Mechanistic model-based approach to Skin Sensitisation Risk Assessment


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Abstract

Despite our understanding of the key events that drive skin sensitisation our ability to combine non-animal hazard data with exposure information to establish a safe level of human exposure for a sensitisng chemical remains a key gap. Our aim is to apply mechanistic understanding of skin sensitisation to improve our ability to make risk assessments in more predictive manner. Central to our approach is a toxicokinetic-toxicodynamic (TKTD) model designed to capture the key events in the skin sensitisation adverse outcome pathway (AOP) that underpin naive CD4+  T-cell activation as a surrogate measure for sensitisation induction in humans. Chemical-specific model parameters are derived from bespoke in vitro experiments designed to measure reactivity rate and skin bioavailability, while biological parameters are taken from the immunological literature.

The model has been used to simulate a study published previously by Friedmann et al. in which 165 healthy volunteers were exposed to one of five doses of the contact allergen 2,4-dinitrochlorobenzene (DNCB). As a significant proportion of each dose cohort were sensitised to DNCB within this study, comparison of model simulation results to these clinical data have provided an opportunity to explore the relationship between naive CD4+ T-cell activation and clinical sensitisation. To do so, the model was parameterised for the relevant biological pathways and simulations were performed to cover the range of dose concentrations used in the study. Dynamic dosimetry analysis was then performed to calculate the dose threshold sensitisation for the study, and the proportion of the average individual acquiring contact allergy at any given dose.

Importantly, uncertainty due to both parameter uncertainty (limitations in our knowledge of parameter values) and model uncertainty (limitations due to validity of modelling assumptions) has been characterised. The uncertainty in model predictions for the DNCB case study is significant, therefore additional historical case studies are underway to address this finding.

1. Model Scope

Objectives: TKTD model scope should be simple representation of the chemistry and biology capable of simulating the induction of contact allergy (DNCB) to enable prediction of a safe level of skin exposure

2. Model Schematic

Panel A: A TOXICOKINETIC MODEL (Reynolds, 2016) (I) diffusion and partitioning into the stratum corneum and skin; (II) sensitiser clearance by dermal capillaries; (III) covalent modification of protein nucleophiles by hapten.

Panel B: A TOXICODYNAMIC MODEL (Reynolds, 2016) (I) proteasome processing of protein nucleophiles to form small peptides and transport to the endoplasmic reticulum (ER); (II) binding of peptides and hapten-peptide complexes to Class I MHC and transport to plasma membrane; (III) binding of MHC and hapten-MHC to CD8+ T cells and (IV) activation of naive specific CD8+ T cells.

3. Model Assumptions

Model is based upon the following major assumptions:

1. Extent of naive CD8+ T-cell receptor (TcR) triggering is the key determinant of human allergic status
2. Extent of at least one TcR specific to the ‘hapten’
3. Required TcR co-stimulatory signals are sufficient
4. Accompanying CD4+ T-cell response is critical
5. DC migration from exposure site is sufficient

Uncertainty analysis was considered for all model assumptions (major and minor), and evidence for and against each assumption was systematically documented.

4. Prior parameter uncertainty by Expert Knowledge elicitation

Expert knowledge elicitation is a process for characterising experts’ uncertainty when data/information is lacking (Finch, 1991; O’Hagan, 2006; Rowe and Wright, 1999). EKE was used to obtain prior probability distributions for all TKTD model parameters. Example of hapten-protein degradation rate was shown to illustrate this step—three processes: 1. experts capture evidence related to the parameter of interest, including any sources of uncertainty; 2. experts are asked to make judgements on possible or potential parameters; 3. a probability distribution is used to represent this uncertainty.

5. Posterior parameters by Bayesian inference

A simple compartmental model (Dawes, 2010) was applied to skin penetration data (OECD TD 428 modified to include additional time points and clearance measurements - Pendlington, 2008, Reynolds, 2016) to update prior information on kinetics and partitioning rates using Bayesian analysis.

A similar approach was applied to protein reactivity data to obtain estimates of DNCB reaction rate and protein binding, kinetics within human skin (data and data analysis not shown).

6. Predict probability of skin sensitisation to DNCB

To predict the likelihood of an allergic immune response to DNCB the following sequence of events were explicitly modelled: 1. haptenation of nucleophilic amino acids in the skin; 2. protein degradation by proteasome; 3. presentation of proteosome-derived peptides by Class I MHC; 4. recognition of peptide-MHC by TcR of CD8+ T cells binding

An threshold was defined (using literature data) to enable the model output (average CD8+ Tif triggering rate over time) to be converted into a probability that an individual would become allergic as a result of DNCB exposure. A reverse dosimetry approach (Cowell, 2008) was used to back-calculate the doses of DNCB that would cross the TCR signal threshold and cause allergy. The model prediction was benchmarked against historical clinical data from Friedmann and colleagues (ELU, Skin biobank 100%), and further tested via a single exposure to DNCB, which was found to be 14.5 µg/cm².

7. Model evaluation and next steps

Sensitivity analysis was performed to determine the parameters contributing the most uncertainty to simulated sensitisation dose.

Next Steps:

1. A framework for evaluating a TKTD model-based approach to skin sensitisation assessment is currently under development

2. Model development is ongoing to enable the T cell memory response to be simulated in collaboration with University of Leeds, University of Manchester, Salidlow Royal Nhs Foundation Trust & University of Sheffield.

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References


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