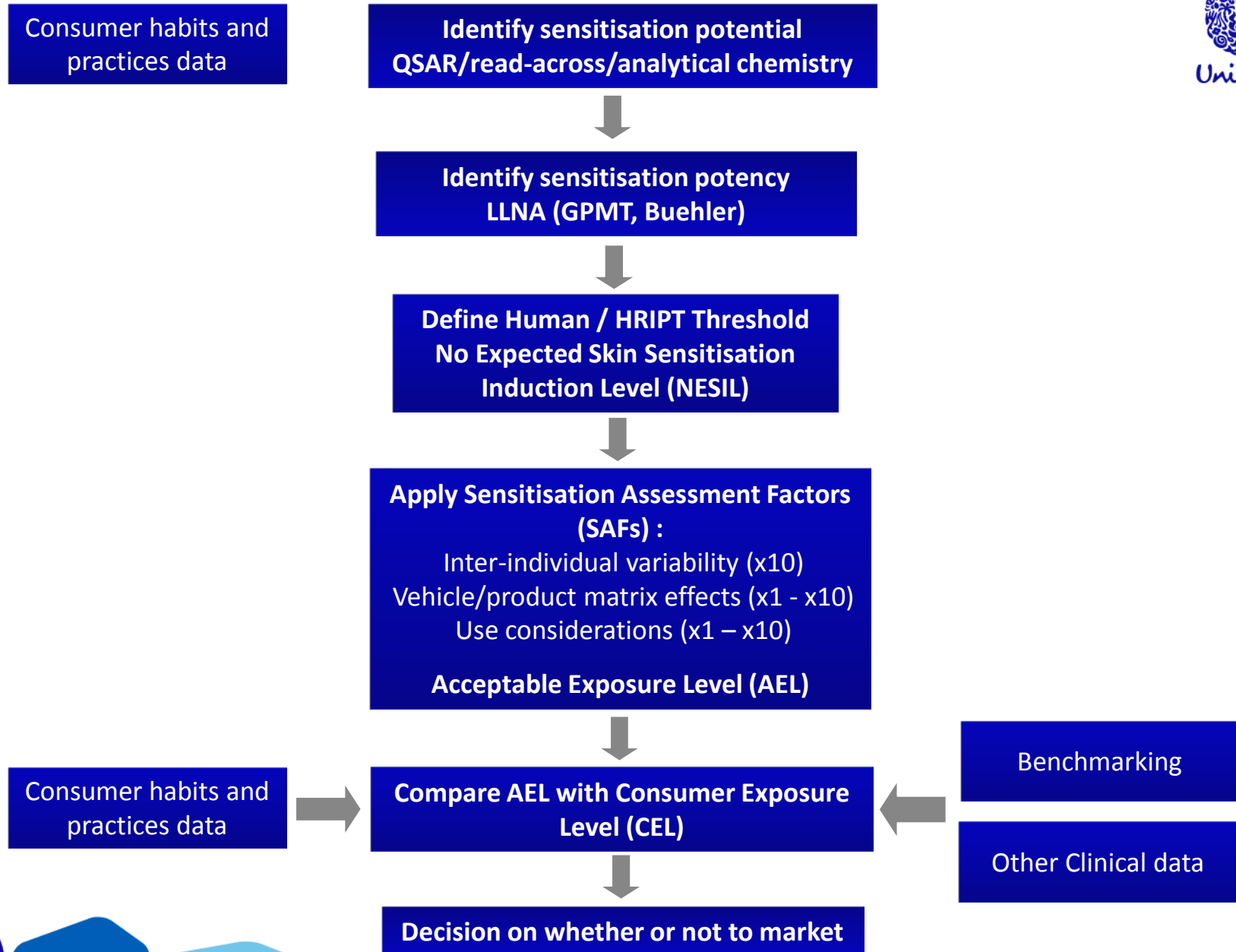# CASE STUDY PRESENTATION:
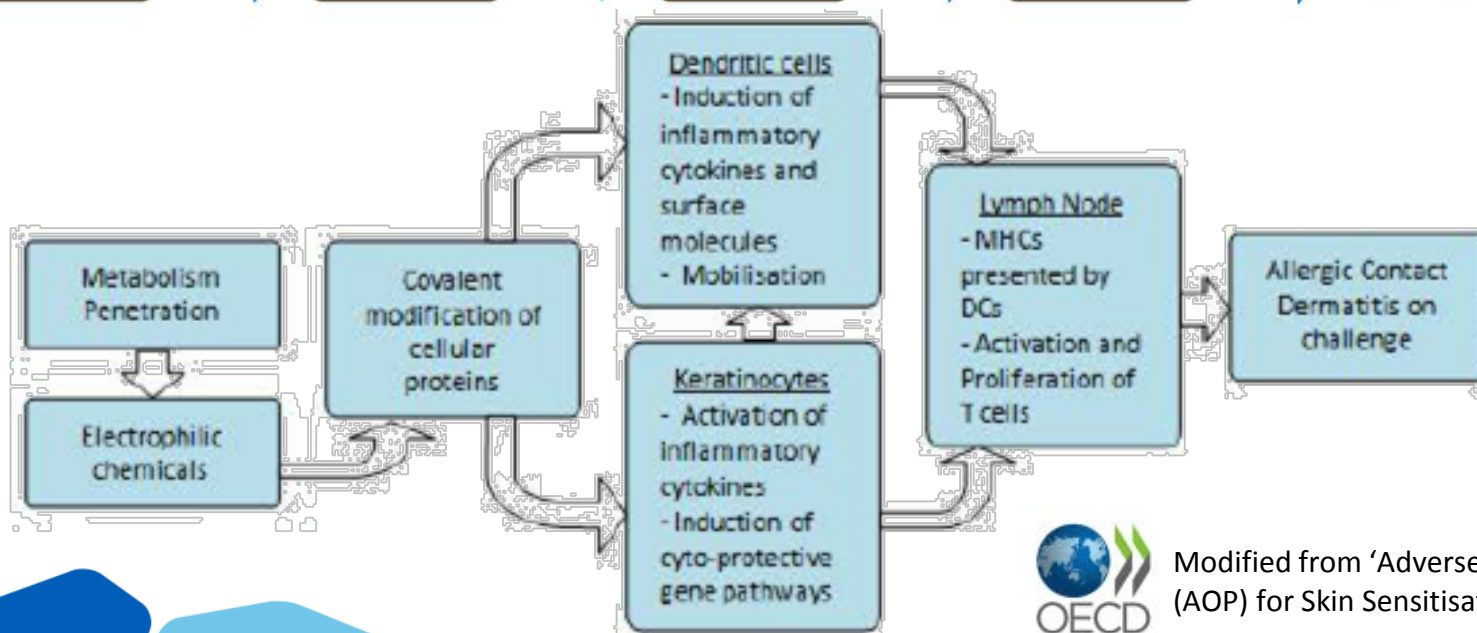