Integrated Safety Testing and Assessment of Topical Drug Products

Human Dermal Safety Testing for Topical Drug Products
FDA Public Workshop

J F. Nash, Ph.D. and Petra Kern, Ph.D.
The Procter & Gamble Company

Outline

I. Summary and Conclusion
II. Photosafety testing
III. Skin irritation testing
IV. Skin sensitization testing
V. References

Summary and Conclusion

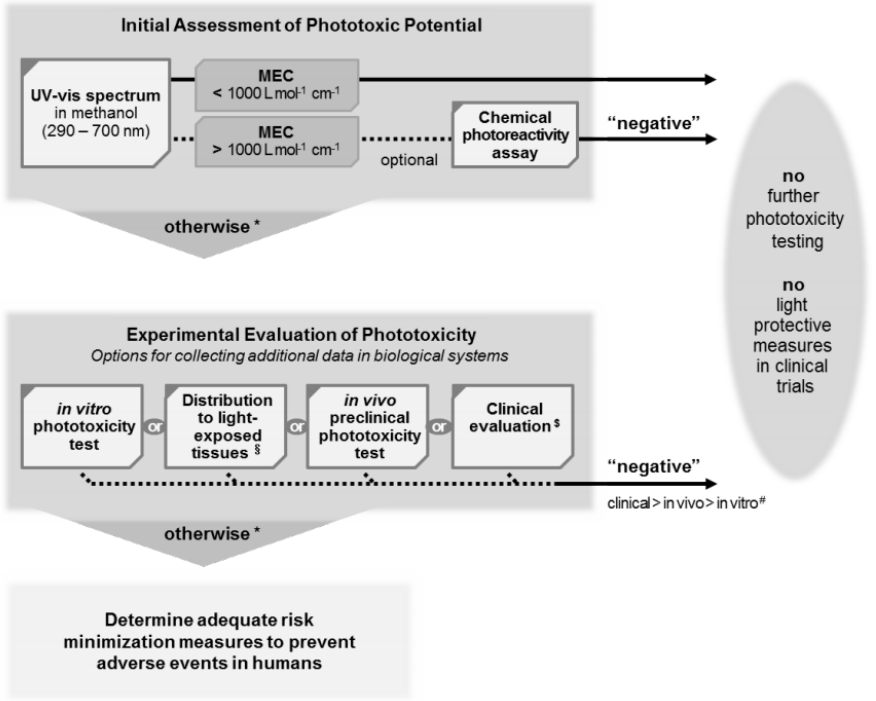
- Assessment of photosafety, skin irritation and skin sensitization potential have integrated testing approaches built from an understanding of adverse outcome pathways (AOP).
- Mechanistic-based dermal toxicity testing has been designed to improve predictivity of adverse events in humans following topical product application.
- Collaboration amongst academics, industry, regulatory authorities and nongovernmental organizations have helped progress such testing approaches and criteria used to assess adverse outcomes.

II. Photosafety Testing

- **Physiochemical properties: UV/visible light absorption**
  - Bauer et al. (2014): "A molar extinction coefficient (MEC) of 1000 L $mol^{-1}cm^{-1}$ has been confirmed as a reliable and sensitive threshold in order to identify compounds that absorb light of 290-700 nm.
    - If MEC < 1000 L $mol^{-1}cm^{-1}$, no further testing
- ***In vitro* Testing**
  - 3T3 Neutral Red Uptake (NRU) Phototoxicity Test - OECD 432 - OECD Guideline for testing of chemicals - Guideline 432: *In vitro* 3T3 NRU phototoxicity test Organization for Economic Cooperation and Development, Paris, adopted 13 April 2004.
  - Epidermis models, e.g., Episkin, phototoxicity testing, i.e., insoluble, finished formulae
    - If "negative" outcome, no further testing is needed. If "positive", next step is *in vivo* testing.
- ***In vivo* Testing**
  - **Preclinical** (for review preclinical models see: Spielmann et al. 2000; Nash, 2009)
    - Photoirritation (ingredient or formulation)
    - Photoallergy (ingredient or formulation)
  - **Human Clinical Testing**
    - Confirmatory phototoxicity/photoirritation – formulation: Kaidbey and Kligman (1978)
    - Confirmatory Photoallergy – formulation : Kaidbey and Kligman (1980)
- **Clinical Trials**
  - Risk assessment and minimization, e.g., light avoidance
  - Biomarkers
    - Noninvasive: erythema, pigment changes
    - Invasive: histopathology, e.g., "sunburn" cells

