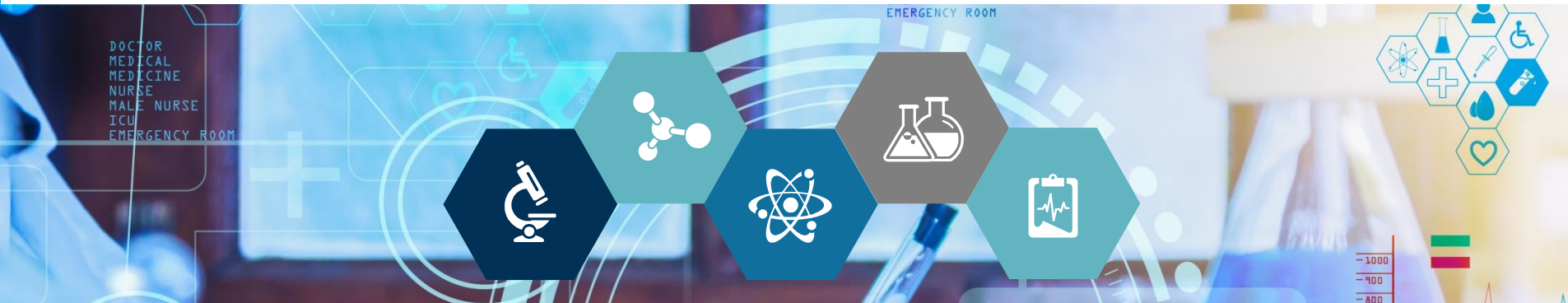


1<sup>st</sup> International Conference

**Modern research trends in biomedical sciences: a holistic approach to healthcare**

Institute of Health Sciences, University of Opole, Poland



# Information technologies as a tool for identification of endocrine disrupting chemicals

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University "Prof. Dr. Assen Zlatarov", Burgas, BULGARIA

April 2024

Marine Science  
Biochemistry  
Material Science  
Microbiology  
Photographic Science and Printing Technology  
Genetics

## Highlights:

- Human health and global chemical safety
- Recent achievements in computational chemistry
- Application of computer tools for identification of estrogen disrupting chemicals (EDC)

# Summary

- **Landmarks in EDC Research and computational chemistry**
- Prediction the binding effect of chemicals toward the estrogen receptor
- Conclusions

