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In This Issue

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Endocrine Disrupters Are Still Here

By Bruce J. Berger

The publication of *Our Stolen Future* in 1996 created a firestorm of publicity and public anguish concerning the possibility that tiny amounts of some widely-used chemicals characterized as "endocrine disrupters" might be causing a variety of adverse human health effects, including among other things cancer and accelerated sexual maturity. Congress took action, directing EPA to commission scientific studies of such low-level effects. Although public anxiety about endocrine disrupters seems to have abated, the government-funded and government-conducted research has ground along and, if anything, seems to be accelerating. These developments cast a dark cloud of potential toxic tort liability for manufacturers of such chemicals and of products incorporating them. This article reviews the concept of endocrine disrupters and describes some of the recent studies that could arguably be used to support future plaintiffs' product and environmental cases.

Endocrine Distupter (ED) Theory

An endocrine disputer is any chemical that, at low levels, can act at endocrine, androgen, or steroid receptors and cause toxic effects. The chemicals that are now alleged to be endocrine disrupters are numerous and include: bisphenol-A ("BPA") (a building block of polycarbonate plastic typically found in baby bottles, compact discs, computer parts, dental sealants, eyeglasses, and food containers), polychlorinated biphenyls ("PCBs"), polyfluorinated octanoic acid ("PFOA") (an ingredient used in the manufacture of some non-stick coatings), brominated flame retardants (PDBEs) (commonly used in many consumer products

such as Styrofoam, carpets, office equipment), dioxin, and foods containing high soy proteins and isoflavones. Essentially, endocrines are chemicals (commonly known as hormones) secreted by various bodily organs such as the ovaries, the testes, the adrenal gland, or the pituitary gland and serve as messengers to other cells throughout the body when they attach to receptors on the surface of such cells. EDs are chemicals that interfere with the normal signaling of the endogenous hormones at these receptors. For example, by occupying the receptor itself, the ED might block the body's own hormone (*e.g.* estrogen or androgen) and prevent the physiologically "correct" response of the target cell. Similarly, an ED might by occupying the receptor cause the cell to overreact (or underreact) and create more (or less) of an effect on bodily function than would the body's own chemical.

According to *Our Stolen Future*, "the most dramatic and troubling sign that hormone disrupters may already have taken a major toll comes from reports that human male sperm counts have plummeted over the past half century" and that "Danish researchers found that the average male sperm count has dropped forty-five (45) percent from 1940 to 1990." EPA now attributes to EDs "decreases in IQ tests and increases in aggression in children" as well as "severe malformations of the genitals of boys [which] have increased steadily over the last two decades and fertility [which] has decreased in young males."[1] EPA Office of Research and Development's Suzanne Fenton points to "precocious puberty," defined as the onset of puberty before the age of eight years, which according to her has increased four-fold in the United States from 1969 to the 1990s.[2]

Where Are the EDs?

Like so many indispensable chemicals that have found wide usage in all manner of products, potential EDs are everywhere, including in our bodies. Given rapid developments in analytical chemistry that allow scientists to find low levels of chemicals in blood and urine, it is now known that many potential EDs are found generally in the population at median levels of about 1 part per billion (ppb).[3]

Current Research on ED Toxicology

Because of Congressional directives and EPA's intense interest in the area, it should not be surprising that research concerning ED toxicology is alive and vibrant. For example, in March 2005, the annual meeting of the Society of Toxicology produced numerous abstracts of recently-completed or near-completed scientific studies directed at this area. Many of the studies are performed by EPA's Office of Research and Development itself, under Fenton's direction.

Human Studies

Typically, courts evaluating the scientific reliability of testimony from plaintiffs' medical causation experts in toxic tort cases have held that human studies are much more significant than animal studies. Therefore, it is chilling in a sense to realize that the ED literature already includes statistically-significant positive human studies, as well as animal studies.

