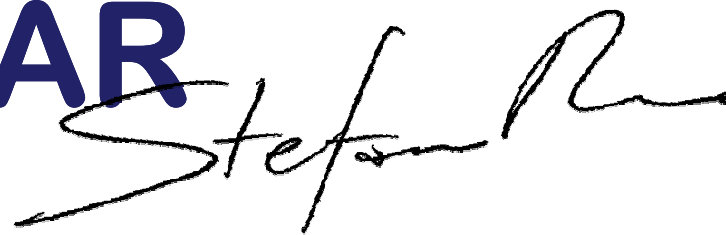


Computational Toxicology and QSAR



by **Stefano Moro**

Molecular Modeling Section (MMS)

Department of Pharmaceutical and Pharmacological Sciences

University of Padova

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How do we organize?

http://mms.dsfarm.unipd.it



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MMS: News & Updates

October 01, 2015

MMS launches the DockBeach tool. [more...](#)

MMS: Events

May 15-19, 2016

33rd Cameron Cyprus Symposium

Receptor Chemistry: Reality and Vision... [more](#)

May 12-13, 2016

3rd GPCR Targeted Screening Conference

Maritim Hotel Berlin - Berlin, Germany... [more](#)

MMS: Latest Hot Publication

Cuzzolin et al. "Deciphering the Complexity of Ligand-protein Recognition Pathways using Supervised Molecular Dynamics (SuMD) Simulations." JCIIM (2016) [more...](#)

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Chimica Farmaceutica 2 (CTF)

Progettazione e Sviluppo di un
Farmaco (CTF) [YouTube channel. more...](#)

Biomodeling (BTF)

Cheminformatica (ISF) [BlackBenck tool. more...](#)

Tossicologia Computazionale
(Master REACH Speciality School) [Supervised Molecular Dynamics](#)
Master, PhD and Advance Courses

Events

11-14, 2016

Annual Meeting in Medicinal Chemistry...

June 13-15, 2016

6th RSC / SCI symposium on GPCRs
in Medicinal Chemistry... [more](#)

MMS: Latest Hot Publication

Cuzzolin et al. "Deciphering the Complexity of
Ligand-protein Recognition Pathways using
Supervised Molecular Dynamics (SuMD)
Simulations." JCIM (2016) [more](#)

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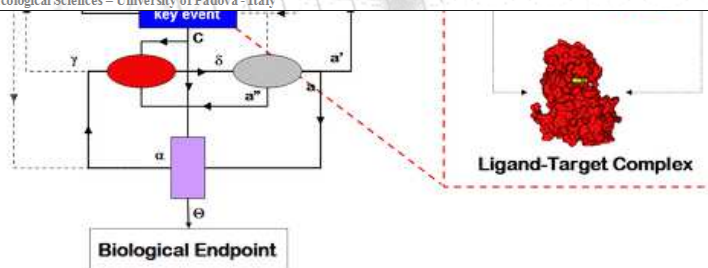


CompuTox & QSAR Agenda:



**CompuTox... mission impossible?
... or just a difficult mission?**

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@sertiamoci: (esercitazioni on-line da usare come "foraggio" cerebrale)

Ecco alcuni strumenti computazionalmente interessanti:

1. VEGA (Ist. Mario Negri - Milano)
2. QSAR ToolBox (ECHA, EU):
3. EPI Suite (EPA, USA):

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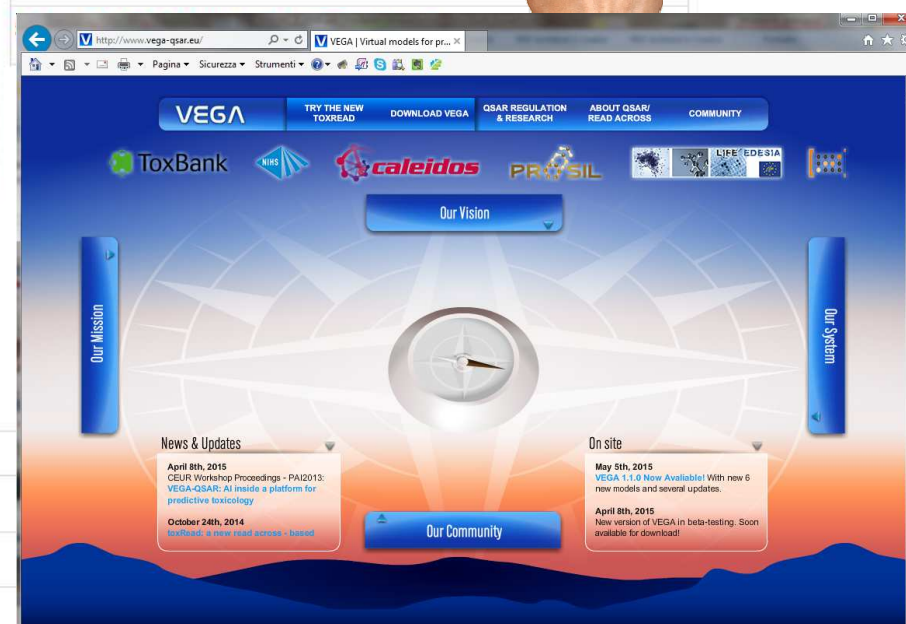
ologie informatiche/computazionali applicate in particolare nell'ambito
a della tossicologica predittiva ed, in particolare, normativa europea REACH.

1. Introduzione alla tossicologia computazionale

2. Rappresentazione e archiviazione molecolare

3. Descrittori molecolari

4. Introduzione alle relazioni quantitative struttura
attività (QSAR)



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Here is when you can find Stefano in the lab:

Where is Stefano?

Oggi	◀	▶	Giugno 2016	Stampa	Settimana	Mese	Agenda
dom	29	30	31	1 giu	2	3	4
	8:30AM Lezione Chir	8:30AM Lezione Chir	8:30AM Lezione Chir	8:30AM Lezione Chir	8:30AM Lezione Chir	8:30AM Lezione Chir	
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12	13	14	15	16	17	18	
	6th RSC / SCI symposium on GPCRs in Medicinal Chemis						
19	20	21	22	23	24	25	
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26	27	28	29	30	1 lug	2	

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CompuTox & QSAR Agenda:



**CompuTox... mission impossible?
... or just a difficult mission?**



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JOINT RESEARCH CENTRE

European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)

European Commission > JRC > EURL ECVAM

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EU-NETVAL Validation Laboratories

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Databases

Glossary

Job vacancies

The **European Union Reference Laboratory for alternatives to animal testing (EURL-ECVAM)** has been formally established in 2011, due to the increasing need for new methods to be developed and proposed for validation in the European Union. **EURL ECVAM** is hosted by the Joint Research Centre, Institute for Health and Consumer Protection (IHCP) located in Ispra, Italy.

EURL ECVAM has a long tradition in the validation of methods which reduce, refine or replace the use of animals for safety testing and efficacy/potency testing of chemicals, biologicals and vaccines. Research laboratories are able to submit to **EURL ECVAM** for scientific validation the alternative methods to animal testing that they have developed.

EURL ECVAM also promotes the development and dissemination of alternative methods and approaches, their application in industry and their acceptance by regulators.

The European Commission's involvement in activities targeted to the validation of alternative approaches to animal testing started in 1991, with the launch of **ECVAM** (the European Centre for the Validation of Alternative Methods), hosted by the **Joint Research Centre, Institute for Health and Consumer Protection (IHCP)**. As from 2011, ECVAM's tasks are assigned to **EURL ECVAM**.



The menu on the left hand side of the page helps you browse through the main content sections of the EURL ECVAM web site.

To contact EURL ECVAM, please use [this interactive form](#).

