



Assessing Computational Approaches for Predicting Estrogen Receptor Binding

Gabriela O. P. Corrêa, PhD
Product Safety Researcher

Safety Assessment Management

ASCCT-ESTIV Award Winners Webinar Series

OBOTICÁRIO

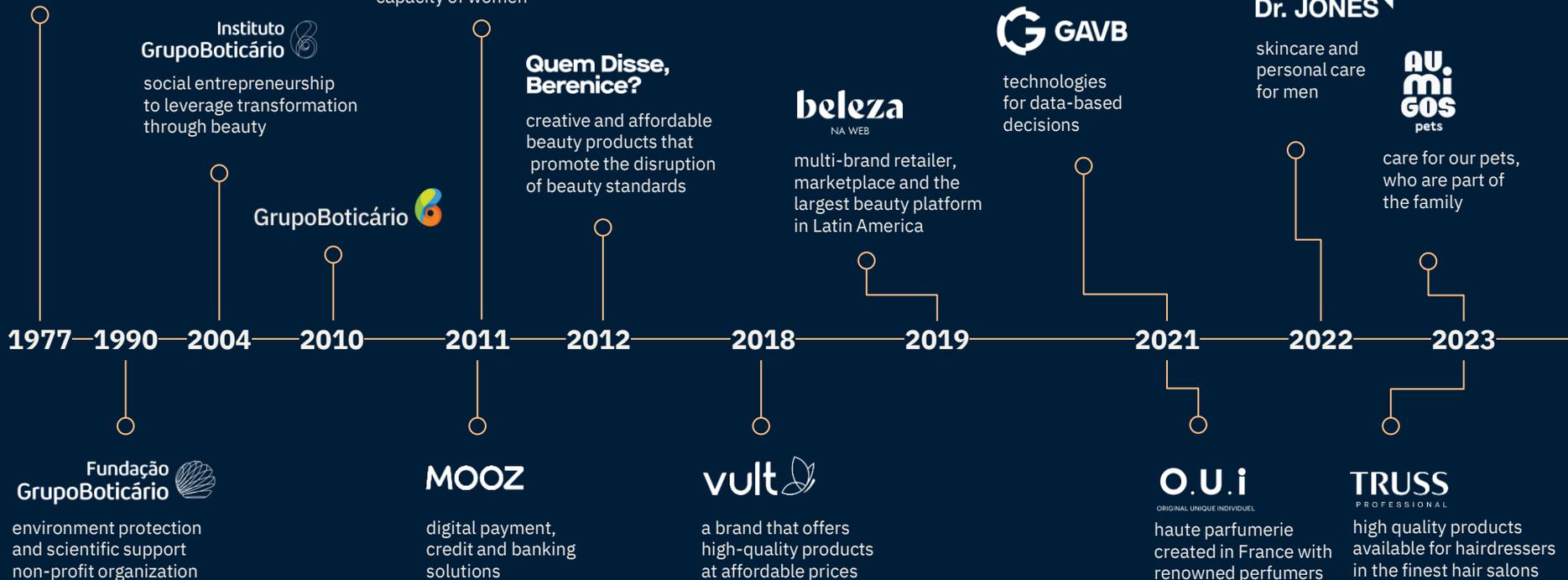
the group's first-born brand and the largest beauty franchise network in the country; it can be found in branded store, direct sales and e-commerce channels

EUDORA

efficient and innovative beauty solutions that encourage the achievement capacity of women



GrupoBoticário



Background

- **Endocrine-disrupting chemicals (EDCs)** are natural or synthetic substances that may **mimic, block, or interfere with the body's hormonal systems**. These chemicals are associated with a wide array of health issues;
- Classical targets of EDCs include nuclear receptors such as estrogen receptors (ER), androgen receptors (AR), thyroid receptors (TR), among others;

