EU scenario on alternatives in cosmetic safety evaluation

State-of-play, impact & recommendations

Dr Gerald Renner
Director Technical Regulatory Affairs
Cosmetics Europe

Overview

I. EU measures affecting animal testing

II. State-of-the-art of science

III. Impact of EU regulatory measures

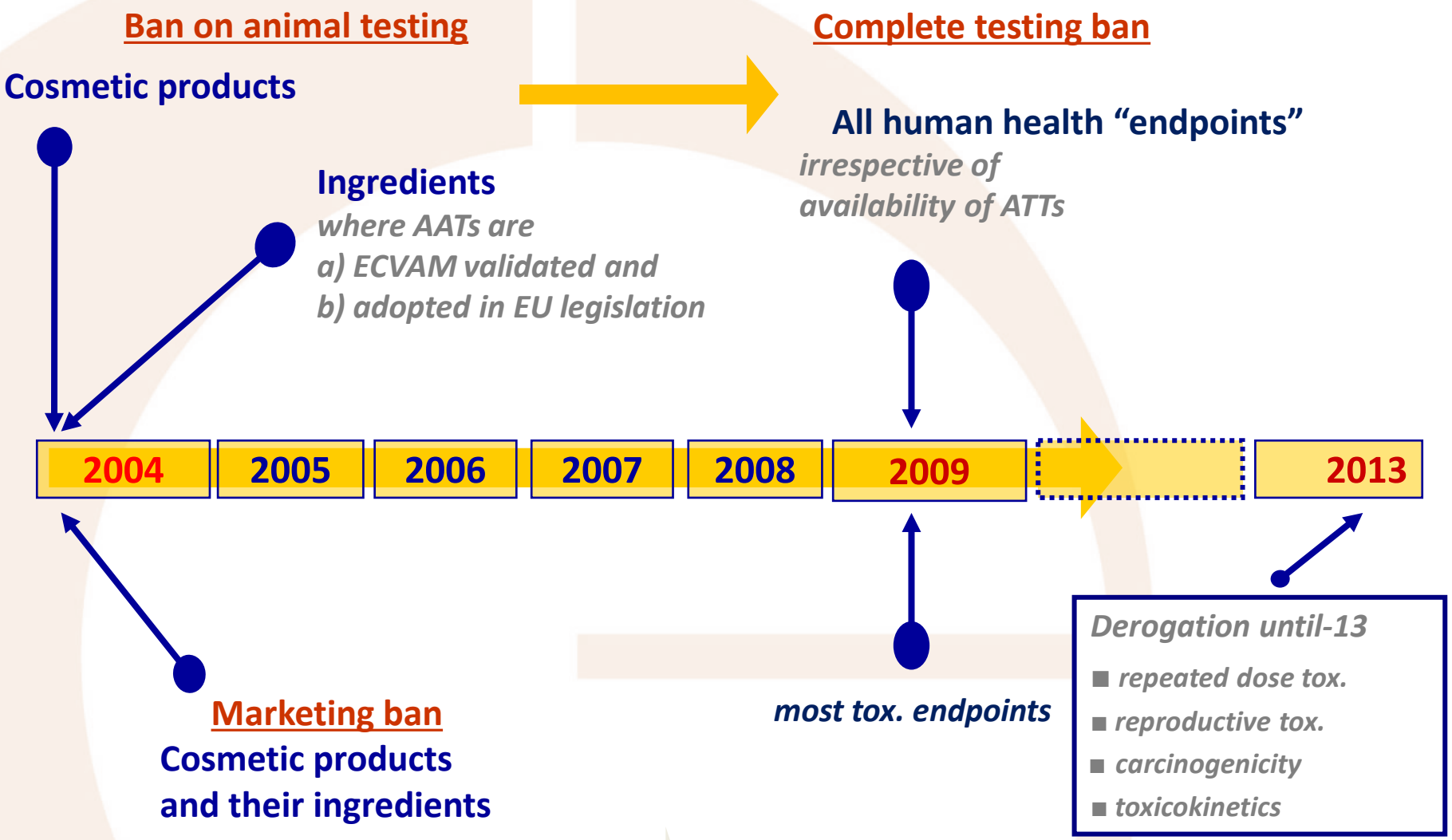
IV. Recommendations

I. EU measures affecting animal testing

EU measures affecting animal testing

Testing and marketing bans "*for the purpose of the Cosmetics Regulation*" successively entering into force between 2004 and 2013

