Center for Alternatives to Animal Testing - Europe

Applicazione di modelli sostitutivi all'animale nell'ambito cosmetologico, in ottemperanza con le linee guida europee

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Genova - 22nd October 2021

TEAM mastery

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Universität Konstanz

The EU's REACH Regulation (EC) No 1907/2006

- The EU's main chemicals regulation
- Stands for Registration, Evaluation, Authorisation, and Restriction of Chemicals
- Purpose: "to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation." (Article 1)

REACH Registration: Who registers and what do they register?

- **EU chemical manufacturers and importers must register any chemical made or imported in a quantity ≥ 1 ton/year.**

- **“One substance, one registration" principle.**

  Manufacturers/importers of same substance submit one, joint registration to avoid duplicate registrations and animal tests.
  Registrants are expected to share existing company data (negotiated).
  New required tests are conducted by one on behalf of all, who share cost.

Toxicity data required for registrations

- **Toxicity data for hazard classification:**
  Basis for the hazard (CLP) information on the chemical Safety Data Sheet (SDS).

- **Toxicity data for risk assessment of potential exposure routes:**
  Basis for Chemical Safety Assessment, which is included in the Chemical Safety Report (CSR) in the registration dossiers for chemicals of quantity ≥ 10 tons/year.

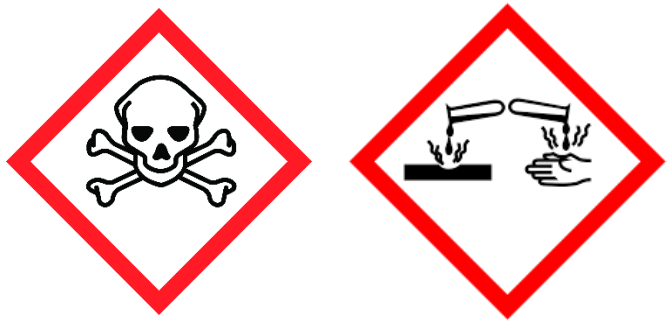
- **Data from in vivo studies provide the NO(A)EL that is the basis for the derivation of the DNELs, necessary to model the exposure scenarios**

Standard toxicity data requirements per tonnage band

8. Toxicological information		VII >1t/y	VIII > 10 t/y	IX > 100t/y	X > 1000 t/y
8.1	Skin irritation/corrosion (in vitro)	VII			
8.1.1	In vivo skin irritation (before 2016)		VIII		
8.2	Eye irritation (in vitro)	VII			
8.2.1	In vivo eye irritation (before 2016)		VIII		
8.3	Skin sensitisation (in vitro after 2016)	VII			
8.4	Mutagenicity				
8.4.1	In vitro gene mutagen study in bacteria	VII			
8.4.2	In vitro cytogenicity study in mammalian cells or in vitro micronucleus study		VIII		
8.4.3	In vitro gene mutation study in mammalian cells		VIII		
	Further Mutagenicity in vivo tests		VIII	IX	X
8.5	Acute toxicity				
8.5.1	Acute toxicity (oral route)	VII			
8.5.2	Acute toxicity (inhalation)		VIII		
8.5.3	Acute toxicity (dermal route)		VIII		
8.6.	Repeated dose toxicity				
8.6.1	Short term repeated dose toxicity (28d)		VIII		
8.6.2	Sub-chronic toxicity study (90d)			IX	
8.6.3	Long term repeated toxicity study (≥ 12 months)				X
8.7	Reproductive toxicity				
8.7.1	One species screening		VIII		
8.7.2	Developmental toxicity study			IX	X
8.7.2	Developmental toxicity study (second species)				X
8.7.3	Two-generation reproductive toxicity study			IX	X
8.7.3	Extended one generation reproductive toxicity study			IX	X
8.8	Toxicokinetics				
8.8.1	Toxicokinetics (available information exept nanoforms)		VIII		
8.9	Carcinogenicity study				X

ECOTOXICOLOGICAL INFORMATION (main in vivo)		VII ≥ 1t/y	VIII≥ 10 t/y	IX≥ 100t/y	X ≥ 1000 t/y
9.1	Aquatic toxicity				
9.1.1	Short-term toxicity testing on invertebrates (Daphnia)	VII			
9.1.2	Growth inhibition study aquatic plants (algae)	VII			
9.1.3	Short-term toxicity testing on fish		VIII		
9.1.5	Long-term toxicity testing on invertebrates (Daphnia)			IX	
9.1.6	Long-term toxicity testing on fish				
9.1.6.1	Fish early-life stage (FELS) toxicity test			IX	
9.1.6.2	Fish short-term toxicity test on embryo and sac- fry stages			IX	
9.1.6.3	Fish, juvenile growth test			IX	
9.3	Fate and behaviour in the environmentFate and behaviour in the environment				
9.3.2	Bioaccumulation in aquatic species, preferably fish			IX	
	Fish Sexual Development Test (OECD TG 234)			IX	

Specific rules for adaptation (Column 2 in Annexes)



