

Science and Strategy

By Benjamin R. Dwyer  
and Samuel Goldblatt

**Defense counsel should recognize that the novel theories advanced by proponents of these claims do not stand up against the tests of established scientific principles.**

# Endocrine Disruption Injury Claims

In recent years, some advocacy groups and scientists have begun to raise alarm about substances—such as bisphenol A (BPA), phthalates, and the herbicide atrazine—which are loosely termed “endocrine disruptors.”

It is claimed that these substances can interfere with the human endocrine system and cause a wide range of adverse health effects. Moreover, it is claimed, conventional dose-response principles do not apply and such effects are possible even at tiny levels of exposure.

Not surprisingly, plaintiffs’ attorneys are seeking clients with illnesses attributed to endocrine disruptors. Several factors make endocrine disruptor theory attractive to them. Most notable is the claim that daily exposure to putative endocrine disruptors among individuals in developed countries is widespread, thus creating a nearly limitless pool of plaintiffs. In addition, the spectrum of illnesses and injuries postulated to relate to endocrine disruptors is broad and includes several types of cancer, reproductive and developmental abnormalities, and even obesity and mental illness. Proponents of endocrine disruption causation posit novel modes of action and theories of low-dose causation for substances such as

dioxin, DDT, PCBs, and other organochlorines. Finally, there has been notoriety in the popular media due to proponents’ victories in the political arena where number of legislatures here and abroad have banned these substances.

This article discusses the general theory of endocrine disruption and the types of substances targeted by its proponents. It assesses the scientific literature proffered to support the theory and, in particular, its shortcomings, and it proposes strategies for defending against claims based on endocrine disruption. The article touches upon the intersection of law and science, but it focuses more on the scientific aspects, and counsel seeking more detailed treatment of the law of scientific evidence may consult one of many excellent DRI publications on that topic.

## The Challenge of Endocrine Disruptors The Endocrine System

A basic working understanding of hor-



■ Benjamin R. Dwyer is a senior associate in the Buffalo, New York, office, and Samuel Goldblatt is a partner in the Boston office, of Nixon Peabody LLP. Both are members of the firm’s Products: Class Action, Trade and Industry Representation Group, have participated in the defense of toxic tort litigation for leading U.S. chemical manufacturers on a national basis, and are experienced in all phases of litigation including trial. Mr. Dwyer and Mr. Goldblatt are members of DRI’s Toxic Torts and Environmental Law Committee.

mones and the endocrine system is helpful before turning to endocrine disruption theory in the section that follows. The endocrine system regulates important physiological functions such as metabolism (including the conversion of food into energy); homeostasis (regulation of the internal environment); growth and development; and fertility and reproduction. Endocrine glands receive stimuli from external and internal sources and prompt the appropriate organs to execute the appropriate response. They do this by producing and secreting hormones.

Hormones are the chemical messengers by which the endocrine glands activate target organs. Hormones are complex molecules that travel via the bloodstream, either freely or attached to transport proteins, to distant organs or tissues. Each hormone subtype has a distinctive molecular shape and structure, enabling it to operate on a “key and lock” principle. Hormone molecules achieve functionality when their “key” reaches a correspondingly shaped “lock”—called a receptor—on a cell or within its nucleus. The activation of the “lock” causes the appropriate physiological response.

For example, we are all familiar with the flight or fight response. Upon suddenly meeting a tiger (external stimulus) one’s adrenal glands immediately produce and release adrenaline, a hormone that rapidly “unlocks” receptors throughout the body stimulating circulation, muscles, and sugar metabolism to produce quick energy.

The hormones of interest here generally relate to internal stimuli (described loosely as the body’s “internal clock”) involved with longer term processes such as homeostasis, reproduction, sexual differentiation, and development *in utero* and after. Estrogens are a class of hormones produced mainly by the ovaries, but also by the adrenal glands (thus their presence in males as well), whose function is related to female reproduction, development and secondary sex characteristics. Androgens are a class of hormones produced mainly by the testis, but also by the ovaries and adrenal glands (thus their presence in females as well), mainly related to male reproduction, development, and secondary sex characteristics. Although estrogens and androgens receive the most attention regarding endocrine disruption, other classes of hor-

mones, such as thyroid and pituitary hormones, are potentially implicated as well.