EU measures affecting animal testing



European Commission Interpretation

In 2013, the European Commission clarified its own interpretation of the scope of the ban explaining that it is not a blanket ban:

«*The Commission considers that animal testing that has clearly been motivated by compliance with non-cosmetics related legislative frameworks should not be considered to have been carried out 'in order to meet the requirements of this Directive/Regulation'* »

«*The Commission considers that the marketing ban is triggered by the reliance on the animal data for the safety assessment under the Cosmetics Directive/Regulation, not by the testing as such . In case animal testing was carried out for compliance with cosmetics requirements in third countries, this data cannot be relied on in the Union for the safety assessment of cosmetics.* »

European Commission Interpretation

- Products are banned only if ingredients or products tested for cosmetics purposes (in or outside of the EU)
- Possibility to market products if ingredients tested for multiple purposes (in and outside of the EU)
- The marketing ban is only triggered by the use of data
- In exceptional circumstances: derogation for existing, non-replacable ingredient of which the use raises a specific human health problem (substantiation required)

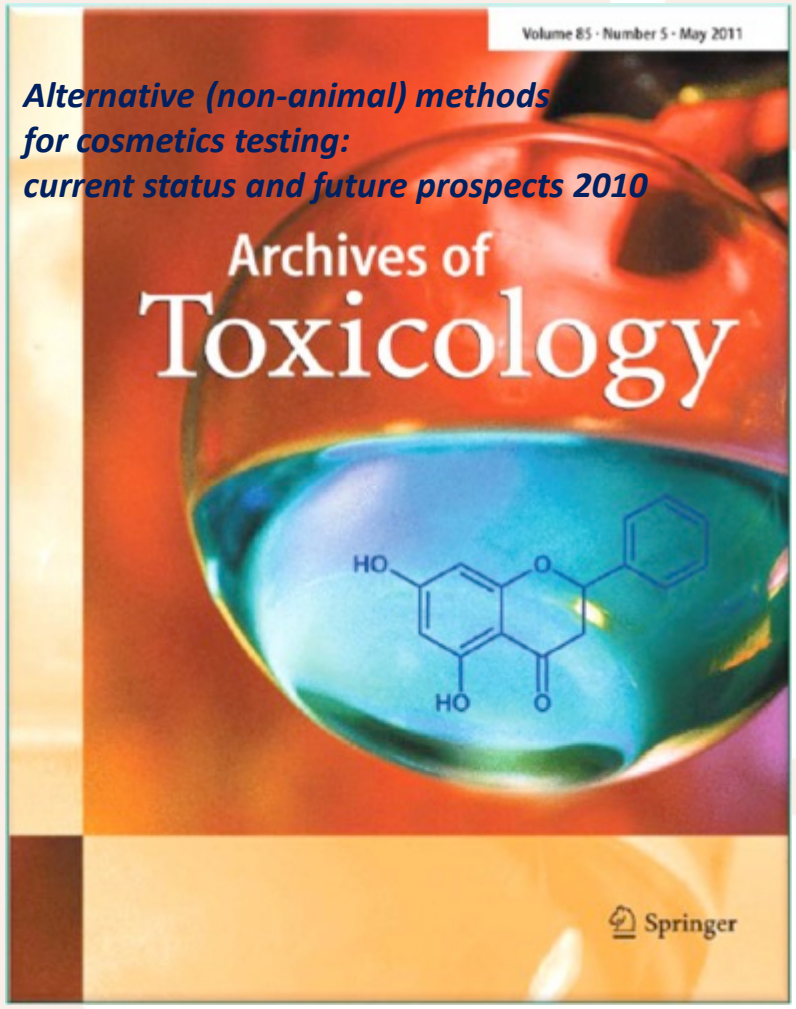
II. State-of-the-art of science

Timetables for phasing out Animal tests

- A *first technical report on timetables for the* phasing out of animal testing was prepared by nominated independent experts in 2003 and published in 2005
- Covered all toxicological endpoints relevant for cosmetics (ingredients) testing

Toxicological Endpoint	Cut-off-dates according article 4a "Testing Ban"	Cut-off-dates according article 4a "Marketing Ban"	2004 EU estimate Availability of Alternatives
Acute toxicity	11 March 2009	11 March 2009	> 2014
Skin corrosion	11 March 2009	11 March 2009	-
Skin irritation	11 March 2009	11 March 2009	> 2009
Eye irritation	11 March 2009	11 March 2009	2010
Genotoxicity / Mutagenicity	11 March 2009	11 March 2009	> 2016
UV induced effects (Allergy)	11 March 2009	11 Mach 2013	> 2016
Skin sensitization	11 March 2009	11 March 2013	2016 - 2018
Subacute / Subchronic toxicity	11 March 2009	11 March 2013	not estimated
Reproductive toxicity	11 March 2009	11 March 2013	not estimated
Carcinogenicity	11 March 2009	11 March 2013	not estimated
Toxicokinetics and Metabolism	11 March 2009	11 March 2013	> 2016

Current status and Outlook beyond the ban



- Adler, S. *et al.* (2011) Arch. Toxicol., 85: 367-485.
- Review considered the toxicological endpoints important for the 2013 marketing ban deadline
- Revealed that the scientific basis to fully replace animal testing for the five toxicological key areas is still not established (*additional time beyond 2013 needed)*
- Confirmed that it could take at least another 7 – 9 years for the replacement of some of the current *in vivo animal* tests necessary for the safety assessment

OECD Guidelines for Toxicology studies

Cosmetics Europe
the personal care association

N°	Type
401	Acute Oral Toxicity
402	Acute Dermal Toxicity
403	Acute Inhalation Toxicity
404	Acute Dermal Irritation/Corrosion
405	Acute Eye Irritation/Corrosion
406	Skin Sensitisation
407	Repeated Dose 28-Day Oral Toxicity Study in Rodents
408	Repeated Dose 90-Day Oral Toxicity Study in Rodents
409	Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents
410	Repeated Dose Dermal Toxicity:90-Day
411	Subchronic Inhalation Toxicity: 90-Day
412	Subacute Inhalation Toxicity: 28-Day Study
413	Subchronic Inhalation Toxicity: 90-Day Study
414	Prenatal Developmental Toxicity Study
415	One-Generation Reproduction Toxicity
416	Two-generation Reproduction Toxicity Study
417	Toxicokinetics
418	Delayed Neurotoxicity of Organophosphorus Substances Following Acute Exposure
419	Delayed Neurotoxicity of Organophosphorus Substances: 29-Day Repeated Dose Study
420	Acute Oral toxicity – Fixe Dose Procedure
421	Reproduction/Developmental Toxicity Screening Test
422	Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
423	Acute Oral Toxicity – Acute Toxic Class Method
424	Neurotoxicity Study in Rodents
425	Acute Oral Toxicity: Up-and-Down Procedure
426	Developmental Neurotoxicity Study
427	Skin Absorption: *In Vivo* Method
428	Skin Absorption: *In Vitro* Method
429	Skin Sensitisation: Local Lymph Node Assay

