

3. Physiochemical characteristics

At present, there are several sources listing suspected endocrine disruptors. Some chemicals appear in all lists, but others appear only in some lists. There are wide variations in the selection of chemicals for these lists. This variability suggests that many aspects have not been clarified, such as those on whether a certain chemical has endocrine-disrupting action, as well as the type and degree of the action. These chemicals include the active ingredients of pesticides, industrial chemicals, and pharmaceuticals. The production, use, or import of some of them (e.g., PCB, DDT, Chlordane) have already been prohibited in Japan. The number of suspected endocrine disruptors may be changed, after test methods for such substances, which are under discussion, are established and investigations have progressed.

The paragraphs below outline the characteristics of the major estrogenic chemicals discussed in “A Study on the Crisis Management of Chemicals” under the 1996 Health Sciences Research Program.

Pharmaceuticals: Synthetic hormones are pharmaceutical compounds administered for their possible pharmacological actions on the endocrine system. Therefore, these hormones have endocrine disrupting actions. They include progestogen androgen, ecdysteroid, farnesyl, and diethylstilbestrol (DES), which caused the so-called “DES-daughters” after it was given to pregnant women. It is pointed out that these pharmaceuticals could be released into the environment via human excretions. Also, certain pharmaceuticals, which are sometimes administered to beef cattle, exert estrogenic actions. Estrogen acts as an anabolic steroid (protein-assimilating steroid) in beef cattle.

The Joint FAO/WHO Codex Alimentarius Commission has established residue limits for zeranol and trenbolone (i.e., synthetic hormone preparations) in beef. Japan also has limits for these preparations. However, the Commission has no residue limits for preparations derived from natural hormones because they occur naturally in cattle.

Organochlorine insecticides: Organochlorine insecticides are known to be typical endocrine disruptors which are dispersed in the environment. Among them, DDT^{*3}

has long been known to have estrogenic actions. These insecticides include dichlorodiphenylethane-class pesticides (e.g., DDT and its metabolites, such as DDD and DDE), cyclodyene-class pesticides (e.g., chlorane, oxychlorane, t-nonachlor, heptachlor, heptachlor epoxide, aldrin, and dieldrin), hexachlorobenzene, and hexachlorocyclohexane. Many of these only slightly decompose, and they concentrate and accumulate in the body. Therefore, their decay rate is known to be extremely low. Low-level and long-term exposure to organochlorine chemicals results in their accumulation in human and animal tissues.*⁴

Polychlorinated biphenyls: Polychlorinated biphenyls (PCBs) have widely been applied over a long period for various purpose, from industrial to household, including heat-exchange mediums, adhesives, flame-resistant agents, and insulating solutions. Their production reached several hundreds of thousands of tons in 1970.

PCBs, along with dioxin, which are chemical industrial byproducts, are problematic because of their accumulative properties and strong toxicity. PCBs consist of up to 209 types of homologues, most of which are remarkably stable and biocumulative.*⁵ Therefore, PCB's persistence in the environment has been of particular note. Most of the products on the marketplace are mixtures of various homologues, which makes it difficult to assay environmental and biological samples and to analyze the results obtained.*⁷

The European Parliament presently defines "PCB" as a fluid containing PCBs at 0.005% or more. According to a report from the Environment Health Institute in the UK,*⁸ PCBs' estrogenic actions were originally thought to be about one millionth that of estradiol.*⁹ However, a mouse-uterus estrogen receptor-binding test*¹⁰ determined that hydroxy bodies were compounds with estrogen activity.*¹¹ Such bodies include 4-hydroxy-2',4',6'-trichlorobiphenyl, 4-hydroxy-2',3',4',5'-tetrachlorobiphenyl, and 4,4'-dihydroxy-2'-chlorobiphenyl, which have an activity 1/42 to 1/90 that of estradiol. S.K. Korach showed that these substances more readily dissolve in water and are more readily excreted from the body than their parent compounds. The endocrine-disrupting mechanisms of these substances are known to be expressed mainly through aryl-hydrocarbon (Ah). This finding indicates that there could be endocrine disruptors which exert their actions

through unknown receptors. This indication is reflected in the fact that cognate-type substances of a PCB have conflicting characteristics, such as estrogenic and anti-estrogenic actions.^{*12} Among the anti-estrogenic actions, 3,4,3',4'-tetrachlorobiphenyl inhibits the induction of a 52kDa protein in MCF-7 human breast-cancer cells.

Alkyl phenols: Alkyl phenols are microbial-degradation products of alkyl phenol polyethoxylates (APEs) which are nonionic surfactants. APEs have been manufactured worldwide in large amounts for various uses, including synthetic detergents, paints, herbicides, and insecticides. The worldwide yearly production of APEs is expected to exceed 300,000 tons for 1998.^{*13}

These chemicals are released into the water system through the sewage system, and are very stable. They are known to be taken into by organisms in the inland water system and to be stored in their fatty tissues. Their basic chemical structure is alkyl phenol, which does not easily degrade. It was suggested that their residues released in rivers can have toxic effects on aquatic life. Under such circumstances, a gradual-diminution plan is being implemented, targeted for the end of the 20th century.^{*14} The activities of p-nonyl phenol and p-octyl phenol, which account for 80% of the compounds with ethoxylates, can be determined in several assays, including the proliferation activity of human breast cancer cells, such as MCF-7, gene transcription in genetically transformed chick-embryo fibroblasts, and the expression of vitellogenin gene in rainbow trout-hepatic cells. These assays reveal that the activity of octyl phenol is slightly higher than that of nonyl phenol, but as low as 1/1000 that of estradiol.

Phytoestrogens: Phytoestrogens from plants differ from other chemicals in that they are natural compounds. These environmental substances can become problematic, especially when livestock consume them. It has long been known that when sheep consume red clover (*Trifolium pratense*) that contains a large amount of genistein, they develop reproductive abnormalities.^{*16} Phytoestrogens in plant products, such as soy beans, are taken in by humans through foods in everyday life. Their main active ingredients are isoflavones (genistein and daidzein) and coumestan (coumesterol).^{*15} Certain kinds of fungal metabolites of cereal grains, such as zearalenone-like substances, also have estrogenic actions.^{*17} In addition to substances called exogenous estrogens, there may be other endocrine disruptors,

such as those with androgenic actions. However, these substances have not been systematically categorized.

Note: Bisphenol A, styrene dimers, styrene trimers, and phthalic acid esters will be discussed in a later section (appendix).