AUTHOR COMMENTARIES - From Special Topics

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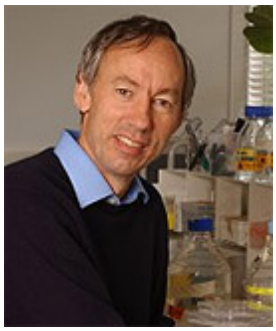

John Sumpter
From the Special Topic of Bisphenol A (BPA)

Bisphenol A (BPA) is a chemical used to make polycarbonate bottles and epoxy resins. Global production of BPA now exceeds three million tons a year. Humans can ingest BPA that has leached from bottles and the epoxy resins used to coat food cans. Consumer groups and government agencies have been taking an increasing interest in the environmental and health risks associated with BPA.

According to our Special Topics analysis of papers published on BPA over the past decade, the work of Professor John Sumpter ranks at #5 by total cites. In Essential Science Indicators℠ *from Thomson Reuters, he ranks among the 100 most-cited scientists in the field of Environment & Ecology, based on 38 papers cited a total of 2,137 times between January 1, 1999 and October 31, 2009. Professor Sumpter is Distinguished Professor of Ecotoxicology at the Institute for the Environment, Brunel University, one of the few campus-based colleges in Greater London.*

In this interview, ScienceWatch.com *European correspondent Dr. Simon Mitton examines the key contributions made by Professor Sumpter and his colleagues on the effects of chemicals in the aquatic environment.*

SW: You have a strong interest in biologically active pollutants, and the effect that these have on fish. Can you explain how you entered this field of research?

I started by accident! I started as a classical zoologist interested in fish and fish hormones, primarily from an aquaculture point of view, examining the control of reproduction, and how to make reproduction more efficient in fish farming. By accident I got involved in some studies of wild fish that appeared to be reproductively abnormal because they were intersex fish—part male, part female. From that discovery

we asked: what might be the cause of this intersexuality?

The answer turned out to be exposure to chemicals that either were or mimicked estrogen. Bisphenol A (BPA) is one of a group of chemicals that are not strictly estrogen (they are not steroid hormones) but under the right circumstances mimic estrogen. I then became interested in chemicals of that kind, of which BPA is a representative. I stumbled into this field rather than entering from a conventional toxicological point of view.

SW: You've been with Brunel University for 31 years. What is the present standing of the group you set up in 1978?

There are only four academics in the team working on ecotoxicology. Essentially we ask: what do chemical contaminants in the environment do to wildlife? We do have an international reputation in this area, particularly with chemicals that either are hormones or behave like hormones. We built our reputation on the chemicals that can feminize fish. That rather specialized story somehow grabbed the attention of many other scientists and also the media. It became an international story. In most mixtures, it appears that steroid estrogens, not xenoestrogens like BPA, are responsible for the feminization of fish. However, within ecotoxicology, there's probably not a chemical anywhere in the world that is higher up the scientific and political agenda than BPA.

SW: In our ranking of your key papers on bisphenol A, the top paper compares short-term assays of the estrogen-like actions of chemicals (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). Who is interested in these tests?

This is a straightforward experimental study that compared many different ways of assessing whether a chemical behaved like an estrogen. We describe many different methods: some of these use animals, some do not, some involve computation. Now let's consider the regulators: they would like to know which tests are the best. This paper gives a fairly comprehensive analysis of all the tests available. It is highly cited because it is the most comprehensive comparison of the different tests.

SW: The second paper tells us that wild intersex roach have reduced fertility (Jobling S, *et al*., "Wild intersex roach (*Rutilus rutilus*) have reduced fertility," *Biol. Reprod*. 67[2]: 515-24, February 2002). Is that a concern?

The title of the paper says it all! Concerning the issue of intersexuality in fish (and other wildlife), the key question is: So what? Does intersexuality actually matter to the fish? This paper was the first one to address that question, and to show that it does matter, because intersex fish are less fit reproductively. This means there is a biological phenomenon out there in the wild that is reducing the ability of animals to reproduce.

SW: In 2000 your group published a paper, with Dr. Edwin Routledge as lead author, on the effects of xenoestrogens (Routledge EJ, *et al*., "Differential effects of xenoestrogens on coactivator recruitment by estrogen receptor (ER) alpha and ER beta," *J. Biol. Chem*. 275[46]: 35986-93, 17 November 2000). Would you talk a little about this work?

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step-by-step."

This is undoubtedly a highly technical paper. It moved our research from grand philosophical issues, such as whether intersexuality matters to wild animals, right down to the fine molecular details. It is widely known that different estrogenic chemicals have different effects on different tissues. This is well known, for example, in the case of women who take estrogen postmenopausally. The issue becomes, why is that? What are the fine technical details that mean that estrogens have different effects on different tissues?

