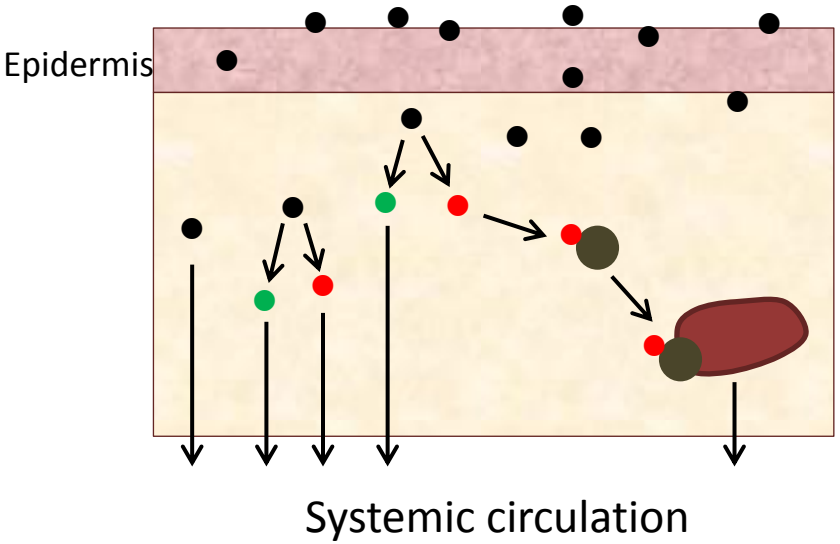
Factors that may impact on skin sensitisation



Frequency/duration **Area of application** **Dose per unit area**	Consumer habits
Penetration into skin	Occlusion Matrix Skin integrity Genetic factors
Metabolic activation/inactivation	Genetic factors
Binding to protein	Chemical reactivity
Activation of Keratinocytes	Danger signals Inflammation
Activation of Dendritic cells	Genetic factors Site of application
Activation of immune system (T cell proliferation)	Genetic factors

Overview

- Part 1: (re)consideration of underlying science
  - led by David
- Part 2: impact of the above on QRA/SAFs
  - led by Bob
- Discussions/telecons have informed this work

