EASTMAN

Comprehensive third-party research results

Eastman Tritan™ copolyesters are free of estrogen and androgen activity.

Estrogen and testosterone are essential hormones to many important biological processes in animals and humans, including sexual differentiation and development. Studies have shown that certain synthetic and naturally occurring chemicals can interfere with these processes and lead to adverse effects.

To support the safety of Tritan copolyesters, Eastman asked various reputable, independent third-party laboratories to use well-recognized scientific methods to test Eastman Tritan™ copolyester for potential estrogenic or androgenic activity. This battery of tests included:

- **Quantitative structure activity relationships (QSAR)**[1]
  Computer modeling of monomers to assess each substance's molecular structure and its ability to bind to human estrogen and androgen (testosterone) receptors in a manner that could lead to their activation.
- **Receptor transactivation assays**[2,3]
  The estrogenic and androgenic activity of both the monomers and concentrated extracts of Tritan were also evaluated in vitro using both yeast and mammalian cell assays performed by two separate labs. These tests evaluate a substance's ability to bind to a hormone receptor and induce gene expression. Extracts were generated using FDA and European Union recommendations for food contact migration testing. Additional extracts were derived following a dishwasher simulation environment (10 days, 70°C, in Cascade™ solution).
- **Competitive binding assays**[2]
  Despite the fact that neither the QSAR nor transactivation studies showed any evidence of binding or gene expression by estrogenic or androgenic pathways, a second tier of tests based on competitive binding assays was conducted. These tests confirm a substance's ability to specifically bind to a specific hormone receptor and can be used to calculate the Relative Binding Affinity (RBA).
- **Uterotrophic assay/Hershberger assay**[4]
  These studies are considered the most definitive tests for assessing a chemical's potential to elicit estrogenic or androgenic responses in living biological systems. These two in vivo tests are part of the Tier I Endocrine Disruption Screening Program of the U.S. Environmental Protection Agency (EPA).

In addition, the monomers were tested in 13-week repeated exposure studies assessing their systemic toxicity potential as well as studies assessing their developmental toxicity potential. The results revealed no evidence of androgen- or estrogen-related effects at any dose level. The results of the monomer studies assessing endocrine activity and an explanation of the scientific approach to testing compounds for estrogenic and androgenic activity have been recently published in Food and Chemical Toxicology, Vol. 50, Issue 2, pages 2196–2205 (2012).

The uniformly negative responses seen in these complementary third-party studies overwhelmingly demonstrate that Eastman Tritan monomers and copolyesters are free of estrogenic and androgenic activity. These studies assessed a wide variety of receptor mediated mechanisms and biological end points. It is important to note that Tritan was evaluated by testing multiple end points using a battery of tests, including more definitive in vivo studies, which is the recommended approach by the Endocrine Disruption Screening Program, Office of Economic and Cooperative Development (OECD) and other international organizations. These studies were also submitted and reviewed by the USFDA which expressed no concerns for estrogenic or androgenic activity by Tritan for its intended end uses.

Furthermore, Eastman Tritan™ copolyesters have been reviewed independently and approved by regulatory agencies, including:

- Health Canada, which issued a Letter of No Objection allowing the use of Eastman Tritan™ copolyester in food contact applications.
- U.S. Food and Drug Administration, which cleared Tritan for use in food contact applications.
- European Food Safety Authority and the European Commission, which cleared Tritan and a key Tritan monomer for repeat-use food contact applications under the new Plastics Regulation.
- Japan Hygienic Olefin and Styrene Plastics Association (JHOSPA), which amended its list of certified polymers to include the composition of Tritan.

[1]*Conducted by Dr. William Welsh, Department of Pharmacology, UMDNJ-Robert Wood Johnson Medical School, Piscataway, New Jersey*

[2]*Conducted by CeeTox, Inc., Kalamazoo, Michigan*

[3]*Conducted by the Center for Environmental Biotechnology, University of Tennessee, Knoxville, Tennessee*

[4]*Conducted by WIL Research Laboratories, LLC, Ashland, Ohio*

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The results of **insight**™

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Safety Data Sheets providing safety precautions that should be observed when handling and storing Eastman products are available online or by request. You should obtain and review the available material safety information before handling any of these products. If any materials mentioned are not Eastman products, appropriate industrial hygiene and other safety precautions recommended by their manufacturers should be observed.

It is the responsibility of the medical device manufacturer ("Manufacturer") to determine the suitability of all component parts and raw materials, including any Eastman product, used in its final product to ensure safety and compliance with requirements of the United States Food and Drug Administration (FDA) or other international regulatory agencies.

Eastman products have not been designed for nor are they promoted for end uses that would be categorized either by the United States FDA or by the International Standards Organization (ISO) as implant devices. Eastman products are not intended for use in the following applications: (1) in any bodily implant applications for greater than 30 days, based on FDA-Modified ISO-10993, Part 1, "Biological Evaluation of Medical Devices" tests (including any cosmetic, reconstructive, or reproductive implant applications); (2) in any cardiac prosthetic device application, regardless of the length of time involved, including, without limitation, pacemaker leads and devices, artificial hearts, heart valves, intra-aortic balloons and control systems, and ventricular bypass assisted devices; or (3) as any critical component in any medical device that supports or sustains human life.

For manufacturers of medical devices, biological evaluation of medical devices is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body. The ranges of tests under FDA-Modified ISO-10993, Part 1, "Biological Evaluation of Medical Devices" include cytotoxicity, sensitization, irritation or intracutaneous reactivity, systemic toxicity (acute), subchronic toxicity (subacute), implantation, and hemocompatibility. For Eastman products offered for the medical market, limited testing information is available on request. The Manufacturer of the medical device is responsible for the biological evaluation of the finished medical device.

The suitability of an Eastman product in a given end-use environment is dependent on various conditions including, without limitation, chemical compatibility, temperature, part design, sterilization method, residual stresses, and external loads. It is the responsibility of the Manufacturer to evaluate its final product under actual end-use requirements and to adequately advise and warn purchasers and users thereof.