„How can Alternatives to Animal Testing bring benefit to Chemical Industry“

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Experimental Toxicology and Ecology, BASF SE

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EUSAAT Virtual Seminar Series 2021

BASF’s segments

Chemicals

Petrochemicals

Intermediates

Materials

Performance Materials

Monomers

Industrial Solutions

Dispersions & Pigments

Performance Chemicals

Surface Technologies

Catalysts

Coatings

Construction Chemicals*

Nutrition & Care

Nutrition & Health

Care Chemicals

Agricultural Solutions

* We are considering the possibility of merging our construction chemicals business with a strong partner, as well as the option of divesting this business. The outcome of this review is open. The Construction Chemicals division will be reported under the Surface Technologies segment until signing of a transaction agreement.

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Global Chemical Safety

Consumer

Worker

Chemicals

REACH (EG 1907/2006)

Pesticides:

EG 1107/2009

Cosmetics:

EG 1223/2009

22.12.2009 EN Official Journal of the European Union L 342/59

REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 30 November 2009
on cosmetic products
(recast)
(Text with EEA relevance)

Environment

Population

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Regulatory Toxicology – Risk Assessment

RISK = EXPOSURE x HAZARD

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BASF – Experimental Toxicology and Ecology

- **Ludwigshafen**
  - 1,200 m² for ecology studies
  - 10,800 m² for toxicology studies
  - 1,000 m² for in vitro studies
  - 1,800 m² air-conditioned rooms for laboratory animals
  - 1,350 m² for dog facilities
  - ~ 240 employees (30 scientists)
- **Berlin – BASF metabolome solutions GmbH**
  - Analytical services under GLP
  - Metabolomics in plants, fish and mammalian matrices
  - >40 employees

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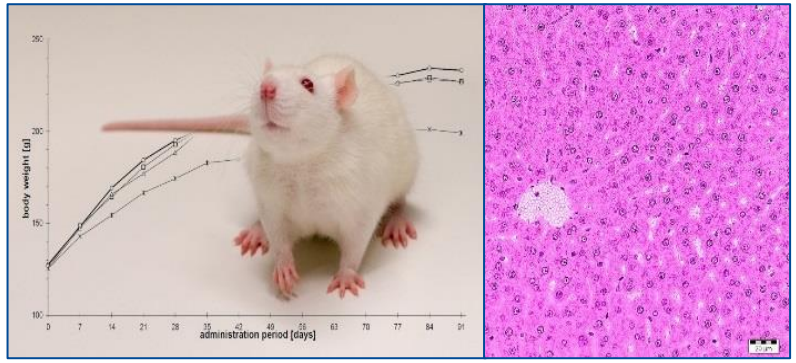
Animal Testing - In accordance to Test Guidelines (OECD)



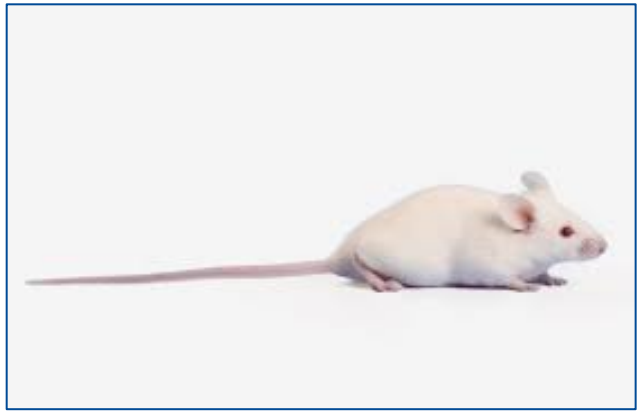
Acute, subchronic, chronic toxicity and cancerogenicity

Inhalation toxicity

Reproductive toxicity

Ecotoxicity

Biokinetics



Genotoxicity

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Animal testing - Animal Welfare (EU 63/2010)

DIRECTIVES

DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 22 September 2010

…imals used for scientific purposes

(…with EEA relevance)

Article 1

Subject matter and scope

1. This Directive establishes measures for the protection of animals used for scientific or educational purposes.

To that end, it lays down rules on the following:

(a) the replacement and reduction of the use of animals in procedures and the refinement of the breeding, accommodation, care and use of animals in procedures;

(b) the origin, breeding, marking, care and accommodation and killing of animals;

(c) the operations of breeders, suppliers and users;

(d) the evaluation and authorisation of projects involving the use of animals in procedures.

Article 4

Principle of replacement, reduction and refinement

1. Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure.

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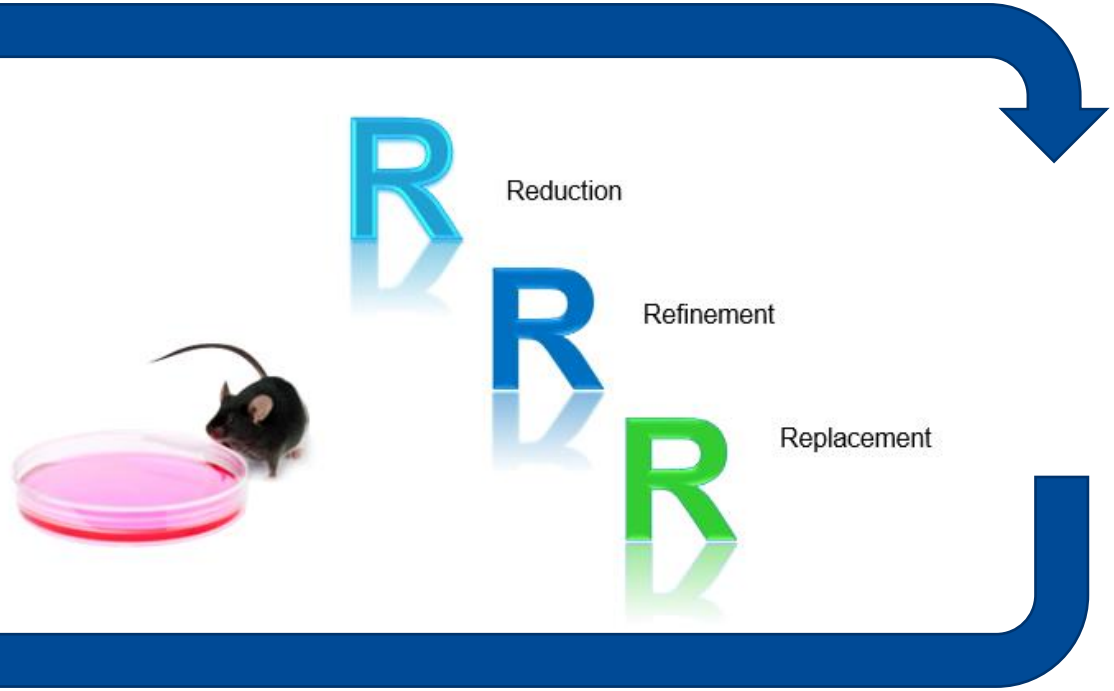
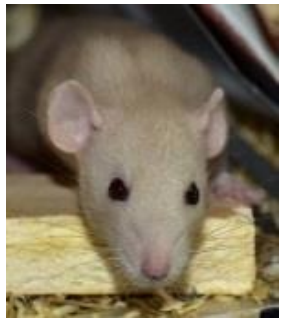
Safety assessment by Alternatives to Animal Testing

Consumer

Worker



Laboratory Animal



Environment

Population

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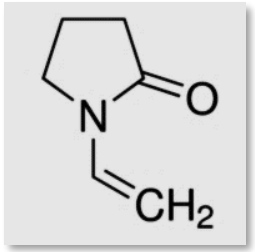
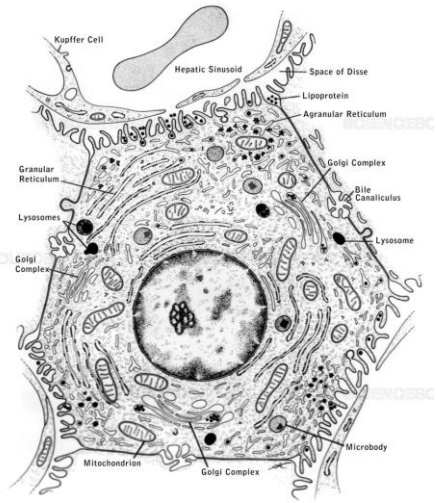
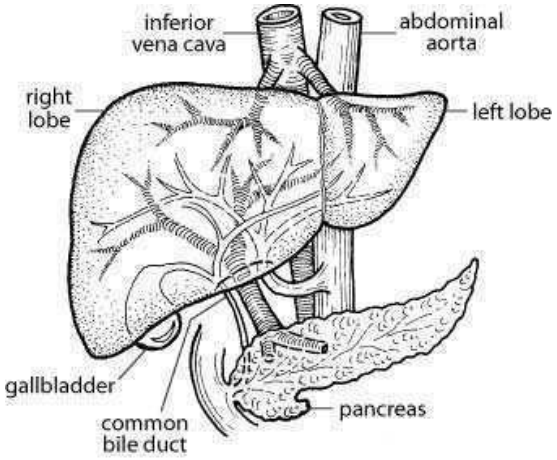
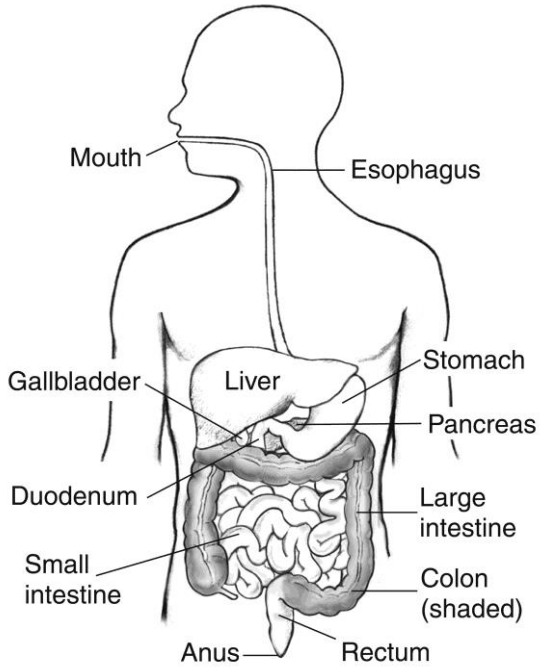
Modern Toxicology - Adverse Outcome Pathways