N°	Type
430	*In Vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test (TER)
431	*In Vitro* Skin Corrosion: Human Skin Model Test
432	*In Vitro* 3T3 NRU Phototoxicity Test
435	*In Vitro* Membrane Barrier Test Method for Skin Corrosion
436	Acute Inhalation Toxicity - Acute Toxic Class Method
437	Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants
438	Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants
440	Uterotrophic Bioassay in Rodents: A short-term screening test for oestrogenic properties
441	Hershberger Bioassay in Rats: A short-term Screening Assay for (Anti)Androgenic Properties
451	Carcinogenicity Studies
452	Chronic Toxicity Studies
453	Combined Chronic Toxicity/Carcinogenicity Studies
455	Stably Transfected Human Estrogen Receptor-α Transcriptional Activation Assay for the Detection of Estrogenic Agonist-Activity of Chemicals
471	Bacterial Reverse Mutation Test
472	Genetic Toxicology: *Escherichia coli*, Reverse Assay
473	*In Vitro* Mammalian Chromosome Aberration Test
474	Mammalian Erythrocyte Micronucleus Test
475	Mammalian Bone Marrow Chromosome Aberration Test
476	*In Vitro* Mammalian Cell Gene Mutation Test
477	Genetic Toxicology: Sex-Linked Recessive Lethal Test in *Drosophilia melanogaster*
478	Genetic Toxicology: Rodent dominant Lethal Test
479	Genetic Toxicology: *In Vitro* Sister Chromatid Exchange assay in Mammalian Cells
480	Genetic Toxicology: *Saccharomyces cerevisiae*, Gene Mutation Assay
481	Genetic Toxicology: *Saccharomyces cerevisiae*, Mitotic Recombination Assay
482	Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells *In Vitro*
483	Mammalian Spermatagonial Chromosome Aberration Test
484	Genetic Toxicology: Mouse Spot Test
485	Genetic Toxicology: Mouse Heritable Translocation Assay
486	Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *In Vivo*