From: ICH S10 Photosafety Evaluation of Pharmaceuticals. Guidance for Industry (January 2015)

Figure 1: Outline of Possible Phototoxicity Assessment Strategies for Pharmaceuticals Given via Systemic and Dermal Routes



* "otherwise": data do not support a low potential for phototoxicity or have not been generated (assay/test/evaluation not conducted)

\# A "negative" result in an appropriately conducted *in vivo* phototoxicity study supersedes a positive *in vitro* result. A robust clinical phototoxicity assessment indicating no concern supersedes any positive nonclinical results. A positive result in an *in vitro* phototoxicity test could also, on a case-by-case basis, be negated by tissue distribution data (see text). In the United States, for products applied dermally, a dedicated clinical trial for phototoxicity on the to-be-marketed formulation can be warranted in support of product approval.

$ Clinical evaluation could range from standard reporting of adverse events in clinical studies to a dedicated clinical photosafety trial.

§ Tissue distribution is not a consideration for the phototoxicity of dermal products.

III. Skin Irritation: Testing*

- Physicochemical properties
  - e.g., pH, acid/alkaline reserve, oxidants, exothermic
- *In silico*
  - (Q)SAR, read-across, expert rules-based systems, e.g., DEREK, TOPKAT
- *In vitro*
  - OECD 430, 431 & 435: *In vitro* skin corrosion testing
  - OECD 439: *In vitro* skin irritation: reconstructed human epidermis (RHE) test method.
- *In vivo*
  - Preclinical
    - OECD 404 Acute dermal irritation/corrosion
  - Human Clinical Testing:
    - Confirmatory formulation testing: Acute (3, 24 or 48 hr) and/or cumulative (4 – 21 day) irritation patch test
- Clinical Trials
  - Biomarkers
    - Noninvasive: IL-1α, IL-1ra
    - Invasive: histological evidence of inflammation

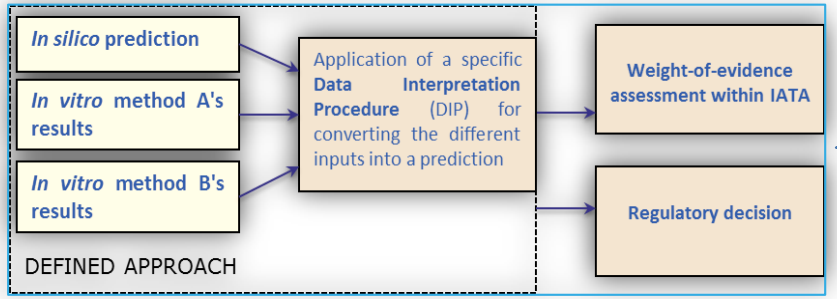
*OECD (2017) *Guidance Document on an Integrated Approach on Testing and Assessment (IATA) for Skin Corrosion and Irritation*.

IV. Skin Irritation: Testing

- Integrated Approach on Testing and Assessment (IATA) modules
- Application possible for formulations