Photo: Cell culture under sterile conditions in the EURL ECVAM microbiology laboratory. Copyright: EU 2012.

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Featured article



Review of the Availability of In Vitro and In Silico Methods for Assessing Dermal Bioavailability [Read more...](#)

Watch our video!

Our scientists show you what they are doing to advance safety assessment of chemicals without relying on animal testing



VALERIE ZUANG
EURL ECVAM

ISPRA

Istituto Superiore per la Protezione
e la Ricerca Ambientale

<https://eurl-ecvam.jrc.ec.europa.eu/>

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Some preliminary definitions:

CompuTox... or Predictive Toxicology:

It is a discipline for the implementation of chemicals policy (including the safety assessment of industrial chemicals, chemicals in consumer products, pesticides and biocides) through the development, assessment and application of computational, or *in silico*, methods. These methods, sometimes referred to as *non-test methods*, can be used to reduce our reliance on experimental testing, and *in particular animal testing*.

Source: European Union Reference Laboratory for alternatives to animal testing (EURL-ECVAM)



Some preliminary definitions:

in silico methods:

The expression *in silico* is used to mean "performed on computer or via computer simulation." The phrase was coined in 1989 as an analogy to the Latin phrases *in vivo* and *in vitro* which are commonly used in biology and refer to experiments done in living organisms and outside of living organisms, respectively.

Source: European Union Reference Laboratory for alternatives to animal testing (EURL-ECVAM)



Some preliminary definitions:

non-test methods:


A *non-test method* refers to any non-experimental method or approach that can be used to provide data for the assessment of chemicals. Data, produced by a non-test method, are called *non-test data*. Non-test methods include *QSAR models* and *read-across/grouping approaches* and can be used to predict in a quantitative or a qualitative manner the physicochemical, biological, i.e. (eco)toxicological, and environmental fate properties of substances from knowledge of their chemical structure and other properties. Both QSARs and read-across/grouping approaches are based on the principle that the properties of substances, including their biological activities, depend on their chemical structure and hence can be predicted from it (*similar substances have similar properties*).

Source: ECHA, Expert Workshop “Dealing with Uncertainty of Non-Test Methods under REACH” 23-24 September 2010.



Why *in silico*?

Experiment Typical Cost per Compound (€)

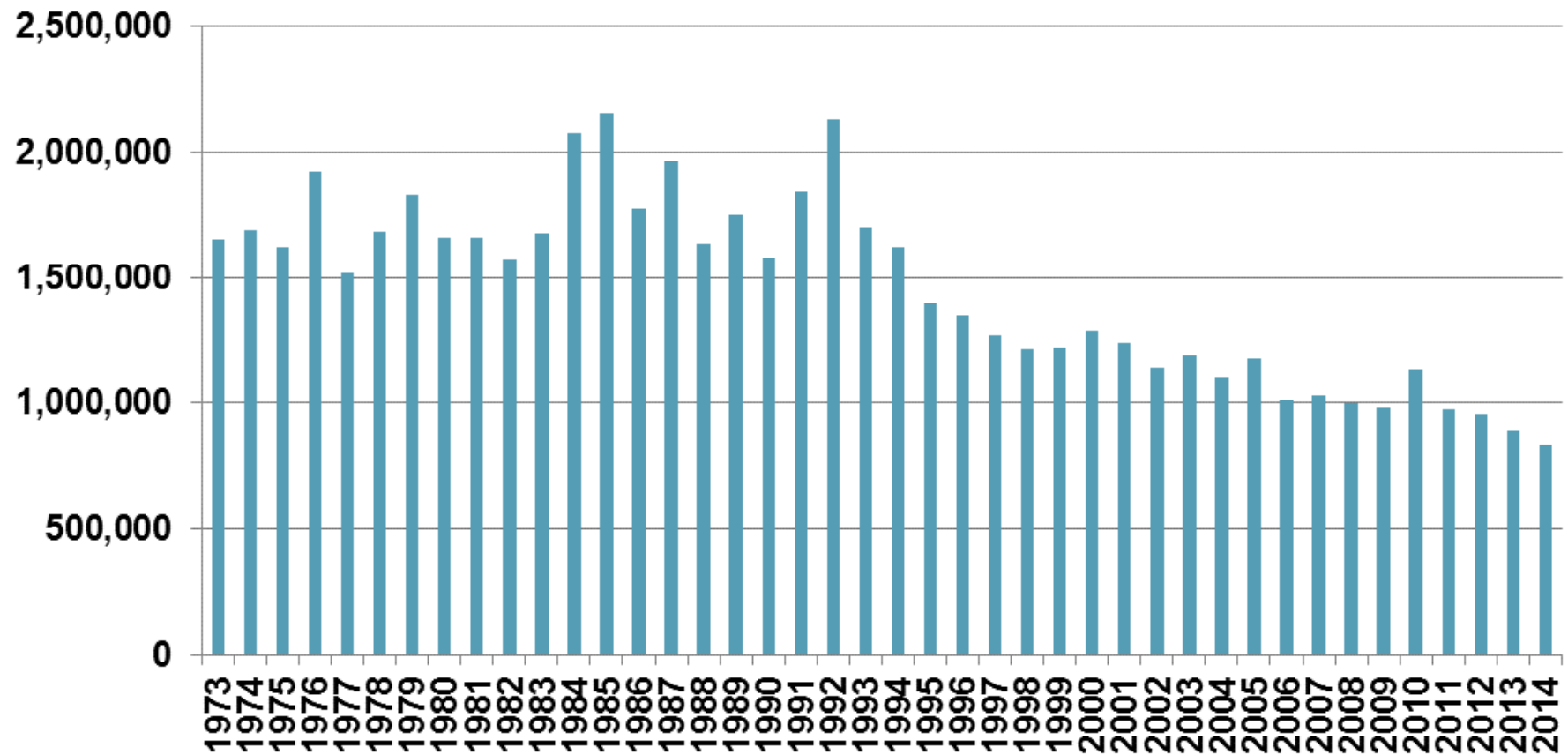
Computer modeling	7	
Biochemical assay	270	
Cell culture assay	2.700	
Rat acute toxicity	8.100	
Protein crystal structure	68.000	
Animal efficacy trial	200.000	
Rat 2-year chronic oral toxicity	550.000	
Human clinical trial	3.500.000	

Source: D.C. Young in "Computational Drug Design: A Guide for Computational and Medicinal Chemists" Wiley, 2009.



the real drama with *in vivo* exp:

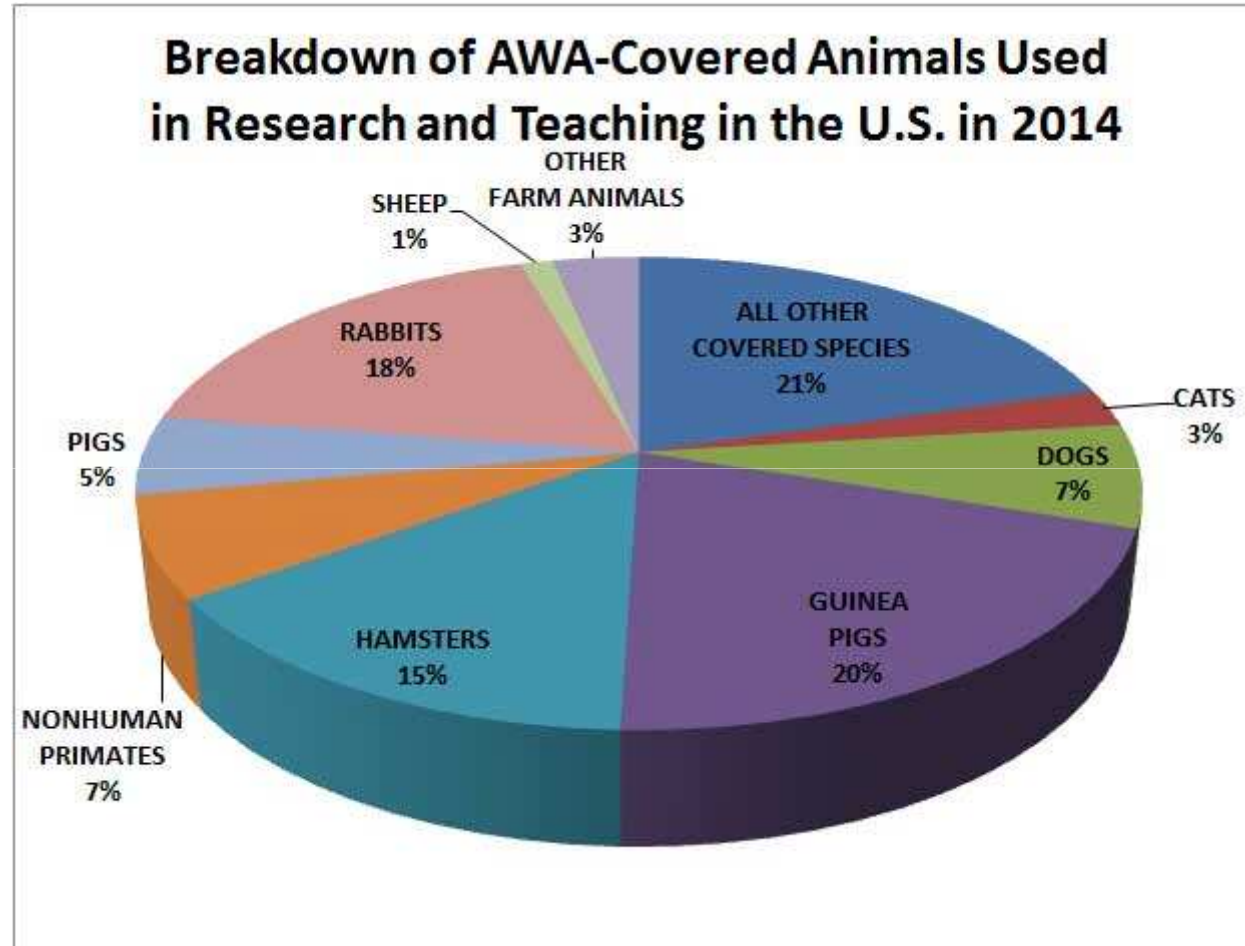
Total Number of AWA-Covered Animals Used in Research, Testing and Teaching in the U.S. 1973-2014



Source: <http://www.navs.org/animal-research-numbers-continue-downward-trend-according-to-newly-released-report/>



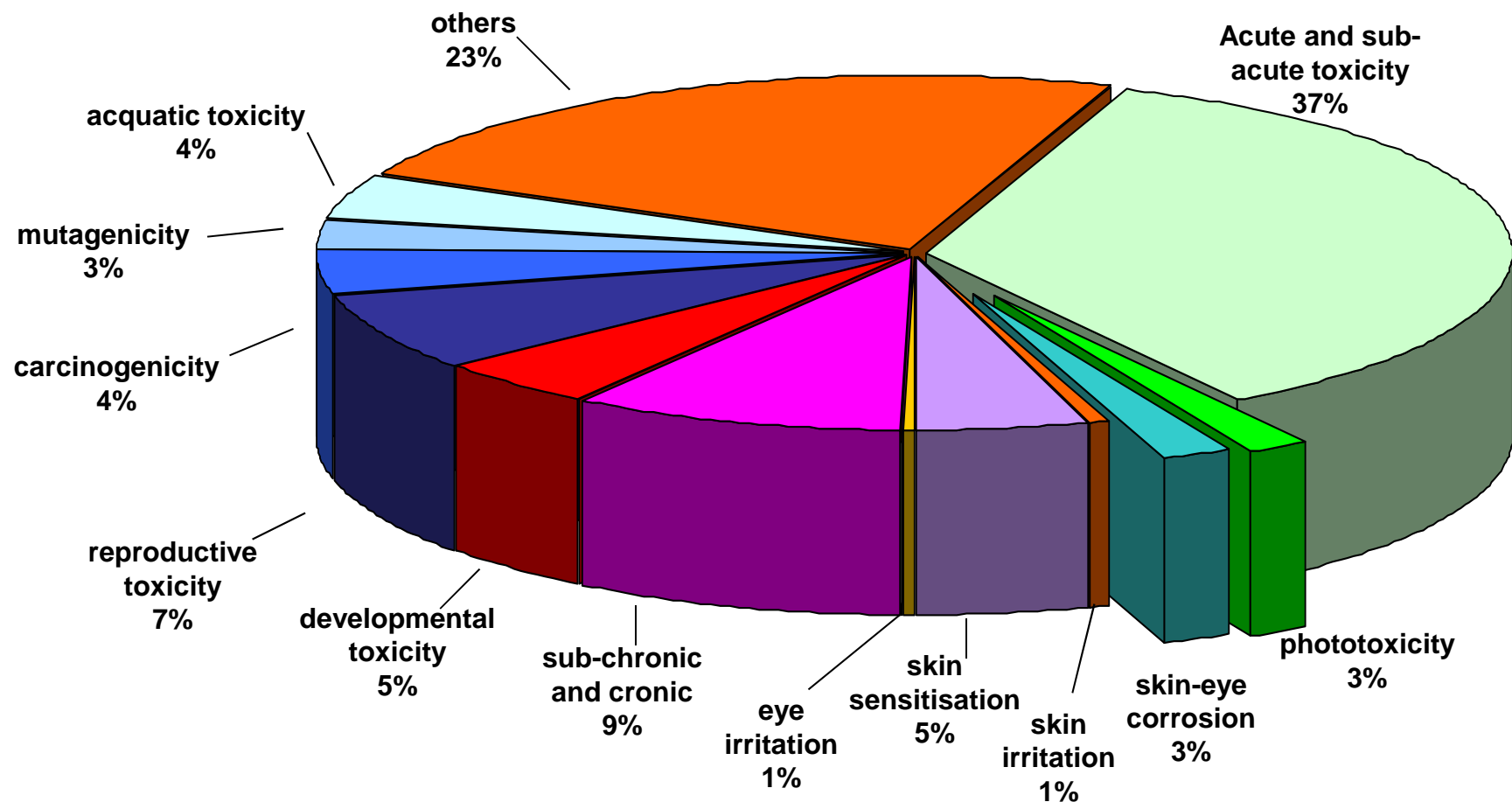
the real drama with *in vivo* exp:



Source: <http://www.navs.org/animal-research-numbers-continue-downward-trend-according-to-newly-released-report/>