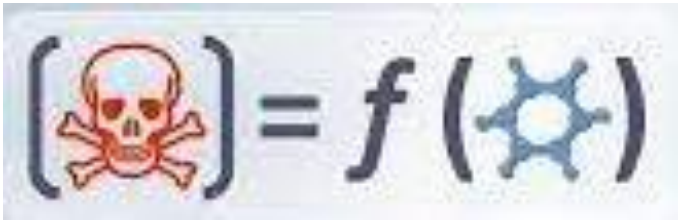
- Serious eye damage/eye irritation
  - The substance is a strong acid (pH ≤ 2.0) or base (pH ≥ 11.5)
  - The substance is classified as acute toxicity by the dermal route

- Skin Sensistisation
  - The substance is a strong acid (pH ≤ 2.0) or base (pH ≥ 11.5)
  - The substance is classified as skin corrosion (Category 1)
  - An in vivo study shall be conducted only if in vitro/in chemico test methods are not applicable, or the results obtained from those studies are not adequate for classification and risk assessment

- Acute Toxicity
  - The substance is classified as corrosive to the skin
  - Other routes: If there is only one route of exposure, information for only that route needs to be provided
  - Dermal: the substance does not meet the criteria for classification as acute toxicity or STOT SE by the oral route
  - no systemic effects have been observed in in vivo studies with dermal exposure

General rules for adaptation (Annex XI)

- **Weight of evidence using existing data and non-animal methods**
- **Mathematical models/QSARs**
- **"Suitable" *in vitro* methods**
- **Grouping and Read-across**



REACH pioneered use of such alternative methods to replace animal testing.

REACH Evaluation

1. Dossier evaluation: ECHA checks that registration dossiers contain the information on chemicals required by the legislation.
2. Substance evaluation: Member states evaluate substances after they have identified any concerns.

Following one of these assessments (or both), registrants may be required to submit or generate additional information on the substance.

3. Evaluation of new animal testing proposals from registrants (Annex IX, X only): ECHA usually approves the tests.

REACH Evaluation

Dossier Evaluation status

ECHA's dossier evaluation process covers compliance checks and the examination of testing proposals. By consulting the table below, you can find out whether ECHA has started to evaluate dossiers for a particular substance and follow the progress through the evaluation process.

The table below displays the type, scope and status of the assessment undertaken for a given dossier. The decision date and the non-confidential version of the decision are published shortly after the decision has been adopted.

Before publishing the non-confidential version of an adopted decision on its website, ECHA consults the addressees of the decision on this version. ECHA systematically removes any personal data from the non-confidential version of a decision. Some sections may also be redacted based on justified claims by registrants, regarding information confidential or deemed to harm their commercial interest if disclosed.

Check the expandable boxes below for more details.

FURTHER INFORMATION

- Evaluation Process
- Dossier Compliance Checks
- Testing Proposals examination
- Testing Proposals consultation

See a problem or have feedback?

> **Content of the table**

> **How to read the table**

Last updated 01 October 2021. Database contains 3569 unique substances/entries.

Filter the list

Gap between REACH principle and practice

In principle, use of alternative approaches is a core REACH principle:

- In its statement of purpose
- In its Annex XI adaptations to replace standard animal-based requirements with alternatives
- In its requirement that new animal testing be done only as a last resort

In practice:

- *In vitro* method sometimes gives positive or equivocal result that, per REACH, must be confirmed by an *in vivo* test.
- ECHA or the Member states often reject alternative approaches during the evaluation process, typically citing lack of scientific justifications, Read-across especially.

The EU Cosmetic Regulation (EC) No 1223/2009

Purpose: "to ensure the functioning of the internal market and a high level of protection of human health" (Article 1).

What is prohibited (Article 18a,b): placing on the market cosmetic products or any of their ingredients that are tested on animals "*in order to meet the requirements of this Regulation*".

PRODUCT INFORMATION FILE (PIF)

- Description of the cosmetic product
- Cosmetic Product Safety Report (CPSR)
  - Part A: Cosmetic Product Safety information
  - Part B: Cosmetic Product Safety assessment
- Method of manufacturing and GMP compliance
- Proof of the effect claimed
- **Data on any animal testing for the development or safety of the cosmetic product**

Limitations of Cosmetic Regulation animal testing ban

- **Excludes ecotoxicity testing from the ban.**

  Cosmetic regulation states that environmental effects will be considered under REACH.

- **Allows marketing of product if the animal test was done for a purpose other than the Cosmetic Regulation, e.g., a dual use or a different regulation.**

  Tests conducted for a dual use (a use other than cosmetics) can be used for the cosmetic safety assessment, but only if the test was done specifically and only for the dual use. Simply having a dual use doesn't permit a test.

  Tests conducted for a different regulation may not be used for the cosmetic safety assessment. Using such a test results in a marketing ban on the product.

- **Does not address production worker exposure.**

  Cosmetic regulation states only that the cosmetic safety assessment is to account for "the intended use of the cosmetic product and the anticipated systemic exposure to individual ingredients in a final formulation."

Relationship of REACH and Cosmetic Regulation

- A cosmetic ingredient is just another chemical under REACH.
- As for other chemicals, the dossiers for cosmetic ingredients must meet REACH requirements for hazard classification data and risk assessment data.
- For ingredients registered according to Annex VIII onward (≥ 10 tons/yr), the dossier must include a full chemical safety report (CSR) that addresses potential exposure scenarios.
- Cosmetic ingredients are exempted only from an assessment for consumer/professional worker exposure, because this assessment is performed under the Cosmetic Regulation.
- Cosmetic ingredients are not exempted from an assessment for worker exposure during manufacture of the ingredient or the final cosmetic product or for environmental effects.

