# GLOSSARY

**what we mean by…**

**Acute toxicity** – the harmful effects of a chemical that result from a single or short-term exposure.

**Alternative methods** – methods for testing toxicity which can (i) replace animal testing or (ii) reduce it or (iii) refine it to reduce animal suffering (the 'three Rs').

**Chemicals** – substances either occurring naturally or purified or manufactured by industry, which can range from being harmless to being highly toxic. Some chemicals are the constituent parts of familiar things in our daily lives such as cleaning agents; others are used in agriculture and in the manufacture, packaging and distribution of daily objects from computer screens to medication.

**Chronic toxicity** – the harmful effects of a chemical resulting from repeated exposures, often cumulatively over months or years, and often at lower levels.

**Ecotoxicity** – the potential for a chemical to affect an ecosystem, such as by changing the natural biochemistry, physiology, behaviour and/or interactions of living organisms.

**Endpoint** – a type of adverse effect, such as eye irritation, birth defects or cancer. Toxicity tests are carried out for specific chemicals (or groups of chemicals) in relation to specific endpoints.

**QSAR** – the use of QSAR models is an important example of *in silico* methods. Quantitative Structure-Activity Relationship models correlate the properties and molecular structure of a chemical with its biological effect on human health and/or on relevant species in an ecosystem. The correlation can then be used in the prediction and assessment of new substances. QSAR / *in silico* methods are applicable to organic (carbon-based) compounds, not to inorganic substances.

**REACH** – (explained in the text) replaced nearly forty previous EU directives and regulations with a single regulation that makes manufacturers and importers responsible for registering chemicals with the European Chemicals Agency (ECHA), as well as for understanding and managing the risks associated with their use. REACH also aims to promote the use of existing data, and of alternative methods of assessment, such as QSAR methods.

**Stakeholder** – professionals, organisations and citizens who are affected by an action or decision, and/or can affect it, and so have an interest or 'stake' in it. As citizens we are all stakeholders in chemical testing because we are affected by the quality of that testing. Regulators, researchers and users are particular kinds of stakeholders who may inform debate in the public interest or their institutional interest.

**Toxicity** – the potential of a chemical substance to cause damage to humans and/or the environment.

**Toxicology** – research and routine industry testing of the effects of substances on health and the environment at different doses and concentrations, traditionally by tests on animals.

ORCHESTRA

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# IN SILICO METHODS

## for testing the toxicity of chemicals

## An introduction

**www.in-silico-methods.eu**

ORCHESTRA

Available online: version française, versione italiana, deutsche Version

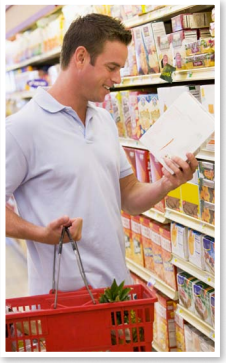
# Testing the Toxicity of Chemicals

**Almost everything we buy as European consumers involves the presence of chemical substances in its production, manufacture or use. This includes food and additives, cosmetics, medicines, household goods, packaging, mobile phones and electronics.**

Introducing those chemicals into our environment has consequences, whether they enter as manufacturing waste, accidental spillage or post-consumer waste. They can enter the air we breathe and the things we eat and drink, and can accumulate in the ecosystem (animals, plants, water, soil, etc.).

Incidents, accidents, health concerns and reports of impacts on wildlife have led to a growing focus on the consequences of chemical accumulation in the environment. Public demand for 'cleaner' products has reinforced regulation around the manufacture, distribution, use and disposal of chemicals, and increased the effort by industry to reduce hazards and improve safety.

## Protecting Health and the Environment



*"The challenge is to have scientifically sound information on the potential hazards of substances whilst at the same time minimising unnecessary animal testing. One of the fundamental aims of REACH is to promote alternative methods for assessing hazards of substances and to see animal testing as a last resort."*

Geert Dancet, Executive Director of ECHA, Press Release: August 2009 [3]



# REACH: The Challenge

**The European Union response to the public demand for 'cleaner' products is the 2007 REACH regulation. REACH deals with Registration, Evaluation, Authorisation and Restriction of Chemical substances.[1]**

REACH requires industry to provide information to users on the risks of every chemical which they manufacture and market, so that better decisions can be made about their use. For substances on the market in volumes of at least one tonne per year, data about the toxicity must be registered with the European Chemicals Agency (ECHA).

