occupational factors a variety of health outcomes will be assessed, including markers or physiologic alterations that may be considered intermediate stages on the pathway to CVD, and including both sub-clinical and clinical CVD outcomes. These types of studies will likely involve selected worker populations, for example, those wearing ambulatory blood pressure monitors at work, but also will require innovation and advancement in laboratory science; novel and emerging research fields should be explored and encouraged [49]. Among the specific biologic mechanisms in need of study, for example, are mechanisms related to acute and chronic inflammatory changes associated with particulate exposure [50, 51].

Objective 11: Understand risk factors associated with CVD.

Research is needed to better understand the magnitude of risks of CVD among workers, the prevalence of risk factors, the proportion of CVD attributable to occupational exposures (population attributable risk %) and the relationship of occupational risk factors with known non-occupational risk factors for CVD.

Exposure assessment and epidemiology studies of high-priority, high-feasibility populations (for example, bus drivers, emergency personnel, human service workers and shift workers) should be conducted and communicated to identify and quantify risk of CVD associated with workplace exposures and the relationship of occupational risks to non-occupational risks. There are many well known risk factors for CVD; evidence indicates that workplace factors are also associated with several different CVD outcomes. The prevalence of these risk factors in various occupational groups, the magnitude of associations of these workplace factors with CVD, and differential effects on different working populations, need to be further assessed [50, 52-54].

There remains a challenge to develop sufficiently simple (but still reliable) population-level indicators, constructed using available/routine data for monitoring workplace risk factors for CVD, which can be used for research and surveillance by authoritative organizations throughout the world. Surveys such as the periodic NIOSH national Quality of Work Life surveys (https://www.cdc.gov/niosh/topics/stress/qwlquest.html), or other efforts to collect data representative across a range of occupational settings, are needed. An important step toward creating a nationally representative database of workplace factors associated with CVD would be to merge (to the extent possible) datasets from multiple currently existing projects. A more comprehensive (and more costly) approach would be to develop and administer surveys of the prevalence and distribution of work-related factors known to contribute to CVD. A critical factor in newly-developed surveys would be the use of common sets of key exposure variables and outcomes. The availability of representative data across industries would play an important role in informing the development and evaluation of interventions to minimize work-related risk factors for CVD (Objective 12).

11A. Investigate interactions between occupational psychosocial and physical hazards associated with CVD.

It is important to further investigate interactions between occupational psychosocial and physical hazards (for example, shift work, job strain, noise, and toxic chemicals), and between occupational and non-occupational risk factors for CVD [55, 56]. The interactions of potential work-related mechanisms with biologic response mechanisms (e.g., blood pressure elevation, metabolic syndrome, altered circadian rhythm, lowered heart rate variability, coagulation, inflammation, cortisol) and relationships to CVD endpoints are emerging areas of study [57-61]. Epidemiologic studies are also needed to increase knowledge about the extent to which occupational factors are independently associated with CVD, are primarily markers for other more well understood risk factors, or are a combination of these [55, 61-63].

11B. Investigate changes in the nature of work as potential occupational risk factors for CVD.

Changes in workplace demographics, the changing nature of the employee-employer relationship, precarious employment, downsizing/restructuring, privatization, and new systems of production and management (such as

lean production) are currently impacting work organization and the nature of workplace psychosocial stressors [64, 65].

11C. *Investigate effects of existing CVD.*

The effects that existing CVD may have on work capacity and performance, on return-to-work factors and worker safety, and on workers' families, and the contribution of CVD to issues such as medical retirement, disability, or separation from the workplace are emerging issues in need of study.

11D. *Investigate potential uses of wearable technology to mitigate CVD risk factors.*

Research is encouraged which takes advantage of the developing fields of wearable technology – for example, studies which may combine self-reports and biomonitoring to improve sensitivity and specificity of occupational exposure measurement in terms of CVD prediction/ identification of exposed individuals.

Objective 12: Develop and evaluate workplace interventions for CVD.

