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Review

Polycyclic aromatic hydrocarbons and female reproductive health: A scoping review

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are a class of common persistent environmental pollutants found in water, air, soil, and plants and can be released by natural sources. However, the majority of atmospheric PAHs are from vehicular emissions, coal-burning plants, and the production and use of petroleum-derived substances. Exposure to PAHs has been implicated in cancer and other diseases, including reproductive disorders. This scoping review is a preliminary step that explores the utility and feasibility of completing a systematic review evaluating the effect of PAHs on female reproduction. We performed literature searches in PubMed, Web of Science, and Scopus, then screened, identified, and categorized relevant studies. Our results identified fertility and pregnancy/fetal viability as outcomes with sufficient research for systematic review. In addition to presenting the relevant studies, the review identifies data gaps, and provides the groundwork to develop the most appropriate research questions for systematic review.

Contents

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a diverse class of organic compounds that are common persistent pollutants [1]. PAHs are predominantly emitted from combustion sources such as vehicular emissions, coal-burning plants, and via the production and use of petroleum-derived substances (e.g., lubricants and fuels). They are also released from tobacco smoke, the burning of biomass (e.g., forest fires, controlled burns), the cooking of certain foods, and other natural sources (e.g., volcanoes, erosion of sedi-

Abbreviations: 1-HP, 1-hydroxypyrene; BaP, benzo(a)pyrene; BghiP, benzo(ghi)perylene; BoE, body of evidence; Chr, chrysene; Cr, creatinine; Fluo, flouranthane; grp, group; n/a, not applicable; Naph, naphthalene; NHANES, National Health and Nutrition Examination Survey; n/r, not reported; OHAT, Office of Health Assessment and Translation; PAH, polycyclic aromatic hydrocarbon; Phe, phenanthrene; Pyr, pyrene; reps, replicates; UOG, unconventional oil and gas.

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Table 1
Detailed description of outcome categories.

Outcome category	Description
Fertility	lack of conception, no/less offspring, implantation sites, egg production
Pregnancy/fetal viability	gestational length, fetal loss, spontaneous abortion
Reproductive organ cancer	cancer of the ovaries, uterus, cervix
Breast cancer	cancer of the mammary glands
Reproductive organ weight	weight of ovaries, uterus, cervix
Reproductive behavior	production of pheromones, reproductive receptivity
Uterine physiology	changes to the endometrium, myometrium, and cervix
Ovarian physiology	changes to the ovaries, oocyte development and maturation
Placental physiology	changes to placental function and development
Menstruation/estrus	cyclicity, amenorrhea
Time to puberty	timing of reproductive activity

ments) [2–5]. Further, recent studies have detected PAHs near sites of unconventional oil and gas development (UOG) activity [6–8]. UOG includes hydraulic fracturing, which is a method of injecting water, sand, and chemicals underground at high pressure to release oil and gas from various types of geological formations [6,9].

PAHs released into the atmosphere are deposited into soils and aquatic systems [1]. Environmental monitoring has detected PAHs in air, soils, sediments, plants, and water [2,10–14]. Due to their ubiquitous and persistent nature, these compounds have been detected in human and wildlife populations. Biomonitoring of humans in the general population, performed by the National Health and Nutrition Examination Survey (NHANES), showed evidence of exposure to all four of the PAHs in their screening battery: fluorene, phenanthrene, naphthalene, and pyrene [15,16]. Exposure to these compounds may occur via inhalation, ingestion of food and water, and absorption through the skin and other mucosal barriers [13,17]. In wildlife populations, PAHs have been detected in mammalian and non-mammalian species, with sources of exposure attributed to both combustion sources (e.g., recent forest fires) and releases from sites of oil and gas production [17–19].

