Estimating human skin sensitization potential with an assembly of human and animal QSAR models

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Abstract

Estimating the potency values for contact allergens is of considerable importance when determining proper risk labels. The computational approaches for assessing skin sensitization are gaining wider regulatory acceptance. This presentation will present a workflow to assess the quantitative risk of skin sensitization for humans using QSAR models developed from animal and human data. An assembly of classification models for LLNA and Guinea Pig Maximization Test, Buehler test, Human Maximization Test, and Human repeat Insult Patch Test, as well as three categorical LLNA models, are used. The workflow consists of three steps and is very intuitive and highly interpretable. To validate this approach, the initial set of known human sensitizers and non-sensitizers was assembled. After removing the chemicals already present in the learning sets of the used QSAR models and additional data curation, the final external set consists of 19 compounds, 14 sensitizers, and five non-sensitizers. This set was predicted with coverage 94.74%; sensitivity 92.31%; specificity 80.00%; concordance 88.89%, positive accuracy 92.31%, and negative accuracy 80.00%. Thus, we suggest a highly predictive workflow to assess the risk and potency of human skin sensitizers.

Regulatory Context: OECD 429 and 497 Guideline on Defined Approaches for Skin Sensitization

According to OECD TG497: A Defined Approach (DA) consists of a selection of information sources (e.g in silico predictions, in chemico, in vitro data) used in a specific combination, and resulting data are interpreted using a fixed data interpretation procedure (DIP) (e.g. a mathematical, rule-based model). DAs use methods in combination and are intended to overcome some limitations of the individual, stand-alone methods.

According to OECD TG429: The basic principle underlying the Local Lymph Node Assay (LLNA) in mouse is that sensitizers induce a primary proliferation of lymphocytes in the auricular lymph nodes draining the site of chemical application. Results are expressed as the Stimulation Index (SI). A chemical is considered a sensitizer when the stimulation index exceeds 3 (SI > 3). ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) recommends the following ranges for four categories of sensitizers.

Category	EC3 (%)
1 Extreme	< 0.1
2 Strong	≥0.1 - <1
3 Moderate	≥1 - < 10
4 Weak	≥10 - ≤100

Objective

- Build optimized workflow using high quality (Q)SAR models developed from animal and human data to produce a high confidence assessment and support expert reviews and regulatory submissions.

Software and Training Sets for (Q)SAR Models

- An assembly of classification models for LLNA and Guinea Pig Maximization Test, Buehler test, Human Maximization Test, and Human repeat Insult Patch Test, as well as three categorical LLNA models, are used.
- The external set consists of 19 compounds, 14 sensitizers and 5 non-sensitizers for humans
- CASE Ultra (CU) v1.8.0.5 (MultiCASE, Inc.) software was used to build statistical and rule-based models.

Model Name	Version	System Level	Modeled Event	Model Description	Training Set Size
SKIN_SENS_LLNA	1.8.0.2	ORGAN	Activation of immune response	Skin Sensitization based on murine local lymph node (LLNA) assay	1821
SKIN_SENS_NON_LLNA	1.7.0.5	ORGAN	Allergic response	Guinea Pig Maximisation Test (GPMT), and Buehler test. Human Maximisation Test(HMT) and Human Repeat Insult Patch Test (HRIPT)	2000
SKIN_IRRITATION		ORGAN	Skin irritation	24h Draize skin test in rabbit	6505
SKIN_CARC	1.7.0.5	ORGANISM	Skin cancer	Carcinogenicity by skin application	1297
SKIN_CORROSION		ORGAN	Skin Corrosion	In-vivo Skin Corrosion	2051
LLNA_CAT2_STRONG	1.8.0.2	ORGAN	Activation of Immune Response	Strong sensitizers (LLNA EC3<1%)	383
LLNA_CAT3_MODERATE				Moderate and strong sensitizers (LLNA EC3<10%))	792
LLNA_CAT4_WEAK				Weak, Moderate and Strong sensitizers (LLNA EC3<100%)	891