Molecular
initiating event

Cellular
key events

Organ
key events

Organism
adverse outcome

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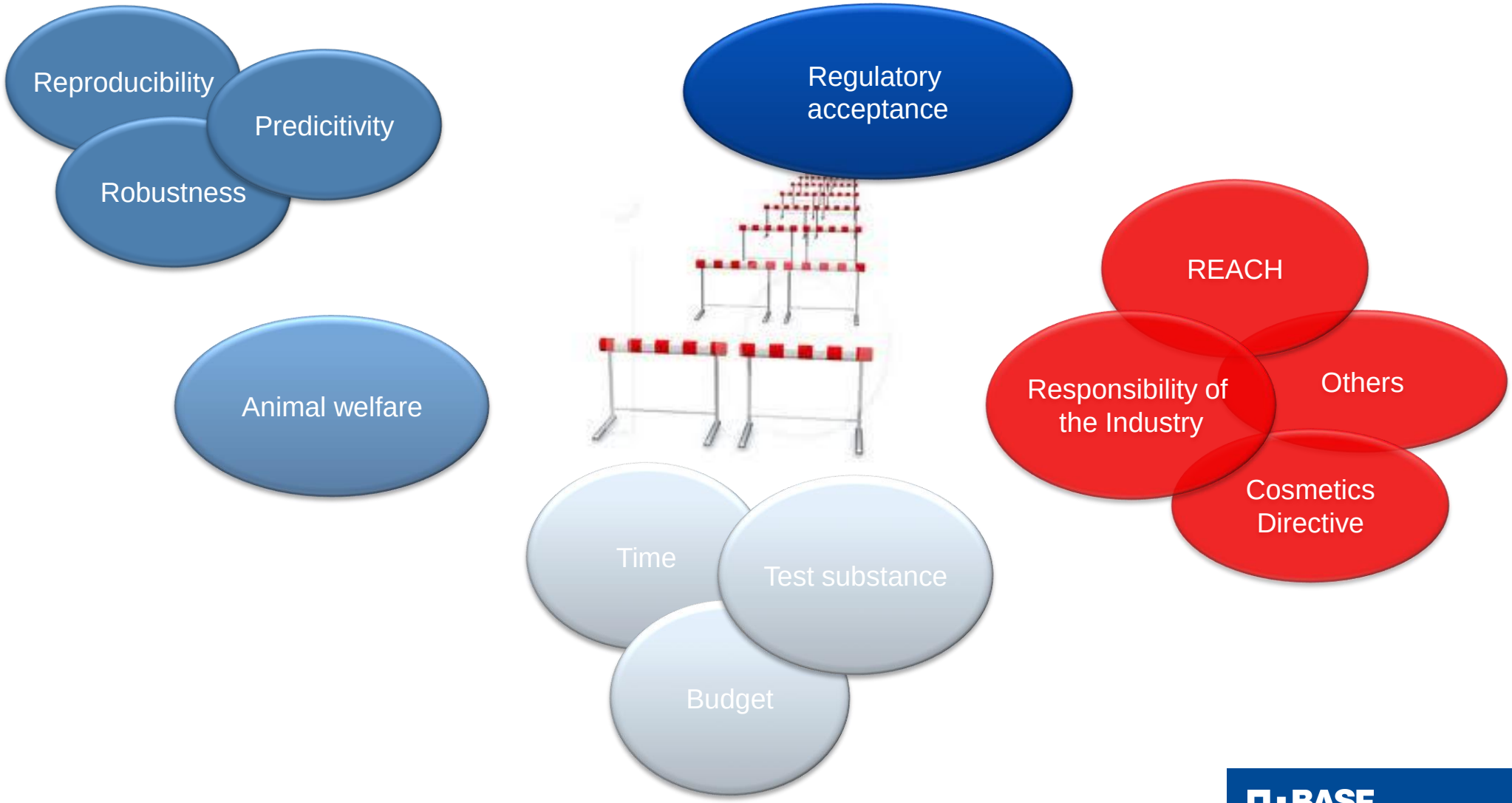
From research to regulation - challenges



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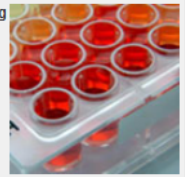
Alternative toxicological methods at BASF - A success story

Innovation Award 2012

Toxikologische Untersuchungen: Mit Alternativmethoden zum Erfolg

Chemikalien, Pflanzenschutzmittel und Pharmawirkstoffe müssen sicher sein und dürfen die Gesundheit nicht gefährden. Um dies zu gewährleisten, schreibt der Gesetzgeber unter anderem umfangreiche toxikologische Tests vor, die oftmals den Versuch an Tieren erfordern. Doch es gibt auch Alternativen. Der Aufgabe, diese zu entwickeln widmet sich das BASF-Projektteam der Experimentellen Toxikologie und Ökologie.



»mehr

TRADE NEWS | DEC 2, 2013

BASF receives 2013 Animal Protection Research Prize

- **German Federal Ministry of Food, Agriculture and Consumer Protection honors research team for developing alternative methods**
- **About one third of all toxicological studies at BASF are conducted using alternative methods**

OECD/OCDE **442D**
Adopted:
25June 2018

KEY EVENT BASED TEST GUIDELINE 442D

IN VITRO SKIN SENSITISATION ASSAYS ADDRESSING THE AOP KEY EVENT ON KERATINOCYTE ACTIVATION

GENERAL INTRODUCTION

Keratinocyte activation Key Event based Test Guideline

1. A skin sensitiser refers to a substance that will lead to an allergic response following repeated skin contact as defined by the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (UN GHS) (1). There is general agreement on the key biological events underlying skin sensitisation. The current knowledge of the chemical and biological mechanisms associated with skin sensitisation has been summarised as an Adverse Outcome Pathway (AOP) (2), starting with the molecular initiating event through intermediate events to the adverse effect, namely allergic contact dermatitis. This AOP focuses on chemicals that react with thiol (i.e. cysteine) and primary amines (i.e. lysine) such as organic chemicals. In this instance, the molecular initiating event (i.e. the first key event) is the covalent binding of electrophilic substances to nucleophilic centres in skin proteins. The second key event in this AOP takes place in the keratinocytes and includes inflammatory responses as well as changes in gene expression associated with specific cell signalling pathways such as the antioxidant/electrophile response element (ARE)-dependent pathways. The third key event is the activation of dendritic cells, typically assessed by expression of specific cell surface markers, chemokines and cytokines. The fourth key event is T-cell proliferation (3).

2. This Test Guideline describes in vitro assays that address mechanisms described under the second Key Event of the AOP for skin sensitisation, namely keratinocyte activation (2). The Test Guideline comprises test methods to be used for supporting the discrimination between skin sensitisers and non-sensitisers in accordance with the UN GHS (1). The test methods currently described in this Test Guideline are:

- The ARE-Nrf2 luciferase KeratinoSens™ test method (Appendix IA), and
- The ARE-Nrf2 luciferase LuSens test method (Appendix IB).

3. These two in vitro ARE-Nrf2 luciferase test methods have been considered scientifically valid. The KeratinoSens™ test method first underwent a validation study followed by an independent peer-review by EURL ECVAM Scientific Advisory Committee (ESAC) and positive recommendations by EURL ECVAM, and is considered the validated reference method (VRM) (3) (4) (5) (6). The LuSens test method later

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In accordance with the decision of the Council on a delegation of authority to amend Annex I of the decision of the council on the Mutual Acceptance of Data in the assessment of chemicals [C(2018)49], this Guideline was amended by the OECD's Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology by written procedure on 25 June 2018.

2012 **2013** **2016** **2018**

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Status quo Regulatory Acceptance of Alternative Methods

- Skin irritation and corrosion
- Eye irritation
- Skin sensitization
- Acute systemic toxicit
- Repeated exposure systemic/organ toxicity
- Reproductive toxicity
- Mutagenicity
- Carcinogenicity

NOT TESTED ON ANIMALS

2006	EU animal testing as „last resort“ for REACH
2013	EU ban for cosmetic ingredients
2017	UK restriction for plant protection products
2025	NL to end the use of animals in safety testing
2035	US EPA to phase-out the use of animals

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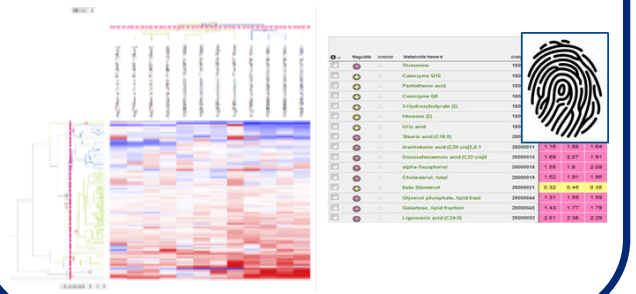
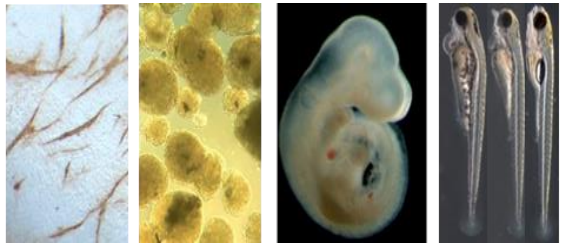
Alternative Toxicological Methods – Projects (2020-2023)

Metabolome and Microbiome Platform



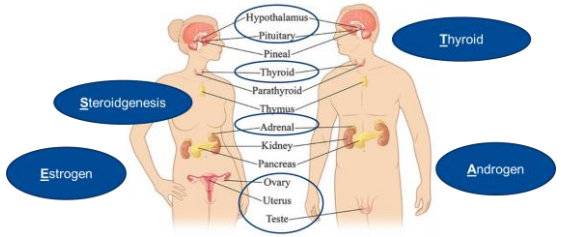
Reproductive Toxicity



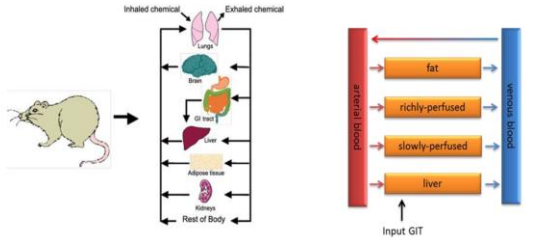
Computational Toxicology

NanoGrouping

Endocrine Effects



IVIVE (in vitro to in vivo extrapolation)



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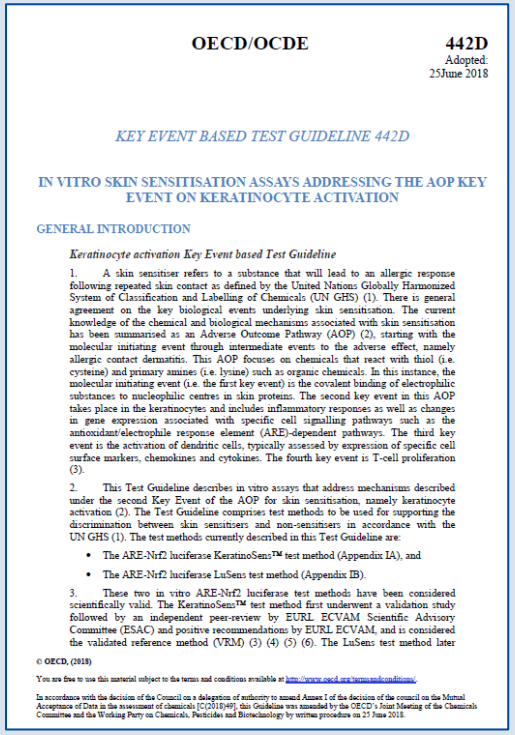
Safety assessment by Alternatives to Animal Testing

