Practical Considerations for Incorporating Skin Penetration Data into a Risk Assessment for a Consumer Product Launch

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Conflict of Interest Statement

- Employment and research has been funded by Johnson & Johnson Consumer Products, Inc.

Outline/Objectives

- Typical consumer ingredient exposure- and safety assessments are predicated on application to healthy, intact skin with a robust barrier function
- OECD 428 and SCCS (2010) require testing on samples with intact barrier.
- There are currently no standard dermal penetration models for assessing penetration through less-than-robust skin barrier, such as newborn skin and potentially compromised barriers in diaper rash, eczema, acne and psoriasis.

Outline/Objectives

- Without such data, additional safety factors may (?) be considered for the risk assessment for these applications, as the consumers could be considered Sensitive Sub-Populations, but the specific values to be used will be arbitrary and could vary among regulatory authorities.
- Data generated to determine the magnitude of difference (if any) vs. healthy, intact skin

Tethering Pre-clinical to Clinical

Clinical, non-invasive measures of barrier function appear to be inexact proxies for chemical penetration.

Trans-Epidermal Water Loss (TEWL) is the most commonly used clinical tool. Clinical measures of compromised skin indicate 3-4x increase in TEWL.

We have developed two *ex vivo* models to address chemical penetration through skin with less-than-robust barriers to refine our assessments of ingredients for these impacted product categories.

Dermal Penetration Models

The static Franz chamber was used for both models. Pig skin from animals euthanized for other purposes was the tissue source.

For the newborn skin model, 4-day old pig skin was treated intact and compared with pubescent pig skin and human cadaver skin.

For the compromised skin model, suckling pig skin was paired into untreated or tape-stripped skin groups.

Markers of Barrier Function

- **Trans-Epidermal Water Loss** (TEWL) – evaporative water loss;
  increases with damage
- **Electrical Impedance** – measure of skin capacitance;
  decreases with damage
- **Electrical Resistance** (ER) – measure of current conduction;
  decreases with damage
- **Tritiated Water** (T_2O) – absorption of water *into* the skin;
  increases with damage
- **^{14}C-octanol** – measures absorption of an externally applied hydrophobic molecule;
  increases with damage

Markers of Barrier Function

For the newborn skin model, the penetration of a caffeine solution was compared with multiple markers of barrier function among the various skin sources.

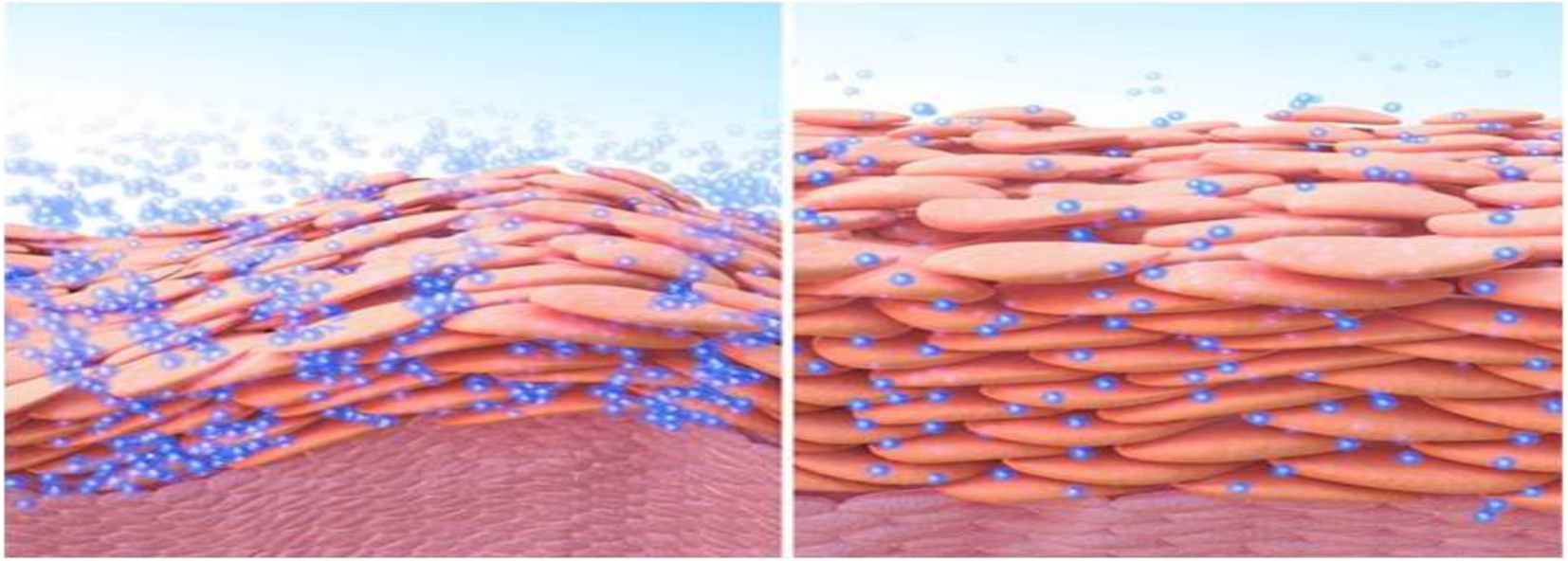
For the compromised skin model, multiple markers of barrier function were assessed in intact skin versus paired skin with various numbers of tape stripping to assess the change in barrier function with differing intensities of insult.

