| About section of a profiler |
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| **Name of the profiler** |
| rtER Expert System – USEPA |
| **Developer; date; version** |
| ***Developer:***<br>Pat Schmieder, Rick Kolanczyk, Mike Hornung, Mark Tapper, Jeff Denny, and Gil Veith<br><br>***Donator:***<br>Mid-Continent Ecology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, US EPA, 6201 Congdon Boulevard, Duluth, Minnesota 55804 US<br><br>***Version:*** 1.0<br>December 2016 |
| **Relevance/Applicability to endpoint(s)** |
| The rtER Expert System – USEPA profiler consists of molecular definitions mimic the structural criteria of chemical classes potential estrogen receptor-binders covered by US EPA Estrogen Receptor Expert System (ERES) The ERES profiler is an effects-based automated system used to predict estrogen receptor binding affinity.<br>The ERES was originally developed to address a defined regulatory purpose, specifically for prioritizing chemicals from two specific inventories, food use pesticidal inerts (FI) and antimicrobial pesticides (AM) which do not include any chemicals with steroidal-type chemical structures, and thus not capable of higher affinity ER interactions. This system was built upon a training set of chemicals to cover the defined regulatory inventories using in vitro assays specifically optimized to pick up any indication of binding by testing up to chemical solubility or cytotoxicity within the assays to increase confidence that a chemical predicted negative is unlikely to bind ER. A chemical class-based approach was designed to allow extrapolating from a limited number of well-characterized TrSet chemicals to a broader inventory of chemicals by employing effects-based chemical category and read-across concepts.<br>The ERES is a logic rule-based decision tree that encodes the experts' mechanistic understanding with respect to both the chemical and biological aspects of the well-defined endpoint, or the ER bioassay domain. The transparency (relationship of predicted chemicals to tested chemicals) and usefulness of the system for the intended purpose (predictions provided for FI and AM chemicals) was emphasized in the approach to develop the ERES. For example, the relationship between relative binding affinity (RBA) and LogKow that was identified for the ERES chemical groups was used within each group to ensure the predicted chemical was bounded by TrSet chemicals. Chemicals falling outside the boundaries of known ability to predict (whether active or inactive) were considered to have "Unknown Binding Potential" (UnkBP). The automated version of the ERES enables users to compare the predicted chemical to TrSet chemicals within each chemical group (i.e., the decision tree node).<br>In the Toolbox, the rtER Expert System ver.1 – USEPA profiler is used for the purpose of categorization based on the structural definitions of the original ERES chemical classes. The rtER Expert System ver.1 – USEPA profiler is introduced for categorization purpose and not for predicting relative binding affinity (RBA). |
| **Relevance/Applicability to particular chemical classes** |
| This profiler is applicable for organic chemicals having a fictional group able to bind to estrogen receptor (such as Phenols, Anilines, Tamoxifen type compounds and other). The |

structural alerts are separated into three general types depending on the site of interaction with the receptor: Special Rules Groups; Site A, Contains Phenol Fragment and Site B, Contains Specific Fragment.

**Approach used to develop the profiler -** Concise but informative description of:

a) The rtER Expert System – USEPA profiler was developed to flag potential estrogen receptor binders. It can be used for grouping of analogues according to fictional group able to interact with estrogen receptor.

b) The profiler consists only of structural boundaries organized in logical sequence. The structural categories included in this profiler are based on chemical classes with known toxicity data. The Profiler is oorganized in a dendro-type profiling scheme based on the original US EPA ERES decision tree.

c) Each of the categories related to the specific class is associated with training set chemicals.

d) Summary list of the categories is provided below.

**Summary list of categories and associated classes**

| Category/structural alert | No. analysed chemicals | Positive/Negative Chemical (associated with skin sensitisation) |
|---|---|---|
| Acyclic Perfluoro | 0 | 0/0 |
| DDT-Like compounds | 8 | 8/8 |
| 4-Alkylchlorobenzenes | 0 | 0/0 |
| Multi Cyclic Hydrocarbons | 11 | 4/11 |
| Tamoxifen-Like compounds | 3 | 3/3 |
| Thiophosphate Esters | 2 | 2/4 |
| Alkylphenols | 24 | 24/24 |
| Phenylphenols | 5 | 5/5 |
| Alkoxyphenols | 6 | 6/6 |
| Parabens | 8 | 8/8 |
| Salicylates | 7 | 7/8 |
| Gallates | 1 | 1/2 |
| Mixed Phenols | 5 | 5/5 |
| 4-Alkylanilines | 0 | 0/0 |
| 4-Alkoxyanilines | 3 | 3/4 |
| Phthalates | 6 | 6/8 |
| Alkylcyclohexanols | 3 | 3/5 |
| Phenones (Branched) | 4 | 4/6 |
| 2-;4-; or2,4,6-Benzoates | 3 | 3/6 |
| Mixed Organics | 8 | 8/8 |
| **Total 20 categories** | | |

**Similar to other profilers**

This profiler is similar to Estrogen Receptor Binding profiler, since both schemes are related to classification of chemicals based on their ER binding potential. However in difference of last, the rtER Expert System – USEPA scheme belongs to the Endpoint specific profilers. In this respect it is a more appropriate for secondary categorization purposes.

**Short description of update version**

SMARTS language for describing molecular patterns, i.e. structural boundaries, structural alerts has been implemented in OECD QSAR Toolbox 4.0. As a result the ***rtER Expert***

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| ***System - USEPA*** profiler has been rewritten. Only small distinctions are expected in the profiling results between Toolbox v.3.4 and v 4.0 due to different interpretation of the molecular structures, e.g. for heterocyclic/heteroaromatic compounds. |
| Disclaimer |
| The structural boundaries used to define the chemical classes (e.g. “Alcohol” – chemical class from “Organic functional group” profiler) or alerting groups responsible for the binding with biological macromolecules (e.g. “Aldehydes” – structural alert for protein binding), represent structural functionalities in the molecule which could be used for building chemical categories for subsequent data gap filling. They are not recommended to be used directly for prediction purposes (as SARs). |