Regulatory Studies



OECD/OCDE 442D
Adopted: 25June 2018

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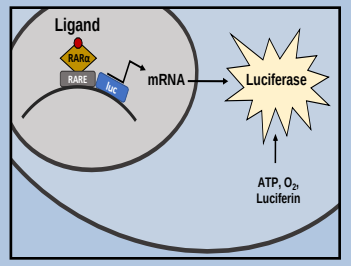
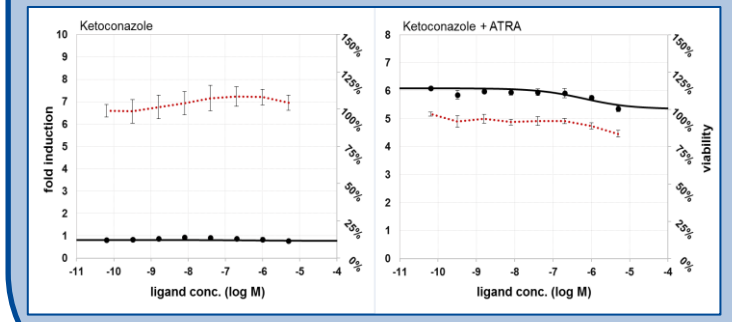
Mechanistical studies





Screening

>100 000 compounds

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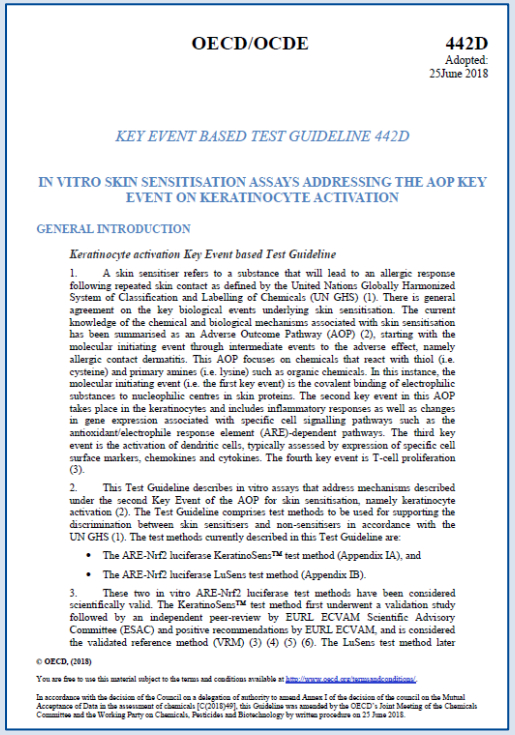
Safety assessment by Alternatives to Animal Testing

Regulatory Studies



OECD/OCDE

442D
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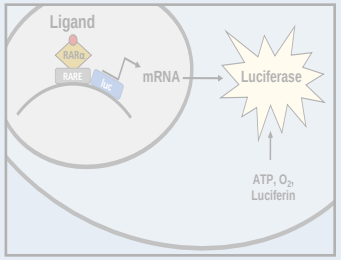
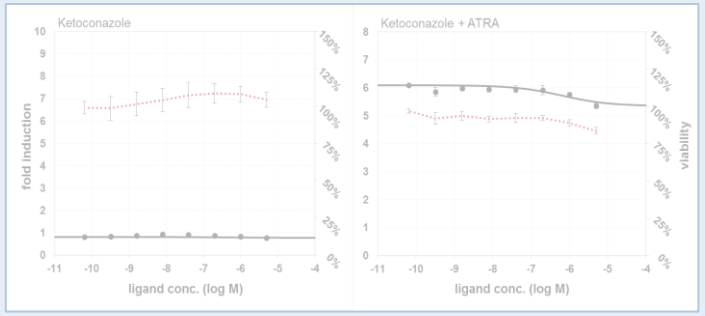
Mechanistical studies





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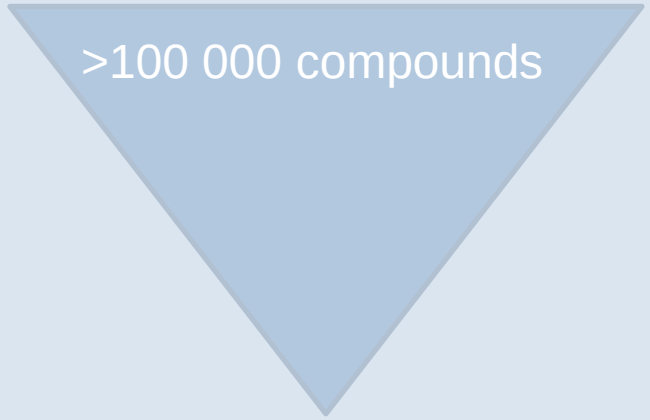

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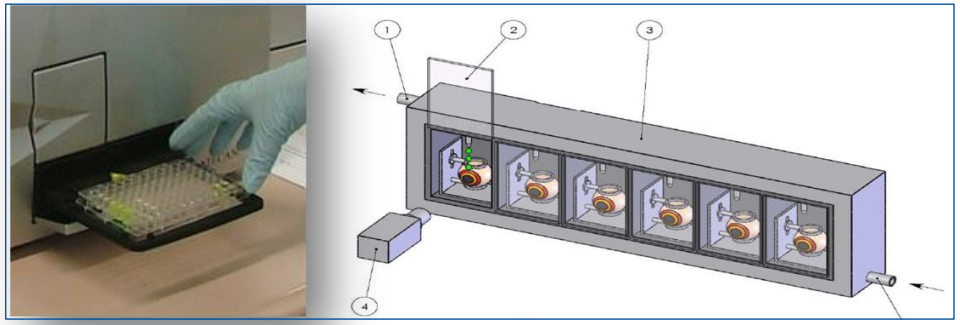
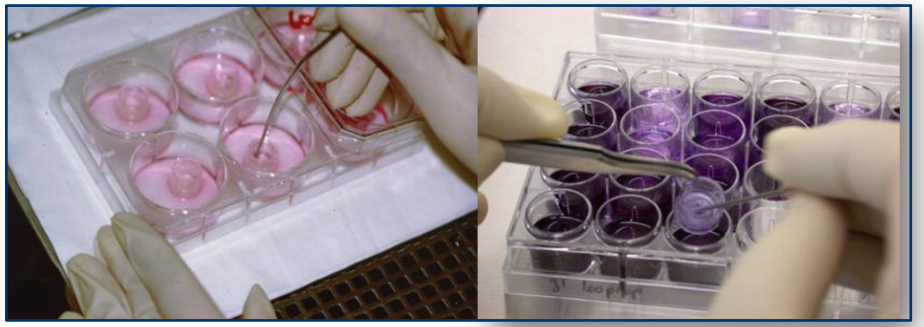
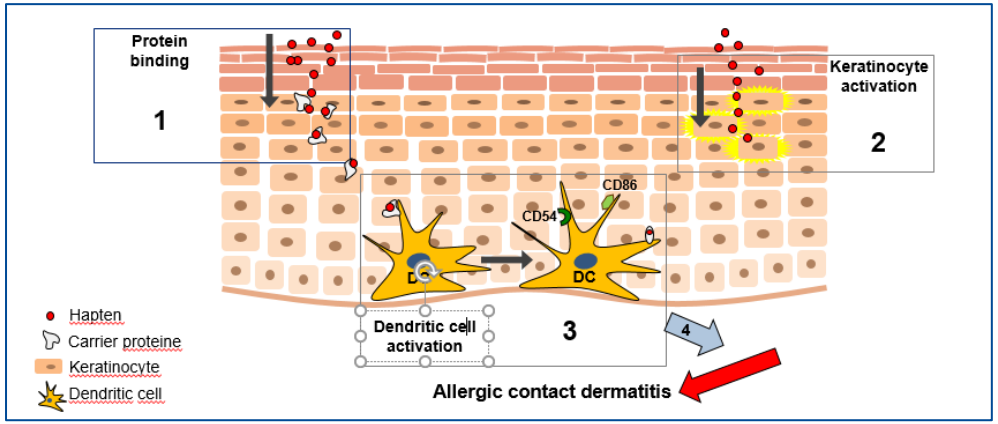
OECD in vitro studies



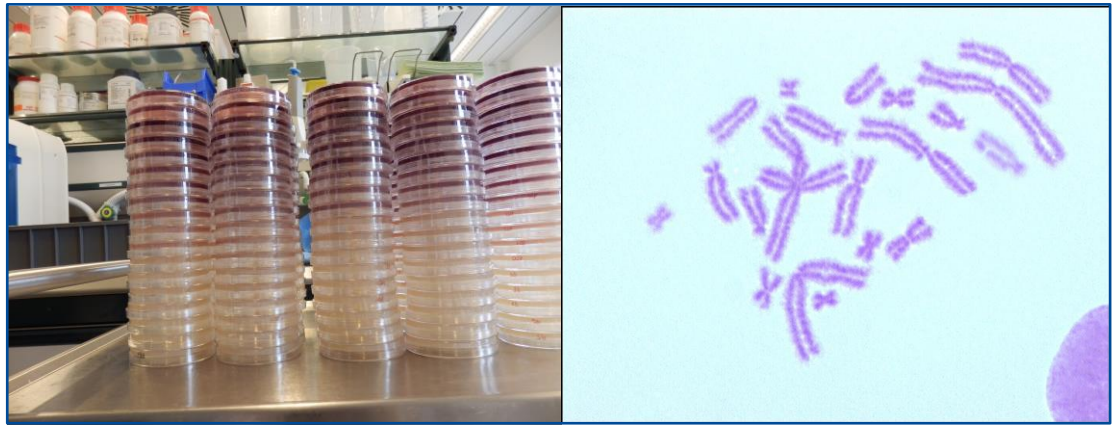
Eye Irritation



Skin corrosion and irritation



Skin sensitization



Genotoxicity

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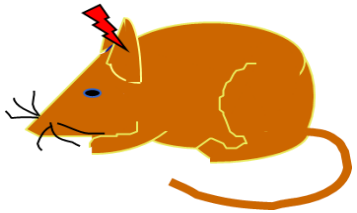
Skin sensitization – Animal testing