In addition to production and release of hormones, the endocrine system reduces their levels when necessary through a negative-feedback pathway. Hormones are distinguishable from other chemical messengers by their ability to accomplish their purpose in relatively small concentrations. The endocrine system is sensitive to disruptive influences particularly in an organism’s early stages of development, it is theorized, due to less developed metabolism.

Substances with properties like hormones also exist in the environment and may interact with an organism’s endocrine system. Such exogenous substances can occur naturally, for example in some fruits, grains, legumes and fungi. In addition, synthetic (man-made) hormone-like substances are theorized to interact with the endocrine system. Such synthetic substances are the focus of this article and the subject to which we turn next.

### Theories of Endocrine Disruption

Endocrine disruptors are substances that can interfere with the production or activity of hormones. Whether and at what degree of exposure they may cause adverse health effects is the subject of robust debate. Endocrine disruption as a pathway for adverse health effects is a relatively new subject of intensive research compared, say, to carcinogenesis. Interest dates to the early- to mid-1990s when reports surfaced of substantially altered sexual characteristics in wildlife exposed to massive accidental releases of organochlorines and when studies appeared to show reduced human sperm counts worldwide.

Endocrine disruptors can operate in a number of ways. Molecules may resemble or mimic certain hormones and bind with the corresponding hormone receptors, thereby overproducing an unintended endocrine response. These are termed *agonists*. Alternatively, by binding to hormone receptors, they may block hormone binding, thereby inhibiting hormone action. These are *antagonists*. Others inhibit hormone production or transport through the bloodstream. Still others may degrade receptors or inhibit expression of genes controlled by hormones. It is theorized

that by mimicking or thwarting the action of natural hormones, endocrine disruptors artificially increase or decrease hormonal activity and/or confound its timing, causing excesses or deficits at inappropriate points in the natural cycle. This, in turn, is said to cause adverse effects in reproduction and development, and increase susceptibility to certain hormonally mediated

Those among the general population with BPA exposure are exposed primarily through the diet.

cancers such as breast or prostate cancer. The endocrine system’s enmeshment with a broad range of physiological functions enables proponents to make broad assertions of its effects. For example, it is postulated that early exposure to endocrine disruptors may cause excess production of fat cells and disrupt weight homeostasis, exacerbating obesity.

The fact that estrogen levels are associated with certain hormonally mediated cancers is cited by proponents of endocrine disruptor causation in support of their claims that exogenous hormones also may have deleterious health effects. This raises the question whether synthetic estrogens and other man-made substances that may mimic hormones can have such effects at low levels of exposure.

The most controversial aspect of endocrine disruption theory purports to overturn long accepted dose-response principles. Dose-response is a fundamental tenet of causation science: as Paracelsus famously stated in the 16th Century, “the dose makes the poison.” Expressed graphically, the dose-response curve is *monotonic*—*i.e.*, a line that travels in one direction, away from the intersection of the x- and y-axes representing dose and incidence of observed effects. Related to dose-response is the concept of a threshold—*i.e.*, that no adverse effects occur below a certain level of exposure, due in part to biological systems’ ability to neu-



tralize modest amounts of toxins without adverse effect or repair damage at a cellular or genetic level.

The science of toxicology rests on these bedrock principles. In animal models, a substance's potential effects are established through controlled exposure to unrealistically high doses. A no-effect level is equated with the exposure below which no effect is

**The plaintiffs' personal injury bar has taken notice. Some are actively seeking clients with illnesses attributed to endocrine disruptors, as evidenced by their websites.**

observed in animals and, by extrapolation, no effects are anticipated in humans.

Proponents of endocrine disruptor causation, relying on a limited number of studies, assert that conventional dose-response theory does not apply to endocrine disruptors. They claim that adverse effects are seen in lab animals at relatively low exposure levels—even below the modest levels of background exposure to which we are all exposed. They claim that the dose-response curve for exposure to endocrine disruptors is not linear or monotonic, but rather *non-monotonic*—i.e., expressed graphically, “U” shaped. It is claimed that the lowest exposure levels have substantial causal effects through a cascade effect of endocrine action. The impact is said to fall as exposures increase but rise again as exposure rises into higher levels. The proponents claim that conventional toxicology models fail to test for effects at low exposure levels.

