

An Interim Report of the RIFM AAT Dermal Sensitization Research Program

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Human Health Scientist**



Overview

- **Brief Overview of RIFM**
- **Long Range Research Plan**
- **RIFM AAT Dermal Sensitization Research Program**
 - **Human Potency Categorization**
 - **Correlation between animal vs. human data**
 - ***In chemico* and *in vitro* research program**
 - **Collaborations to enhance *in silico* models**
 - **Dermal Sensitization Threshold (DST)**

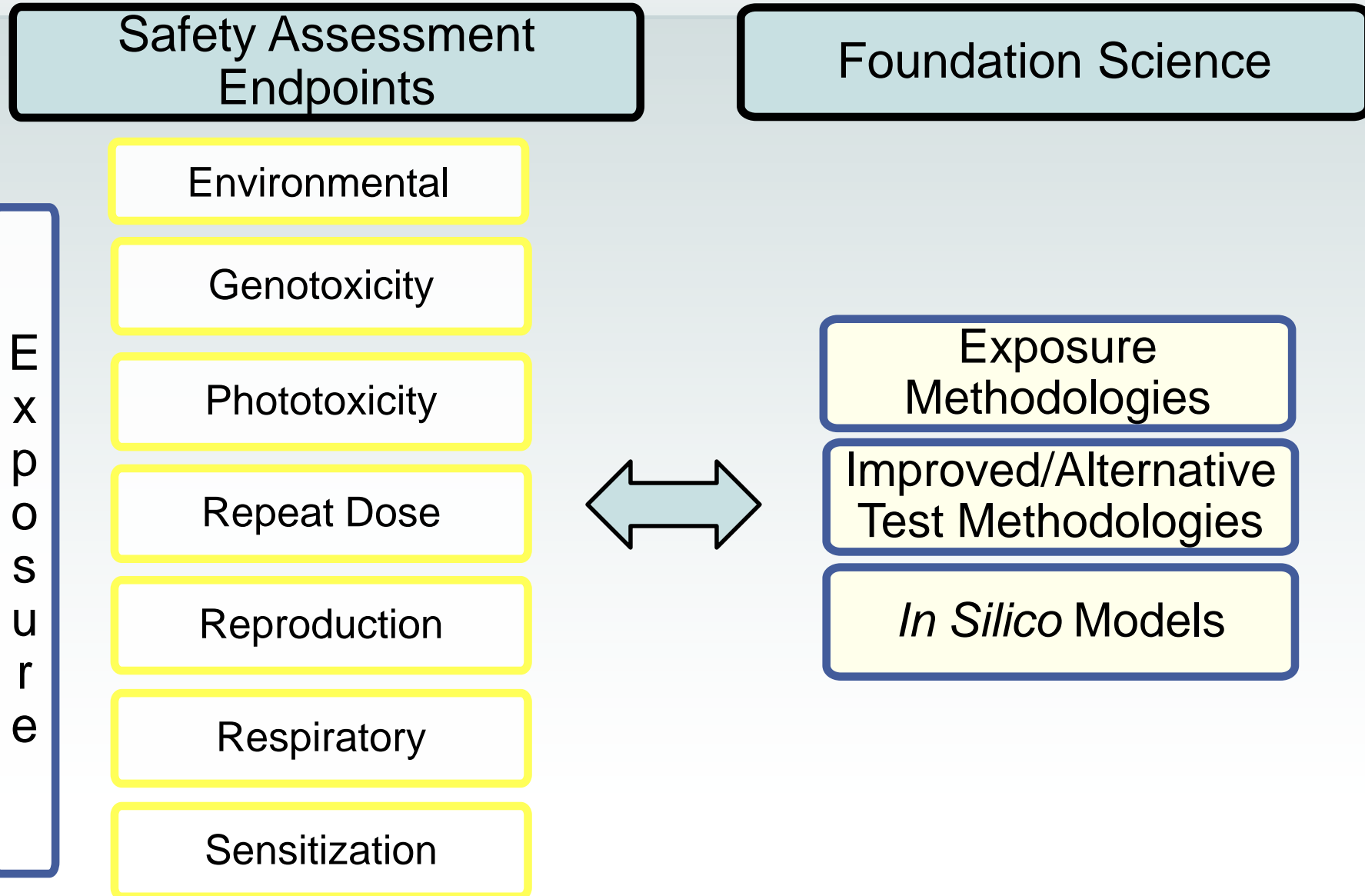


RIFM's Mission Statements defines the organization's role as a research institution:

- **Engage in research and evaluation of fragrance materials through an independent Expert Panel**
- **Determine safety in use for fragrance materials**
- **Gather, analyze, and publish scientific information**
- **Distribute scientific data and safety assessment judgments to RIFM members, industry associations and other interested parties**
- **Maintain an active dialogue with official international agencies**
- **Take input from our stakeholders (e.g., Core Teams, Expert Panel, external collaborators) with a focus on research that:**
 - ◆ **Improves the SA Process**
 - ◆ **Addresses other endpoints**
 - ◆ **Supports sustainability efforts**



RIFM Safety Evaluation Process



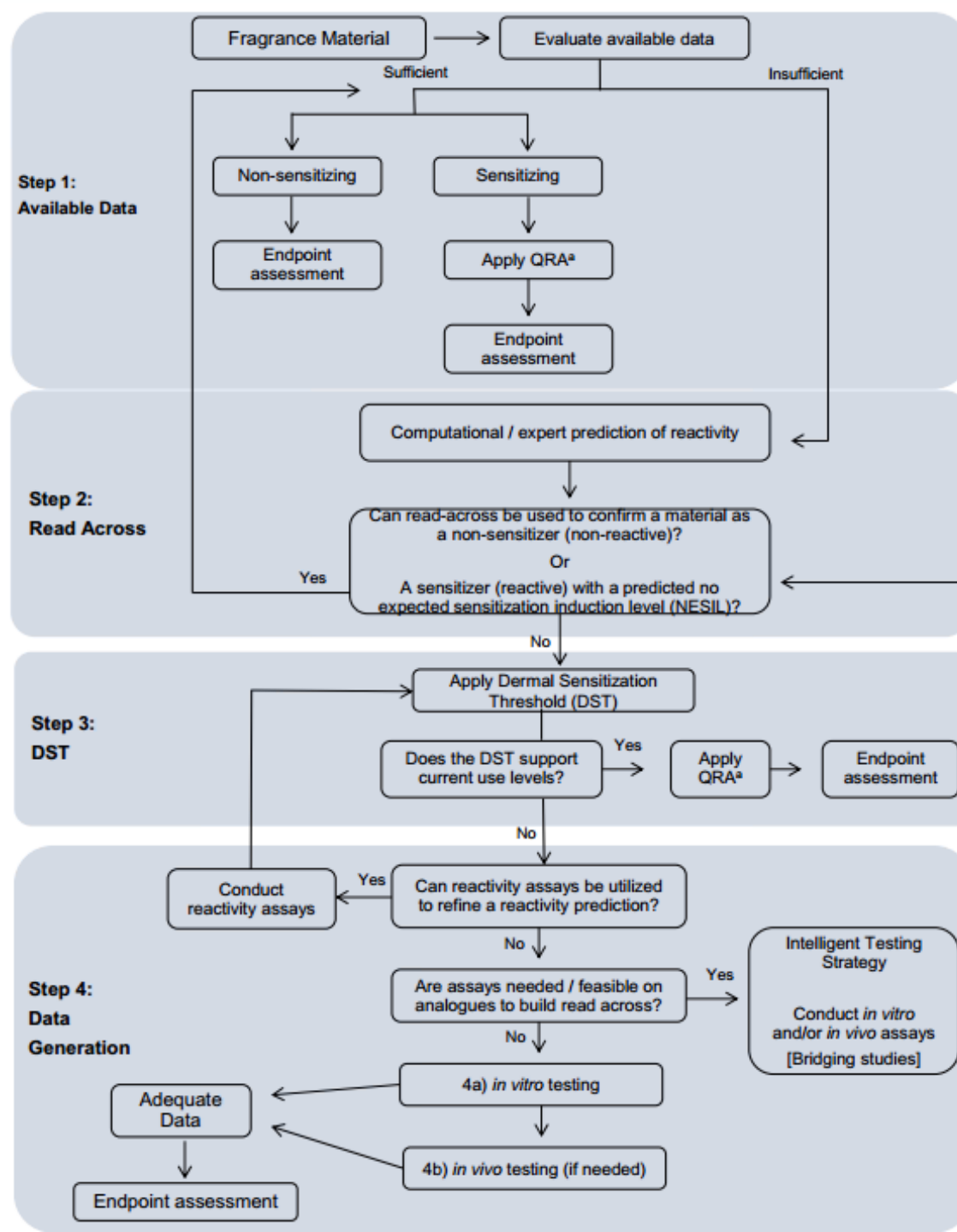


Step 1: Evaluate available data

Step 2: Read across

Step 3: Apply the Dermal Sensitization Threshold (DST)

