OECD Skin Sensitization AOP

Development and Supporting Evidence

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OECD AOP Programme

- "Learning by doing"
- Linked to regulatory need
  - QSAR Toolbox
  - IATA
- Broad international participation
- http://www.oecd.org/env/ehs/testing/

- First published AOP (May 2012)
- Consensus document

Unclassified ENV/JM/MONO(2012)10/PART1

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

04-May-2012

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Cancels & replaces the same document of 27 April 2012

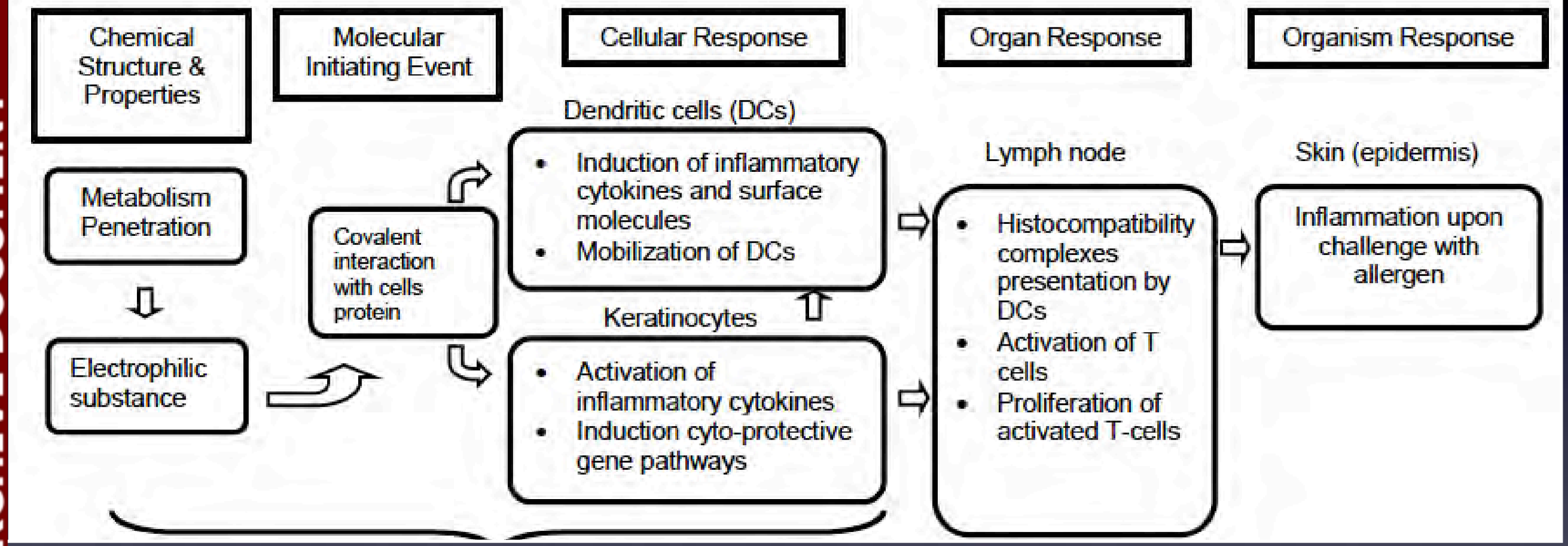
The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins Part 1: Scientific Evidence

