Red Española para el Desarrollo de Métodos Alternativos a la experimentación animal

Los métodos alternativos a la experimentación animal ante las nuevas normativas internacionales

IV Jornada de REMA, X Aniversario

Colegio Oficial de Veterinarios de Madrid

1 de diciembre de 2009

Documentos disponibles en http://www.remanet.net/

REACH

EL VALOR DE LA SEGURIDAD

THE VALUE OF SAFETY

Acceptability of alternative methods

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¿Why we need a Regulation internationally accepted.

To guarantee

- **the safety and confidence of citizens**
- **free circulations of goods**

Clasification and labelling of dangerous substances

Sustancias nuevas	**New chemicals**	**EC Directiva 67/548/EEC**
Datos requeridos	Data requierement	Directiva 92/32/EEC
Criterios de evaluación	Principles	Directva 93/67/EEC
Guias tecnicas	Technical Guidance Documents	TGD, EC, 1993

(30 adaptations)

Methods of testing

Not in he inventory of Existing substances (EINECS) antes de Sept de 1981

Evaluation on the basis of data requiered to be presented by the Notifier

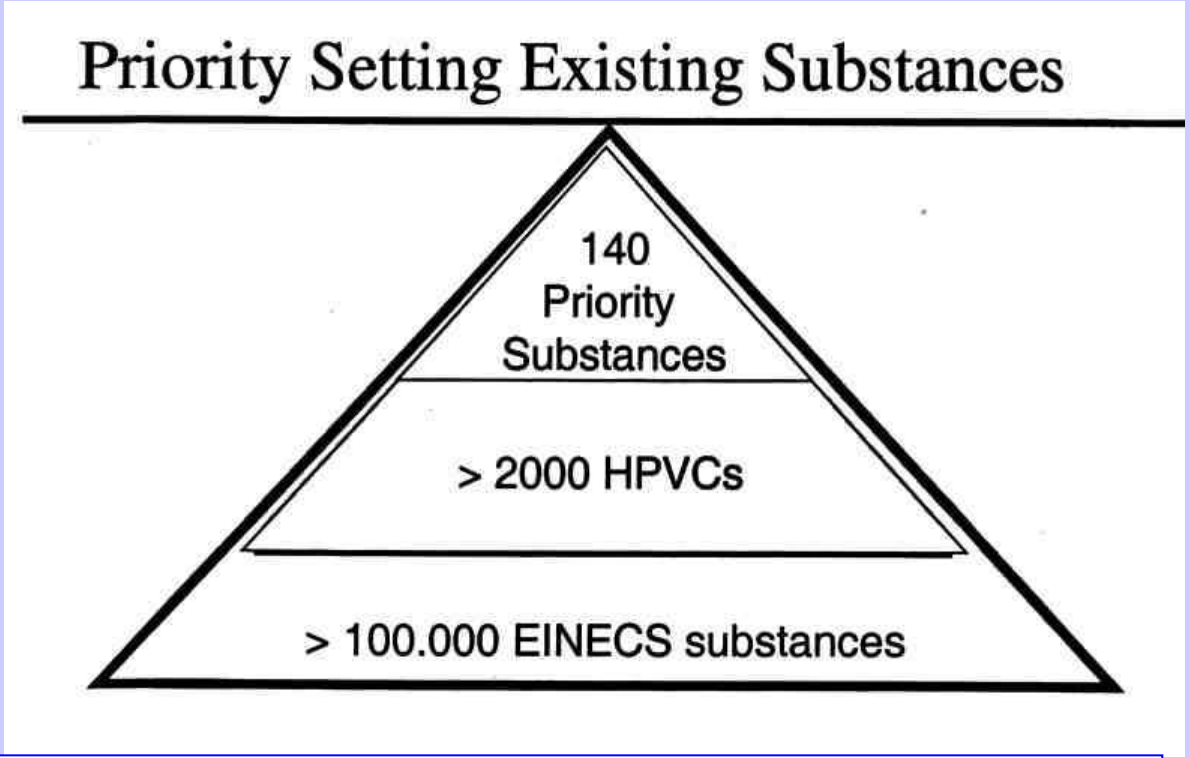
Sustancias existentes	**Existing chemicals**	**EC Reg. Consejo 793/93**
Principios de evaluacion	Risk assesment principles	EC Reg 1488/94
TGDs	TGDs	TGDs for EC Reg 1488/94
TGDs para armonización criterios de evaluación de sustancias Nuevas y Existentes.	TGDs package for harmonization of the evaluation of News and Existing Chemicals	TGDs EC, 1996