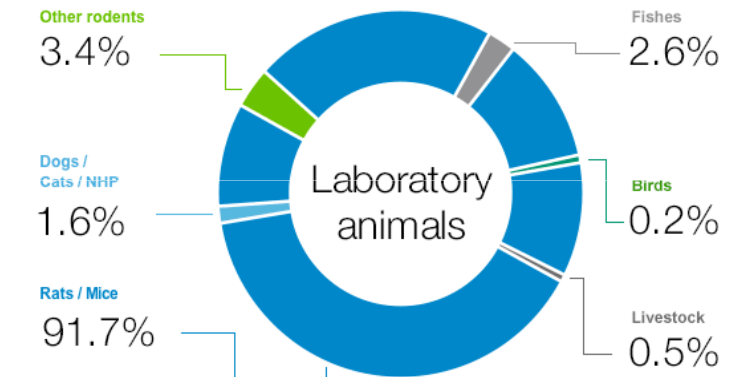
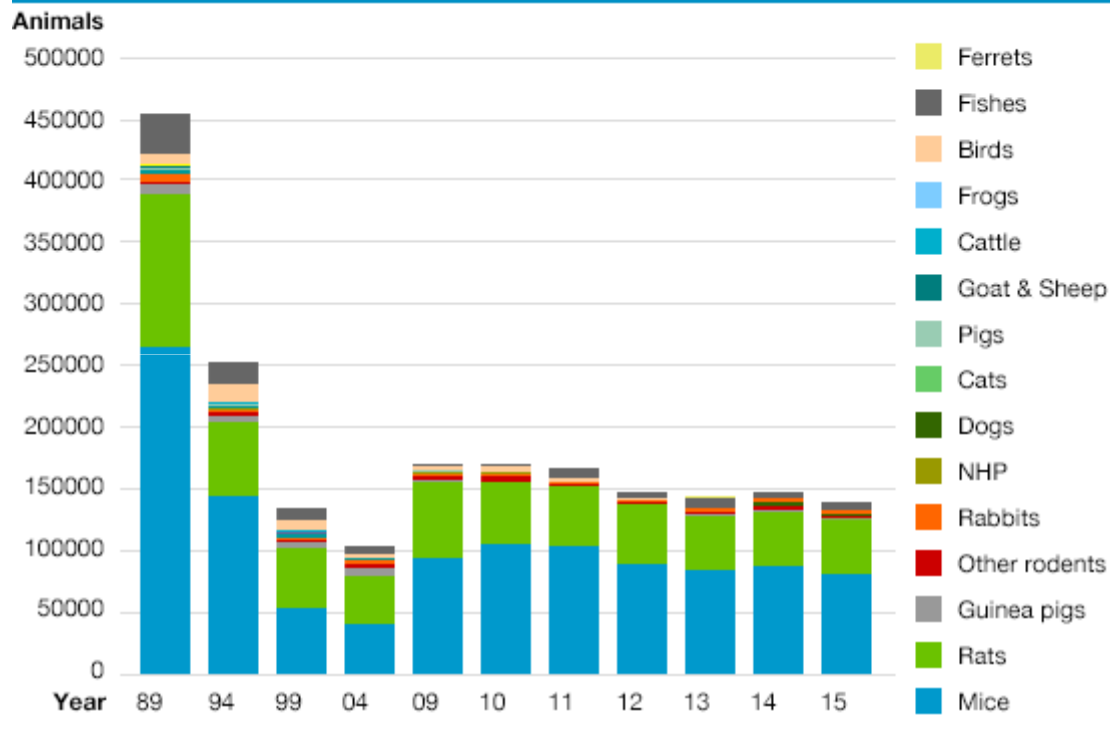
the real drama with *in vivo* exp:



Source: <http://www.navs.org/animal-research-numbers-continue-downward-trend-according-to-newly-released-report/>



the real drama with *in vivo* exp:



Source: <http://www.animalstudies.bayer.com/en/numbers.aspx>

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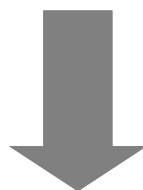
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REACH: the new European chemicals legislation

According to the European Commission (EC) a new European chemicals legislation is needed.



REACH

(**R**egistration, **E**valuation, **A**uthorization of
Chemical substances)

Source: [ECHA web site](#) /



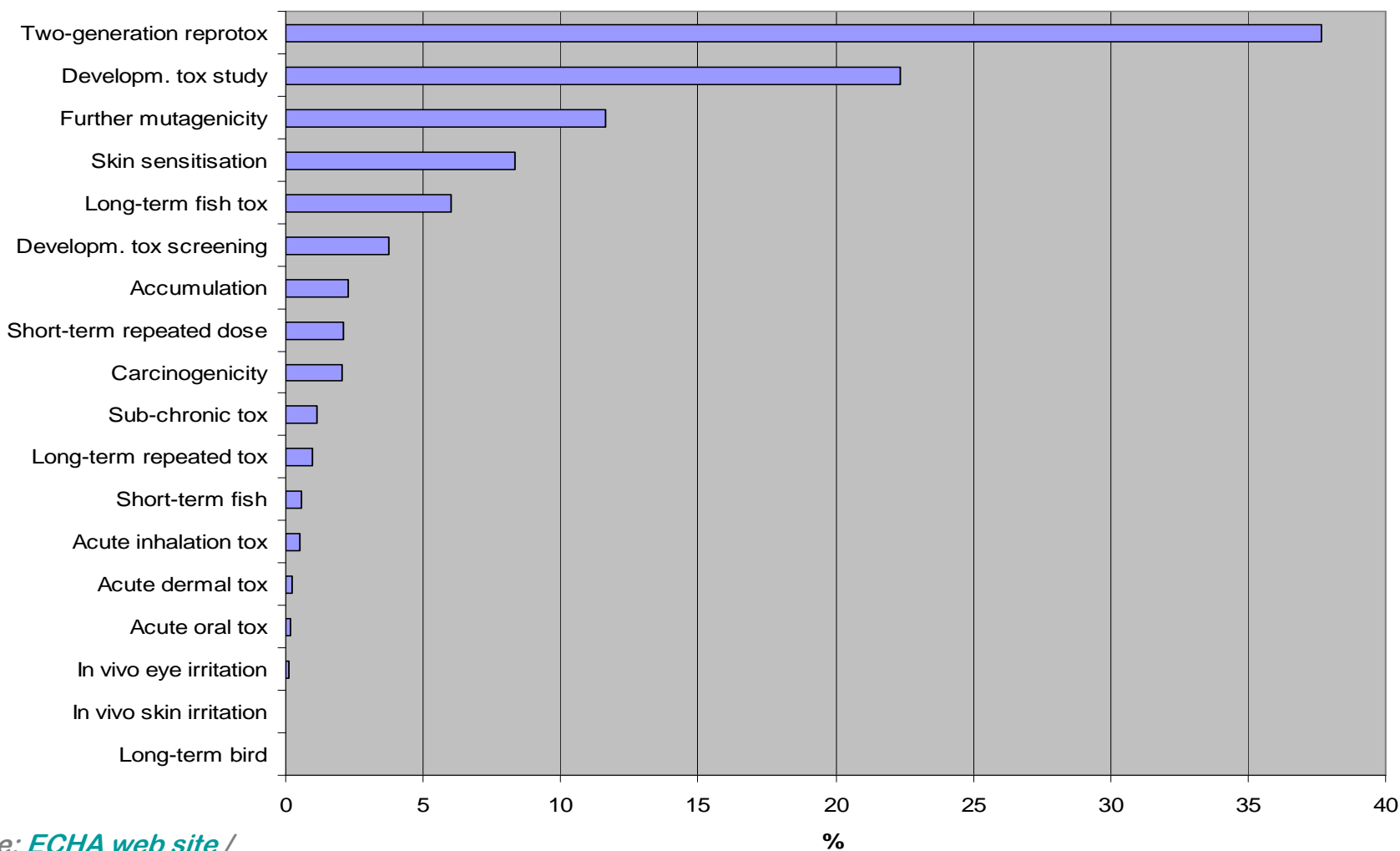
REACH: screening for what?