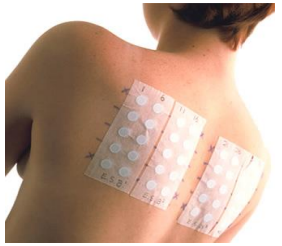
Animal tests



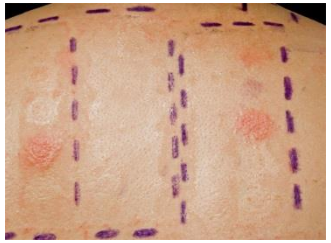
Local lymph node assay (LLNA; OECD TG 429, 442A & B)

Buehler & guinea pig maximization test (GPMT; OECD TG 406)

Human tests



princetonconsumer.com



http://www.cliantha.in

e.g. Human Repeated Insult Patch Test (HRIPT)

- **Regulatory aspects:**
  - Chemicals: REACH prescribes the LLNA for all chemicals (≥ 1 t/a)
  - Cosmetics: EU Cosmetic Directive/Regulation imposed a full ban on animal tests

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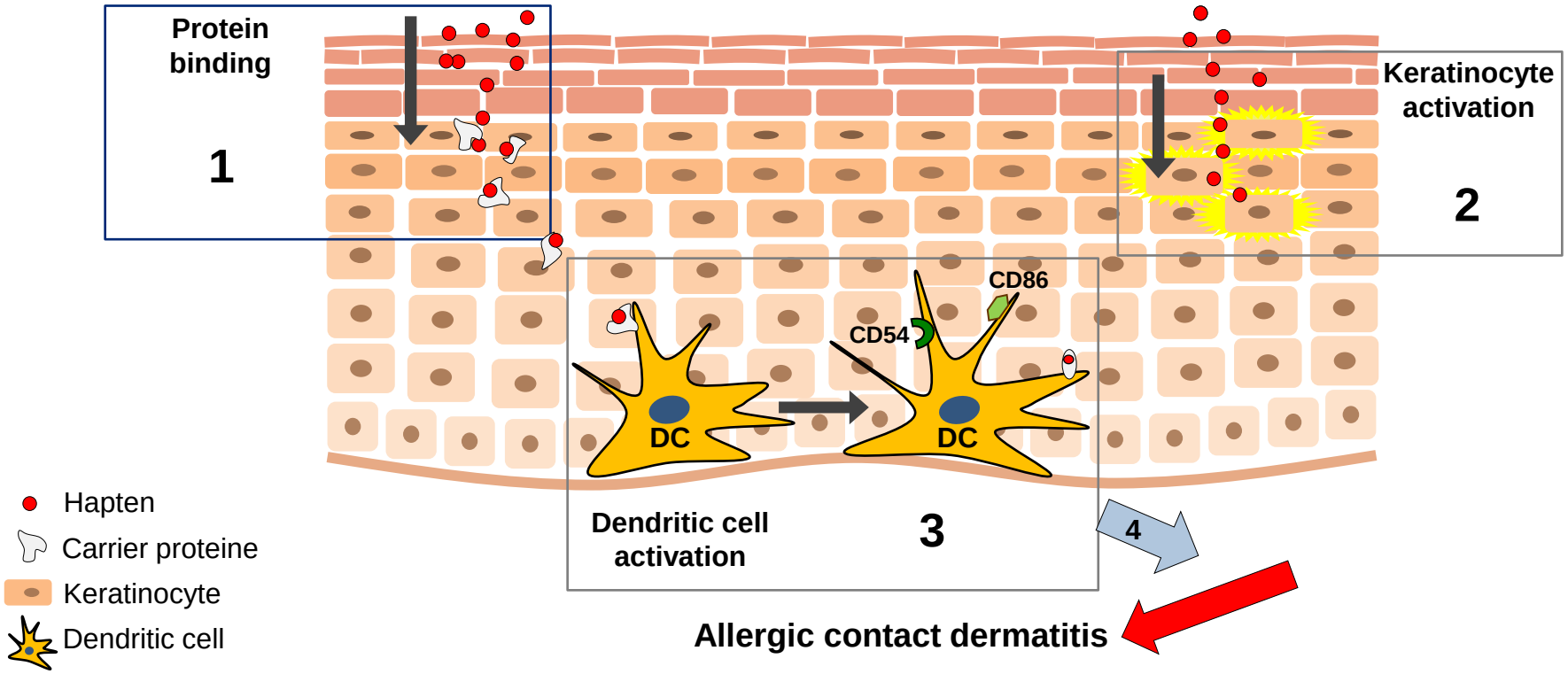
Skin sensitization – Adverse outcome pathway (AOP)



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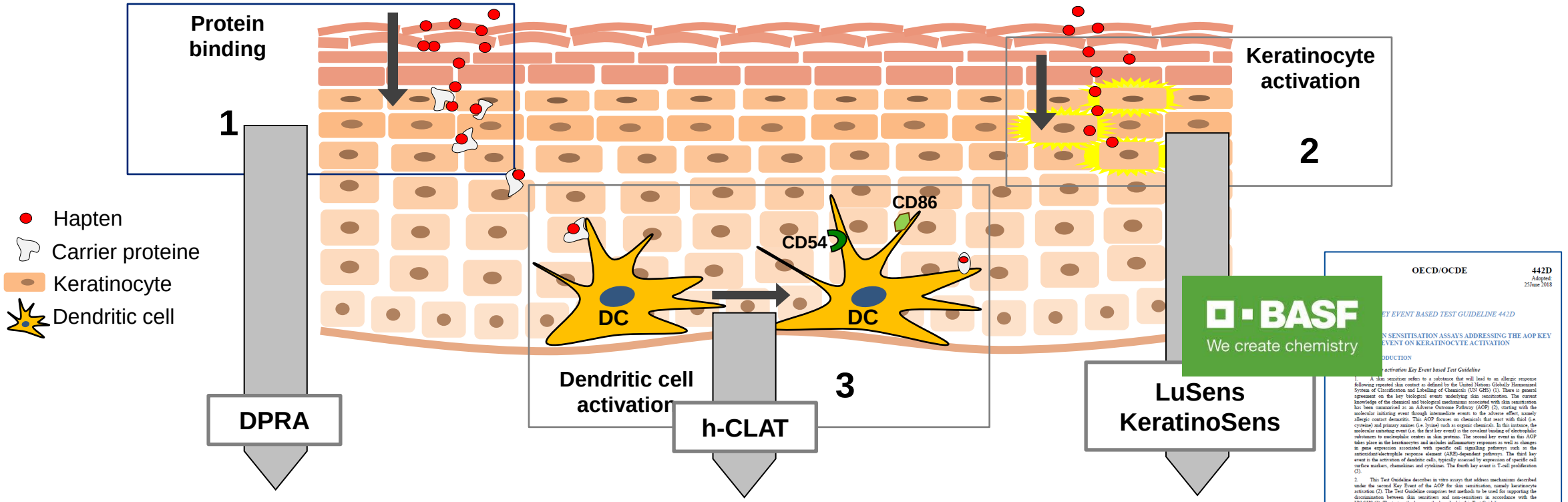
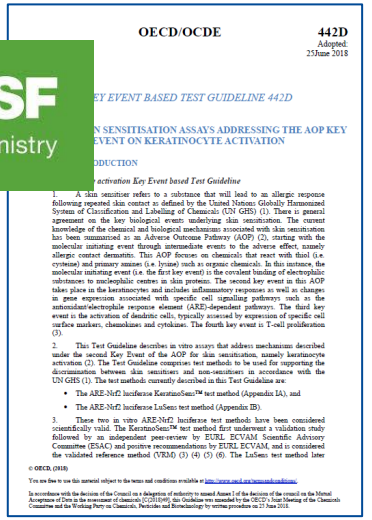
Skin sensitization – IATA




OECD/OCDE 442D
Adopted: 25June 2018

"2 out of 3" integrated testing strategy
IATA case no. 1 (ENV/JM/HA(2016)11)

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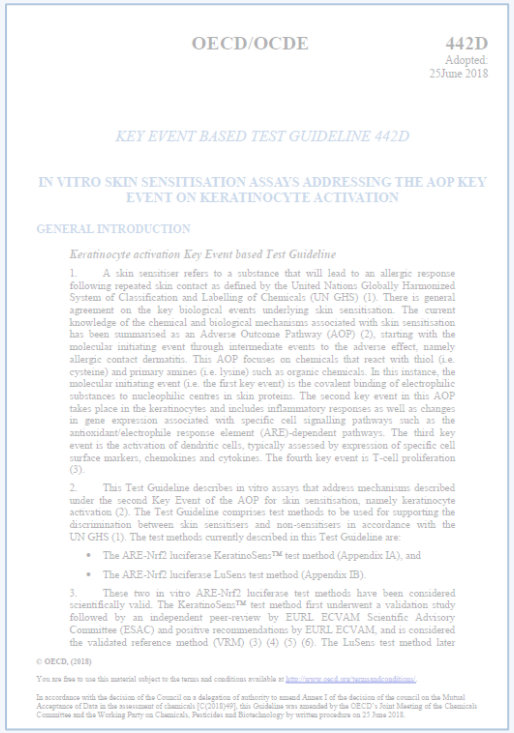
Safety assessment by Alternatives to Animal Testing

Regulatory Studies



OECD/OCDE 442D
Adopted: 25June 2018

KEY EVENT BASED TEST GUIDELINE 442D

IN VITRO SKIN SENSITISATION ASSAYS ADDRESSING THE AOP KEY EVENT ON KERATINOCYTE ACTIVATION

GENERAL INTRODUCTION

Keratinocyte activation Key Event based Test Guideline

1. A skin sensitiser refers to a substance that will lead to an allergic response following repeated skin contact as defined by the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (UN GHS) (1). There is general agreement on the key biological events underlying skin sensitisation. The current knowledge of the chemical and biological mechanisms associated with skin sensitisation has been summarised as an Adverse Outcome Pathway (AOP) (2), starting with the molecular initiating event through intermediate events to the adverse effect, namely allergic contact dermatitis. This AOP focuses on chemicals that react with thiol (i.e. cysteine) and primary amines (i.e. lysine) such as organic chemicals. In this instance, the molecular initiating event (i.e. the first key event) is the covalent binding of electrophilic substances to nucleophilic centres in skin proteins. The second key event in this AOP takes place in the keratinocytes and includes inflammatory responses as well as changes in gene expression associated with specific cell signalling pathways such as the antioxidant/electrophile response element (ARE)-dependent pathways. The third key event is the activation of dendritic cells, typically assessed by expression of specific cell surface markers, chemokines and cytokines. The fourth key event is T-cell proliferation (3).

