Evaluation of Potency Prediction by SENS-IS Assay, Using Weight of Evidence-based Potency Category as a Benchmark

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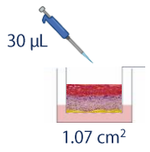
Introduction

Potency determination of potential skin sensitizers in humans is crucial. The information on potency dictates the amount of a material that can be safely used, without inducing skin sensitization. **SENS-IS is a non-animal test method based on a reconstructed human skin model**, that was developed to predict the hazard and potency of potential skin sensitizers. In this work, the performance of the SENS-IS assay in potency prediction for 174 materials was evaluated. To that end, the potency determined by collectively considering all well-established test data, including human, animal, *in chemico*, *in vitro*, and *in silico* data was used as the benchmark. Based on this weight of evidence approach, the dataset was composed of 5, 19, 34, 54, and 38 extreme, strong, moderate, weak, and very weak sensitizers, respectively, as well as 24 non-sensitizers. SENS-IS precisely predicted the potency category for 46% of the materials, and it closely approximated the potency category for another 39%. Our analysis showed that SENS-IS provides a good approximation of the skin sensitization potency.

Materials and Methods

SENS-IS Assay and its prediction model (Cottrez et al., 2016)



EpiSkin™-Large

RT-PCR

17 ARE genes → **7+** Sensitizer

21 SENS-IS genes → **7+** Sensitizer

24 Irritation genes → **21+** Too irritating to conclude

Weight of Evidence-based (WoE) potency category as benchmark data: (Na et al., 2022)

Main Drivers

- **Human data (CNIH, HMT)***: NOELs, LOELs
- **Local lymph node assay data**: EC3
- ***in silico* data**: OECD Toolbox, OASIS TIMESS
- ***in chemico* & *in vitro* data**: DPRA, KeratinoSens, h-CLAT

Supporting factors

- **Other *in vivo* data**: Guinea pig studies
- **Exposure data**: Creme-RIFM aggregate exposure model
- **Diagnostic patch test data**

→ **WoE Potency Category**

*CNIH: Confirmation of no induction in humans; HMT: human maximization test

Results/Conclusion

SENS-IS provided a good estimation of WoE potency category

SENS-IS approximated the WoE potency category for 85% (46% exact match, 39% approximate) of the 174 materials evaluated.

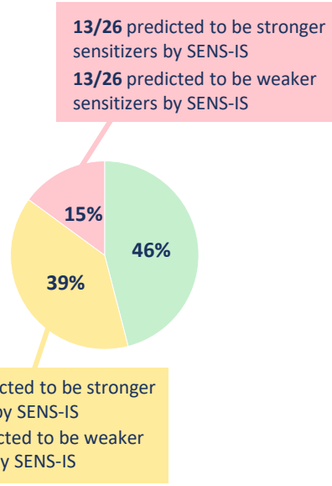
WoE \ SENS-IS	Extreme	Strong	Moderate	Weak	Very Weak	NS
Extreme	2	2	0	1	0	0
Strong	1	12	5	1	0	0
Moderate	0	5	18	6	3	2
Weak	1	1	14	27	5	6
Very Weak	0	0	7	17	2	12
NS	0	0	0	4	1	19

NS: Non sensitizer

Exact match: same potency category

Approximate: one potency category difference

Off: 2+ potency categories difference

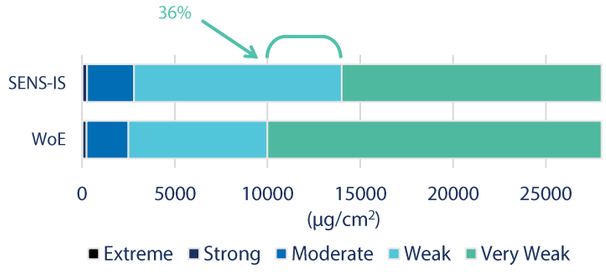


Concentrations used in SENS-IS assay can be converted to dose per skin area

A better alignment of potency comparison could be achieved if dose per skin area values are used.

Potency category	Concentration leading to Pos. (%)	SENS-IS Range (µg/cm²)	Human Potency Range (µg/cm²)
Extreme	0.1%	<28	<25
Strong	1%	28 - 2 0	25-500
Moderate	10%	280 – 2803	500-2500
Weak	50%	2803 – 14000	2500-10000
Very Weak	100%	14000 - 28000	>10000
NS	Negative	Negative	Negative

(Adapted from Api et al., 2017)



References

Cottrez F, Boitel E, Ourlin JC, et al. SENS-IS, a 3D reconstituted epidermis based model for quantifying chemical sensitization potency: Reproducibility and predictivity results from an inter-laboratory study. *Toxicol In Vitro. Apr 2016;32:248-60.*
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Api AM, Parakhia R, O'Brien D, Basketter DA. Fragrances Categorized According to Relative Human Skin Sensitization Potency. *Dermatitis. Sep/Oct 2017;28(5):299-307.*

Questions? Contact Mihwa Na (mna@rifm.org)
And check out the full manuscript in RTP.