Considerations about how the reproductive toxicity has been managed in the REACH registration dossiers. What will happen in the future?

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Linz, EUSAAT 2012, 6th September 2012

REACH deadlines

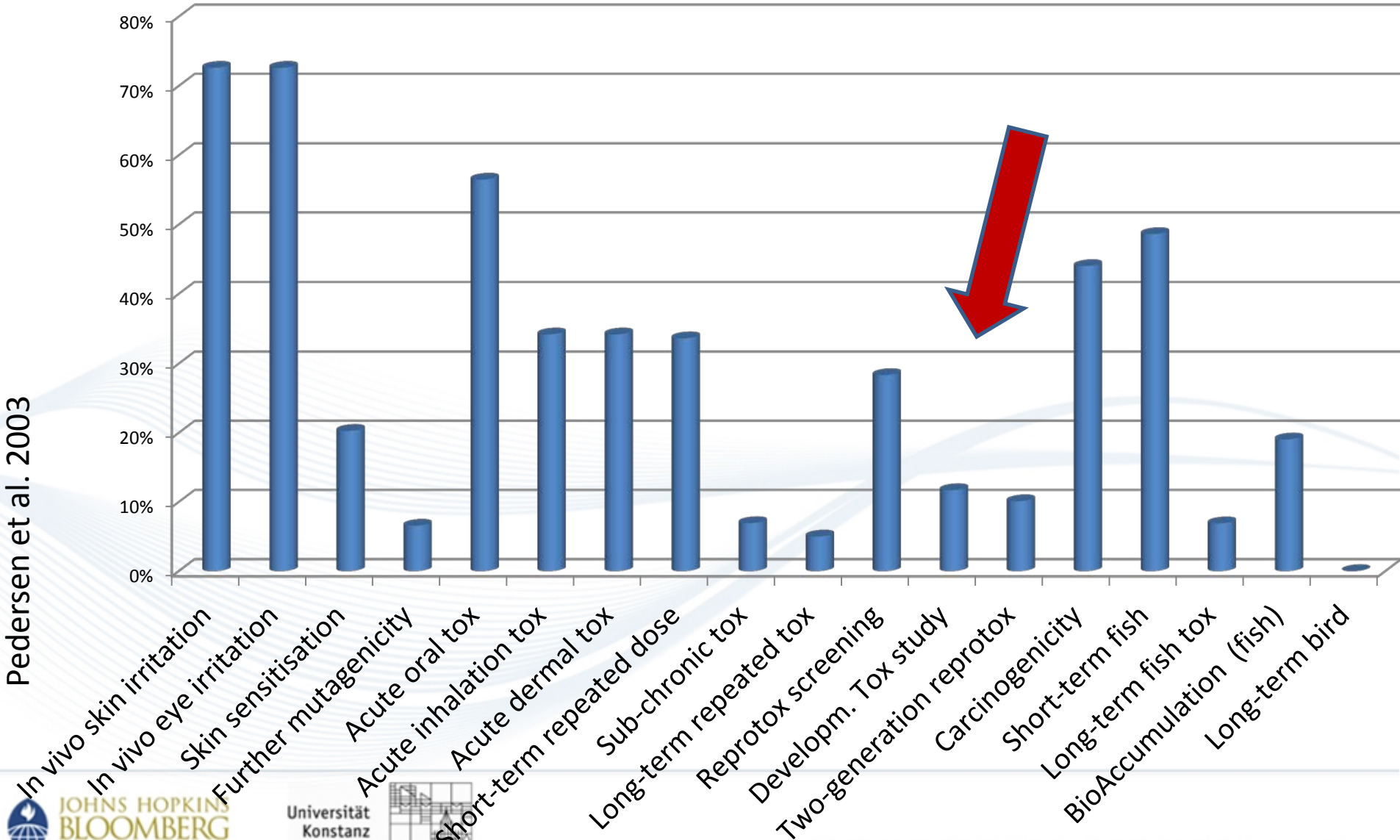
Date	Event
1 December 2010	Deadline for Registration of substances under the provision of Annex X: ≥ 1000 t/y - ≥ 100 t/y (substances which may cause long term adverse effects in the environment and classified as H400 or H410 - ≥ 1 t/y (substances classified as CMRs Category 1a or 1b
1 June 2013	Deadline for Registration of substances under the provision of Annex IX: ≥ 100 t/y
1 June 2018	Deadline for Registration of substances under the provision of Annex VII and VIII: ≥ 1 t/y