Las que estaban en el inventario europeo de sustancias existentes (EINECS) antes de Sept de 1981 (**100.106**)

EXISTING SUBSTANCES

A challange for the evaluation of substances

Guarantee of safety for human health and the environment



White Book (2001)

REACH Regulation (2007)

Industria submit existing data

Competente Authority: responsability of evaluation (the charge of the proof)

Charge of the proof on industry (Estudies and risk assessment)

Substances with specific regulations		
Nombre	*Name*	*Reference*
Directiva de Plaguicidas	Directive of Pesticides (or PPP Directive)	EC Dir 91/414/EEC
Medicamentos veterinarios	Veterinary drugs	EC Reg 2377/90
Aditivo alimentarios	Feed additives	EC Dir 70/524/EEC
Aditivos de alimentos	Food additives	89/107/EEC
Cosméticos	Cometics	SCP/803/90
Materiales de embalaje	Packaging materials	EC Dir CSIPM/1025
Biocidas	Biocides	EC Dir 98/8/EEC
TGDs		

Notifier submitting a dossier with proposed evaluation

REACH?

- **R**egistration, **E**valuation, **Authorization** and Restriction of **Ch**emicals.
  - **Directive 121/2006 (modify Dir. 67/548 for adapting to REACH)**
  - **Regulation 1907/2006 (direct executive consequence in all EU)**
  - **Technical guides**
- 1 June 2007. (Pre-register until dic 2008)
- REACH gives higher responsibility to industry

Objetives:

- Protect human health en environment
- Registering about **30.000 substances**
- Increase competitivity
- Free circulation of substances
- **Industry higher responsability**
- Communication commertial chain
- **Safe use of chemicals**
- Development of new technologies
  Use of **alternative methods of animal testing**
- transparency

Procesos de la normativa REACH

- **ECHA**: European Chemical Agency (1 June 2007)
- **PRERREGISTER**: Prerregistro de sustancias susceptibles de registro.
- **SHARING DATA (Forum)**
- **REGISTER**
- **EVALUATION**
- **AUTORIZATION**
- **RESTRICTION**

CLASIFICATION , LABELLING AND PACKAGE (CLP)

(Reg. 1272/2008)

ECHA

Agencia Europea de Sustancias y Preparados Químicos

- Controlará todos los procesos relacionados con la normativa REACH.
- 1 de junio de 2007
- Comités
  - Comité de Evaluación de Riesgos (RAC) – expertos
  - Comité socioeconómico (SEC) -expertos
  - Comité de Autoridades competentes –representación estados

PRERREGISTRO

- Periodo: **1 junio 2008** → 1 diciembre 2008.

Press Release. Helsinki, 19 December 2008

LIST OF PRE-REGISTERED SUBSTANCES PUBLISHED

Today, ECHA has published on its website **a list of pre-registered substances.**

- **2.75 million preregistrations,**
- **by 65,000 companies**
- **about 150,000** substances
- between 1 June and 1 December 2008.
- cover **all the EU "existing substances" (EINECS) and the list of notified new substances (ELINCS), together**
- **about 105,000 substances**.

