Bristol-Myers Squibb

UTILIZATION OF DEREK NEXUS DERMAL SENSITIZATION PREDICTIONS FOR HAZARD ASSESSMENT AT BRISTOL-MYERS SQUIBB

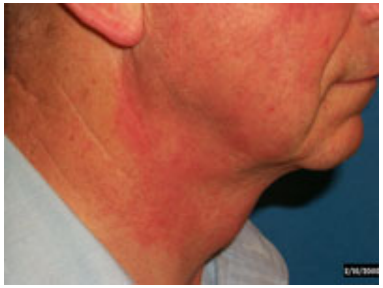
Jedd Hillegass, Ph.D., DABT
Bristol-Myers Squibb, Drug Safety Evaluation
International Collaborative Group Meeting
March 16, 2017

Overview

- Dermal sensitization background and predictive tools currently utilized
- Use of the Derek Nexus *in silico* model data for hazard assessment purposes at Bristol-Myers Squibb (BMS)
- Derek Nexus' alert-based model and outcome of data sharing on predictivity within the BMS chemical workspace
- Derek Nexus' EC3 model and performance within the BMS chemical workspace
- Conclusions and future directions

Dermal Sensitization

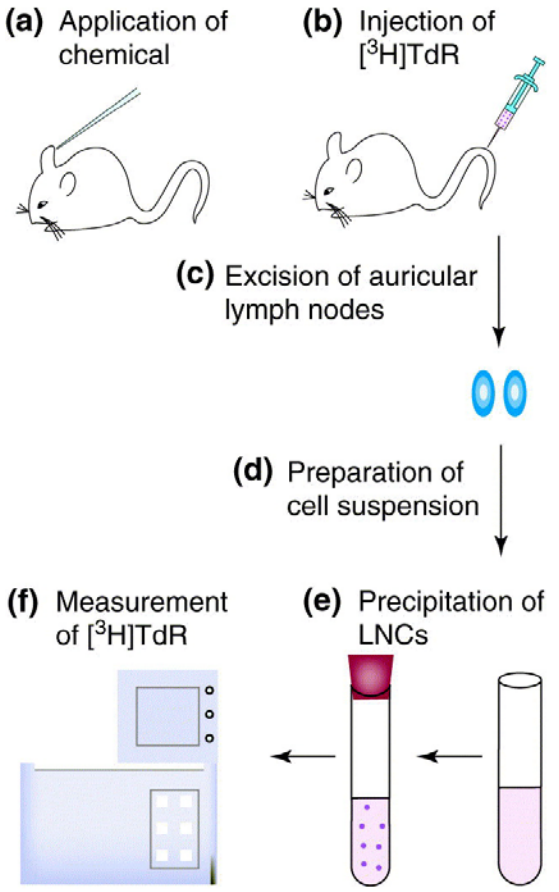
- A dermal sensitizer is a chemical that, following repeated exposure, causes subjects to develop contact allergic dermatitis / delayed-type skin hypersensitivity reactions
- Dermal sensitization reactions are one of the most commonly encountered occupational diseases



- Available tools for predicting dermal sensitization potential:
  - *In silico* models (Derek Nexus, OECD QSAR Toolbox, Case Ultra, TIMES-SS)
  - *In vitro* assays (DPRA, KeratinoSens™, hCLAT)
  - *In vivo* assays (LLNA, GPMT)

Current Tools – *In Vivo*

- Local Lymph Node Assay (LLNA)
  - Assay in mice which is the most widely accepted *in vivo* method for assessing dermal sensitization
  - Advantages: Provides potency prediction, good positive predictivity of dermal sensitization potential
  - Disadvantages: Cost, turnaround time, significant compound requirements, over-predicts weak positives
  - Predictivity of LLNA*:
    - Accuracy: 72-77%
    - Sensitivity (TP rate): 96%



** TRENDS in Pharmacological Sciences

** Source: ICCVAM, National Institute of Environmental Health Sciences, NIH Publication no. 99-4494*
*** Source: Basketter et al. 2001. Trends Pharmacol Sci 22(6): 264-265*