Series on Testing and Assessment
No.168

Unclassified ENV/JM/MONO(2012)10/PART1

Adapted from Schultz et al. 2011

Key Events	Experimental Support	Strength of Evidence
Key Event I (MIE)	Site of action proteins (Karlberg et al., 2008; Wong & Liebler, 2008). Covalent binding at cysteine &/or lysine (Roberts & Natsch, 2009; Schwöbel et al., 2011)	Strong; well accepted mode of toxic action associated with skin sensitisation (Gerberick et al., 2008; Aeby et al., 2010); 100s of chemicals evaluated for binding; quantitative endpoints
Key Event 2	Gene expression of antioxidant response element in keratinocytes (Natsch & Emter, 2008; Emter et al., 2010; McKim et al., 2010)	Strong/Adequate; well accepted cell signalling pathway associated with skin sensitisation; 10s of compounds evaluated; quantitative endpoints
Key Event 3	Activation of dendritic cells (dos Santos et al., 2009; Vandebriel et al., 2010; Ashikaga et al., 2010)	Adequate; well accepted expressions of co-stimulatory molecules & cytokines associated with skin sensitisation; various endpoints; 10s of compounds evaluated; tend to be qualitative rather than quantitative
Key Event 4	T-cell proliferation (Gerberick et al., 2005; Kern et al., 2010)	Strong; two decades of development & testing with the Local Lymph Node Assay (LLNA); 100s of chemicals evaluated; quantitative endpoint
Adverse Outcome	Allergic contact dermatitis in humans or its rodent equivalent contact hypersensitivity	In vivo data sets for human & guinea-pig



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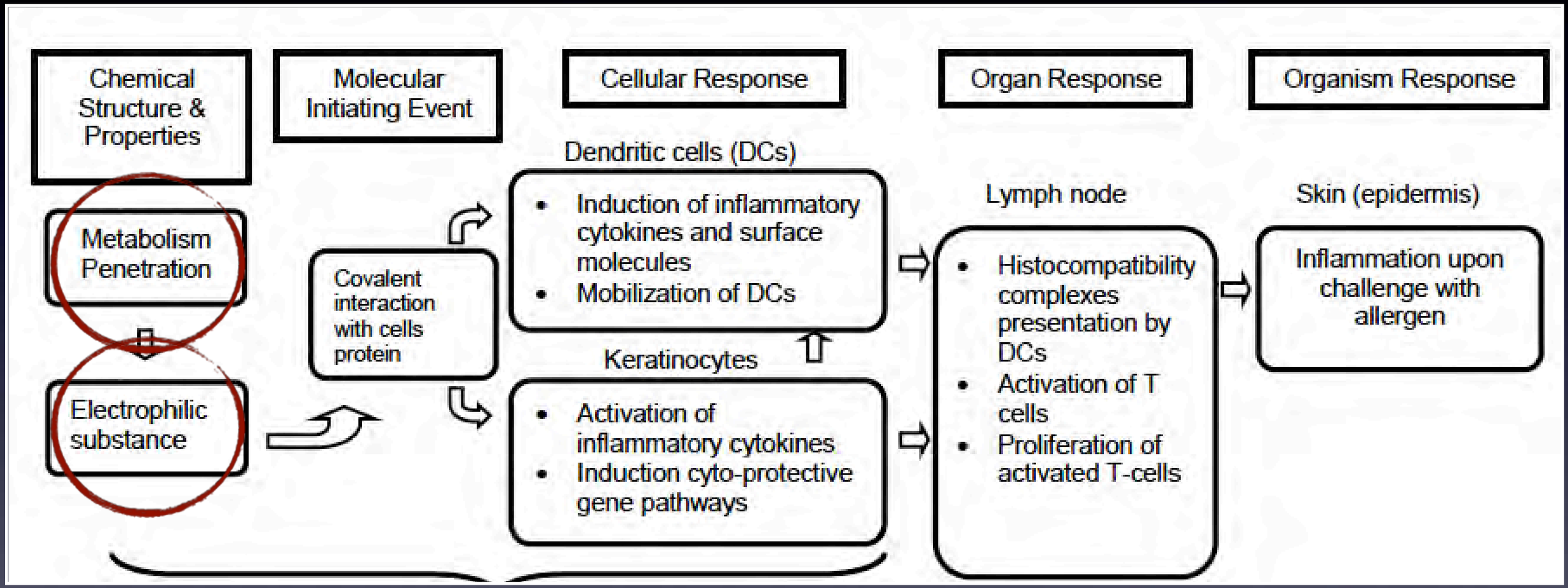
Considerations



Exposure Applicability Domain

Quantitative Elements

- Yes/No result can be acceptable
- For this AOP, quantitative measurements are possible for three of the four key events
- Evidence behind activation of dendritic cells more qualitative
- Determination of thresholds or potency is a function of the regulatory context

1-Chloro-2,4-Dinitrobenzene (DNCB)