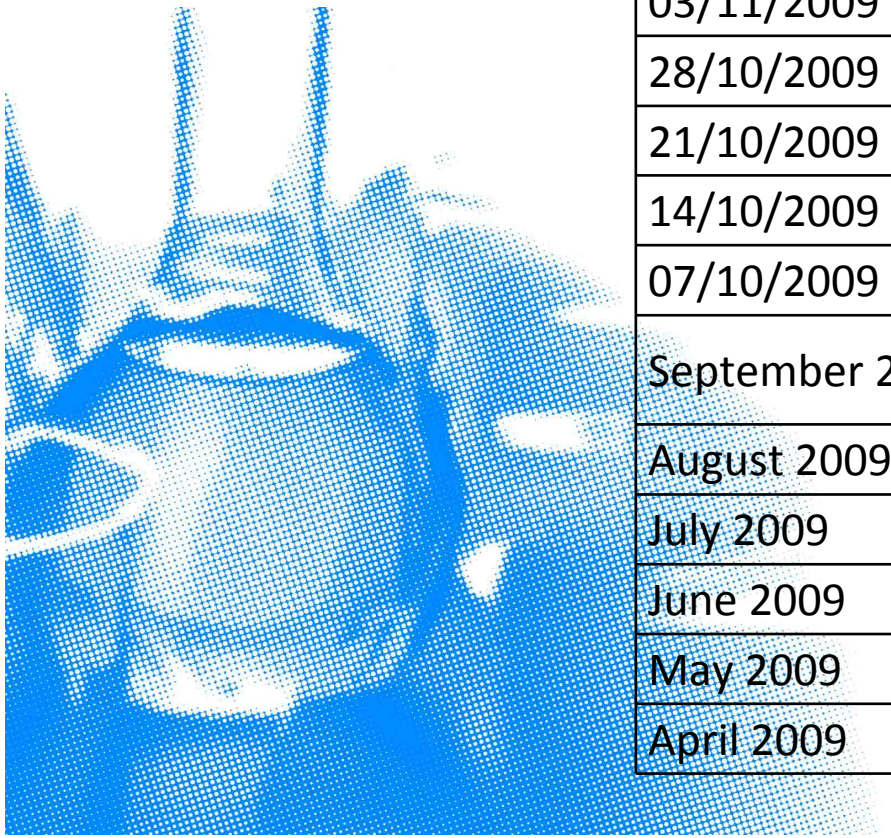
Helsinki, 27 March 2009

ECHA PUBLISHES AN UPDATED LIST

around **143 000 substances of them**, pre-registered by **some 65 000 companies**..

ECHA does not expect all of these substances to be registered.

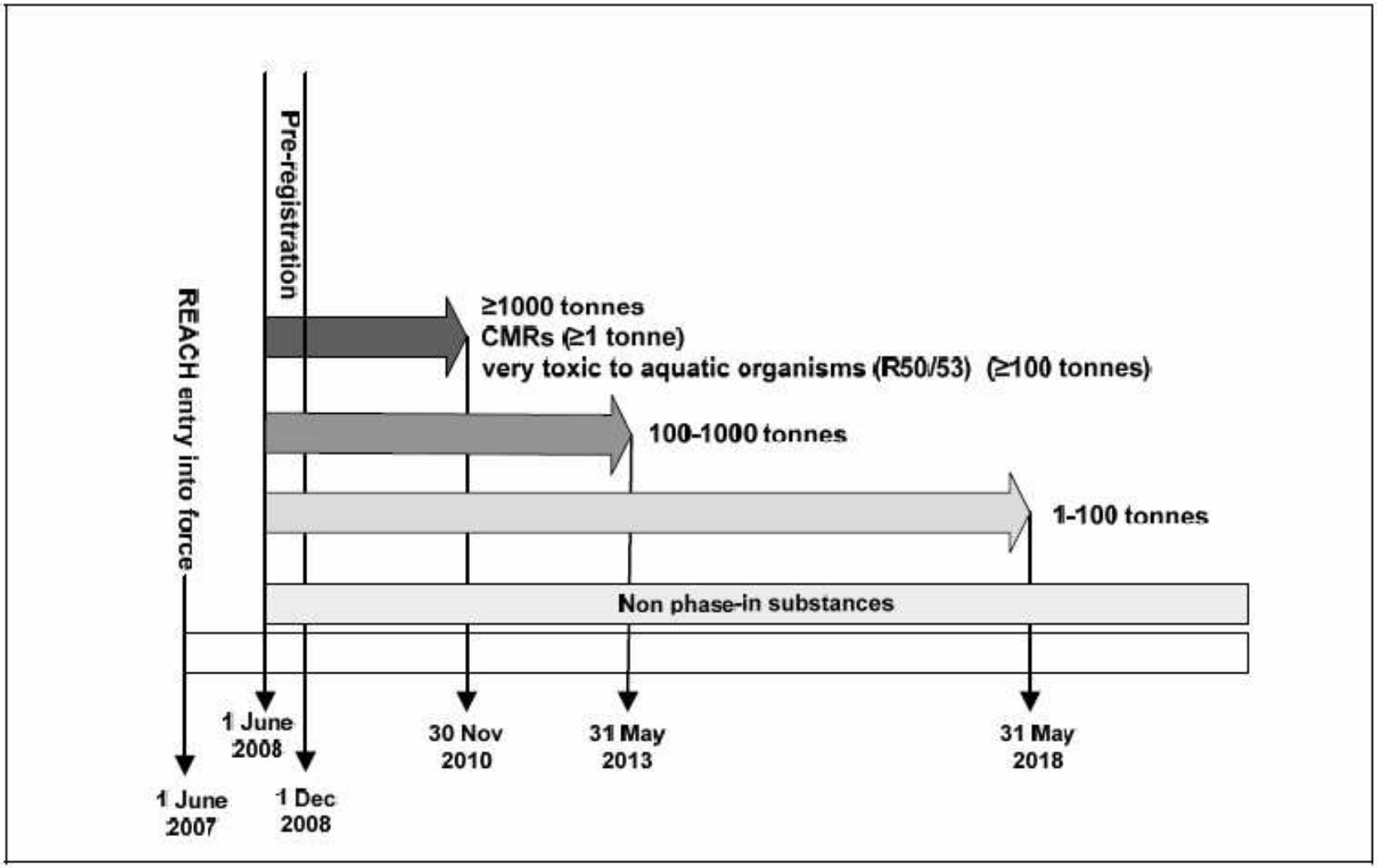
Substance Information Exchange Forum (SIEF)



