# Proestrogenic Chemicals in Cosmetics

Yuri Eaves, Nalini Lall and Bareera Qazi
Department of Environmental and Occupational Health, California State University, Northridge

## ABSTRACT

Over the past several years, the discussion of endocrine disrupting chemicals (EDC) being present in everyday products has been more prominent. While there has been discussions, there have been few regulations banning the use of endocrine disruptors in consumer products. Endocrine disruptors are chemicals that disrupt the natural hormones produced by the endocrine system of the body. Endocrine disruptors can affect many mechanisms of action in the body through, inhibition of a hormone's normal function, mimicking a hormone, or by altering the function of the endocrine system entirely having the most dangerous effects [3]. The structure of estrogenic chemicals is strongly related to their estrogenic activity and can be evaluated by appropriate grouping of the responsive genes by focused microarray analysis [13]. These chemicals are present in a variety of consumer products, specifically cosmetics.

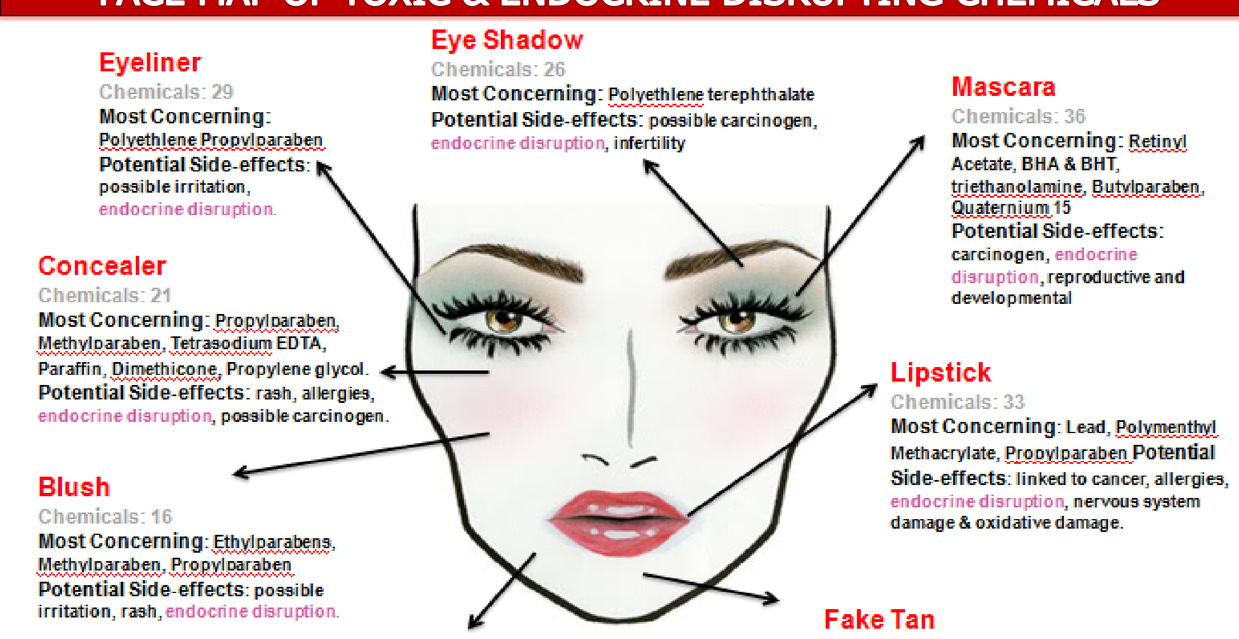
The focus will be on pro-estrogenic endocrine disruptors. Through various cell functions and signaling mechanisms such as apoptosis, carcinogenesis, cell growth and proliferation, differentiation and development and inflammation, there is a potential for additive effects and even synergistic effects may occur in the endocrine system . [9][20]