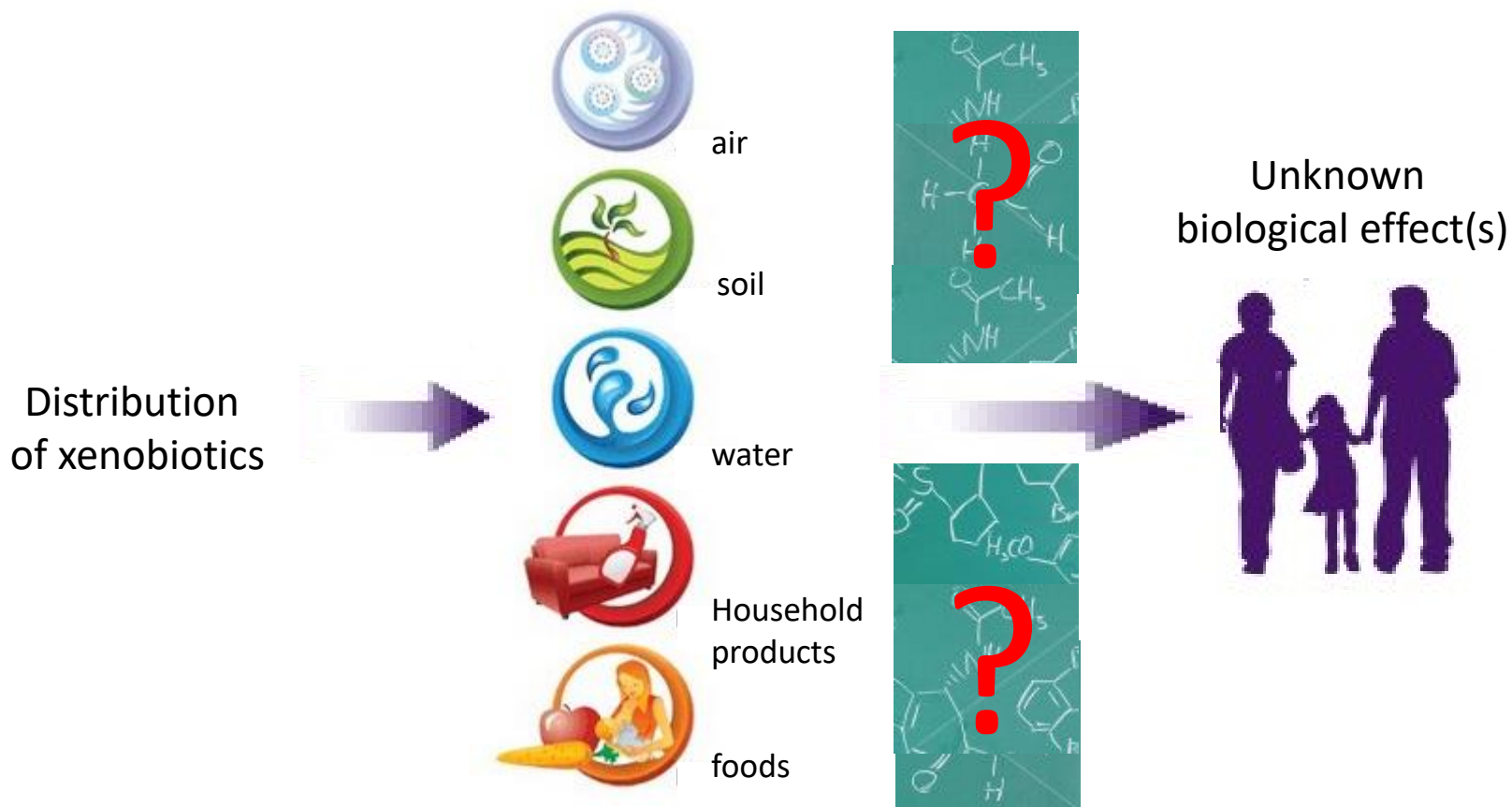
# EDC Research Timeline

## Historical landmarks in the EDCs Research

<p><b>Silent Spring</b> The book "Silent Spring" by the American biologist Rachel Carson was published.</p>	<p>The "DES catastrophe"</p>	<p>The term "Endocrine Disruptor" is firstly introduced.</p>	<p>WHO Issues First Global Assessment of the State of the Science of EDCs</p>	<p>First use of the term "obesogen"</p>	<p>Endocrine Society issues Position Statements on EDCs</p>	<p>Introduction of the term "metabolism-disrupting chemicals"</p>
<p><b>1962</b></p>	<p><b>1971</b></p>	<p><b>1991</b></p>	<p><b>2002</b></p>	<p><b>2006</b></p>	<p><b>2009</b></p>	<p><b>2015</b></p>
<p>Its publication was a seminal event for the environmental movement and resulted in a large public outcry that eventually led, in 1972, to a ban on the agricultural use of DDT in the USA.</p>	<p>Children born to mothers prescribed DES were found to have increased risk of a rare reproductive tract cancer in their early 20's. DES is recognized as a transplacental carcinogen.</p>	<p>During Wingspread meeting, where 21 international scientists from 15 different disciplines convened to share their research relevant to transgenerational health impacts, the term "endocrine disruption" was coined.</p>	<p>The document examined human health impacts on reproduction, neurobehavior, cancer, the immune system, and other endocrine systems potentially vulnerable to EDCs</p>	<p>In 2006, researchers at the University of California, Irvine, highlighted the role of environmental chemicals in the emerging obesity epidemic and coined the term "obesogen".</p>	<p>The Task Force's work resulted in a comprehensive scientific document published in 2009 as the Society's first Scientific Statement.</p>	<p>Parma consensus statement proposed the term "metabolism-disrupting chemicals (MDCs)" to describe the environmental chemicals that have the ability to promote diabetes, obesity and fatty liver, through perturbing metabolism at multiple levels.</p>

# Computational chemistry and human health

## Xenobiotics in the environment



A map of Europe with country borders outlined in black. The map is positioned on the left side of the slide.

How many chemicals are available in the EU environment

?

**Do we know their possible biological/toxic effect(s)**

# Computational chemistry and human health



## European Chemicals Agency Helsinki, Finland

**REACH** is the European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals.

It entered into force in 2007, replacing the former legislative framework for chemicals in the EU.



# Computational chemistry and human health



## European Chemicals Agency Helsinki, Finland

**REACH** is the European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals.

It entered into force in 2007, replacing the former legislative framework for chemicals in the EU.

**The Aim** is to evaluate the potential risk to human health of **30,000 chemicals** used in sufficiently high volume (1 tonne or more per year).