Active Lead Registrants

Date	Formed SIEF
25/11/2009	**2051**
18/11/2009	2025
11/11/2009	2004
03/11/2009	1974
28/10/2009	1928
21/10/2009	1893
14/10/2009	1834
07/10/2009	1793
September 2009	1766
August 2009	1327
July 2009	982
June 2009	574
May 2009	293
April 2009	57

Registration deadlines



ESTUDIOS TOXICOLÓGICOS Y METABÓLICOS

Toxicidad aguda (Oral. Dérmica. Por inhalación. Irritación cutánea y ocular Sensibilización dérmica.

Estudios metabólicos en mamíferos.

Toxicidad a corto plazo, dosis repetida (28 días) (oral, dérmica, inhalacion)

Toxicidad subcrónica (2 especies)

Toxicidad crónica

Estudios de mutagenicidad (in vitro, in vivo)

Estudio de carcinogenicidad

Toxicidad para reproducción(teratogenicidad, fertilidad)

Datos adicionales (neurotoxicidad, mechanismos; otras rutas parentales

Datos en humanos

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ANNEX VI
INFORMATION REQUIREMENTS

STEP 1 – GATHER AND SHARE EXISTING INFORMATION

The registrant should gather all existing available test data
… test data to be shared, thereby avoiding unnecessary testing…
… from (Q)SARs, read-across from other substances, …

STEP 2 – CONSIDER INFORMATION NEEDS

STEP 3 – IDENTIFY INFORMATION GAPS

STEP 4 – GENERATE NEW DATA/PROPOSE TESTING STRATEGY

… new data shall be generated (Annexes VII and VIII),
or a **testing strategy shall be proposed** (Annexes IX and X),

New tests on vertebrates shall only be conducted or proposed as a last resort when all other data sources have been exhausted.

Tonelaje:	[1,10]	[10,100]	[100,1000]	?1000
8.1. IRRITACIÓN O CORROSIÓN CUTÁNEAS				
in vitro corrosión cutánea	X	X	X	X
in vitro irritación cutánea (no si corrosivo)	X	X	X	X
in vivo irritación cutánea (no si corrosivo)		X	X	X
8.2. IRRITACIÓN OCULAR				
in vitro de la irritación ocular	X	X	X	X
In vivo irritación ocular		X	X	X
8.3. Sensibilización cutánea				
Ensayo in vivo.	X	X	X	X
8.4. Mutagenicidad				
Estudio **in vitro** de la mutación génica en bacterias	X	X	X	X
Si 1+ => nuevos estudios de mutagenicidad	X	X	X	X
in vitro citogenicidad en células de mamífero o **in vitro** ensayo **micronucleico**.		X	X	X
Si "-" => **in vitro mutación génica** en células de mamífero Si "+" considerar ensayos in vivo		X	X	X
8.5. Toxicidad aguda				
Por vía oral	X	X	X	X
Por inhalación		X	X	X
Por vía cutánea		X	X	X