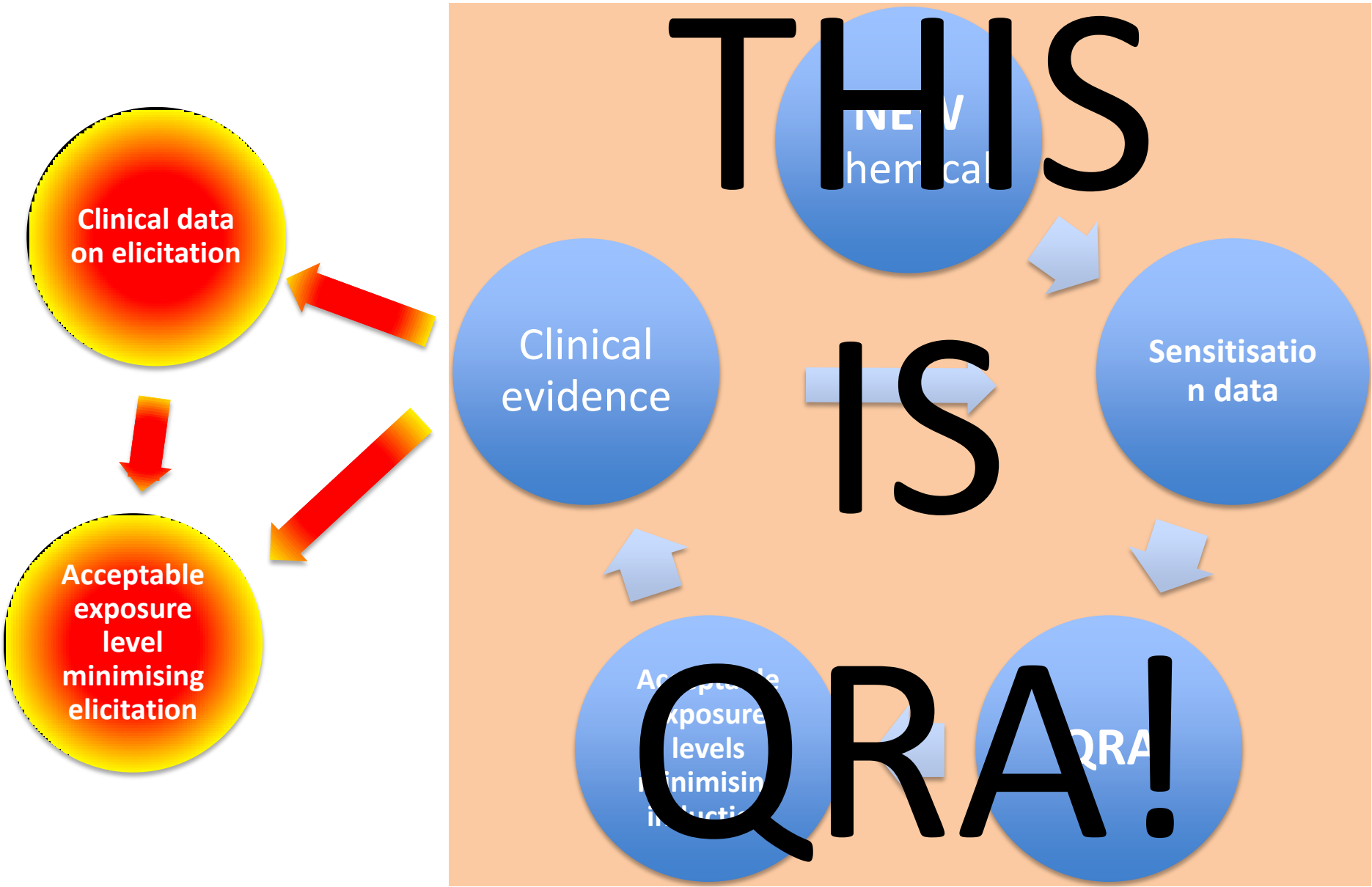
Background to the QRA Review 2014

- Toxicological risk assessment is normally based on the extrapolation of an experimentally derived threshold to an acceptable use level

- Perhaps we should have a discussion on what is meant by “acceptable”

- ***Evidence*** to date indicates that current toxicology risk assessment works, if it is done properly....

Skin sensitisation risk assessment



QRA, MDGN and MIT

What happens if you apply the current QRA properly to these problem preservatives? Adapted from Basketter DA, 2010; Cut Ocul Toxicol, 29: 4-9.

Product type	MDGN (ppm)	Overall for MDGN	MIT (ppm)	Overall for MIT
Non-aerosol deodorant	25	Leave on limit: 25 ppm	**5**	Leave on limit: 5 ppm
Face cream/body lotion	50		**10**	
Liquid soap	100	Rinse off limit: 100 ppm	**15**	Rinse off limit: 15 ppm
Shampoo	1000		**150**	

The weight of evidence sensitisation data for MIT leads to a NESIL of 15 µg/cm^2. Using this with information from published QRA analyses on other preservatives, suggests the current MIT epidemic could have been avoided?

So what is at fault? Is it the QRA, or is it its application/acceptance?

Scientific review regarding QRA SAFs

- ***Safety assessment factors (SAFs):*** a trio of numerical adjustments applied to an experimentally derived skin sensitisation induction threshold to account for:
  - *Interindividual variation in susceptibility – all aspects of biological variability*
  - *The impact of the exposure matrix – in effect to account for vehicle differences*
  - *Use considerations – any aspects not accommodated in the exposure calculation*

Some words of caution

- Skin sensitisation QRA is comparable to other toxicology risk assessments
- …but let's avoid pre-conceptions on whether QRA2014 will be like/unlike QRA2013
- Expert judgment is unavoidable at times:
  - *Use of a 2 - 3 fold factor is applied when variability is judged to be low, but worth accommodating*
  - *Use of (a) 10x factor(s) is associated with where we judge there are order of magnitude effects*

Things we don't know include

- The relative importance of prolonged (low dose) exposure compared to experimental exposure
- *Whether 24 hours is really the best compromise for the accumulating skin exposure dose*
- Does a generally sensitive sub-population exists, and ***IF*** it does, how do we identify it

Interindividual variability

- Intrinsic (endogenous) variability
- Age
- Ethnicity
- Gender
- Genetics
- Skin state, including inflammation and barrier disruption

Interindividual variability

- Intrinsic variability
- Age
- Ethnicity
- Gender
- Genetics
- Skin state, including inflammation and barrier disruption

- We are well aware that in practice measures of interindividual variability may incorporate several of these aspects, although to an unknown extent
- Older age, gender and the presence of inflamed skin are not included in all the historical human test data