2. This Test Guideline describes in vitro assays that address mechanisms described under the second Key Event of the AOP for skin sensitisation, namely keratinocyte activation (2). The Test Guideline comprises test methods to be used for supporting the discrimination between skin sensitisers and non-sensitisers in accordance with the UN GHS (1). The test methods currently described in this Test Guideline are:

- The ARE-Nrf2 luciferase KeratinoSens™ test method (Appendix IA), and
- The ARE-Nrf2 luciferase LuSens test method (Appendix IB).

3. These two in vitro ARE-Nrf2 luciferase test methods have been considered scientifically valid. The KeratinoSens™ test method first underwent a validation study followed by an independent peer-review by EURL ECVAM Scientific Advisory Committee (ESAC) and positive recommendations by EURL ECVAM, and is considered the validated reference method (VRM) (3) (4) (5) (6). The LuSens test method later

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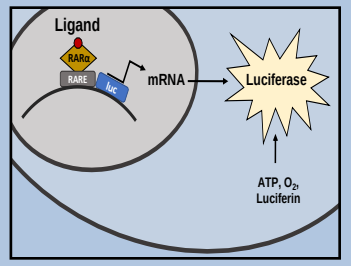
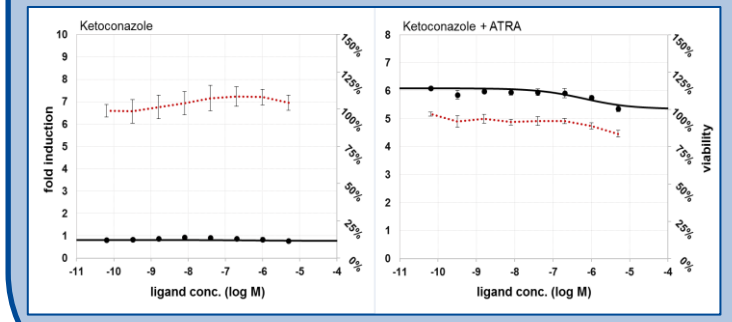
Mechanistical studies





Screening

>100 000 compounds

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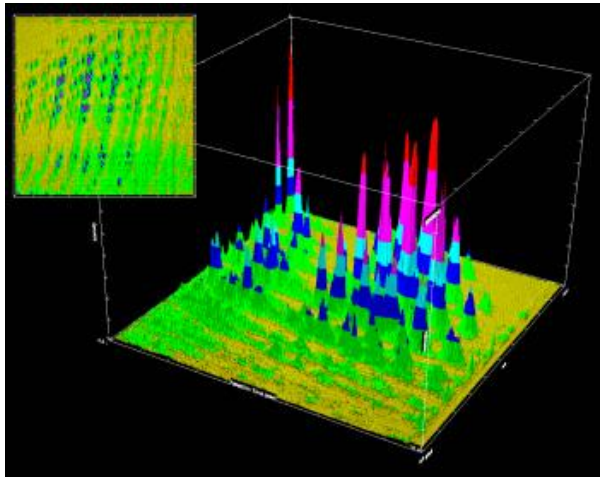
Alternative Toxicological Methods – Metabolomics for Read-Across

Treatment (28 days)

Blood sampling (d7, d14, d28)

Metabolite
Tryptophan
Arginine
Tyrosine
Thyroxine (T4)
Linolenic acid (C18:cis[9,1...
alpha-Tocopherol
Lignoceric acid (C24:0)
Campesterol
Tricosanoic acid (C23:0)
Phytosphingosine
14-Methyl-Pentadecanoic aci...
17-Methyloctadecanoic acid
Eicosatrienoic acid (C20:3)...
O-Methylsphingosine No1 (pl...
O-Methylsphingosine No2 (pl...
erythro-Sphingosine
Cholesterol
5-Oxoproline
Citrate
Glutamate
Creatinine
Sphingomyelin No 01 (putative)
Sphingomyelin (d18:1, C16:0...



Metabolom
9000 signals
~300 known metabolites

MetaMap®Tox

Sample **Reference**

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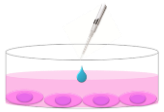
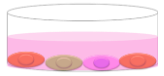
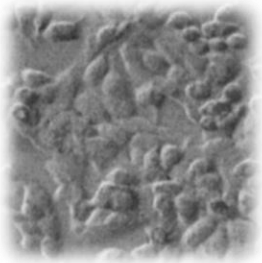
Alternative Toxicological Methods – Metabolomics in vitro



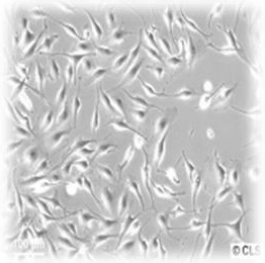
Treatment

Sampling
(48h)



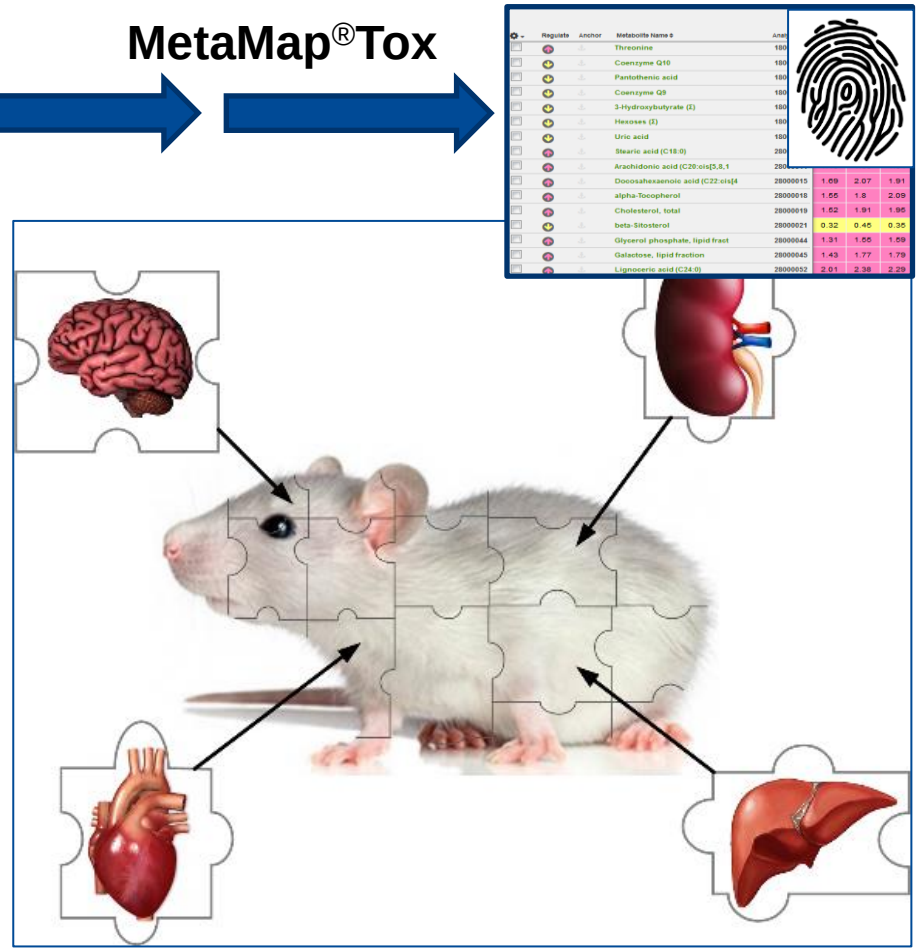


Liver Cells



Kidney Cells

MetaMap®Tox



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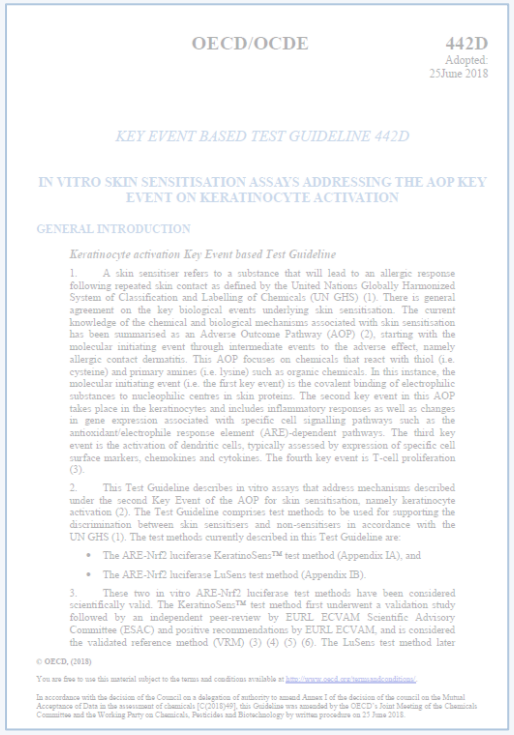
Safety assessment by Alternatives to Animal Testing

Regulatory Studies



OECD/OCDE 442D
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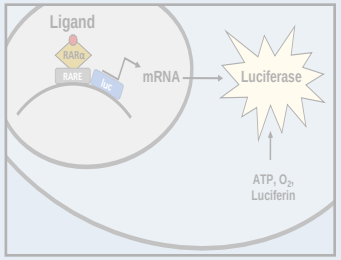

