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Review

Exposure to benzophenone-3 and reproductive toxicity: A systematic review of human and animal studies

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ABSTRACT

Hydroxy-4-methoxybenzophenone, also known as benzophenone-3 (BP-3), is a commonly used ultraviolet filter in skincare and as a food additive. Large concentrations of similar phenolic compounds have been detected in urine, amniotic fluid, and placental tissue, thereby raising questions about its impact on reproduction. The objective of this paper was to investigate the reproductive toxicity of BP-3 in humans and animals. In humans, studies showed that high levels of BP-3 exposure could be linked to an increase in male birth weight but a decline in female birth weight and male gestational age. In fish, BP-3 exposure resulted in a decline in egg production, hatching, and testosterone, along with a down-regulation of steroidogenic genes. In rats, a decrease in epididymal sperm density and a prolonged estrous cycle for females was observed. These positive associations may be attributed to an altered estrogen and testosterone balance as a result of endocrine disrupting effects of BP-3. However, the current body of literature is limited by non-uniform exposure and outcome measurements in studies both across and within species and future studies will need to be conducted in a standardized fashion to allow for a more significant contribution to the literature that allows for better comparison across studies.

Contents

1. Introduction

Hydroxy-4-methoxybenzophenone, also known as benzophenone-3 (BP-3), is a phenolic compound found naturally in flowering plants. BP-3 is frequently used as an organic sunscreen agent, photoinitiator, indirect food additive, and fragrance enhancer [1]. According to the Centers for Disease Control and Prevention, the prevalence of exposure to BP-3 in the United States is reported to be 96.8% due to the fact that phenolic compounds like BP-3 are prevalent in the air, drinking water, food, and personal care products [2,3]. In fact, a recently-published systematic review found that BP-3 was detected in the majority of urine and breast milk samples collected, with average concentrations of >0.4 μg/L [2]. Phenolic compounds have also been detected

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in blood, amniotic fluid, follicular fluid, placental tissue, semen, umbilical cord blood, fetal serum, and adipose tissue [3].

Though BP-3 has been on the market for several decades, it has recently received increased attention from the public as a potentially harmful toxicant due to increased public awareness of the impacts from environmental exposures upon fertility and child develop-ment [4,17,18]. Previous experimental studies have shown associations between exposure to phenol compounds with increased abortions and arrested development of embryos; however, most studies have focused on Bisphenol-A (BPA) [18]. BPA, with a similar chemical structure to BP-3, can pass though the blood-placenta barrier [5], leading investigators to theorize that BP-3 may also pass though this barrier, inducing reproductive toxicity [5]. The focus on BP-3 arose predominately after studies reported a systematic absorption of BP-3 in humans at a rate of up to 2% after dermal application [4,6–8]. This rate of absorption became a cause for concern given the increased use of sunscreen in the general public to prevent skin cancer [9], as well as the high prevalence of BP-3 in water supplies [2], resulting in both dermal and oral exposure.

The mechanism of toxicity of phenol compounds leading to adverse birth outcomes has been theorized to be through, in part, alterations in endocrine function during critical periods of development [18]. Studies have linked endocrine-disrupting chemicals, which includes BP-3, with adverse birth outcomes via alterations in sex hormone activity during development [16,9,10]. The first study to publish the potential biological impacts of BP-3 exposure was by Schlumpf et al. [11] which showed an in vitro increase in estrogen receptor activity in human breast cancer cells and an in vivo increase in uterine weight in immature rats exposed to BP-3 [11,12]. Several years later, Wang et al. [4] published a paper critiquing this study, claiming that the public inappropriately interpreted the in vivo results from this animal model study, generating considerable contro-versy [4]. Since the studies by Schlumpf et al. [11] and Wang et al. [4], several more studies have been conducted on both human and animal models to assess reproductive effects of exposure to BP-3.

This paper is a systematic review consolidating the key human and animal model studies to date assessing the impacts of BP-3 on reproductive outcomes. A systematic review approach was taken for two reasons: 1) evidence-based decision making in clinical settings rely heavily on systematic reviews to arrive at synthesized conclusions from the available literature, usually on human subjects and 2) there is an increasing preference in the scientific community to conduct systematic reviews of animal studies to further inform us on potential human outcomes. [13] This study is the first systematic review to inform investigators on reproductive toxicity induced by BP-3 exposure. Study limitations, health implications, and future research directions are also identified.

2. Methods

A literature search was conducted for all relevant publications using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, Cumulative Index to Nursing & Allied Health Literature (CINAHL Plus), the Wiley Cochrane Library, the Cochrane Database, Science Citation Index Expanded (SCI-EXPANDED), ToxCast, EMBL, and the Centre for Reviews and Dissemination database. All databases were searched up to February 21, 2017 and non-English studies were excluded. PubMed Reminer was used to help refine the search strategy and ensure all appropriate and relevant terms were included. Included search terms are detailed in Table 1. A separate grey literature search was done to find any conference proceedings or company or government reports.

Table 1
MeSH Headings Used to Identify Relevant Studies.

Exposure	
1. "Benzophenone-3"	
2. "BP-3"	
3. "2-Hydroxy-4-methoxybenzophenone"	
4. "Escalol 567"	
5. "Eusolex 4360"	
6. "Oxybenzone"	
7. "Oxybenzon"	
8. "Benzophenone-1"	
9. "Benzophenone-8"	
10. "2,4-Dihydroxybenzophenone"	
11. "2,2'-dihydroxy-4-methoxybenzophenone"	
12. "2,3,4-trihydroxy-benzophenone"	
13. "Advastab 45"	
14. "Uvinul"	
15. "Cyasorb"	
16. "Chimassorb"	
17. "Tinosorb"	
18. "2-Benzoyl-5-methoxyphenol"	
19. "4-Methoxy-2-hydroxybenzophenone"	
20. "Viosorb 110"	
21. "Aduvex 24"	
22. "2-Benzoyl-5-methoxyphenol"	
23. "3-Benzopheonone"	
24. "HMB"	
25. "Neo Heliopan BB"	
26. "Prosorb UV 200"	
27. "4-Methoxy-2-hydroxybenzophenone butyric acid"	
28. "Advastab 45"	
29. "1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 Or 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28"	
Outcome	
30. "Endocrine"	
31. "Hormone"	
32. "Hormonal"	
33. "Estrogenic"	
34. "Genital system"	
35. "Estrogen"	
36. "Antiandrogenic"	
37. "Testosterone"	
38. "Reproduction"	
39. "Reproductive"	
40. "Fetus"	
41. "Uterus"	
42. "Uterine"	
43. "Embryo"	
44. "Gonadal"	
45. "Sex"	
46. "Fertility"	
47. "Infertility"	
48. "Developmental"	
49. "Sexual function"	
50. "Estrogenic"	
51. "Uterotrophic"	
52. "30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52"	
Combined Terms	
53. "29 AND 52"	

Abbreviations: MeSH, Medical Subject Headings.

All retrieved studies were combined and two independent reviewers screened all titles and abstracts in accordance to the Preferred Reporting System for Systematic Reviews and Meta-Analyses (PRISMA)[14] guidelines. As abstracts were reviewed, the following inclusion criteria were applied: 1) study conducted on either humans or animals; 2) English language only; 3) direct or indirect reproductive outcome(s) reported; and 4) exposure to BP-3. The table of contents of selected studies were hand searched