2796/
P262

Application of clinical benchmarks to NexGen Risk Assessment (NGRA) decision-making for skin allergy: use of historical clinical experience to define low risk cosmetic product market exposures

Reynolds, J., Gilmour N., Baltazar. M., Reynolds, G., Windebank, S., Spriggs, S. and Maxwell, G - SEAC, Unilever, Colworth Science Park, Sharnbrook, Bedford, MK44 1LQ, UK

Background

NGRA is an exposure-led, hypothesis-driven approach integrating new approach methodologies (NAMs) to ensure safety without generating animal data. We have developed an NGRA framework (Figure 1) for skin allergy that is based upon ICCR principles (Dent *et al.*, 2018) and aligns with the Cosmetics Europe Skin Allergy NGRA framework (Gilmour *et al.*, 2020).

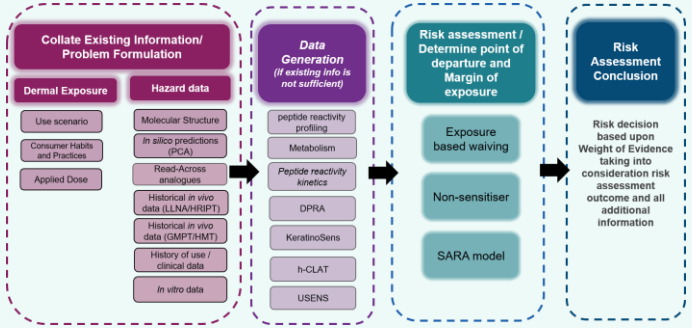

Figure 1. NGRA framework for Skin Allergy

This framework uses the Skin Allergy Risk Assessment defined approach (SARA DA – see Figure 2 below – Reynolds et al. 2019.) to estimate human potency using historical *in vivo* data [human repeat insult patch test (HRIPT) and mouse local lymph node assay (LLNA, OECD TG 442B) data] and new approach methodology (NAM) data [Direct Peptide Reactivity Assay (DPRA, OECD TG 442c); KeratinoSens™ (OECD TG 442D); human Cell Line Activation Test (hCLAT, OECD TG 442E); U-Sens™ (OECD TG 442E)].

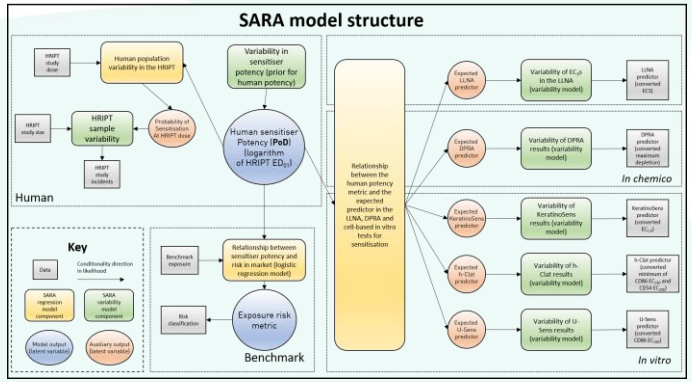

Figure 2. Overview of SARA DA model structure

Approach

Traditional quantitative risk assessment approaches (QRA) for skin allergy use safety factors to rescale points of departure, such as No Expected Sensitisation Induction Levels (NESILs), to market-equivalent safe doses which can be compared against consumer exposure estimates to inform safety decisions. Justifications for the appropriate size of safety factors are drawn retrospectively and are largely based upon historical precedent of use. For NGRA, benchmark exposure information may be leveraged to derive empirical support that an exposure is low risk and can be considered safe. To apply this concept to NGRA for skin allergy we established 62 low or high risk benchmark exposures using 10 human contact allergens [methyl- chloroisothiazolinone / methylisothiazolinone (MCI/MI) (See Table 1), MI, methyl-dibromoglutaronitrile (MDBGN), phenoxyethanol, iodo-propynylbutylcarbamate (IPBC), propyl paraben, benzoyl alcohol, sodium benzoate, propyl gallate and hydroxyisohexyl-3-cyclohexane carboxaldehyde (HICC)] with an established history of use in 7 cosmetic products (deodorants, face cream, body lotion, liquid hand soap, shampoo, body wash and lipstick).