Physico-chemical properties		Environmental fate and ecotoxicity		Human health	
melting point		photodegradation		acute toxicity	oral
boiling point		hydrolysis		skin irritation	
density		biodegradation		eye irritation	
vapour pressure		bioaccumulation		skin sensitisation	
partition coefficient		acute tox to fish		chronic mammalian toxicity	
water solubility		acute tox to invertebrates		mutagenicity	<i>in vitro</i>
		acute tox to algae		carcinogenicity	
		acute tox to bacteria		teratogenicity	
		chronic toxicity			

Source: [ECHA web site](http://echa.europa.eu) /

Estimated test animal need for the different endpoints (*van der Jagt et al., 2004*)

Test animal need for different endpoints
(% of total test animals needed)



Source: [ECHA web site](#) /



REACH: testing costs and testing needs *(van der Jagt et al., 2004; IHCP EUR report 21405).*

- ⇒ Direct testing costs: € 2,4 billion (max. scenario)
- ⇒ Animals numbers: 3,9 million (max. scenario)
- ⇒ Time foreseen: 11 years (<http://ecb.jrc.it>)

This corresponds to a 3% increase of the total number of vertebrate test animals used if no alternative intelligent approaches are applied

Source: [ECHA web site](http://echa.europa.eu) /



REACH: and remember...

≈ 85% of toxicological data on 'old' chemicals are lacking.

Source: [ECHA web site](#) /



REACH: the Commission is invited to...

- develop screening procedures to effectively identify chemicals with potentially harmful properties or uses of concern for the purposes of prioritising substances for which further information is urgently needed ...(*Conclusion 40*)
- **develop procedures** ... to simplify the identification of the relevant testing strategies and **reduce the need for animal testing**, including the use of decision trees and specific screening methods for all chemicals, such as **validated computer modelling**...(*Conclusion 43*)

Source: [ECHA web site](#) /



The principle of 3R's (Directive 86/609/EEC)

Refinement: reduce suffering and distress;

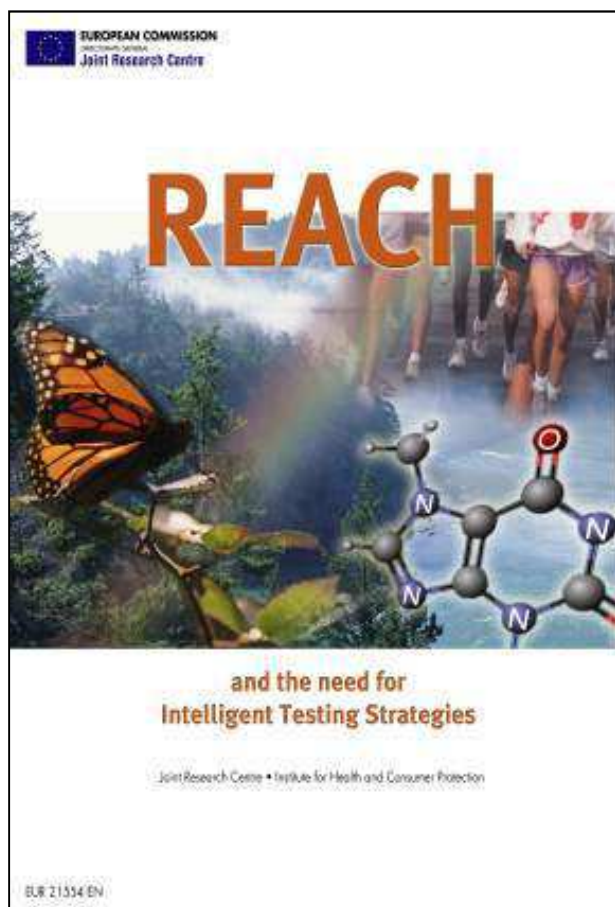
Reduction: reduce number of animals needed to obtain equivalent information;

Replacement: substitution of animal tests, either completely or partially (certain chemical types and/or endpoints).

Source: [ECHA web site](#) /



Intelligent Testing Strategy, ITS. (Bradbury et al., 2004)

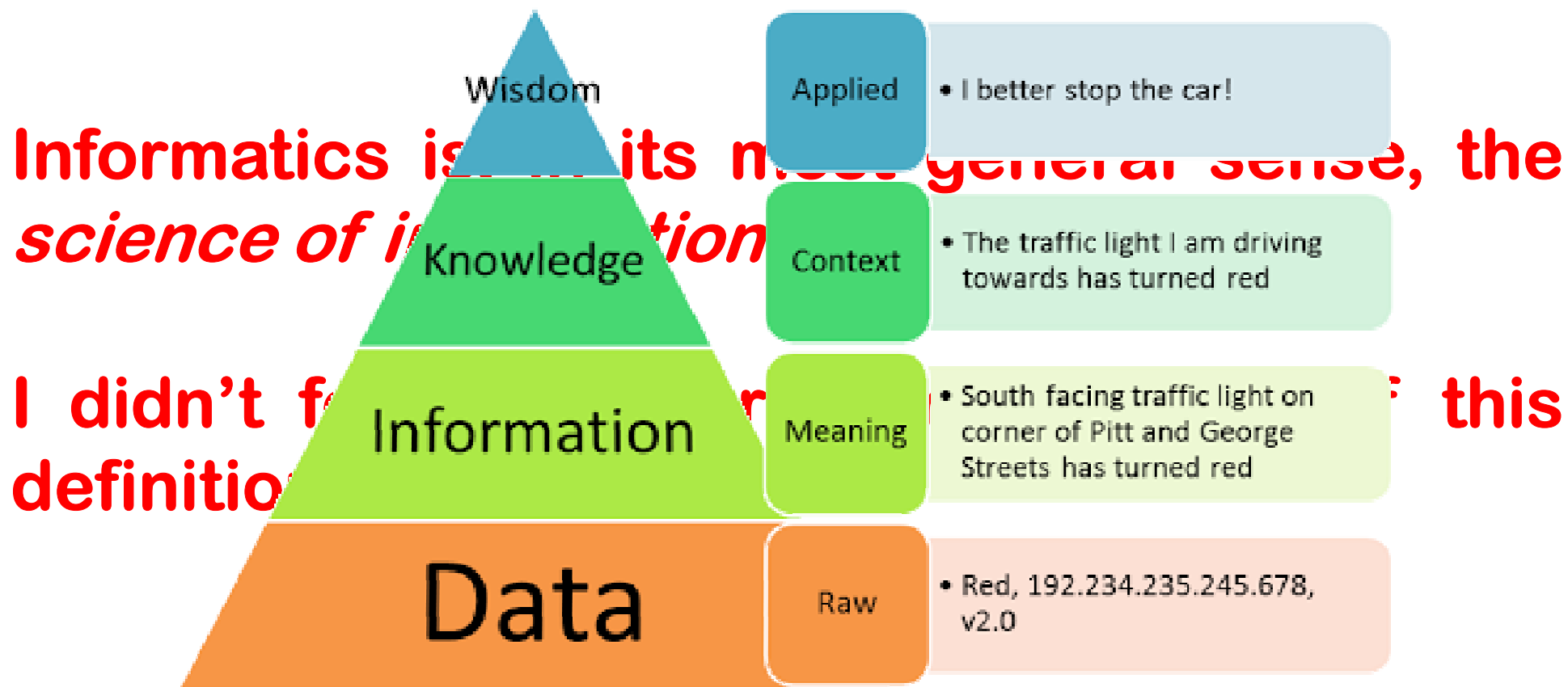


- (i) *In-vitro* tests
- (ii) Optimised *in-vivo* tests
- (iii) Thresholds of toxicological concern
- (iv) SARs and QSARs
- (v) Read-across and chemical categories
- (vi) Exposure assessment/exposure-based waiving

Source: [ECHA web site](#) /



in silico and informatics...

