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The Banned Sunscreen Ingredients and Their Impact on Human Health: A Systematic Review

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Abstract

Background: Recent evidence of high systemic absorption of sunscreen ingredients has raised concerns regarding the safety of sunscreen products. Oxybenzone (BP-3) and octinoxate (OMC), two common sunscreen ingredients, were recently banned in Key West and Hawaii due to their toxic effects on marine ecosystems. Their impact on human health requires a careful assessment.

Objective: To summarize the current evidence on the association between the systemic level of BP-3 or OMC and its health impact.

Methods: A primary literature search was conducted using PubMed database in February 2019.

Results: There are 29 studies that address the impact of these ingredients on human health. Studies show that elevated systemic level of BP-3 has no adverse effect on male and female fertility, female reproductive hormone level, adiposity, fetal growth, child's neurodevelopment and sexual maturation. However, the association of BP-3 level on thyroid hormone, testosterone level, kidney function and pubertal timing has been reported and prompts further investigations to validate a true association. The systemic absorption of OMC has no reported effect on thyroid and reproductive hormone levels.

Conclusions: Current evidence is not sufficient to support the causal relationship between the elevated systemic level of BP-3 or OMC and adverse health outcomes. There are either contradictory findings among different studies or insufficient number of studies to corroborate the observed association. To accurately evaluate the long-term risk of exposure to BP-3 and OMC from sunscreen, a well-designed longitudinal randomized controlled trial needs to be conducted.

Keywords

benzophenone-3; oxybenzone; sunscreen; octyl methoxycinnamate; octinoxate; toxicity; endocrine; reproductive; fertility; endocrine disrupting compounds; EDC; systemic absorption

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1. Introduction

The concern for safety and effectiveness of sunscreen ingredients has been heightened after recent evidence of their measurable systemic absorption following topical application ^{1,2}. Indeed, the US Food and Drug Administration (FDA) emphasized the importance of the safety assessment on all sunscreen ingredients with systemic absorption greater than 0.5 ng/mL ³. In the recent randomized controlled trial, 4 out of 4 tested sunscreen ingredients were found in the subjects' blood at concentrations exceeding the FDA threshold for waiving toxicology assessment, thereby raising concerns among sunscreen users ¹. In fact, concerns regarding the safety of sunscreen ingredients were growing even before the study was published. In 2018 and 2019, the state of Hawaii and Key West, Florida banned the sale of sunscreen containing oxybenzone (BP-3) or octinoxate (OMC) due to their detrimental threat to the marine ecosystems ⁴⁻⁶. Their toxic effects on other species has alarmed the general public about their potential to impact human health when applied to human skin ⁷.

BP-3 and OMC are two common sunscreen ingredients that are also known to have endocrine-disrupting potential ⁸. While they are mainly used as UV filter in sunscreens, they are also prevalent in air, drinking water, cosmetics, fragrances and plastic packagings, providing additional routes of exposure to humans ⁹. Numerous studies have shown that they can penetrate through the skin and enter the systemic circulation ^{1,10-15}. They have been detected in urine, blood, semen, and even amniotic fluid and breast milk, thereby raising concerns about their negative consequences on fetal development as well as other organ systems ^{9,16}. However, whether the presence of these ingredients in systemic circulation poses risks to human health is unclear. To answer whether systemic absorption of sunscreen poses risks to human health, further investigation is needed.

In this review, we evaluated current evidence on the association between the systemic levels of BP-3 and OMC in humans, and altered health outcomes and fetal development to help provide an insight into the potential clinical significance of the sunscreens' systemic absorption.

2. Methods

A literature search was conducted for all relevant publications in the Pubmed using the following search term: (benzophenone-3 OR oxybenzone OR octinoxate OR octyl methoxycinnamate) AND (endocrine OR reproductive OR kidney OR liver OR cancer OR brain OR hormone OR skin OR hair OR gastrointestinal OR defect OR embryo OR pregnant OR nervous system OR autoimmune disease) AND (animal OR mice OR rat OR rabbit OR human). All articles were searched from January 1, 1979 to February 22, 2019. A total of 423 studies were retrieved, and two independent reviewers screened all titles and abstracts in accordance to the Preferred Reporting System for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). The following exclusion criteria were applied: 1) non-evidence-based studies including review articles, letters and commentaries; 2) *in vitro* studies using cultured cell or tissue; 3) animal studies using non-mammalian species such as insects and amphibians; 4) studies written in languages other than English; 5) studies that do not focus on physiological outcome. The following inclusion criteria were applied: 1)

studies conducted on either humans or mammalian species (e.g. mice, rats); 2) studies that included univariate analysis between BP-3 (or OMC) level and physiological outcome.