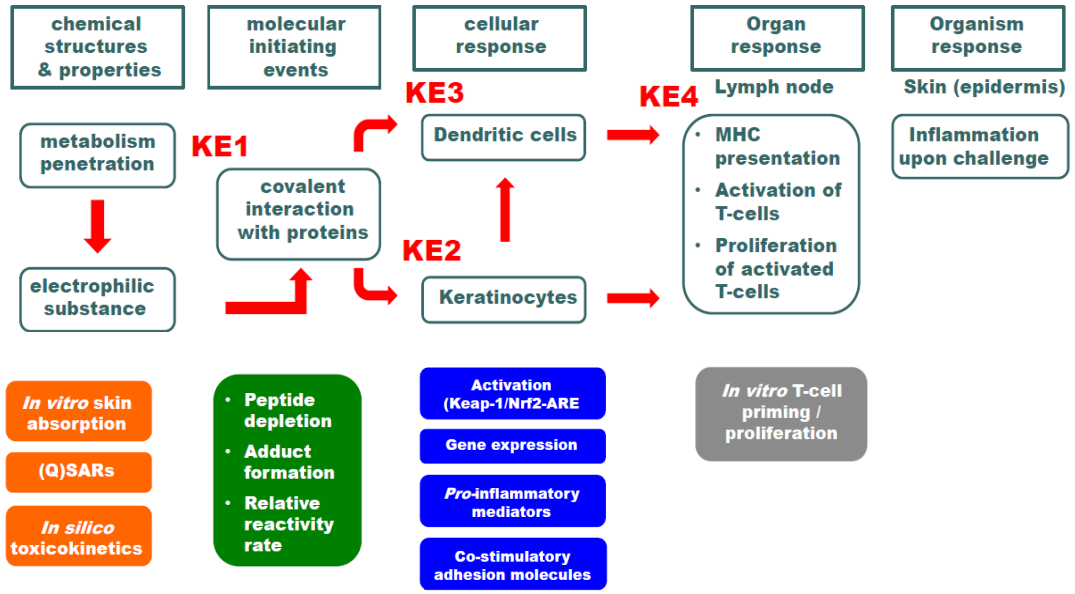
Part (*)	Module	Data
Part 1 (Existing information, physico-chemical properties and non-testing methods)	1 2 3 4 5	Existing information - Existing human data *a)* Non-standardised human data on local *skin effects* *b) Human Patch Test (HPT)* - *In vivo* skin irritation and corrosion data (OECD TG 404) - *In vitro* skin corrosion data *a) OECD TG 430* *b) OECD TG 431* *c) OECD TG 435* - *In vitro* skin irritation data (OECD TG 439) - Other *in vivo* and *in vitro* data a) *In vitro* skin corrosion or irritation data from test methods not adopted by the OECD b) Other *in vivo* and *in vitro* dermal toxicity data
	6	Physico-chemical properties (existing, measured or estimated) - e.g., pH, acid/alkaline reserve
	7	Non-testing methods - for substances: (Q)SAR, read-across, grouping and prediction systems; - for mixtures: bridging principles and theory of additivity
Part 2 (WoE analysis)	8	Phases and elements of WoE approaches
Part 3 (Additional testing)	(5b)	*Other in vivo* and/or *in vitro* dermal toxicity testing (if required by other regulations)
	(3)	*In vitro* skin corrosion testing
	(4)	*In vitro* skin irritation testing
	(5a)	*In vitro* skin irritation testing in test method not adopted by the OECD
	(2)	*In vivo* skin irritation and corrosion testing

IV. Skin Sensitization: Testing



- Physicochemical Assessment
  - Log P (oil/water partition coefficient), pKa, Wat solubility etc.
- *In silico*
  - Structural alerts, (Q)SAR, read-across, expert rules-based systems, e.g., DEREK, TOPKAT, TIMES etc.
- *In chemico*
  - Direct Protein Reactivity Assay (DPRA) – OECD TG 442c. Screening method for evaluation of skin sensitization potential (haptens, prehaptens)
- *In vitro*
  - Keratinocyte response: ARE-Nrf2 Luciferase Test Method KeratinoSens™- OECD TG 442d
  - Dendritic cell response: h-CLAT (Human Cell Line Activation Test) – OECD TG 442e
- *In vivo*
  - Preclinical: Local lymph node assay (LLNA) – OECD 429
  - Human: Repeat Insult Patch Testing (HRIPT) – Formulation testing. Confirmatory
- Clinical Trials
  - Formulation testing
  - No established biomarker

IV. Skin Sensitization: AOP



OECD, 2012. The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins. Series on Testing and Assessment No. 168.