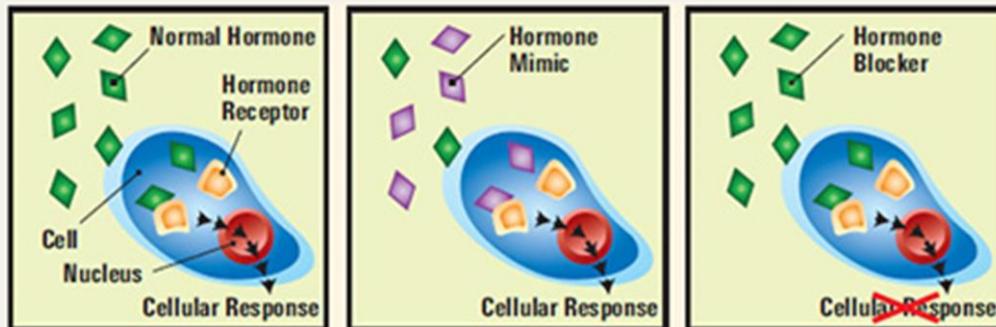


Figure 1. Sources of endocrine disruptors (NIH, 2024)



Figure 2. When absorbed in the body, an EDC can decrease or increase normal hormone levels (left), mimic the body's natural hormones (middle), or alter the natural production of hormones (right) (NIH, 2024)

Review Article |  Open Access |  

Interference Mechanisms of Endocrine System and Other Systems of Endocrine-Disrupting Chemicals in Cosmetics—In Vitro Studies

Yixuan Zhang, Lihong Tu, Jian Chen , Lihong Zhou 

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Academic Editor: Malgorzata Kotula Balak

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Review

Endocrine Disruptors in Cosmetic Products and the Regulatory Framework: Public Health Implications

by Paraskevi Kalofiri* , Foteini Biskanaki* , Vasiliki Kefala , Niki Tertipi , Eleni Sfyrí  and Efsthios Rallis 

Department of Biomedical Sciences, School of Health Sciences and Welfare, University of West Attica, 12243 Athens, Greece

* Authors to whom correspondence should be addressed.

Cosmetics 2023, 10(6), 160; <https://doi.org/10.3390/cosmetics10060160>

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Review

Synthetic Endocrine Disruptors in Fragranced Products

by Sawyer Ashcroft 1 , Noura S. Dosoky 1 , William N. Setzer 2,3  and Prabodh Satyal 2,* 

¹ Essential Oil Science, dōTERRA International, Pleasant Grove, UT 84062, USA

² Aromatic Plant Research Center, 230 N 1200 E, Suite 100, Lehi, UT 84043, USA

³ Department of Chemistry, University of Alabama in Huntsville, Huntsville, AL 35803, USA

* Author to whom correspondence should be addressed.

Endocrines 2024, 5(3), 366–381; <https://doi.org/10.3390/endocrines5030027>

> *Eur J Dermatol.* 2024 Feb 1;34(1):40–50. doi: 10.1684/ejd.2024.4615.

Market analysis of the presence of endocrine disrupting chemicals in cosmetic products intended for oncological patients and other vulnerable groups

María-Elena Fernández-Martín ¹, José V Tarazona ²

Affiliations + expand

PMID: 38557457 DOI: [10.1684/ejd.2024.4615](https://doi.org/10.1684/ejd.2024.4615)

This study aimed to assess the **sensitivity** and **specificity** of *in silico* tools in **predicting the binding of chemicals to estrogen receptor**;

This is an important endpoint for cosmetic products, considering human health and the environment

Methodology

Training set - 20 proficiency chemical substances

- **OECD Test No. 455:** Performance-Based Test Guideline for Stably Transfected Transactivation *In Vitro* Assays to Detect Estrogen Receptor Agonists and Antagonists;
- **OECD Test No. 493:** Performance-Based Test Guideline for Human Recombinant Estrogen Receptor (hrER) *In Vitro* Assays to Detect Chemicals with ER Binding Affinity;

- ★ **Positive substances:** 14 (70%) - exhibit affinity for the receptor;
- ★ **Negative substances:** 6 (30%) - do not exhibit affinity for the receptor;