3. Results

3.1 Selection of Studies

29 studies met our criteria. 16 studies evaluated the association between the systemic levels of BP-3 (n=16) or OMC (n=2, also included in BP-3) and various outcomes in organ systems, whereas 13 studies evaluated the association between the prenatal systemic levels of BP-3 (n=13) and outcomes in child development (Table 1). We quantified the number of supporting and refuting evidences into Tables 2 and 3.

3.2 Oxybenzone

3.2.1 Effects on Organ Systems—We have found 29 studies that assess the impact of high systemic level of BP-3 on endocrine, reproductive, metabolic, renal systems and neonatal development during pregnancy (Table 1). The effect on thyroid hormone levels was most extensively studied (n=5) most likely due to its endocrine disrupting potential shown in animal studies. Despite the amount of evidence, the association between elevated systemic level of BP-3 and thyroid hormone levels in humans is still inconclusive, because the observed association from each study was not consistent throughout all other studies. Two studies showed an association of higher urinary BP-3 concentrations with decreased thyroid hormones, yet one study showed an inverse association with T4, and another showed the association with T3 only^{17,18}. Interestingly, the two most recent studies with a cohort of 1560 and 439 demonstrated no statistically significant association ($p<0.05$) between urinary BP-3 concentration and thyroid hormone levels, disputing the results from two previous studies^{19,20}. Of the five studies referenced above, only one study assessed the thyroid hormone level after sunscreen application. In this single-blinded clinical trial, 32 volunteers applied cream formulated with 10% of three active ingredients in sunscreen (OMC, BP-3, and 4-methylbenzylcathinone) for one week, and the plasma thyroid levels before and after treatment were measured²¹. No biologically significant effects on thyroid hormone levels were observed after one week, indicating that the maximum allowable concentration of BP-3 in sunscreen was not capable of disturbing the homeostasis of thyroid hormones, at least during the short duration of the study.

The effect of BP-3 concentration on fertility was the second most common potential outcome studied (n=4 studies)²²⁻²⁵. All four studies demonstrated that there was no association between BP-3 exposure and fertility although different parameters were used for measuring fertility, which included semen analysis, the number of menstrual cycles required to achieve pregnancy, and a hazard ratio for spontaneous abortion.

The estrogenic and anti-androgenic activities of BP-3 have frequently been reported in *in vitro* and animal studies, but its impact on human reproductive endocrine systems has not been addressed in great detail. We found four studies that investigated the effect of elevated systemic level of BP-3 on reproductive hormone levels^{14,18,26,27}. In males, the urinary BP-3 concentration was found to be associated with significantly lower serum total testosterone

levels in a cross-sectional study with 588 adolescents²⁷. The same association was also observed in a single-blinded study, which measured the plasma testosterone levels of 15 males after topical application of BP-3 containing cream¹⁴. The author, however, indicated that the difference was more likely due to normal biological variations in hormone levels, because the statistical difference was also evident in blood samples drawn prior to sunscreen application. The clinical significance of BP-3 effect on testosterone level may require further studies as two other studies found no association between BP-3 level and male semen quality or infertility^{23,25}. In females, on the other hand, there was no statistically significant association between urinary BP-3 concentration and reproductive hormone levels, such as estradiol, progesterone, FSH and LH^{14,18,26}.

Besides analysing the reproductive hormone levels, the endocrine disrupting potential of BP-3 was evaluated by measuring the age of pubertal onset by two prospective cohort studies. Each study found contradicting association, one showing a positive and the other showing a negative association between the BP-3 urine levels and the age of pubertal onset^{28,29}. Therefore, the effect on pubertal development is inconclusive.

