USE OF NAMS IN NGRA: CASE STUDIES FROM THE CONSUMER PRODUCTS INDUSTRY

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基本问题: CAN WE USE A NEW INGREDIENT SAFELY?

Can we safely use $x\%$ of ingredient $y$ in product $z$?
INCREASING NUMBERS OF GLOBAL CONSUMERS WANT THEIR CONSUMER PRODUCTS NOT TESTED ON ANIMALS
2007-2018: USING 21ST CENTURY SCIENCE
BUT SO MANY TECHNICAL ABBREVIATIONS!

- AOP
- IATA
- TOX21
- NAMs
- ITS
- NGRA

Pathways-based toxicology
Defined Approaches
This Cooperative Research and Development Agreement (CRADA) entered into by and between UNILEVER U.K., a company incorporated in England and Wales (registered office is at Unilever House, 100 Victoria Street, London SW1E 6QG, a member of the Unilever group of companies) and the National Center for Computational Toxicology of the United States Environmental Protection Agency ("EPA") under §§3710a-3710d (commonly known as the Federal Insecticide, Fungicide, and Rodenticide Act) was entered into with the express purpose of advancing the state of the art of toxicity assessment. The overarching goal of this CRADA is to develop comprehensive methods for assessing and managing the health and environmental safety of chemicals. This includes addressing potential health effects of chemicals from occupational and consumer sources, as well as environmental impacts.
New Case studies in 2018 - The Selection Strategy

Rationale

During the first two years of this project we have been working on a number of case studies. There are more or less approaching completion, and are to be finalized in 2018. As announced at our last face-to-face meeting in Exeter in September we are to make decisions on a new series of case studies that are to start (early) 2018. Partners have been invited to come with suggestions for new case studies, fulfilling at least one of the four outlined criteria. Three page maximum proposals, with a clearly defined objective of regulatory relevance, should shortly describe a number of key issues, but also the proposed case study (level, and estimated resources needed). Proposals will then have been reviewed by the WG, and discussed and decided upon within the Steering Team.

Selection criteria

- compounds having one very specific mode of action
- compounds having in any target organs at LOAEL
- compounds having or non-target compounds
- compounds that affect “exotic” targets: organs not covered in EU-ToxRisk like e.g. thymus, adrenal
- “non-specific effects” like change of organ, and/or body weights
- non-organ targets like e.g. hematological or vascular effects.
- compounds for which their metabolism is critical for toxicity (toxinitation or degradation)
- compounds that address one of the selected 15 AOPs of this project (not yet addressed)
- compounds with no clear identified MOH
- compounds which have T2D/innato data/break data
- compounds with well-defined exposure data
- compounds that have a tendency to accumulate in specific target organs in vivo
- compounds that show an increase of toxicity over time (increase NOAEL / increase severity)

Proposal template

- Case study objectives
- Toxicological endpoint addressed: T2D, or DART
- Toxicological effect addressed
- Test compounds (name, POS)
- Describe available in vivo toxicity data
- Mode of action information
- Describe available toxicokinetic data
- Describe availability of information in other relevant databases (T2D, ToxicBank, TRAVERSE...)
- Describe care study approach
- Who will be case study leader
- When the case study is to start and end
- The estimated whole budget
- What selection criteria this case study addresses
CAT-APP CASE STUDIES FOR BIOLOGICAL READ ACROSS OF PETROCHEMICALS

141 SUBSTANCES
& 20 REFERENCE CHEMICALS
39 Phenotypes measured on iCells (some unique to the cell line in question)

~340,000

4 DIFFERENT PHYSICAL CHEMICAL CHARACTERIZATIONS ON ALL 141 SUBSTANCES
3-4 ASSAYS CONDUCTED ON HUMAN CELL LINES

~35,000,000

4 IPS* derived cells
2 human cell line

www.concawe.eu/cat-app

• Cat-App is the largest to date "case study" that was aimed at testing whether and how in vitro bioactivity (including transcriptomics) can be used to support grouping of UVCBs
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 transparently and documented
A CASE STUDY APPROACH – HYPOTHETICAL PRODUCTS
IMAGINE WE HAD NO DATA...