For example, Zhang, et al., published a study in 2004 in the American Journal of Epidemiology on EDs and the risk of breast cancer.[4] The authors reported a higher risk of breast cancer in some women – those with a particular genetic variant -- having higher blood levels of PCBs. For such women, increased levels of PCBs resulted in a statistically-significant Odds Ratio of 4.2, *i.e.*, suggesting that exposure to PCBs increased the risk of breast cancer by a factor of four. Similarly, Yang, et al., published the abstract of a case-control study in 2005 of girls with early puberty.[5] They reported a statistically-significant increase in this condition among girls with higher levels of BPA in their urine than in girls with lower levels of BPA.[6]

Animal Studies of Potential Relevance to Human Health

Much of the animal research concerning EDs has been published only over the last couple of years. There are scores of such studies that now purport to show adverse effects from EDs at low-levels. A recent review by Vom Saal, et al., claims that there are at least 94 such studies showing positive effects.[7] One such study, by Viberg, et al., purports to show that PDBEs are toxic to mice and rat brains at low levels.[8] The alleged effects of such toxicity include learning and memory deficits.

As Vom Saal, et al., make clear, however, the research does not go only in one direction. Studies funded by industry and conducted by the Harvard Center for Risk Analysis, for example, have failed to show adverse effects at low levels. Vom Saal, et al., level multiple criticisms of the industry-funded studies, suggesting, *inter alia*, that insensitive animal assays have been used and that effects of EDs have been masked by confounding due to feed products that themselves cause endocrine disruption.

Environmental Impacts of EDs

In addition to potential problems related to human health, research currently suggests that environmental impacts may direct future agency action to restrict or eliminate certain widely-used EDs. According to EPA, "evidence is continuing to mount that wildlife [as well as humans] may be at risk from exposure to chemicals operating through an endocrine mediated pathway."[9] "Wildlife effects have been more thoroughly documented [than human effects]. Abnormalities in birds, marine mammals, fish, amphibians, alligators, and shellfish have been documented [and] linked to specific chemical exposures." *Id.* In short, EPA policy statements apparently take the view that the same effects attributed to DDT when Rachel Carson published *Silent Spring* are now due to potentially hundreds of other chemicals dispersed at minuscule levels in the environment. How EPA has managed to attribute specific effects to "specific chemical exposures," and which effects it attributes to which exposures, has not been spelled out.

Future Direction and Anticipated Developments

Although many chemicals presently in mass production have been deemed EDs, the likelihood is that even more chemicals – perhaps scores -- will be added to the list over the next few years. Congress directed EPA to develop a screening program that could potentially reach any chemical to which a "substantial population" may be exposed.[10] EPA regards its screening program to identify EDs as part of its formal agenda "necessary to protect public health and the environment."[11] The screening program eventually will be a high-velocity system running hundreds of chemicals in short term tests.[12] Although EPA guidance offers a caveat that a positive result in any of the screening programs will not mean that the subject chemical is in fact an ED – and that the screening will only lead to more sophisticated testing – the likelihood is that public opinion and the fear of liability may create intense pressure for companies using such chemicals to find alternatives quickly.

Implications for Future Toxic Tort and Product Liability Cases

How will the research now being funded by EPA and pursued in various academic centers be used a decade from now in toxic tort litigation? Clearly, scientists will continue by using multiple linear and logistic regression to find or attempt to find correlations between levels of particular chemicals in various bodily organs or substances (placental blood, breast milk, urine, etc.) and adverse effects. At the standard level of statistical significance ($p < 0.05$), one out of every 20 studies would be expected to show a correlation even if there is no such correlation in reality. With implications as broad as breast and prostate cancer, neurotoxicity, precocious puberty, and

given the voracious appetite of plaintiffs' attorneys for new substances upon which to frame essentially the same kinds of personal injury and class action law suits that they have pursued for decades with respect to substances as diverse as asbestos, benzene, and prescription drugs, it seems only a matter of time before "endocrine disrupter" litigation joins the list.

These future toxic tort cases will be fought primarily on the battlefield of medical causation. In all federal courts and in most state courts, proponents of expert testimony bear the burden of establishing that the opinions they offer are scientifically reliable and based upon scientifically-relevant evidence. *Daubert v. Merrell-Dow Pharms., Inc.*, 509 U.S. 573 (1993). Even in state courts where *Daubert* has not officially been adopted, scientific reliability (or lack thereof) has still been argued as the basis for excluding opinion testimony. And, in other states, the general acceptance test of *Frye v. United States*, 293 F. 1013 (D.C. Cir. 1923), thrives. These rubrics provide a basis to exclude testimony that various EDs can or did cause the alleged harm about which a plaintiff complains.