There is growing evidence suggesting that exposure to environmental chemicals, such as phthalates, bisphenol A and multiple endocrine disrupting chemicals (EDCs), could have adverse consequences on renal function and might contribute to cumulative renal injury. One case-control study evaluated whether the exposure to BP-3 can be a risk factor for chronic kidney diseases³⁰. When they measured the albumin-to-creatinine ratio (ACR), a kidney function marker, and the urinary concentrations of BP-1, a BP-3 metabolite, of 441 female participants, they found a significant association between BP-1 and ACR, suggesting BP-3 as a potential contributing factor to kidney injury.

Xue et al. compared the urinary concentration of BP-3 in 49 obese Indian children and 27 non-obese controls to examine whether exposure to BP-3 is associated with childhood obesity³¹. The results showed no significant association between BP-3 and childhood obesity.

3.2.2 Effects on Fetal and Neonatal Development—The developing embryo and fetus are particularly vulnerable to endocrine disrupting chemicals (EDCs) such as BP-3, because they can potentially interfere with the hormones, neurotransmitters and growth factors that are critical for normal development^{32,33}. Since BP-3 is known to cross blood-placenta barrier and enter amniotic fluid and breast milk, the safety concern regarding the use of sunscreen in pregnant women has increased³⁴. Thirteen studies assessed the association between prenatal BP-3 exposure and offspring's development. In all studies, the level of prenatal BP-3 exposure was determined by the mother's urinary concentration of BP-3 during pregnancy, and the target outcome was evaluated from the offspring through post-birth follow-up. Overall, the prenatal concentration of BP-3 did not have biologically significant effects on the development of offspring (Table 3). Studies found no statistically significant association between prenatal BP-3 exposure and the offspring's sex ratio, birth weight, pubertal development, body fat mass, intelligence quotient and behaviour³⁵⁻⁴⁴. However, a few studies reported the potential risk of prenatal BP-3 exposure on offspring development⁴⁵⁻⁴⁷.

The study by Wolff et al. found that prenatal BP-3 exposure was associated with increased birth weight in boys, but four other studies reported no association between prenatal BP-3 and offspring's birth weight⁴⁵. In a case control study, Huo et al. compared the urinary concentration of BP-3 from 101 mothers with children diagnosed with Hirschsprug's disease (HSCR) and 322 controls, and reported that maternal BP-3 urinary level was associated with higher odds of having a child with HSCR⁴⁶. However, the urine samples from mothers were collected after child was born, and therefore the observed concentration does not necessarily reflect the prenatal BP-3 level. Buckley et al. studied the association between prenatal BP-3 exposure and the risk of developing allergy or immune disorders in offspring⁴⁷. The results actually shows that the higher prenatal exposure of BP-3 was associated with a lower risk of wheeze in children.

3.3 Octinoxate

3.3.1. Effects on Organ System—Octinoxate (octyl methoxycinnamate; OMC), like BP-3, is also considered as EDC^{8,48,49}. However, the effect of OMC exposure on human health is insufficiently investigated compared to that of BP-3. A paucity of studies may be attributed to its relatively low dermal penetration and systemic absorption compared to that of BP-3¹¹. When female participants applied the same amount of cream containing either 10% OMC or BP-3 containing cream, the maximum plasma concentration was 7 ng/mL for OMC, whereas 187 ng/mL for BP-3¹¹.

Only two studies were found on the effect of OMC on human physiology, which were published by the same author. In both studies, 32 participants applied a cream with 10% of BP-3, OMC and 4-MBC for a week, and its effect on the levels of reproductive hormones and thyroid hormones was reported in 2004 and 2007, respectively^{14,21}. Neither reproductive hormone nor thyroid hormone levels were remarkably affected, indicating that short-term topical application of OMC did not disrupt the regulation of thyroid hormone.

3.3.2. Effects on Fetal and Neonatal Development—We could not find any human study that evaluated the effect of high systemic levels of OMC on fetal and neonatal development.

