COMMENTARY

The Structural Pervasiveness of Estrogenic Activity

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A remarkably wide variety of chemical structures, produced both by nature and by man, have estrogenic activity. While the molecular details of this structural pervasiveness of estrogenic activity are not known, it is less surprising if one considers that assays for estrogenic activity are extremely sensitive and can operate over a potency range of 10 million, that most estrogens share the common structural motif of a phenol or the functional equivalent of a phenol, and that most estrogens are lipophilic and thus can be resistant to metabolism and undergo bioconcentration. Evaluating the effect and potential risk of this structurally pervasive estrogenic activity is a complex issue, and a number of factors should be considered: *a*) while excessive and aberrant exposure of humans and animals to estrogens may be detrimental, a certain degree of exposure to natural estrogens from both endogenous and exogenous natural sources is unavoidable; *b*) estrogens from various sources may have beneficial as well as undesirable effects; *c*) their action may be selective on certain target sites; and *d*) they may have other nonestrogenic toxic or beneficial effects. Thus, one must be aware of the widespread potential for compounds to have estrogenic activity, and one must evaluate individually whether the activity of each of these estrogenic substances and our exposure to them is a benefit or a detriment to animal and human health.

Compounds with a remarkable array of chemical structures—of natural origin or produced by humans—have estrogenic activity. Estrogens of natural origins include not only the ovarian estrogenic steroids, but many natural products produced by plants and microbes. Some of these latter compounds are derived from components of normal dietary foodstuffs (legumes and grains) and have their activity enhanced by the activity of gut microflora of animals and humans; others enter the diet of humans or livestock only via contamination. Synthetic estrogens include not only nonsteroidal hormone mimics but phenolic impurities found in pH indicator dyes and phenolic components used in the fabrication of polycarbonate plastics and as the core components of nonionic detergents. A number of industrial chemicals and agricultural pesticides and their metabolites, some of which are multiply chlorinated, also have estrogenic activity. Representative structures of estrogens from these diverse sources are shown in Figure 1.

How can it be that compounds from so many different sources have estrogenic activity? In fact, the variety of chemical structures that elicit an estrogenic response in sensitive test systems is enormous; in this regard the estrogen receptor system may well be unique in terms of the structural diversity of its effective stimulants. Without a greater knowledge of the molecular details of the structure of the estrogen receptor and its interaction with ligands, it is difficult to speculate as to the reason for this tolerance of structural diversity. Nevertheless, some points of interest should be made.

- Potent estrogens show cell growth stimulatory activity at exceedingly low concentrations. When using the growth rate of estrogen-sensitive cells to assay for estrogenic activity, growth stimulation by estradiol can be observed at a concentration of 10^{-12} M, and half-maximal stimulation is usually observed at 3×10^{-11} M. (In fact, the potency of estrogens in this assay appears to exceed their affinity for the estrogen receptor by a factor of about 10.) Since other compounds can be assayed at concentrations of up to 10^{-5} to 10^{-4} M in these cell systems, it is not surprising that even those with very weak activity can give a detectable response. It is rare to have a functional assay system that can operate over a concentration range of 10 millionfold.
- There are some common structural motifs among compounds with estrogenic activity. Most compounds that have estrogenic activity are phenols. Others, however, are nonphenolic aromatic compounds, which in some cases may undergo bioactivation by metabolism to phenols (e.g., methoxychlor). Some of these may act even without this bioactivation, but these compounds are generally of relatively low potency (e.g., *o,p'*-DDT). Some compounds with estrogenic activity are not even aromatic, but this is unusual, and these compounds are often of quite low potency (e.g., endosulfan, kepone, toxaphene). One should also note that even some of these compounds may bear the functional equivalent of a phenol; for instance, the cyclic sulfite group in endosulfan is a polar function that can act as a hydrogen bond acceptor, and the ketone group in kepone, because of ring strain, is likely to be partially hydrated, affording a gem diol function that can participate in hydrogen bonding. Thus, the most rudimentary structural motif that elicits

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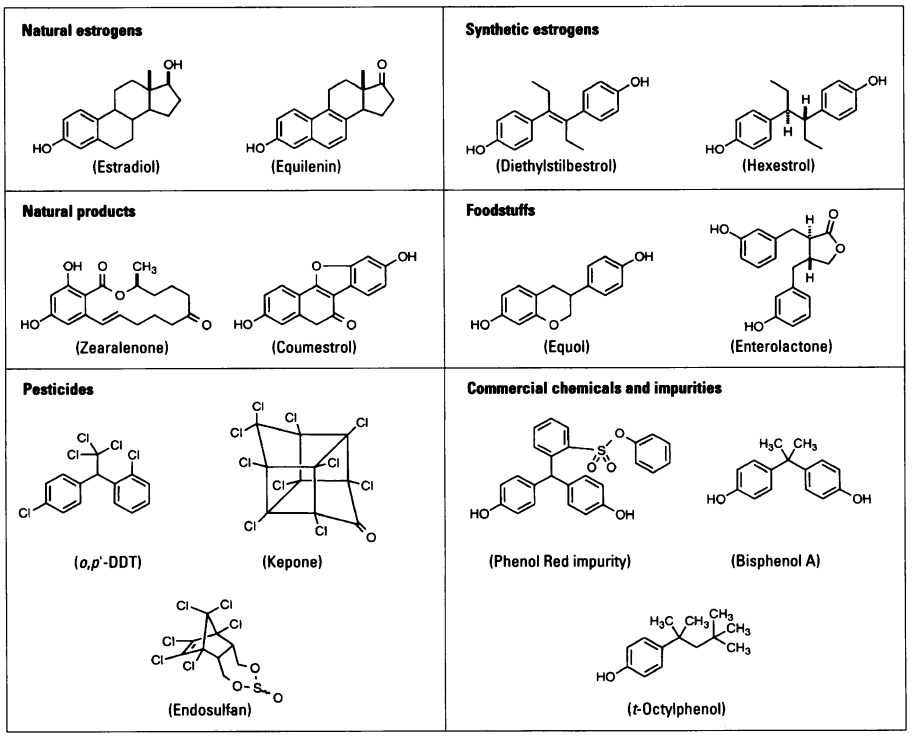