Given the long latency period of CVD, it is not surprising that there have been no published intervention studies designed to reduce CVD by mitigating occupational risk factors [66]. Only four work organization intervention studies have been published, and these have shown reductions in biological intermediaries associated with CVD, such as blood pressure, catecholamines or lipids [66]. However, there is an extensive knowledge base on strategies to improve work organization and reduce workplace psychosocial stressors [67-69]. These strategies need to now be applied in studies with cardiovascular outcomes. Intervention studies are needed to supplement the current evidence base of work-related CVD, which is dominated by observational studies [61]. Such intervention studies, with strategies to alter workplace factors, improve screening, and manage personal risk factors, are particularly needed to improve currently available data [27, 53, 54, 56, 58, 70].

12A *Develop interventions for occupations where exposures are difficult to control.*

Special consideration may be needed for prevention strategies applicable to workers in occupations where exposures to agents or workplace factors are difficult to control and are, at least to some extent, an inherent feature of the occupation, such as firefighters, police officers and emergency medical technicians.

12B. *Develop interventions for groups with high risk for CVD.*

The cost-effectiveness (and feasibility) of interventions targeted to high risk groups is not known. Research is needed addressing occupational interventions targeted to those people with high CVD risk (e.g., high Framingham score), to potentially learn whether health benefits and/or reductions in disability will result. Research is similarly needed among groups with higher levels of exposure to occupational psychosocial and physical risk factors, or who may have a higher incidence of CVD, and possibly stronger associations between exposures and CVD outcomes, such as workers with lower socioeconomic status [64, 71]. As the American Heart Association (AHA) recommended: we should "consider targeted….interventions for their more vulnerable employees…..engage those who are economically challenged, less educated, or underserved" [72].

12C. *Develop return-to-work practices for workers with CVD.*

Given the increasing proportion of workers in developed countries working past age 65, and resulting increasing prevalence of CVD in the workforce, research is needed to learn more about increasing the ability of workers with CVD to stay at work or return to work and designing and promoting healthy working conditions for workers returning to work after having had a cardiac event [73, 74]. Research indicates an increased risk of heart disease recurrence if workers return to a job in which an adverse psychosocial work environment persists [75].

12D. *Develop work environment interventions to mitigate CVD risk factors.*

The workplace has been shown to be an effective setting to evaluate interventions to reduce cardiovascular risk factors, even for those which may not be primarily occupational in nature [76]. However, worksite wellness or

health promotion programs are less likely to reach those workers at higher risk, such as lower SES workers [77, 78]. A Total Worker Health® approach promoted by NIOSH has the potential to identify and change barriers to healthier behaviors such as inflexible schedules, shiftwork and long work hours, and to reduce risks of chronic disease caused by stressful work. Similarly, the AHA calls for "changes in the work environment to encourage healthy behaviors and promote occupational safety and health" [72] and that "worksite wellness programs should help working families balance work & family commitments….policies around child/elder/care, telecommuting and flexible work schedules" [72]. Evaluation of these more global approaches in the workplace setting, with attention to higher-risk or difficult-to-access workers, is warranted.

12E. *Develop innovative approaches to evaluating CVD interventions.*

Future research needs to consider the wide variety of forms that interventions can take. Randomized controlled trials are nearly impossible for occupational psychosocial and physical risk factors. Quasi-experimental studies (with control groups and pre- and post-assessments) in a workplace or workplaces are a more feasible option. In addition, the evaluation of "natural experiments" affecting working conditions can play an important role and will require the establishment of worksite-based and regional or national surveillance systems. Natural experiments can include work organization changes implemented by employers to improve productivity or efficiency (such as lean production, lean healthcare or new public management), or bargained by employers and labor unions. They can also include legislative or regulatory efforts to improve working conditions, such as U.S. state laws banning mandatory overtime or requiring minimum staffing levels for nurses in hospitals [79].

REFERENCES

1. American Cancer Society [2016]. Cancer Facts & Figures 2016. Atlanta: American Cancer Society.

2. Straif K [2008]. The burden of occupational cancer. Occ Env Med 65(12):787-788.

3. Driscoll T, Takala J, Steenland K, Corvalan C, Fingerhut M [2005]. Review of estimates of the global burden of injury and illness due to occupational exposures. Am J Ind Med 48:491-502.

4. Rushton L, Hutchings SJ, Fortunato L, et al [2012]. Occupational cancer burden in Great Britain. Br J Cancer 107(Suppl 1):S3-7.