Molecule penetration assessed using Caffeine, 3-Aminophenol, Sucrose and Benzoic Acid in an emulsion.

Neonatal Skin Study

Baby Skin

Adult Skin



L. Telofski et al. Derm Res Practice 2012

Barrier Integrity Tests
ex vivo Human Trunk Skin, and Neonatal and Pubescent Porcine Skin

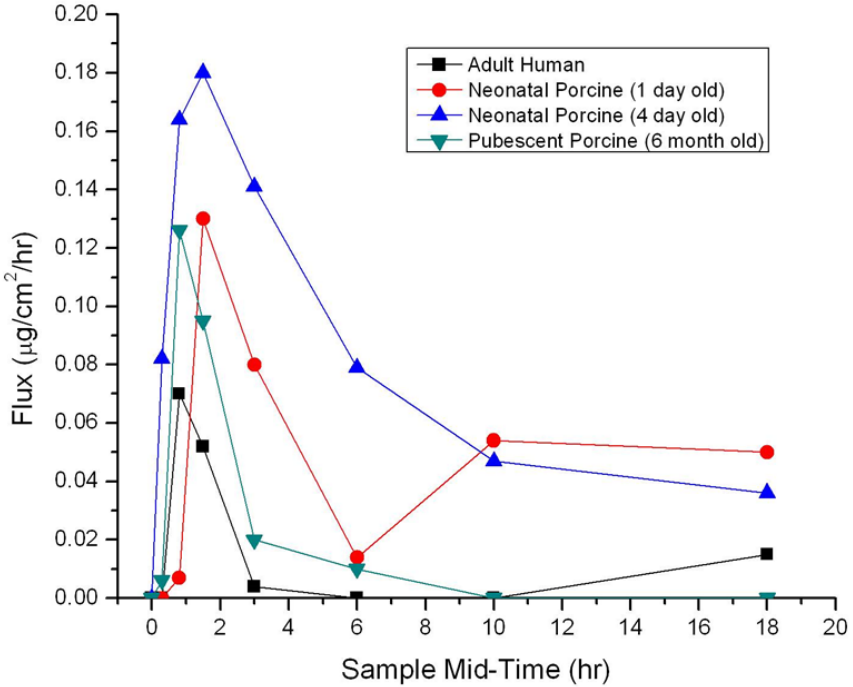
	Neonatal Porcine Skin (4 day old)	Pubescent Porcine Skin (6 month old)	Adult Human Skin (42 – 55 yrs)	Relative 4-day vs pubescent	Relative 4-day vs human
$^{3}H_2O$ (µL/cm^2/5 min)	0.23 ± 0.08	0.90 ± 0.22	0.30 ± 0.06	0.26	0.77
^{14}C-Octanol (µL/cm^2/5 min)	3.25 ± 0.97	3.26 ± 0.60	8.43 ± 2.18	1.00	0.39
TEWL (g/m^2/hr)	2.5 ± 0.5	8.9 ± 1.4	9.8 ± 1.9	0.28	0.26
Impedance (no units)	98.8 ± 6.2	93.1 ± 1.6	100.1 ± 1.5	1.06	0.99

