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BPS and Cell Fusion in the Human Placenta: A Separate Mechanism of Action?

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During the past decade, the plasticizer bisphenol S (BPS) has been replacing the endocrine-disrupting chemical bisphenol A (BPA) in numerous consumer products.[1,2] As an example of its prevalence, a survey conducted in the United States and seven Asian countries found BPS in 81% of human urine samples collected.[3] Despite the two chemicals' general similarity, some of their biochemical properties differ.[4,5,6] This raises the possibility that BPS may affect endocrine organs—including the human placenta—differently than BPA does. Researchers led by Almudena Veiga-Lopez, a visiting associate professor in the Department of Pathology at the University of Illinois at Chicago, explored one such mechanism in a recent *in vitro* study published in *Environmental Health Perspectives*.[7]

Veiga-Lopez and colleagues studied cell fusion processes human placentas collected at the end of healthy pregnancies. The results of their analyses suggest that BPS may interfere with the formation of the syncytiotrophoblast (STB), a layer of epithelial cells in the placenta. The STB prevents the rejection of fetal cells by the maternal immune system, enables the exchange of nutrients and gases between mother and fetus, protects the fetus from some (although not all) harmful chemicals in maternal blood, and secretes its own hormones, such as hCG and progesterone.[8]

The STB is composed of trophoblasts, which are the first cells to differentiate after an egg is fertilized. The authors proposed that BPS interferes with the fusion of trophoblasts into the STB by competing with the epidermal growth factor (EGF) for binding to the EGF receptor (EGFR). EGF is a protein that stimulates cell growth and differentiation throughout the body.[9] The researchers analyzed trophoblasts from six term placentas and found that 200 ng/mL of BPS blocked EGF-mediated cell fusion *in vitro* by binding to EGFR. That concentration is at the upper end of the reported urinary range for the U.S. general population.[10]

Importantly, spontaneous cell fusion was not blocked by this dose, suggesting alternative mechanisms may be involved in the interference with STB formation. "Even if BPS were to block all of the cell fusion events that are induced by EGF, cells that were to fuse spontaneously—not through EGF—could still do so," Veiga-Lopez explains.

Although human trophoblasts from term placentas still fuse *in vitro*, they no longer divide.[11,12] So the researchers also analyzed

BPS is used in thermal receipt paper and linings of food and beverage cans. It has been found in canned foods, indoor dust, sewage sludge, groundwater, and river sediment. Image: © Robert Hoetink/Shutterstock.

proliferating breast cancer cells, which are an established model for testing the EGFR-binding activity of environmental chemicals. The results provided additional evidence that BPS acts as an EGFR antagonist.

The study raises the possibility that BPS may adversely affect fetal development or increase the risk of pregnancy complications. However, those possibilities hinge on the role of EGF in the cell fusion process *in vivo*.

"The placenta has one of the body's highest EGFR expression levels, and EGF is among the dominant factors regulating the proliferation, uterine [attachment], and fusion of human trophoblasts," says Veiga-Lopez. "But other factors are involved as well. Our understanding of these processes is limited, as they are very difficult to study."

EGF likely plays a variety of roles throughout pregnancy.[13,14,15] In the first trimester, EGF helps the developing placenta attach to the uterus. To nourish the rapidly growing fetus in later pregnancy stages, EGF and other factors primarily control the cell fusion process to keep up with the increasing complexity the villi—the finger-like structures that maximize the embryo's contact with maternal blood.

Any role of BPS in that fusion process is currently uncertain, says R. Michael Roberts, a professor emeritus of reproductive biology at the University of Missouri, who was not involved in the study. "The researchers proposed a new mechanism of action for BPS that is different from alterations of the classical steroid receptor pathway," he says. "Although intriguing, I think it remains a hypothesis until confirmed by other studies at environmentally relevant doses."

Graham Burton, a professor emeritus of reproductive physiology at the University of Cambridge, United Kingdom, who also was not involved in the study, agrees with the authors' conclusion that BPS blocks EGF-mediated cell fusion *in vitro*. However, extrapolating that finding to human pregnancies is difficult, he notes.

"BPS may affect trophoblast proliferation early in the course of placental development, but I think it is less likely to affect *in vivo* syncytialization, as spontaneous fusion was not blocked in their experiments," says Burton. "At the end of the day, we just don't know enough about the role of EGF in regulating this complex process."

Recently generated organoid trophoblast cultures[16,17] form structures similar to villi, differentiate into the STB and other cell types, and secrete placenta-specific peptides and hormones. These cultures closely resemble first-trimester placentas and may help clarify the regulation of cell fusion, says Burton.

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