## INTRODUCTION

Chemicals found in cosmetics are regulated by the United States Food and Drug Administration, (FDA), specifically the Federal Food, Drug and Cosmetic Act (FD&C) passed in 1938 [15]. Although the FDA regulates the chemicals in cosmetics, the FDA does not have the legal authority to approve cosmetics before they go on the market. Cosmetic companies can use any ingredient or raw material in their products without the government review or approval. However, the FDA can take legal action against a cosmetics that has sufficient and reliable information proving that the cosmetic is adulterated or misbranded, [6]. People are exposed to cosmetic ingredients in many ways including inhalation of powders, swallowing chemicals on the lips or hands, or absorbing the chemicals through the skin. Many of the cosmetic chemicals that are making their way into the human body are potential hormone disruptors.[8,16, 7, 17]. There are many routes of exposure when it comes to cosmetics. The FDA relies on the cosmetic companies to report any injuries voluntarily [6,15].

As compared to the European Union (EU) and their regulation on chemicals, the Council Directive has banned over 1300 chemicals for use in cosmetics while the US FDA has only banned nine. Through extensive research on endocrine disrupting chemicals, it is clear that the FDA should consider the negative effects of chemical mixtures in the cosmetics industry.

## FACE MAP OF TOXIC & ENDOCRINE DISRUPTING CHEMICALS

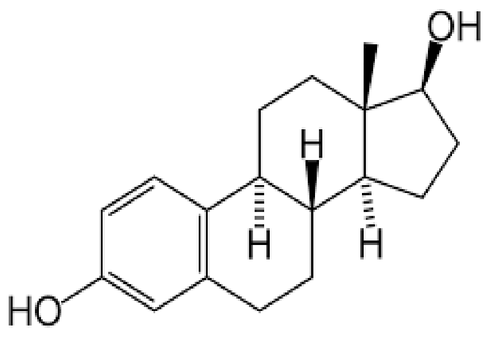



## Examples of Concerning Chemicals in Cosmetics

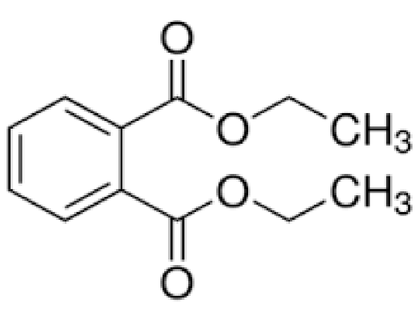
| | | |
|---|---|---|
| 2-ethylhexyl-4-methoxycinnamate | Carbomer | octyl-dimethyl-p-aminobenzoic acid |
| 2-hydroxy-4-methoxy-benzophenone | Cadmium | Oxybenzone |
| 2,2',4,4'tetrahydroxybenzophenone | **Chloroform** | **Parabens*:** |
| 2,4-dihydroxybenzophenone | **Chlorofluorocarbon propellants** | p-hydroxybenzoic acid (common metabolite of paraben esters) |
| 2,4,6-trinitro-1,3-dimethyl-5-tert-butylbenzene | Coal Tar | Methyl paraben |
| 3-(4-methylbenzylidene)camphor | di-n-butyl phthalate (DBP) | Butyl paraben |
| 4-acetyl-6-tert-butyl-1,1-dimethylindan | di(2-ehtylhexyl phthalate (DEHP) | Ethyl paraben |
| 4-chloro-4'-hydroxybenzophenone | dimethicone | Propyl paraben |
| 4-hydroxyazobenzene | Ethylene glycol monomethyl Ethers | Paraffin |
| 6,7-dihydro-1,1,2,3,3-pentamethyl-4-(5H)indanone | **Formaldehyde Resin*** | PEG-6 sorbitan oleate |
| acetyl methyl tetramethyl tetralin | Genistein | Polyethlene |
| Alcohol denats | Glycerin | Perchlorate |
| Aluminum | **Halogenated salicylanilides** | **Petroleum*** |
| Ammonium acrylates | Homosalate | Polymenthyl |
| Arsenic | **Hydroquinone*** | **Progesterone*** |
| Atrazine | Lanolin | Propylene glycol |
| Benzidine | Sodium Lauryl Sulfate (SLS) | **Pthalates*** |
| Benzoic Acid | **Lead*** | **Quaternium-15*** |
| Benzophenone | Magnesium silicate | **Retinyl Acetate*** |
| **Bithionol** | Monoethanolamine (MEA) | **Talc*** |
| Butylated hydroxyanisole (BHA) | Mercury | **Titanium Dioxide*** |
| Butylene Glycol (PG) | **Methylene chloride** | Tetrasodium EDTA |
| | Methacrylate | **Toluene** |
| | Methylisothiazolinone | **Triclosan*** |
| | Nickel | triethanolamine (TEA) |
| | nordihydroguariaretic acid | Tocopherols |
| | octamethylcyclotetrasiloxane | **Vinyl chloride** |
| | | **Zinc Sterate*** |
| | | **Zirconium-containing complexes** |