Current Tools – *In Silico*

- Derek Nexus (Version 5.0.1)
  - An expert rule-based system for various toxicological endpoints
    - Skin sensitization, mutagenicity, chromosome damage, teratogenicity, eye/skin/respiratory irritation, respiratory sensitization, phototoxicity, photoallergenicity, etc.
  - Alerts are limited by the amount of publicly available data and the number of companies contributing proprietary data to the dataset
  - Advantages: Immediate readout, capable of predicting multiple endpoints, no animals/compound required
  - Disadvantages: Originally observed poor predictability for skin sensitization within the BMS chemical workspace
    - False positive predictions may result in additional costs by triggering unnecessary *in vivo* testing
    - Incorrect/false negative predictions may result in inaccurate hazard identification
  - Recent data sharing exercises have significantly improved predictivity

Exposure Control Banding (ECB)

- Sets requirements for handling compounds in an occupational setting
- Correlated to an airborne concentration (µg/m^3) of compound that workers may be exposed to daily (8-10 hrs) for years without experiencing an adverse health effect

Sensitization Potential	EC3* Value	BMS ECB	Range (µg/m^3)
Weak	>1%	2	100 - 1000
Moderate	0.1% ≤ EC3 ≤ 1%	3	10 - <100
Potent	0.01% ≤ EC3 < 0.1%	4	1 - <10
Extremely Potent	<0.01%	5	0.1 - <1
~ In silico ~			
Negative	---	3	10 - <100
Positive	---	4	1 - <10

**EC3 value represents the effective concentration of test material needed to elicit a 3-fold increase in lymph node cell proliferation in treatment mice compared to control mice*

ECB and Surface Wipe Tests

- ECB is also correlated with a surface wipe test limit, which is defined as the maximum amount of material that can contaminate a laboratory surface without eliciting a dermal sensitization response
- Calculation of the surface wipe test limit is based on the EC3 value obtained in the LLNA and incorporates an additional safety factor (minimally 5x)
- Assumes that the air concentration in the workplace (driven by the ECB) controls to the surface limit

Sensitization Potential	EC3* Value	BMS ECB	Range (µg/m^3)	Surface Wipe Test Limit
Weak	>1%	2	100 - 1000	Not required
Moderate	0.1% ≤ EC3 ≤ 1%	3	10 - <100	500 µg/100 cm^2
Potent	0.01% ≤ EC3 < 0.1%	4	1 - <10	50 µg/100 cm^2
Extremely Potent	<0.01%	5	0.1 - <1	5 µg/100 cm^2

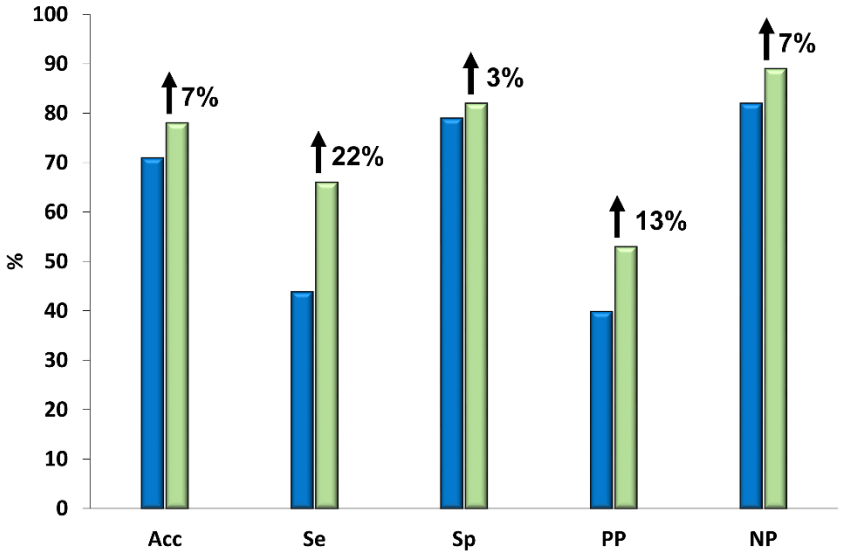
Current BMS Approach – Alert-Based Model