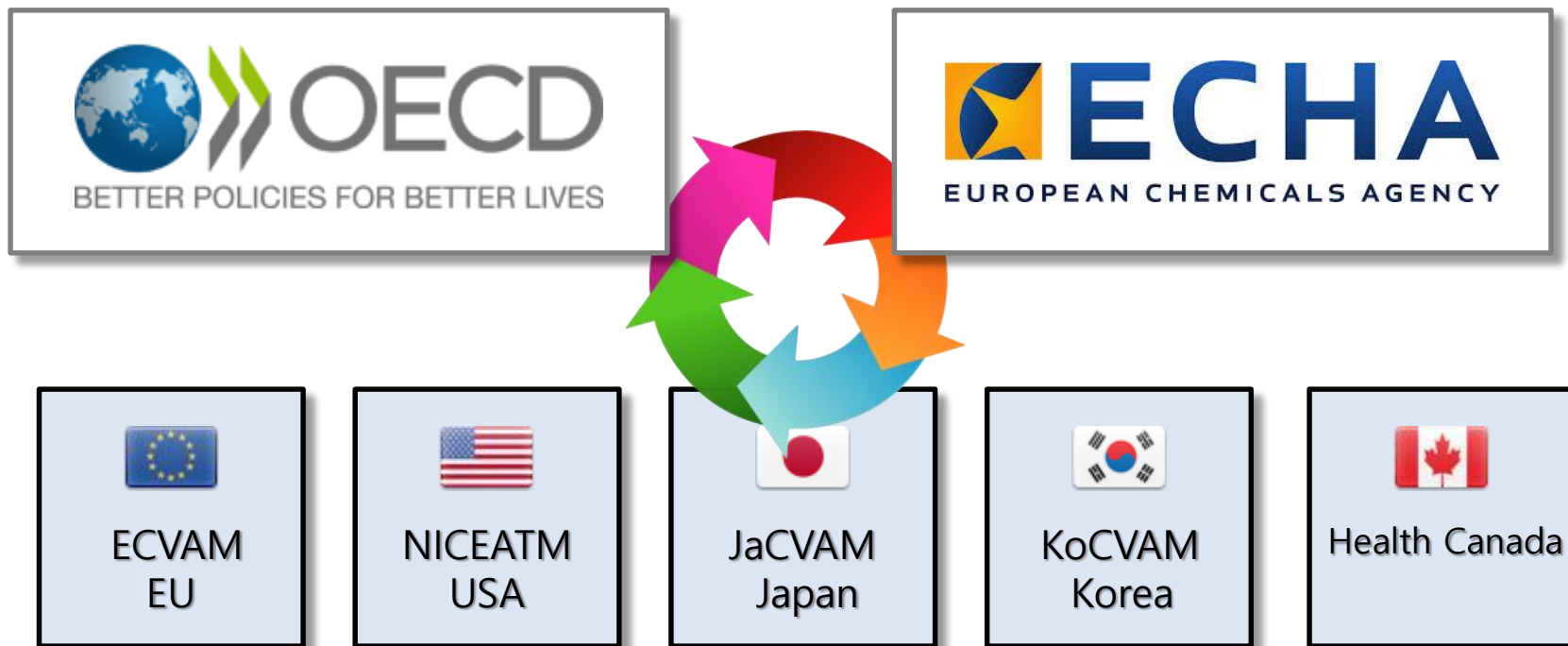


## Computational chemistry and human health

The main question is how to assess the potential risk of those **30,000 chemicals** to harm human health?



## Computational chemistry and human health



The REACH legislation allows assessment of the chemicals based on alternative non-testing methods. In this respect a non-commercial software tool called OECD QSAR TOOLBOX have been developed and used for prediction of variety biological/toxic effects.



### **Main actions performed by the Toolbox:**

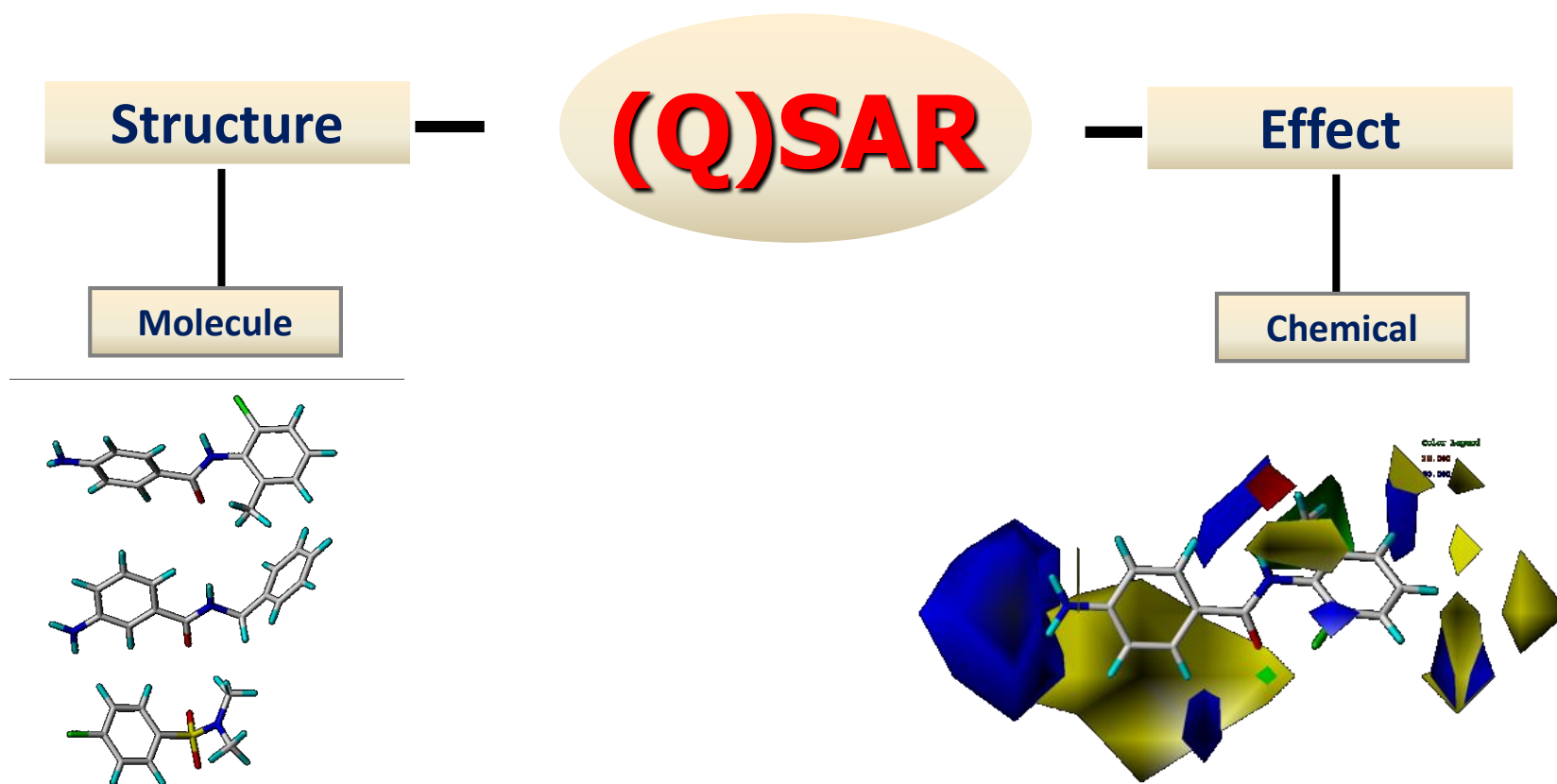
- Indicates if a chemical is included in national/regional regulatory inventories or existing chemical categories.
- Searches for available experimental results for the chemical of interest.
- Explores a chemical list for possible similar chemicals.
- Extracts experimental data for similar chemicals.
- Allows user to construct and apply their own models

