TECHNICAL WHITE PAPER

3D reconstructed skin models: Transforming clinical and safety testing

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Reconstructed human epidermis (RHE) models have become indispensable tools in clinical and pre-clinical research due to their ability to closely mimic the structural and functional properties of human skin. These in vitro 3D tissue models provide a scientifically robust and ethically sound alternative to animal testing, supporting regulatory safety assessments and advancing our understanding of skin biology and barrier function. Their applications extend across dermatology, dermo-cosmetics, toxicology and drug development, making them highly relevant for clinical research.

Structure and characteristics of RHE models

RHE is generated by culturing normal human keratinocytes on inert polycarbonate or collagen substrates at the air-liquid interface, which induces differentiation into a multilayered epidermis resembling in vivo human skin histologically and functionally. RHE models replicate the multilayered architecture of the human epidermis, including (from the outermost barrier layer) – stratum corneum (cornified layer), stratum granulosum (granular layer), stratum spinosum (spiny layer) and stratum basale (basal layer).

These models express key differentiation markers such as filaggrin, keratin 5 and 10 and loricrin, which are critical for maintaining skin barrier integrity and function. The precise structure and differentiation status can be tailored depending on the intended application, such as irritation testing, toxicity evaluation or absorption studies.

Commercially available RHE models include SkinEthic™, EpiSkin™ and EpiDerm™, which have been validated for a variety of regulatory toxicity tests, such as skin irritation, corrosion and phototoxicity according to OECD guidelines (e.g. TG 431, TG 439, TG 498).

Applications in clinical research

Immature epidermis models for neonatal skin

Between birth and puberty, the skin evolves to fully perform all the functions of adult skin. Although newborn skin comprises the same number of layers as adult skin, each layer is approximately five times thinner, making it more fragile and susceptible to dehydration. The upper epidermal layers, especially the stratum corneum, are less developed and provide a weaker barrier against water loss and infections. Newborn skin is also more sensitive to UV radiation and more permeable to potentially harmful chemicals.

As a result, hygiene and skincare products for newborns and young children must be extremely gentle and protective. Dermo-cosmetic companies cannot rely on adult skin for product testing. Instead, they must utilize models that closely replicate the unique properties of neonatal skin.

To address these differences, immature epidermis models are reconstructed similarly to standard epidermis models but used earlier in the development process – typically after 10 days of growth versus 17 days for standard models. This shortened growth period results in a significantly thinner stratum corneum, making the model especially valuable for assessing product tolerance in babies. Roso et al. (2021) demonstrated that immature epidermis models are more sensitive than standard RHE models, allowing for more accurate evaluations of product tolerance in neonatal skin.

Testing protocols for these models often follow OECD Test Guideline No. 439. In standard procedures, the product is applied for 42 minutes, followed by a 42-hour post-treatment incubation. Cell viability is then assessed using the MTT assay. Depending on the formulation, the application and post-treatment conditions can be customized. Additionally, inflammatory mediators such as IL-1α and histological analysis can be used to complement the assessment.

A multiparametric approach – incorporating cytotoxicity testing, inflammatory markers and histological analysis – ensures a thorough and reliable assessment of dermo-cosmetic products designed for young children, thereby enhancing safety.

Safety and irritation testing

RHE models are widely used to evaluate skin irritation and the corrosion potential of chemicals, pharmaceuticals and cosmetic products. They comply with internationally recognized guidelines, such as OECD Test Guideline No. 439 for skin irritation testing and TG 431 for skin corrosion, providing validated, reproducible and human-relevant data. This approach reduces reliance on animal models and human volunteers, accelerating product development while ensuring safety.

Impaired epidermis models for dermatological conditions

In clinical settings, many products are applied to impaired skin, such as in cases of atopic dermatitis, psoriasis and wounds. Additional scenarios include product use following procedures such as microdermabrasion or tattooing.