4. Discussion

The primary goal of our review was to understand whether elevated systemic levels of BP-3 and OMC can cause negative health consequences in humans. Among many sunscreen ingredients, we focused on BP-3 and OMC as their toxicity to aquatic species and their endocrine-disrupting potential make them high-priority candidates for safety assessment. The endocrine disruptive effect and developmental toxicity of BP-3 and OMC in cell line and animals are well documented, but their impact on humans has not been addressed in great detail. Aside from sunscreens, BP-3 and OMC are frequently used in cosmetics, shampoo, lip balms and fragrances, so the safety assessment of these compounds are of particular importance. As previously mentioned, the number of studies that investigated the health impact from systemic absorption of sunscreen is significantly scarce. On the other hand, we found 29 studies that investigated the impact of high systemic level of BP-3 (n=29) or OMC (n=2, also included in BP-3) on a wide range of health outcomes in endocrine,

reproductive, metabolic, renal, dermatologic, and developmental systems. Our systematic review demonstrated that current evidence does not strongly support a causal relationship between the systemic level of BP-3 or OMC and adverse health outcome in humans.

The major limitation of our study, however, is that we could not determine the actual contribution of sunscreen on the systemic levels of BP-3 and OMC, and therefore cannot verify the long-term risk of using sunscreen containing BP-3 or OMC. Most studies included an analysis of urinary concentration as an exposure biomarker, which may result from exposure to environmental means other than sunscreen absorption. None of the studies, except 2, evaluated the health outcome using sunscreen as a main route of exposure. It remains to identify the systemic levels of BP-3 and OMC among chronic sunscreen users and use those values to re-evaluate its association with health effects.

In fact, the previous study by Janjua et al. provides an insight into the contribution of transdermal absorption on the systemic level of BP-3 and OMC by comparing the plasma and urine concentration before and after sunscreen application in a group of 32 volunteers ¹¹. Prior to sunscreen application, the plasma and urine concentration for BP-3 and OMC were below the level of detection (3.9 ng/mL) in most subjects. However, after the first whole-body application of sunscreens containing 10% of BP-3 and OMC, the median plasma concentrations rose to 238 ng/mL for BP-3 and 16 ng/mL for OMC within the first two hours. The dramatic increase of plasma concentrations after sunscreen application suggests that a large amount of systemic circulation of BP-3 and OMC could be attributed to sunscreen absorption.

The most recent study by Matta et al. indeed replicates the results reported by Janjua et al. When participants applied sunscreen products containing 6% BP-3, the geometric mean maximum plasma concentration was elevated to 209.6 ng/mL from undetectable level of concentration within two hours, resembling the pharmacokinetics observed from the previous study. Their study also highlighted a long terminal half-life of BP-3 and drug accumulation by measuring the plasma concentration at constant intervals over 7 days after first sunscreen application.

A substantial accumulation of BP-3 in the body from repeated sunscreen application was also mentioned in a previous study by Gonzalez et al. When subjects applied sunscreen containing 4% BP-3 for five days, they continued to excrete significant amounts of BP-3 up to five days after the last application ¹⁰.

The evidence of substantial systemic absorption and accumulation of BP-3 prompts a thorough investigation of the long-term risks of BP-3 containing sunscreen use. Although current evidence does not show a significant correlation between the systemic level of BP-3 and adverse health effects, further studies need to be done to determine the systemic effects resulting from long-term sunscreen use and whether steady state levels exceed the threshold for toxic biological effects.

OMC, unlike BP-3, exhibits low dermal penetration and systemic absorption compared to that of BP-3, which may explain a lack of investigation into its potential health impact ¹¹. Nevertheless, the median toxic dose (TD₅₀), the dose at which toxicity occurs in 50% of

cases, is different for each compound, so the low systemic absorption of OMC does not prove its relative safety. More importantly, the topical application of OMC results in systemic absorption greater than 0.5 ng/mL, a threshold established by the FDA for waiving toxicology assessment, and therefore further drug safety assessment on OMC is crucial.

5. Conclusion

In this systematic review, we did not find a strong support for a causal relationship between the systemic level of BP-3 or OMC and adverse health outcomes. The elevated systemic level of BP-3 did not have adverse effect on fertility, childhood adiposity, and fetal and neonatal development, but its impact on thyroid and reproductive hormone levels, pubertal development, kidney function and the immune system will require further investigations. The health consequences of an elevated OMC level has been less extensively studied presumably due to its poor dermal absorption and low serum concentrations relative to other sunscreen compounds. The current evidence shows that topical application of OMC does not have biologically significant effect on thyroid and reproductive hormone levels. To evaluate the long-term risk of exposure to BP-3 or OMC from sunscreens, a well-designed longitudinal randomized controlled trial is of high priority.