TEWL and Impedance demonstrated consistent changes across the groups. Tritiated Water- and Octanol flux were not consistently altered

Mass Balance: Penetration of Caffeine through *ex vivo* Human Trunk Skin, and Neonatal and Pubescent Porcine Skin

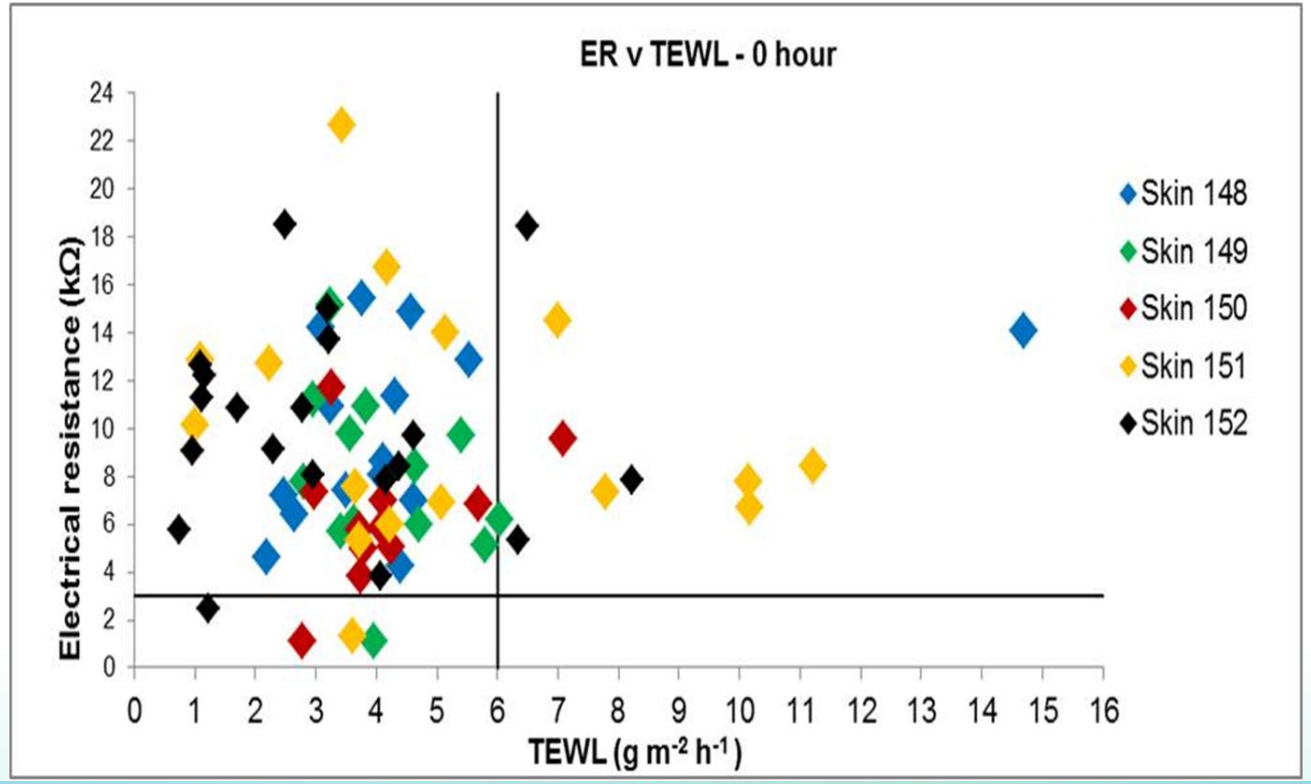
	Neonatal Porcine Skin (4 day old)	Pubescent Porcine Skin (6 month old)	Adult Human Skin (42 – 55 yrs)	Relative 4-day vs pubescent	Relative 4-day vs human
Source	4.0 mg/mL Caffeine in 50:50 EtOH:H_2O	4.0 mg/mL Caffeine in 50:50 EtOH:H_2O	4.0 mg/mL Caffeine in 50:50 EtOH:H_2O		
Receptor (%)	3.79 ± 1.77	0.59 ± 0.27	0.70 ± 0.18		
Dermis (%)	0.10 ± 0.05	0.71 ± 0.19	0.01 ± 0.00		
Epidermis (%)	0.24 ± 0.07	1.52 ± 0.41	0.24 ± 0.05		
Stratum Corneum (%)	0.83 ± 0.51	1.28± 0.16	0.19 ± 0.16		
Surface (%)	90.36 ± 3.21	83.13 ± 2.93	87.02 ± 1.97		
Total Recovery (%)	95.32 ± 2.54	87.24±2.18	88.16 ± 1.87		
Σ Bioavailable (%)	4.13%	2.82%	0.95%	1.46	4.35
Bioavailable/Recovery	4.33%	3.23%	1.08%	1.34	4.02