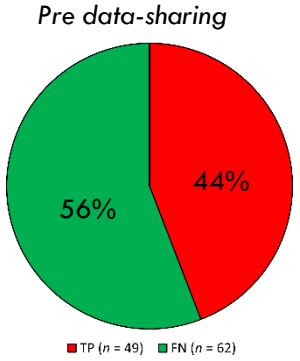
- Early Screening Evaluation (Tier I – Preclinical development)
  - *In silico* analysis of entire API synthesis scheme
    - Positive *in silico* readout for dermal sensitization = ECB 4
    - Negative *in silico* readout for dermal sensitization = ECB 3
  - Conduct reduced LLNA (1% concentration only) on API and intermediates of concern
    - Assign an ECB based partly on sensitization potency (other factors include *in silico* mutagenicity readout and pharmacological activity)

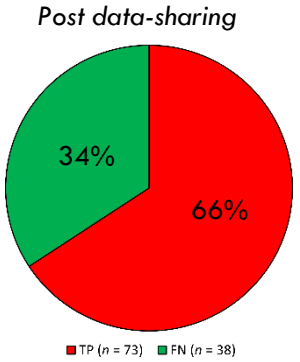
- Full Evaluation (Tier II – Phase II clinical development)
  - Conduct full LLNA on all intermediates
  - Alter ECB if necessary based on EC3 value obtained

Data Sharing Results

- Lhasa Limited was provided access to a BMS proprietary data set containing 467 compounds (355 LLNA neg, 1 GPMT neg, and 111 LLNA pos)
- Results
  - Six new alerts were generated and five established alerts were modified, thereby increasing the chemical workspace coverage
  - Overall predictivity improved appreciably:







Macmillan et al, 2016 (SOT Poster Abstract 2629)

Derek Nexus' EC3 Model

Research article

Journal of AppliedToxicology

Received: 9 November 2016, Revised: 4 January 2017, Accepted: 4 January 2017 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/jat.3448

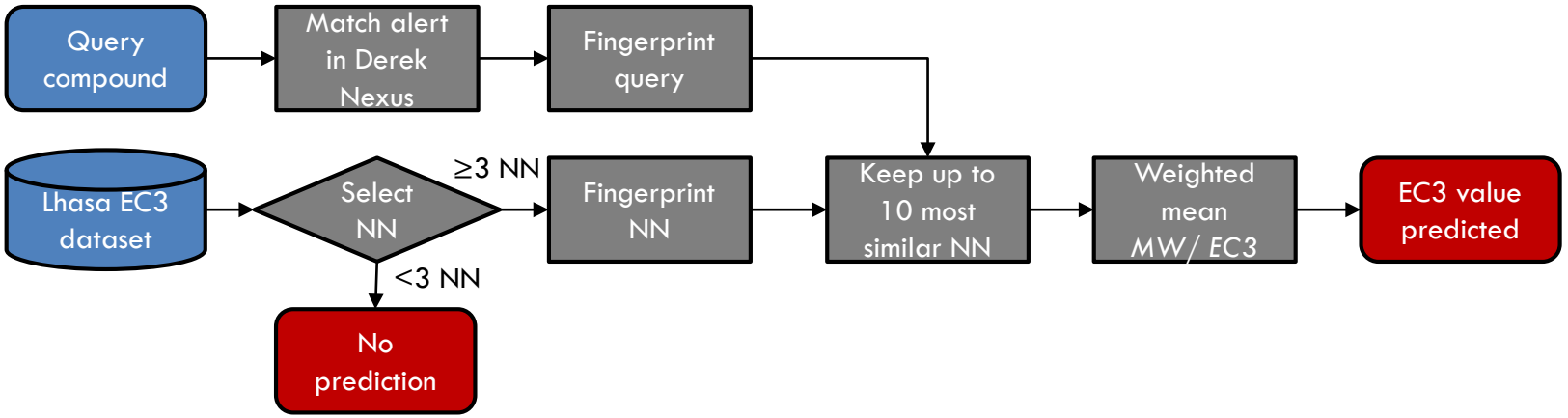
A quantitative *in silico* model for predicting skin sensitization using a nearest neighbours approach within expert-derived structure–activity alert spaces

