Reproductive Toxicology xxx (xxxx) xxx-xxx

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com

Can oxybenzone cause Hirschsprung's disease?

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ARTICLE INFO

Keywords:
Embryogenesis
Hirschsprung's disease
Inhibition of neural crest cell migration
Oxybenzone

ABSTRACT

Oxybenzone is a ultraviolet (UV) absorber used in 70% of sunscreen products, is a recognized endocrine disrupting chemical (EDC) and is small enough to pass through skin and placenta barriers. Numerous studies have identified this chemical in the urine/blood of pregnant women as well as in fetal and umbilical cord blood. A recent study demonstrated that women with medium to high levels of oxybenzone in their urine was associated with giving birth to neonates with Hirschsprung's Disease (HSCR). Testing in human cell lines confirmed that low levels of oxybenzone has the potential to disrupt cell migration and function in a manner similar to what is associated with HSCR. Analysis of human exposure levels to oxybenzone from sunscreen use, under normal conditions, demonstrates that enough chemical can cross into the mother's blood making it available to the fetus at high enough levels that can indeed inhibit migration of neural crest cells during critical embryonic development.

1. Short communication

Oxybenzone (also know as benzophenone-3) is a chemical ultraviolet (UV) absorber commonly used at 6% in sunscreen and anti-aging skincare products. The Center for Disease Control studied 2517 participants aged 6 years and older and found 15 ppb–3 ppm in the urine of 96.8% of the population studied making this chemical one of the most commonly found substance in the human body [1]. Hirschsprung's disease (HSCR) is a neonatal intestinal abnormality that is derived from a failure of enteric neural crest cells migration during embryogenesis from 5 to 12 weeks. Depending on global location, the incidence of HSCR varies from 1:2000 to 1:5000 with a 4-fold increase occurring in males over females. The knowledge of environmental factors contributing to HSCR is still quite limited and this information is the first known associating the disease to oxybenzone exposure [2]. Regardless, other studies making oxybenzone suspect relate it to being an endocrine disrupting chemical [3–5] commonly detected in breast milk [6,7] with prenatal exposure reducing pregnancy duration [8] and suboptimal fetal growth [9–11]. Oxybenzone also causes apoptosis of neuronal cells inhibiting autophagy and disruption their epigenetic status [12–14].

Huo et al. [2], investigated the levels of oxybenzone in urine and the incidence of HSCR in 423 Chinese patients. All patients were tested for oxybenzone via a spot urine test and then divided into groups based on the presence of HSCR. Group 1 consisting of 101 neonates diagnosed with HSCR that presented with intestinal obstruction and chronic constipation that were diagnosed by barium enema and anorectal manometry prior to surgery and were confirmed with pathological analysis after surgery, Group 2 consisted of a non-HSCR surgical control made up of 103 infants requiring surgery for intussusception or incarcerated/strangulated inguinal hernia without ischemia or necrosis and Group 3 was a non-HSCR and non-surgical control consisting of 219 neonates. Subject demographics were equally matched within the population (age, weight, education) and behaviors (smoking, drinking). Based on the data obtained there was a positive association between women identified with medium to high levels (maximum detection level of 400.72 ppb) of oxybenzone in urine and the incidence of HSCR.

Concurrently, in vitro studies were conducted in 293T and SH-SY5Y cells lines, which are widely used in HSCR research because they mirror abnormal migration involved in the disease pathway. They observed a consistent statistically significant expression of several receptors/genes after oxybenzone exposure ranging from 0.1 μM (22.8 ppb) to 100 μM (22,800 ppb) concentrations (Table 1). The variability between the two cell lines to react to the same concentrations of oxybenzone maybe associated with their sensitivity to the chemical under the conditions of the tests. Regardless, maternal con-

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https://doi.org/10.1016/j.reprotox.2019.02.014
Received 18 October 2018; Received in revised form 16 February 2019; Accepted 28 February 2019
Available online xxx
0890-6238/

Table 1
Lowest Observable Adverse Effect Level (LOAEL) of Oxybenzone Tested Yielding Significance.