In researching that question, you get into the technicalities of how estrogens work at a molecular level, which is relatively well-known. Edwin Routledge and myself at Brunel combined our expertise on estrogenic chemicals with that of molecular biologists Roger White and Malcolm Parker, who are now at the Institute of Reproductive and Developmental Biology, Imperial College London. What we were able to show is that different xenoestrogens, including BPA, have different effects at the level of fine detail. Those differences might explain why estrogens have tissue-specific effects. Putting it rather technically, we conclude that ligand-dependent differences in the ability of estrogen receptors to recruit coactivator proteins may contribute to the complex tissue-dependent responses observed with certain xenoestrogens.

SW: And is that investigation also the topic of the 2000 *Toxicol. Appl. Pharm*. paper, "Issues arising when interpreting results from an in vitro assay for estrogenic activity" (Beresford N, *et al*., 162[1]: 22-33, 1 January 2000)?

To a degree, yes. This paper is about one particular test for estrogen, which we developed with the pharmaceutical corporation Glaxo (now GSK). They developed a beautiful test for estrogen. The paper uses a recombinant yeast strain (*Saccharomyces cerevisiae*) to investigate a number of issues that could potentially lead to the mislabeling of chemicals as endocrine disruptors. We have more experience of this test than any other group—we have now given the test to over 200 laboratories worldwide. Sometimes they do not know how to use it or how to interpret the data, so we thought it would be helpful to publish a paper saying, "Here is a summary of our experience of the test, and here are some of the issues that might occur that you should be aware of if you are going to test lots of chemicals." The paper was well received and therefore highly cited by practitioners using this specific test.

SW: In 2005 you published a remarkable paper that predicts the response of wild fish to estrogens (Brian JV, *et al*., "Accurate prediction of the response of freshwater fish to a mixture of estrogenic chemicals," *Environ. Health Perspect*. 113[6]: 721-8, June 2005). What is its main message?

Toxicology is a subject essentially based on the premise that individual chemicals have effects. In simple terms: in toxicology we take chemical A, and then discover if it is toxic to humans or animals. Then we move on to chemical B, and so on. That's fine at one level, but the problem is that you and I, and indeed every animal in the world, are not exposed to individual chemicals. Instead we are exposed to highly complex mixtures. So an individual probably has hundreds of non-natural chemicals in their body; I actually think it might be tens of thousands!

SW: Oh really? That's scary!

Yes, really, and you should be scared. So right now there is a big push in toxicology away from assessing individual chemicals towards assessing complex mixtures. No toxicology lab knows how to do that at present, so we are trying to go step-by-step.

"...within ecotoxicology, there's probably not a chemical anywhere in the world that is higher up the scientific and political agenda than BPA."

This paper is about step 1: if we had a mixture of different estrogenic chemicals that all caused the same biological effect, do we know enough to predict the effect of the mixture, in the sense of how does the cocktail differ from its individual ingredients? I am proud of this paper because we looked at five individual estrogens including BPA, and we were able to show we could predict their effects in combination. That then allows a regulator to say if chemicals have the same biological effect we should sum them, and we should regulate on the mixture rather than the individual chemicals.

SW: How do you interact with regulators? Do they read your papers and then take action?

Not very much. The last time a regulator contacted me was five years ago to talk about a group of chemicals. There is not that good a link between the scientists writing the paper and the regulators reading them.

SW: What has your present research in ecotoxicology achieved?

In the toxicology of environmental chemicals we have moved on from concerns about killing wildlife with mass-produced chemicals such as oils and pesticides. What we have realized in the last 10 years is that we have contaminated the natural world with many chemicals that we all get exposed to, that do not cause acute toxicity, but they might cause important effects on reproduction, for example.

And many of these effects occur at extraordinarily low concentrations. I am talking here about 100,000 times lower than what we thought was the risk. A chemical in the contraceptive pill is present in the aquatic environment at parts per trillion. At these extraordinary low concentrations it has dramatic effects on fish reproduction. We have made people realize that chemicals at minute proportions in the environment can have specific effects on animals; they may not kill them, but reproduction is affected.

SW: What is your current focus?

Most of the research I am concerned with is about pharmaceuticals, not just estrogens, that are present in the aquatic environment, and what their effects might be. There are many more biologically important chemicals in the environment than we thought hitherto. They are there at extraordinarily low levels but we should not dismiss them. They might adversely affect wildlife. But also possibly humans too! I am currently applying for funding to investigate the public health consequences of pharmaceuticals in drinking water.

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John Sumpter's current most-cited paper in *Essential Science Indicators*, with 225 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:

Read an interview with Ana Soto, coauthor of the paper above.

KEYWORDS: BISPHENOL A, BPA, ESTROGENICITY TESTS, HORMONE-DISRUPTING CHEMICALS, INTERSEX FISH, FEMINIZED FISH, REPRODUCTIVE FITNESS, XENOESTROGENS, TISSUE-DEPENDENT RESPONSES, ENDOCRINE DISRUPTORS, SACCHAROMYCES CEREVISIAE, PHARMACEUTICALS, AQUATIC ENVIRONMENT.

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