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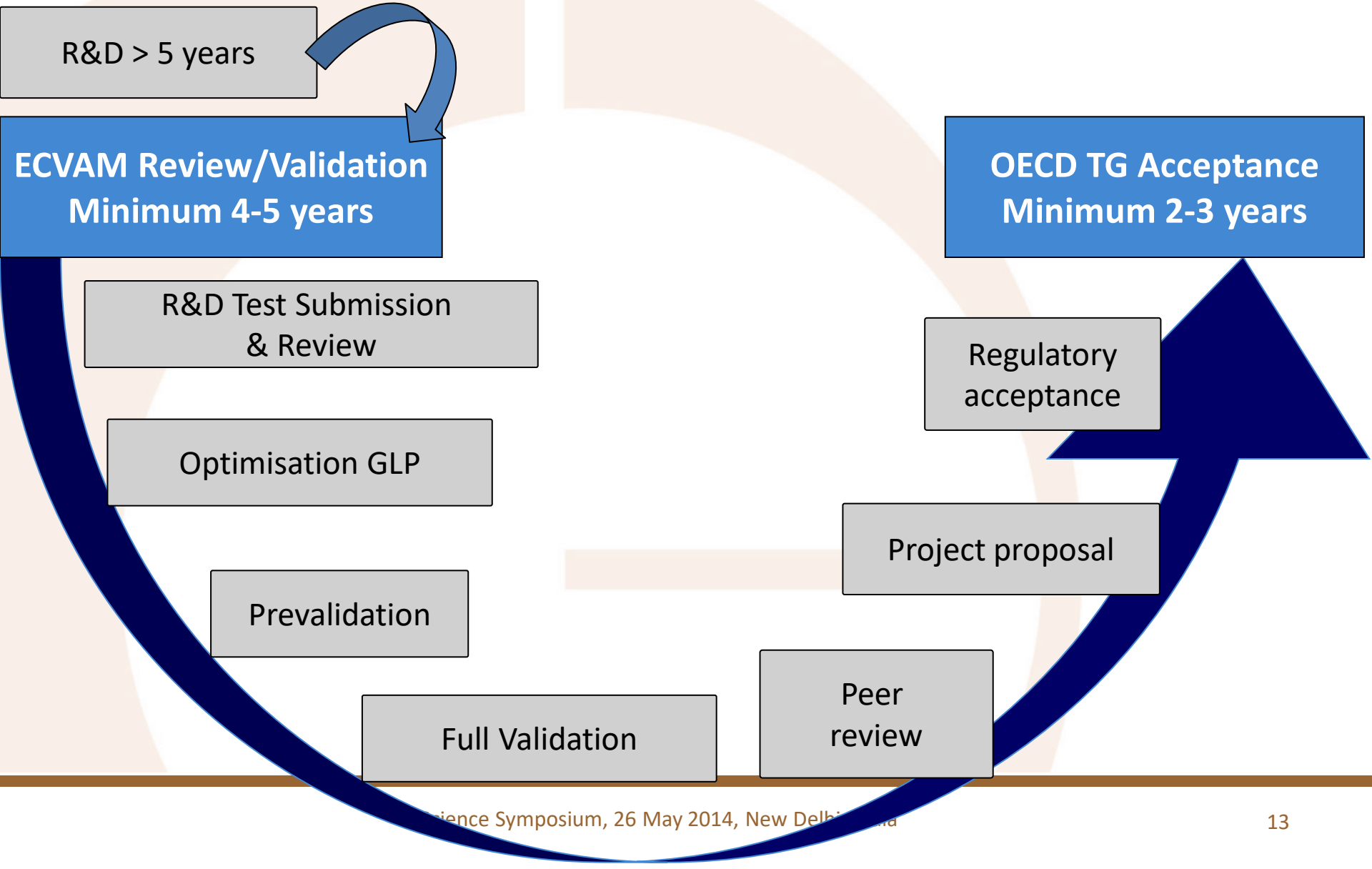