ECHA

GUIDANCE

Guidance on Information Requirements and Chemical Safety Assessment

Chapter R.7a: Endpoint specific guidance

Version 5.0

December 2016

AOP Key event measured[59]	Test method	Validation status, regulatory acceptance	EU Test Methods/ OECD test guideline	Outcome according to the test method/guideline	EURL ECVAM DB-ALM protocol Nr.
Skin sensitisation					
Key Event 1 Peptide/protein binding	DPRA	Validated and regulatory acceptance	B.59/TG 442C	SS or NS with complementary information	154
Key Event 2 Keratinocyte response	KeratinoSens™	Validated and regulatory acceptance	B.60/TG 442D	SS or NS with complementary information	155
	LuSens[60]	Under validation assessment	N.A/N.A	SS or NS with complementary information	184
	SENS-IS[61]	Under validation assessment	N.A/N.A	SS or NS with complementary information	N.A
Key Event 3 Monocytic /Dendritic cell response	h-CLAT	Validated and regulatory acceptance	N.A/TG 442E	SS or NS with complementary information	158
	U-SENS™[60]	Validated and under regulatory adoption	N.A/draft TG available	SS or NS with complementary information	183
	IL-8 Luc Assay[62]	Validated and under regulatory adoption	N.A/draft TG available	SS or NS with complementary information	N.A.
Key Event 4[63] T-cell response	N.A	N.A	N.A/N.A	N.A.	N.A.

V. References: Photosafety

BAUER, D., AVERETT, L. A., DE SMEDT, A., KLEINMAN, M. H., MUSTER, W., PETTERSEN, B. A. & ROBLES, C. 2014. Standardized UV-vis spectra as the foundation for a threshold-based, integrated photosafety evaluation. *Regul Toxicol Pharmacol,* 68**,** 70-5.

CERIDONO, M., TELLNER, P., BAUER, D., BARROSO, J., ALEPEE, N., CORVI, R., DE SMEDT, A., FELLOWS, M. D., GIBBS, N. K., HEISLER, E., JACOBS, A., JIROVA, D., JONES, D., KANDAROVA, H., KASPER, P., AKUNDA, J. K., KRUL, C., LEARN, D., LIEBSCH, M., LYNCH, A. M., MUSTER, W., NAKAMURA, K., NASH, J. F., PFANNENBECKER, U., PHILLIPS, G., ROBLES, C., ROGIERS, V., VAN DE WATER, F., LIMINGA, U. W., VOHR, H. W., WATTRELOS, O., WOODS, J., ZUANG, V., KREYSA, J. & WILCOX, P. 2012. The 3T3 neutral red uptake phototoxicity test: practical experience and implications for phototoxicity testing--the report of an ECVAM-EFPIA workshop. *Regul Toxicol Pharmacol,* 63**,** 480-8.

EUROPEAN, AGENCY, FOR, THE, EVALUATION, OF, MEDICINAL & PRODUCTS 2002. Note for Guidance on Photosafety Testing. *In:* (CPMP), C. F. P. M. P. (ed.). London.

FOOD & DRUG ADMINISTRATION, H. H. S. 2015. International Conference on Harmonisation; S10 Photosafety Evaluation of Pharmaceuticals; guidance for industry; availability. Notice. *Fed Regist,* 80**,** 4282-3.

HENRY, B., FOTI, C. & ALSANTE, K. 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? *J Photochem Photobiol B,* 96**,** 57-62.

KAIDBEY, K. H. & KLIGMAN, A. M. 1978. Identification of topical photosensitizing agents in humans. *J Invest Dermatol,* 70**,** 149-51.

KAIDBEY, K. H. & KLIGMAN, A. M. 1980. Photomaximization test for identifying photoallergic contact sensitizers. *Contact Dermatitis,* 6**,** 161-9.

NASH, J. F. 2009. Phototoxicology. *In:* BALLANTYNE, B., MARRS, T. C. & SYVERSEN, T. (eds.) *General and Applied Toxicology, 6 Volume Set, 3rd Edition.* London: John Wiley & Sons.

