About section of a profiler
Name of the profiler
Keratinocyte gene expression
Developer; Donator; date; version
Developer: Laboratory of Mathematical Chemistry (LMC), Bourgas, Bulgaria, Terry W. Schultz, Ph.D. The University of Tennessee, College of Veterinary Medicine, Knoxville TN USA *Donator:* Terry W. Schultz, Ph.D, The University of Tennessee, College of Veterinary Medicine, Knoxville TN USA *Version***:** 2.0 February 2017
Relevance/Applicability to endpoint(s)
This profile is built in relation with the implementation of the adverse outcome pathway (AOP) for skin sensitization. It is developed on the base of data derived from the KeratinoSens assay, which examined the potential for chemicals to induce the expression of a luciferase reporter gene under control of a single copy of the ARE element of the human AKR1C2 gene stably inserted into immortalized human keratinocytes. Relevance to skin sensitization is inferred from the relationship of Keap1-Nrf2-ARE regulatory pathway and its detection of electrophilic chemicals to sensitization. Experimental data is based on EC1.5 values. No gene induction is observed when EC1.5 is >2000. The profile contains 21 structural alerts extracted from about 300 chemicals comprised with EC1.5 data. The set of 21 structural alerts are separated into four categories: very high gene expression, high gene expression, moderate gene expression and low gene expression. Classification of categories depends on the EC1.5 values and is as follows: chemicals having very high gene expression (EC1.5< = 15 uM); high gene expression (EC1.5 = 15 – 50 uM); moderate gene expression (EC1.5 = 50 – 100 uM); low gene expression (EC1.5 = 100 – 1999 uM). The profiling results outcome assigns a target to the corresponding potency category based on matched structural criteria.
Relevance/Applicability to particular chemical classes
This profiler is applicable to those organic chemicals that have presence of at least one of the 21 structural alerts specified within the profiler. The presence of alerts is not bounded with parametric ranges; it is based on structural boundaries only. The absence of a structural alert should not be taken as an absence of potency to interact with proteins and especially with keratinocytes.
Approach used to develop the profiler - Concise but informative description of:
a) The aim of this profiler is to investigate the potential for chemicals to induce the expression of a luciferase reporter gene especially associated with *in vitro* reactivity.
b) The profiler was developed on a basis of empirical data. The data are extracted from about 300 chemicals comprised within EC1.5 data taken form Keratinocyte gene expression Givaudan database included in the Toolbox.
c) Trainig set constsits of a list with 300 chemicals
d) Reference source
Summary description of profiles/alerts within the profiler

Profile/structural alert	Number of	Number of chemicals

	chemicals analysed	associated with specific toxicity range
High gene expression	**9**	**9/9**
alpha,beta-Unsaturated aldehydes	3	3/3
N-Acylamides	1	1/1
Non-conjugated aldehydes and dialdehydes	5	5/5
Low gene expression	**15**	**15/15**
1,2- and 1,3-Diketones	4	4/4
Alkyl methacrylate esters	2	2/2
Aryl aliphatic and alicyclic mono-ketones	2	2/2
Azlactones	2	2/2
Isocyanates, Diisocyanates and Isothiocyanates	3	3/3
Vaniline derivatives	2	2/2
Moderate gene expression	**7**	**7/7**
1,2- and 1,3-Dialdehydes	1	1/1
Alkylenediamines	2	2/2
Fragrance aldehydes	4	4/4
Very high gene expression	**49**	**49/49**
Activated halo-benzenes	5	5/5
alpha, beta-Unsaturated carbonyl compounds	20	20/20
Benzyl halides	3	3/3
Cyclopropenones	1	1/1
Glycidyl ethers	2	2/2
Isothiazolone derivatives	3	3/3
Polycyclic Aromatic Hydrocarbons	2	2/2
Substituted para- and ortho-phenylenediamines, aminophenols and benzenediols	12	12/12
Thiuram disulfides	1	1/1
Total	**80**	**80/80**

Counter category: Not possible to classify according to these rules

Similar to other profilers

This profiler is focused on possibilities of chemicals to interact with proteins on the in chemico reactivity level and may provide indication for protein binding potency of chemicals based on possibility to induce the expression of a luciferase reporter gene. As such, this profiler should be used not as a primary grouping method, but as a secondary method for refining the primary group of chemicals. As a result of this a stringent and more consistent group of chemical responsible for interaction with cell proteins could be obtained.

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.
Further general modifications are as follows:
Due to training set expansion and newly defined activity ranges based on EC1.5 only all categories definitions have been rewritten.

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).