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REACH

Factsheet

ECHA-14-FS-04-EN

Interface between REACH and Cosmetics regulations

ECHA
EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

A-010-2018 1 (30)

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

18 August 2020

(Compliance check – Sections 8.7.2. and 8.7.3. of Annex IX – Substance used exclusively as an ingredient in cosmetic products – Relationship between the REACH Regulation and the Cosmetics Regulation – Studies on vertebrate animals – Route of administration for an EOGRTS – Section 9.1.6. of Annex IX – Aquatic toxicity testing)

E.C.M.
Educazione Continua in Medicina

"… the Cosmetics Regulation does not restrict testing under REACH, if:

- ***this testing is required for environmental endpoints; or***
- ***the substance is also registered for non-cosmetic uses.***

Even if a substance is registered exclusively for cosmetic use, the animal testing requirements continue to apply to tests needed to assess the risks from exposure to workers in the Chemical Safety Assessment."

"The requested human health tests are justified for the purposes of assessing hazards for workers. Such testing would not trigger the testing and marketing bans under the Cosmetics Regulation as the testing is to be performed for the purposes of meeting the requirements of the REACH Regulation

The REACH Regulation contains no provision that exempts registrants from the requirement to carry out studies on vertebrate animals only because the substance is used as an ingredient in cosmetic products."

ALTEX, accepted manuscript
published August 18, 2021
doi:10.14573/altex.2104221

t[4] Report*

Continuing Animal Tests on Cosmetic Ingredients for REACH in the EU

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Abstract:

*…. We found the REACH database has **3,206 chemical dossiers** with cosmetics as a reported use. Of these, **419** report cosmetics as the only use, and 63 of these have in vivo tests completed after the Cosmetic Regulation ban on in vivo testing. **Registrants largely used alternative, non-animal methods to evaluate ingredients for REACH, but some still conducted new in vivo tests to comply with REACH requirements for toxicity data** and worker safety assessments. In some cases, ECHA, the agency that evaluates REACH dossiers, rejected registrants' alternative methods as insufficient and required new in vivo tests. **As ECHA continues to evaluate dossiers, more requests for in vivo tests are likely**. …*

DOI: https://doi.org/10.14573/altex.2104221

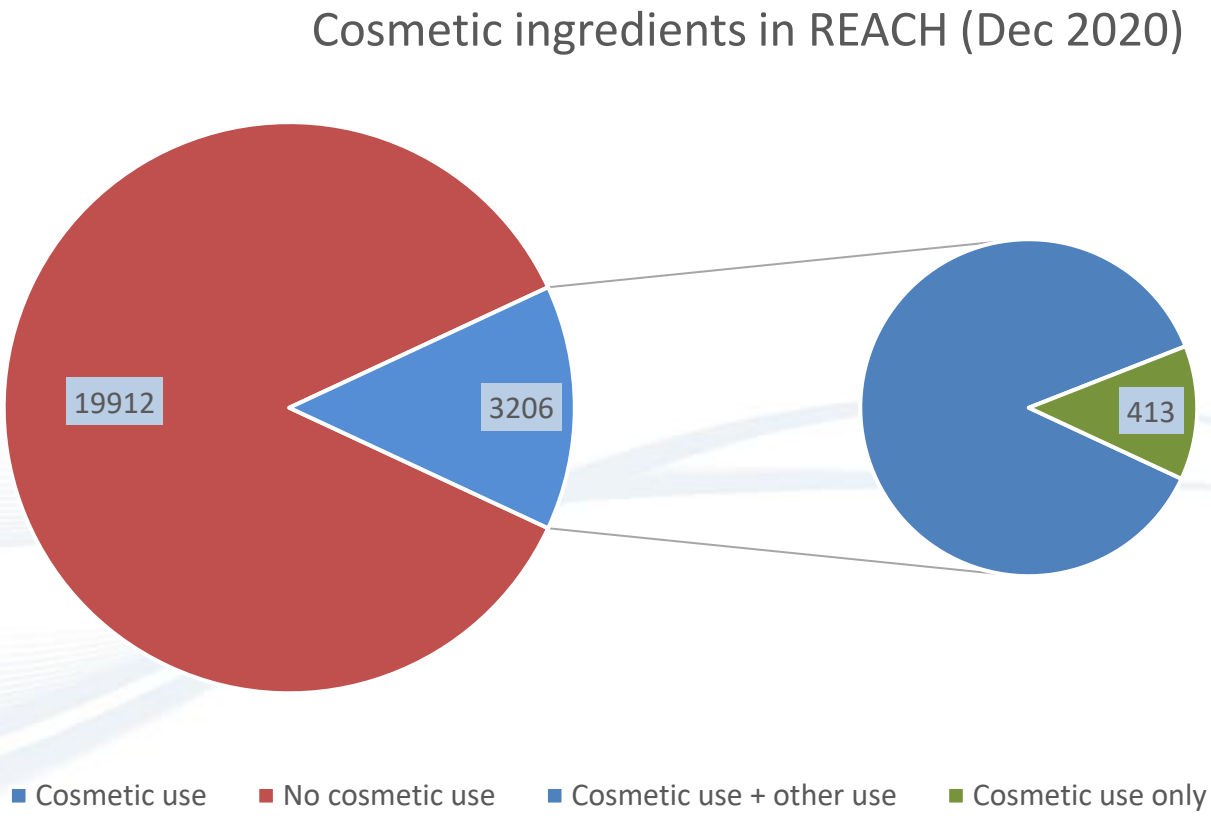
Cosmetic ingredients registered in REACH

Third most common use declared in REACH:

1. **PC 32: Polymer preparations & compounds: 3,505**
2. **PC 0: Other: 3,442**
3. **PC 28 + 39: Perfumes & fragrances; Cosmetics & personal care products: 3,206**

...

of 41 uses in REACH.