“THE OVERALL GOAL IS A HUMAN SAFETY RISK ASSESSMENT”

“THE ASSESSMENT IS DESIGNED TO PREVENT HARM”
CHARACTERISE THE PHYSICOCHEMICAL PROPERTIES

**NAME** | **Curcumin**
---|---
**CAS** | 458-37-7 -Sigma 8024-37-1 (Keto) 115851-80-4 (enol) – Chemspider
**MW** | 368.380 Da (Phys chem prop database)
**Log P** | 3.36 (Phys chem prop database)
**Solubility** | 122 µM (45 mg/L) (Phys chem prop database)
**Log S** | -3.91 (Phys chem prop database)
**Log K_{AW}** | -19.541 (Episuite)
**Log K_{BSA}** | 2.94 (Exposure tool)
**Form** | odourless yellow solid

- **In Silico determinations:**
  - QSAR; ToxTree; OECD Toolbox; DEREK alerts; MIE Atlas; Drugbank; Metacore
- **Chemistry determinations:**
  - Partition coefficient logP
  - Peptide binding potential
- **In vitro determined:**
  - Kinetic solubility
  - Thermodynamic solubility
  - Metabolic & chemical stability
  - Stability in human plasma
  - Plasma protein binding
  - Partitioning in blood
  - Free concentration determinations
USE OF EXISTING OECD IN VITRO APPROACHES

Skin and eye irritation; skin sensitization; phototoxicity; mutagenicity

“FOLLOWING AN APPROPRIATE APPRAISAL OF EXISTING INFORMATION”
**THE ASSESSMENT IS EXPOSURE LED**

Exposure scenario:
- Worst case in US: 32.97 µg/cm²
- Used one time per day
- Skin surface area: 4712.5 cm² (95 percentile)
- Amount of product used per day: 5.18 g/day
- Amount of ingredient in contact with skin: 155 mg/day

<table>
<thead>
<tr>
<th>Laundry scenarios</th>
<th>Systemic exposure (mg/kg bw per day)</th>
<th>Local dermal exposure (ug/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Treatment</td>
<td>0.19</td>
<td>50</td>
</tr>
<tr>
<td>Main wash</td>
<td>0.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Residues on clothes</td>
<td>0.06</td>
<td>0.04</td>
</tr>
<tr>
<td>Total (Main wash+ residues on clothes)</td>
<td>0.36</td>
<td>8.44</td>
</tr>
<tr>
<td>Total (pre-treatment+ main wash+ residues on clothes)</td>
<td>0.55</td>
<td>58.44</td>
</tr>
</tbody>
</table>

### PBK model predicted free concentrations (µM)

<table>
<thead>
<tr>
<th></th>
<th>plasma</th>
<th>heart</th>
<th>liver</th>
<th>brain</th>
<th>adipose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (µM)</td>
<td>3.1 - 41.7</td>
<td>0.6 - 7.2</td>
<td>0.2 - 3.0</td>
<td>0.01 - 0.15</td>
<td>0.002 - 0.03</td>
</tr>
</tbody>
</table>
**“USING A TIERED AND ITERATIVE APPROACH”**

**Tier 0/I**
- Hazard Identification
  - Literature
  - Databases
  - Dashboard
  - In silico alerts
  - MIE atlas
  - AOP wiki

**Tier II**
- Pathway determination
  - Transcriptomics
  - Proteomics
  - Receptor screens
  - Stress panels
  - PBK

**Tier III**
- Pathway characterisation
  - Live cell imaging
  - Systems toxicology models
  - Repeat dose models
  - Organotypic models

- In silico-first approaches for identifying pathways of concern and formulating hypotheses for testing
- Identifying/characterising lead MIEs and pathways through experimental data generation
- Characterisation of response in biologically relevant *in vitro* systems and complex computational models for decision making

**Uncertainty**

HoSU; EBW; Biological Read Across; NAMs; Complex multi-endpoint NGRA

A CONTINUUM OF APPROPRIATE NEED
“USING ROBUST AND RELEVANT METHODS AND STRATEGIES”

- Use of ToxCast data
- Eurofins receptor safety screening
- Cell stress panels
- Discover X Biomap Diversity immune modulation panel
- SARA skin sensitization predictions
- ToxTracker mutagenicity profile
- BioSpyder TempoSeq HTTr and NoTEL prediction
The SARA Weight of Evidence (WoE) human potency model* is a high-dimensional probability distribution describing data from the following sources:

- DPRA OECD TG442D (cys/lys depletion)
- KeratinoSens™ OECD TG442C (EC_{1.5}, EC_{3}, IC_{50})
- H-Clat OECD TG442E (CD54 EC_{200}, CD86 EC_{150}, CV75)
- U-SENS™ OECD TG 442E (CD86)