Results

The SARA DA was extended to incorporate benchmark exposure information as an additional input alongside historic *in vivo* and NAM data. After fitting the model, and given some exposure scenario of interest, the model can then be run in 'forward mode' to calculate the *SARA risk metric*, defined as the probability that the exposure is low risk for sensitisation induction (see Figure 3). This calculation is based on a regression of margins of exposure against the induction risk for each benchmark exposure.

Material	Product type	Use level (ppm)	Consumer exposure to benchmark product (ng cm^{-2})	Induction risk
MCI/MI	Deo	30	350	HIGH
		7.5	87.8	HIGH
	Face cream	30	100	HIGH
		7.5	25	HIGH
	Body lotion	30	18	HIGH
		7.5	4	HIGH
	Liquid hand soap	15	7.3	LOW
	Shampoo	15	1.1	LOW
	Shower gel	15	0.2	LOW

Table 1 Summary of the exposure information, clinical evidence and overall risk ranking for MCI/MI benchmark. MCI/MI is a broad-spectrum preservative. The risk of induction of skin sensitisation from use at both 30ppm and 7.5ppm in leave on products is considered as high risk for induction of skin sensitisation and use at 15ppm in rinse off products is considered as low risk, in-line with SCCS conclusions (Fewings & Menne, 1999; SCCS, 2009).

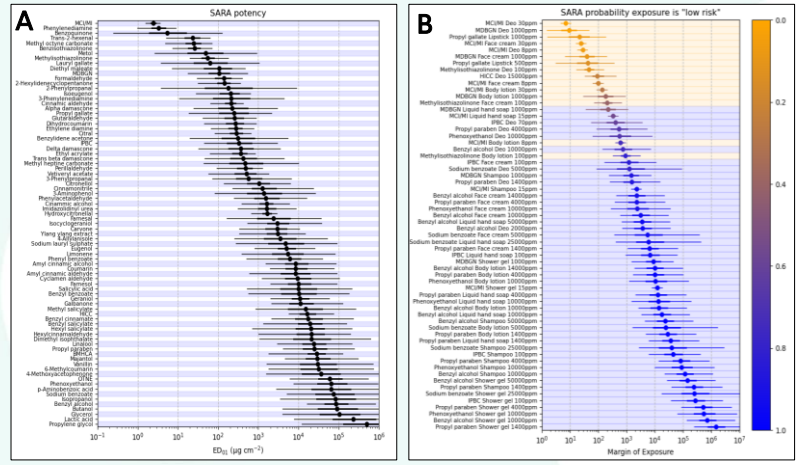

Figure 3; A: SARA DA model predictions of human sensitiser potency; B: estimates of the MoE corresponding to each benchmark exposure Panel B shows distribution generated for the MoE [SARA DA model predicted ED_{01} (see panel A) divided by exposure] for every benchmark exposure, where the risk can be defined as either high or low, based on clinical evidence. Background colours indicate the assigned risk category for each exposure (orange indicating high risk and blue low risk). SARA DA model also infers a probability that a certain exposure is low risk and the line colours indicate this model inferred probability.

Results (cont.) and Discussion

Reliable use of the SARA risk metric within a risk assessment requires that it be *calibrated* - understood in terms of frequencies of correct decisions.

Benchmark exposures were used within a cross-validation exercise to assess calibration of the SARA risk metric. For all SARA probabilities, the frequency of truly low risk exposures was found to be within the expected range irrespective of whether predictions were trained on NAM data, historic in vivo, or a combination of both (see Figure 4).

Based on these promising initial results, extension of and peer review of the risk benchmarking dataset and approach are now sought.

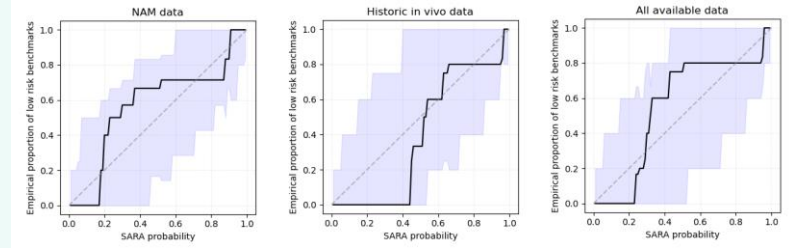

Figure 4: Assessment of calibration of the SARA risk metric

This poster is available at www.tt21c.org/safety

Unilever