Live demonstration
Navigating cosmetic ingredients in the ECHA database and CosIng

- **Ethyl 4-hydroxybenzoate EC number: 204-399-4 | CAS number: 120-47-8**
  INCI: ethylparaben

CosIng database

https://ec.europa.eu/growth/sectors/cosmetics/cosing_en

ECHA database

https://echa.europa.eu/information-on-chemicals/registered-substances

Simple Search

You can search for the name of a substance (displayed in sma
INGREDIENT (displayed in CAPITAL LETTERS), listed in the I
Inventory.

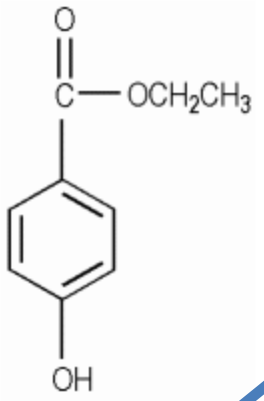
CosIng allows also users to search for relevant CAS and EC n

The current data in the database can be found under the defau

Version	EC Regulation
Name ⓘ or CAS/EC #	Ethylparaben
Scope	All
Status	Active

Search

Please keep us informed of any problems or requests

INCI Name	ETHYLPARABEN
Description	Ethylparaben is the ester of ethyl alcohol and p-hydroxybenzoic acid. It conforms to the formula: 
CAS #	120-47-8
EC #	204-399-4
Cosmetics Regulation provisions ⓘ	V/12
Functions	• FRAGRANCE • PRESERVATIVE
SCCS opinions	• 0873/05 - Extended Opinion on the Safety Evaluation of Parabens • 0874/05 - Opinion on Parabens, underarm cosmetics and breast cancer • 1017/06 - Opinion on Parabens • 1183/08 - Opinion on Parabens • 1348/10 - Opinion on Parabens • 1514/13 - Opinion on Parabens updated request for a scientific opinion on 'propyl-and butylparaben'
Identified INGREDIENTS or substances e.g.	

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Last updated 13 October 2021. Database contains 23445 unique substances and contains information from 104985 dossiers.

Substance identity

Substance name:

CAS number:

EC / List number: 204-399-4

Other Numerical Identifiers:

Type

Administrative data

Substance data

Uses and exposure

View all Registered Substances

Search

Clear all

Name	EC / List no.	CAS no.	Registration Status	Registration type	Submission type	Total tonnage band	Last Updated	Details
Ethyl 4-hydroxybenzoate	204-399-4	120-47-8	Active	Full		≥ 100 to < 1 000 tonnes	21-01-2021	

Ethyl 4-hydroxybenzoate

EC number: 204-399-4 | CAS number: 120-47-8

- General information
  - Substance Identity
  - Administrative Information
- Classification & Labelling & PBT assessment
- Manufacture, use & exposure
- Physical & Chemical properties
- Environmental fate & pathways
- Ecotoxicological information
- Toxicological information

Substance identity

Identification | Type of substance | Substance identifiers | Compositions

- Life Cycle description
  - No identified uses
  - Manufacture
  - Formulation
  - Uses at industrial sites
  - Uses by professional workers
  - Consumer Uses
  - Article service life
- Uses advised against

Consumer Uses

Documents

open all close all

+ Consumer End Use of cosmetic products or pharmaceuticals
+ Consumer end use of cosmetics and pharmaceuticals
+ Consumer End Use of cosmetic products or pharmaceuticals

Type of Substance

Composition:	mono-constituent substance
Origin:	organic

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Ethyl 4-hydroxybenzoate

EC number: 204-399-4 | CAS number: 120-47-8

- General information
- Classification & Labelling & PBT assessment
- Manufacture, use & exposure
- Physical & Chemical properties
- Environmental fate & pathways
- Ecotoxicological information
- Toxicological information

- Toxicological Summary
- **Toxicokinetics, metabolism and distribution**
- **Acute Toxicity**
- **Irritation / corrosion**
  - Endpoint summary
  - Skin irritation / corrosion
  - Eye irritation
- **Sensitisation**
- **Repeated dose toxicity**
- **Genetic toxicity**
- Carcinogenicity
- **Toxicity to reproduction**
- **Specific investigations**
- Exposure related observations in humans
- Toxic effects on livestock and pets
- Additional toxicological data

Skin irritation / corrosion

Currently viewing: 001 Key | Experimental result

Administrative data | Data source | Materials and methods | Results and discussion | Applicant's summary and conclusion

Administrative data

Endpoint:	skin irritation: in vivo
Type of information:	experimental study
Adequacy of study:	key study
Reliability:	1 (reliable without restriction)
Rationale for reliability incl. deficiencies:	other: Comparable to guideline study.