Parameter	LOAEL		Statistical Significance	
	293T Cells	SH-SY5Y Cells	293T Cells	SH-SY5Y Cells
Decrease of RET	0.1 μM (22.8 ppb)	0.1 μM (22.8 ppb)	$P < 0.05$	$P < 0.05$
Decrease of PLAG1	0.1 μM (22.8 ppb)	1 μM (228 ppb)	$P < 0.05$	$P < 0.05$
Increase in miR-218 expression	100 μM (22,800 ppb)	1 μM (228 ppb)	$P < 0.01$	$P < 0.01$
Increase of SLIT2	100 μM (22,800 ppb)	10 μM (2280 ppb)	$P < 0.05$	$P < 0.001$
Increase of ROBO1	10 μM (2280 ppb)	100 μM (22,800 ppb)	$P < 0.05$	$P < 0.01$

centrations of oxybenzone remained consistent delineating the risk probability to the offspring. The negative control, 0.1% Dimethyl Sulfoxide, was not added to the table since no observable toxicity was noted. They concluded that maternal oxybenzone exposure was associated with offspring's HSCR in the population study as well as based on the impact observed in several receptors/genes for the cell lines tested demonstrating that oxybenzone contributed to the pathopoiesis of HSCR via regulating genes signal transduction (Fig. 1).

Understanding the various in vitro impacts that oxybenzone has on cells and identifying it in the urine of pregnant women is important, however, in order for oxybenzone to exert a neurotoxic effect (HSCR) on a fetus, it has to be able to pass into the mother's blood, through the umbilical cord and into the developing offspring. With that said, oxybenzone has a molecular weight of approximately 228 g/Mol which is small enough for the chemical to pass through human skin [15] and placenta [16] barriers. Janjua et al. [17], conducted a single-blinded study in 32 healthy volunteers, 15 young males and 17 postmenopausal females, who applied a sunscreen with oxybenzone daily to their whole-body for 2 weeks using the 2 mg/cm^2 dose recommended by the Food and Drug Administration (FDA) and observed a maximum plasma concentrations of 200 ppb in postmenopausal females and 300 ppb in young men.

Zhang et al. [18], studied oxybenzone and one of its metabolites 4-hydroxybenzonephenone (4-HBP) in maternal blood (1 h before delivery) with fetal cord blood (taken at time of delivery) in 20 subjects. 4-HBP was found in all matched fetal cord blood and maternal blood samples, at concentrations ranging from 0.26 to 0.51 ppb in cord blood, and from 0.32 to 1.78 ppb in maternal blood. Oxybenzone was found in 12 cord blood samples (range: 0.55–2.55 ppb) and 7 maternal blood samples (0.74–2.30 ppb). Total of both benzophenones is 0.81–3.06 ppb fetal cord and 1.06–4.08 ppb maternal blood samples or basically a 3:4 ratio (75%) between fetal and maternal blood levels. Similarly, Krause et al. [19], evaluated oxybenzone levels in 23 fetal cord and maternal blood samples and observed a 1:10 ratio (10%) between fetal and maternal blood levels.

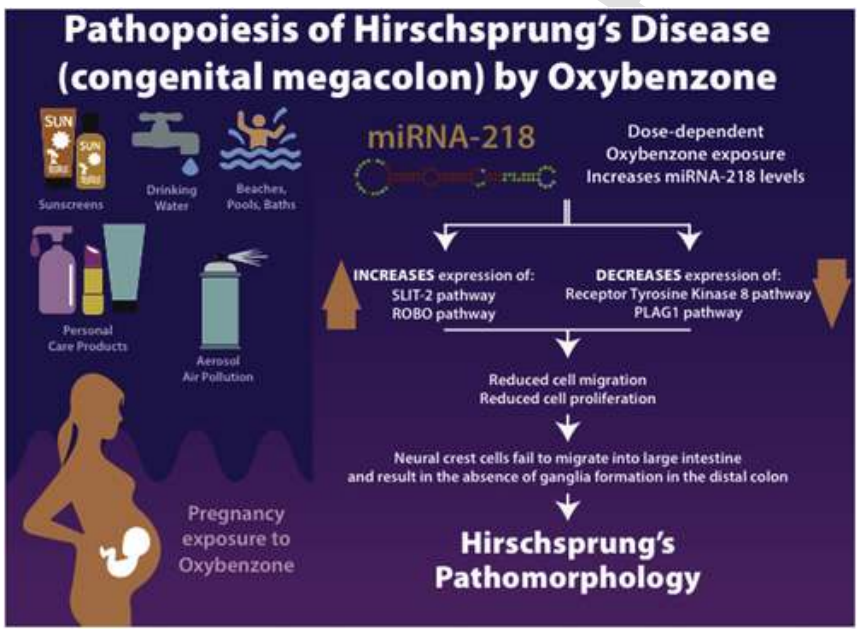

Fig. 1. Pathopoiesis of HSCR by Oxybenzone.