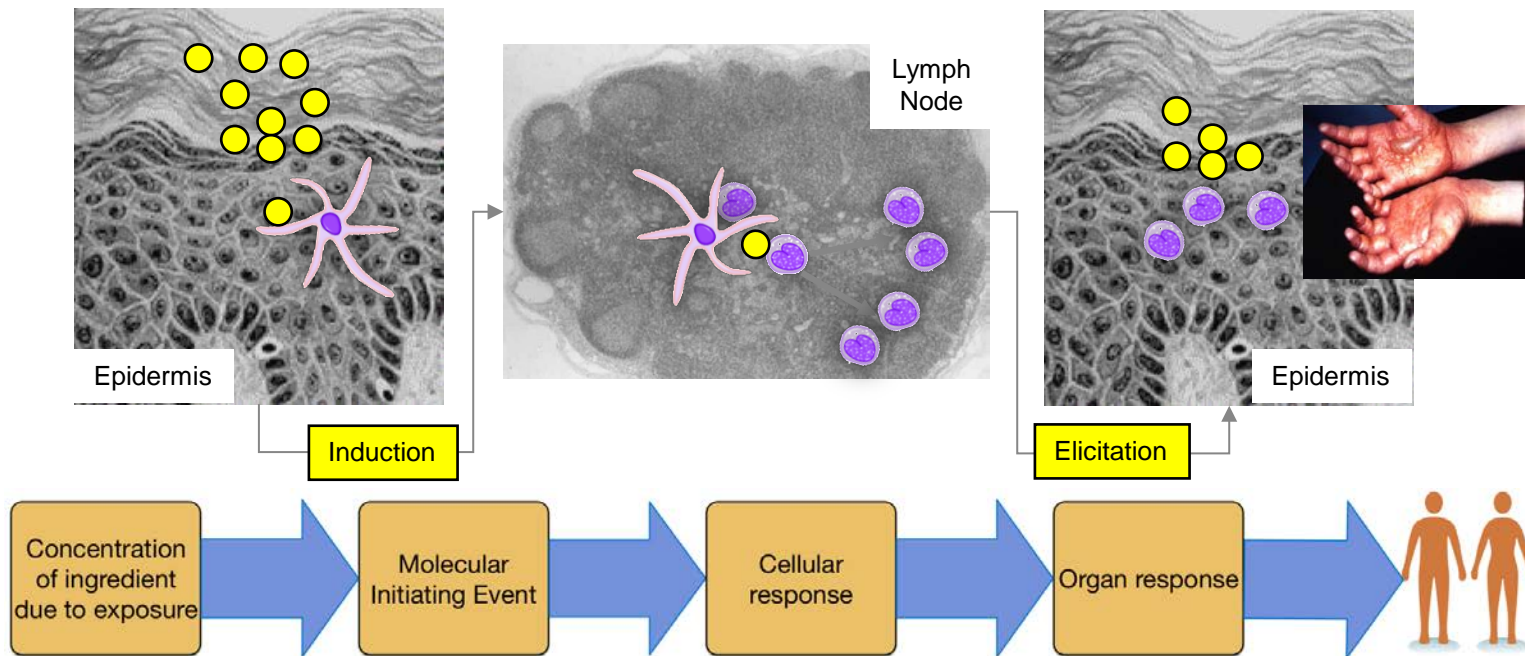# A QUANTITATIVE AOP FOR SKIN SENSITISATION RISK ASSESSMENT