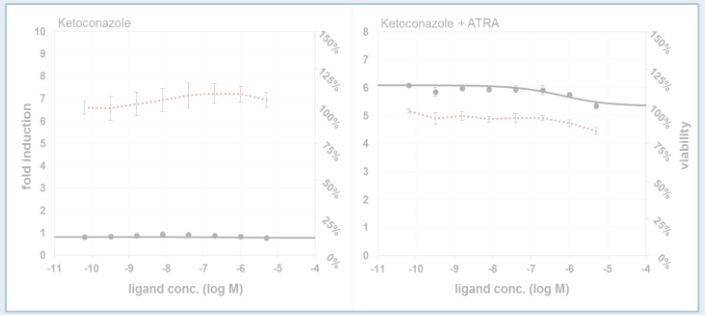

Screening

>100 000 compounds

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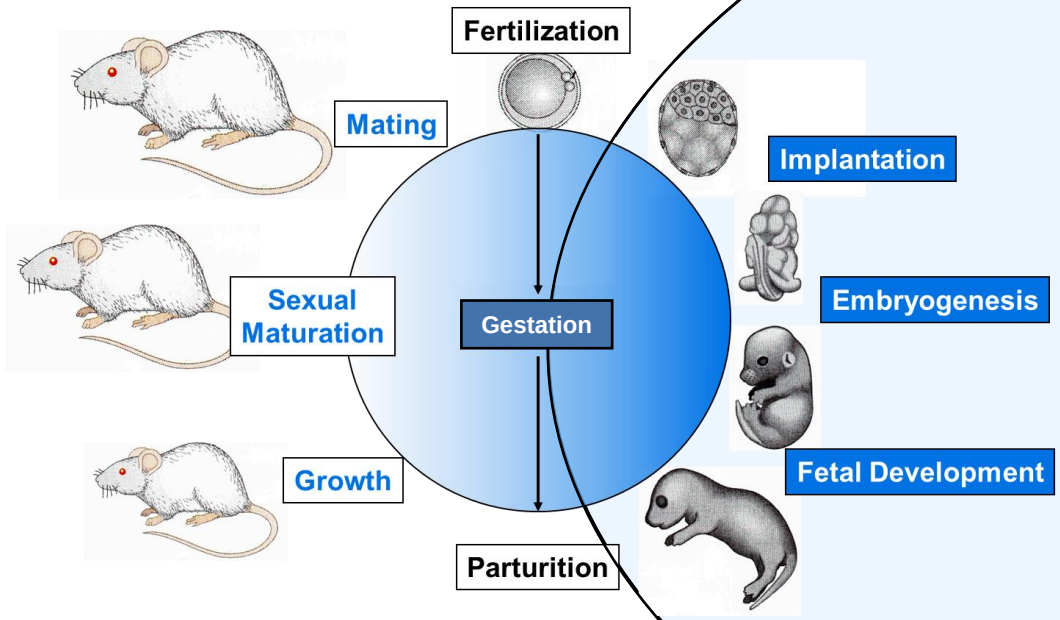
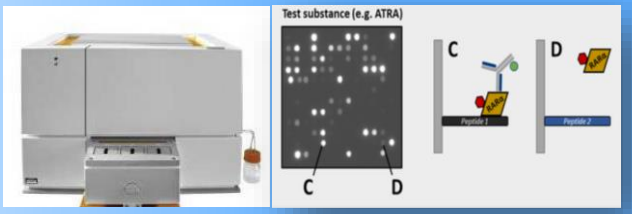
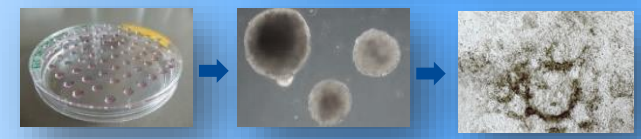
Reproductive Toxicity



RA binding

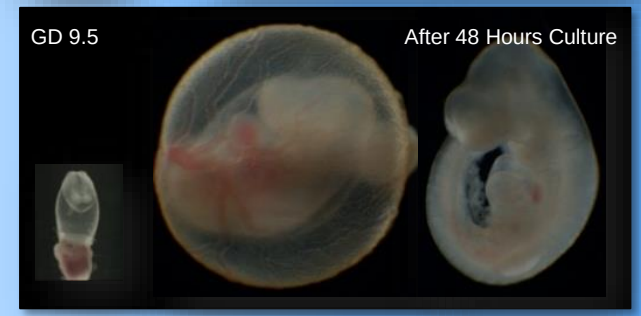


EST



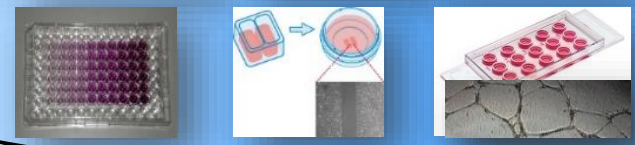
zfTera

WEC



Ex ovo

Angio



→ **BASF develops a toolbox for screening of potential developmental toxicity effects**

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Endocrine effects

Source:
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311

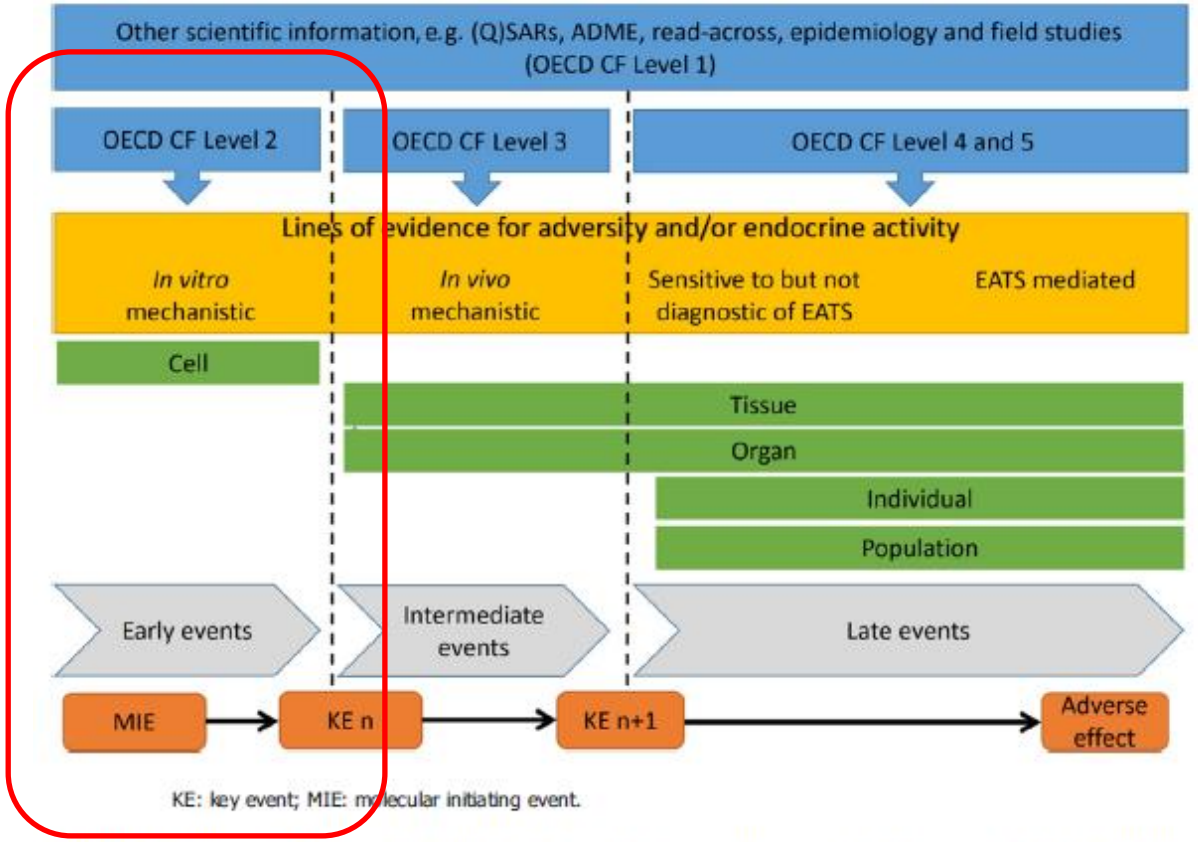
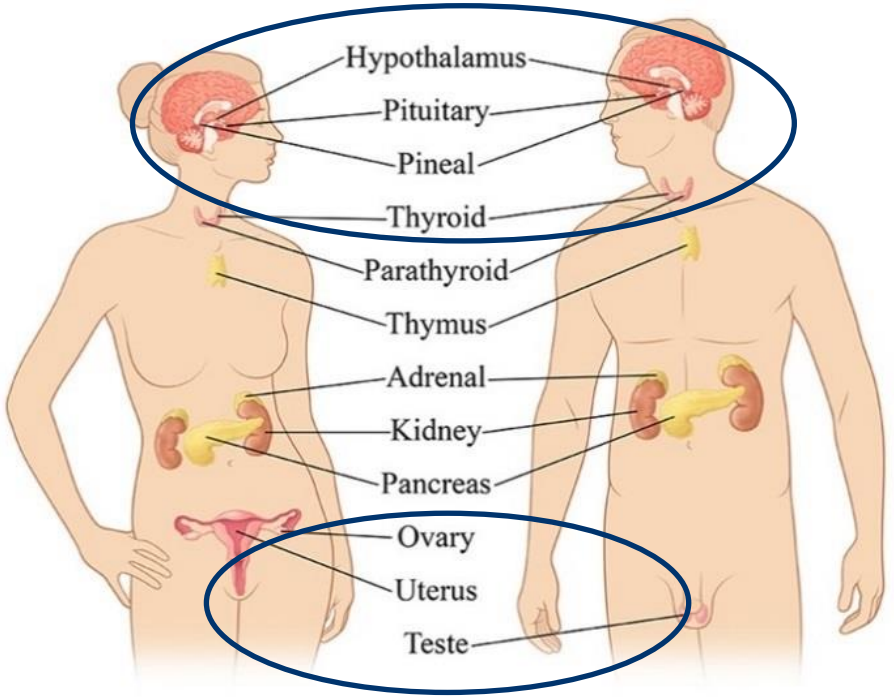


Figure 6: Scheme illustrating how the lines of evidence can be organised to support the postulated mode of action. The arrows linking KEs represent the KE relationships



http://anatomyandphysiologyfinal.weebly.com/endocrine-system.html

→ **BASF address the mechanistical understanding regarding ED properties of the pesticides/ chemicals by in vitro methods**

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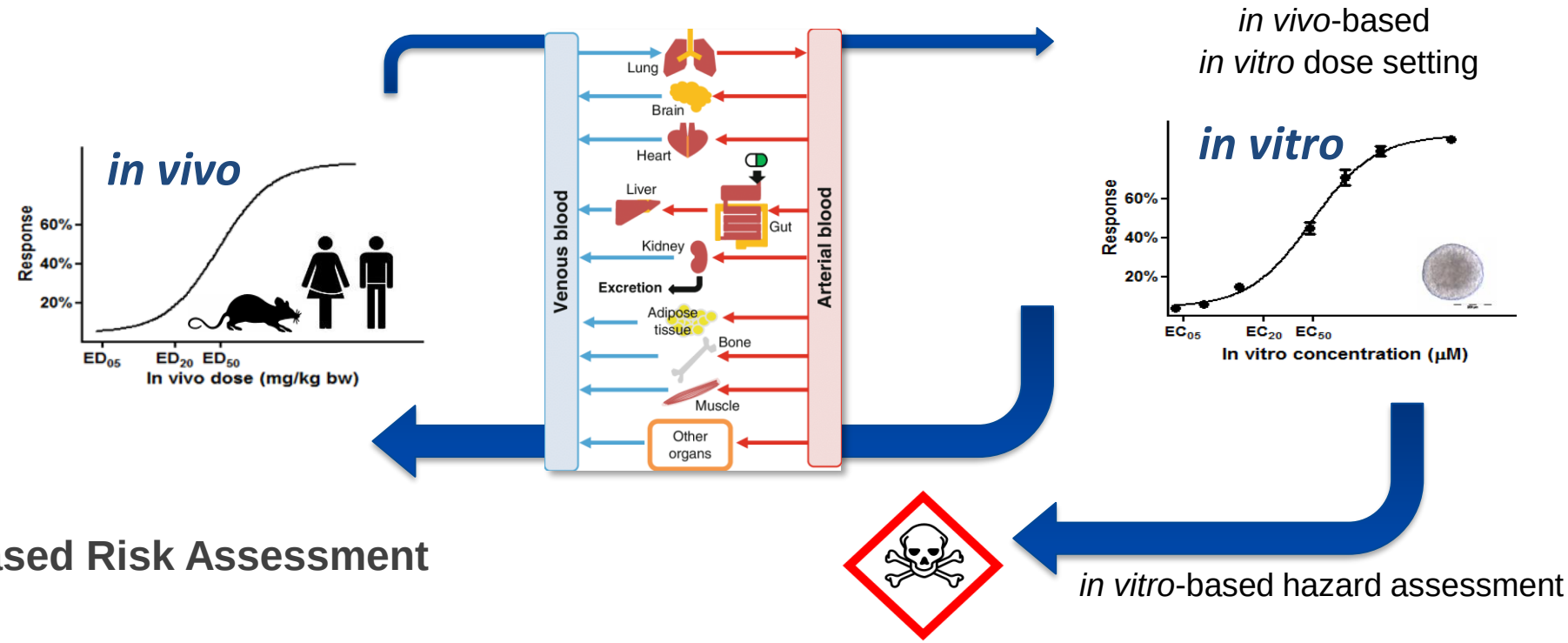
In vitro to *in vivo* Extrapolation (IVIVE)