#### **Putative Endocrine Disruptors and Potential Exposures**

BPA is a high-volume production chemical, ubiquitous in today's marketplace. It is used in the production of polycarbonate plastics—typically clear, hard plastics used

for baby bottles, food and drink containers and other household items. It is also used in the production of epoxy resins used to coat the insides of food cans, bottle caps and water supply pipes. It is a polyvinyl chloride (PVC) plasticizer and is also used in tooth coatings and dental sealants.

Those among the general population with BPA exposure are exposed primarily through the diet. BPA may migrate into food and drinks from container linings and be ingested. It is claimed that most people have exposures on most days, albeit very small. Some individuals may be occupationally exposed through inhalation and/or dermal contact. BPA is also claimed to be “weakly estrogenic”—that is, it is claimed to bind to estrogen receptors with agonist effects.

Phthalates are a class of high-volume production chemicals valued for their ability to make plastics softer and more flexible. Phthalates are found in a wide variety of soft plastic consumer products such as children's toys and care items, garden hoses, pool liners, and food containers, as well as medical devices and commercial and industrial products such as wire insulation. Exposure may occur primarily through ingestion of processed foods containing phthalate particles released from food processing equipment. Phthalates in soft plastic children's toys and child care items—often meant to be mouthed by tiny users—has garnered the most attention, and children with phthalate-containing toys or care products are claimed to have higher exposures than adults. Proponents of endocrine disruptor causation also cite studies showing possible effects on the developing male reproductive tract. A smaller number of individuals may be exposed through inhalation in the workplace or through the use of soft plastic medical devices or supplies.

Some pesticide or herbicide residues are also claimed to have adverse effects through endocrine disruption. Atrazine is one of the most widely used herbicides and is used to eliminate weeds, particularly those that threaten corn crops, and it is found in groundwater, particularly in agricultural areas. It is claimed that atrazine may act as an estrogen agonist or antagonist or disrupt pituitary hormone activity.

Some purported endocrine disruptors—e.g., PCBs and DDT—are familiar to

veteran toxic tort practitioners, although alleged endocrine pathways and effects are new. PCBs and metabolites of DDT are claimed to be endocrine disruptors because they have been observed to be weakly estrogenic or antiestrogenic in experimental assays and this has given rise to new causal claims relating to endocrine-modulated cancers such as breast cancer. Polycyclic aromatic hydrocarbons (PAHs) and dioxins are also widely disseminated and persistent in the environment and are claimed to have endocrine disruptive properties.

#### **Endocrine Disruptors in the Public Arena**

Research into endocrine disruption theory is substantial. Globally, over \$100 million dollars have been spent, with thousands of scientific studies published. The U.S. Environmental Protection Agency is undertaking a large-scale effort to assess endocrine disruption potential on 87,000 known synthetic chemicals. Its Endocrine Disruptor Screening Program (EDSP) was launched in 1998 in response to new theories of endocrine disruption and because of the lack of adequately validated screens or tests for endocrine disrupting effects. The EDSP will develop specific screens to identify potential endocrine disruptors, their dose-response, and their effects on human health and the environment. It recently scheduled the first tests under this program that will include atrazine. (74 Fed. Reg. 54415, 54422 (Oct. 21, 2009)). To date there is no scientific consensus that these substances cause adverse effects in humans through endocrine disruption, particularly at typical exposure levels.

Nevertheless, in recent years, advocacy groups and their political allies have scored some victories in the public arena. Phthalates were targeted in the Consumer Product Safety Improvement Act (CPSIA) of 2008. Under the CPISA, it is now unlawful to sell or distribute certain children's products containing concentrations of six types of phthalates over 0.1 percent of product.

BPA is on the defensive, too. Bills are presently pending in the U.S. Congress that would ban it in food and beverage containers regulated by the FDA and/or the CPSC. Several states have already imposed future bans on BPA in certain children's products; similar legislation is proposed in many more. Canada too has announced its intent

to ban the import, sale and advertising of polycarbonate baby bottles containing BPA. Although the FDA has taken the position that there is no harm to infants using baby bottles containing BPA, it is reconsidering its position in the face of increasing political pressure. On the other hand, the California scientific advisory panel responsible for listing chemicals suspected of causing reproductive and developmental harm pursuant to its Proposition 65 recently declined to list BPA.