GAVIN MAXWELL, CATHERINE CLAPP, RICHARD CUBBERLEY, SERAYA DHADRA, NIKKI GELLATLY, STEPHEN GLAVIN, SARAH HADFIELD, SANDRINE JACQUOILLEOT, AMELIA JARMAN, IAN JOWSEY, SUE LOVELL, JACK MAYNE, CRAIG MOORE, RUTH PENDLINGTON , JULIETTE PICKLES, JOE REYNOLDS. OUARDA SAIB, DAVID SHEFFIELD, RICHARD STARK, WENDY SIMPSON, VICKI SUMMERFIELD. DAWEI TANG, SAM WINDEBANK & CAMERON MACKAY

SAFETY & ENVIRONMENTAL ASSURANCE CENTRE (SEAC), UNILEVER R&D

TRADITIONAL SKIN SENSITISATION RISK ASSESSMENT

Consumer habits and practices data

Identify sensitisation potential QSAR/read-across/analytical chemistry

Identify sensitisation potency LLNA (GPMT, Buehler)

Define Human / HRIPT Threshold No Expected Skin Sensitisation Induction Level (NESIL)

Apply Sensitisation Assessment Factors (SAFs) :
Inter-individual variability (x10)
Vehicle/product matrix effects (x1 - x10)
Use considerations (x1 – x10)

Acceptable Exposure Level (AEL)

Consumer habits and practices data

Compare AEL with Consumer Exposure Level (CEL)

Benchmarking

Other Clinical data
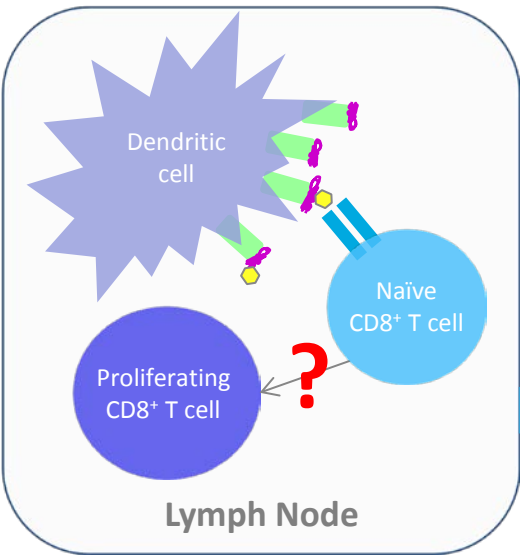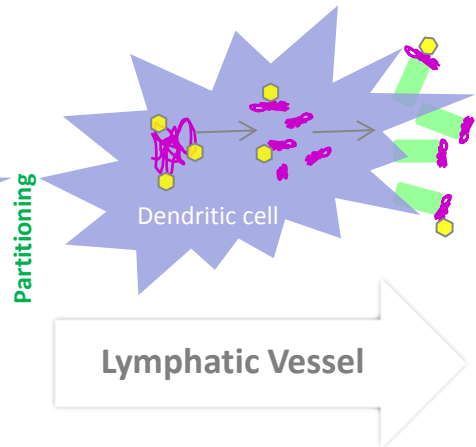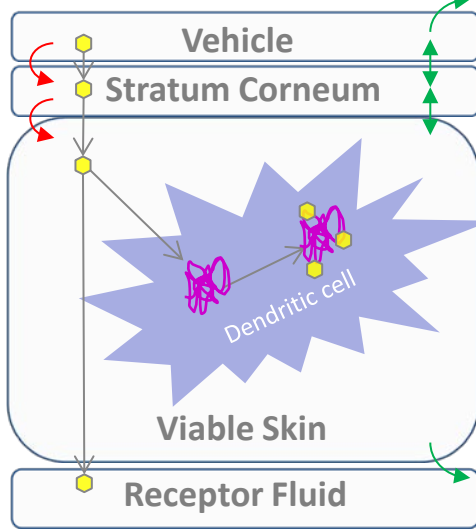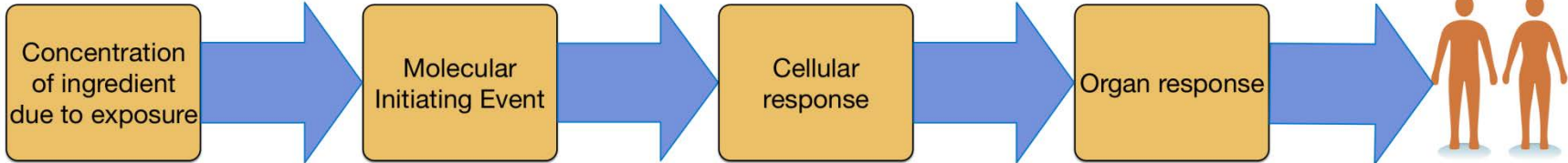
Decision on whether or not to market

NEW SKIN SENSITISATION RISK ASSESSMENT PARADIGM?