6/09/2012

REACH requirements for reproductive toxicity evaluation

Annex VIII; substances ≥ 10t/y
8.7.1. **Screening for reproductive/developmental toxicity**, one species (OECD 421 or 422), if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from in vitro methods that the substance may be a developmental toxicant
Annex IX; substances ≥ 100t/y
8.7.2. **Pre-natal developmental toxicity study, one species**, most appropriate route of administration, having regard to the likely route of human exposure (B.31 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 414). 8.7.3. **Two-generation reproductive toxicity study**, one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure, if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues
Annex X; substances ≥ 1000t/y
8.7.2. **Developmental toxicity study, one species**, most appropriate route of administration, having regard to the likely route of human exposure (OECD 414). 8.7.3. **Two-generation reproductive toxicity study**, one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure, unless already provided as part of Annex IX requirements

Missing information - Forecast in 2003



Foreseen number of expected full registration dossiers

Scenario		Chemical marketed in quantity:				TOTAL
		≥ 1 t/y	≥ 10 t/y	≥ 100 t/y	≥ 1000 t/y	
1	Preregistered substances	29,550		59,599	54,686	143,835
2	Considering only Phase-in substances			53,048	47,858	100,906
3	Considering market increase 1994 to 2008	44,632	11,570	5,721	> 3700	68,208
4	Pedersen et al. (2003) Estimation	19,200	4977	2,461	2,704	29,342

Rovida and Hartung, 2009

t4 Report*

How are Reproductive Toxicity and Developmental Toxicity Addressed in REACH Dossiers?

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Summary

The first deadline for REACH registration has passed and registration data for the first set of substances are now public. According to ECHA, 4,599 substances have been registered so far, and the corresponding dossiers of many of them are now partially available in a public database. A sample of 400 records was randomly selected and analyzed with regard to reproductive and developmental toxicity. Most dossiers do not follow the strict requirements in the official guidelines, and some dossiers lack some very basic information. A broad variety of existing data is used, and the read-across opportunity is very much exploited. Surprisingly, a number of in vivo tests have been performed already, apparently for REACH purposes, in spite of the legal requirement to make a public proposal and wait for authorization by ECHA. The number of animals used so far, plus the number of animals that will derive from testing proposals of the first REACH deadline, is very high; it may add up to 1.6 million animals just to accomplish reproductive and developmental toxicity endpoints if the data collected from 400 dossiers are extrapolated to the total number of registered substances. In vitro tests are completely absent, even though there are many tests that may be used to complement either read-across strategies or partially reliable existing data. It is recommended, in the spirit of REACH, to protect human health through an in-depth assessment of the chemicals and simultaneously, to promote the use of in vitro alternatives.

Keywords: REACH, CLP, reproductive toxicity, developmental toxicity, registration dossiers

ALTEX, 28/4, 2011

ECHA Database

+ About Us
+ Regulations
+ Addressing Chemicals of Concern
− Information on Chemicals
+ Pre-registered substances
− Registered substances
› Identified substances for registration in 2010
› Substances identified by industry to be registered by 31 May 2013
› Classification & Labelling Inventory
+ Testing proposals
+ Transitional Measures
› Community Rolling Action Plan
› Data on Candidate List

Registered substances

Chemical Substance Search

Last updated 19th of July. Database contains 7 663 unique substances and contains information from 30 375 dossiers.

formaldehyde

Enter search string - a Chemical Name, EC No, Cas No, etc. Leave blank and press *'Search'* to view entire database.