→ BASF develops and optimizes kinetic models to predict *in vitro* and *in vivo* concentrations at the target to allow an appropriate risk assessment

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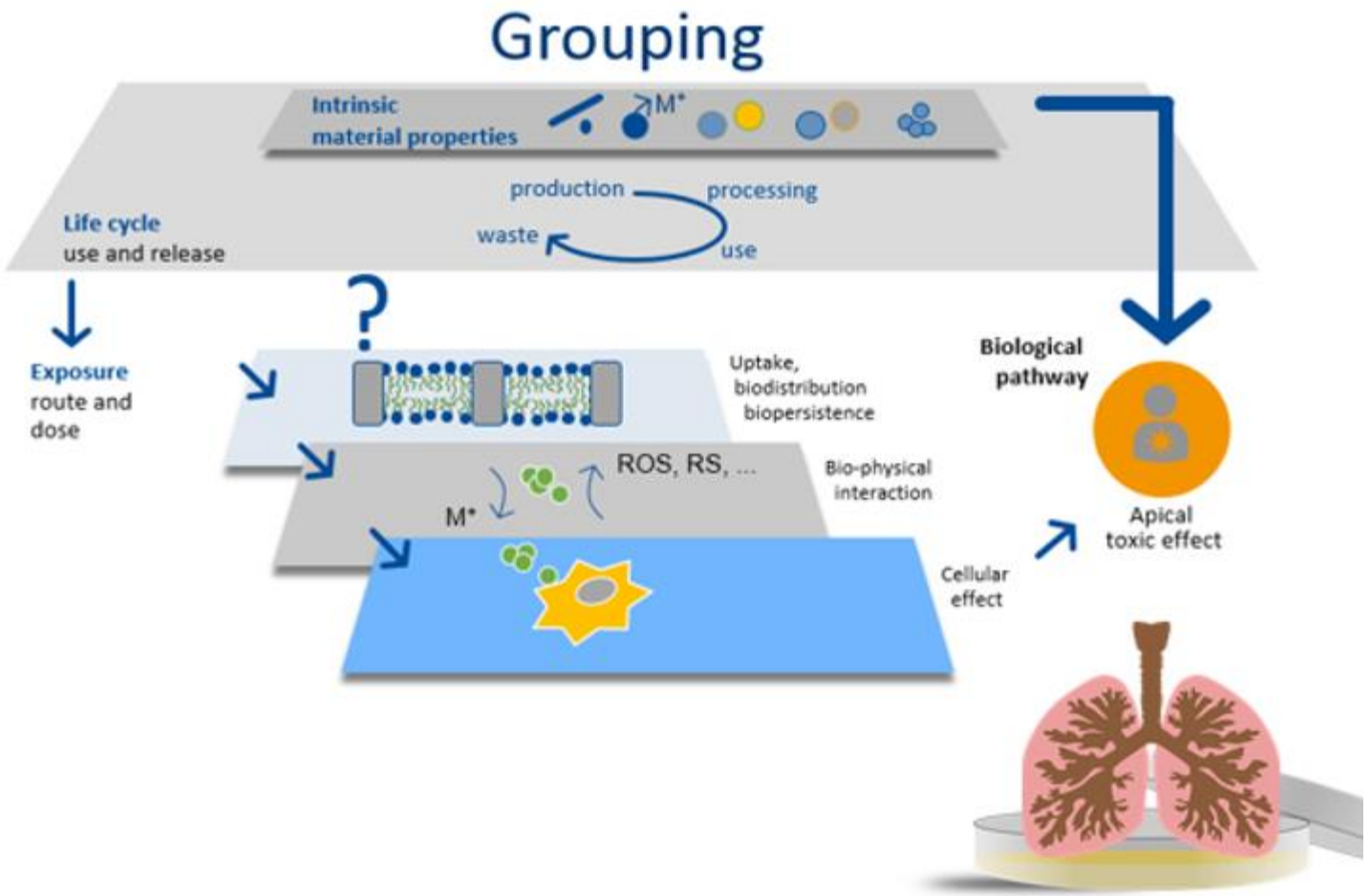
NanoGrouping



→ BASF develops strategies for grouping nanomaterials to reduce the numbers of required animal studies
→ BASF is partner in several EU/BMBF-funded projects
→ BASF develops new methods for in vitro lung toxicity

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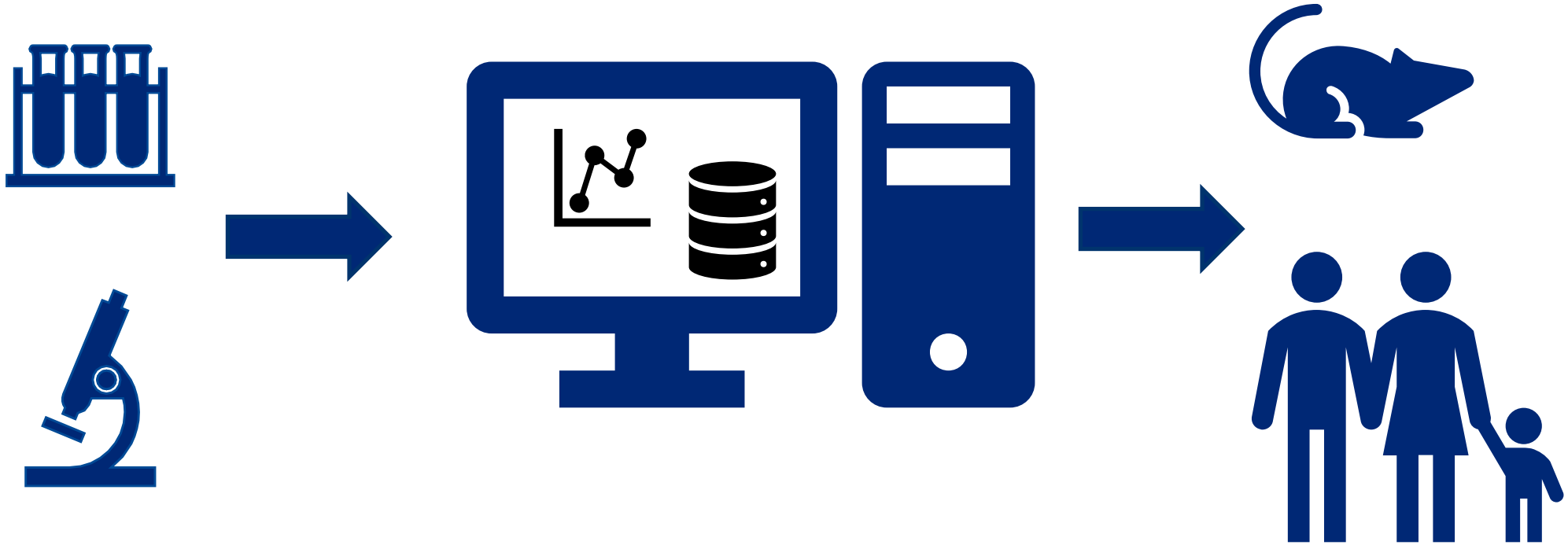
Computational Toxicology



→ **BASF develops tools to predict toxicological endpoints in silico**

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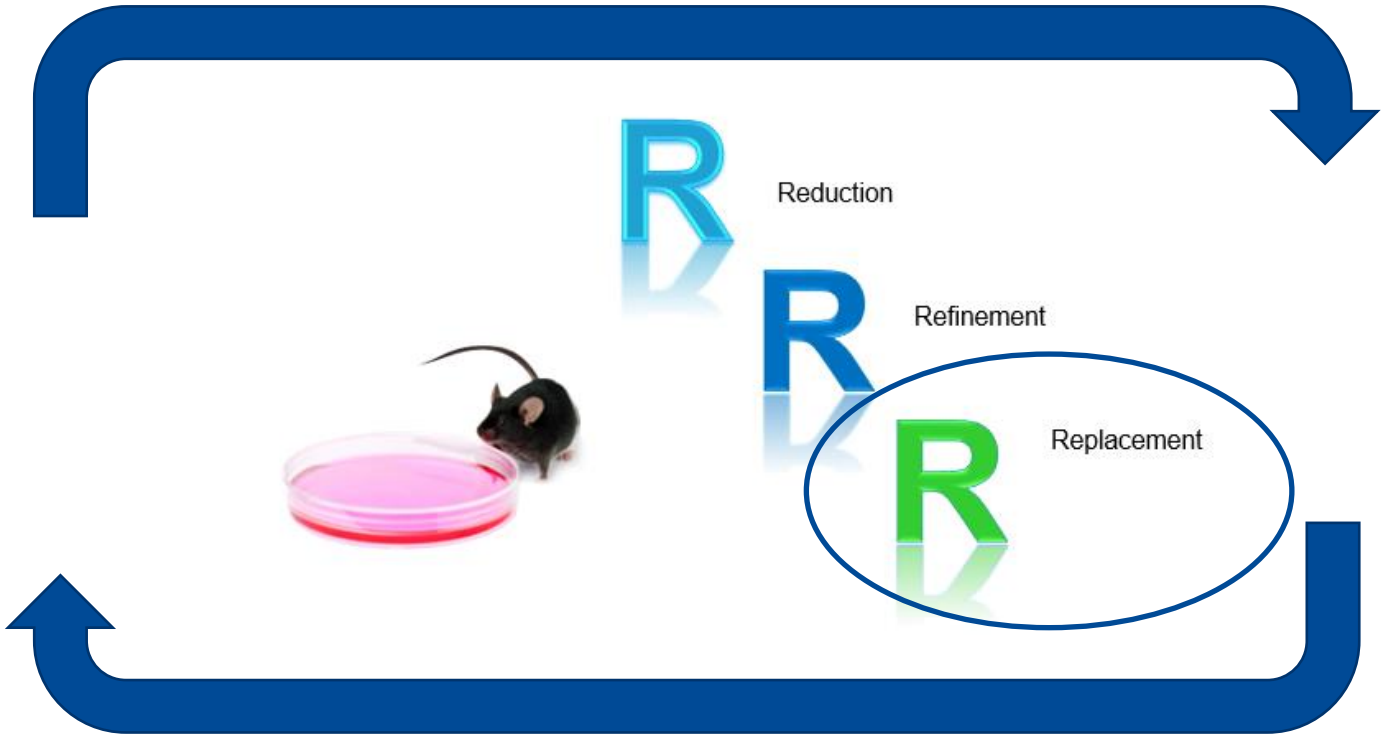
Alternative toxicological methods - final goal

