AUTHOR COMMENTARIES - From Special Topics

Bisphenol A (BPA) - August 2009
Interview Date: September 2009

PDF

Ana Soto

From the Special Topic of Bisphenol A (BPA)

According to our Special Topics analysis of bisphenol A research over the past decade, the work of Dr. Ana Soto ranks at #2 by total cites, based on 27 papers cited a total of 930 times. In Essential Science Indicators℠ *from Thomson Reuters, Dr. Soto's record includes 74 papers cited a total of 1,820 times between January 1, 1999 and April 30, 2009. She is also a Highly Cited Researcher in both Ecology/Environment and Pharmacology.*

Dr. Soto heads up her own lab at the Tufts University School of Medicine, where she is Professor of Anatomy and Cellular Biology.

In the interview below, ScienceWatch.com *correspondent Gary Taubes talks with Dr. Soto about her highly cited research relating to bisphenol A.*

SW: When did you first get interested in the subject of endocrine disruptors and what prompted it?

That was in 1989, when I was working, as I still am, with Professor Carlos Sonnenschein. We had come to the conclusion, contrary to perceived wisdom, that estrogen does not directly induce cells to proliferate, but rather, blocks the action of a plasma-borne inhibitor. This was something really iconoclastic, but really important. Although I'm always being interviewed for my work on endocrine disruptors, this research related to control of cell proliferation is, conceptually speaking, more important. We, like everyone else, thought that in order for cells to proliferate, they had to be stimulated—we thought that's what estrogen did. But we found out, much to our surprise, that cells could proliferate without estrogen *in culture conditions* even though the same cells in animals could only proliferate when estrogen was present. That was a paradox and, to make a long story short, what we found was that estrogens do not actually induce cells to proliferate; rather, they block the action of the above-mentioned plasma-borne inhibitor.

That was very interesting, but it brought us to another puzzle: why everyone was thinking along the positive control of cell proliferation and we were finding just the opposite, i.e., that cell proliferation was under negative control. We started looking at the literature and found a great paucity of data regarding this issue. Eventually we published a book on the implications of this finding: *The Society of Cells*.

Now back to the endocrine disruptors. In 1989, we were trying to determine what it was in serum that inhibited the action of estrogen in the animal. We had developed an assay that worked like this: in the absence of serum, cells would proliferate, but if you added a fraction of the serum that was inhibitory, they wouldn't. Then, if you added estradiol back, these cells proliferated again. So we used this assay for years until all of a sudden it stopped working. The cells would proliferate even in the presence of the

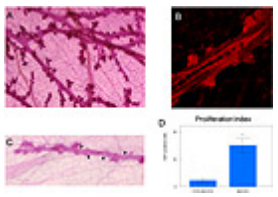
inhibitor. It didn't matter if we added estrogen or not. It smacked of contamination with estrogen. We spent four months trying to figure out where the unknown estrogen came from until we verified that it was something shedding from the test tubes that we used to store the serum components.

How did you identify what the active compound was?

At that point, we called the manufacturers and told them about our strange experience. They said that they didn't know where the estrogen could be coming from, but they agreed to send us four or five batches of these plastic tubes. We called them back two weeks later and told them which batch had the estrogens. They then traced those batches to a change in the formulation of the plastic manufacturing—they had made it sturdier, more impact-resistant. We asked them what it was they had added, but they said it was a trade secret.

We spent another year purifying the "trade secret." It turned out to be nonylphenol, an antioxidant that's also used in the synthesis of detergents. Carlos and I published our findings and then went looking for other places where nonylphenol was used. It turned out that it's also in the spermicides used in condoms and in creams applied with diaphragms…right there we knew it could be a big problem.

Figure 1 [+] details



Fetal and perinatal exposure to...

Figure 2 [+] details

In the lab photo I am at center of the first row...

SW: Was that first paper noticed? Did anyone pay attention at the time?

Theo Colborn became aware of our work and invited us to a conference she organized in 1991 in Wingspread, Wisconsin. At the time, she was concerned about the problems in the Great Lakes with animals that looked feminized. The idea was that DDT is also estrogenic, as are polychlorinated biphenyls. These two chemicals had already been banned; however, if they were the causal agents of these changes, there was nothing to be done but wait until the levels of these chemicals decay, hoping that enough individuals of each species of animals would have survived the consequences of these exposures and reproduce.

If, instead, the problem in the Great Lakes was due to the kind of chemicals we were now studying, additional regulatory measures could be taken to protect the environment. Colborn put together a panel with 20 scientists and I was one of them, and we came up with this term "endocrine disruptors" and shared in the writing of what's called the Wingspread Statement.

We then wrote the first paper on endocrine disruptors together with Theo Colborn and Fred vom Saal, which was published in 1993. We also decided to test other chemicals used in the environment. So Carlos and I tested a battery of these chemicals and found that several of them were estrogenic. They're less potent than the natural ovarian hormone, but it prompted us to ask what would happen if animals are exposed to them.

