Correspondence

Environmental Estrogens

The estrogenic equivalent analysis that Dr. Safe presented recently in *EHP* (103:346–351) is a welcome addition to the literature, and development of this toxicologic approach is an important step in evaluating new endpoints for environmental agents (*1,2*). The hormonal potential of chemical contaminants offers many opportunities for further research, including study of the environmental etiology of breast cancer.

Complex mixtures are of great importance for human environmental exposures, but we understand neither exposure nor effect very well. Safe, as a basis for evaluating one hormonal endpoint, offers estrogenic equivalents acting in an additive fashion. In future research, we need to learn whether these combinations of chemicals, such as DDT and estrogen, may be additive or multiplicative. Examples of both exist. Thus, *in vitro* assays using MCF7 breast tumor cells found an additive effect for 10 pesticides (*3*), and *in vivo* assays of two PCB metabolites produced an apparent multiplicative effect in altering gender determination in turtles (*4*).

We also need to investigate hormonally active compounds for other relevant biological activity. For example, vinclozilin has androgenic potential (*5*); genistein may act as a free radical scavenger (*6*); and *p,p′*-DDE demonstrated potent anti-androgenic responses in the rat (*8*). Estrogenicity of genistein and other phytoestrogens may be relevant to breast cancer, but countries with high dietary intake of such compounds are generally at low risk for breast cancer. Therefore, it is possible that exogenously derived phytoestrogens act differently from steroid hormones, perhaps by altering levels of free versus bound estrogen or by increasing estrogen excretion through the biliary/fecal route (*8*).

It has become more and more apparent that toxicokinetics of chemicals is a critical component of dose–response relationships. Endogenous levels of organochlorines in women today are 10-fold higher than those of estrogen (*9*), and their effects are prolonged because of their persistence in the body. Toxicokinetics are also closely tied to PCB toxicity (*10*); thus 2,2′,5,5′-tetrachlorobiphenyl, an estrogenic compound, is short-lived in the body compared to 2,2′,4,4′,5,5′-hexachlorobiphenyl. The latter has little estrogenic behavior in rats until 20 or more days after exposure (*11*). In addition, PCBs may also have potent antiestrogenic behavior (e.g., 3,3′,4,4′-tetrachlorobiphenyl). Humans and wildlife have been exposed to mixtures of PCBs that possess a range of estrogenic activity, and the interaction of various PCB congeners has not been widely studied. PCBs may be synergistic, as in the example cited above (*4*), but their hormonal activity can also differ in different experiments, as with Aroclor 1254 (*12,13*). Indeed, the ability of chemicals in the body to act both as agonists and antagonists is well known; for example, soy products and tamoxifen can be both estrogenic and antiestrogenic. These contrasting endpoints can be attributed to different mechanism as well as to pharmacokinetics.

As Safe notes, *p,p′*-DDE is the predominant (>90%) residue of DDT in the environment. While DDT may be undetectable in some assay conditions, *p,p′*-DDT is still routinely found in women, albeit at low levels. Other isomers including *o,p′*-DDT may be currently undetectable, but they may have been present at an earlier time, so that measurement of DDE alone can serve as a surrogate for prior exposures to other isomers. Moreover, with respect to breast cancer, the effect of organochlorines may arise from mechanisms not directly involving the estrogen receptor, such as induction of P450 enzymes.

I agree with Safe that the current evidence is far from conclusive about the association of organochlorine exposure and breast cancer risk, and the many confirmatory studies now underway will improve our knowledge in this regard. The connection to male reproduction, including sperm counts, is highly speculative. However, the existing data, along with ample evidence of endocrine disruption in wildlife, provide a clear challenge for basic and epidemiologic researchers to uncover public health risks arising from environmental exposures.

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Response

In her letter, Dr. Wolff correctly points out the difficulties in assessing the potential adverse impacts of chemical mixtures containing compounds which exhibit both common (e.g., estrogenic) and diverse activities. Despite these problems, it is not unreasonable or unprecedented to determine levels and relative potencies of individual compounds in a mixture which elicit common responses and/or act through similar pathways. This method is the toxic equivalency factor (TEF) approach for hazard assessment of chemical mixtures, which by definition focuses only on specific chemical-induced responses. Regulatory agencies use a TEF approach for hazard assessment of 2,3,7,8,-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds (*1*) and estrogen equivalents have previously been used for determining human exposure to