Figure 1. The variety of structures of compounds that have estrogenic activity is displayed according to various designations and sources.

estrogenic activity is a phenol that is relatively unhindered at the *ortho* positions, but then contains a rather bulky, hydrophobic structure attached to the *meta* or *para* positions. The further details of the structure have a major effect on the potency of the compound, but this basic motif will generally ensure some estrogenic activity (at least enough to be detected by an assay that has a potency range of 10 million).

- Estrogens tend to be rather hydrophobic. As the structural mimicry of an estrogen deviates more and more from that of estradiol, some estrogenic activity is generally ensured by having the compound be hydrophobic. This is perhaps why estrogenic activity is found with a number of the chlorinated pesticides and biphenyls such as *o,p'*-DDT, DDE, PCBs, methoxychlor, kepone, and toxaphene. The last of these is perhaps the most unusual structure (or mixture of structures) to display estrogenic activity and is probably the most hydrophobic. Each chlorine substituent is predicted to elevate the lipophilicity by a factor of 2- to 9-fold (as estimated by the octanol–water partition coefficient). It is perhaps a conspiracy of nature that hydrophobic compounds, particularly those resistant to metabolic degradation such as polychlorinated materials or those with highly branched alkyl substituents, persist in the environment and may undergo bioconcentration, thereby amplifying the potential exposure of these agents to those at the end of food chains. In addition, because of their lipophilicity, these compounds can accumulate to high levels in lipids and membranes from which they can slowly be released to provide a low, persistent level of compound in blood; such continuous dosage may be most effective in stimulating certain estrogenic responses.

These three factors—an extremely sensitive assay system with a very wide (10^7-fold) response range, a general responsiveness to phenols, and the added enhancement of activity and environmental persistence due to hydrophobicity—conspire to endow a large variety of chemical structures with some estrogenic activity.

Regardless of the molecular details of ligand receptor interaction or the transduction of the signal of receptor activation into response that are responsible for this fact, the consequences of the structural diversity of estrogens in terms of human and animal health need to be soberly evaluated. Some effects of estrogens in unwanted places, such as impurities in pH indicator dyes used in cell culture media or components that leach out of polycarbonate media bottles, are simply nuisances that confound the results of cell culture experiments. Other exposures such as those of pesticide residues from application and production, in some cases amplified by bioconcentration, may have profoundly detrimental effects on the health and reproductive capacity of wildlife (and possibly of humans).

While estrogenic materials in foodstuffs, either as normal endogenous secondary metabolites of plants or the products of microbial infestation (such as moldy corn), can be destructive to the fertility of livestock, related estrogens (or their precursors from which weak estrogens are produced by the reductive metabolism of gut microflora) may, in fact, be beneficial to humans. These compounds, to which humans are exposed in large doses through the normal intake of healthy foodstuffs, are generally compounds of low potency, and their net effect on the endogenous human endocrine system may actually be that of estrogen antagonism. Weak, short-acting estrogens such as estriol are known to reduce the effect of potent estrogens such as estradiol and thereby have a net protective effect. Furthermore, some of the weak estrogens or their precursors in foodstuffs may have other biological activities that are beneficial to human health, such as the inhibition of angiogenesis. On the other hand, some compounds with estrogenic activity may have a spectrum of toxicities that is fully independent of the estrogen response system. Another facet to consider is the selectivity of estrogen action. Estrogens cause many responses and have myriad effects on health and reproductive function; it is now becoming apparent that alterations in their structure can have variable effects on these activities. Thus, the potency and agonist/antagonist balance of different estrogens can depend on the particular species, tissue, or response being investigated.

These numerous considerations notwithstanding, one should not lose sight of a number of simple facts about human exposure to estrogens—the estrogens may be as good as they are bad, but exposure to estrogenic substances (at least those from natural sources) is, by almost any reasonable standard, inescapable. Most human diets contain large quantities of weak estrogenic

substances (or their precursors) as natural components of our food. Estrogens are produced endogenously by humans (by males as well as females) and, aside from unusual cases, the major exposure that humans have to potent estrogens is to those of their own production.

The bottom line is simply this: one must be aware of the widespread potential for compounds with varying structures, but sharing the general structural motifs outlined above, to have estrogenic activity. On the other hand, one must try—on a case by case basis—to come to a better understanding of whether the activity of these compounds and our exposure to them is a detriment or a benefit to animal and human health.