Step 4: Generate data





Long Range Research Plan: Human Health Sciences

Projects	Notes	Improve the SA Process				Addressing other endpoints	Status
		Method Development or Validation	Increasing Output	Safety In Use/Improve Criteria Document	Improving/advancing Criteria Document		
Dermal Sensitization	In vitro methods & use of data	X	X	X	X		On-going
	LLNA vs. Human	X		X	X		1 st paper published; 2 nd in preparation
	In Silico Methods	X	X	X	X		On-going
Exposure	Enhance Model	X		X	X	X	On-going



Long Range Research Plan: Human Health Sciences

Projects	Notes	Improve the SA Process				Addressing other endpoints	Status
		Method Development or Validation	Increasing Output	Safety In Use/Improve Criteria Document	Improving/advancing Criteria Document		
Genotoxicity	BlueScreen™	X	X	X	X		Manuscript in prep.
	Bio-informatics		X		X		On-going
	Reconstructed Skin MNT Skin COMET	X		X	X		On-going
	In Silico	X	X	X	X		Planned
	In Ovo Models	X		X	X		Planned
	High Throughput Screening for mech of action	X		X	X		Planned



Long Range Research Plan: Human Health Sciences

Projects	Notes	Improve the SA Process				Addressing other endpoints	Status
		Method Development or Validation	Increasing Output	Safety In Use/Improve Criteria Document	Improving/advancing Criteria Document		
TTC	DST (Sensitization), TTC Repeat dose, Reproduction Toxicity, Inhalation	X	X	X	X		On-going
	Internal Oral TTC values:	X	X	X	X		Planned
	Internal Dermal TTC values:	X	X	X	X		Future



Long Range Research Plan: Human Health Sciences

Projects	Notes	Improve the SA Process				Addressing other endpoints	Status
		Method Development or Validation	Increasing Output	Safety In Use/Improve Criteria Document	Improving/advancing Criteria Document		
Repeat Dose, Reproduction Toxicity	Structural alerts	X	X	X	X		Future
	Adverse Outcome Pathway	X	X		X	X	Future
Developmental Toxicity	In vitro methods	X	X	X	X		Exploring methods



Long Range Research Plan: Human Health Sciences

Projects	Notes	Improve the SA Process				Addressing other endpoints	Status
		Method Development or Validation	Increasing Output	Safety In Use/Improve Criteria Document	Improving/advancing Criteria Document		
Respiratory	In silico/In chemico	X	X	X	X		On-going
	U Rochester in vitro systems to characterize respiratory irritants and sensitizers.	X	X	X	X		On-going
	Human lung slice	X	X	X	X		Completed; manuscript in prep.
	Characterizing Initiating Events for Respiratory Sensitization	X	X	X	X		Planned



Long Range Research Plan: Human Health Sciences

Projects	Notes	Improve the SA Process				Addressing other endpoints	Status
		Method Development or Validation	Increasing Output	Safety In Use/Improve Criteria Document	Improving/advancing Criteria Document		
Phototoxicity	Compare test methods Strategic for Safety Assessment Process	X	X	X	X		On-going
Photoallergy	Investigate use of in vitro dermal sensitization assays to test for photoallergy	X	X	X	X		Planned



Long Range Research Plan: Current Environmental Projects

Projects	Notes	Improve the SA Process				Addressing other endpoints	Supporting sustainability efforts	Status
		Method Development or Validation	Increasing Output	Global Applicability of the RIFM Framework	Improving/advancing the RIFM Framework			
Bioaccumulation assessment of NCSs	Stockholm University Phase 1 completed/ Phase 2: 2016-2018	X				X		On Time/On Budget First paper published
in vitro metabolism assessment of fragrance ingredients for bioaccumulation	KJ Scientific/ Wildlife International Phase 1a: 2016/ Phase 1b: 2016-2017	X				X		Phase 1 nearly complete/On Budget
Fate and Effects of personal care ingredients in temperate and subtropical sediments	Roskilde University/ Wageningen University 2013-2018			X		X	X	On Time/On Budget First paper published