5. Purdue MP, et al [2015]. The proportion of cancer attributable to occupational exposures. Ann of Epi 25: 188e192.

6. Steenland K, et al [2003]. Dying for work: the magnitude of US mortality from selected causes of death associated With occupation. Am J Ind Med 43:461–482.

7. Rushton L, Bagga S, Bevan R, et al [2010]. Occupation and cancer in Britain. Br J Cancer 102: 1428 – 1437.

8. Centers for Disease Control and Prevention. U.S. Cancer Incidence Statistics: an Interactive Atlas. https://nccd.cdc.gov/DCPC_INCA/ . Accessed December 20, 2016.

9. European Agency for Safety and Health at Work [2014]. Exposure to carcinogens and work-related cancer: A review of assessment methods.
https://osha.europa.eu/en/tools-and-publications/publications/reports/summary-on-cancer

10. Straif K [2012]. Estimating the burden of occupational cancer as a strategic step to prevention. Br J Cancer 19(107) Suppl 1:S1-2.

11. Boffetta P [2004]. Epidemiology of environmental and occupational cancer. Oncogene 23:6392-6403.

12. Landrigan PJ [1996]. The prevention of occupational cancer. CA Cancer J Clin 46:67-69.

13. Siemiatycki J, Richardson L, Straif K, et al [2004]. Listing occupational carcinogens. Environ Health Perspect 112(15):1447-1459.

14. Raj, P et al [2014]. Recent trends in published occupational cancer epidemiology research: results from a comprehensive review of the literature. Am J Ind Med 57, 259–264.

15. Hutchings S, Cherrie JW, Van Tongeren M, and Rushton L [2012]. Intervening to reduce the future burden of occupational cancer in Britain: what could work? Cancer Prev Res 5(10):1213–22.

16. IARC Technical Publication No. 42 [2009]. Identification of research needs to resolve the carcinogenicity of high-priority IARC carcinogens. http://monographs.iarc.fr/ENG/Publications/techrep42/index.php

17. Ward EM, et al [2010]. Research recommendations for selected IARC-classified agents. Environ Health Perspect 118(10): 1355-1362.). DOI:10.1289/ehp.0901828 http://ehp.niehs.nih.gov/0901828/

18. Macdorman MF, Gregory ECW [2015]. Fetal and perinatal mortality, United States, 2013. National vital statistics reports; 64(8). Hyattsville, MD: National Center for Health Statistics. https://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_08.pdf

19. Centers for Disease Control and Prevention [2008]. Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. MMWR 57(1):1-5. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm

20. Mathews TJ, MacDorman MF, Thoma ME [2015]. Infant mortality statistics from the 2013 period linked birth/infant death data set. National vital statistics reports; vol 64 no 9. Hyattsville, MD: National Center for Health Statistics. https://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_09.pdf

21. Centers for Disease and Control and Prevention Topic Page "Reproductive Health- Infertility FAQs." https://www.cdc.gov/reproductivehealth/infertility/index.htm . Accessed May 16, 2017.

22. Thoma ME, et al [2013]. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertil Steril 99:1324-1331.

23. Heron, M [2016]. Deaths: Leading causes for 2014. National vital statistics reports; 65(5). Hyattsville, MD: National Center for Health Statistics. http://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_05.pdf

24. Mozaffarian D, et al. on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee [2015]. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 131:e29–e322.

25. Cooper R, Cutler J, Desvigne-Nickens P, et al [2000]. Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings from the National Conference on Cardiovascular Disease Prevention. Circulation 102:3137–3147.

26. Leigh PJ, Miller TR [1998]. Job-related diseases and occupations within a large workers' compensation data set. Am J Ind Med 33:197–211.

27. Price A [2004]. Heart disease and work. Heart 90:1077-1084.

28. Kecklund G, Axelsson J [2016]. Health consequences of shift work and insufficient sleep. Br Med J 355:i5210.

29. Vyas M, Garg A, Iansavichus A, Costella J, Donner A, Laugsand L, et al [2012]. Shift work and vascular events: systematic review and meta-analysis. Br Med J 345:e4800.

30. Theorell T, Jood K, Jarvholm LS, Vingard E, Perk J, Ostergren PO, Hall C [2016]. A systematic review of studies in the contributions of the work environment to ischaemic heart disease development. Eur J Public Health 26: 470-477.