Modified from 'Adverse Outcome Pathway (AOP) for Skin Sensitisation', OECD

DEVELOP A MATHEMATICAL MODEL OF ALLERGIC CONTACT DERMATITIS TO ENABLE RISK ASSESSMENT DECISION-MAKING FOR NEW CHEMICALS
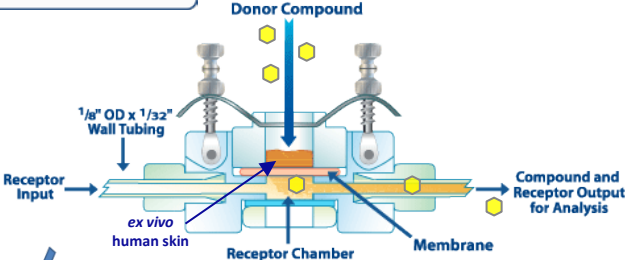
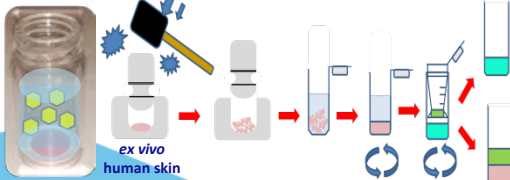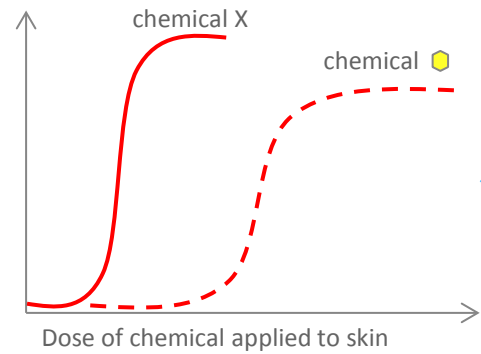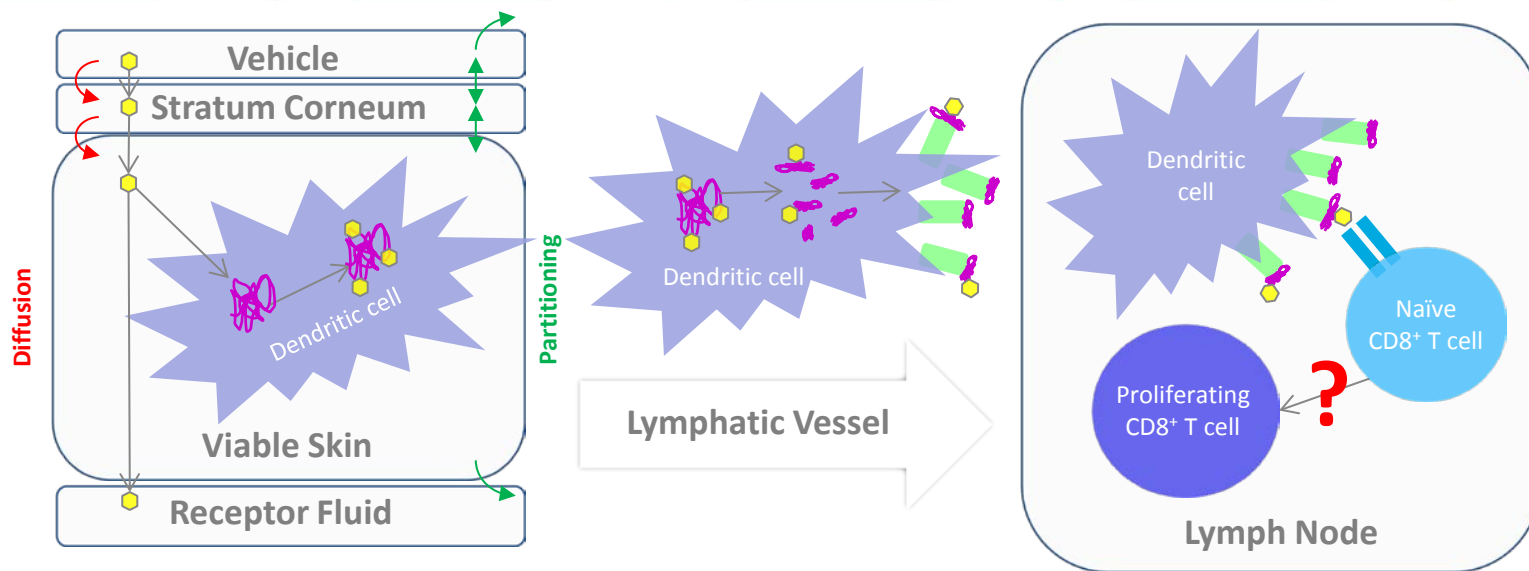# DNCB CASE STUDY – BENCHMARK MODEL PREDICTION USING DATA FROM FRIEDMANN *ET AL.* 1983

MODELLING SKIN BIOAVAILABILITY OF EXPERIMENTAL SENSITISER 2,4-DI-NITRO CHLOROBENZENE (DNCB)