Long Range Research Plan: Current Environmental Projects

Projects	Improve the SA Process				Addressing other endpoints	Supporting sustainability efforts	Status
	Method Development or Validation	Increasing Output	Global Applicability of the RIFM Framework	Improving/advancing the RIFM Framework			
Retrospective Framework Analysis		X		X			On hold/Resources redirected to SA effort
Strategy For Fish Ecotoxicity Testing	X					X	Continue to support HESI efforts/Other activities on hold: resources redirected to SA effort
NCS SA: Research and Testing Needs	X			X			Approach under development. Completion planned 4Q 2017.
Exposure/Effects in D&E Regions			X			X	2018 Workshop in planning to further define next phase and linked with Changes to Exposure Modeling
Bioaccumulation: Terrestrial Organisms					X		First data review at this months ETF meeting
Changes to Exposure Modeling			X	X		X	See note above

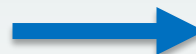


Dermal Sensitization Research Program



Analyses of Human Data

- Categorization of fragrances according to their relative skin sensitization potency
 - All available human data used (HRIPT, HMT, DPT)



- A manuscript of all RIFM generated HRIPT data is in progress!
 - HRIPTs are **only** conducted to confirm a no effect level



LLNA vs. Human Data

681

Cutaneous and Ocular Toxicology <http://informahealthcare.com/cot>
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Cutan Ocul Toxicol, Early Online: 1-5
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RESEARCH ARTICLE

Correlation between experimental human and murine skin sensitization induction thresholds

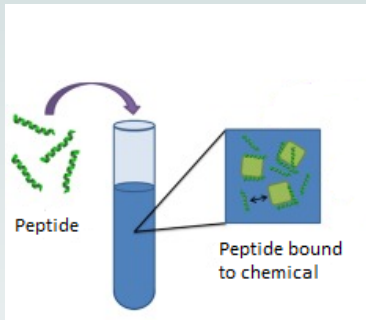
Anne Marie Api¹, David Basketter², and Jon Lalko¹

¹Research Institute for Fragrance Materials, Woodcliff Lake, NJ, USA and ²DABMEB Consultancy Ltd, Sharnbrook, Bedfordshire, UK

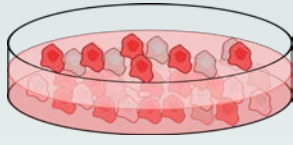


Part 2 in Progress

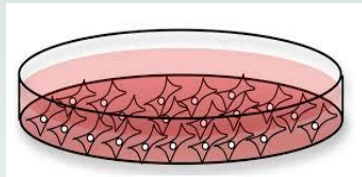
In Chemico and In Vitro Methods



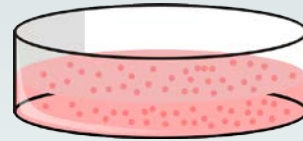
DPRA



KeratinoSens™



h-CLAT



U-Sens™



PPRA



Sens-IS

2013/14

2014

2015/16

~50 RIFM Fragrance Ingredients in Collaboration with Cosmetics Europe

~50 RIFM Fragrance Ingredients



- **Extend the applicability domain of the Bayesian network using RIFM data**
 - **Pilot underway**
 - ◆ **LLNA, HRIPT and RIFM generated DPRA, KeratinoSens™, h-CLAT and SENS-IS data**
 - ◆ **PPRA and U-Sens data to be considered for inclusion upon completion**



Research article

A quantitative *in silico* model for predicting skin sensitization using a nearest neighbours approach within expert-derived structure–activity alert spaces

Steven J. Canipa, Martyn L. Chilton, Rachel Hemingway, Donna S. Macmillan✉, Alun Myden, Jeffrey P. Plante, Rachael E. Tennant, Jonathan D. Vessey, Thomas Steger-Hartmann, Janet Gould, Jedd Hillegass, Sylvain Etter, Benjamin P. C. Smith, Angela White, Paul Sterchele, Ann De Smedt, Devin O'Brien, Rahul Parakhia, ... [See fewer authors](#) ^