31. International Commission on Occupational Health [2013]. The Tokyo declaration on prevention and management of work-related cardiovascular disorders. International Commission on Occupational Health (ICOH) Newsletter 11;(2,3):4.

32. Blair A, Marrett L, Beane Freeman L [2011]. Occupational cancer in developed countries. Environ Health 10(Suppl 1):S9.

33. Stewart BW et al [2016]. Cancer prevention as part of precision medicine: 'plenty to be done.' Carcinogenesis 37(1): 2–9.

34. Takala J [2015]. Eliminating Occupational Cancer. Industrial Health 53: 307-309.

35. Pukkala E, Martinsen JI, Weiderpass E, et al [2014]. Occup Environ Med; 71:398–404.

36. Luengo-Fernandez R, Leal J, Gray A, Sullivan R [2013]. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol 14:1165–74.

37. NTP (National Toxicology Program) [2016]. Report on carcinogens, Fourteenth Edition.; Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. http://ntp.niehs.nih.gov/go/roc14

38. Straif K, Loomis D, Guyton K, et al [2014]. Future priorities for the IARC Monographs. Lancet Oncol, 15:683–684.

39. Doolan GW, Benke G, Giles GG, Severi G, and Kauppinen T [2014]. A case control study investigating the effects of levels of physical activity at work as a risk factor for prostate cancer. Environmental Health. 13:64. http://www.ehjournal.net/content/13/1/64 .

40. van Muijen P, Weevers N, Snels I [2013]. Predictors of return to work and employment in cancer survivors: a systematic review. European Journal of Cancer Care 22:144-60.

41. Zaman A, Tytgat K, Klinkenbijl J, Frings-Dresen M and de Boer A [2016]. Design of a multicentre randomized controlled trial to evaluate the effectiveness of a tailored clinical support intervention to enhance return to work for gastrointestinal cancer patients. BMC Cancer 16:303.

42. Islam T, et al [2014]. Factors associated with return to work of breast cancer survivors: a systematic review. BMC Public Health 14(Suppl 3):S8. http://www.biomedcentral.com/1471-2458/14/S3/S8

43. Laurier D, Richardson DB, Cardis E, et al [2016]. The international nuclear workers study (INWORKS): a collaborative epidemiological study to improve knowledge about health effects of protracted low-dose radiation exposure. Radiation Protection Dosimetry: 1–5.

44. Vargas AJ and Harris CC [2016]. Biomarker development in the precision medicine era: lung cancer as a case study. Nature Reviews Cancer 16: 525–537. doi:10.1038/nrc.2016.56

45. Thomas CC, et al [2015]. CDC Grand Rounds: the future of cancer screening. MMWR 64(12): 324-327.

46. Canadian Medical Association [2016]. Recommendations on screening for lung cancer. Canadian Medical Association Journal 188(6):425-432.

47. Barbiero F, Barbone F, Rosolen V, et al [2016]. Screening with low-dose computed tomography (LDCT) of asbestos exposed subjects is associated with reduced lung cancer mortality. http://dx.doi.org/10.1136/oemed-2016-103951.164 .

48. U.S. Census Bureau [2013]. Men in nursing occupations: American Community Survey highlight report. https://www.census.gov/topics/employment/industry-occupation.html . Accessed May 22, 2017.

49. Tawakol A, Ishai A, Takx RAP, et al [2017]. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet 389:834–45. Lancet. Published online January 11, 2017 http://dx.doi.org/10.1016/S0140-6736(16)31714-7.

50. Fang SC, Cassidy A, Christiani DC [2010]. A systematic review of occupational exposure to particulate matter and cardiovascular disease. Int J Environ Res Public Health 7:1773-1806.

51. Simeonova PP and Erdely A [2009]. Engineered nanoparticle respiratory exposure and potential risks for cardiovascular toxicity: predictive tests and biomarkers. Inh Tox 21(S1):68-73.

52. Landsbergis P, Dobson M, Koutsouras G, Schnall P [2013]. Job strain and ambulatory blood pressure: A meta-analysis and systematic review. American Journal of Public Health 103: e61-e71.