Skin Bioavailability
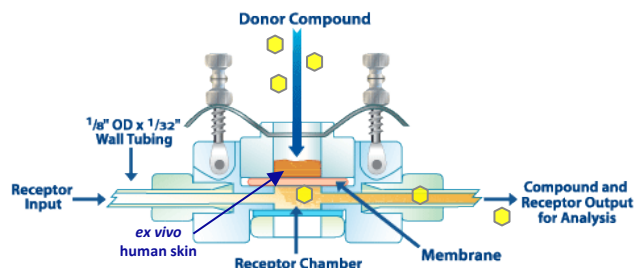
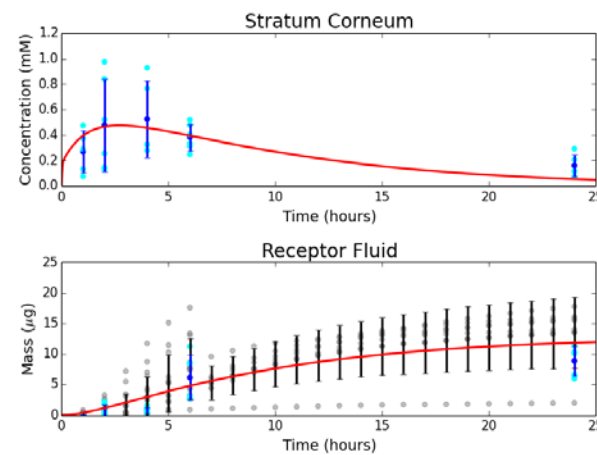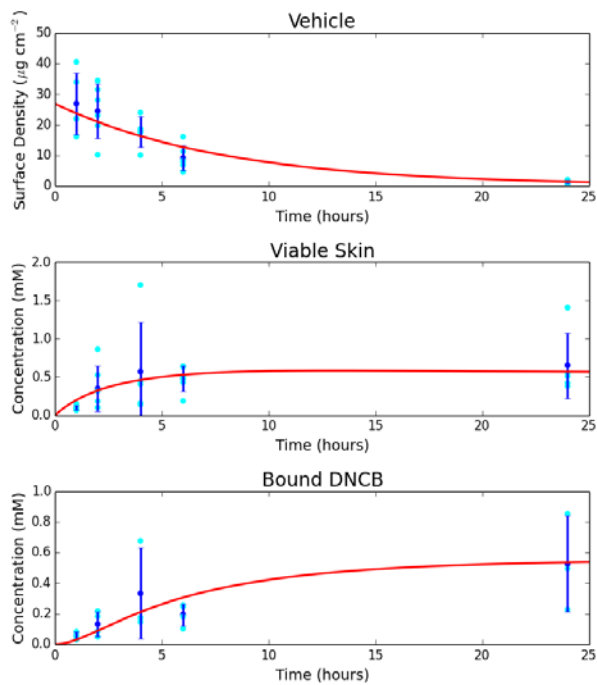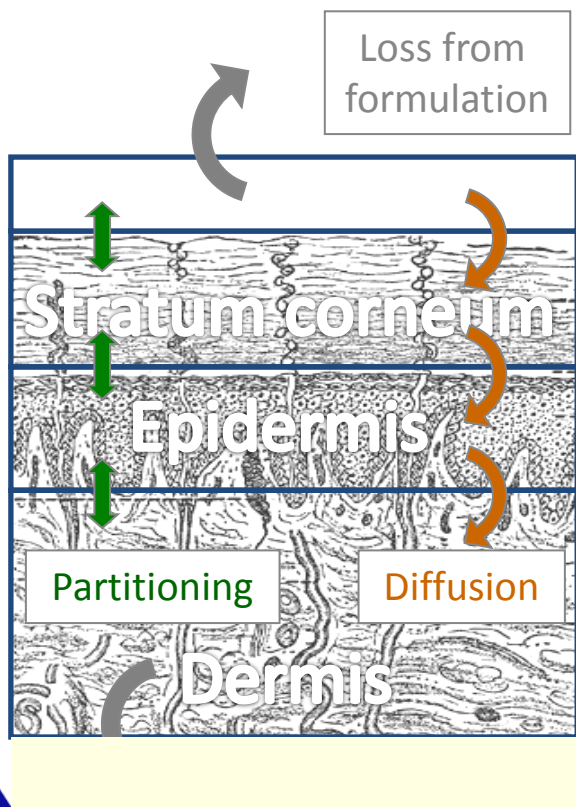| Exposure Scenario	*in vitro* skin pen
Dose	38.25 µg/cm^2
Vehicle Volume	20 µL
Surface area	0.64 cm^2

Loss from formulation

Stratum corneum

Epidermis

Dermis

Partitioning   Diffusion

Loss from skin

Estimation of Bioavailability in Skin - based on OECD Test Guideline 428

- DNCB & ex vivo human skin - Pendlington et al 2008 Cutan. Ocul. Toxicol. 27. 283-94.
- Penetration system modelled and partitioning and diffusion rates determined by fitting - Davies et al 2011 Toxicol. Sci. 119, 308-18