The plaintiffs' personal injury bar has taken notice. Some are actively seeking clients with illnesses attributed to endocrine disruptors, as evidenced by their websites. Plaintiffs' experts have advanced endocrine disruptor theory in support of claims of causation. (See, e.g., *Beck v. Koppers, Inc.*, 2006 U.S. Dist. Lexis 25519 (N.D. Miss. 2006) (wherein plaintiff's expert claimed dioxin caused breast cancer via endocrine disruption). Our firm is defending similar claims involving exposure to similar substances. In addition, several class actions have been filed against manufacturers incorporating BPA in their products under theories of consumer fraud. (See *In re Bisphenol-A (BPA) Polycarbonate Plastic Products Liability Litigation* (MDL No. 08-1967, W.D. Mo.).)

### Defending Against Endocrine Disruption Claims

The challenge posed by endocrine disruptors is formidable, but there are a number of grounds on which defense counsel can attack claims of causation and the proffered scientific opinion evidence on which they are based. The sheer volume of available research data may allow wily plaintiffs' experts to point selectively to a small number of studies that purportedly support their position. It is incumbent upon defense counsel to devote the necessary time and resources, which can be substantial, to master the large body of relevant research, present it as a coherent whole, that is well integrated into a defense strategy. In this way, counsel may expose the "pick and chose" approach often used by plaintiffs' experts.

A plaintiffs' expert's failure to address all the available scientific evidence and to proffer sound reasoning for accepting or discounting contrary data (so-called

"negative" studies) is a strong indicator of unreliability. It is important therefore for practitioners to understand research synthesis, "weight-of-evidence" and other generally accepted methods for evaluating scientific data. It is beyond the purview of this article to review the processes by which scientists evaluate scientific evidence and make causal assessments, but the interested defense lawyer is encouraged to review one of many good sources, including Weed, D.L., *Weight of Evidence: A Review of Concept and Methods*, 25 RISK ANAL. 1545-57 (2005); Guzelian, P.S., *Evidence-Based Toxicology: A Comprehensive Framework for Causation*, 24 HUMAN & EXP. TOX. 161-201 (2005); Cole P., *Causality in Epidemiology, Health Policy, and Law*, 27 ENVIRON. L. REP. 10279-85 (1997); and Hill A.B., *The Environment and Disease: Association or Causation?*, 58 PROC. ROY. SOC. MED. 295-300 (1965).

A number of governmental and international institutions have considered the scientific evidence and concluded that evidence for endocrine disruptor causation of adverse effects in humans is lacking. For example, a review of the data by the World Health Organization's International Programme on Chemical Safety concluded that there is no firm evidence of direct causal associations between low-level exposures (*i.e.*, levels measured in the general population) with endocrine disruptors and adverse health outcomes. WHO/IPCS, *Global Assessment of the State-of-the-Science of Endocrine Disruptors* (2002). The pronouncements of these bodies, and the body of scientific evidence considered by them, can be used to undermine contrary causation claims.

Scientists at several private consulting firms have also published in this area, and their publications may be of interest to defense counsel. One such firm has conducted three comprehensive surveys of toxicology studies of reproductive and developmental effects of low-dose (< 5.0 mg/kg/day) BPA exposure. See Goodman, J.E., *et al.*, *Weight-of-Evidence Evaluation of Reproductive and Developmental Effects of Low Doses of Bisphenol A*, CRIT. REV. TOX. 39:1-75 (2009) (the most recent of the three surveys). Its scientists performed a weight-of-the-evidence analysis weighing the respective studies based on criteria such as

rigor, power, corroboration, relevance, and coherence. The studies that met those criteria tended to show no adverse effects from such exposure. In contrast, studies that did show adverse effects in low-dose exposures were less numerous, were unable to replicate their results, failed to show consistency across species, doses, and time, and did not exhibit coherence or plausibil-

**A plaintiffs' expert's failure to address all the available scientific evidence and to proffer sound reasoning for accepting or discounting contrary data... is a strong indicator of unreliability.**

ity. Similarly, the analysis concluded that the weight of the evidence did not support a non-monotonic dose-response pattern. *Id.* Defense counsel defending claims of endocrine disruptor causation are well advised to consult this and similar bodies of literature.