Interindividual variability

• Intrinsic (endogenous) variability	• Experimental data* suggests a substantial variation
• Age	• Low
• Ethnicity	• Low (Caucasians more sensitive in the HMT; 5 allergens; 77/125 vs 54/120)
• Gender	• Low
• Genetics	• Not identified to any extent
• Skin state, including inflammation and barrier disruption	• Data suggests inflammation, rather than barrier disruption has a 10x effect

*Note this is an indicator of variability based on high dose/low exposure frequency

Monobenzylether of hydroquinone

- Human maximization test results
  - 0.1% gave 12% positive
  - 1.0% gave 30% positive
  - 10% gave 64% positive
  - 25% gave 99% positive

- This study shows a >250 range of susceptibility under these conditions of exposure
- The panel was 90% “Negroes” (*sic*) of 18-50 years
- Six other allergens gave similar/compatible results (Kligman, 1966)

p-Phenylenediamine - 1

- In the human repeated insult patch test:
  - 0.01% gave 7% positive
  - 0.1% gave 11% positive
  - 1.0% gave 53% positive

- This indicates that humans varied by a factor of >100 under the conditions of the study
- The work involved Caucasians of 21-50 years
- 20 other allergens were studied; most did not cover the dose response range adequately (Marzulli and Maibach, 1974)

p-Phenylenediamine - 2

- In the human repeated insult patch test:
  - 0.001% probably would be 0%
  - 0.01% gave 7% positive
  - 0.1% gave 11% positive
  - 1.0% gave 53% positive
  - 10% would probably sensitise 100% (HMT, Kligman 1966)
- These assumptions lead to the conclusion that humans varied by a factor of $>10^4$ under the conditions of the study

Barrier disruption v inflammation

- In the HMT, tape stripping to the glistening layer has only minor impact on induction (Kligman, 1966b); 2% in controls, 8% in test

- In the same assay, the use of SLS to promote irritant inflammation has a substantial and positive effect on induction (2% positive on control skin v 39% on inflamed skin)

Exposure matrix

It is essential not to confuse penetration with skin bioavailability! Penetration enhancers are likely to reduce sensitisation induction.

- Human experimental data approximates to zero
- Limited guinea pig test data exists, but is not quantitative
- LLNA data on the impact of vehicles on EC3 values is the sole significant information set
- Marzulli and Maibach showed a 3 fold variation (2 allergens)
- Limited guinea pig test data exists, but is not quantitative
- The results suggest only modest variation in EC3 value (against a background where EC3 measurement varies too); the maximum effect was 20x.

Exposure matrix

It is essential not to confuse penetration with skin bioavailability!

Penetration enhancers may to reduce sensitisation induction.

	Petrolatum	95% ethanol
Cinnamal	0% (0/53)	2% (1/55)
Costus oil	8% (1/12)	25% (3/12)

- Marzulli and Maibach showed a 3 fold variation (2 allergens) (Contact Dermatitis, 1976)
- I have not done any statistical analysis of this data, but I very much doubt the differences would reach significance

Effect of occlusion – HMT data

Allergen	Response rate		
	No occlusion	Semi-occlusion	Occlusion
0.01% DNCB	17%	48%	60%
0.01% NDMA	ND	36%	72%
0.1% NDMA	84%	ND	100%
0.05% PPD	30%	68%	92%

Effect of occlusion on penetration data

Allergen	% Penetration	
	No occlusion	Occlusion
Cinnamyl anthranilate	24	53
Safrole	15	38
Cinnamic alcohol	34	66
Cinnamic acid	18	61

For a “volatile” chemical in the absence of occlusion less material may be available

Remember – penetration does not equal dermal bioavailability

Use SAF

We need to be careful not to introduce here aspects which will be fully accommodated within the dermal exposure calculation

- Occlusion
  - the limited information that exists shows a surprisingly modest impact of occlusion on the induction of skin sensitisation
  - some body sites, e.g. axilla, genitalia, anus, are likely to provide a degree of occlusion
- Body site considerations
  - clinically, some skin areas appear more likely to express an allergic response, but that does not, per se, mean that they are more likely to be the cause of induction
  - moist toilet tissues/wipes are often the first reports related to new preservative allergies
  - we need to avoid confounding induction v elicitation susceptibility

What are the QRA implications?

- So, over to Bob, who had the thankless task of trying to interpret my ramblings into a practical suggestions for how to approach skin sensitisation risk assessment…