Consumer

Worker



Environment

Population

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Selected Literature

Maternal Toxicity

- Added value of plasma metabolomics to describe maternal effects in rat maternal and prenatal toxicity studies
  J Keller, W Mellert, S Sperber, H Kamp, X Jiang, E Fabian, M Herold, T Walk, V Strauss, B van Ravenzwaay (2019)
  https://doi.org/10.1016/j.toxlet.2018.10.032
  Toxicology Letters 301, 42-52

Microbiome:

- Analysis of metabolome changes in the bile acid pool in feces and plasma of antibiotic-treated rats
  C Behr, M Slopianka, V Haake, V Strauss, S Sperber, H Kamp, T Walk, K Beekmann, IMCM Rietjens, B van Ravenzwaay (2019)
  https://doi.org/10.1016/j.taap.2018.11.012
  Toxicology and Applied Pharmacology 363, 79-87
- Impact of lincosamides antibiotics on the composition of the rat gut microbiota and the metabolite profile of plasma and feces
  C Behr, S Ramírez-Hincapié, HJ Cameron, V Strauss, T Walk, M Herold, K Beekmann, IMCM Rietjens, B van Ravenzwaay (2019)
  https://doi.org/10.1016/j.toxlet.2018.08.002
  Toxicology Letters 296, 139-151
- Microbiome-related metabolite changes in gut tissue, cecum content and feces of rats treated with antibiotics
  C Behr, S Sperber, X Jiang, V Strauss, H Kamp, T Walk, M Herold, K Beekmann, IMCM Rietjens, B van Ravenzwaay (2018)
  https://doi.org/10.1016/j.taap.2018.06.028
  Toxicology and Applied Pharmacology 355, 198-210
- Gut microbiome-related metabolic changes in plasma of antibiotic-treated rats
  C Behr, H Kamp, E Fabian, G Krennrich, W Mellert, E Peter, V Strauss, T Walk, IMCM Rietjens, B van Ravenzwaay (2017)
  https://doi.org/10.1007/s00204-017-1949-2
  Archives of Toxicology 91 (10), 3439–3454

Selected Literature

Metabolome in vitro and in vivo:

- Prediction of liver toxicity and mode of action using metabolomics in vitro in HepG2 cells
  T Ramirez, A Strigun, A Verlohner, HA Huener, E Peter, M Herold, N Bordag, W Mellert, T Walk, M Spitzer, X Jiang, S Sperber, Thomas Hofmann, Thomas Hartung, H Kamp, B van Ravenzwaay (2018)
  https://doi.org/10.1007/s00204-017-2079-6
  Archives of Toxicology Volume 92 (2), 893–906
- Metabolomics as read-across tool: A case study with phenoxy herbicides
  B van Ravenzwaay, S Sperber, O Lemke, E Fabian, F Faulhammer, H Kamp, W Mellert, V Strauss, A Strigun, E. Peter, M Spitzer, T Walk (2016)
  Regulatory Toxicology and Pharmacology 81, 288-304
- Detection of hepatotoxicity potential with metabolite profiling (metabolomics) of rat plasma
  W Mattes, K Davis, E Fabian, J Greenhaw, M Herold, R Looser, W Mellert, S Groeters, H Marxfeld, N Moeller, G Montoya-Parra, A Prokoudine, B van Ravenzwaay, V Strauss, T Walk, H Kamp (2014)
  https://doi.org/10.1016/j.toxlet.2014.07.021
  Toxicology Letters 230 (3), 467-478
- The sensitivity of metabolomics versus classical regulatory toxicology from a NOAEL perspective
  B van Ravenzwaay, GA Montoya, E Fabian, M Herold, G Krennrich, R Looser, W Mellert, E Peter, V Strauss, T Walk, H Kamp (2014)
  https://doi.org/10.1016/j.toxlet.2014.03.004
  Toxicology Letters 227, 20–28

Selected Literature

In vitro- in vivo extrapolation

- In vitro-to-in vivo extrapolation (IVIVE) by PBTK modeling for animal-free risk assessment approaches of potential endocrine-disrupting compounds

  E Fabian, C Gomes, B Birk, T Williford, T Ramirez, C Haase, R Zbranek, B van Ravenzwaay, R Landsiedel (2019)
  https://doi.org/10.1007/s00204-018-2372-z)
  Archives of Toxicology 93 (2), 401–416
- Use of physiologically based kinetic modeling-facilitated reverse dosimetry of in vitro toxicity data for prediction of in vivo developmental toxicity of tebuconazole in rats.

  Li H, Zhang M, Vervoort J, Rietjens IM, van Ravenzwaay B, Louisse J.
  doi: 10.1016/j.toxlet.2016.11.017.
  Toxicol Lett. 2017 Jan 15;266:85-93.

Developmental Toxicity

- A comparison of the embryonic stem cell test and whole embryo culture assay combined with the BeWo placental passage model for predicting the embryotoxicity of azoles

  M Dimopoulou, A Verhoef, CA Gomes, CW van Dongen, YMCM Rietjens, AH Piersma, B van Ravenzwaay B (2018)
  https://doi.org/10.1016/j.toxlet.2018.01.009
  Toxicology Letters 286, 10-21
- Extended evaluation on the ES-D3 cell differentiation assay combined with the BeWo transport model, to predict relative developmental toxicity of triazole compounds

  H Li, B Flick, IMCM Rietjens, J Louisse, S Schneider, B van Ravenzwaay (2016)
  https://doi.org/10.1007/s00204-015-1541-6
  Archives of Toxicology 90 (5), 1225-1237

Selected Literature

Nanotoxicology

- Decision-tree models to classify nanomaterials
  A Gajewicz, T Puzyn, K Odziomek, P Urbaszek,A Haase, C Riebeling, A Luch, MA Irfan, R Landsiedel, M van der Zande, H Bouwmeester (2018)
  https://doi.org/10.1080/17435390.2017.1415388
  Nanotoxicology 12 (1), 1-17
- Safety assessment of nanomaterials using an advanced decision-making framework, the DF4nanoGrouping
  R Landsiedel, L Ma-Hock, K Wiench, W Wohlleben, UG Sauer (2017)
  https://doi.org/10.1007/s11051-017-3850-6
  Journal of Nanoparticle Research 19 (5), 171
- Grouping and Read-Across Approaches for Risk Assessment of Nanomaterials.
  Oomen AG, Bleeker EA, Bos PM, van Broekhuizen F, Gottardo S, Groenewold M, Hristozov D, Hund-Rinke K, Irfan MA, Marcomini A, Peijnenburg WJ, Rasmussen K, Jiménez AS, Scott-Fordsmand JJ, van Tongeren M, Wiench K, Wohlleben W, Landsiedel R.(2015)
  doi: 10.3390/ijerph121013415.
  Int J Environ Res Public Health. 2015 Oct 26;12(10):13415-34.
- Application of short-term inhalation studies to assess the inhalation toxicity of nanomaterials.
  Landsiedel R, Ma-Hock L, Hofmann T, Wiemann M, Strauss V, Treumann S, Wohlleben W, Gröters S, Wiench K, van Ravenzwaay B. (2014)
  doi: 10.1186/1743-8977-11-16.
  Part Fibre Toxicol. 2014 Apr 4;11:16.

Selected Literature

Local Tolerance

- The kinetic direct peptide reactivity assay (kDPRA): Intra- and inter-laboratory reproducibility in a seven-laboratory ring trial
  Britta Wareing, Susanne N Kolle, Barbara Birk, Nathalie Alépée, Tina Haupt, Rishil Kathawala, Petra S Kern, Laurent Nardelli, Hans Raabe, Marián Rucki, Cindy A Ryan, Sjoerd Verkaart, Walter M A Westerink, Robert Landsiedel, Andreas Natsch
  Doi: 10.14573/altex.2004291
  ALTEX 2020;37(4):639-651
- A review of substances found positive in 1 of 3 in vitro tests for skin sensitization
  Susanne N Kolle, Andreas Natsch, G Frank Gerberick, Robert Landsiedel
  doi: 10.1016/j.yrtph.2019.05.016.
  Regul Toxicol Pharmacol. 2019 Aug;106:352-368
- Prediction of skin sensitization potency sub-categories using peptide reactivity data
  B Wareing, D Urbisch, SN Kolle, N Honarvar, UG Sauer, A Mehling, R Landsiedel (2017)
  https://doi.org/10.1016/j.tiv.2017.08.015
  Toxicology in Vitro 45 (1), 134-145
- Intra- and inter-laboratory reproducibility and accuracy of the LuSens assay: A reporter gene-cell line to detect keratinocyte activation by skin sensitizers
  T Ramirez, N Stein, A Aumann, T Remus, A Edwards, KG Norman, C Ryan, JE Bader, M Fehr, F Burleson, L Foertsch, X Wang, F Gerberick, P Beilstein, S Hoffmann, A Mehling, B van Ravenzwaay, R Landsiedel (2016)
  https://doi.org/10.1016/j.tiv.2016.01.004
  Toxicology in Vitro 32, 278-286
- Assessing skin sensitization hazard in mice and men using non-animal test methods
  D Urbisch, A Mehling, K Guth, R Landsiedel, J Jaworska, PS Kern, F Gerberick, A Natsch, R Emter, T Ashikaga, M Miyazawa, H Sakaguchi (2015)
  https://doi.org/10.1016/j.yrtph.2014.12.008
  Regulatory Toxicology and Pharmacology 71, 337-351
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