**Chemicals banned in the United States** [6]
***Chemicals Banned in the European Union but not banned in the United States [4,6]**

## Pro-Estrogenic Synergism

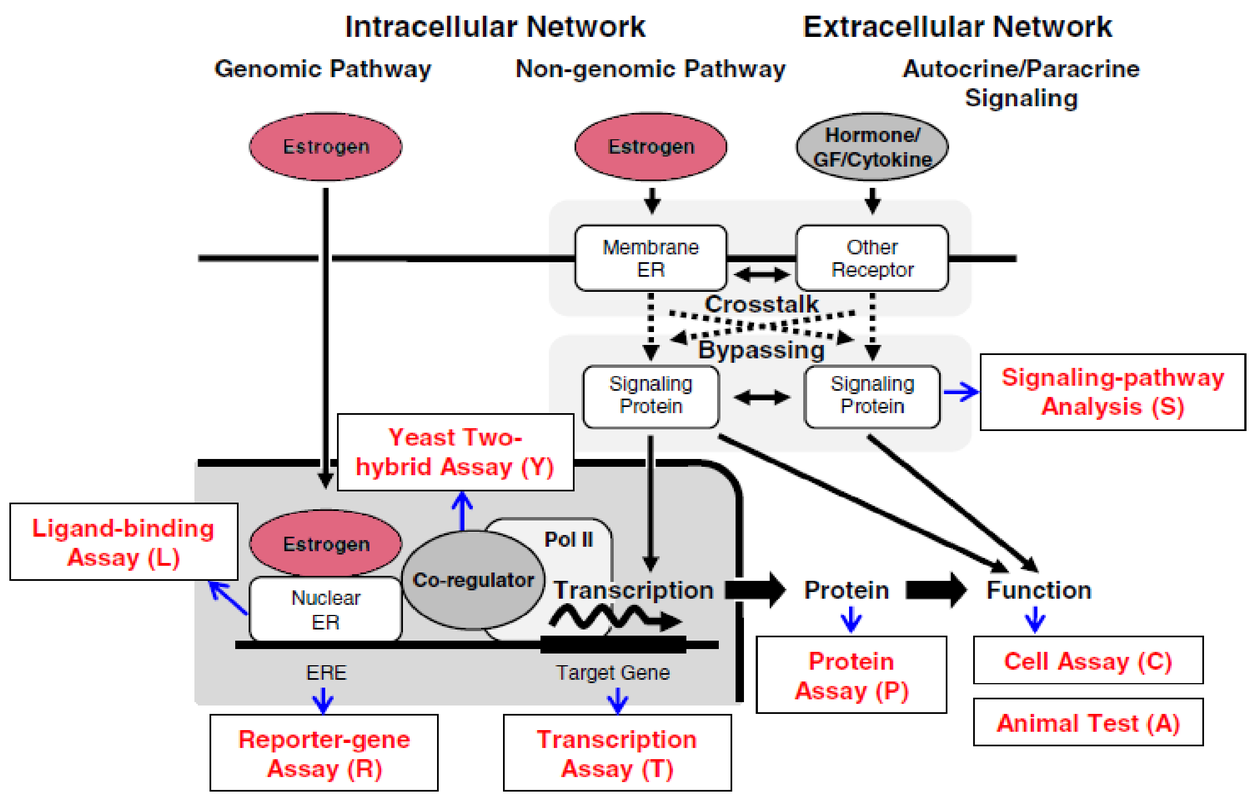



**Estrogen**




**Diethyl Phthalate**

When absorbed in the body, an endocrine disruptor, specifically a pro-estrogenic chemical, can increase normal hormone levels, by mimicking the body's natural hormones. It can bind to a receptor within a cell and block the endogenous hormone from binding. The normal signal then fails to occur and the body fails to respond properly. Specifically, Diethyl Phthlate, part of the Phthalate group, which are hormone disrupting chemicals. Phthalates compete with estrogen to bind to estrogen receptor sites. A key structural basis of estrogenicity is due to the phenolic ring that is indispensable for its ability compete for receptors. Phthalate esters were found to show estrogenicity as well as up regulate already present estrogen in the body.