# Summary

- Landmarks in EDC Research and computational chemistry
- **Prediction the binding effect of chemicals toward the estrogen receptor**
- Conclusions

# Quantitative Structure – Activity Relationship

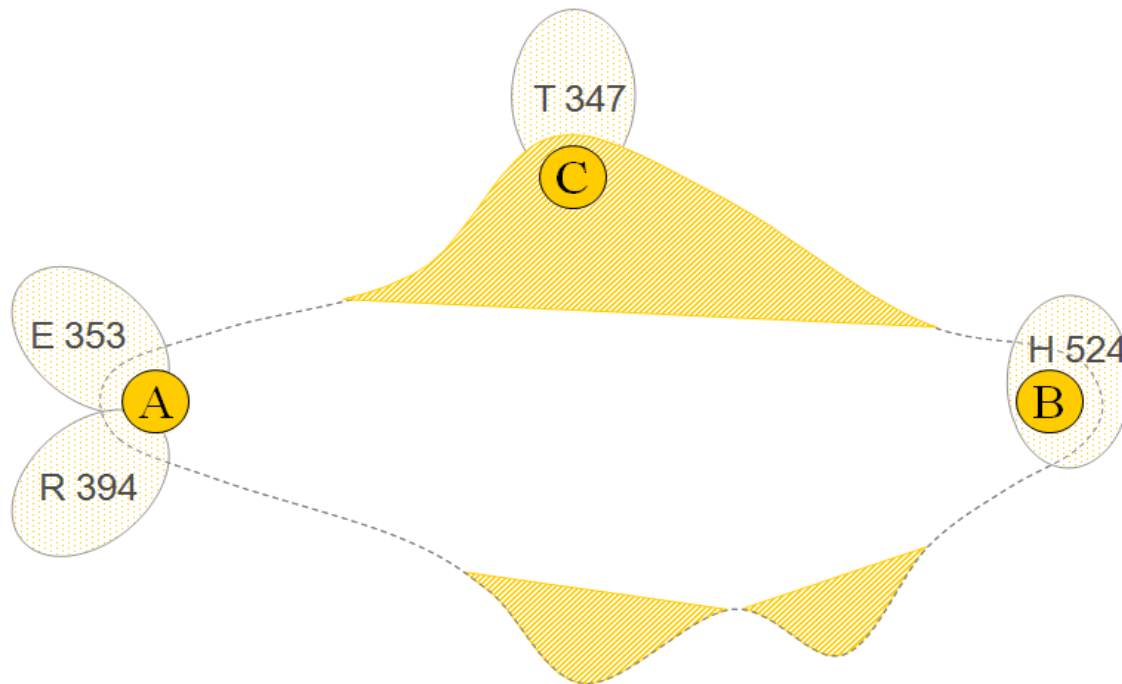
## QSAR method for identification of EDCs