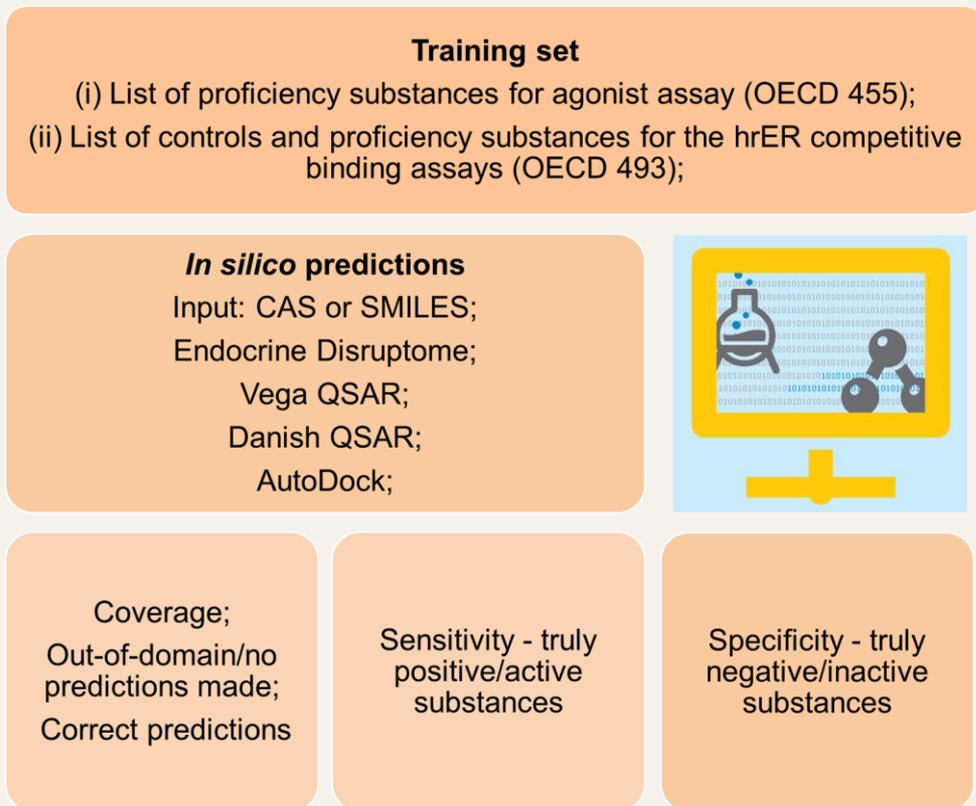
Table 1. OECD proficiency chemical substances

Substances	CAS RN
Diethylstilbestrol	56-53-1
17 α -estradiol	57-91-0
meso-Hexestro	84-16-2
4-tert-Octylphenol	140-66-9
Genistein	446-72-0
Bisphenol A	80-05-7
Kaempferol	520-18-3
Butylbenzyl phthalate	85-68-7
p,p'-Methoxychlor (Methoxychlor)	72-43-5
17 α -ethynylestradiol	57-63-6
Norethynodrel	68-23-5
Zearalonone	17924-92-4
Butylparaben	94-26-8
Ethylparaben	120-47-8
Atrazine	1912-24-9
Spirolactone	52-01-7
Ketoconazole	65277-42-1
Reserpine	50-55-5
Octyltriethoxysilane	2943-75-1
Corticosterone	50-22-6

CAS RN: Chemical Abstracts Service Registry Number.

Methodology

Figure 4. Study design



Models:

- **Endocrine Disruptome**
 - ER α and ER β ;
- **Vega QSAR**
 - Estrogen Receptor-mediated effect (IRFMN-CERAPP) 1.0.1;
 - Estrogen Receptor Relative Binding Affinity model (IRFMN) 1.0.2;
- **Danish QSAR**
 - Estrogen Receptor α Binding, Full training set (Human *in vitro*);
 - Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*);
 - Estrogen Receptor α Activation (Human *in vitro*);
 - Estrogen Receptor Activation, CERAPP data (*in vitro*);

Methodology

- **AutoDock** was used to perform **molecular docking**, polar hydrogens and Kollman charges were added to the protein structure (Estrogen receptor - PDB code: 1a52) and the number of torsions in the ligand was established;
- For results → Substances were considered **positive**, indicating a high probability of binding, when the **binding affinity was ≥ -7.5** . Substances that obtained values **< -7.5 were classified as negative**;