☑ I have read and I accept the disclaimer.

Search

Lower limit(tonnes): Upper limit(tonnes):

You can narrow the search results by entering a total tonnage band (per annum)

Search results

Records per page 25

EC Number	CAS Number	Name	Total Tonnage Band	
200-001-8	50-00-0	formaldehyde	1,000,000 + tonnes per annum	View
200-001-8	50-00-0	formaldehyde	Intermediate Use Only	View
293-659-0	91081-53-7	Rosin, reaction products with formaldehyde	1,000 - 10,000 tonnes per annum	View

http://echa.europa.eu

formaldehyde

Exp Supporting Toxicity to reproduction.001

Administrative Data | Data source | Materials and methods | Results and discussions

Administrative Data

Purpose flag	supporting study
Study result type	experimental result
Reliability	2 (reliable with restrictions)
Rationale for reliability incl. deficiencies	peer reviewed secondary literature

Data source

Reference

Reference type	review article or handbook
Author	IARC
Year	2006
Title	Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol
Bibliographic source	Lyon, International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Vol. 88, pp 39-325

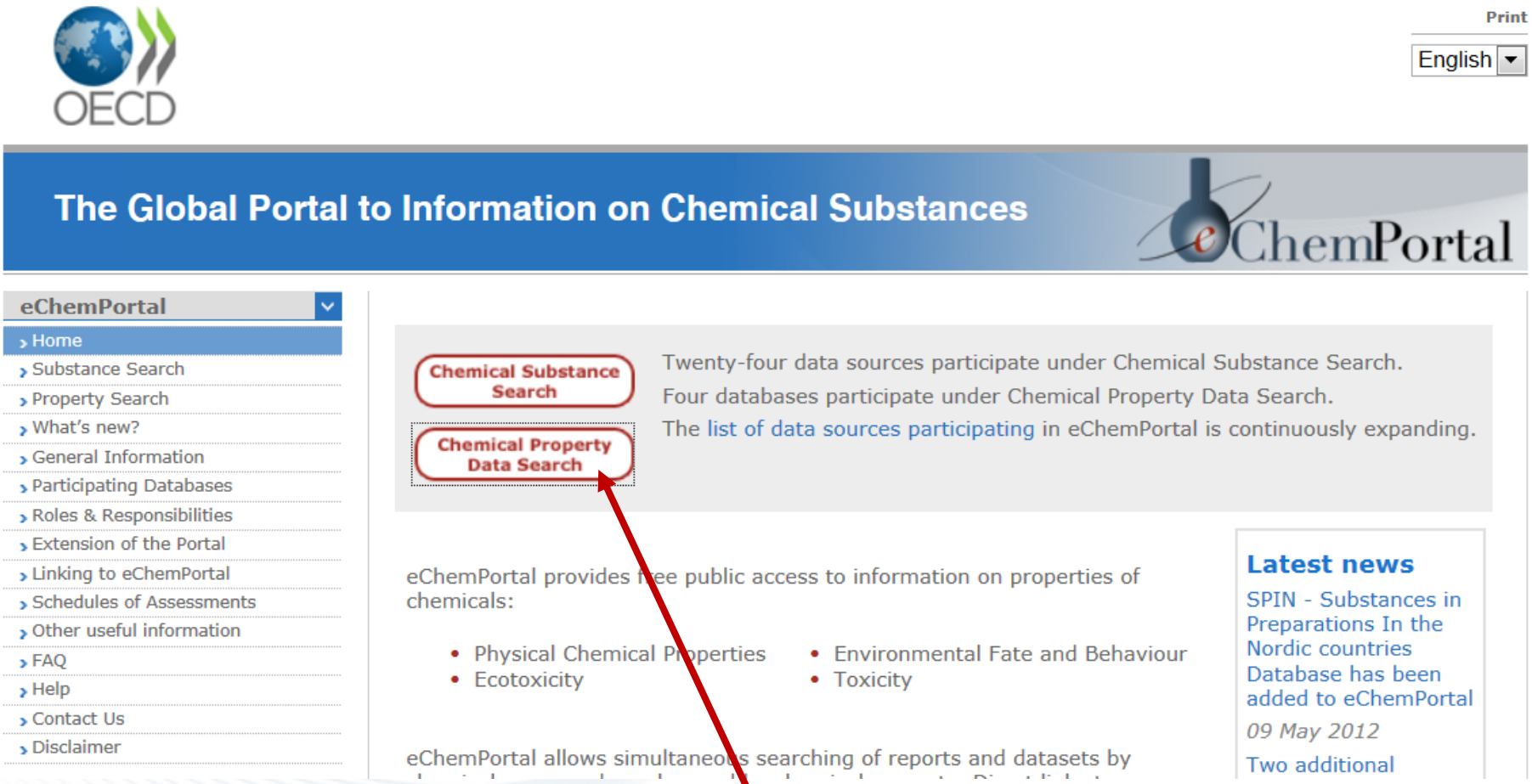
Materials and methods

Principles of method if other than guideline

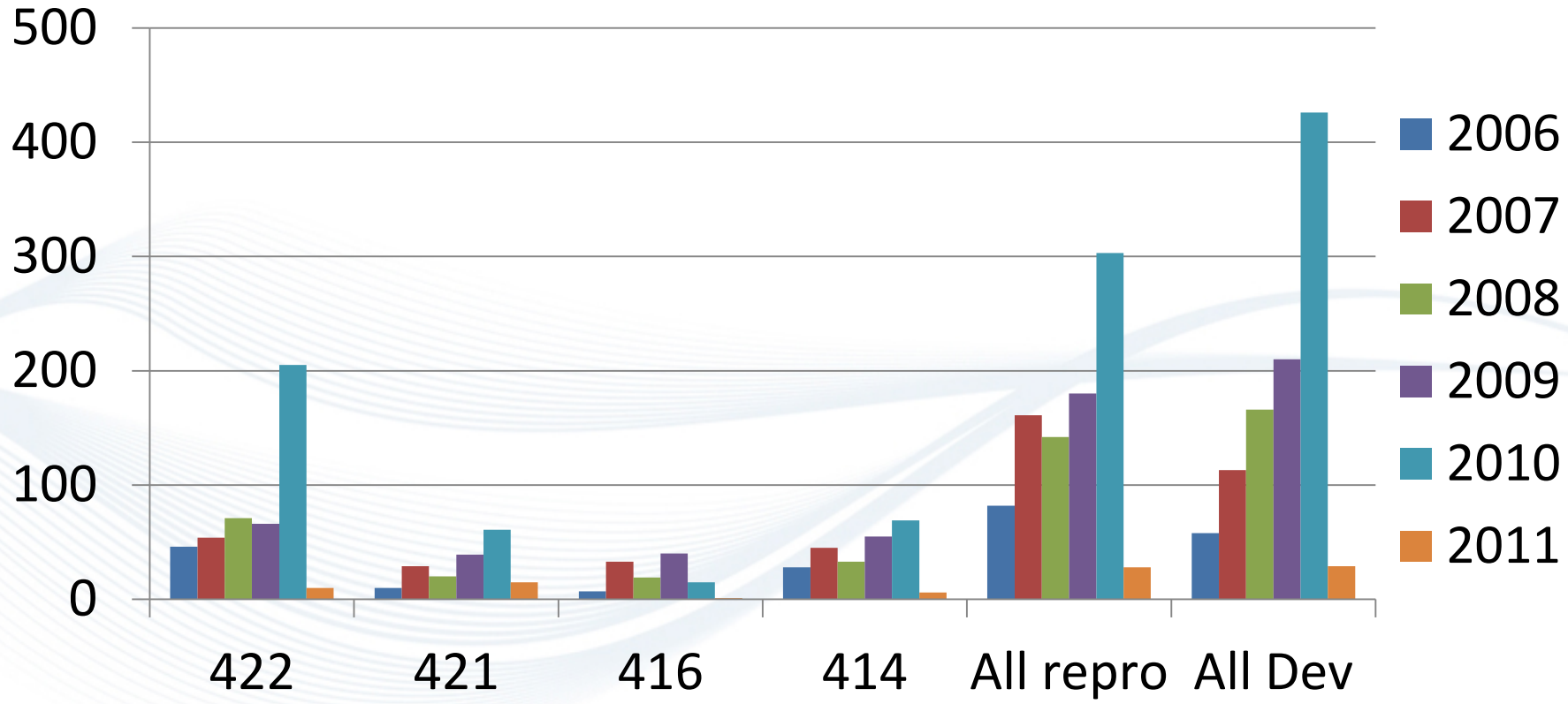
Category of IUCLID entries for reproductive toxicity and developmental toxicity in the 400 analyzed dossiers