REACH has therefore created an urgent demand for the testing of large numbers of chemicals for toxicity. Around 100,000 chemicals may be registered under REACH from 2010 to 2018 for which toxicity test data will be required.

Legislators, scientists and industry have agreed that chemical testing must respect the "3R's" – the commitment to reduce, refine and replace animal testing wherever possible. REACH has made the major step of requiring manufacturers and importers of chemicals to share their existing and new test data, so that tests are not repeated unnecessarily. Plus, when tests on vertebrate animals are proposed, ECHA publishes a request for existing data that could be used instead of new tests being carried out. [2]

The European Commission have nevertheless estimated that to complete registration in the coming decade could involve the use of up to 9 million laboratory animals, and cost around € 1.3 billion.[3]

REACH therefore provides possibilities to use alternative assessment methods as well as existing data.[2] *In silico* methods are one important way forward.

[1] ECHA 2009, 'REACH - The most ambitious chemical legislation in the world' http://tinyurl.com/ECHA-REACH-EN

[2] ECHA 2010, 'Practical guide 10: How to avoid unnecessary testing on animals' http://tinyurl.com/ECHA-PG10

[3] ECHA Press Release, August 2009 http://tinyurl.com/ECHA-PR0911

# What are *in silico* methods

**Traditional toxicology testing is carried out in laboratories using live animals (*in vivo* testing). Around a million animals are used every year in Europe in such tests (2005 data[4]). Alternative methods include *in vitro* testing, where small quantities of chemicals are mixed with living cell cultures in test tubes.[5]**

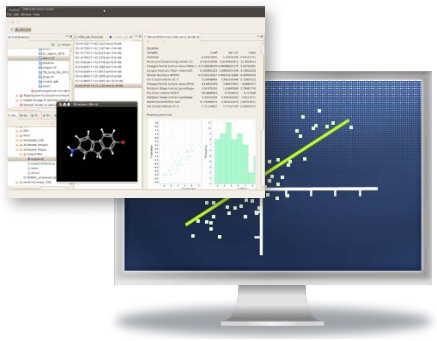
*In silico* methods are a new development in chemical testing that relies on computer simulation or modelling. Results from existing tests are used to model the ways in which a chemical may be hazardous in the body and/or in the environment. In this way the toxicity of a particular chemical used in a particular setting can be predicted and assessed without further tests on animals or living cells.

*In silico* methods are widely used (including by regulators in the US) to screen and identify chemicals for priority testing in the laboratory. They are also used in addition to laboratory data to add another line of evidence or argument. For many scientists, the goal is also to replace and improve on animal tests.

[4] Abbott, Alison. "Animal testing: More than a cosmetic change" Nature 438, 144-146, November 10, 2005.

[5] Overview at http://alttox.org/ttrc/tox-test-overview/

***In silico* methods use computer simulation or modelling to predict and assess the toxicological properties of chemicals in the body and the environment.**



## Examples

The EU-funded CAESAR project has developed *in silico* predictive models (QSAR) for five types of endpoints (adverse effects). The software for the models is freely available online through the www.caesar-project.eu website.

The EU-funded CHEMOMENTUM project has developed a platform to build QSAR models in an automated way using workflows based on grid technologies.

The EPI (Estimation Programs Interface) Suite is a suite of physical/chemical property and environmental fate estimation programs developed by the US Environment Protection Agency (EPA) Office of Pollution Prevention Toxics and the Syracuse Research Corporation (SRC). EPI Suite uses a single input to run 17 estimation programs. It is used by the EPA as a screening-level tool. www.epa.gov/opptintr/exposure/pubs/episuite.htm



# Advantages of *in silico* methods

**The EU has funded research into the development of *in silico* methods because the advantages are potentially immense.**

## Reducing the testing on animals

*In silico* methods use the findings from *in vivo* and *in vitro* laboratory tests (explained on facing page). But they allow scientists to reduce the repetition of animal testing, by replacing further tests with computer modelling. This reduces both animal suffering and the chemical waste from further laboratory tests.