Steven J. Canipa[a], Martyn L. Chilton[a], Rachel Hemingway[a], Donna S. Macmillan[a]*, Alun Myden[a], Jeffrey P. Plante[a], Rachael E. Tennant[a], Jonathan D. Vessey[a], Thomas Steger-Hartmann[b], Janet Gould[c], Jedd Hillegass[c], Sylvain Etter[d], Benjamin P. C. Smith[e], Angela White[f], Paul Sterchele[g], Ann De Smedt[h], Devin O'Brien[i] and Rahul Parakhia[i]

Affiliations: (a) Lhasa Limited, (b) Bayer Pharma, (c) Bristol-Myers Squibb, (d) Firmenich S.A., (e) Firmenich Inc., (f) GlaxoSmithKline, (g) International Flavors & Fragrances, (h) Janssen Research and Development, (i) RIFM

Derek Nexus' EC3 Model

- Released as a component of Derek Nexus v.5.0.1 (Jan 2016)
- k-Nearest Neighbors model using weighted average scaled by the Tanimoto distance (statistical similarity) between the query and dataset compounds
- Model rules:
  - A valid neighbor is one which fires the same dermal sensitization structural alert
  - Minimum number of neighbors required is three, otherwise no EC3 prediction is given
  - Up to 10 most similar neighbors are considered
  - Predicted EC3 value is the weighted average of all the valid neighbors



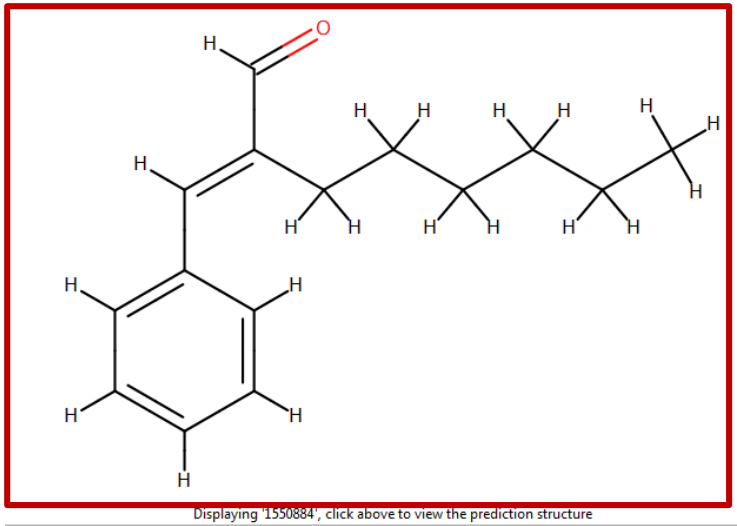
EC3 Model Example

Hexyl cinnamic aldehyde (CAS# 101-86-0)

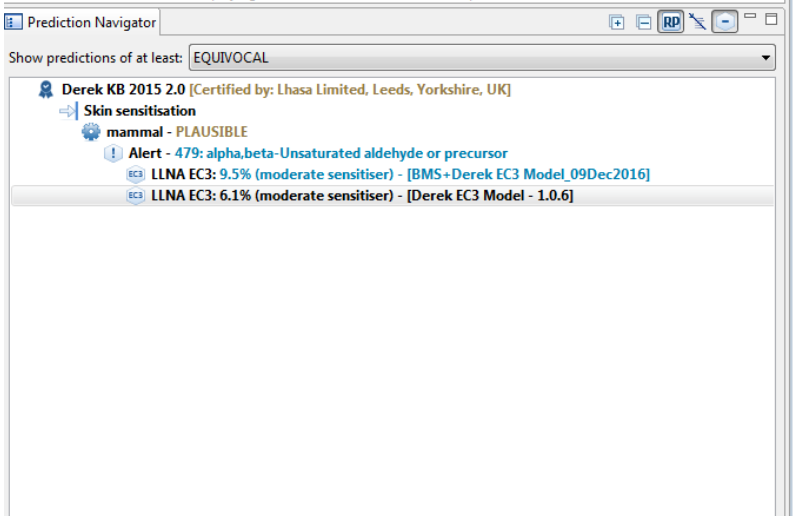
OECD recommended positive control for LLNA

