APPLYING ICCR PRINCIPLES TO NEXT GENERATION RISK ASSESSMENT (NGRA)

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WHAT IS THE ICCR?

The International Cooperation on Cosmetics Regulation

5 member regulators (Brazil, Canada, EU, Japan, USA) providing a multilateral framework to maintain and enable:

• High level of global consumer protection
• Promoting regulatory convergence
• Minimizing barriers to international trade

https://www.iccr-cosmetics.org/
BACKGROUND TO JOINT WORKING GROUP

• Non-animal test data can no longer be considered ‘alternative’
• Basing a risk assessment on non-animal test data requires a fundamental change in approach
• Because science in this area is rapidly evolving, formal guidance for cosmetic ingredients is not yet available
A group of scientists from regulatory authorities and industry tasked by the ICCR Steering Committee to outline the principles that underpin the use of novel methods and data in cosmetic ingredient risk assessment (Next Generation Risk Assessment)
ICCR NINE PRINCIPLES OF NGRA

4 Main overriding principles:
- The overall goal is a human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

3 Principles describe how a NGRA should be conducted:
- Following an appropriate appraisal of existing information
- Using a tiered and iterative approach
- Using robust and relevant methods and strategies

2 Principles for documenting NGRA:
- Sources of uncertainty should be characterized and documented
- The logic of the approach should be transparent and documented
JOINT WORKING GROUP TASK 2

Provide further information on the types of new methodologies that may be useful in the risk assessment of cosmetics (Part 2)

For the benefit of risk assessors more familiar with traditional toxicological datasets

➢ Which approaches can be used?
➢ What are their strengths and limitations?
➢ Where could they be used in the risk assessment?
Continue through tiers until sufficient information to make a decision: assessment may be complete at any tier

https://doi.org/10.1016/j.comtox.2017.10.001
ONE EXAMPLE NGRA WORKFLOW

1. Identify use scenario
2. Identify molecular structure
3. Collect existing data
4. Identify analogues, suitability assessment and exiting data
5. Systemic bioavailability (parent vs. metabolite(s), target organs, internal concentration)
6. MoA hypothesis generation (weight of evidence based on available tools)
7a. Targeted testing
7b. Biokinetic refinement (in vivo clearance, population, in vitro stability, partition)
8. Points of departure, in vitro in vivo extrapolation, uncertainty estimation, margin of safety
9. Final risk assessment or summary on insufficient information approach

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Read across
Exposure-based waiving
*In silico* tools
Metabolism and metabolite identification
Physiologically-based kinetic modelling
*In chemico* assays
‘Omics
Reporter gene assays
*In vitro* pharmacological profiling
3D culture systems
Organ-on-chip
Pathways modelling
Human studies
In chemico assays
Pathways modelling
Organ-on-chip
Human studies

ONE EXAMPLE NGRA WORKFLOW

TIER 0: IDENTIFY USE SCENARIO, CHEMICAL OF CONCERN AND COLLECT EXISTING INFORMATION

1. IDENTIFY USE SCENARIO
2. IDENTIFY MOLECULAR STRUCTURE
3. COLLECT EXISTING DATA
4. IDENTIFY ANALOGUES, SUITABILITY ASSESSMENT AND EXITING DATA

TIER 1: HYPOTHESIS FORMULATION FOR AB INITIO APPROACH

5. SYSTEMIC BIOAVAILABILITY (PARENT VS. METABOLITE(S), TARGET ORGANS, INTERNAL CONCENTRATION)
6. MoA HYPOTHESIS GENERATION (WEIGHT OF EVIDENCE BASED ON AVAILABLE TOOLS)

TIER 2: APPLICATION OF AB INITIO APPROACH

7A. TARGETED TESTING
7B. BIOKINETIC REFINEMENT (IN VIVO CLEARANCE, POPULATION, IN VITRO STABILITY, PARTITION)
8. POINTS OF DEPARTURE, IN VITRO IN VIVO EXTRAPOLATION, UNCERTAINTY ESTIMATION, MARGIN OF SAFETY
9. FINAL RISK ASSESSMENT OR SUMMARY ON INSUFFICIENT INFORMATION APPROACH

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CONCLUSION

• Workflows like the SEURAT-1 ab initio workflow provide a flexible framework upon which to build an NGRA
• These frameworks can be used in a way that exemplifies the 9 ICCR principles
• Using exposure-led frameworks it is possible that for cosmetic ingredients some of the higher-tier approaches may only rarely be needed
NEXT GEN. RISK ASSESSMENT FOR SKIN ALLERGY: USE OF 0.1% COUMARIN IN FACE CREAM

**Context:**
- **Hypothetical case study** created using publicly available data
- All steps of **Ab Initio workflow** considered but steps 4-7 not required to complete this assessment
- **Historical published in vivo data** [HRIPT & LLNA] for coumarin was excluded from risk assessment to simulate NGRA for a novel ingredient

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**Coumarin** 0.1% in face cream
NEXT GEN. RISK ASSESSMENT FOR SKIN ALLERGY:
STEP 1 - IDENTIFY USE SCENARIO
NEXT GEN. RISK ASSESSMENT FOR SKIN ALLERGY:
STEP 2: IDENTIFY MOLECULAR STRUCTURE

TIER 0: IDENTIFY
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CHEMICAL OF CONCERN
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INFORMATION

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2. IDENTIFY MOLECULAR STRUCTURE

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- Toxtree predicts coumarin can bind proteins via Michael addition and/or acyl transfer mechanisms.
- OECD QSAR Toolbox predicts an SN2 mechanism of protein binding after oxidation to epoxide.