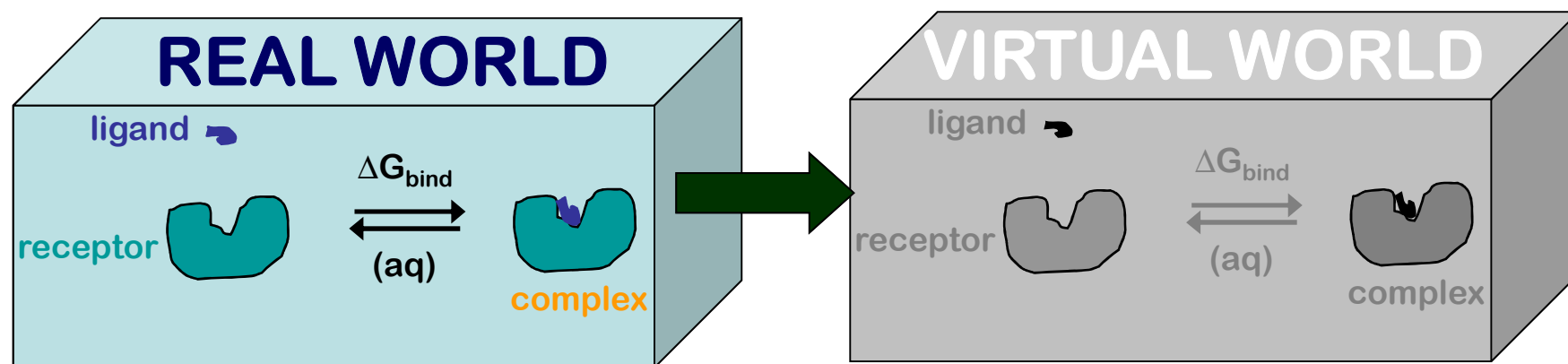


© 2011 Angus McDonald



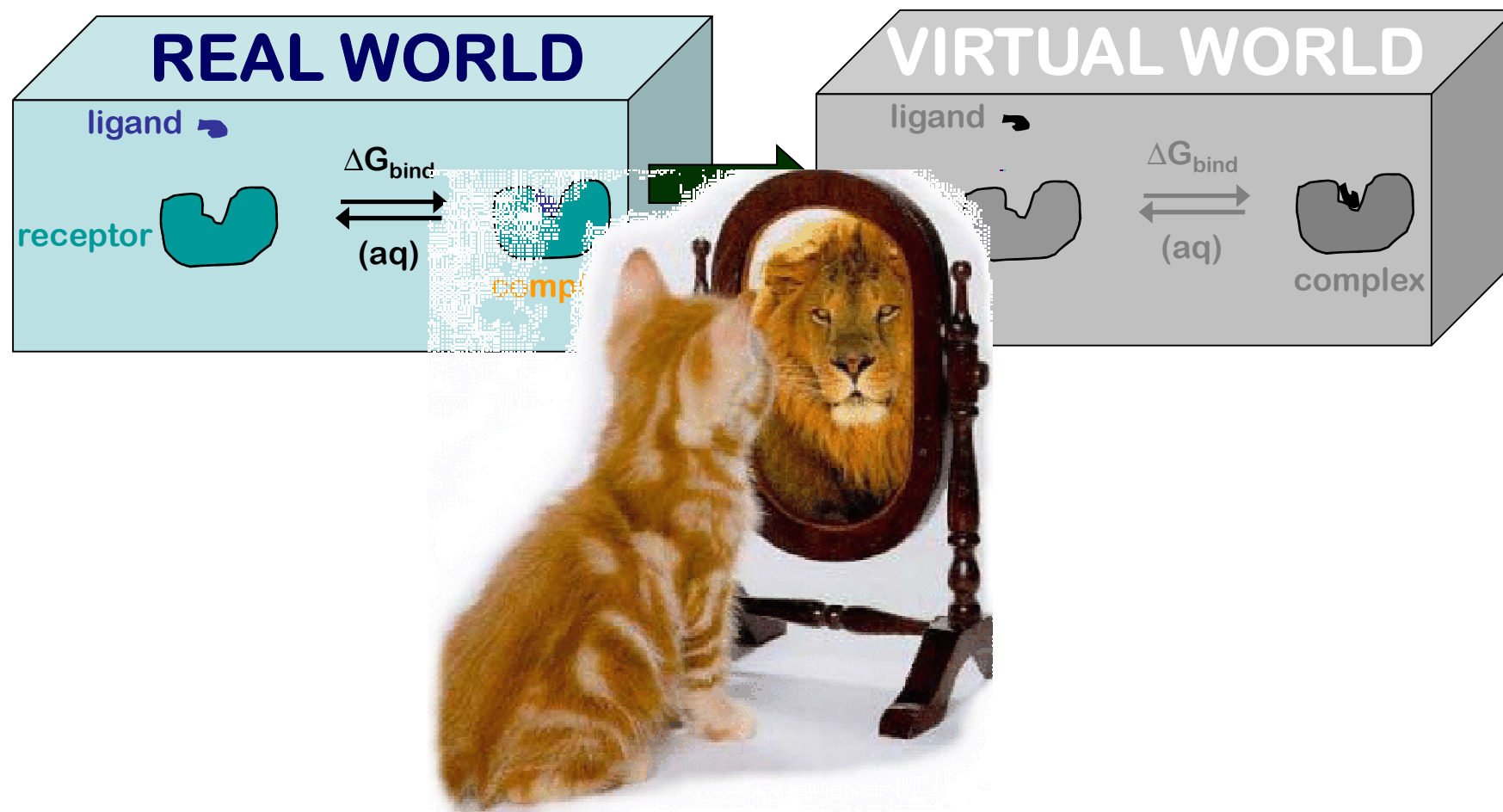
Informatics is the basic science of any *virtualization process*:

From an informatics point of view, any computational tool is a virtualization process: the creation of a virtual version of the real process.



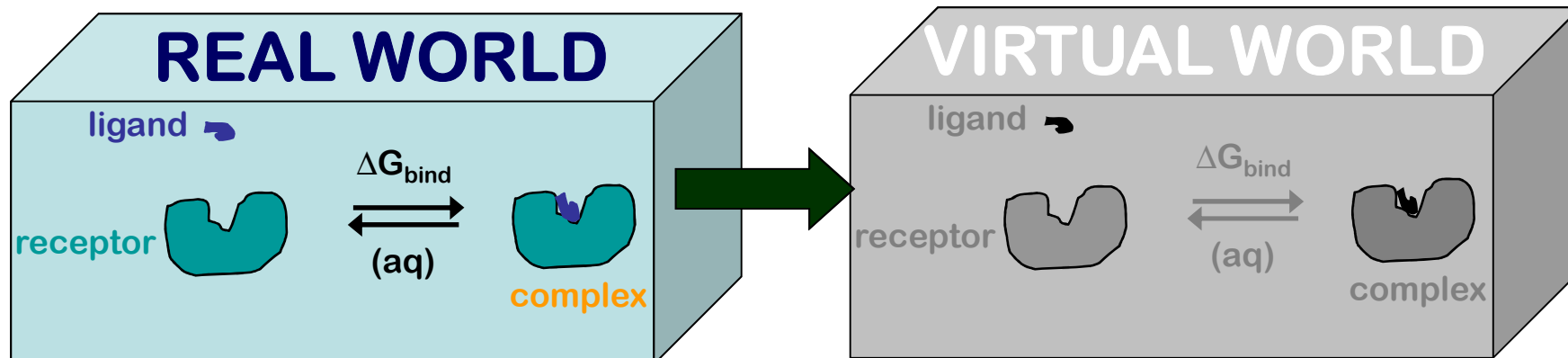


The *accuracy* of this virtualization process is crucial:





My favorite example:



C₆H₆

Hydrogen (H) 1.00794 atomic mass

Carbon (C) 12.0107 atomic mass

Molecular weight calculation:

$$12.0107 \times 6 + 1.00794 \times 6$$

$$= 78.11184 \text{ g/mol}$$

Q: determine the molecular weight of benzene?