# Prediction the binding effect of chemicals toward the estrogen receptor

## Specificity of receptor-ligand interactions Schematic representation of ER binding pocket

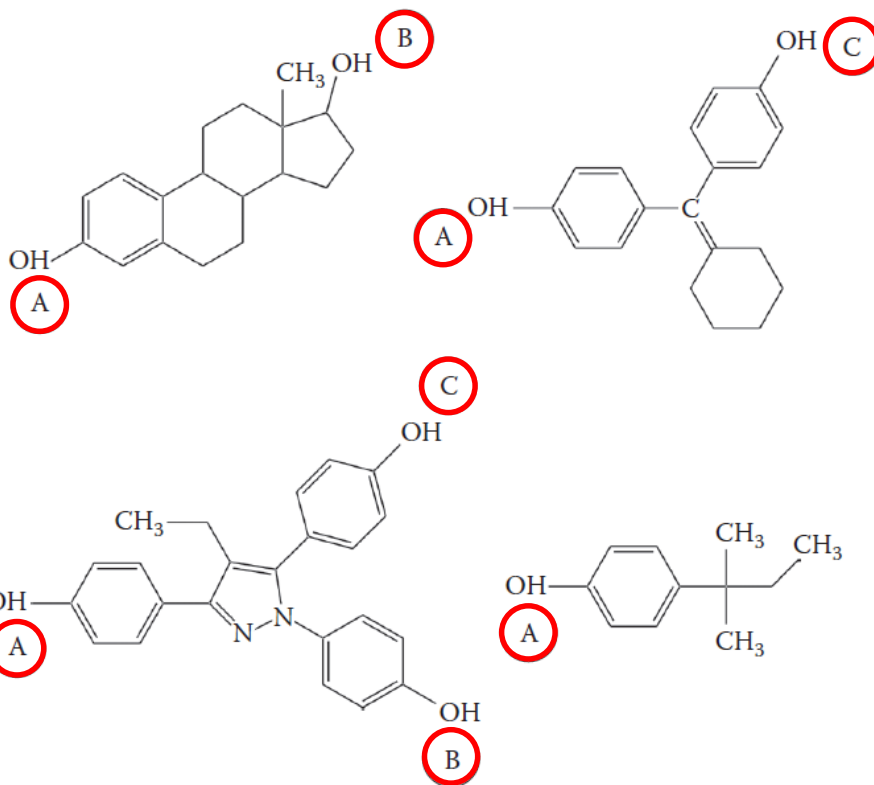
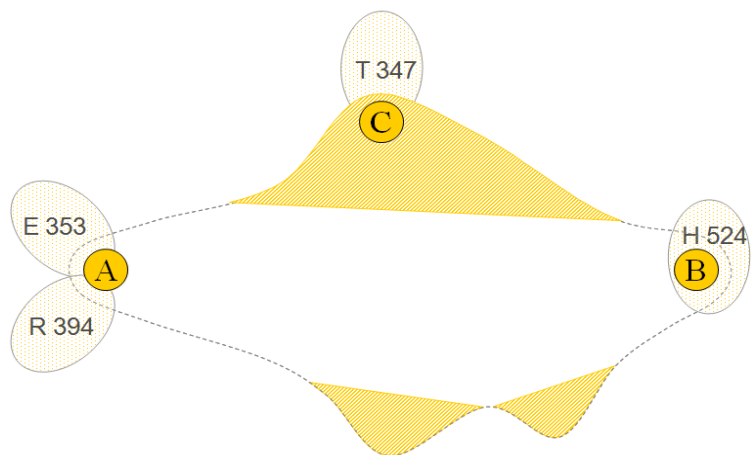
- Recognized are three sites of interaction within the pocket\*