PAHs have an extensive body of literature describing their endocrine disruptive activity [20,21]. Several studies have shown that these compounds act as antiestrogens and/or antiandrogens by interacting directly with the estrogen receptor or androgen receptor. For example, benz[a]anthracene, benzo[a]pyrene, fluoranthene, and chrysene were shown to inhibit androgenic activity [22]. PAHs have also been shown to activate aryl hydrocarbon responsive genes resulting in widespread antiestrogenic effects [8,23,24]. Further, hydroxylated metabolites of PAHs such as 2-hydroxynaphthalene, 2-hydroxydibenzofuran, 2-hydroxy-9-fluorenone, 2-hydroxyfluorene, 1-hydroxypyrene, and 1-hydroxynaphthalene have shown estrogenic activity *in vitro* [25]. Many of these hydroxylated metabolites have been detected in human urine [26,27].

Given the widespread exposure of humans to PAHs, and the ability of PAHs to disrupt endocrine signaling, we conducted a preliminary search of the PAH literature to examine all the physiological effects of PAHs in humans and animals. The goal was to identify the endocrine relevant endpoints with the most health effect literature. Among other endpoints, this search identified a substantial body of literature that evaluated non-cancer reproductive effects in both males and females. Outcomes included sperm quality, testicular function [28–30], egg viability [31,32], DNA damage in oocytes [33], and reproductive disease [34]. We also found several narrative reviews discussing cancers of reproductive organs, such as the breast [35,36], as well as ovarian damage [37,38], and male reproductive function [39]. Female reproductive

Table 2
Overall summary of studies evaluating female reproductive endpoints following exposure to polycyclic aromatic hydrocarbons (PAHs).

	Number (%)
Total number of studies	75
Publication date	
2010–2016	34 (45)
2009–2005	25 (33)
2004–2000	10 (13)
1999–1996	6 (8)
Models	
Human	10 (13)
Rodent	18 (24)
Fish	19 (25)
Crustacean	16 (21)
Mollusk	3 (4)
Insect	2 (2)
Annelid	1 (1)
Echinoderm	2 (2)
Age of Exposure	
Prenatal	5 (7)
Neonatal	11 (14)
Prepubescent	7 (9)
Pubescent	7 (9)
Adult	61 (81)
Senescent	5 (7)
Outcomes	
Fertility	36 (48)
Pregnancy/fetal viability	15 (20)
Ovarian physiology	26 (34)
Uterine physiology	7 (9)
Reproductive organ weight	22 (30)
Reproductive behavior	3 (4)
Breast cancer	2 (2)
Reproductive organ cancer	3 (4)
Placental physiology	1 (1)
Menstruation/Estrus	3 (4)
Time of puberty	2 (2)
PAH	
Naphthalene	14 (19)
C2-naphthalene	1 (1)
Acenaphthylene	2 (2)
Acenaphthene	1 (1)
Fluorene	2 (2)
Anthracene	1 (1)
Phenanthrene	10 (13)
Fluoranthene	6 (8)
Pyrene	9 (12)
Benz[a]anthracene	6 (8)
Chrysene	3 (4)
Benzo[k]fluoranthene	5 (7)
Benzo[a]pyrene	42 (56)
Indeno(1,2,3-c,d)pyrene	1 (1)
Dibenz(a,h)anthracene	3 (4)
Benzo(g,h,i)perylene	3 (4)
PAH mixture	11 (15)

effects were selected for the focus of the current review because these endpoints are sensitive indicators of disrupted endocrine function. The female reproductive system may be particularly vulnerable to environmental chemical exposures, in part due the fact that oocytes are the longest-lived non-regenerating cells in the body and thus subject to a lifetime of chemical exposures. Female reproduction is also perhaps less well-studied compared to male reproduction, due to more challenging and invasive outcome assessments, and less research detailing how to create controlled experiments that take into account factors such as estrus cyclicity [40].

Although our search identified several primary studies evaluating the impacts of PAHs on female reproduction, none of the endpoints had been assessed in a systematic review in order to determine the confidence and strength of the evidence. Therefore,