### Lack of Epidemiological Evidence

Epidemiology is the study of disease in human populations. "Epidemiology, a field that concerns itself with finding the causal nexus between external factors and disease, is generally considered to be the best evidence of causation in toxic tort actions." *Rider v. Sandoz Pharmaceuticals*, 295 F.3d 1194, 1198 (11th Cir. 2002). In fact, some courts have held that toxic tort plaintiffs' expert opinion lacking epidemiological support is unreliable. See, e.g., *Brock v. Merrell Dow Pharm.*, 884 F.2d 166 (5th Cir. 1989); *Chambers v. Exxon Corp.*, 81 F. Supp. 2d 661 (M.D. La. 2000), *aff'd*, 247 F.3d 240 (5th Cir. 2001). Epidemiologists study groups of individuals and look for and evaluate the strength of associations between, say, a putative carcinogen and an elevated



incidence of cancer in the subject study population relative to unexposed control populations. Such associations, if found, are analyzed in the context of other criteria to evaluate whether a true cause and effect connection exists.

In the case of phthalates, there is little epidemiological data relating to general toxicity or developmental or reproductive

**The toxicology literature**  
relied upon by proponents  
of endocrine disruptor  
causation is insufficient  
to support causation.

effects in humans. The National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction and Development (NTP-CERHR) surveyed the available scientific data on seven types of phthalates and found few studies of the effects in humans. Accordingly, it concluded, there is no direct evidence that phthalate exposure adversely affects reproduction or development in humans.

BPA too has not been as widely studied in humans, but a few epidemiological studies have been completed, typically comparing human subjects' BPA levels and various markers of reproduction and development. For example, a study of pregnant woman found no association between BPA levels and birth weight, birth length, head circumference, or gestational age. Wolff, M.S., *et al.*, *Prenatal Phenol and Phthalate Exposures and Birth Outcomes*, 116 ENVIRON. HEALTH PERSP. 1092-97 (2008). A study of pregnant women at delivery found no association between BPA levels and gestational length or birth weight. Padmanabhan, V., *et al.*, *Maternal Bisphenol-A Levels at Delivery: A Looming Problem?*, 28 J. PERINATOL. 258-63 (2008). A study of adolescent girls found no significant association between BPA levels and development of secondary sex characteristics. Wolff, M.S., *et al.*, *Environmental Exposures and Puberty in Inner City Girls*, 107 ENVIRON. RES. 393-400 (2008).

Organochlorines such as PCBs and DDT, which persist for long periods in human tissues (BPA and phthalates are rapidly excreted), have been the subject of epidemiological study at least since the early 1970s. More recently it has been claimed that they are estrogenic. This, combined with rising incidence in developed countries of breast cancer, a disease associated with levels of natural estrogens, led to intensive epidemiological study of organochlorines in the late 1990s and early 2000s in the northeastern U.S., especially Long Island. Researchers compared blood serum levels of organochlorines in breast cancer patients with healthy controls; approximately thirty such studies were published between 1993 and 2002. Collectively these studies found no difference in levels of organochlorine residues in women with breast cancer and those without. Calle, E., *et al.*, *Organochlorines and Breast Cancer Risk*, 52 CANCER J. CLIN. 301-09 (2002).

While epidemiology-based evidence is not essential to demonstrate reliability of expert opinion in support of causation, its absence places a significant burden on the proponent of the evidence. *See, e.g., Rider, supra.* The dearth of such evidence relating to endocrine disruption undercuts the reliability of proffered expert opinions regarding causation through endocrine disruption. The proponents of endocrine disruption rely heavily on animal studies, the topic to which we turn next.

#### Meeting the Challenge of Toxicology Data

The vast majority of the studies relating to putative endocrine disruptors are toxicological: *in vivo* animal model studies or *in vitro* test tube studies. Proponents of endocrine disruptor causation rely heavily on a small number of toxicological studies and attempt to extrapolate observed adverse effects to humans. In fact, recent governmental restrictions on the use of BPA and phthalates have largely been based on such studies. Defense counsel must consult the relevant precedent in their jurisdictions regarding the sufficiency of toxicology studies to support causal inferences in toxic tort cases, but leaving that aside, the toxicology literature relied upon by proponents of endocrine disruptor causation is insufficient to support causation. Defense counsel may employ several strategies by which to counter causation claims based on such studies.