Data source

Reference

Reference Type:	study report
Title:	Unnamed
Year:	1983
Report date:	1983

Materials and methods

Test guideline

Qualifier:	equivalent or similar to guideline

Ethyl 4-hydroxybenzoate

EC number: 204-399-4 | CAS number: 120-47-8

Toxicity to reproduction

Currently viewing: 001 Key | Experimental result

Administrative data

Endpoint:	extended one-generation reproductive toxicity - with both developmental neuro- and immunotoxicity (Cohorts 1A, 1B without extension, 2A, 2B, and 3)
Type of information:	experimental study

Test material

- Test material information

Constituent 1

Reference substance name:	Propyl 4-hydroxybenzoate
Cas Number:	94-13-3
IUPAC Name:	Propyl 4-hydroxybenzoate
Test material form:	solid
Details on test material:	Composition: Propyl 4-hydroxybenzoate: 99,7 % 4-Hydroxy-benzoic acid: 0.1 % unspecified impurity: 0.2 % Ethanol: < 200 ppm Propanol: < 200 ppm melting point: 98 °C

20% of all cosmetic-only dossiers used alternative methods for *all* endpoints

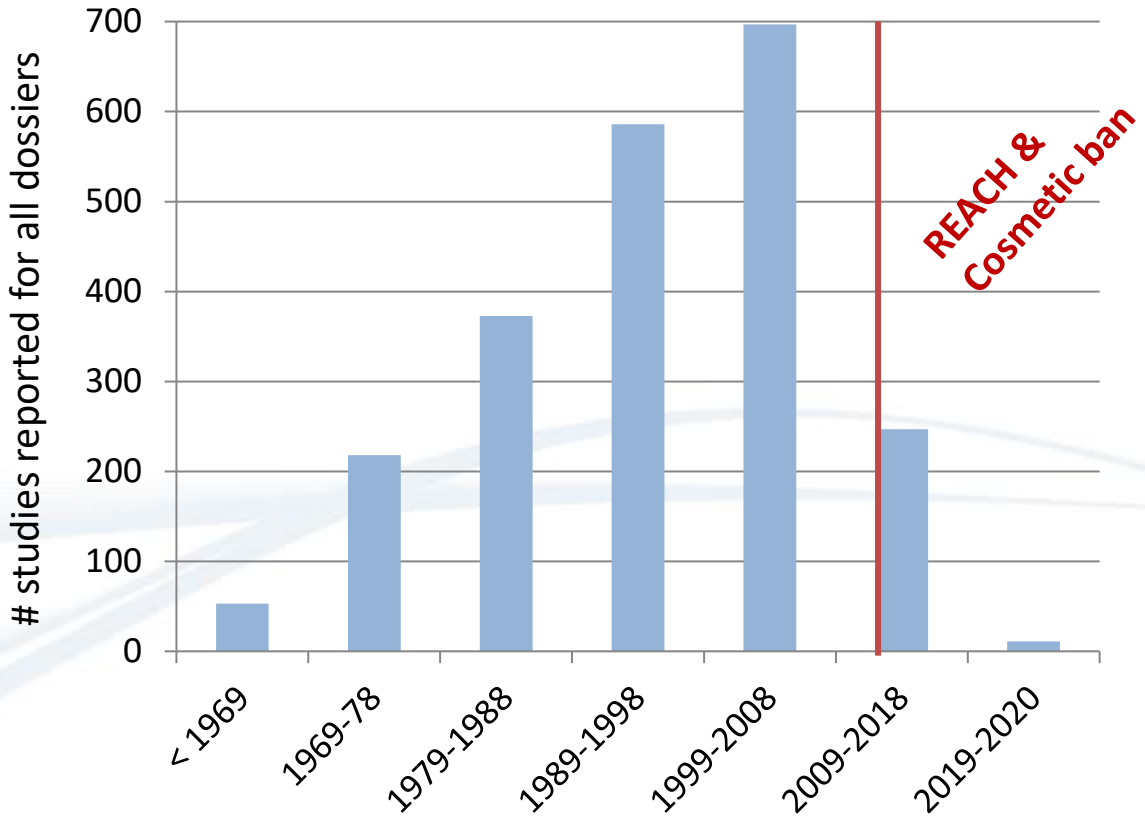
Many other dossiers used alternative-only methods for at least some endpoints

Endpoint	% of cosmetic-only dossiers using only alternative methods for this endpoint
Skin irritation	46%
Eye irritation	47%
Skin sensitization	41%
Genetic toxicity	83%
Acute toxicity - Oral	29%
Acute toxicity - Dermal	40%
Repeated dose toxicity - Oral	33%
Reproductive toxicity	50%
Developmental toxicity	40%
Toxicokinetics	77%
Acute Fish toxicity	32%

Most common study type is in vivo study

Endpoint	Most common study type	Second most common type
Skin Irr	In vivo – 41%	In vitro – 29%
Eye Irr	In vivo – 39%	In vitro – 32%
Skin Sens	In vivo – 41%	Read across – 18%
Genetic Tox	In vitro – 59%	Read across – 18%
Acute Tox - Oral	In vivo – 55%	Read across – 25%
Acute Tox - Dermal	In vivo – 38%	Read across – 24%
Rep Dose Tox - Oral	In vivo – 52%	Read across – 34%
Reproductive Tox.	Read across – 36%	In vivo – 32%
Developmental Tox.	In vivo – 48%	Read across – 39%
Toxicokinetics	Expert statement – 32%	In vivo – 18%
Acute Fish Tox	In vivo – 51%	Read across – 22%
Acute tox - inhalation, repeated dose - dermal, and repeated dose - inhalation primarily had waivers and are not included here.		