Coumarin’s major metabolites also have in silico alerts for SN2, Michael addition and acyl transfer protein binding mechanisms.

Coumarin 0.1% in face cream
NEXT GEN. RISK ASSESSMENT FOR SKIN ALLERGY: STEP 3: COLLECT EXISTING DATA

Published in vitro data obtained from Cosmetics Europe database:
- DPRA – OECD TG 442C - negative
- h-CLAT – OECD TG 442E - negative
- KeratinoSens™ – OECD TG 442D - positive
- U-Sens™ – OECD TG 442E - positive
NEXT GEN. RISK ASSESSMENT FOR SKIN ALLERGY: STEP 8: DERIVE A POINT OF DEPARTURE

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EXIT TTC
EXIT READ-ACROSS
EXIT INTERNAL TTC
EXIT AB INITIO

Coumarin 0.1% in face cream

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Skin Allergy Risk Assessment (SARA) Defined Approach (DA) model

NEXT GEN. RISK ASSESSMENT FOR SKIN ALLERGY: STEP 8: DERIVE A POINT OF DEPARTURE

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NEXT GEN. RISK ASSESSMENT FOR SKIN ALLERGY:
STEP 8: DERIVE A POINT OF DEPARTURE

NEXT GEN. RISK ASSESSMENT FOR SKIN ALLERGY:
STEP 9: RISK ASSESSMENT DECISION

We conclude there is a low risk of coumarin inducing skin allergy at 0.1% in a face cream.
Probabilistic prediction of Human Skin Sensitiser Potency for use in Next Generation Risk Assessment (NGRA)

Gavin Maxwell, Nora Aptula, Maria Baltazar, Richard Cubberley, Nicola Gilmore, Thomas Green, Julia Head, Chris Lucas, Georgia Reynolds, Joe Reynolds, Sandrine Spriggs, Evita Vandenbosche, David Vlismak & Cameron MacKay

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Abstract No. 1769 | P145

Our aim is to develop an next generation approach to skin allergy risk assessment that do not require new animal test data, address naïve exposure scenarios and better quantity uncertainty. We have developed a Bayesian multi-scale, regression models to estimate the human population with sensitisation threshold (defined as the chemical- specific exposure level at which 1% of the population would not react). Sensitisation threshold varies from 0 to 10000 ppb, depending on the chemical. The model is a regression model that uses a Bayesian framework to estimate the parameters of the model. The model is a regression model that uses a Bayesian framework to estimate the parameters of the model. The model is a regression model that uses a Bayesian framework to estimate the parameters of the model. The model is a regression model that uses a Bayesian framework to estimate the parameters of the model.

SARA defined approach

1) Objective & modelling approach A Bayesian multivariate, hierarchical regression model was developed to estimate the human population with sensitisation threshold (defined as the chemical-specific exposure level at which 1% of the population would not react). Sensitisation threshold varies from 0 to 10000 ppb, depending on the chemical. The model is a regression model that uses a Bayesian framework to estimate the parameters of the model. The model is a regression model that uses a Bayesian framework to estimate the parameters of the model. The model is a regression model that uses a Bayesian framework to estimate the parameters of the model. The model is a regression model that uses a Bayesian framework to estimate the parameters of the model.

Applying ICCR principles to NGRA case study

Step 1: Hypothetical scenario: react or protective type

1. Define the exposure scenario: Which exposure scenario would you like to compare? (e.g., skin contact, oral, inhalation)
2. Identify the chemical: Which chemical is being assessed for sensitisation potential?
3. Determine the exposure concentration: What is the concentration of the chemical that is being assessed?
4. Calculate the exposure duration: How long will the exposure occur for?

Step 2: Structural properties of protein and epitope

1. Identify the protein: Which protein is being assessed for sensitisation potential?
2. Determine the epitope: What is the epitope that is being assessed for sensitisation potential?
3. Compare the epitope to the protein: How do the epitope and the protein compare in terms of structure and function?

Step 3: Selecting data

1. Choose data set: Select a data set that contains the chemical and the protein of interest.
2. Check for validation: Ensure that the data set is validated and appropriate for the assessment.
3. Evaluate the data: Evaluate the data to ensure that it is relevant and accurate for the assessment.

Step 4: Derive a point or domain using SARA OA

1. Use SARA OA to derive a point or domain for the chemical and the protein.
2. Evaluate the domain: Evaluate the domain for relevance and accuracy.
3. Compare the domain to the exposure scenario: Compare the domain to the exposure scenario to determine if it is appropriate.

SAFETY SCIENCE IN THE 21ST CENTURY

For more info: [www.f21.org/assets/2019]