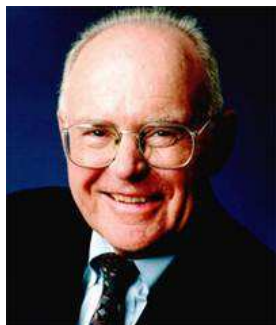
A:



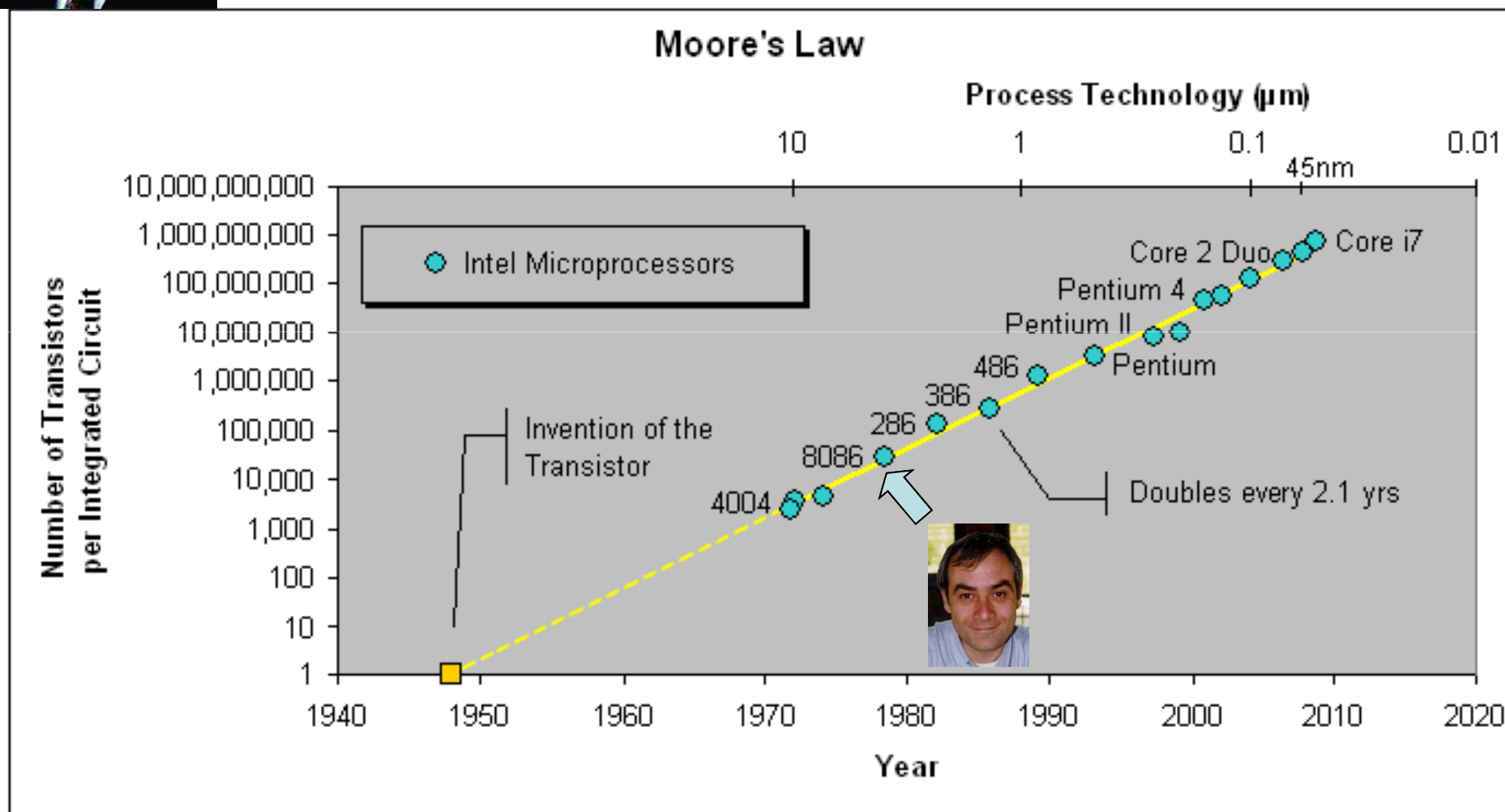
**Now, in what informatics has
influenced more in our daily life?**

**Well, we probably summarize the
answer in only one word:**

Time

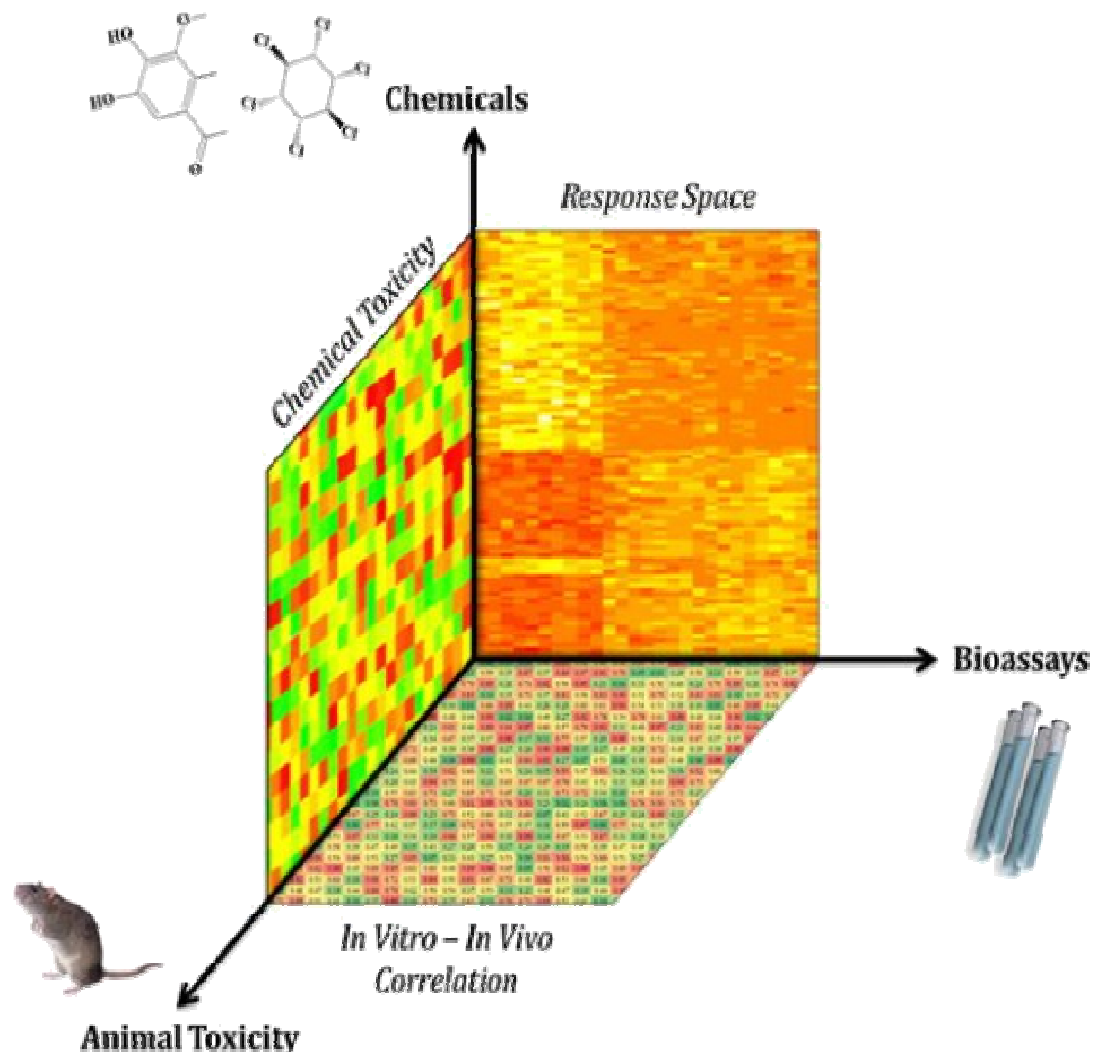


Informatics... synonymous of speed?