MODELLING OF SKIN PROTEIN HAPTENATION → SKIN DENDRITIC CELL ANTIGEN PROCESSING, PRESENTATION & MIGRATION TO DRAINING LYMPH NODE
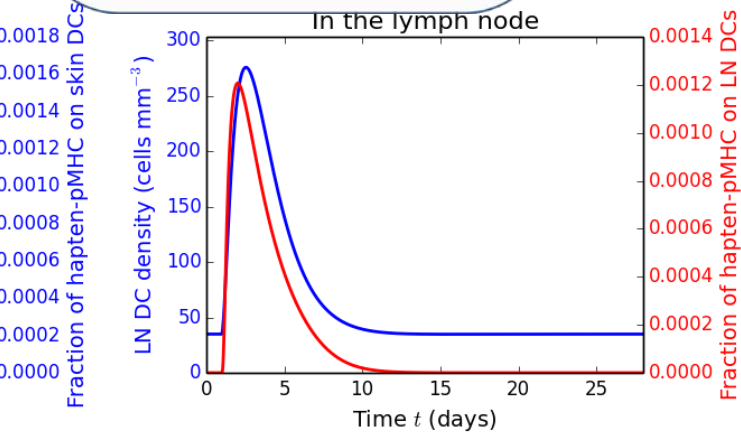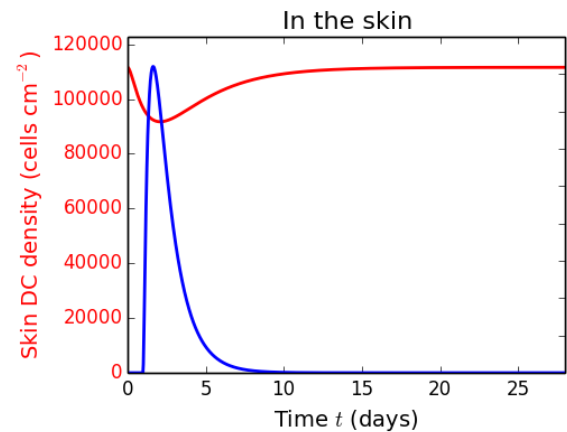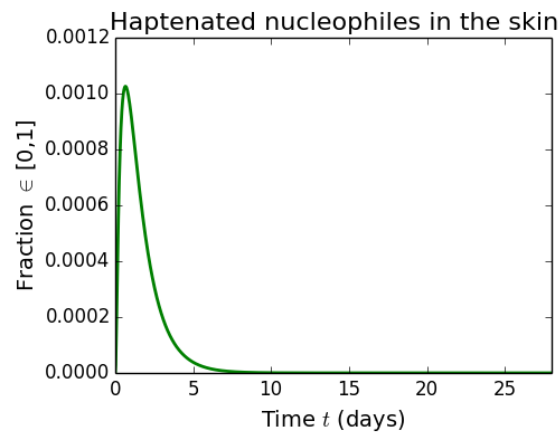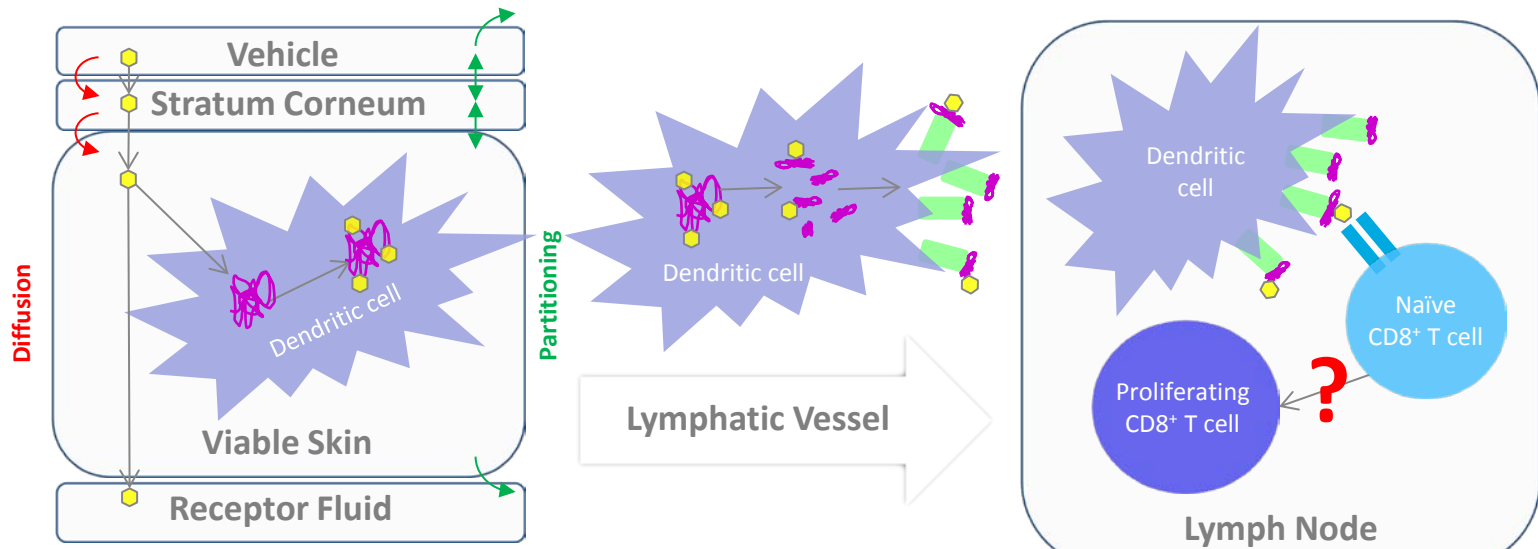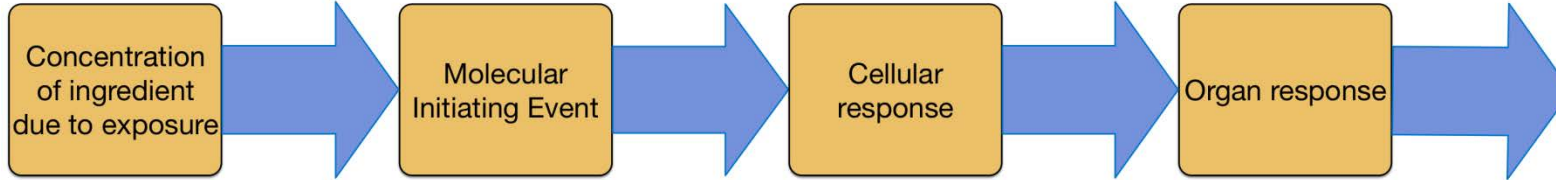
PREDICTING THRESHOLD OF T CELL ACTIVATION VIA MODELLING OF DC: T CELL IMMUNE SYNAPSE