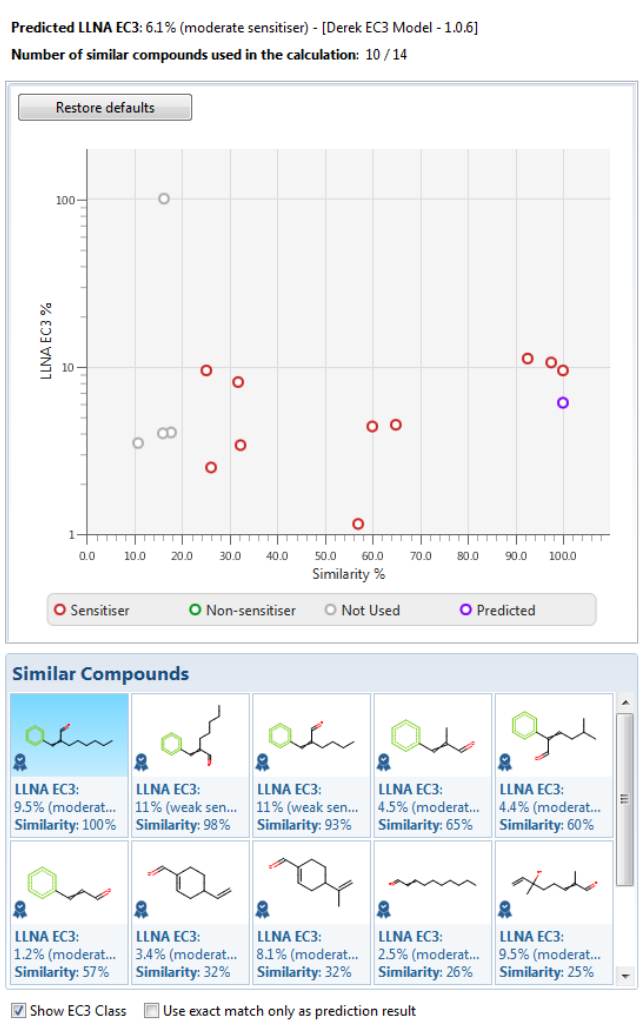
Mean EC3: 9.5%

LLNA: Positive
GPMT: Positive
Human: Positive



Displaying '1550884', click above to view the prediction structure





EC3 Model Performance Parameters

ECETOC Classification		BMS Handling Practices	
EC3 (%)	**Category**	**ECB**	**Wipe Test**
≥ 10	Weak	2	Not required
≥ 1 - < 10	Moderate	2	Not required
≥ 0.1 - < 1	Strong	3	500 µg/100 cm^2
< 0.1	Extreme	4 (<0.1) 5 (<0.01)	50 µg/100 cm^2 5 µg/100 cm^2

GHS Classification	
EC3 (%)	**Category**
≤ 2	1A – Strong sensitizer
>2	1B – Other sensitizer