Details on the external validation

- The initial set of known human sensitizers and non-sensitizers was combined from David A. Basketter et al (2014, DOI: 10.1097/DER.0000000000000003) and Vinicius M. Alves et al (2016, doi:10.1039/C6GC01836J)
- The set consisted of 127 unique chemical structures, 85 sensitizers and 42 non-sensitizers.
- An assembly of SKIN_SENS_NON_LLNA, SKIN_SENS_LLNA and 3 categorical LLNA models were used
- Out of 127 initial skin sensitizers, 103 were present in the SKIN_SENS_NON_LLNA model. Out of these, 61 human sensitizers and 15 human non-sensitizers were correctly labeled as Positive or Negative, with overall concordance 73.8%
- From the remaining 24 external compounds 5 inorganic salts were removed
- The final external set consists of 19 compounds, 14 sensitizers and 5 non-sensitizers

Results

- Coverage 94.74%
- Sensitivity 92.31%
- Specificity 80.00%
- Concordance 88.89%
- Pos accuracy 92.31%
- Neg accuracy 80.00%

Skin Sensitization Assessment Workflow

- Step 1. Test with SKIN_SENS_NON_LLNA. If predicted inconclusive or out of domain, go to Step 2
- Step 2. Test with SKIN_SENS_LLNA, accept the outcome as final.
- Step 3. Use LLNA_CAT2_STRONG, LLNA_CAT3_MODERATE and LLNA_CAT4_WEAK to assess the potency. All predicted in the Step 2 sensitizers are tested with LLNA_CAT2_STRONG, LLNA_CAT3_MODERATE and LLNA_CAT4_WEAK models. For each query compound the predicted ECOTOC category is derived from the most conservative prediction

Name	Registry #	Human sensitizer	LLNA_CAT2_STRONG	LLNA_CAT3_MODERATE	LLNA_CAT4_WEAK	SKIN_SENS_LLNA	SKIN_SENS_NON_LLNA	Predicted Sensitizer	Potency
Bacitracin	1405-87-4	yes	Positive	Positive	Out of Domain	Positive	**Positive**	**yes**	strong
Bisphenol A diglycidyl ether	1675-54-3	yes	Positive	Known Positive	Positive	Known Positive	**Positive**	**yes**	moderate
Squaric acid dibutylester	2892-62-8	yes	Inconclusive	Out of Domain	Inconclusive	**Positive**	Out of Domain	**yes**	no call
Quaternium-15	4080-31-3	yes	Inconclusive	Out of Domain	Out of Domain	Inconclusive	Out of Domain	no call	no call
Atranol	526-37-4	yes	Known Positive	Negative	Positive	**Known Positive**	Inconclusive	**yes**	strong
Diphencyclopropenone	886-38-4	yes	Known Positive	Negative	Out of Domain	**Known Positive**	Out of Domain	**yes**	strong
2-Aminophenol	95-55-6	yes	Known Positive	Positive	Positive	**Known Positive**	Inconclusive	**yes**	strong
Butylene glycol	107-88-0	no	Negative	Negative	Negative	Negative	**Negative**	**no**	non-sens
Cetylpyridinium chloride	123-03-5	no	**Positive**	Positive	Positive	Positive	**Negative**	**no**	strong
Triclosan	3380-34-5	no	**Positive**	Positive	Inconclusive	Positive	**Positive**	**yes**	strong
Cetrimide	57-09-0	no	Known Negative	Known Negative	Known Negative	Known Negative	**Negative**	**no**	non-sens

Conclusions

- We present a highly interpretable and well performing suite of Categorical LLNA models designed to assess the ECETOC category of skin sensitizers
- The models can be used standalone or as a part of MultiCASE SkinEye suite of statistical models.
- The highly predictive workflow to assess the risk and potency of human skin sensitizers is suggested as an initial concept.

Sources of Data

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- ECHA Database, https://echa.europa.eu via eChemPortal https://www.echemportal.org
- NICEATM LLNA Database, ICCVAM Evaluations of the Murine Local Lymph Node Assay (LLNA) https://ntp.niehs.nih.gov/whatwestudy/niceatm/test-method-evaluations/immunotoxicity/llna/index.html#NICEATM-LLNA-Database