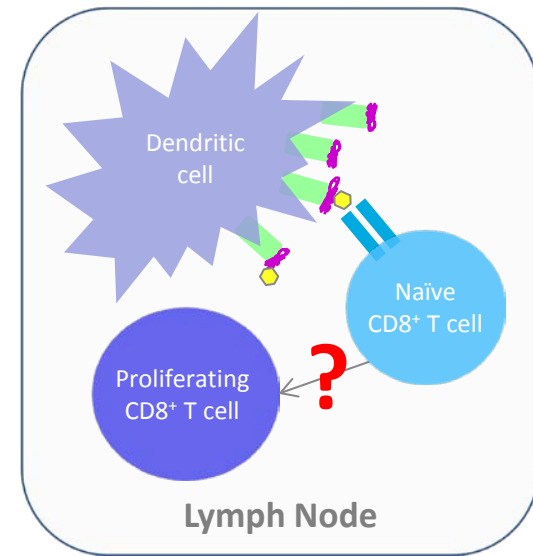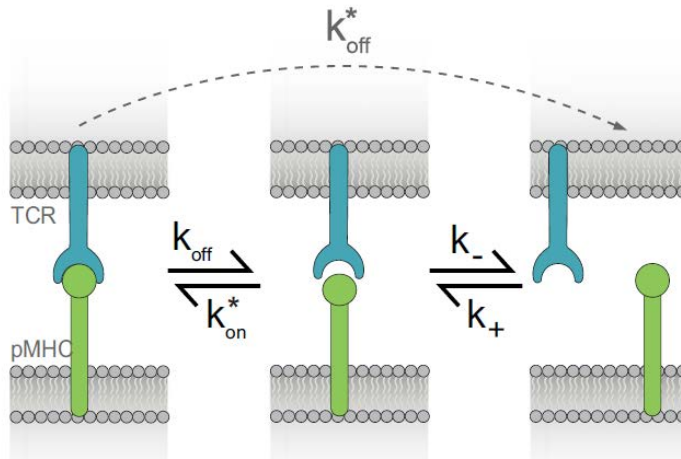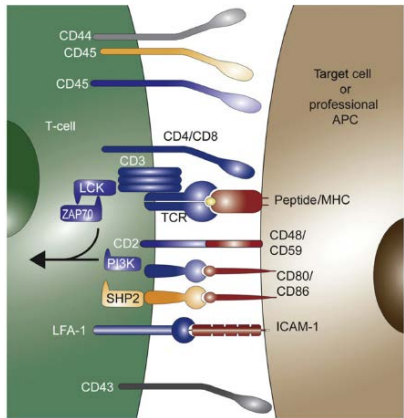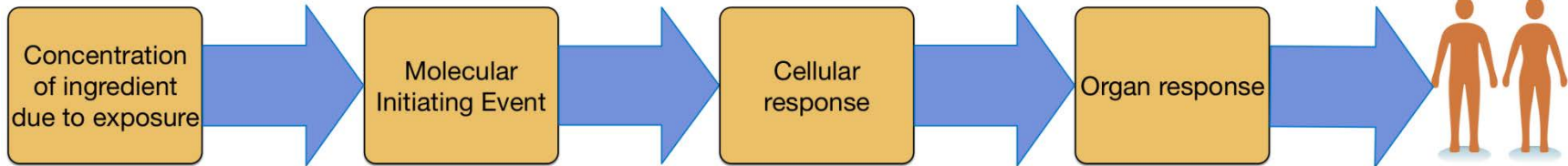
Explore effect of pMHC surface density and k_{on}/k_{off} on probability of T-cell triggering with the available models (Zarnitsyna & Zhu, 2012). Simulations generated using 'confinement time' model of Dushek, et al, 2009.
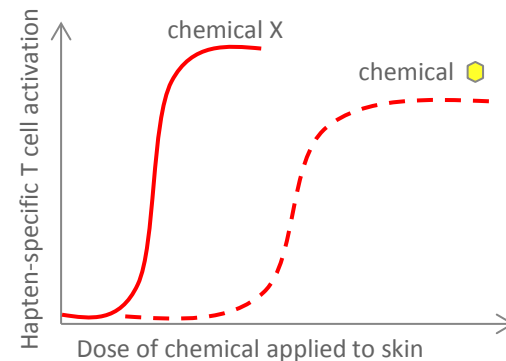
DNCB CASE STUDY – MODEL OUTPUT & CLINICAL DATA