	7.8.1 Reproductive toxicity		7.8.2 Developmental/ teratogenicity	
Existing	158	39.5%	169	42.3%
Read Across	107	26.8%	112	28.0%
QSAR/*in vitro*	3	0.8%	2	0.5%
Waived	71	17.8%	53	13.3%
Void	18	4.5%	20	5.0%
Planned new	43	10.8%	44	11.0%

ECHEM Portal



Test method/Year (OECD eChem portal)



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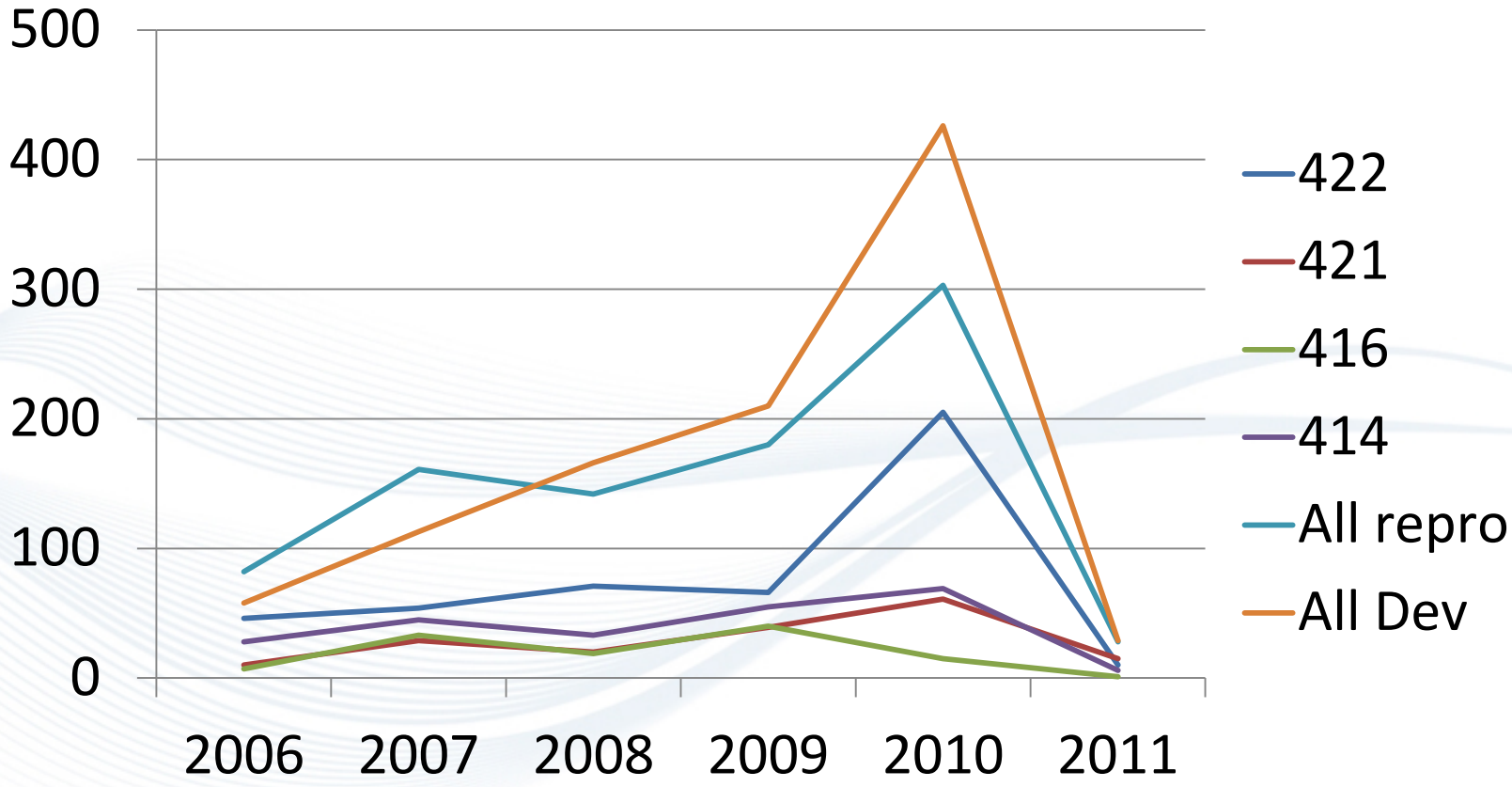
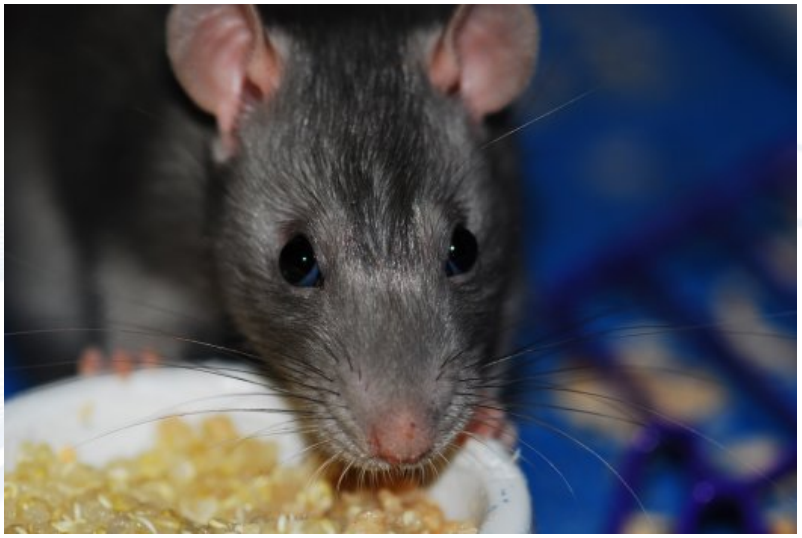


Testing Proposals

- On September 2011, only 159 testing proposals were submitted in the area of reproductive Toxicity, which represents 4.4% of the REACH registration dossier. However, this will lead to the use of more than 500,000 animals

Another important consideration concerns the strong differences between some registration dossiers. It seems unfair that diligent submitters admitted that their dossiers were lacking important information and asked for the permission to perform new tests, while others simply did the test without permissions or used data of limited scientific relevance just to fill a box.



What will happen in the future? (2013 deadline)

- Many more dossiers will contain data from OECD 422 study
- Read-across and grouping will be applied in the same % or more
  - No in vitro approaches will be applied
  - EOGRTS (OECD TG 443) performed instead of OECD 416?

What may change the scenario

- CoRAP (Community Rolling Action Plan)
  - 91 dossiers are under evaluation. Among those 11 were selected because of reproductive concern and 18 as possible endocrine disruptors
- Performing OECD 443 (Extended One Generation Reproductive Toxicity Study) instead of OECD 416 in testing proposals