The strategy need not be simply countering "their" studies with "our" studies.

A defense to a claim of causation that relies on toxicology must account for issues such as: Do the proponents of causation employ rigorous and reliable assessments of the toxicology data that supports their opinions as opposed to that which does not? Do the toxicology studies meet the test of "coherence"? Do the doses employed in the toxicology studies relate to typical real-world exposures? Do the animal toxicology studies account for real differences in pharmacokinetics between species? Do proponents account for alternative bases for causation? Do they account for problems with biologic plausibility?

#### Dosing: The Laboratory vs. Reality

Many toxicology studies cited by proponents of endocrine disruptor causation expose laboratory animals to levels many times greater than typical human exposures. Defense counsel must be prepared to show how studies relied upon by plaintiffs do not reliably represent realistic exposure levels or correlate to expected effects in human beings.

The NTP-CERHR monographs for the various types of phthalates addressed typical exposures. Phthalate exposure in the general population is less than 0.03 mg/kg per day. Young children mouthing products containing phthalates may be exposed up to 0.28 mg/kg per day. (People undergoing intensive medical treatment may be exposed in higher amounts to one type of phthalate used in soft plastic medical care products.) No-observed adverse effect levels (NOAELs) in animal studies were orders of magnitude higher than typical human exposures. In the case of di(2 ethylhexyl) phthalate (DEHP), for example, the NTP-CERHR survey of animal data found NOAELs of no less than 1.0 mg/kg per day—in many cases it was hundreds of times higher. Thus highest estimated typical DEHP exposure in children is one-fourth to hundreds of times lower than the NOAEL. In the case of di-isononyl phthalate (DINP), the NTP-CERHR found that studies showing adverse developmental effects in rodents employed exposure levels about 1,000 times higher than the upper range of estimated exposure in children. *See* NTP-CERHR Monograph on

the Potential Human Reproductive and Developmental Effects of Di(2 Ethylhexyl) Phthalate (2006) and NTP-CERHR Monograph on the Potential Human reproductive and Developmental Effects of Di-isononyl Phthalate (2003). Moreover, even simultaneous exposures to multiple types of phthalates results in cumulative doses well below typical human exposures. Benson, R., *Hazard to the Developing Male Reproductive System from Cumulative Exposure to Phthalate Esters*, 53 REGUL. TOX. PHARMACOL. 90–101 (2009).

According to the NTP-CERHR, BPA exposure in the adult general population is no greater than 0.0015 mg/kg/day. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A (2008). Because of their greater food intake per body weight, children may be exposed up to 0.014 mg/kg/day. *Id.* The actual exposures to BPA may be much less. Two of the largest, most scientifically rigorous studies conducted found NOAELs for BPA-exposed rodents of 5.0 mg/kg/day for systemic effects and 50.0 mg/kg/day for reproductive and development effects. Tyl, R., *et al.*, *Two-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD-1 Mice*, 104 TOXICOL. SCI. 362–84 (2008); Tyl, R., *et al.*, *Three-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague-Dawley Rats*, 68 TOXICOL. SCI. 121–46 (2002). See also, Goodman, *supra* (assessing quality of BPA toxicology studies). These NOAELs are hundreds to thousands times higher than typical exposures of children and adults. Based on the Tyl studies, the European Union (EU) calculated that typical levels of exposures to BPA in children and adults is not a cause for concern. European Union, *Updated European Risk Assessment Report for Bisphenol-A* (2008).

### Unrealistic Modes of Exposure

Many of the studies cited by proponents of endocrine disruptor causation are based on exposure through inhalation or subcutaneous injection. These studies do not “fit” the normal human exposure to these substances and therefore provide an unreliable basis for causal claims.

Virtually all of human exposure to phthalates and BPA is oral. In the case of phthalates, small particles enter processed food from processing equipment or pack-

aging or are ingested by children mouthing toys. In the case of BPA, small amounts in food container linings migrate into food.

Not all modes of exposure have equal results, however. Ingestion results in a much smaller biologically active dose, due to the effects of what is termed first-pass metabolism. Ingested particles enter the digestive tract and, like all food, are absorbed through the intestinal wall to the liver where these undergo *conjugative metabolism*. Conjugative metabolism is a process in which certain chemical substances including estrogens, pharmaceuticals, and toxic products of digestion, are rendered biologically inactive and made ready for excretion.