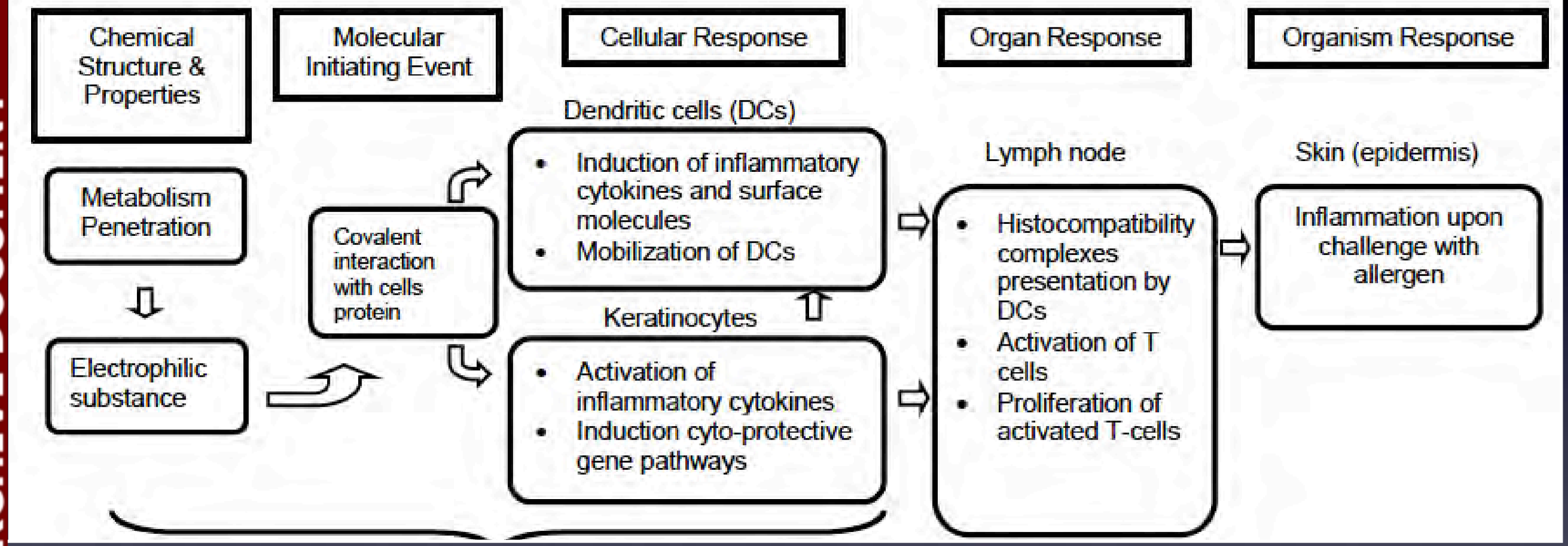
- Skin penetration and metabolism are not mitigating factors
- Highly reactive aromatic ring electrophile
- Reacts preferentially with thiol-rich cellular proteins and shown to react within Dendritic Cells
- Key pathways (NF-kappaB, JNK, p38 MAPK, and ERK1/2) in DC maturation are affected by DNCB

1-Chloro-2,4-Dinitrobenzene (DNCB)

- Shown in multiple in vitro keratinocyte assays to upregulate genes related to DC maturation
- In multiple DC lines and primary models DNCB exposure resulted in expression of cytokines and cell surface markers known to be associated with sensitization response (e.g. IL1β, IL-8, and TNFα; CD54 and CD86)
- Led to internalization of MHC Class II antigens by DCs

1-Chloro-2,4-Dinitrobenzene (DNCB)

- RHE models of human skin with DCs show increased levels of CD86 expression
- Led to cell proliferation, including of T cells, in lymph tissue
- DNCB is considered a sensitizer in the LLNA
- GPMT and Buehler tests classify DNCB as causing a strong sensitized response upon challenge



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OECD Vision for Use of SS AOP

- Develop structural alerts and category/read-across approaches for the OECD QSAR Toolbox
- Lead to development of *in vitro* assays
- Support development of Integrated Approaches to Testing and Assessment
- Looking ahead: AOP Wiki