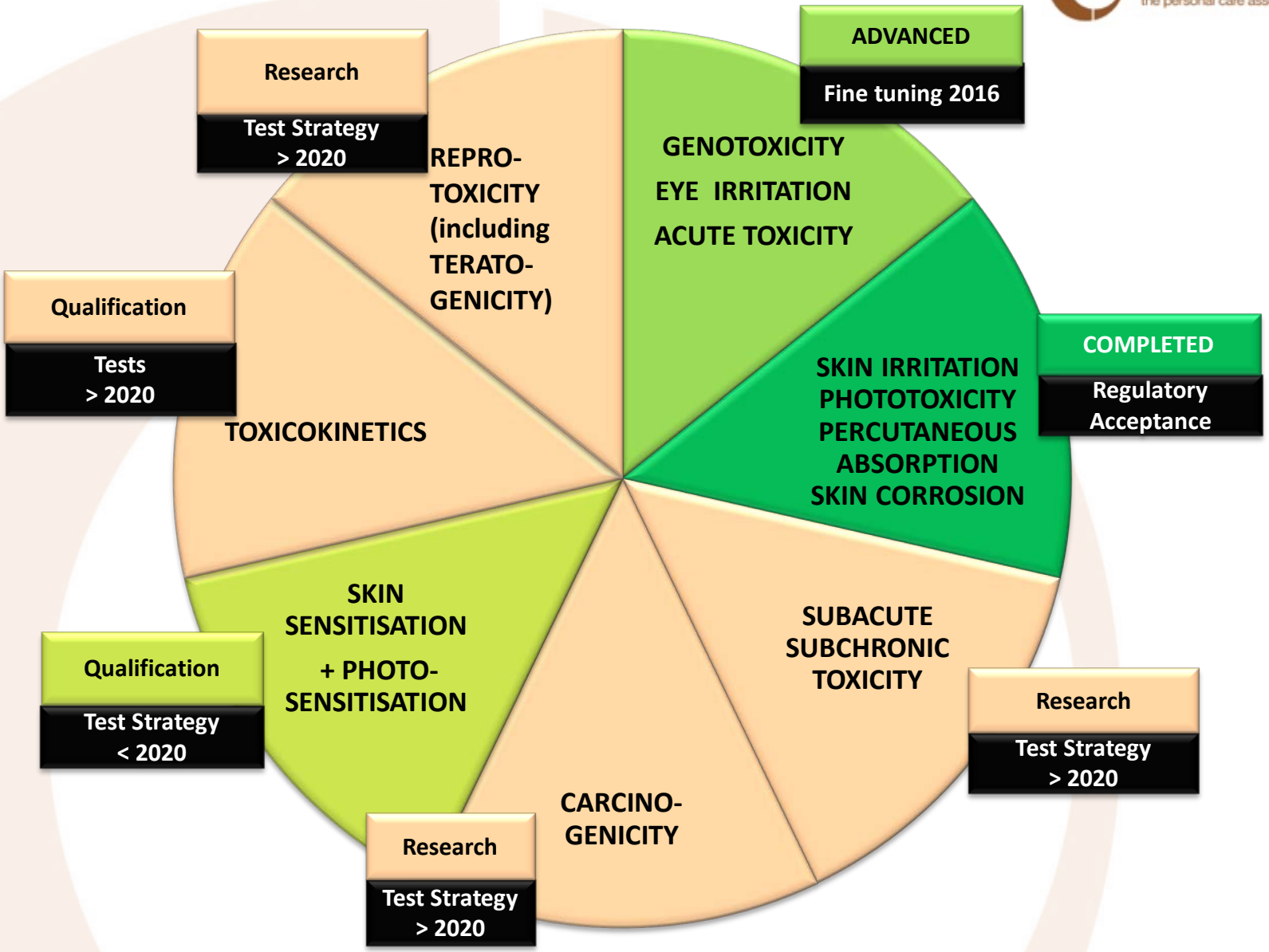
The OECD tool box still mainly contains *in vivo* studies. These concern studies on rodents.