SW: What other evidence was there that these compounds could be problematic?

There was the diethylstilbestrol story. That's DES, the synthetic estrogen given to pregnant women in the 1950s with the stated purpose of preventing miscarriages. Some of the women exposed to DES during fetal life developed cancer of the vagina. This finding led to the banning of its use in pregnancy in 1971. This unintended consequence demonstrated that the fetal system is exquisitely sensitive and a target of these hormonally active chemicals. So we had to figure out what else could happen to fetuses exposed to estrogenic chemicals released from plastics.

Instead of using nonylphenol, we used bisphenol A (BPA), which another group had identified as estrogenic and also present in plastic. The use of BPA is also more widespread than that of nonylphenol. We exposed animals to what, to us, seemed to be environmentally relevant doses during pregnancy, and then followed their offspring development. The first thing we noticed was that we got much more than we bargained for; namely, we saw some things you'd expect with estrogens—that is reproductive effects—but in addition we also noticed obesity and even behavioral problems. It also produced masculinization of the female hypothalamus, alterations in control of ovulation, alterations in development of the mammary gland, and increased propensity of the mammary gland to develop cancer. This portion of our studies was done in collaboration with Professor Beverly Rubin. Meanwhile, research done by Dr. Antonia Calafat and her colleagues at the CDC revealed high levels of BPA in human urine from a cross-section of the American population. These studies confirmed that the BPA

levels used in our experiments were environmentally relevant.

SW: When was this follow-up work published?

These were all published between 2001 and now. The cancer papers were published in 2007.

SW: And this work was in rodents, not humans?

Yes, mice and rats.

SW: What was the context of your highly cited 1999 paper on tests for endocrine disruptors that was published in *Environmental Health Perspectives* (Anderson HR, *et al*., "Comparison of short-term estrogenicity tests for identification of hormone-disrupting chemicals," 107:89-108, Suppl. 1, February 1999)?

I mentioned before the contamination with the plastic tubes. We realized that the assay we were using to purify the serum-borne inhibitor of the proliferation of estrogen-sensitive cells could also be used to detect estrogen. As the saying goes, if you've got lemons, make lemonade. Thus, we further reasoned, "Fine, if we discovered nonylphenol with it, we can use this method to detect all types of estrogen; so, let's make it an assay."

"These chemicals are ubiquitous in modern life and thus very difficult to avoid, even with conscious effort."

We developed an assay called E-SCREEN, which we described in *Environmental Health Perspectives* in 1991, together with the discovery of nonylphenol in plastic. The 1999 paper by Anderson is a comparison of all the tests that existed then for estrogenicity. E-SCREEN was the oldest of all these *in vitro* assays and the one used most widely, this is the "reference" assay. Most of the environmental estrogens discovered in the '90s were identified using the E-SCREEN assay.

SW: Why do you think that paper has been so influential and cited so frequently?

I'm guessing, but maybe people considered the assay in this paper as one of the most sensitive and reliable assays available. The first *Environmental Health Perspectives* paper on nonylphenol and the E-SCREEN have been cited well over 1,000 times, as has the 1993 paper with Theo Colborn about endocrine disruptors.

SW: How much has the thinking on endocrine disruptors evolved in the past decade? What do we know now that we didn't know in 1999?

Things have changed a lot. In 1999, we didn't have a lot of information about any of these chemicals. There's now a body of evidence that has led countries like Canada, for example, to regulate exposure of BPA, so newborns are not exposed. Denmark has done the same. I also mentioned DES earlier, which was given during pregnancy to avoid miscarriages, and it was then discovered that of girls born to these mothers, one in 1,000 developed vaginal cancer. This had been an exceedingly rare cancer until then, only seen before in elderly women. In 2006, it was reported that women exposed to DES *in utero* have an increased risk of breast cancer. What our work is showing is that this fetal period is exceedingly important, and that exposure *in utero* to estrogens may have long-term implications for offspring—significant increased risk of breast cancer being one of them. This is one of the take-home messages of this work.

The other message is that chemicals that are not mutagens can cause cancer. This finding points to a very current and important issue, namely, that there has been a shift in the way we study cancer. While the dominant view is still that cancer is a cell-based problem allegedly caused by mutations in genes that control cell proliferation, we have proposed an alternative theory. It considers cancer a problem of tissue organization comparable to organogenesis. From this perspective, it is expected that abnormal morphogenesis due to exposure to endocrine disruptors may increase the risk to develop cancer.

SW: What message would you like to give to the general public about your research and about endocrine disruptors in general?