Figure 5. Molecular docking design

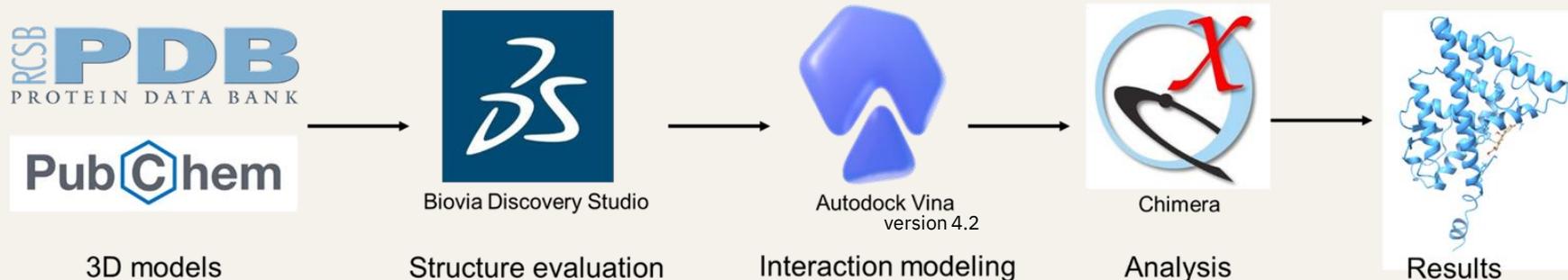


Table 2. *In silico* predictions results

Substances	OECD 493/455	VEGA QSAR	Danish QSAR	Endocrine Disruptome	AutoDock
Diethylstilbestrol	POS	POS	POS	POS	POS
17 α -estradiol	POS	POS	POS	POS	POS
meso-Hexestro	POS	POS	POS	POS	POS
4-tert-Octylphenol	POS	POS	POS	NEG ←	NEG ←
Genistein	POS	POS	POS	POS	POS
Bisphenol A	POS	POS	POS	POS	POS
Kaempferol	POS	POS	POS	POS	POS
Butylbenzyl phthalate	POS	POS	POS	NEG ←	POS
p,p'-Methoxychlor (Methoxychlor)	POS	POS	POS	NEG ←	POS
17 α -ethynylestradiol	POS	POS	POS	POS	POS
Norethynodrel	POS	POS	POS	POS	POS
Zearalonone	POS	POS	POS	POS	POS
Butylparaben	POS	POS	POS	NEG ←	NEG ←
Ethylparaben	POS	POS	OUT	NEG ←	NEG ←
Atrazine	NEG	NEG	NEG	NEG	NEG
Spironolactone	NEG	OUT	NEG	NEG	NEG
Ketoconazole	NEG	NEG	NEG	POS	POS
Reserpine	NEG	NEG	NEG	NEG	NEG
Octyltriethoxysilane	NEG	NEG	OUT	OUT	NEG
Corticosterone	NEG	NEG	NEG	NEG	NEG

Results

- **VEGA and Danish** → QSAR tools - similar results;
- **Endocrine Disruptome and Autodock** → Molecular docking tools - similar results;

POS: Positive; NEG: Negative; OUT: Out-of-domain / No predictions made.

Results

Table 3. Agreement percentages (%) between OECD proficiency substances and *in silico* predictions

Parameters	VEGA QSAR	Danish QSAR	Endocrine Disruptome	AutoDock
Coverage	95,00	90,00	95,00	100,00
Out-of-domain / No predictions made	5,00	10,00	5,00	0,00
Correct predictions	95,00	90,00	65,00	80,00
Sensitivity	100,00	100,00	64,28	78,57
Specificity	100,00	100,00	80,00	83,33