Tonelaje:	[1,10]	[10,100]	[100,1000]	?1000
8.6. Toxicidad por dosis repetidas				
toxicidad por dosis repetidas a **corto plazo (28 días**), [1 especie, vía según exposición] [salvo ensayo a 90 días]		X	X	X
toxicidad subcrónica (90 días), de **una especie, roedores**, [vía según exposición]			X	X
a largo plazo (>1 año) [podrá proponerse según exposición]				¿?
8.7. Toxicidad para la reproducción				
toxicidad para el desarrollo, de una especie [Para 10-100, solo si no pruebas por (Q)SAR o in vitro de tóxica para el desarrollo].		X	X	X
toxicidad para la reproducción dos generaciones, [Si no carcinógena genotóxica o mutagéna células germ.] [Para 100-1000 ton, solo si no hay efecto en órganos reproductores a 28 o 90 días]			X	X
8.8 Toxicocinética				
alcance dependerá de la información pertinente disponible		X	X	X
8.9.1. Estudio de carcinogenicidad				
				X

Example of data requiered

(Subchronic toxicity

COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
8.6.2. Sub-chronic toxicity study (90 days), one species, rodent, male and female, most appropriate route of administration, having regard to the likely route of human exposure.	8.6.2. The sub-chronic toxicity study (90 days) **does not need to be conducted if:** – a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure; or – a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used; or – a substance undergoes immediate disintegration and there are sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake); or – the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day "limit test", particularly if such a pattern is coupled with limited human exposure.

EJEMPLO DATOS REQUERIDOS

COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
8.9.1. Carcinogenicity study	**8.9.1. A carcinogenicity study <u>may be proposed</u>** by the registrant or may be required by the Agency in accordance with Articles 40 or 41 if: – the substance has a widespread dispersive use or there is evidence of frequent or long-term human exposure; and – the substance is classified as mutagen category 3 or there is evidence from the repeated dose study(ies) that the substance is able to induce hyperplasia and/or pre-neoplastic lesions. **If the substances is classified as mutagen category 1 or 2, the default presumption would be that a genotoxic mechanism for carcinogenicity is likely. In these cases, a carcinogenicity test will normally not be required.**

SHARING DATA

- Pre-registrants can find other pre-registrants of the same substance for sharing data
  - Pre-registrants of the same substance are obliged to sharing data (paying rights) of existing studies in vertebrates
  - Forum (SIEF) (Substance Information Exchange Forum)

TITLE III

DATA SHARING AND AVOIDANCE OF UNNECESSARY TESTING

Article 25

Objectives and general rules

1.In order to avoid animal testing, **testing on vertebrate animal**s for the purposes of this Regulation shall be undertaken **only as a last resort**. It is also necessary to take measures limiting duplication of other tests.

2…..

Art 26.3

1.If the same substance has previously been registered **less than 12 years** earlier, the Agency shall inform the potential registrant ….

2.Studies involving vertebrate animals shall not be repeated.

Initial calender

REACH

Table 1.1: The proposed schedule for the registration of 30,100 existing substances (6)

Number of substances	Volume (tonnes per annum)	Deadline for registration
2600	>1000	end of 2005
2900	100–1000	end of 2008
4600	10–100	end of 2012
20,000	1–10	end of 2012

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ALTERNATIVE METHODS. ACCEPTABILITY OF RESULTS ?

- No guideline but scientifically valid studies?
- **In vitro alternative** validated methods?
- **In vitro non validated** but scientifically valid methods?

- Further development of QSAR, read across (USE OF DATA ACCUMULATED IN ECHA BY REGISTRATION?)

WHO WILL PARTICIPATE IN DECISSIONS PROCESS?

- Experts in staff of ECHA
- Expert in committees
- Competent authorities

NEED for INCREASING ACCEPTABILITY !!

- Promoting Research
- Interaction among European Institutions (ECHA-ECVAM, Other committees)
- Interaction of European Institution with Academia, Industry, Society, National administrations
- **Role of Consensus Platforms at national and international levels (REMA, ECOPA)**


VILLENA 8:45 PM

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GRACIAS POR SU ATENCIÓN