Clin. exp. Immunol. (1983) **53**, 709–715.

Quantitative relationships between sensitizing dose of DNCB and reactivity in normal subjects

P. S. FRIEDMANN, CELIA MOSS, S. SHUSTER & JUDY M. SIMPSON* *Department of Dermatology and *Department of Medical Statistics, University of Newcastle upon Tyne, Newcastle upon Tyne, UK.*

Friedmann *et al* 1983

- Single exposure to DNCB
- 7.1cm^2 volar forearm
- 100µL acetone vehicle

Sensitisation assessed by challenge with DNCB 4 weeks after application

Prediction of maximum immune synapse rate in the 4 weeks following application
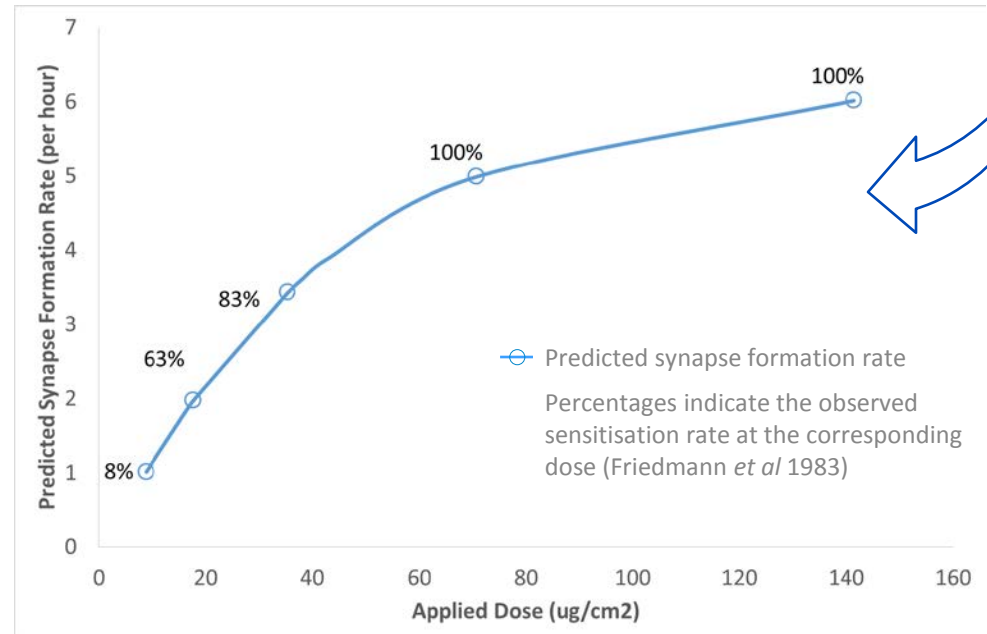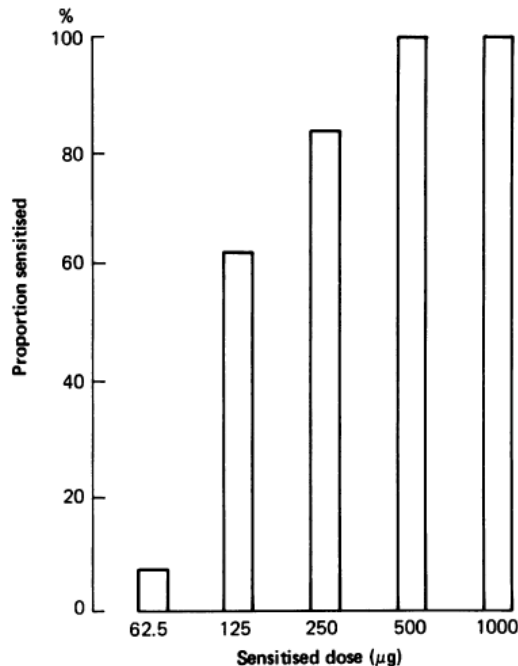
DNCB CASE STUDY – MODEL OUTPUT & CLINICAL DATA

REVIEW ARTICLE   DOI 10.1111/J.1365-2133.2007.08162.x

The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans
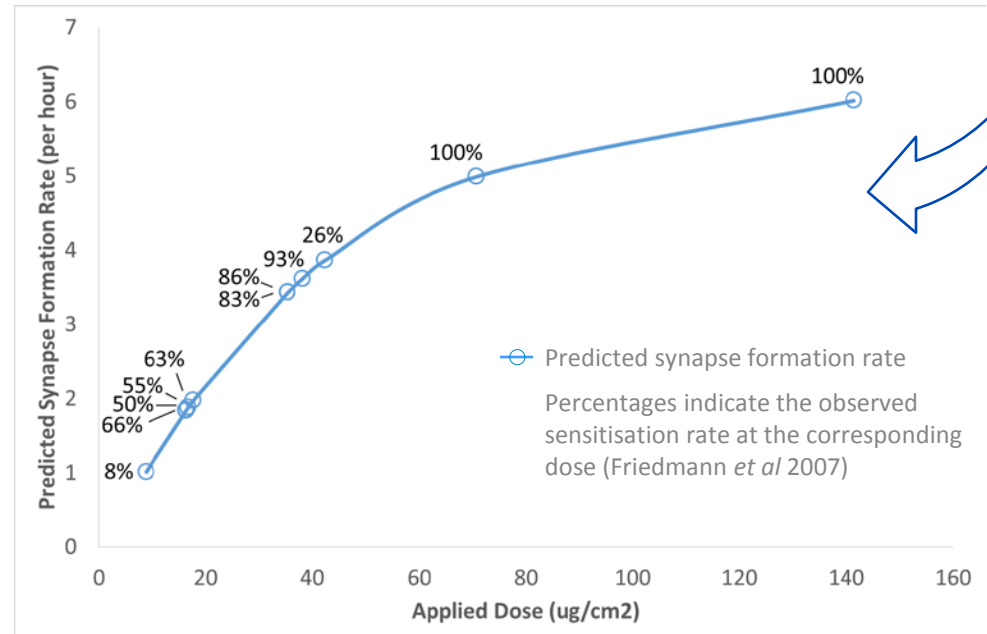
P.S. Friedmann

Friedmann 2007
- Single exposure to DNCB
- Various exposure areas, sites, vehicles & volumes

Sensitisation assessed by challenge with DNCB 4 weeks after application

Prediction of maximum immune synapse rate in the 4 weeks following application

Diameter (cm)	Area (cm^2)	Total (µg)	Concentration (µg cm^{-2})	Number of subjects	Percentage sensitised
3	7.1	1000	142	24	100
3	7.1	500	71	40	100
3	7.1	250	35.4	30	83
3	7.1	125	17.7	30	63
3	7.1	62.5	8.8	24	8
1.5	1.8	62.5	35.4	7	86
2.1	3.5	58	16.4	22	55
3	7.1	116	16.4	34	50
4.25	14.2	232	16.4	15	66
1 cm paper	0.8	30	38	28	93
3 mm paper	0.08	3	38	15	26

Predicted synapse formation rate

Percentages indicate the observed sensitisation rate at the corresponding dose (Friedmann *et al* 2007)

OVERALL SUMMARY

- We have developed a mechanistic, mathematical model of DNCB-induced CD8$^+$ T cell activation in humans with the purpose of informing skin sensitisation risk assessment

- The model predicts various measures of sensitiser-induced CD8$^+$ T cell activation for different DNCB exposure scenarios using a combination of chemical- & exposure-specific non-animal data on skin bioavailability and reactivity

NEXT STEPS

1. Progress human CD8$^+$ T cell response model development to allow mechanistic prediction of allergic contact dermatitis

2. Determine the uncertainty in our model predictions through characterising parameter & model uncertainty

ACKNOWLEDGEMENTS