6. Questions (answers highlighted)

1. Which two sunscreen ingredients did Hawaii and Key West ban?
 - a. Avobenzone and octisalate
 - b. Oxybenzone and octinoxate
 - c. Zinc oxide and titanium dioxide
 - d. Octocrylene and trolamine salicylate
2. Why did Hawaii and Key West ban two sunscreen ingredients?
 - a. Studies showed that they can cause damage on coral reef and marine species.
 - b. Studies showed that they can lead to higher risk of melanoma.
 - c. Studies showed that they can monopolize the sale of sunscreens.
 - d. Studies showed that they can cause digestive problems when ingested.
3. Oxybenzone and octinoxate can penetrate through the skin and enter the systematic circulation.
 - a. True
 - b. False
4. FDA recommends toxicology assessment on sunscreen ingredients with systemic absorption greater than which of the following?
 - a. 0.1 ng/mL

- b. 0.5 ng/mL
 - c. 10 ng/mL
 - d. 50 ng/mL
5. Humans can be exposed to oxybenzone and octinoxate from other sources besides sunscreen.
 - a. True
 - b. False
6. Oxybenzone has been detected in which of the following in human body?
 - a. Blood
 - b. Urine
 - c. Breast milk
 - d. All of the above
7. The evidence exists for an association between systemic level of oxybenzone and all of the following except ____.
 - a. Thyroid hormone level
 - b. Testosterone level
 - c. Kidney function
 - d. Heart failure risk
8. Oxybenzone and octinoxate are considered as endocrine disrupting chemicals (EDCs).
 - a. True
 - b. False
9. Current evidence shows that there is a significant correlation between the systemic level of oxybenzone and fertility.
 - a. True
 - b. False
10. There is sufficient amount of evidence that sunscreen absorption causes detrimental effect on human health.
 - a. True
 - b. False

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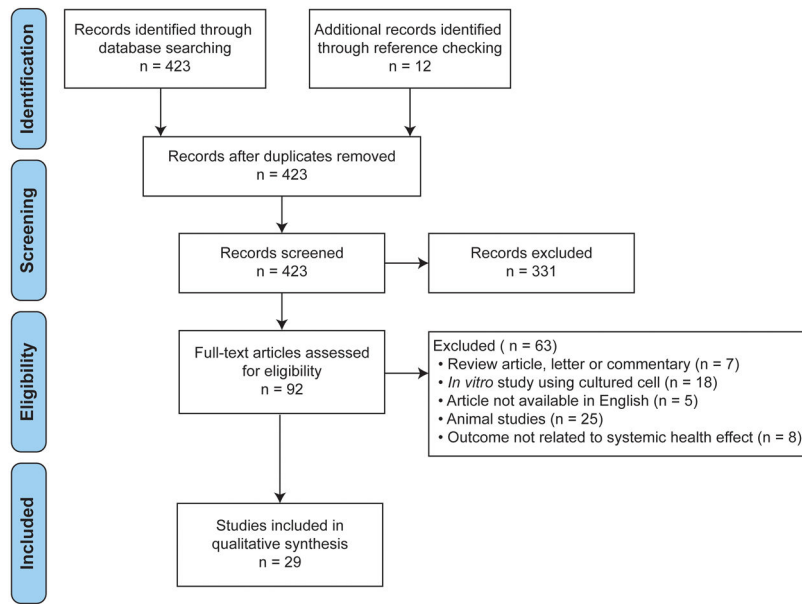


Figure 1. PRISMA Diagram.
Process of inclusion of studies

Table 1. Human studies on the association between the systemic levels of oxybenzone (BP-3)/octinoxate (OMC) and health outcome