53. Charles LE, Fekedulegn D, Burchfiel CM, et al [2016]. Shiftwork and diurnal salivary cortisol patterns among police officers. JOEM 58(6): 542-549.

54. Violanti J, Fekedulegn D, Andrew ME, et al [2017]. The impact of perceived intensity and frequency of police work occupational stressors on the cortisol awakening response (CAR): Findings from the BCOPS study. Psychoneuroendocrinology 75:124-131.

55. Choi B, Schnall P, Dobson M, et al [2014]. Very long (> 48 hours) shifts and cardiovascular strain in firefighters: a theoretical framework. Ann Occ Env Med 26(1):5.

56. Kivimaki M and Kawachi I [2015]. Work stress as a risk factor for cardiovascular disease. Curr Cardiol Rep 17:74.

57. Wiebert P et al [2012]. Occupational exposure to particles and incidence of acute myocardial infarction and other ischaemic heart disease. Occup Environ Med 69:651-657.

58. Landsbergis PA et al [2015]. Job strain, occupational category, systolic blood pressure, and hypertension prevalence. JOEM 57(11):1178-1184.

59. Fransson EI et al [2015]. Job strain and the risk of stroke: an individual-participant data meta-analysis. Stroke 46:557-559.

60. Steenland K [1996]. Epidemiology of occupation and coronary heart disease: research agenda. AJIM 30:495-499.

61. Kivimaki M et al [2015]. Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603,838 individuals. Lancet 386:1739-1746.

62. Cullen M [2209]. The search for preventable causes of cardiovascular disease – whither work? Am J Epi 169(12):1422-1424.

63. MacDonald LA et al [2009]. Occupational as socioeconomic status or environmental exposure? A survey of practice among population-based cardiovascular studies in the United States. Am J Epi 169(12):1411-1421.

64. Schnall P, Dobson M, Landsbergis P. 2017. Work, Stress and Cardiovascular Disease. In: Quick J, Cooper C editors. Handbook of Stress and Health Chichester: Wiley.

65. Schnall P, Dobson M, Landsbergis P. 2016. Globalization, work and cardiovascular disease. International Journal of Health Services 46: 656-692.

66. Theorell T, Brisson C, Vézina M, Milot A, Gilbert-Ouimet M. 2015. Psychosocial factors in the prevention of cardiovascular disease. In: Gielen S, De Backer G, Piepoli M, Wood D editors. The ESC Textbook of Preventive Cardiology London: Oxford University Press. p 238-250.

67. LaMontagne AD, Keegel T, Louie AM, Ostry A, Landsbergis PA. 2007. A systematic review of the job stress intervention evaluation literature: 1990—2005. Intl J Occup & Environ Health 13: 268-280.

68. LaMontagne AD, Keegel TG. 2012. Reducing Stress in the Workplace (An Evidence Review: Full Report). Creating Healthy Workplaces evidence review series Melbourne, Australia: Victorian Heath Promotion Foundation (VicHealth). p 58 pages.

69. Bourbonnais R, Brisson C, Vezina M. 2011. Long-term effects of an intervention on psychosocial work factors among healthcare professionals in a hospital setting. Occup Environ Med 68: 479-486.

70. Soteriades ES et al [2011]. Cardiovascular disease in US firefighters: a systematic review. Card in Review 19(4):202-215.

71. Kristensen TS, Kornitzer M, Alfredsson L. Social factors, work, stress and cardiovascular disease prevention. Brussels: The European Heart Network, 1998.

72. Carnethon M, Whitsel LP, Franklin BA, Kris-Etherton P, Milani R, Pratt CA, Wagner GR. 2009. Worksite wellness programs for cardiovascular disease prevention: a policy statement from the American Heart Association. Circulation 120: 1725-1741.

73. Dreyer RP, et al. 2016. Return to Work After Acute Myocardial Infarction: Comparison Between Young Women and Men. Circ Cardiovasc Qual Outcomes. http://circoutcomes.ahajournals.org
DOI: 10.1161/CIRCOUTCOMES.115.002611

74. Li J, et al. 2016. Work stress and cardiovascular disease: a life course perspective. J Occup Health 2016; 58: 216-219.

