

TRANSLATIONAL ANDROLOGY AND UROLOGY

Peer Review File

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Reviewer A

The authors present a well written manuscript detailing the effects of environmental toxins on male fertility. I only have a few comments:

Comment 1. Can the authors please include the specific toxins that they will be discussing in the body of the text in the abstract? Perhaps as a concluding sentence to state "... in this review we will be focusing upon..."

Reply 1: We thank the reviewer for the comment and agree that adding this information will facilitate an understanding of the scope of the review through reading of the abstract.

Changes in the text: We have added the following two sentences to the end of the abstract, Page 2, lines 24-30: "The aim of this review is to examine the literature linking changes in male fertility to some of the most common environmental exposures. Specifically, pesticides and herbicides such as dichlorodiphenyltrichloroethane (DDT), dibromochloropropane (DBCP), organophosphates and atrazine, endocrine disrupting compounds including plastic compounds phthalates and bisphenol A (BPA), heavy metals, natural gas/oil, non-ionizing radiation, air and noise pollution, lifestyle factors including diet, obesity, caffeine use, smoking, alcohol and drug use, as well as commonly prescribed medications will be discussed."

Comment 2. The first sentence of the introduction is a little dramatic. I'm not sure if fertility is a 'public health crisis'.

Reply 2: We thank the reviewer for the comment have agreed to change the wording in the first line of the introduction.

Changes in the text: The first sentence of the introduction on Page 3, line 2, now reads "The previously debated male fertility decline is no longer controversial."

Comment 3. Is there any data available for specific locations where environmental toxins have specifically caused an effect? For example, the BRIO superfund site in Texas?

Reply 3: The authors agree that this is an interesting question. On literature review, the authors were unable to identify much literature on the impact of large-scale environmental contamination. We have added the following text to discuss this point:

Changes in the text: Page 3 lines 25-32 and Page 4 lines 1-5 "Many compounds implicated are ubiquitous in our modern society and men may routinely encounter them during their daily activities. Alternatively, exposure may be following a larger scale environmental contamination such as that encountered after a nuclear accident or in situations requiring government Superfund cleanup. While data on long-term fertility outcomes following exposures to Superfund cleanup or nuclear accident sites are limited, data do note a link

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between prenatal exposure and preterm birth and congenital abnormalities,(5,6) suggesting that exposure to environmental toxins in these situations may negatively impact other fertility parameters. In addition, the Environmental Protection Agency (EPA) has acknowledged that certain compounds found at Superfund cleanup sites may have adverse fertility effects, that fertile men and women are at greater risk for negative effects, and suggest screening for exposure take fertility potential into account.(7) Though exposure to high volumes of toxins in the setting of large-scale environmental contamination may affect male fertility...

Comment 4. The authors mention radiation in the form of laptops but not in the form of Chernobyl. Maybe a few lines on this?

Reply 4: We thank the reviewer for the comment. As the Chernobyl nuclear disaster resulted in exposure to ionizing radiation, a full discussion of this is beyond the scope of the current review, where we are focusing on non-ionizing radiation. However, we acknowledge that exposure through nuclear accidents warrants mention, and have changed the text to reflect this as below.

Changes in the text: Page 9, lines 31-32 "Ionizing radiation in the form of medical diagnostic imaging, radiotherapy, or even through nuclear accidents is well known to have a negative impact on spermatogenesis via induction of oxidative stress..."

Comment 5. there is an excellent article on smoking and male fertility that appears to have been accidentally overlooked and should be included. PMID: 25697426.

Reply 5: We thank the reviewer for suggesting the addition of this valuable manuscript to our review. We have added several sentences to our manuscript referenced to the suggested article as indicated below.

Changes in the text: Page 14, lines 18-21 "Tobacco is considered a known cause of male factor infertility, with cigarette smoking linked to decreases in semen volume, sperm count, and sperm motility in a dose-dependent and reversible manner, as well as to impaired assisted reproduction technique (ART) outcomes.(107)" Page 14, lines 30-31 "In addition to toxins found in cigarette smoke, nicotine is also thought to independently have a negative impact on semen parameters.(107)" Page 17, lines 19-21 "Specifically, prenatal exposure to cigarette smoking has been associated with decreased sperm concentration and testicular size in adults.(107)"

Comment 6. Similarly, for page 14, line 5, another article could be included PMID: 30929329

Reply 6: We thank the reviewer for their comment and have included the suggest reference as below.

Changes in the text: Page 16, line 15 "....(124)"

Comment 7. Could the authors include a small section on vaping and e-cigarettes into

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the smoking subsection is there anything known about this? It is very popular.

Reply 7: We agree with the reviewer that e-cigarettes are of interest here. We kindly direct the reviewer to the existing second paragraph within the smoking section on Page 15 for a brief discussion of the limited literature on the topic. We have added a line addressing the link between nicotine and male fertility as below.

Changes in the text: Page 15, lines 4-6 “However, given the negative link between nicotine and semen parameters, electronic cigarettes still pose a theoretical risk to male fertility.”

Reviewer B

This is an excellently written narrative review investigating the most common toxins affecting fertility. While the authors present evidence suggesting the link between these toxins and negative effects on semen parameters, the authors also measure these statements suggesting evidence is still limited. The article may be accepted as is.

We thank the reviewer for their comments.