SCHUMANN, J., BOUDON, S., ULRICH, P., LOLL, N., GARCIA, D., SCHAFFNER, R., STREICH, J., KITTEL, B. & BAUER, D. 2014. Integrated preclinical photosafety testing strategy for systemically applied pharmaceuticals. *Toxicol Sci,* 139**,** 245-56.

SPIELMANN, H., MULLER, L., AVERBECK, D., BALLS, M., BRENDLER-SCHWAAB, S., CASTELL, J. V., CURREN, R., DE SILVA, O., GIBBS, N. K., LIEBSCH, M., LOVELL, W. W., MERK, H. F., NASH, J. F., NEUMANN, N. J., PAPE, W. J., ULRICH, P., VOHR, H. W. & EUROPEAN CENTRE FOR VALIDATION OF ALTERNATIVE, M. 2000. The second ECVAM workshop on phototoxicity testing. The report and recommendations of ECVAM workshop 42. *Altern Lab Anim,* 28**,** 777-814.

V. References: Skin Irritation

BASKETTER, D. A., WHITTLE, E., GRIFFITHS, H. A. & YORK, M. 1994. The identification and classification of skin irritation hazard by a human patch test. *Food Chem Toxicol,* 32**,** 769-75.

OECD 2006. *Test No. 435: In Vitro Membrane Barrier Test Method for Skin Corrosion*.

OECD 2010. *Test No. 439: In Vitro Skin Irritation*.

OECD 2015a. *Test No. 404: Acute Dermal Irritation/Corrosion*.

OECD 2015b. *Test No. 430: In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test Method (TER)*.

OECD 2016. *Test No. 431: In vitro skin corrosion: reconstructed human epidermis (RHE) test method*.

OECD 2017. *Guidance Document on an Integrated Approach on Testing and Assessment (IATA) for Skin Corrosion and Irritation*.

PERKINS, M. A., OSBORNE, R., RANA, F. R., GHASSEMI, A. & ROBINSON, M. K. 1999. Comparison of in vitro and in vivo human skin responses to consumer products and ingredients with a range of irritancy potential. *Toxicol Sci,* 48**,** 218-29.

YORK, M., GRIFFITHS, H. A., WHITTLE, E. & BASKETTER, D. A. 1996. Evaluation of a human patch test for the identification and classification of skin irritation potential. *Contact Dermatitis,* 34**,** 204-12.

*EPISKIN™, EpiDerm™, and SkinEthic™ accepted by US via OECD guideline 439

V. References: Skin Sensitization

BUEHLER, E. V. 1994. Occlusive patch method for skin sensitization in guinea pigs: the Buehler method. *Food Chem Toxicol,* 32**,** 97-101.

JAWORSKA, J., DANCIK, Y., KERN, P., GERBERICK, F. & NATSCH, A. 2013. Bayesian integrated testing strategy to assess skin sensitization potency: from theory to practice. *J Appl Toxicol,* 33**,** 1353-64.

KLIGMAN, A. M. 1966a. The identification of contact allergens by human assay. 3. The maximization test: a procedure for screening and rating contact sensitizers. *J Invest Dermatol,* 47**,** 393-409.

KLIGMAN, A. M. 1966b. The identification of contact allergens by human assay. II. Factors influencing the induction and measurement of allergic contact dermatitis. *J Invest Dermatol,* 47**,** 375-92.

OECD 2010. *Test No. 429: Skin Sensitisation*.

OECD 2014. *The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins*.

OECD 2015. *Test No. 442C: In Chemico Skin Sensitisation*.

OECD 2016. *Guidance Document on the Reporting of Defined Approaches to be Used within Integrated Approaches to Testing and Assessment*. No. 255

OECD 2017. *Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be Used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation*. No. 256

OECD 2018a. *Test No. 442D: In Vitro Skin Sensitisation*.

OECD 2018b. *Test No. 442E: In Vitro Skin Sensitisation*.