	Author, Year	Study type (LOE)	# of Subjects ^a	Study Characteristics	Measure of Outcome	Conclusion
<i>Thyroid Hormone Level</i>	Przybyla et al., 2018, ²⁰	Cross-sectional study (4)	850 M, 710 F	Measurement of urinary BP-3 concentration and serum thyroid hormone levels	T3, T4, TSH levels	No significant association between BP-3 and thyroid hormone levels
	Aker et al., 2018 ¹⁹	Case-control study (3)	439 pregnant F	Measurement of urinary BP-3 concentration and serum thyroid hormone levels	T3, T4, T3/T4 ratio, TSH, FT4 levels	No significant association between BP-3 and thyroid hormone levels, although the author reported an inverse trend with T3 and T4
	Kim et al., 2017 ¹⁷	Retrospective cohort study (3)	1829 M/F	Measurement of urinary BP-3 concentration and serum thyroid hormone levels	T3, T4, FT3, FT4, TSH levels	High BP-3 concentration was associated with decrease FT4 and T4
	Aker et al., 2016 ¹⁸	Prospective cohort study (2)	106 pregnant F	Measurement of urinary BP-3 concentration and serum hormone levels at two time points (16-20 wks and 24-28 wks) during pregnancy	FT3, FT4, TSH levels	An IQR increase in BP-3 was significantly associated with 3% decrease in free T3; no significance with TSH or T4
	Janjua et al., 2007 ²¹	Single-blinded clinical trial (4)	32 M/F	Measurement of serum thyroid hormone levels before and after whole-body topical application of sunscreen + 10% of BP3, OMC and 4-MBC for QD for one week	TBG, TSH, T3, T4, FT3, FT4 levels	No biologically significant change in thyroid hormone levels, although statistical difference was observed likely due to normal hormonal variation
<i>Fertility</i>	Buck Louis et al., 2015 ²⁵	Case-control study (3)	413 M	Measurement of urinary BP-3 concentration and semen analysis	Semen parameters	No significant association between BP-3 concentration and semen quality
	Buck Louis et al., 2014 ²²	Prospective cohort study (2)	501 couples	Measurement of urinary BP-3 concentration and fecundity	The number of menstrual cycles required to achieve pregnancy	No significant association between BP-3 concentration and fecundity
	Chen et al., 2013 ²³	Case-control study (3)	877 idiopathic infertile male, 713 controls	Measurement of urinary BP-3 concentration and semen analysis	Semen parameters (volume, sperm concentration and number)	No significant association between BP-3 concentrations and idiopathic male infertility and semen parameters
<i>Reproductive hormone level</i>	Chen et al., 2013 ²⁴	Case-control study (3)	70 couples with spontaneous abortions, 180 control couples	Measurement of urinary BP-3 concentration and the rate of spontaneous abortions	Rate of spontaneous abortions	No significant association between BP-3 and spontaneous abortions
	Pollack et al., 2018 ²⁶	Prospective cohort study (2)	143 premenopausal F	Measurement of urinary BP-3 concentration and reproductive hormones over two menstrual cycles	Reproductive hormone levels (estradiol, progesterone, FSH, LH)	Single-chemical exposure model: No significant association between BP-3 and reproductive hormones Multi-chemical exposure model: Negative association between BP-3 and FSH and LH