* Reynolds, J, MacKay C, Gilmour N, Miguel-Vilumbrales D and Maxwell G (Submitted for publication: Computational Toxicology) Probabilistic prediction of human skin sensitisser potency for use in next generation risk assessment

AOP for skin sensitisation
https://aopwiki.org/aops/40
PREDICTION OF PROBABILITY OF SENSITISATION OCCURRING IN HRIPT*
FOR CASE STUDY CHEMICALS

*Human Repeat Insult Patch Test

= No Expected Sensitization Induction Level
(www.ifraorg.org)
PROBABILITY OF CONSUMER BECOMING SENSITISED (DIFFERENT PRODUCT TYPES)

**Face cream**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (µg cm⁻²)</th>
<th>Chance of inducing sensitisation in at least one individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNCB</td>
<td>10⁻¹ to 10³</td>
<td>p=1.00</td>
</tr>
<tr>
<td>Methyl heptine-carbonate</td>
<td>10⁻¹ to 10³</td>
<td>p=0.19</td>
</tr>
<tr>
<td>Coumarin</td>
<td>10⁻¹ to 10³</td>
<td>p=0.00</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>10⁻¹ to 10³</td>
<td>p=0.00</td>
</tr>
</tbody>
</table>

**Shampoo**

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</tr>
</thead>
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<td>Lactic acid</td>
<td>10⁻¹ to 10³</td>
<td>p=0.00</td>
</tr>
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**HUMAN RECEPTOR PANELS**

**SafetyScreen44™ Panel**

*In silico prediction tool*
BioMAP systems contain **human primary cell types** (or combinations) that are stimulated to replicate complex cell and pathway interactions normally found in disease physiology.

**Curcumin is active with 9 annotated readouts:**

- Antiproliferative to human primary coronary artery smooth muscle cells and endothelial cells (grey arrows).
- Inflammation-related activities: VCAM-1 (down), sPGE2 (down); IL-8 (up)
- Immunomodulatory activities: HLA-DR (down)
- Tissue remodeling activities: Collagen IV (down), PAI-1 (down); uPAR (up)
- Hemostasis-related activities: TF (up)
Range of biomarkers covering ~10 cell stress pathways:

**Mitochondrial Toxicity:** MitoSOX, PGC1α, MMP, ATP, Glu/Gal

**Oxidative Stress:** GSH, ROS, SRXN1, NRF2

**DNA damage:** pH2AX, p53

**Inflammation:** TNFAIP3, ICAM1, NFkB p65, IL-1β, IL-8, HMGB1

**ER Stress:** PERK, ATF4, CHOP, XBP1, BiP, ER Tracker

**Metal Stress:** MTF-1, Metallothionein

**Osmotic Stress (NFAT5); Heat Shock (HSP70); Hypoxia (HIF1α)**

**Cell Health:** LDH, Phospholipidosis, Steatosis, pHrodo indicator, apoptosis (caspase-3/7) & necrosis (ToPro-3)
INTERPRETING THE DATA IN CONTEXT OF EXPOSURE

Blood plasma FREE concentration (shaded region indicates uncertainty)

Positive biomarkers ‘hits’

Mean FREE concentration PoD (*) and 95% uncertainty range (o)

Colours indicate pathway
COMPARING A CASE STUDY CHEMICAL WITH A WELL-KNOWN TOXIC AGENT