The average of sensitivity and specificity, indicating a models performance across both positive and negative substances

$$\frac{\text{Sensitivity} + \text{Specificity}}{2}$$

×

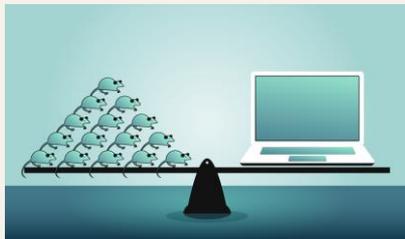
Balance accuracy

Vega QSAR □ 100,00%

Danish QSAR □ 100,00%

Endocrine Disruptome □ 72,14%

Autodock □ 80,95%



Conclusions

***In silico* approaches**

Fast and cost-effective
alternative to animal
testing



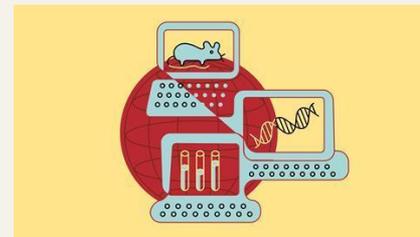
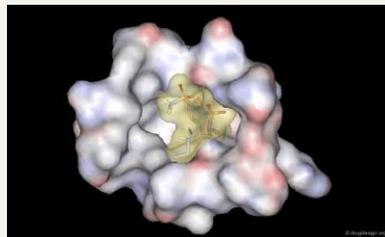
Estrogen Receptor Binding

QSAR tools performed
well



Bridging the Gap

This results can complement *in vitro* and
literature data, and offer valuable pre-
screening for new substances with
endocrine-disrupting potential



The logo for the FDA (Food and Drug Administration) is displayed in white, bold, sans-serif font on a blue rectangular background.

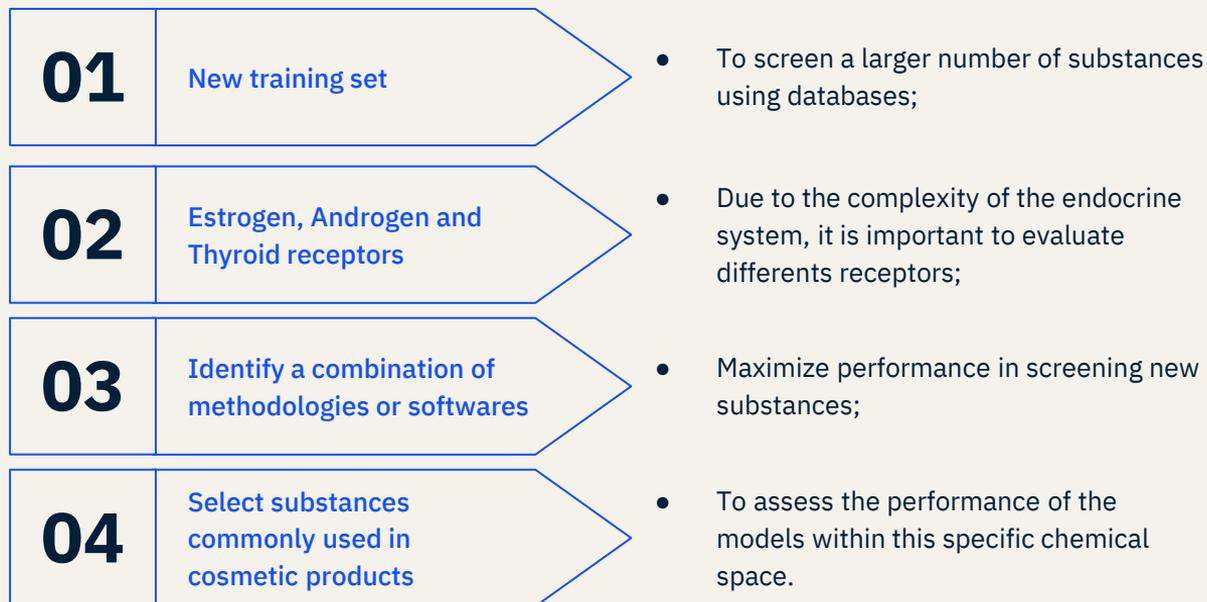
Endocrine Disruptor
Knowledge Base
(EDKB)

Endocrine
Disruptor
Lists

The logo for ECHA (European Chemicals Agency) features a stylized yellow and blue square icon to the left of the text "ECHA" in large, bold, black letters, with "EUROPEAN CHEMICALS AGENCY" in smaller black letters below it.

Endocrine disruptor assessment list

Future Directions



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Thank you for listening



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Contacts

- ❖ <https://www.linkedin.com/in/gabrielapradocorrea/>
- ❖ gabriela.correa@grupoboticario.com.br



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