Author, Year	Study type (LOE)	# of Subjects ^a	Study Characteristics	Measure of Outcome	Conclusion
Scinicariello et al., 2016 ²⁷	Cross-sectional study (4)	588 M/F	Measurement of urinary BP-3 concentration and serum testosterone levels	Serum testosterone	Male adolescents in the 3rd and 4th quartiles of BP-3 had significantly lower total testosterone (-38.74%; 95% CI: -58.52, -10.42) and (-36.87%; 95% CI: -59.34, -1.98)
Aker et al., 2016 ¹⁸	Prospective cohort Study (2)	106 pregnant F	Measurement of urinary BP-3 concentration and serum hormone levels at two time points (16-20 wks and 24-28 wks) during pregnancy	estradiol, progesterone, SHBG levels	IQR inc in BP-3 was signif. associated with 10.3% dec. in SHBG at second time point but not first time point; no significance w/ estradiol or progesterone
Janjua et al., 2004 ¹⁴	Single-blinded clinical trial (1)	32 M/F	Plasma reproductive hormone levels were measured before and after whole-body topical application of sunscreen for a week	Reproductive hormone levels (testosterone, estradiol, progesterone, FSH, LH)	Decrease in plasma testosterone after the application, but likely due to normal hormonal variation. No association with other female reproductive hormones
Binder et al., 2018 ²⁸	Prospective cohort study (2)	200 F	Measurement of urinary BP-3 concentration at two time points: prior to the onset of breast development (B1) and during adolescence (B4); age of menarche was recorded	Age of menarche	A higher BP-3 concentration at B1 was associated with earlier menarche (HR: 1.17; 95% CI: 1.06, 1.29)
Wolff et al., 2015 ²⁹	Prospective cohort study (2)	1239 girls at age 6-8 years old	Measurement of urinary BP-3 concentration at enrollment. Subjects were followed annually for 7 years to determine the age at first breast or pubic hair development.	Pubertal onset	BP-3 concentration was associated with later onset of breast development 5-6 months later, (AOR: 0.80; 95% CI: 0.65, 0.98)
Xue et al., 2015 ³¹	Case-control study (3)	49 obese children 27 non-obese control	Measurement of urinary BP-3 concentration and clinical evaluation of obesity	Rate of obesity	No significant association between BP-3 concentration and the likelihood of obesity
Kang et al., 2019 ³⁰	Cross-sectional study (4)	441 F	Measurement of urinary BP-3 concentration and albumin-to-creatinine ratio (ACR) at a single time point	Urinary albumin-to-creatinine ratio (AR)	Positive association between the concentration of BP-1, a metabolite of BP-3, and ACR
Messerlian et al., 2018 ³⁵	Prospective cohort study (2)	346 mother-child cohorts	Measurement of urinary BP-3 concentration from both men and women prior to conception and second measurement from women during pregnancy; birth weight and head circumferences of infants were assessed	birth weight and size	No significant association between maternal BP-3 and the birth weight
Ferguson et al., 2018 ³⁶	Prospective cohort study (2)	476 mother-child cohorts	Measurement of paternal and maternal prenatal urinary BP-3 concentration and newborn's size and weight at delivery	birth weight and size	No significant association between maternal BP-3 and the birth weight
Tang et al., 2013 ⁵⁰	Prospective cohort study (2)	567 mother-child cohorts	Measurement of maternal prenatal urinary BP-3 concentration prior to delivery and newborn's weight, length and gestational age	birth weight, size and length of gestation	No significant association between BP-3 concentrations and the birth weight and size. Prenatal BP-3 concentration was associated with decreased length of gestation (-0.45

Author, Year	Study type (LOE)	# of Subjects ^a	Study Characteristics	Measure of Outcome	Conclusion
Philippat et al., 2012 ³⁸	Prospective cohort study (2)	191 mother-child cohorts	Measurement of paternal and maternal prenatal urinary BP-3 concentration and newborn's size and weight at delivery	birth weight and size	No significant association between maternal BP3 and the birth weight (26g; CI: -2, 54), but author mentioned that a positive trend exists.
Wolff et al., 2008 ⁴⁵	Prospective cohort study (2)	404 mother-child cohorts	Measurement of paternal and maternal prenatal urinary BP-3 concentration and newborn's size and weight at delivery	birth weight and size	BP3 was associated with increasing birth weight in boys (44 g; 95% CI: 5.4, 84) per 1 ln-transformed biomarker, but decreasing birthweight in girls (but no statistical data shown for girls)
Harley et al., 2019 ⁴⁰	Prospective cohort study (2)	179 mother-daughter cohorts 159 mother-son cohorts	Measurement of maternal prenatal urinary BP-3 concentration. Children were followed up for pubertal assessments	Pubertal onset in children	No significant association of prenatal urinary BP3 concentrations with pubertal onset
Huo et al., 2016 ⁴⁶	Case-control study (3)	101 Hirschsprung's disease (HSCR) patient's mother-child 322 control	Measurement of urinary BP-3 concentration from HSCR patient's mother and control	The odds of giving birth to child with HSCR	Higher BP-3 exposure groups were more likely to give birth of HSCR children (adjusted OR = 2.39; 95% CI=1.10, 5.21). However, the urine sample was not collected during pregnancy.
Chevrier et al., 2012 ⁴¹	Case-control study (3)	5200 mother-child cohorts	Urine samples were collected from mothers who gave birth to boys with hypospadias and undescended testes, and three controls per case were selected among male singleton live births	The odds of giving birth to child with hypospadias and undescended testes	No significant association between maternal BP-3 and male genital abnormalities
Buckley et al., 2016 ⁴²	Prospective cohort study (2)	173 mother-child cohorts	Prenatal BP-3 was measured from pregnant women's urine samples; body fat mass of child was measured from 1998 to 2002.	Percent body fat	No significant association, but prenatal BP-3 concentrations were inversely associated with percent fat mass in girls (beta=-1.51, 95% CI=-3.06, 0.01) but not in boys (beta=-0.20, 95% CI=-1.69, 1.26)
Nakiwala et al., 2018 ⁴³	Prospective cohort study (2)	452 mother-son cohorts	Urine samples were collected from pregnant women at 22-29 gestational weeks. Verbal and performance IQ of children were assessed at 5-6 years old	verbal and performance IQ	No significant association between prenatal BP-3 exposure and the boys' verbal or performance IQ (uncorrected p-value 0.09)
Philippat et al., 2017 ⁴⁴	Prospective cohort study (2)	529 mother-son cohorts	Prenatal BP-3 was measured from mother's urine samples; child's behavior was assessed by the Strength and Difficulties Questionnaire (SDQ) completed by mothers	Child's behavior	No significant association between BP-3 and child's behavior
Bae et al., 2016 ³⁹	Prospective cohort study (2)	220 parent-child cohorts	Preconception urinary BP-3 was measured from both father and mother, and the sex of child was reported	Sex ratio of child	No significant association between BP-3 and secondary sex ratio
Buckley et al., 2018 ⁴⁷	Prospective cohort study (2)	164 mother-child cohorts	Urine samples were collected from pregnant women in the third trimester;	Risk of developing atopic dermatitis, asthma, and wheeze	Wheeze was inversely associated with low BP-3 exposure in all children. No