75. Li J, Zhang M, Loerbroks A, Angerer P, Siegrist J. 2014. Work stress and the risk of recurrent coronary heart disease events: A systematic review and meta-analysis. International Journal of Occupational Medicine and Environmental Health.

76. Groenveld IF, et al [2010]. Lifestyle-focused interventions at the workplace to reduce the risk of cardiovascular disease – a systematic review. Scand J Work Environ Health 36(3):202-215.

77. Anderson LM, Quinn TA, Glanz K, Ramirez G, Kahwati LC, Johnson DB, Buchanan LR, Archer WR, Chattopadhyay S, Kalra GP, Katz DL. 2009. The effectiveness of worksite nutrition and physical activity interventions for controlling employee overweight and obesity: a systematic review. Am J Prev Med 37: 340-357.

78. Soler RE, Leeks KD, Razi S, Hopkins DP, Griffith M, Aten A, Chattopadhyay SK, Smith SC, Habarta N, Goetzel RZ, Pronk NP, Richling DE, Bauer DR, Buchanan LR, Florence CS, Koonin L, MacLean D, Rosenthal A, Matson Koffman D, Grizzell JV, Walker AM. 2010. A systematic review of selected interventions for worksite health promotion. The assessment of health risks with feedback. Am J Prev Med 38: S237-262.

79. Landsbergis P, Dobson M, LaMontagne A, Choi BK, Schnall PL, Baker D. Occupational Stress. In Levy B, Wegman D, Baron S, Sokas R (Eds.) Occupational and Environmental Health (7th edition). Oxford University Press 2017 (in press).

Other Reference Material

Centers for Disease Control and Prevention [2014]. National Public Health Action Plan for the Detection, Prevention, and Management of Infertility, Atlanta, Georgia: Centers for Disease Control and Prevention; June 2014. https://www.cdc.gov/reproductivehealth/infertility/pdf/drh_nap_final_508.pdf

Connor TH, Lawson CC, Polovich M, McDiarmid MA [2014]. Reproductive health risks associated with occupational exposures to antineoplastic drugs in health care settings: A review of the evidence. J Occup Environ Med 56(9): 901–910.

de Queiroz EKR and Waissmann W [2006]. Occupational exposure and effects on the male reproductive system. Cad. Saude Publica 22(3):485-493.

Hauser R [2006]. The environment and male fertility: recent research on emerging chemicals and semen quality. Semin Reprod Medicine 24:156-167.

Hogue CJ [2016]. Invited commentary: preventable pregnancy loss is a public health problem. Am J Epidemiology 183(8):709–712.

Lawson CC, Schnorr TM, Daston GP, et al [2002]. An occupational reproductive research agenda for the third millennium. Env Health Persp 111:584-592.

Lawson CC, Grajewski B, Daston GP ,et al [2006]. Workgroup report: implementing a national occupational reproductive research agenda-decade one and beyond. Env Health Persp 114(3):435-441.

Moorman WJ, Ahlers HW, Chapin RE, et al [2000]. Prioritization of NTP reproductive toxicants for field studies. Reproductive Toxicology 14: 293-301.

Monte LM and Ellis RR [2014]. Fertility of women in the United States: June 2012, Current Population Reports, P20-575. Washington, DC: US Census Bureau.

Paul M [1997]. Occupational reproductive hazards. Lancet 347:1385-1388.

Practice Committee of the American Society for Reproductive Medicine [2013]. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril 99:63.

Raju TN, Pemberton VL, Saigal S, et al [2017]. Long-Term Healthcare Outcomes of Preterm Birth: An Executive Summary of a Conference Sponsored by the National Institutes of Health. J Pediatr. 181:309-318.

Rosenberg MJ, Feldblum PJ, Marshall EG [1987]. Occupational influences on reproduction: a review of recent literature. JOEM 29(7):584-591.

Sheiner, EK, Sheiner E, Hammel RD, Potashnik G, Carel R [2003]. Effect of occupational exposures on male fertility: literature review. Industrial Health 41: 55–62.

Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM, et al [2016]. Male reproductive disorders and fertility trends: influences of environment and genetic susceptibility. Physiol Rev 96:55-97.

Swan SH, Elkin EP, Fensteral L [2000]. The question of declining sperm density revisited: an analysis of 101 studies published 1934-1996. Env Health Persp 108(10):961-966.