Traditional Regulatory Acceptance Process at ECVAM and OECD



Status of Science



Available validated Alternative Methods for Human Health Safety Assessments in the SCCS Notes of Guidance

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Endpoints	3Rs
Acute toxicity	Reduction/refinement (oral/inhalation)
Skin corrosivity	Full replacement (TG 430, 431)
Skin irritation	Full replacement (TG 439)
Eye irritation	Partial replacement[1] (TG 437, 438, 460)
Skin sensitisation	No replacement
Phototoxicity	Full replacement (TG 432)
Toxicokinetics	No replacement
Repeated dose toxicity	No replacement
Reproduction toxicity	No replacement
Mutagenicity/Genotoxicity	Partial replacement[2]
Carcinogenicity	No replacement

[1] Only for compounds causing "serious eye damage" (category 1 of the GHS), or not requiring classification for eye irritation or serious eye damage according to the GHS.
[2] Only for negative results, not possible to follow-up positive/false positive results since animal data would be required.

Science - Concluding remarks

- Only for a limited number of toxicological endpoints, replacement methods are available and validated
  (Report by the European Commission Joint Research Centre (JRC)[1])
- Replacement methods for skin allergy testing potentially available within 2-4 years but for the more complex endpoints a timeline is difficult to anticipate
- State-of-the-art of regulatory accepted test methods
  (OECD Test Guidelines[2])

[1] http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/eurl-ecvam-releases-2013-progress-report-development-validation-regulatory-acceptance-alternative-methods

[2] http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

Science - Concluding remarks

More time and efforts are needed to develop the complete set of alternative methods:

- New internationally agreed tools and testing approaches required for successful development of replacements
- New streamlined validation criteria required for mechanistic tests; not realistic that a single screening test should take 6-8 years to reach regulatory acceptance