Mean Flux (μg/cm²/hr) Results

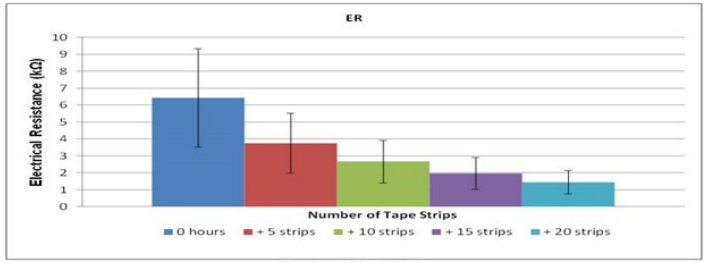


Compromised Skin Study

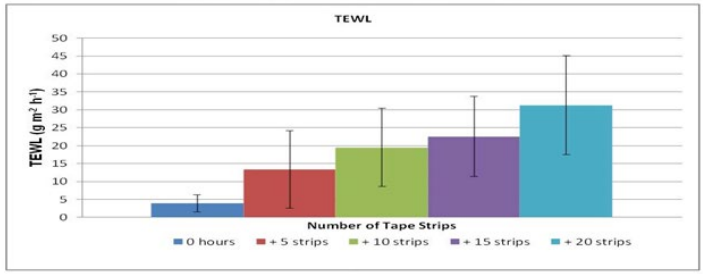
Comparing TEWL vs. ER for Intact Skin



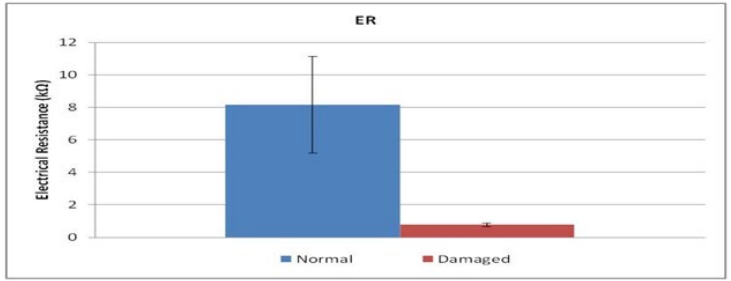
Barrier Function Following Differing Severities of Tape Stripping



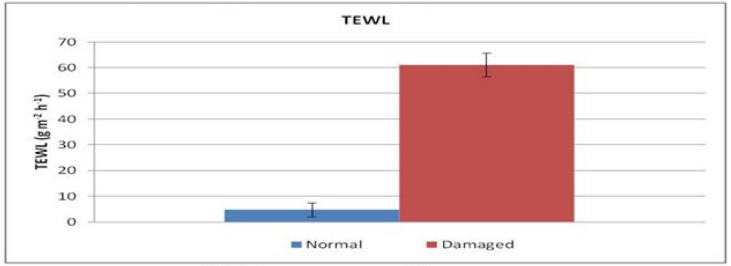
Number of Tape Strips	0 hours	5 strips	10 strips	15 strips	20 strips
Mean	6.43	3.75	2.66	1.97	1.44
SD	2.91	1.75	1.25	0.94	0.70
SEM	0.35	0.21	0.15	0.13	0.10
n	69	68	68	53	53
Min	1.85	1.26	0.95	0.73	0.66
Max	13.49	8.91	7.10	5.32	3.77