In the case of BPA, for example, through conjugative metabolism, estrogenic molecules are biotransformed into non-estrogenic BPA metabolites and eventually passed harmlessly with other digestive wastes in the urine. While some BPA molecules may escape conjugative metabolism and enter general systemic circulation, this proportion is small—between 0.4 and 6.0 percent of orally administered doses in rodents. The proportion is even less in humans, in whom BPA metabolism and toxicokinetics filter still more biologically active BPA than rodents. In rodents, metabolized BPA recirculates in the liver, whereas it is more rapidly excreted in humans. Thus in humans virtually all of ingested BPA is converted by the liver into a harmless by-product that is excreted from the body along with other digestive wastes in a relatively short time period. Moreover, that portion of ingested BPA that does enter the systemic circulation is mostly bound to plasma proteins, restricting its access to tissues where BPA might otherwise exert an estrogenic effect. Similarly, BPA levels in surveys of humans as measured in urine samples must be discounted. Such measurements are of total BPA, not just free BPA. Thus most of what is measured in urine is BPA conjugates (*i.e.*, BPA metabolites), which are biologically inactive. See Goodman, *supra*; Völkel, W., *et al.*, *Metabolism and Kinetics of Bisphenol A in Humans at Low Doses Following Oral Administration*, 15 CHEM. RES. TOXICOL. 1281–87 (2002).

Thus through first-pass metabolism, the biologically active dose is far smaller even than the initial exposure dose. Many

so-called low-dose animal studies involve exposure through inhalation or subcutaneous injection—methods that allow toxins directly into the systemic circulation and result in unrealistically elevated biologically active dosages. Because of the effects of first-pass metabolism, oral doses in animals lead to internal doses that are over a hundred times less than doses admin-

## Defense counsel

challenging endocrine disruptor causation opinion should be cognizant of the use of studies with exposure routes that do not “fit” the facts.

istered by injection directly into the systemic circulation. In humans, the level of unconjugated BPA is usually below detection levels and, when detectable, is hundreds of times below animal NOAELs. See Goodman, *supra*; Völkel, W., *Determination of Free and Total Bisphenol A in Human Urine to Assess Daily Uptake as a Basis for Valid Risk Assessment*, 179 TOX. LETT. 155–62 (2008). Similarly, 75 percent of DEHP is rapidly excreted through urine within 24 hours and blood/serum DEHP is usually below the level of detection. NTP-CERHR DEHP monograph, *supra*.

Defense counsel challenging endocrine disruptor causation opinion should be cognizant of the use of studies with exposure routes that do not “fit” the facts. See, *e.g.*, *General Electric Co. v. Joiner*, 522 U.S. 136, 144 (1997) (expert opinion relying on animal studies with different routes of exposure than plaintiff’s was unreliable). For example, proponents of endocrine disruptor causation point to widespread exposure to BPA as measured by its presence in human urine, but the effects of first-pass metabolism and the lack of detectable unconjugated BPA in those samples undermine the “fit” of the proponents’ argument.



### The Unreliability of Extrapolation

Proponents of endocrine disruptor causation extrapolate animal toxicology data to humans, but doing so is often unreliable, due mainly to significant species differences in pharmacokinetics and metabolism.

For example, ingested BPA is metabolized and excreted differently. Because rodents and humans differ in the pro-

## Courts have recognized

that basing expert opinion on comparisons of similarly structured chemical molecules may be unreliable.

cess by which conjugated—*i.e.*, biologically inactive—BPA is excreted, humans excrete it much quicker. As a result, the oral dosing of rodents results in more systemic exposures to free BPA than in humans.

Also, different species' hormone receptors have different structures. Therefore an exogenous agonist or antagonist binding to a specific receptor in an animal model does not necessarily mean the same substance exhibits the same action in humans. International Union of Pure and Applied Chemistry, *IUPAC Technical Report: Endocrine Disruptors in the Environment*, 75 PURE APPL. CHEM. 631–81 (2003). Notably, adverse effects to reproduction and development seen in rodents with high DEHP exposures were not seen in similarly dosed laboratory primates. NTP-CERHR DEHP monograph, *supra*.