This is a summary of the estrogenic signaling network. It is separated into the intracellular network and the extracellular network. Within the intracellular network is the genomic pathway is the classical pathway. Here, the ligand bound estrogen receptors can act as transcription factors and bind to up regulate or down regulate the estrogenic genes. The non-genomic pathway communicates signals though membrane bound estrogen receptors, (as seen in the figure). The extracellular network includes autocrine and paracrine signaling. Disruptions can occur through cross talk and or bypassing between intracellular and extracellular networks [9] [20]

## ESTROGENIC CHEMICALS ROLE IN CELL FUNCTIONS

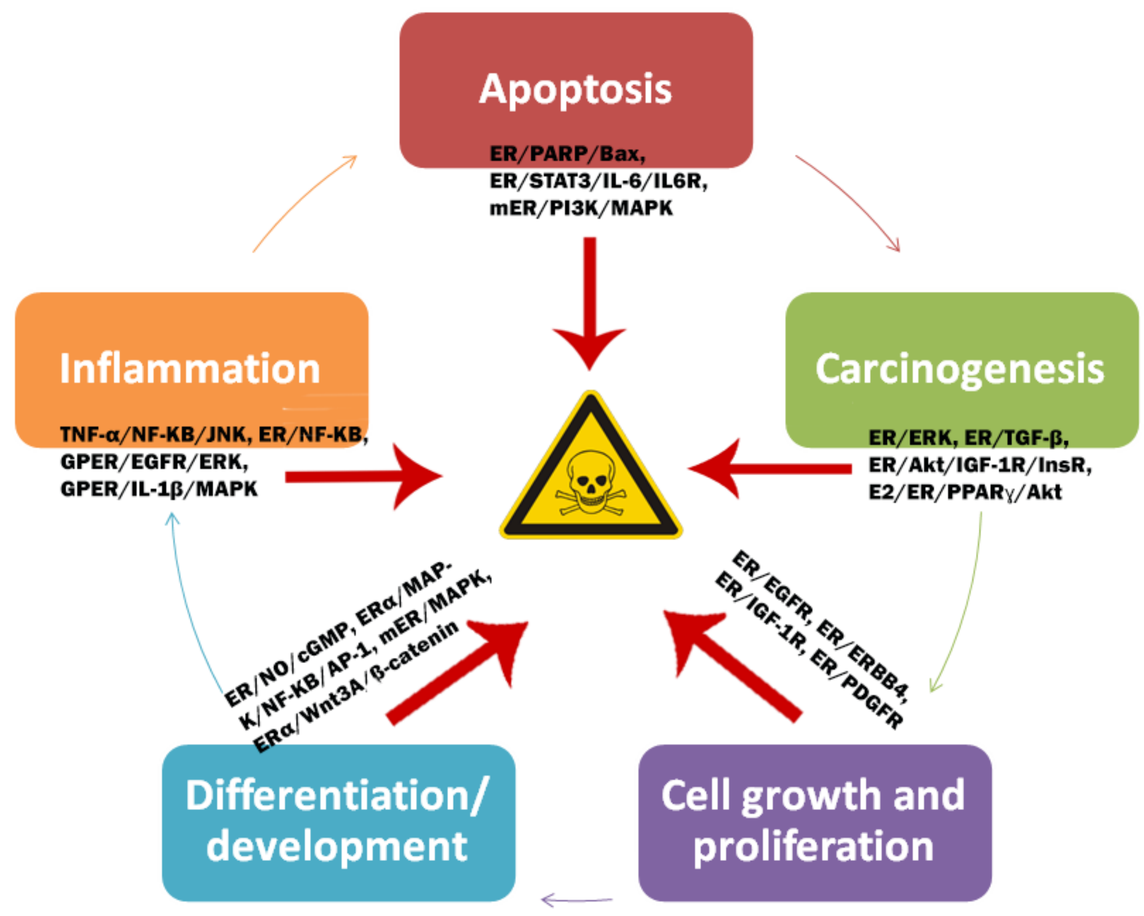
**Apoptosis**
Programmed cell death, otherwise known as apoptosis is a naturally occurring phenomenon in mammals. When cells do not self-destruct in response to a foreign inhibition is when health problems arise. Estrogen is well known to stimulate growth and inhibit apoptosis by several pathways, [9]. These pathways include Fas/FasL mitochondrial, NF-κB and PI3K/Akt pathways [11]. Triclosan [9], and Phthalates [13], are known to inhibit apoptosis. ERα prevents apoptosis by controlling both the extrinsic and intrinsic apoptotic pathways and by promoting cell survival [11].