**Coumarin**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular ATP 6h</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>IL-6 6h</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>XBP1 6h</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>LDH release 6h</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>Intracellular pH 6h</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Doxorubicin**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRXN1 6h</td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
</tr>
<tr>
<td>Glutathione content 5h</td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
</tr>
<tr>
<td>AHR Translocation 5h</td>
<td><img src="image15" alt="Graph" /></td>
<td><img src="image16" alt="Graph" /></td>
</tr>
<tr>
<td>Oxidative stress 5h</td>
<td><img src="image17" alt="Graph" /></td>
<td><img src="image18" alt="Graph" /></td>
</tr>
<tr>
<td>Mitochondrial mass 5h</td>
<td><img src="image19" alt="Graph" /></td>
<td><img src="image20" alt="Graph" /></td>
</tr>
<tr>
<td>Cellular ATP 5h</td>
<td><img src="image21" alt="Graph" /></td>
<td><img src="image22" alt="Graph" /></td>
</tr>
<tr>
<td>Metallothionein 6h</td>
<td><img src="image23" alt="Graph" /></td>
<td><img src="image24" alt="Graph" /></td>
</tr>
<tr>
<td>Heat Shock Response (Hsp70) 5h</td>
<td><img src="image25" alt="Graph" /></td>
<td><img src="image26" alt="Graph" /></td>
</tr>
<tr>
<td>HIF-1alpha 6h</td>
<td><img src="image27" alt="Graph" /></td>
<td><img src="image28" alt="Graph" /></td>
</tr>
<tr>
<td>Mitochondrial mass 6h</td>
<td><img src="image29" alt="Graph" /></td>
<td><img src="image30" alt="Graph" /></td>
</tr>
<tr>
<td>Cellular ATP 6h</td>
<td><img src="image31" alt="Graph" /></td>
<td><img src="image32" alt="Graph" /></td>
</tr>
<tr>
<td>Mitochondrial mass 6h</td>
<td><img src="image33" alt="Graph" /></td>
<td><img src="image34" alt="Graph" /></td>
</tr>
<tr>
<td>HIF-1alpha 6h</td>
<td><img src="image35" alt="Graph" /></td>
<td><img src="image36" alt="Graph" /></td>
</tr>
<tr>
<td>Mitochondrial mass 6h</td>
<td><img src="image37" alt="Graph" /></td>
<td><img src="image38" alt="Graph" /></td>
</tr>
<tr>
<td>Cellular ATP 6h</td>
<td><img src="image39" alt="Graph" /></td>
<td><img src="image40" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Comparisons**

- **6 hours**
  - Coumarin:
    - Cellular ATP 6h
    - IL-6 6h
    - XBP1 6h
    - LDH release 6h
    - Intracellular pH 6h
  - Doxorubicin:
    - SRXN1 6h
    - Glutathione content 5h
    - AHR Translocation 5h
    - Oxidative stress 5h
    - Mitochondrial mass 5h
    - Cellular ATP 5h
    - Metallothionein 6h
    - Heat Shock Response (Hsp70) 5h
    - HIF-1alpha 6h

- **24 hours**
  - Coumarin:
    - Cellular ATP 24h
    - IL-2 24h
    - ICAM-1 24h
    - HIF-1alpha 24h
    - Phospholipidosis 24h
  - Doxorubicin:
    - SRXN1 24h
    - Glutathione content 24h
    - AHR Translocation 24h
    - Oxidative stress 24h
    - Mitochondrial mass 24h
    - Cellular ATP 24h
    - Metallothionein 24h
    - Heat Shock Response (Hsp70) 24h
    - HIF-1alpha 24h
    - Telomere 24h
    - PERK 24h
    - ATF4 24h
    - p53 24h
    - p21 24h
    - p27 24h
    - p24 24h
    - HIF-1alpha 24h
    - Mitochondrial mass 24h
    - Cellular ATP 24h
    - Phospholipidosis 24h
COMPARING A CASE STUDY CHEMICAL WITH A WELL-KNOWN TOXIC AGENT

**Coumarin**

- 6 hours
  - Cellular ATP 6h
  - IL-6 6h
  - XBP1 6h
  - LDH release 6h
  - Intracellular pH 6h

- 24 hours
  - Glutathione content 24h
  - Cellular ATP 24h
  - IL-10 24h
  - ICAM-1 24h
  - HIF-1alpha 24h
  - Phospholipidosis 24h

**Doxorubicin**

- 6 hours
  - SRFK1 6h
  - Glutathione content 6h
  - Akt Translocation 6h
  - Oxidative stress 6h
  - Mitochondrial mass 6h
  - Cellular ATP 6h
  - Metallothionein 6h
  - Heat Shock Response (Hsp70) 6h
  - HIF-1alpha 6h
  - ATF4 6h
  - DNA damage (p-H2AX) 6h
  - DNA structure 6h
  - Caspase 3/7 intensity 6h

- 24 hours
  - Apoptosis 24h
  - Cleavage 24h
  - Splicing 24h
  - p-Chk1 24h
  - p-Chk2 24h
  - p-CREB 24h
  - p-ERK 24h
  - p-JNK 24h
  - p-Stat3 24h
  - p-PI3K 24h
  - p-P70S6K 24h
  - p-mTOR 24h
  - p-Akt 24h
  - Total Akt 24h
  - Total mTOR 24h
  - Total S6 24h
  - Total p70S6K 24h
  - Cleavage 24h
  - DNA damage 24h
  - DNA repair 24h
  - DNA synthesis 24h
  - DNA replication 24h
  - DNA integrity 24h
  - DNA damage 24h
  - DNA repair 24h
  - DNA synthesis 24h
  - DNA replication 24h
  - DNA integrity 24h
HIGH THROUGHPUT TRANSCRIPTOMICS

*NOTEL* is the derived concentration of a compound that does not elicit a *meaningful* change in gene expression (i.e. the threshold of the concentration that elicits minimal mechanistic activity).

