REPRODUCTIVE TOXICOLOGY

Reproductive toxicology: emerging toxicants and cellular targets Aileen F Keating¹ and Adam J Watkins^{ID}²

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This paper forms part of a special section on Reproductive toxicology. The guest editors for this section were Dr Adam Watkins (The University of Nottingham, UK) and Dr Aileen Keating (Iowa State University, IA, USA)

Reproduction (2021) **162** E5–E6

Female reproductive toxicity as a result of environmental toxicants has been recognized for decades and was particularly highlighted in the teratological effects of thalidomide and diethylstilbestrol. Since these defining events, modes of toxicity of environmental exposures have been identified and include endocrine disruption, atresia, primordial follicle growth hyperactivation, DNA damage to the somatic and germ cells, and hyperproliferation of cellular structures. This special series was designed to provide further insight into female reproductive toxicity with review papers on emerging toxicants and emerging cellular targets (Video 1).

Video 1

An overview of the special issue on Reproductive Toxicology and the papers included in this series by Prof Adam Watkins. This video (<http://movie-usa.glencoesoftware.com/video/10.1530/REP-21-0373/video-1>) is available from the online version of the article at <https://doi.org/10.1530/REP-21-0373>.

In the first paper, the topic of male breast disease is examined with a focus on two pathologies, gynecomastia and male breast cancer by Szabo & Vandenberg (2021). A mouse model with which to study the etiology of breast cancer and gynecomastia is described with discussion on phytoestrogen exposure and the sensitivity and importance of considering the stage of development. A rationale for gynecomastia as an outcome of estrogenic chemical exposures is also provided. The second paper by Mourikes & Flaws (2021) delves into the arena of chemical mixtures and their effects on the female gonad. The targets within the ovaries that poise them to be vulnerable to toxicant exposures are reviewed and the information available on environmental, occupational, and medical mixture exposures are described. In addition,

the transgenerational impacts of mixture exposures are presented. The third paper from Khoshkherdar *et al.* (2021) switches gear to address the link between paternal lifestyle and maternal health. This review described the evidence that paternal age and diet can influence gestational maternal well-being. Also, mechanisms specific to sperm and seminal plasma that may be causative for paternal health impacts are described.

The next article from Patisaul (2021) is focused on how endocrine disruption can impact neuroendocrine pathways that are sexually dimorphic. The biology of how the endocrine environment shapes brain development has become more established in recent decades, permitting elucidation of if and how environmental exposures can affect normal developmental physiology and the importance of the window of development at which such an exposure occurs. The challenges presented by the latency of phenotype relative to the exposure and examples of endocrine disruption chemical impacts on neurodevelopmental outcomes are addressed. This leads elegantly to an analysis by Roepke & Sadlier (2021) of the neuroendocrine impacts of endocrine-disrupting chemicals with specific effects on gonadotropin releasing hormone, kisspeptin, and the gonadotropins. As the hypothalamic–pituitary–gonadal axis is regulated normally by endocrine positive and negative inputs, not surprisingly, exposure to endocrine-disrupting chemicals can disrupt this delicate balance. This review paper describes the scientific literature in this area and details needed for further explorations in this area of reproductive neuroendocrinology.

Switching from the brain to the fetal male gonad, Li & Spade (2021) describe the impacts of phthalate exposures on the fetal testis with attention to the importance of windows of developmental exposure for phenotypic and functional outcomes. In addition,

commonalities and differences between modes of action of phthalate exposures with other known testicular toxicants are provided. The special series culminates with a paper by Haggerty *et al.* (2021) in which the long-term consequences for female health of gestation exposure to endocrine disrupting chemicals are discussed. Additionally, the logistical and experimental design challenges to thoroughly evaluate these linkages are explored and the deficits in the currently knowledge base related to women's health is provided.

This special issue is designed to describe several aspects of reproductive toxicity and to highlight where deficits remain and how specific developmental windows of exposure can be critical for the resultant outcomes.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this editorial.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 17 September 2021

Accepted 23 September 2021