I don't believe that the general public can individually accomplish very much just by trying to decrease their own exposure to these chemicals. Each of us can try to do it by not using plastics, eating organic food, etc., but at the end of the day you don't know by how much you have decreased your exposure (95% or 5%). These chemicals are ubiquitous in modern life and thus very difficult to avoid, even with conscious effort. Instead, we believe that an effective community approach is desirable.

Take water, for example. We want to be ecologically sound so we buy the water in glass bottles rather than in plastic ones—water in the glass bottle has less estrogen, but it won't have zero, because it depends on how the water was filtered. Usually the holder of the filter is made out of plastic, and some filters are still made of polycarbonate, which contains BPA. So the fact that you buy water that doesn't

come in a plastic bottle or comes in plastic that doesn't contain BPA, doesn't mean it doesn't have estrogens in it.

If we're going to decrease our exposure significantly, it has to be a societal measure. We are all dealing here with a public health problem, not an individual one. Governments have to get involved. You may reduce your exposure by doing what I said, but you may be better off, ultimately, by calling your representative or senator and saying "I want you to regulate this stuff. I want to get my exposure decreased. This action will benefit me and my community." The technology and the required know-how to tackle the related problems are beyond a well-meant but isolated approach. This type of effort can only happen reliably if the government assumes its natural responsibility to take care of the welfare of its citizens.

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Ana Soto's current most-cited paper in *Essential Science Indicators*, with 221 cites:

Andersen HR, *et al.*, "Comparison of short-term estrogenicity tests for identification of hormone-disrupting chemicals," *Environ. Health Perspect.* 107: 89-108, Suppl. 1, February 1999. Source: *Essential Science Indicators* from Thomson Reuters.

Additional Information:

Ana Soto is featured in ISIHighlyCited.com

KEYWORDS: BISPHENOL A, ESTROGEN DISRUPTORS, PLASMA-BORN INHIBITOR, PLASTIC, NONYLPHENOL, WINGSPREAD STATEMENT, DIETHYLSTILBESTROL, EXPOSURE, PREGNANCY, OBESITY, BEHAVIORAL PROBLEMS, FEMALE HYPOTHALAMUS, MAMMARY GLAND, CANCER, E-SCREEN, ESTROGENICITY TESTS, IN UTERO EXPOSURE, PUBLIC HEALTH, REGULATION.

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Figures and descriptions:

Figure 1:

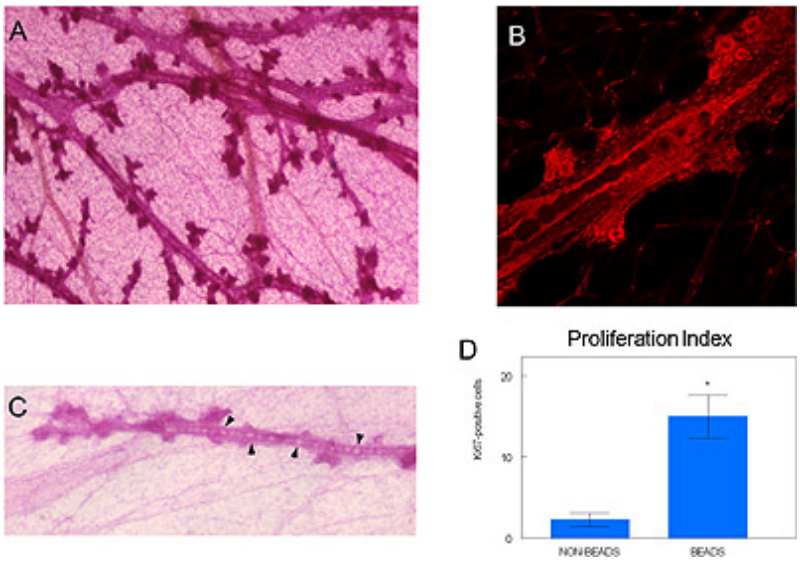

Figure 1:

Fetal and perinatal exposure to environmentally relevant doses of BPA induce a precancerous lesion, intraductal hyperplasias, during adult life. A. Mammary gland whole-mounts from a 3-month old mouse exposed perinatally to 250 ng BPA/kg/day. Most ducts in the field look like a string of beads (Beaded ducts). B. Confocal image of a beaded duct in BPA-exposed females demonstrate the presence of cells inside the ductal lumen. C. Beaded ducts in a whole-mounted mammary gland from BPA-exposed offspring. Glands from 9-month-old females exposed to BPA during perinatal development; beads are marked by arrowheads D. Quantification of the proliferative index in normal ducts (non-beads) and beaded ducts , indicate an almost 5-fold increase in proliferation in beaded ducts ($p = 0.001$). View a larger image (please allow extra load time on slower connections).

Figure 2:

Figure 2:

This photo was taken in the lab. I am at center of the first row, between my partners, professors Beverly Rubin and Carlos Sonnenschein. View a larger image (please allow extra load time on slower connections).

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