EASTMAN

Eastman Tritan™ copolyester

Lack of estrogenic and testosterone activity

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Based on the results from a comprehensive body of research conducted by various reputable third-party research laboratories, using well-recognized methods to screen chemicals for hormonal activity, Eastman Tritan™ copolyester is free of estrogenic and androgenic (testosterone) activity.

Background

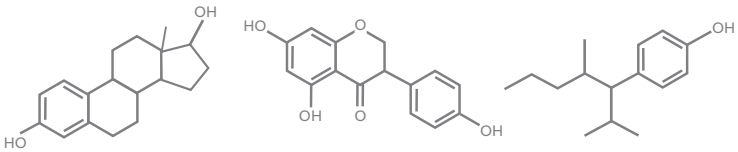
Estrogen and testosterone are two essential hormones found in animals and humans that are utilized in many biological processes (e.g., sexual differentiation and development, reproduction, behavior, and bone health). Studies have shown that certain natural and synthetic chemicals are capable of interfering with these hormone systems and lead to adverse effects in wildlife, experimental animals, and humans. Chemicals that mimic estrogens and testosterone to the extent that they induce adverse responses are commonly referred to as endocrine disrupting chemicals (EDCs). The biological effects from exposure to EDCs vary widely as the potencies of these chemicals to activate hormone receptors can also vary over many orders of magnitude. Determining whether a specific chemical possesses estrogenic or androgenic activity can be accomplished by conducting a complementary battery of screening tests.

EDCs elicit their biological response through hormone receptors that are highly specific for their natural ligands (i.e., estrogen and testosterone). For a chemical to be considered an EDC, multiple steps must occur within a cell. First, the chemical must have sufficient affinity to bind to the hormone receptor. Second, the binding must occur in such a manner that the receptor-chemical complex becomes functionally activated and translocates to the cell's nucleus. This receptor-chemical ligand complex must then be able to bind to specific DNA sequences where it induces synthesis of specific proteins just as if the receptor was bound to its natural ligand.

An initial screen to assess a chemical's potential estrogenic or androgenic activity can be performed by simply comparing its structure to that of the natural ligands (e.g., 17β-estradiol). As previously discussed, the structure of a chemical strongly affects whether the chemical can bind to a specific receptor.

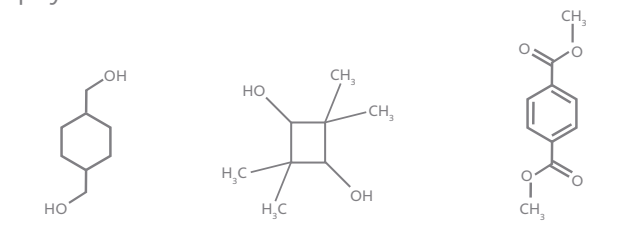
For example, Figure 1 shows several estrogenic compounds and illustrates the presence of a common structural feature associated with some estrogenic compounds. Specifically, many EDCs contain a six-membered aromatic ring with a hydroxyl group (–OH) in the para position. Such a functional trait is not present in the structures of Tritan (Figure 2). Thus, based on structural comparisons alone, the monomers in the manufacture of Tritan would not be expected to possess estrogenic activity. While valuable, evaluating endocrine activity based on structural comparisons alone is still speculative and cannot be used to make any definitive statements about a chemical's potential to have hormonal activity. Accordingly, to more thoroughly validate an absence of estrogenic and androgenic activity, Eastman conducted a battery of screening assays on both the monomers used to manufacture Tritan and on concentrated extracts from finished polymer. These extracts were obtained using very harsh extraction conditions. All studies were performed by independent third-party laboratories and have been standardized and validated using a wide range of known endocrine active compounds.

Figure 1. Estrogen (estradiol) and estrogenic compounds



Estradiol | Genistein | *p*-nonylphenol

Figure 2. Structures of monomers used in Eastman Tritan™ copolyester



Cyclohexanedimethanol | Tetramethyl cyclobutanediol | Dimethyl terephthalate

Battery of methods used to screen for hormonal activity potential

Computer modeling based on Quantitative Structure Activity Relationships (QSAR) is commonly performed to predict the potential of compounds to bind to ligand specific receptors. Similar to a key fitting a lock, the unique structural features of the natural ligand and its natural receptor are evaluated against test chemicals to assess their ability to "fit" and bind. Its propensity to bind is quantified in terms of its "relative binding affinity" (RBA). Accordingly, QSAR models have been demonstrated to be a very useful tool to screen for receptor binding potential because a low likelihood to bind (low-binding affinity) also means a low likelihood to turn the receptor on to its functionally active state. Therefore, as a preliminary assessment, QSAR models were used to evaluate whether the monomers associated with Eastman Tritan™ copolyester have structural characteristics similar to other chemicals known to bind and functionally activate either the estrogenic (α or β) or testosterone receptors.