As to general causation, *i.e.*, whether the substance at issue can cause the specific human health problem at issue, human studies will be attacked by epidemiologists, among other reasons, as not properly controlling for confounding, *i.e.,* other exposures of the subject population that could provide full explanations for any reported effects; and the extrapolation of animal studies by plaintiffs' experts to human causation will be attacked by toxicologists as not scientifically defensible. An argument could be mounted as well that ED theory is not "generally accepted," notwithstanding the groundswell of research in support, because it contravenes general theories of toxicology such as the principle that the dose makes the poison and that for each toxic effect there is a threshold level below which the effect is not seen. As to specific causation, *i.e.*, whether (assuming general causation can be established) the substance at issue did *in fact* cause the specific effect in the plaintiff, the opinions of plaintiffs' experts will be attacked as not scientifically-reliable because, among other reasons, they cannot rule out the possibility of causation by factors wholly separate from the product or chemical at issue.

Additionally, product identification will be a key litigation hurdle for plaintiffs. Given the multiplicity of sources of EDs into the environment, plaintiffs may have difficulty tracing the chemicals that allegedly caused them harm to specific products of the named defendants. These kinds of difficulties, however, are not stopping plaintiffs' firms now from suing every possible manufacturer in site, even in the absence of product identification evidence.[13]

Conclusion

In-house counsel and risk managers need to recognize that substantial scientific work continues on endocrine disruption issues. In other words, *Our Stolen Future* marches on, with disturbing implications. EPA pushes the agenda with its own funding and research. Undoubtedly, the results of initial screenings expected to start rolling in within a year or two will be misinterpreted. There is a high likelihood that ED lawsuits will turn into a constant drain on litigation budgets for many companies, if not a direct threat to the health of some.

The cases will be defensible under *Daubert* and its progeny. In a future article next spring, we plan to lay out in more detail how a scientific defense might likely be mounted against some of the troubling studies that have been published so far.

Endnotes

1. 69 Fed. Reg. 72819 (Dec. 4, 2004).

2. "Environmental Toxicants and Disrupted Mammary Gland Development," Proceedings from Fifth Annual Conference on Sex and Gene

Expression.

3. Vom Saal, et al., An Extensive New Literature Concerning Low-dose Effects of Bisphenol-A Shows the Need for a New Risk Assessment, Env. Health Persp. 113:926-933 (2005).

4. Zhang, et al., Serum polychlorinated biphenyls, cytochrome P-450 1A1, and risk of breast cancer in Connecticut women, Am, J. Epid. 160: 1177-1183 (2004).

5. Yang, et al., Bisphenol-A Exposure and Endocrine Disorders in Children, (SOT Abstract 2005).

6. In this study, the results of concern were significant at a level of $p = 0.04$, *i.e.*, suggesting that the likelihood that the results are spurious is only four percent.

7. Vom Saal, et al., An Extensive New Literature Concerning Low-dose Effects of Bisphenol-A Shows the Need for a New Risk Assessment, Env. Health Persp. 113:926-933 (2005).

8. Viberg, et al., Developmental Neurotoxicity of PDBEs in Mice and Rats, (SOT 2005 Abstract).

9. 69 Fed. Reg. 72819 (Dec. 4, 2004).

10. 21 U.S.C. § 346a(p)(3)(A) & (B); 42 U.S.C. § 300j-17.

11. 69 Fed. Reg. 72819 (Dec. 4, 2004).

12. Systems being developed include "Development and Application of a Bioluminescent Yeast-Reporter System for Screening Chemicals for Estrogenic and Androgenic Effects" (University of Tennessee, due 2006), "Biomarkers for the Assessment of Exposure and Toxicity in Children" (EPA, due 2006), "Mechanistic Approach to Screening Chemicals and Mixtures for Endocrine Activity Using an Invertebrate Model," (North Carolina State University, due 2007), and "A High Throughput Zebrafish Embryo Gene Expression System for Screening Endocrine Disrupting Chemcials," (Boston University, due 2007).

13. Cases of this nature, *e.g.*, are being filed in Madison County, Illinois, against all manufacturers of "benzene-containing products" in the United States – alleging that such products caused various kinds of leukemia or other blood cancers – even apparently without evidence connecting the product of the defendant to the plaintiff.