Author, Year	Study type (LOE)	# of Subjects ^a	Study Characteristics	Measure of Outcome	Conclusion
			allergy and immune system of children was assessed by questionnaire		significant association exists for other allergic conditions.

^a All subjects are adults unless otherwise stated.

Abbreviations: LOE, Level of Evidence; M, male; F, female; y/o, year-old; T3, Total triiodothyronine; T4, Total thyroxine; TSH, Thyroid Stimulating Hormone; FT3, Free triiodothyronine; FT4, Free thyroxine; QD, once a day; 4-MBC, 4-Methylbenzylidene camphor; QD, once a day; FSH, Follicle Stimulating Hormone; LH, Leutinizing Hormone; IQR, Interquartile Range; SHBG, sex hormone-binding globulin; AOR, adjusted odds ratio

Table 2.

Number of human studies about the association between urinary concentration of oxybenzone (BP-3) or octinoxate (OMC) and the physiological outcomes. n=16 (duplicate excluded)

Target effect	Statistically significant association		No statistically significant association	
	BP-3	OMC	BP-3	OMC
Thyroid hormone level	2 (↓↓)	0	3	1 ^a
Pubertal onset	2 (↑)	0	0	0
Male reproductive hormone level	1 (↓)	0	1	1 ^a
Female reproductive hormone level	0	0	2	1 ^a
Kidney function	1 (↓)	0	0	0
Fertility	0	0	4	0
Childhood adiposity	0	0	1	0

In parenthesis, ↓ indicates a negative correlation with elevated BP-3 level. ↑ indicates a positive correlation with elevated BP-3 level.

^aThe results are from the same paper that is also included in BP-3 column.

Table 3.

Number of human studies about the association between maternal prenatal urinary concentration of oxybenzone (BP-3) or octinoxate (OMC) and the target effects in child. n=13 (duplicate excluded)

Target effect	Statistically significant association		No statistically significant association	
	BP-3	OMC	BP-3	OMC
Offspring's birth weight	1 (↑ in boys)	0	4	0
Offspring's birth defect	1 (↑)	0	1	0
Offspring's allergic outcome	1 (↓)	0	0	0
Offspring's pubertal onset	0	0	1	0
Offspring's body fat mass	0	0	1	0
Offspring's intelligence quotient (IQ)	0	0	1	0
Offspring's behavior	0	0	1	0
Offspring's sex determination	0	0	1	0

In parenthesis, ↓ indicates a negative correlation with elevated BP-3 level. ↑ indicates a positive correlation with elevated BP-3 level.