Number of Tape Strips	0 hours	5 strips	10 strips	15 strips	20 strips
Mean	3.86	13.31	19.47	22.56	31.25
SD	2.38	10.84	10.87	11.18	13.79
SEM	0.27	1.25	1.28	1.75	2.33
n	76	75	72	41	35
Min	1.38	3.06	4.51	7.33	5.68
Max	17.90	53.71	47.62	50.16	62.56

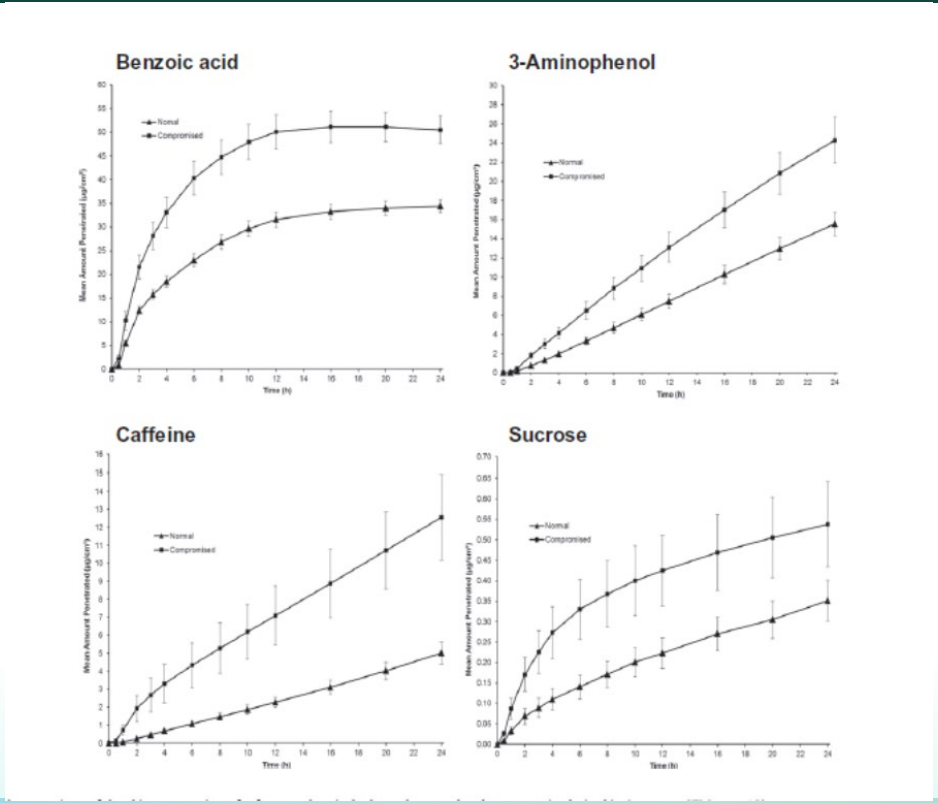


	ER 0hrs	HS
Mean	8.16	0.79
SD	2.97	0.11
SEM	0.66	0.02
n	20	20
Min	3.57	0.62
Max	14.97	1.00



	ER 0hrs	HS
Mean	4.72	61.07
SD	2.69	4.62
SEM	0.60	1.03
n	20	20
Min	1.94	48.54
Max	11.21	71.33

Molecular Transdermal Penetration



Summary

- These data confirm that non-invasive measures of barrier function may be indicative, but are not definitive, for determining the absorption of topical compounds.
- The current 10x intra-species safety factor used in risk assessment adequately captures the difference in neonatal barrier function.
- Only ER was robust enough to discriminate between the barrier property changes effected by sequential tape stripping, while TEWL, T_2O proved to be unsuitable as a short term test.

Summary, continued

- Analysis of the data revealed that removal of 10 tape strips provided a loss of barrier function approximately equivalent to a 3-4 fold increase in TEWL, which approximates the altered barrier function clinically observed in atopic dermatitis, psoriasis, and diaper dermatitis.

- Individual molecules, with different physical-chemical properties, had higher penetration in compromised skin. Magnitudes changed, but not drastically

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Important Background

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Important Background, cont.

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