In the reproductive setting, because of differences in the physiology of gestation in rodents vs. humans, human fetuses are exposed to much higher levels of estrogen during normal gestation and, as a consequence, the effects of estrogen-mimicking chemicals has less effect on human fetuses compared to rodent fetuses. Witorsch, R.J., *Endocrine Disruptors: Can Biological Effects and Biological Risks be Predicted?*, 36 REGUL. TOX. & PHARMACOL. 118–30 (2002).

Causal opinions based on extrapolation may be held to be unreliable and inadmissible. *Sorenson v. Shaklee Corp.*, 31 F.3d 638, 646 n.12 (8th Cir. 1994); *In re Human Tissue Products Liab. Litig.*, 582 F. Supp. 2d 644 (D.N.J. 2008) (experts' extrapolation from animal data held unreliable).

### Problems with Biologic Plausibility

As described above, proponents of endocrine disruptor causation rely on the resemblance of exogenous molecules to natural hormones such as estrogen. Despite some similarities in molecular structure, such as an identical phenolic ring that may cause estrogen-mimicking molecules to bind to estrogen receptors, such binding is incomplete. Differences in the overall molecular structure result in an imperfect fit in the receptor's binding pocket. As a result, putative endocrine disruptors may have many orders of magnitude less potency than the hormones they purport to mimic. Witorsch, *supra*. For example, a review of studies of *in vitro* and *in vivo* studies of atrazine demonstrated insufficient binding with estrogen receptors for agonistic or antagonistic activity, even at concentrations well above normal human exposure. Eldridge, J.C., *et al.*, *Atrazine Interaction with Estrogen Expression Systems*, 196 REV. ENVIRON. CONTAM. TOX. 147–60 (2008).

Courts have recognized that basing expert opinion on comparisons of similarly structured chemical molecules may be unreliable. *See, e.g., McClain v. Metabolife*, 401 F.3d 1233 (11th Cir. 2005) (noting that even small differences in chemical structure may have divergent effects, and excluding expert evidence relying on chemical structure analysis). Counsel defending endocrine disruptor causation claims should be familiar with this type of approach.

### Alternative Sources of Endocrine Disruptors

Exposure to synthetic estrogens must be viewed in the context of the much more significant exposure to naturally occurring exogenous estrogens such as phytoestrogens. Phytoestrogens are natural compounds found in plants and fungi and which have estrogenic properties. Humans are exposed through dietary consumption of fruits, grains, legumes, and fungi. Compared to the presence of synthetic estrogens

such as organochlorine in human blood samples, the presence of phytoestrogens is much higher. In fact, the oenophiles among us would be interested to know that a single glass of red wine contains significantly higher natural estrogen equivalents than the daily intake of any organochlorine residues in food. Due to their estrogenic and anti-estrogenic characteristics, phytoestrogens have been the subject of significant epidemiological research into whether dietary intake of phytoestrogens is related to breast cancer risk. As a whole the epidemiology is inconclusive and thus no such link has been established. *See, e.g., Safe, S.H., and Papineni, S., The Role of Environmental Estrogenic Compounds in the Development of Breast Cancer*, 27 TRENDS PHARMACOL. SCI. 447–54 (2006) and Gaido, K., *et al., Comparative Estrogenic Activity of Wine Extracts and Organochlorine Pesticide Residue in Food*, 106 ENVIRON. HEALTH PERSPEC. 1347–51 (1998).

The significance of phytoestrogens for defense counsel is twofold. First, with the presence in human blood serum of phytoestrogens several times the level of synthetic estrogens, the failure to link dietary phytoestrogen intake and breast cancer significantly undercuts any theory that exposure to synthetic estrogens like organochlorines affects breast cancer risk. Second, it complicates attempts to blame illness on synthetic endocrine disruptors. For example, a plaintiff's expert's claim that exogenous estrogens (*e.g.*, PCBs) cause breast cancer would have to account for the alternate possibility of causation by dietary phytoestrogens.

### Conclusion

Although the challenge presented by proponents of endocrine disruptor causation is formidable, defense counsel are aided by important scientific and legal principles. Most fundamentally, the novel approaches advanced by proponents do not stand the tests of established scientific principles. Rules relating to the admissibility of scientific evidence should be employed in attacking these novel theories. As famously stated by Judge Richard Posner, "The courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). 