But most are historical in vivo studies

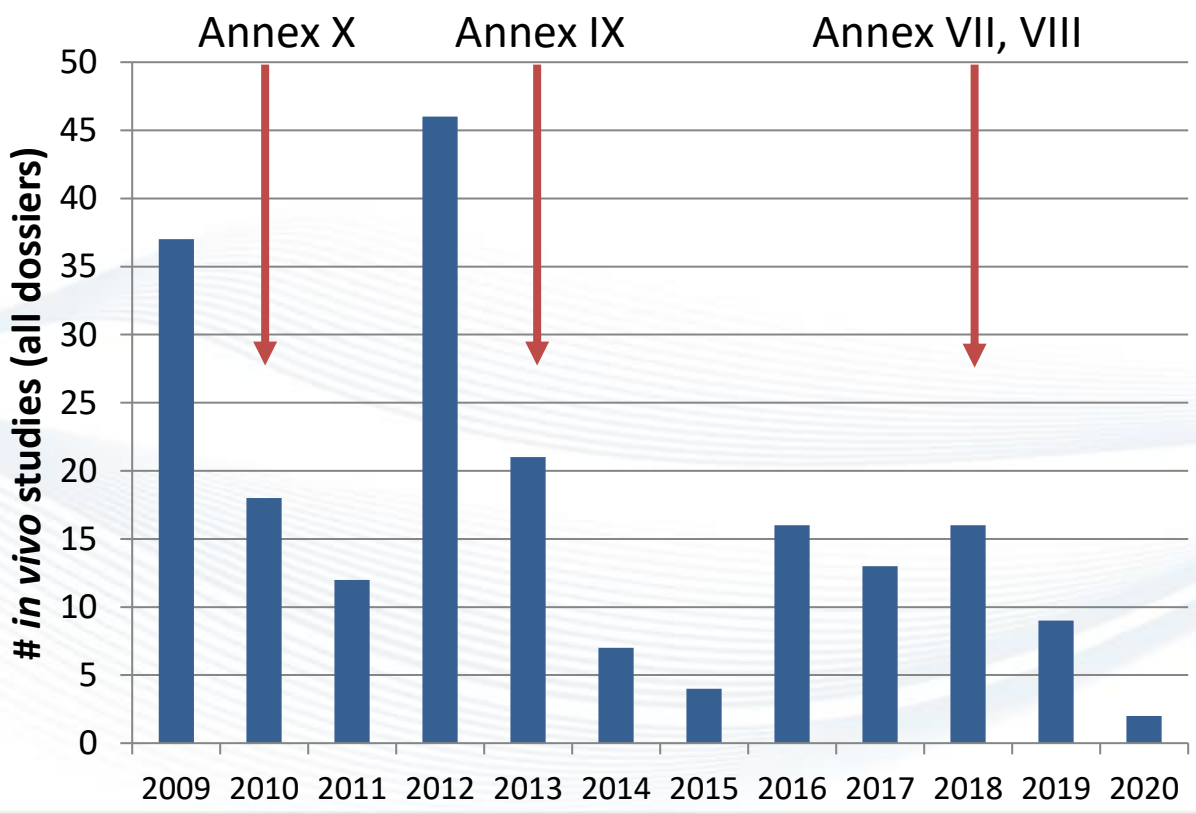


Study dates of *in vivo* studies for cosmetic-only substances

Cosmetic-only ingredients with newer in vivo tests

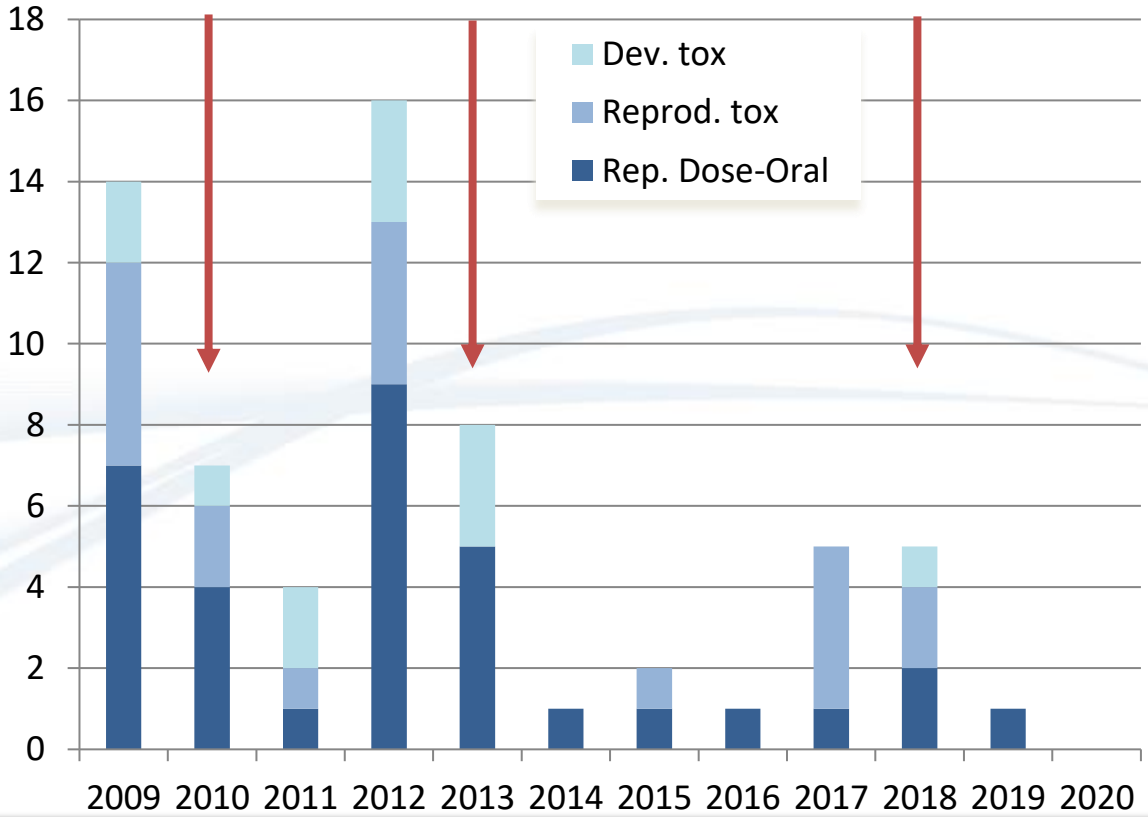
All in vivo tests since 2009: 121 tests

Peak ~year before REACH registration deadlines



Endpoint example:

In vivo for repeated dose endpoints



In vivo tests after Cosmetic Regulation deadlines

	Tests since 2009	after cosmetic ban	REACH confirmed / likely	non-REACH confirmed	OECD Test Methods
Cosmetic ban = 11 March 2009					
Skin Irr	10	8	6	2	404
Eye Irr	9	9	8	1	405
Genetic Tox	3	2	1	1	474
Acute Tox - Oral	44	41	36	5	423 (31); 420 (5)
Acute Tox - Dermal	8	7	5	2	402
Cosmetic ban = 11 March 2013					
Skin Sens	44	16	15	1	429 (13), 406 (2)
Rep Dose Tox – Oral[(5)]	37	9	7	2	407 (3), 408 (1), 422 (3)
Reproductive Tox	20	8	7	1	421 (6), 443 (1)
Developmental Tox	13	3	3	0	414
Toxicokinetics	4	1	0	1	None
TOTAL	**192**	**104**	**88**	**16**	

63 cosmetic-only ingredients had in vivo tests after the Cosmetic Regulation test ban dates

Other results