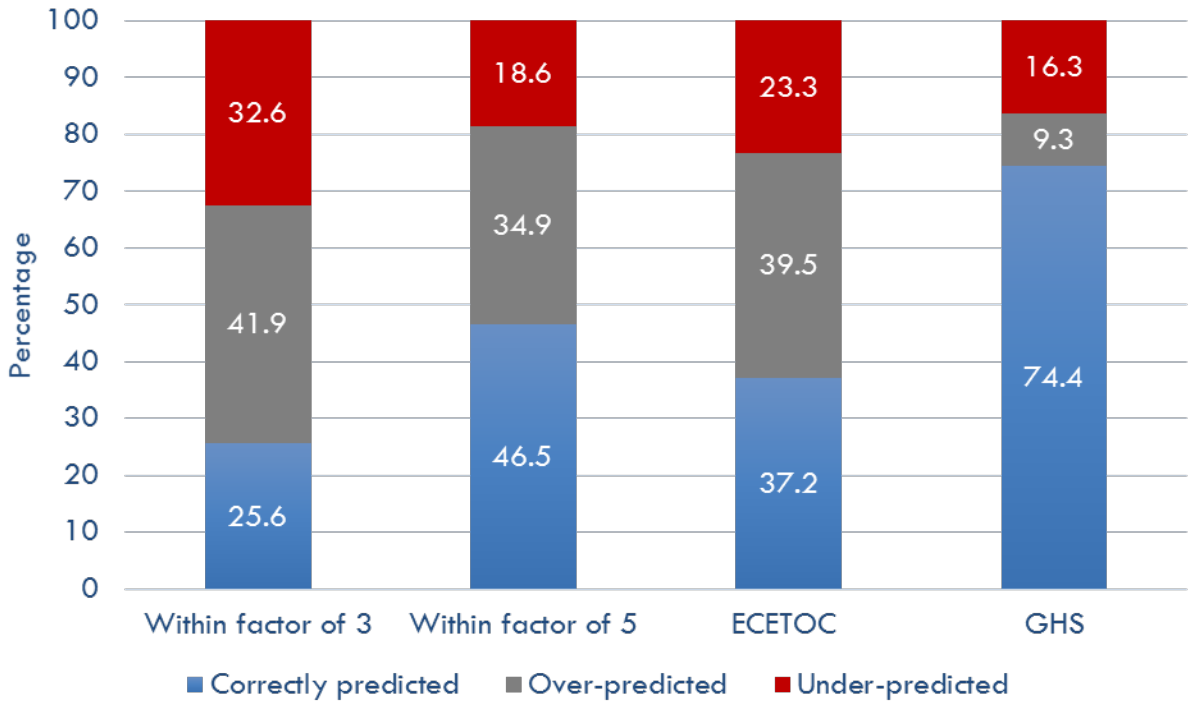
- European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) has assigned specific categories based on the EC3 value determined in the LLNA
- Globally Harmonized System (GHS) classification typically communicated on hazard communication documents is driven by the EC3 value determined in the LLNA

EC3 Model Performance

BMS cmpds donated	Unique cmpds w/ LLNA / EC3 data	Unique cmpds w/ DX alert	Unique cmpds w/ DX alert AND EC3 prediction	EC3 3-fold	EC3 5-fold	ECETOC	GHS	Prediction (N)
473	116	125	43	11	20	16	32	Correct
				18	15	17	4	Over
				14	8	10	7	Under

Model Descriptors:

Nexus v.2.1.0
Derek Nexus v.5.0.1
Derek EC3 Model v.1.0.5



Current BMS Approach - EC3 Model

- As a standalone application, the current Derek Nexus EC3 model does not yet cover enough of BMS' chemical workspace to reliably drive BMS banding decisions

- The Derek Nexus EC3 model could contribute to a weight-of-evidence approach for justifying additional *in silico* modeling and/or accelerated *in vivo* testing

- As a standalone application, the current Derek Nexus EC3 model can be used to drive GHS classification for dermal sensitization

Conclusions / Future Directions

- Data sharing exercises have significantly improved the predictivity of the Derek Nexus software (both the alert-based and EC3 models)
- Use of the alert-based model only is conservative in that ANY positive prediction results in an ECB 4 classification; however, use of the EC3 model as a standalone application for banding is not being pursued at this time given the current performance within the BMS chemical workspace
- BMS is currently exploring the possibility of utilizing a BMS-specific knowledge base alongside the default Lhasa knowledge base to improve the predictivity of the EC3 model
- BMS anticipates that ongoing data sharing exercises will continue to improve the predictive performance of the alert-based and EC3 models in the BMS chemical workspace

Acknowledgements

Bristol-Myers Squibb

- Gene Schulze
- Janet Gould
- Jessica Graham
- Wendy Luo

Lhasa Limited

- Donna Macmillan
- Martyn Chilton
- Steven Canipa
- Laura Wirpsza