Informatics... the Big Data's era!



1 PetaB = 1000000000000000B = 10^{15} bytes = 1000 terabytes.



Informatics... the Big Data's era!

Dropbox has grown enormously since launching in 2008, surpassing 500 million signups and **500 petabytes** (i.e., 5 followed by 17 zeroes!) of user data. That's almost 14,000 times the text of all the books in the Library of Congress. To give you a sense of the incredible growth we've experienced, we had only about 40 petabytes of user data when I joined in 2012. In the 4 years since, we've seen over 12x growth.

The experiments in the Large Hadron Collider produce about 15 petabytes of data per year, which are distributed over the Worldwide LHC Computing Grid. In July 2012 it was revealed that CERN amassed about **200 petabytes** of data from the more than 800 trillion collisions looking for the Higgs boson.

It is estimated that the human brain's ability to store memories is equivalent to about **2.5 petabytes** of binary data.



The principle of 3R's (Directive 86/609/EEC)

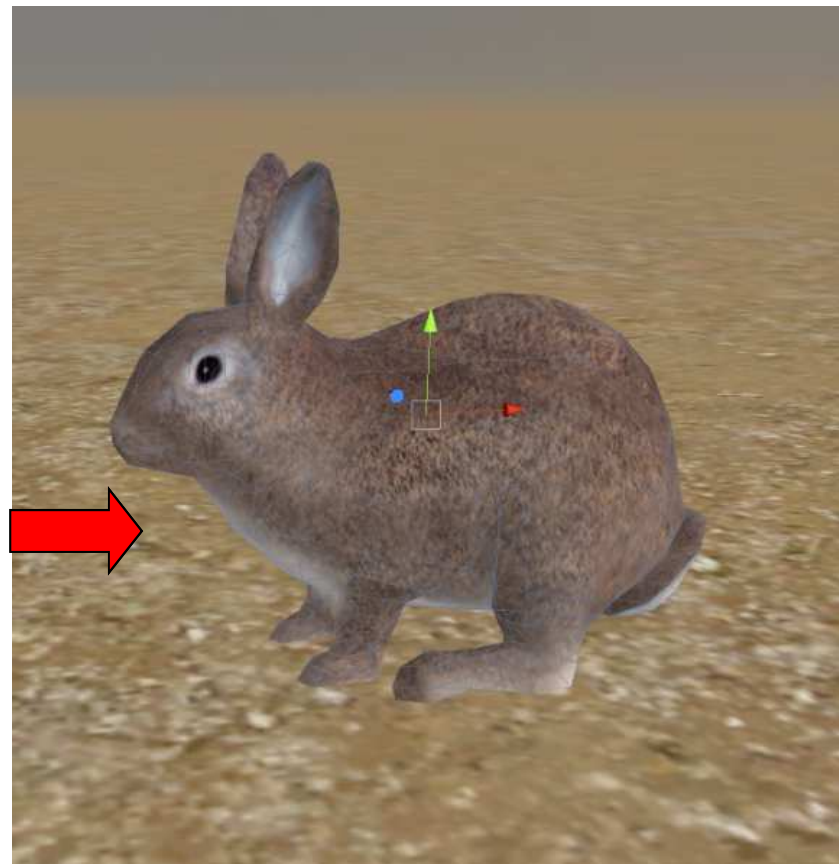
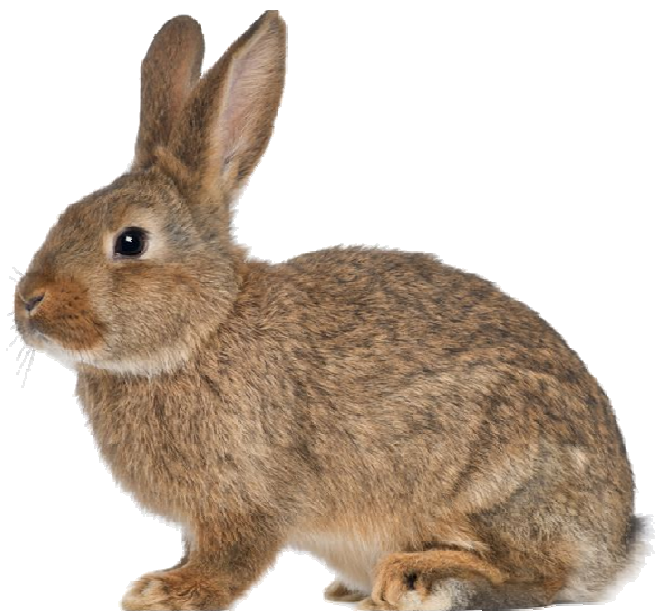
Refinement: reduce suffering and distress;

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Substitution: a “magic” word!

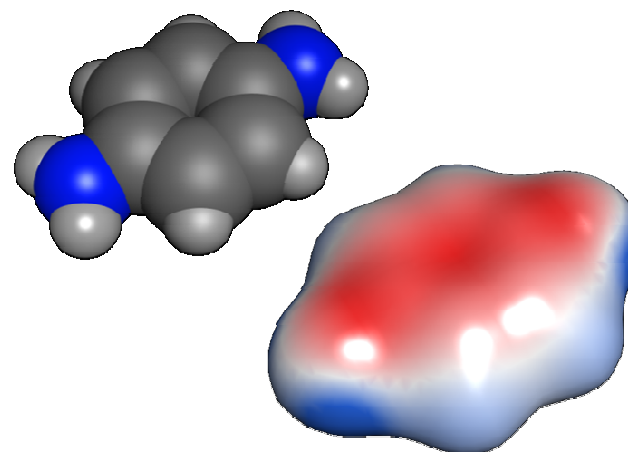
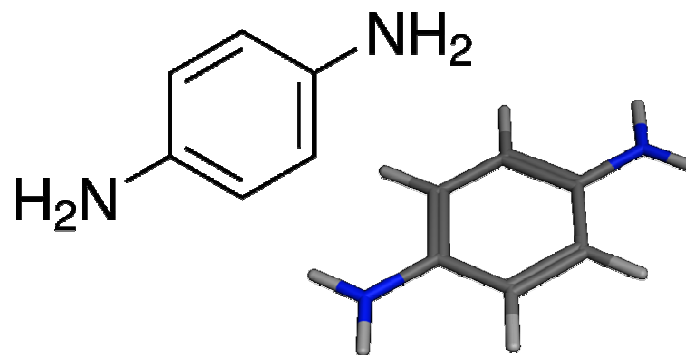


**from the real
world**

**to the virtual
world**



Substitution: a “magic” word!



from the real
world

to the virtual
world



(Q)SAR: a paleo version of the Bunny Avatar!

In the real world:



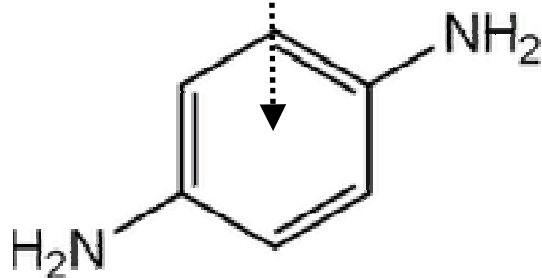
cause



effect



In the virtual world:



(alphanumeric) chemical
properties

$f(x)$?



(alphanumeric) toxicity
data