- **"In vitro first" principle generally followed. Where alternative methods were available, most registrants followed the principle of in vitro first, but ultimately had to test in vivo to comply with REACH.**

  Key reasons were positive or equivocal results from in vitro tests, or chemical properties that made in vitro tests infeasible.

- **Some tests could have been avoided by using Annex XI adaptation strategies.**

  Missed opportunities to use non-animal test strategies for acute toxicity. Also waiver opportunities for acute toxicity were missed in three cases: two based on skin corrosion test results and one dermal test base on the acute oral test result.

The story is continuing…

More new *in vivo* testing for REACH is likely unless conflict resolved:

- **More tests as ECHA reviews more dossiers.**

  As part of its dossier evaluations to date, ECHA has already requested new in vivo tests for cosmetic-only ingredients. Now on going:

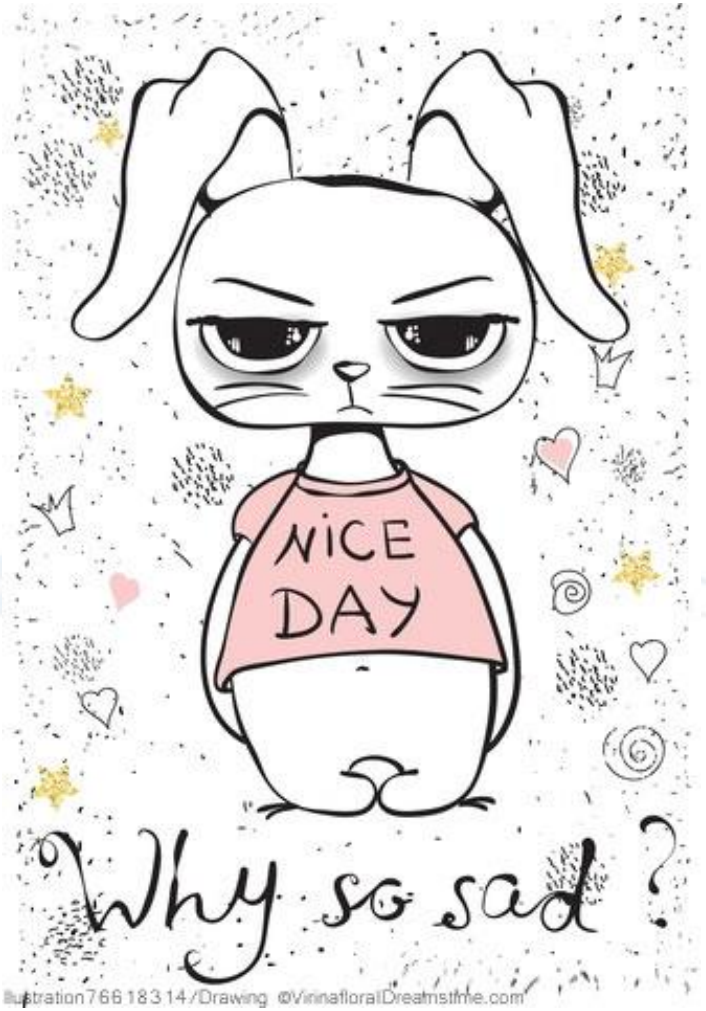
  - **7 tests for 90d oral repeated dose toxicity studies**
  - **7 tests for developmental toxicity studies**
  - **3 combined screening test according to OECD 422**
  - **3 extended one generation reproductive toxicity studies**