\*Katzenellenbogen et al., 2002

# Prediction the binding effect of chemicals toward the estrogen receptor

## Specificity of receptor-ligand interactions

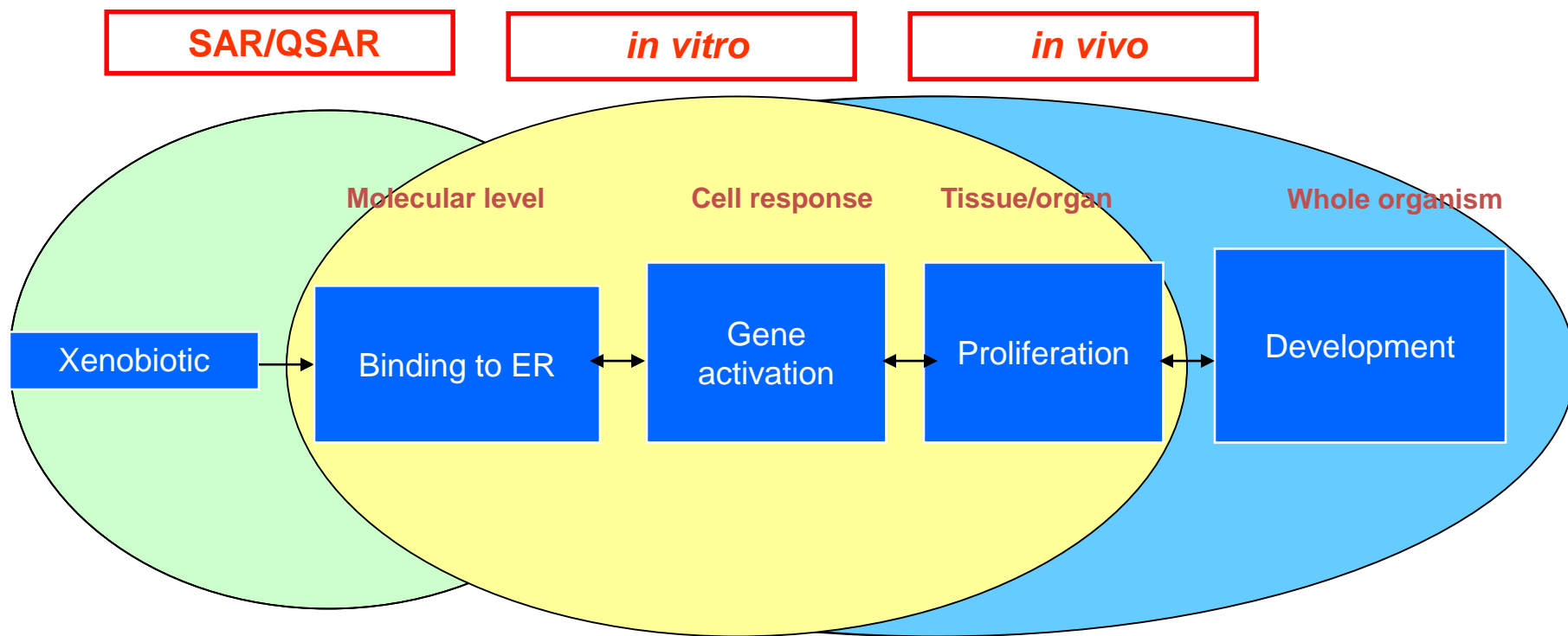




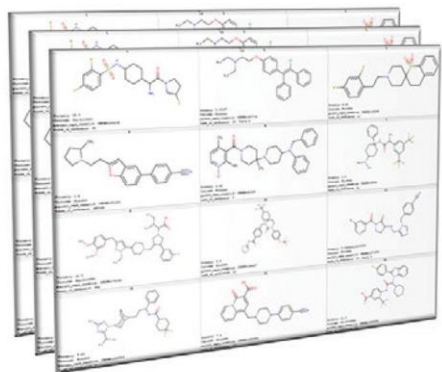
# Prediction the binding effect of chemicals toward the estrogen receptor

## Steps in Estrogen hormon-receptor function

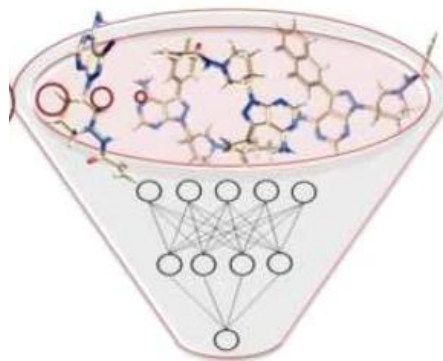
Stimulates development and maintenance of female sexual characteristics.



# Modelling steps and prediction of EDCs



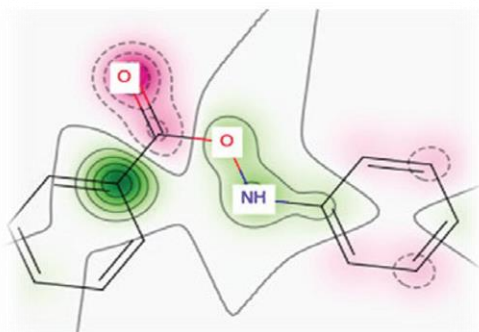
Databases  
(experimental data)



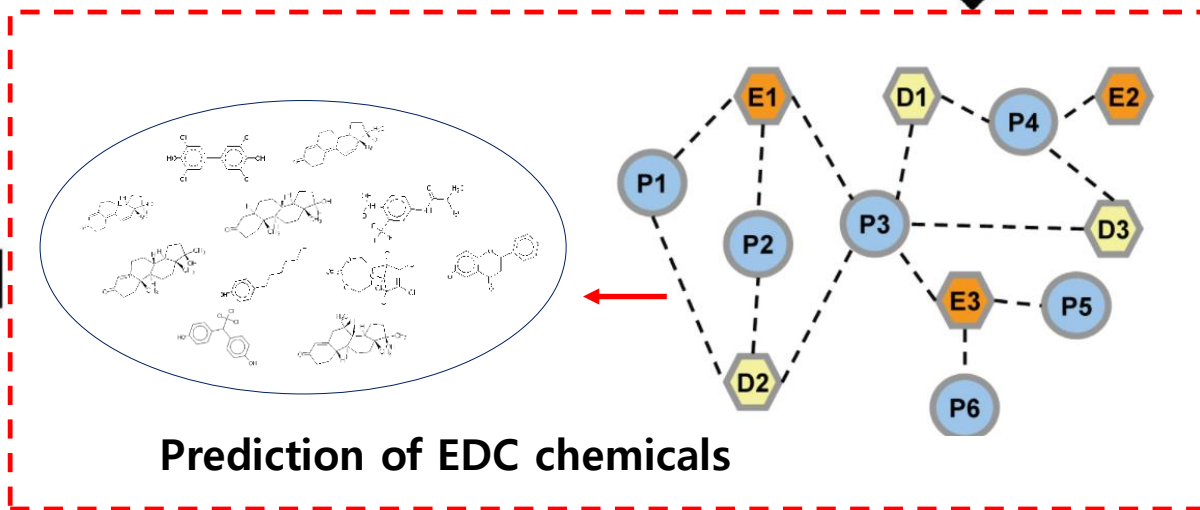
Model building



*In silico* model



Explanation the  
mechanism of effect



Prediction of EDC chemicals

# Prediction the binding effect of chemicals toward the estrogen receptor

QSAR Toolbox 4.2 [Document 1]

**QSAR TOOLBOX**

Input Profiling Data Category definition Data Gap Filling Report

Profiling Custom profile

Apply View New Delete

The OECD QSAR Toolbox for Grouping Chemicals into Categories  
Developed by LMC, Bulgaria

Documents Estrogen Receptor Binding (General Mechanistic) - Profiling Scheme Browser

Save Scheme Export Scheme Save Tests View Tests Run All Tests

Categories Definition Properties Training Set Literature MetalInfo Table Scheme

Filter:

Categories

- Estrogen Receptor Binding
  - Moderate binder, NH2 group
  - Moderate binder, OH group
  - Non binder, impaired OH or NH2 group
  - Non binder, MW>500
  - Non binder, non cyclic structure
  - Non binder, without OH or NH2 group
  - Strong binder, NH2 group
  - Strong binder, OH group
  - Very strong binder, OH group
  - Weak binder, NH2 group
  - Weak binder, OH group