Despite a low likelihood for the monomers to even bind to estrogenic and androgenic receptors, an evaluation was done to assess the functionality of any binding that may result from exposure to Tritan copolyester monomers or extracts. This assessment was completed using a widely accepted assay known as a "receptor transactivation assay." In this assay, human estrogenic (α or β) and androgenic receptors are bioengineered into yeast cells. On binding with a ligand (foreign or natural), the receptor becomes activated and turns on a hormone-dependent gene in the yeast cell similar to what occurs in higher level organisms. In this yeast assay, the gene product resulting from the activation of the estrogenic or androgenic receptor is a bioluminescent protein similar to that found in the common firefly. Thus, if a chemical binds to the receptor in a functionally active manner, the yeast cell emits light that can be quantified and compared to the amount of light given off by the natural ligand to assess its relative potency. Using this system, studies were conducted with all three of the monomers, as well as with extracts derived from finished Tritan. Extracts were prepared by incubating either polymer pellets or molded articles in water or with ethanol (10%–50%) for various times (2 hours–10 days) and temperatures (40°–70°C) to simulate (and/or exaggerate) conditions encountered in household and commercial use. The resulting extraction sample containing substances that could potentially leach from Tritan was concentrated and used in the yeast assay to determine whether compounds possessing any functional activity were present.

Additional studies have also been conducted on three Tritan monomers in an intact biological system (laboratory rodents) to assess their potential to elicit an estrogenic or androgenic response. These assays are termed the "Uterotrophic Assay" and the "Hershberger Assay." In these studies, laboratory rodents that have been surgically castrated were orally exposed to all three monomers simultaneously using a wide range of dose levels (0.001–10 mg/kg). When these castrated animals are exposed to a chemical with endocrine disrupting potential, a measurable physiological response similar to that of the natural ligand will be observed. These tests are regarded by the scientific community to be very sensitive in their ability to detect compounds that possess estrogenic or androgenic activity and are regarded as being a "gold standard" screen for assessing the endocrine disrupting potential of a compound as they take into account all the factors associated with exposure to a chemical in a living system (e.g., adsorption, distribution, metabolism, and elimination).

Table 1. Summary of test results

	QSAR[a]	Yeast[b]	Rats[c]	Rats[c]
	Estrogenic/androgenic binding affinity	Estrogenic/androgenic receptor activation	Uterotrophic assay	Hershberger assay
Monomers[d]				
DMT	Negligible affinity	No activation	No activity	No activity
TMCD	Negligible affinity	No activation	No activity	No activity
CHDM	Negligible affinity	No activation	No activity	No activity
Extracts				
Pellets		No activation		
Molded articles		No activation		

[a]*QSAR analysis conducted by Dr. William Welsh, Professor, Dept. of Pharmacology, UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ*

[b]*Yeast assays conducted by Dr. John Sanseverino; Managing Director, Center for Environmental Biotechnology, University of Tennessee, Knoxville, TN*

[c]*Uterotrophic and Hershberger Assays conducted at WIL Research Laboratories, LLC, Ashland, OH*

[d]*DMT (dimethyl terephthalate); TMCD (2,2,4,4 tetramethyl-1,3-cyclobutanediol); CHDM (1,4 cyclohexanedimethanol)*

Results

The results of the three tests are shown in Table 1. QSAR computer modeling showed that Eastman Tritan™ copolyester lacks the physical and chemical structure to both bind, and hence, activate the endocrine receptors. The hormone transactivation assay conducted with the bioluminescent yeast indicated that neither the monomers nor substances extracted from Tritan possessed estrogenic or androgenic activity. Furthermore, the highly definitive studies using laboratory animals also showed absolutely no evidence of estrogenic or androgenic effects in any of the measured tissue parameters evaluated in this assay.

Conclusion

The results from these three complementary approaches all demonstrate that the monomers and potential extract migrants from Eastman Tritan™ copolyester do not have structural or functional features that are conducive to being able to bind to and activate estrogenic or testosterone hormone receptors. In addition, no other chemicals utilized in the production of Tritan (e.g., catalyst) are known or suspected to be EDCs. Thus, there is minimal risk to humans for the induction of such an adverse effect with the use of Tritan. Accordingly, there is a considerable body of scientific information to support a conclusion that Tritan, as supplied by Eastman, is free of estrogenic and androgenic activity.

EASTMAN
The results of **insight**™

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