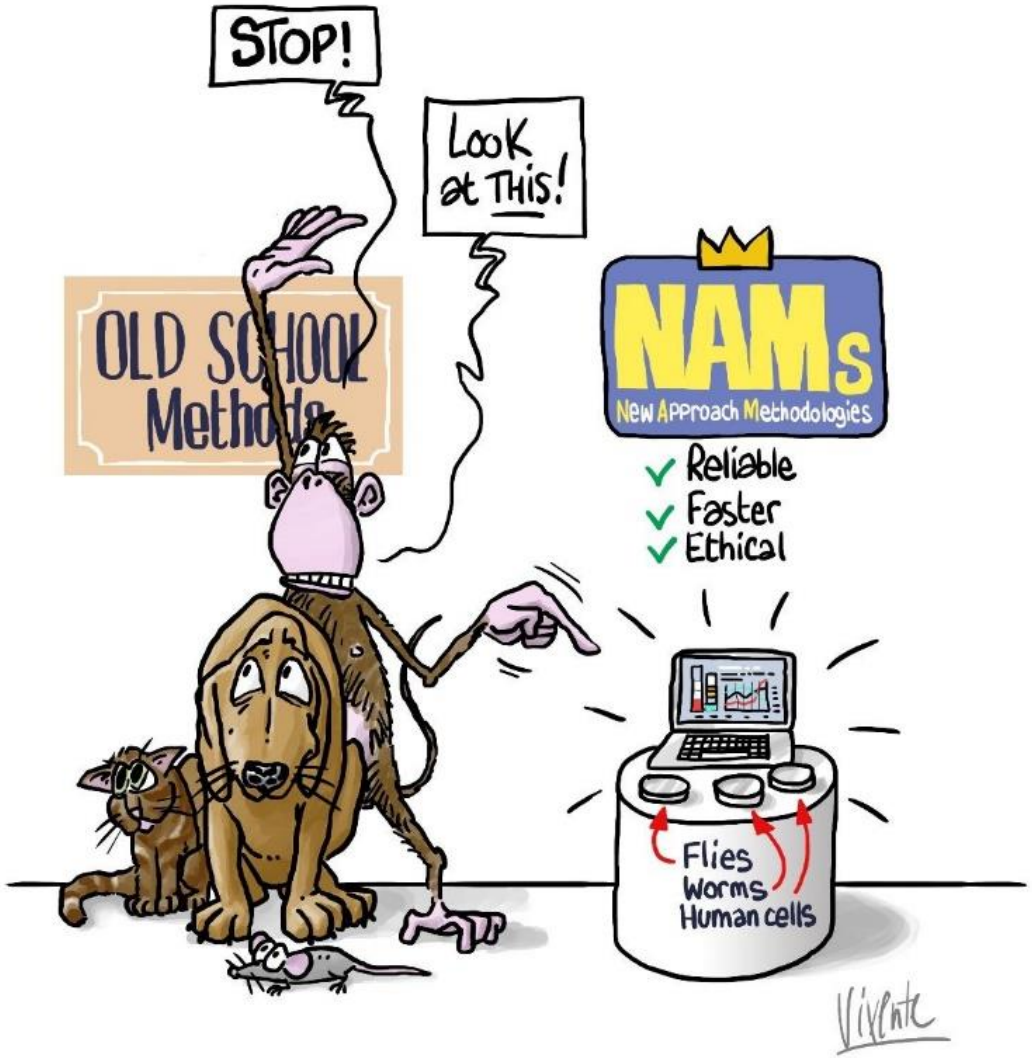
ECHA has promised to review all dossier by 2027

Next Year REACH will be amended to ask for the CSR in Annex VII dossiers and registration of polymers

Consequences for cosmetic industry

- **Global ingredient supply chain now contains REACH animal-tested ingredients.**
- **Ingredient supply chains are often complex, not easily traced to the original manufacturer. This makes identification of the REACH testing difficult.**
- **Large impact on brands if they cannot identify the testing. Reputation relies on consumer trust.**
- **Consumers no longer know who to trust.**





Grazie per l'attenzione!