To establish a cogent argument that the exposure levels and risks of oxybenzone, when used as recommended are of concern the following summary of premises are offered:

1) Oxybenzone is considered to be an endocrine disrupting chemical (EDC).
2) Oxybenzone has a molecular weight of approximately 228 g/Mol, small enough to pass through human skin and placenta barriers.
3) Oxybenzone is commonly used in sunscreen formulas at 6% and as much as 8% of the chemical is absorbed through the skin and into the body via blood stream, partially stored in fat and eventually excreted in urine [20].
4) Studies have demonstrated that 200 ppb of oxybenzone can be found in blood serum when applied topically at a 2 mg/cm^2 FDA dose or 1 ounce (30 g) of sunscreen for every 2 h of sun exposure (average exposure 4 h) to avoid skin cancer.
5) Paired fetal cord and maternal blood samples range from a 1:10 (10%) to a 3:4 (75%) ratio.

Calculation:

60 g (amount of product applied/4 h) * 0.06 (6% oxybenzone in product) / 75 kg (average weight women) = 0.048 g/kg or 48 mg/kg or 48 ppm/exposure.

48 ppm/exposure * 0.08 (8% oxybenzone absorbed topically) = 3.84 ppm or 3840 ppb absorbed over 4 h.

Using the ratio of fetal to maternal blood levels (10% and 75%) after just 2 applications over a 4-h period (1 day's exposure) with a sunscreen containing 6% oxybenzone, exceeded the Lowest Observable Adverse Effect Level (LOAEL) doses in half to three quarters of the parameters evaluated by Huo (Table 2). Since the embryonic period of neural crest cell migration associated with HSCR does not occur until weeks 5–12 of pregnancy, women can unintentionally exposure their fetus to extremely high levels of oxybenzone over time. This is in stark contrast to previously believed use levels requiring 34.6–277 years of sunscreen application before an endocrine disruption effect can be observed in humans [21].

In conclusion, there is a direct association of oxybenzone maternal exposure and HSCR in neonates under normal conditions of use of sunscreen products. Based on the data presented, it would appear

Table 2
Comparison Between Available Maternal/Fetal Blood Levels and Oxybenzone Use.

Exposure[a]	Maternal Exposure	10% Fetal Exposure	75% Fetal Exposure
After 1 Day	3840 ppb	384 ppb	2,880 ppb
After 1 Week	26,880 ppb	2688 ppb	20,160 ppb
After 5 Weeks[b]	134,400 ppb	13,400 ppb	100,800 ppb
After 12 Weeks[b]	322,600 ppb	32,260 ppb	241,950 ppb

[a] Exposure is based on 4 h of sun exposure/day with two 1 ounce applications (60 g) of sunscreen.

[b] Embryogenesis period of neural crest cell migration.

that oxybenzone, a known EDC, should be avoided during pregnancy and/or in the event conception is desired. Based on the lack of EDC data published on non nano-particle size mineral based sunscreens (zinc oxide and titanium dioxide), it maybe a safer choice for mother's that have to protect themselves from sun exposure, minimizing unnecessary chemical exposure to the developing embryo/fetus, in additional to practicing sun avoidance, using protective clothing/hats/sunglasses and utilizing oversized umbrellas/cabanas when outside, at pools or on the beach.

Conflict of interest

Joseph C. DiNardo: no conflict(s) of interest.

Craig A. Downs: Haereticus Environmental Laboratory received a donation $1,100 from the W.S. Badger Company to cover the costs of 105 T-shirts for a "Save The Reef" Rally at 5:00 pm EST on January 15, 2019 in Key West, Florida. This donation had no influence on this on the data, arguments or conclusions stated in this manuscript.

Funding

The authors have no other financial relationships relevant to this article to disclose.

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