*NOTEL* = No observed transcriptional effect level


Farmahin *et al.* (2017) Arch Tox 91, 2045-65

Recommended approaches in the application of toxicogenomics to derive points of departure for chemical risk assessment
HIGH-THROUGHPUT GENE EXPRESSION PROFILING PERFORMED AT BIOSPYDER

• Working with Cyprotex for treatments

CELL LINES:
- MCF-7 – human breast adenocarcinoma
- HepG2 – human liver carcinoma
- HepaRG – terminally differentiated hepatic cells that retain many characteristics of primary human hepatocytes
- N-HEK – Primary Normal Human Epidermal Keratinocytes

DEFINING A SAFE OPERATING EXPOSURE FOR SYSTEMIC TOXICITY USING A NOTEL (NO TRANSCRIPTIONAL EFFECT LEVEL)

[1732] Adipogenesis

<table>
<thead>
<tr>
<th>Compound</th>
<th>BMD50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>33.29</td>
</tr>
<tr>
<td>Bisdemethoxycurcumin</td>
<td>29.23</td>
</tr>
<tr>
<td>Tetrahydrocurcumin</td>
<td>--</td>
</tr>
<tr>
<td>6-Gingerol</td>
<td>--</td>
</tr>
</tbody>
</table>
HIGH THROUGHPUT TRANSCRIPTOMICS

Fold change >1.5
Genes in pathway >3
Fishers exact test >0.1
(3 independent experiments)

HepG2
MCF7
HepaRG

Conc Phenoxyethanol (µM)

POD - NOTEL value
Plasma concentration

Uncertainty

100x - 10x -

Exposure / Dose

High

Low

TOXICITY MARKERS FROM SPECIFIC CELL-BASED ASSAYS:

- Marker 1: 1.97 µM
- Marker 2: 2-3 µM
- Marker 3: 2.9-3.3 µM

Tissue conc

1.5 µM

0.05 µM

Uncertainty

PBK prediction

0.0001 µM

Uncertainty

POD

from various in vitro assays (range from multiple cell lines)

BER Plot

cytotoxicity

e.g. 20 µM

Tissue conc

1.5 µM

0.05 µM

Refinement of internal exposure
do ADME studies

without clearance

with clearance

Broader biological coverage

in vitro assays e.g.

BioSpyder

NOTEL

Oxidative Stress

NOAEC

Uncertainty

Unicell

High

Low

THREE LAYERS OF EXPOSURE / EFFECT RELATIONSHIP:

- Tissue concentration
- PBK prediction
- POD from various in vitro assays (range from multiple cell lines)

SOURCES OF UNCERTAINTY SHOULD BE CHARACTERIZED AND DOCUMENTED
NGRA – EXPOSURE-DRIVEN CASE STUDIES

Log (10) Consumer Exposure (µM)

Log (10) POD (µM)
NGRA – EXPOSURE-DRIVEN CASE STUDIES

暴露量在安全值区域内吗？
ICCR PRINCIPLES OF RISK ASSESSMENT AND WHAT WE’RE LEARNING FROM CASE STUDIES

• Importance of understanding consumer exposure including the relevance of metabolism
• Non-standard, bespoke data generation driven by the risk assessment question
• Ensuring quality, robustness of non-standard work including in silico modelling approaches and bespoke in vitro solutions
• Importance of defining points-of-departure and understanding adverse vs. adaptive responses for less conservative assurance
• Understanding uncertainty in risk assessments to allow informed decision-making
Advances in science are transforming toxicology risk assessment from A system based on using data from tests in live animals to One founded on understanding the effects of chemicals in humans using computational approaches and methods that evaluate changes in biologic processes using human cells.
PUBLICATIONS IN PREPARATION ON ALL THESE TO ILLUSTRATE THE USE OF NAMS IN NGRA SAFETY ASSURANCE
ACKNOWLEDGEMENTS

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