**Carcinogenesis**
Exposure to estrogenic chemicals over a lifetime affects the risk of developing cancer. Cancer development is dependent on exposure time, dose of the chemical and duration of exposure[20]. When the estrogen receptor is falsely up regulated or down regulated it is linked to signaling promoting that promotes the development of various cancers [21] There are several chemicals present in cosmetics that are involved in the estrogen related carcinogenic pathway such as phthalates, estrogen, cadmium and tocopherols. Phthalates have been linked to premature breast development in girls (CHEN) Additional, chemical that have not been classified may add synergistic properties to the pathway. Example pathways for the carcinogenic pathways can be seen in the figure. [1,2,9]

**Cell Growth and Proliferation**
In addition to apoptosis, a proliferation or growth of cells can occur. Estrogen Receptors alpha (ERα) prevents apoptosis by controlling both the extrinsic and intrinsic apoptotic pathways and by promoting cell survival [11]. The genes belonging to signaling, proliferation, and transport clearly exhibited different degrees of variation in their expression level in response to the estrogenic activities of phthalate esters. [13]

**Differentiation and Development**
Estrogen plays a major role in cell differentiation and cell development. It is especially important in sexual differentiation during puberty [14]. With the wide range in age of cosmetics users, this is particularly concerning for young children exposed to these chemicals. Estrogenic activity is modulated by ERα and ERβ. When these pathway mechanisms are activated improperly, developmental and differentiation disease and problems occur [12].

**Inflammation**
Inflammation is an innate immune response that occurs when tissues are damaged in response to exogenous agents. It is the second line of defense without specificity. Estrogenic chemicals can affect the inflammatory response negatively or modulate the signal induced by estrogen. Chemicals such as baicalein, genistein, 4-hydroxyphenyl sulfonamides, niacin, p-n-nonylphenol, p-n- octylphenol, oroxylin-A and resveratrol, are estrogenic chemicals in which signals inflammation and activates specific pathways. The signaling pathways for inflammation involve ER/NF-κB, R/NF-κB/NO, ER/NF-κB/NO/TNF-α, ER/TNF-α/IL-1β/IL-6/NO, and ERα/TNF-α/NO. For example, Resveratrol, a stilbenoid found in cosmetics, shows pathway-selective ER signaling, where it activates the inflammatory pathway [10].




## CONCLUSION

The exposure and risk of endocrine disrupting chemicals, specifically pro-estrogenic, is rampant in the human population because they are found in products that are used daily. These chemicals can be found in various cosmetics, and at different concentrations. Cosmetics are primary used in conjunction with other cosmetics, which can increase the amount of exposure to an individual through inhalation, oral, or dermal contact. The greatest risk of being exposed to these chemicals is disrupting the endocrine system, which has the potential to cause adverse health effects. Approximately 70% of breast cancers are ERα positive and estrogen-dependent [1]. Since a majority of the chemicals in cosmetics are pro-estrogenic, this leads one to speculate that there could be a correlation between the chemicals, their endocrine disrupting properties, and carcinogenicity.

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