First published: 28 February 2017 | <https://doi.org/10.1002/jat.3448>

Regulatory Toxicology and Pharmacology

Volume 95, June 2018, Pages 227-235



Making reliable negative predictions of human skin sensitisation using an *in silico* fragmentation approach

Martyn L. Chilton ^a ✉, Donna S. Macmillan ^a, Thomas Steger-Hartmann ^b, Jedd Hillegass ^c, Phillip Bellion ^d, Anna Vuorinen ^d, Sylvain Etter ^e, Benjamin P.C. Smith ^f, Angela White ^g, Paul Sterchele ^h, Ann De Smedt ⁱ, Milica Glogovac ^j, Susanne Glowienke ^j, Devin O'Brien ^k, Rahul Parakhia ^k

[Show more](#)



DERMAL SENSITIZATION THRESHOLD (DST)

- **Identifies an exposure below which there is a low concern for the induction of sensitization**
- **RIFM collaborated with R Safford and D Roberts to extend DST for reactive chemicals and identify high potency chemicals**
 - Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015b. Extension of the Dermal Sensitisation Threshold (DST) approach to incorporate chemicals classified as reactive. *Regulatory Toxicology and Pharmacology*, 72, 694-701.
 - Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of High Potency Category Chemicals for which the Dermal Sensitisation Threshold (DST) approach should not be applied. *Regulatory Toxicology and Pharmacology*, 72, 683-693



- **Supported integration of rules to identify high potency category chemicals for which DST should not be applied into TIMES-SS software**
 - **Resulted in the release of version 2.28.1**
- **Working to refine/strengthen DST with Dr. Safford by expanding the dataset**



Thank you!



Woodcliff Lake, New Jersey, USA



Applicability Domain of the LLNA



Chemical applicability domain of the Local Lymph Node Assay (LLNA) for skin sensitization potency. Part 1. Underlying physical organic chemistry principles and the extent to which they are represented in the LLNA validation dataset

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^c DuPont Haskell Global Centers, 1090 Elkton Road, Newark, DE 19711, USA

^d The University of Tennessee, College of Veterinary, 2407 River Drive, Knoxville, TN 37996, USA

Chemical applicability domain of the Local Lymph Node Assay (LLNA) for skin sensitisation potency. Part 2. The biological variability of the murine Local Lymph Node Assay (LLNA) for skin sensitisation[☆]

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^b Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, United States

^c Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedford, MK44 1LQ, United Kingdom

Chemical applicability domain of the Local Lymph Node Assay (LLNA) for skin sensitisation potency. Part 3. Apparent discrepancies between LLNA and GPMT sensitisation potential: False positives or differences in sensitivity?[☆]

David W. Roberts ^{a,*}, Terry W. Schultz ^b, Anne Marie Api ^c

^a School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, L3 3AF, United Kingdom

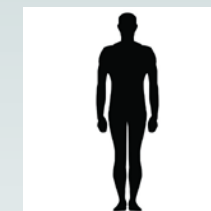
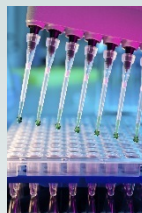
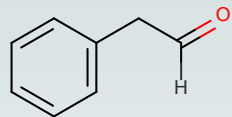
^b The University of Tennessee, College of Veterinary, 2407 River Drive, Knoxville, TN, 37996, USA

^c Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA





Information Sources



Phys-chem, Reactivity, Absorption & Metabolism, In silico tools	In chemico In vitro studies	Mouse and Guinea pig Studies	Human data
<u>OECD QSAR Toolbox</u>	<u>DPRA</u> (KE 1)	<u>Local Lymph Node Assay</u> (KE 4)	<u>Human Repeated Insult Patch Test (HRIPT)</u> (AO)
TIMES-SS DEREK NEXUS	<u>KeratiNoSens™</u> , <u>LuSens™</u> <u>hCLAT</u> , <u>U-Sens™</u> (KE 2 + 3)	<u>GP Maximization Test</u> <u>GP Buehler Test</u> (AO)	
Toxtree, SAM	PPRA, Sens-IS®	GP: OET, CET, FCAT, DT	H-Maximization test
		Mouse ear swelling test	Diagnostic Patch tests