Query details

[0] Structure Query Metabolism

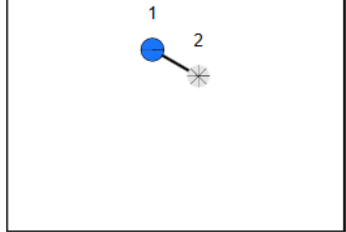
Contents

- Queries
  - Search 1: SMARTS
- Masks

SMARTS

[NH2,N+H3][\$([#6HR]1[#6H2] Edit

View mode: Facade Navigation m



Left click on any marked atom to explore

Metabolism/Transformations

7920

# Prediction the binding effect of chemicals toward the estrogen receptor

QSAR Toolbox 4.2 [Document 1]

QSAR TOOLBOX

Input Profiling Data Category definition Data Gap Filling Report

Data Import Export Delete

Gather Import IUCLID6 IUCLID6 Database Inventory

Documents

Document 1

Genotoxicity OASIS

Filter endpoint tree...

Structure

- Bioaccumulation
- Carcinogenicity
- Developmental Toxicity / Teratogenicity
- Genetic Toxicity

1 2 3 4 5 6 7

M: Negative M: Negative

M: Negative

M: 0 %

Profile

- Endpoint Specific
  - Keratinocyte gene expression

Not possible to c...High gene expre...Not possible to c...Not possible to c...Not possible to c...Not possible to c...Very high c

- DSS I O X
- ECHA PR
- EINECS
- HPVC OECD
- METI Japan
- NICNAS
- REACH ECB
- TSCA
- US HPV Challenge Program

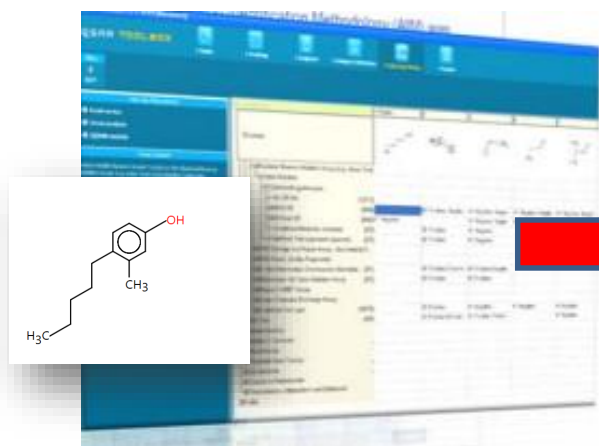
7920

In current version of the OECD Toolbox (v. 4.6) there are 62 available databases containing more than 100 000 chemicals with above 3 million measured data points.

Experimental data for estrogen binding is available for more than 2800 chemicals .

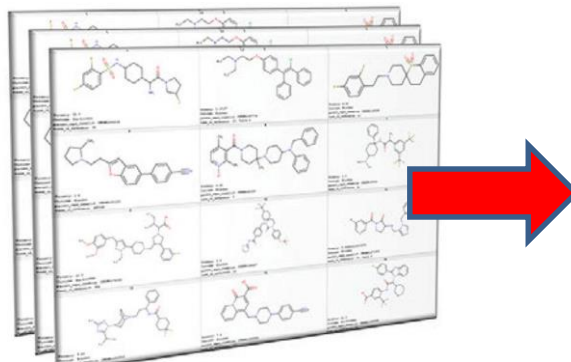
# Prediction the ER binding effect of specific chemical

## Case study for *3-methyl-4-pentylphenol*

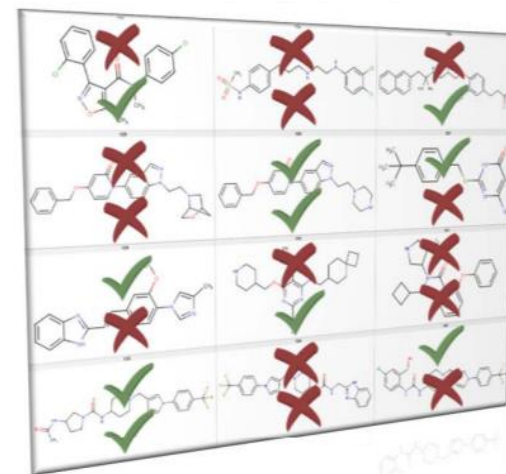


1) Input target chemical

If data is not available



2) Search for experimental data



3) Applying rules or model for prediction

# Prediction the ER binding effect of specific chemical

## Case study for *3-methyl-4-pentylphenol*

QSAR Toolbox 4.4 [Document 1]

Q SAR TOOLBOX

Input Profiling Data Category definition Data Gap Filling Report

Define Define with metabolism Subcate

Documents

Estrogen Receptor Binding

Options

- Select All
- Unselect All
- Invert
- Abc

Biodegradation probability (Biowin 1)

Biodegradation probability (Biowin 2)

Biodegradation ultimate (Biowin 3)

DNA binding by OASIS

DNA binding by OECD

Estrogen Receptor Binding

Hydrolysis half-life (Ka, pH 7)(Hydrowin)