## Reducing costs and delays

For industrial manufacturers, importers and users of chemicals, *in silico* testing can help to avoid the costs and delays associated with animal experiments. Some *in silico* tools are freely available online.

## Enabling the testing of large numbers of chemicals

For regulators and citizens, *in silico* methods can reduce the costs and increase the feasibility of testing, and so make it more possible to evaluate the safety of the wide range of chemical substances in use.

*In silico* methods therefore become important, as now under REACH, when the requirement is to assess whole inventories of chemicals, rather than just a few priority substances.

## Increasing the quality of information

Computer models can potentially integrate findings from both *in vivo* and *in vitro* research, and from a number of laboratory studies, to generate a more sophisticated and more reliable understanding in the future of how a chemical may affect humans and the environment. This may increase the scientific intelligence in chemical planning and reduce the number of unforeseen toxic effects.

*In silico* methods assess probability in a way that is useful to regulators when they are assessing risk and uncertainty.

*In silico* methods can address particular hazards or adverse effects (endpoints) for which animal testing methods are not fully accepted.

# Current limitations in the use of in silico methods

### The models available

*In silico* models are developed from existing data from laboratory tests, so a model can only be as reliable as the data it is based on.

In some key areas, such as long term toxicity to mammals, the available laboratory data is limited, so the range of *in silico* models is also currently limited.

While laboratory tests exist for both acute and chronic toxicity, tests for chronic toxicity take longer and are more expensive. *In silico* methods have correspondingly been developed and become effective in modelling, predicting and assessing acute toxicity, while remaining less developed for the more pervasive problem of chronic toxicity.

Current *in silico* methods cannot evaluate the toxicity of mixtures of chemicals, or of impure substances.

### Progress and uptake

*In silico* methods are an inter-disciplinary area of work, in which models are developed by experts in chemo-informatics for use by toxicologists. The strength and use of a model depends on whether it clearly provides what industry toxicologists and regulators need in their decision-making.

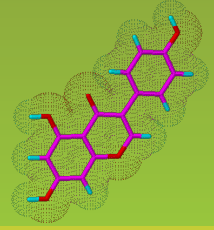
The level of use of *in silico* methods primarily depends on industry. Under REACH, it is the responsibility of the registrant of a chemical to select the assessment methods and to show that their application to a particular case is scientifically valid.

### Regulatory acceptance

The scientific validity of *in silico* methods depends on an *in silico* model being rigorously developed, and then used solely for what it was intended. It also depends on the model being documented well enough by the developers, and by the industry users, for ECHA to carry out an independent and transparent review.

While REACH welcomes alternative methods, ECHA inevitably has to be cautious in accepting their use. If a chemical is wrongly assessed, there may be serious consequences for human health or the environment. That same caution is also important for the future of *in silico* methods; if particular models are applied incorrectly or overused, then *in silico* methods may wrongly lose credibility.





# Find out more

Whether you are a regulator, scientist, policy maker, NGO, journalist or citizen, or a producer or user of chemicals, you may want to keep informed about *in silico* methods and contribute to the discussions around their development and use.

### ORCHESTRA

The EU has funded the ORCHESTRA project to promote a wider understanding, awareness and appropriate use of *in silico* methods. The project team includes chemists and social scientists. We interact directly and online with a range of organisations and individuals. This leaflet provides a first level of information for all.

The ORCHESTRA project will support good practice and regulation by bringing together EU research on *in silico* methods and practical experience of their use.

### Information online

From late 2010 the web portal will become a central information resource. It is designed to improve the transfer and sharing of knowledge and experience between professionals who are developing and using *in silico* models. For industry users and regulators, it will also provide downloadable software for *in silico* models reviewed by the project.

***See the online information at***

**www.in-silico-methods.eu**

*and register to keep up to date.*

### Tell us the information you need

From September 2010 we are consulting with regulators, chemical manufactures, importers and their associations, academic and other researchers, small business users, NGOs and citizen groups in the EU, to find out the information they need about *in silico* methods. To contribute, please visit the website.

### Workshops, seminars and other events

Register online to learn about the seminars and workshops to be organised during 2010-2012.

### Resources for Higher Education

Materials are being developed to generate scientific discussion and understanding of *in silico* methods.

### ORCHESTRA project partners

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