Impaired epidermis models (Roso et al., 2021) are created by mechanically abrading the stratum corneum to simulate a compromised skin barrier. This model demonstrates increased sensitivity to irritation, mimicking real-world conditions in which the skin barrier is weakened. A multiparametric approach is employed for these models, incorporating cell viability assessments, barrier function measurements (e.g. transepithelial electrical resistance (TEER), biotin permeability) and histological analysis.

This strategy allows for a comprehensive evaluation of the tolerance of ingredients or formulations, particularly for products intended for sensitive or damaged skin.

Drug absorption and bioequivalence studies

RHE models serve as reproducible surrogates for human skin in percutaneous absorption studies, overcoming limitations associated with human skin variability and availability. They are instrumental in evaluating the bioequivalence of topical drug formulations, providing consistent data on drug permeation and supporting regulatory submissions.

Use of reconstructed human epithelium models

In addition to epidermis models, reconstructed human epithelium models replicate mucosal tissues such as vaginal, oral, ocular and nasal epithelia. These models are critical for testing product tolerance in specific anatomical sites, including intimate care products, toothpaste, ophthalmic formulations and medical devices.

For example, SkinEthic™ provides various epithelium models and protocols to assess cell viability following product application. The test involves applying a sample to the surface of the epithelial tissue for different durations (10 minutes, 1 hour, 3 hours and 24 hours). Viability is assessed by measuring the tissue color with the MTT assay, where a blue color indicates living cells and a white color indicates dead cells. Results are quantified using spectrophotometric measurements.

The interpretation of results follows this scale:

Cellular viability				**Conclusion**
10 min.	1 hour	3 hours	24 hours	
> 50%	> 50%	> 50%	> 50%	Non-irritant
> 50%	> 50%	> 50%	< 50%	Very slightly irritant
> 50%	> 50%	< 50%	< 50%	Slightly irritant
> 50%	< 50%	< 50%	< 50%	Irritant
< 50%	< 50%	< 50%	< 50%	Very irritant

This protocol is especially useful for testing intimate care products before in-use evaluation under gynecological supervision, as well as for assessing toothpaste formulations. It enables the comparison of tolerance levels between different ingredient combinations or concentrations, supporting research and development while optimizing time and making resource use more efficient. Moreover, it provides an ethical alternative to clinical testing for tolerance evaluation during product development.

Ocular epithelium models are similarly applied in the development of products such as shampoos and eye care products. OECD Test Guideline 492 is typically followed for these models to ensure product safety around the eye area. This approach also supports claims such as ‘does not sting the eye’, although it is important to note that cytotoxicity results do not directly correlate with the subjective stinging sensation.

Conclusion

RHE models represent a powerful and ethical tool in clinical research, offering human-relevant, reproducible platforms for safety testing, drug delivery studies, disease modeling and more. Their versatility – from modeling neonatal and impaired skin to supporting regulatory safety testing – makes them essential in the development and evaluation of dermatological and dermo-cosmetic products.

However, current models do have limitations. RHE systems lack key skin components such as dermal fibroblasts, vasculature and immune cells, which limit their ability to fully replicate complex skin physiology and systemic interactions.

Additionally, differences in permeability compared to native human skin necessitate careful data interpretation.

Ongoing research will continue to advance RHE models, with further refinement and validation helping to reduce reliance on animal testing while accelerating progress in dermatological research and therapeutic development.

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References

- OECD Guidelines for the Testing of Chemicals, Section 4 - Test No. 439: In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method, 14 June 2021
- OECD Guidelines for the Testing of Chemicals, Section 4 - Test No. 492: Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage
- Roso A, Puginier M, Bergal M, Nunzi F, Alonso A. In vitro Approach to Assess Local Tolerance of Ingredients Dedicated to Specific Topical Care Applications. J. Dermatol & Skin Sci. 2021;3(1):30-48
- Hofmann E, Schwarz A, Fink J, Kamolz LP, Kotzbeck P. Modelling the Complexity of Human Skin In Vitro. Biomedicines. 2023 Mar 6;11(3):794. doi: 10.3390/biomedicines11030794. PMID: 36979772; PMCID: PMC10045055.
- SkinEthic RHE Reconstructed Human Epidermis

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