Hydrolysis half-life (Ka, pH 8)(Hydrowin)

Hydrolysis half-life (Kb, pH 7)(Hydrowin)

Hydrolysis half-life (Kb, pH 8)(Hydrowin)

Hydrolysis half-life (pH 6.5-7.4)

Ionization at pH = 1

Ionization at pH = 4

Ionization at pH = 7.4

Ionization at pH = 9

Protein binding by OASIS

Protein binding by OECD

Protein binding potency Cys (DPRA 13%)

Protein binding potency GSH

Protein binding potency Lys (DPRA 13%)

AW SWAOP

Toxicity to Reproduction

- Relative ARBA 21/22 M: NaN %
- Relative ERBA
  - Human 42/42 M: 0.013 % M: 0.018 % M: 0.0747 % M: 0.0147 % M: 0 %
  - Rat 7/7 M: 0.0009 %
  - Recombinant human estrogen r... 58/58 M: 0.013 % M: 0.018 % M: 0.0747 % M: 0.0147 % M: NaN %
  - Trout 11/11 M: 0.00042 %

Toxicokinetics, Metabolism and Distribution

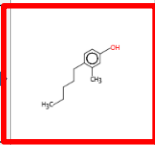
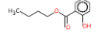
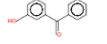
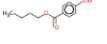
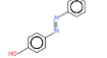
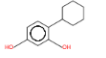

Profiling

- General Mechanistic
- Estrogen Receptor Binding Moderate binder...

The OECD QSAR Toolbox for Grouping Chemicals into Categories

Developed by LMC, Bulgaria

1 [target] 2 3 4 5 6 7

1 [target]	2	3	4	5	6	7
						

67

# Prediction the ER binding effect of specific chemical

## Predicted as weak binder to the estrogen receptor

QSAR Toolbox 4.4 [Document 1]

**QSAR TOOLBOX**

Input Profiling Data Category definition Data Gap Filling Report

Document Single Chemical Chemical List Search Target Endpoint

New Open Close Save CAS# Name Structure Composition Select ChemIDs Database Inventory List Substructure (SMARTS) Query Define

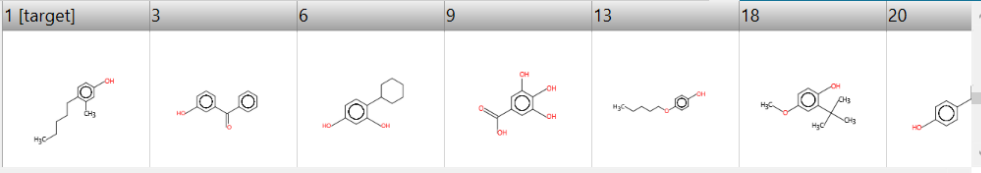
The OECD QSAR Toolbox for Grouping Chemicals into Categories  
Developed by LMC, Bulgaria

Documents

- Document 1
  - [C: 1;Md: 0;P: 0] Search chemical
  - [C: 67;Md: 140;P: 0] Moderate binder, O
    - [C: 52;Md: 117;P: 0] Enter GF(TA)
      - [C: 5;Md: 13;P: 0] Subcategorize
      - [C: 33;Md: 68;P: 0] Subcategoriz
      - [C: 20;Md: 42;P: 0] Subcat

Filter endpoint tree... 1 [target] 3 6 9 13 18 20

Structure



Descriptors

Prediction

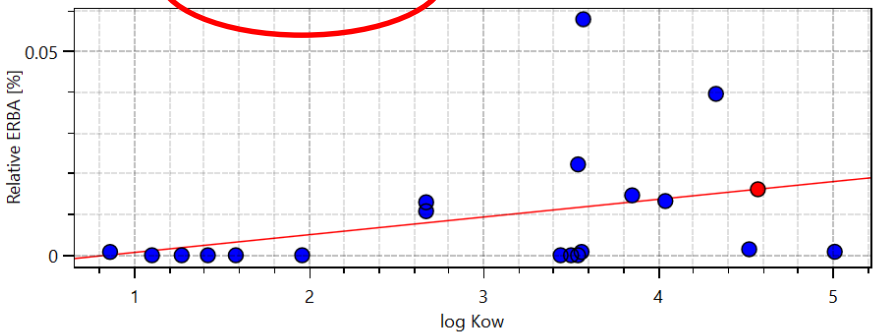
Adequacy

Cumulative frequency

Residuals

Statistics

**Trend analysis prediction for Relative ERBA, based on 19 values**  
**Predicted: 0.0162 %**  
Model equation:  $\text{Relative ERBA} = -3.67\text{E-}3 (\pm 0.0193) + 4.35\text{E-}3 (\pm 6.01\text{E-}3) * \log \text{Kow}, \%$



Select / filter data

- Subcategorize
- Mark chemicals by WS
- Mark chemicals by descriptor value
- Mark outliers
- Filter points by test conditions
- Mark focused chemical
- Mark focused points

Accept prediction



## CONCLUSIONS

- Computational tools could be used successfully for identification of EDCs
- Users of the QSAR Toolbox software are able to apply different techniques for predictions
- Theoretical predictions reduces significantly financial resources for experimental tests





**Thank you for  
your attention!**



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**Milen Todorov**  
University "Prof. Dr. Assen Zlatarov", Burgas, BULGARIA