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**A report of barriers to disseminating results of environmental  
research, and stakeholders needs related to the use of *in silico*  
models.**

**REPORT OF ON-LINE STAKEHOLDER SURVEY**

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**Dissemination Level**

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| <b>PU</b> | Public  | <b>X</b> |
| <b>PP</b> | Restricted to other programme participants (including the Commission Services)        |          |
| <b>RE</b> | Restricted to a group specified by the consortium (including the Commission Services) |          |
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### History of amendments

| Issue | Date       | Section / page(s)                         | Cause of change                      | Implemented by        |
|-------|------------|---|--------------------------------------|-----------------------|
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| 2.0   | 2010-11-01 | Notes for current barriers section        | --                                   | IRFMN                 |
| 3.0   | 2010-11-11 | Proposed report structure: link with D2.3 | --                                   | PublicSpace           |
| 4.0   | 2011-02-09 | Draft report of method & results          | Actual data available                | Symlog                |
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| 4.2   | 2011-03-23 | Identifying conclusions                   |                                      | Symlog                |
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# A Report of Stakeholders' Needs Related to the Use of *In Silico* Models

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## Preface: The ORCHESTRA project

In recent years the EU has funded research into developing **computer-based methods for evaluating the toxicity of chemicals**, called '***in silico* methods**'. The methods generally rely on so-called QSAR or 'Quantitative structure-activity relationship' models (the terms are used almost interchangeably in this report).

These computerized models and methods are potentially important in making it possible to evaluate large numbers of chemicals (as required by the EU REACH legislation) while also reducing the numbers of tests on animals.

The ORCHESTRA project is funded by the EC to communicate some of the research findings to regulators, industry users and others. The intention is to promote the wider understanding, awareness and appropriate use of *in silico* methods.

The ORCHESTRA project brings together natural and social scientists; these disciplines collaborated on all phases of the survey and its reporting.

More information about the project, and also about REACH and *in silico* methods, etc., may be found online at [www.orchestra-qsar.eu](http://www.orchestra-qsar.eu).

## 1 Survey of stakeholders' views, needs and practices regarding *in silico* methods

This deliverable document analyses and reports the findings of a survey of stakeholders to identify the perceived benefits, barriers and needs in relation to the regulatory use of *in silico* methods. On this basis, the findings are also briefly summarised in deliverable 2.3 "Dissemination Plan".

Responses to the questionnaire consultations will continue during the ORCHESTRA project, and provide insight into:

- The current awareness of, and interest in, *in silico* methods
- The perceived benefits and attractions of *in silico* methods
- The current barriers to the use of *in silico* methods
- The current professional and policy needs
- Stakeholders' current sources of information on methods in toxicology.

Reported here are responses received from September 2010 through April 2011.

The total sample of responses is unfortunately small (see §1.2), and thus the authors' interpretations are not viewed as highly supported or robustly validated statements regarding the full population that was approached for this survey. However, some trends or groupings in response seem to appear, and great care has been taken to interpret these at an appropriate level.

## 1.1 Method

Three questionnaires were developed by project partners. These were:

- I. **“Benefits and barriers to the use of QSAR methods”**. This “technical survey” contained 8 questions and was intended principally “for those involved in Toxicology or Chemicals Regulation”, i.e., technical or specialist stakeholders (regulators, industry users, academics and consultants...). See **Annex I**.
- II. **“Use of QSAR / In-silico methods”**. This was a very short instrument (2-4 questions) targeting the same stakeholders. See **Annex II**.
- III. **“Policy issues around ‘in silico’ methods as alternatives to animal testing”**. The 6 questions were intended for all interested persons and particularly, those without specialist knowledge. See **Annex III**. The results are not reported in the present deliverable centred on technical “needs and barriers”.

Each instrument was constructed with a mix of multiple-choice and open questions. All three questionnaires were implemented online (facilitating data entry, compilation and analysis). They can be viewed in annex or online at the (identical) project websites: [www.orchestra-qsar.eu](http://www.orchestra-qsar.eu) or [www.in-silico-methods.eu](http://www.in-silico-methods.eu).

## 1.2 Sample (and limitations)

The invitation to respond to Questionnaire I took the form of a letter in English (**Annex I**) that was circulated by email to 280 potential respondents across Europe and beyond. These had been identified in an earlier step of the ORCHESTRA project (deliverable 2.1, “Stakeholders list”). Recipients could choose to respond online or on paper (no paper entries were received). The invitation was circulated in September 2010.

A further invitation was distributed as an email in Italian to more than 2000 contacts of CentroReach in mid January 2011 with a deadline for online response dated at 31 January.

It was observed that the flow of responses was small and so Questionnaire II was created as a quick alternative for professionals who might feel too busy to respond to a survey. This was sent in mid December 2010 to all members of the first email group (above) who had not responded to the first invitation.

Finally, after a successful Orchestra Workshop<sup>1</sup> gathered consultants, industry scientists, and representatives of competent national and international authorities, a new invitation to fill out Questionnaire I was sent to these persons in April 2011.

<sup>1</sup> ORCHESTRA Workshop: “REACH and QSAR - What can we learn from case studies?”, 6 April 2011 at IRFMN, Milan.  
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In the interim between January and April, the project team reflected on the stakeholder categories that had been developed for Questionnaire I. It was decided, on the basis of analysing the first 24 replies, and in light of interviews and other accumulated project experience, to alter the categories proposed in the questionnaire. The online questionnaire was thus amended in April 2011 with a new category structure. All 24 prior responses were carefully reassigned by hand to the most appropriate categories, on the basis of survey data but also by perusing respondents' own institutional websites to better understand their positioning.

Even with implementation of the new category structure, it was decided for this report to reassign some new (April) respondents (verified on the same bases). The insight from this sequence is: **the survey population clearly arises from a scientific community. The scientists who responded have very different roles, duties and activities, but these cut across typical institutional lines.** (Indeed the very development of QSAR models appears to take place in each stakeholder context; see footnote 2, this page.) After careful analysis of all available data including websites, it was decided to present the results using the following combinatory categories based on primary stake:

- **ACACON** - These subjects' research, development and/or application of *in silico* methods take place in an **academic** or **consultancy** context. They display many different roles and stakes within the REACH process, but they are not direct employees of an industrial manufacturer of chemical products, nor are they tasked as protectors of public health.
- **REGUL** - These subjects' research, development and/or application of *in silico* methods take place in a governmental **regulatory** context. Their primary stake and national (or international) mission lie in protecting public health or well-being.
- **INDUS** – These subjects' research, development and/or application of *in silico* methods take place directly within a commercial **industrial** context. Manufacturers of chemical products, their company has a primary economic stake in the outcome of specific REACH dossiers. (A chemical manufacturers' federation is also represented in this category.)

Subjects for whom some doubt arose were assigned to categories based on a) greatest likeness of institutional mission, and b) greatest likeness of individual responses when compared to typical response profiles of each category.

As of 27 April 2011, Questionnaire I had yielded **33** exploitable responses, falling or assigned into the following categories:

- **ACACON: 13 subjects<sup>2</sup>**
- **REGUL: 12 subjects**
- **INDUS: 8 subjects.**

These abbreviated stakeholder category labels are used in this report, highlighting the fact that **no claim is made to describe stakeholder populations at large**. The data are interpreted with scrupulous care and some suggestive trends or observations appear, but would demand testing on a larger survey population. This said, systematically collected survey data from 33 specialists may be

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<sup>2</sup> Among ACACON respondents, 5 mention they actually **develop** *in silico* methods; for REGUL and INDUS one respondent in each case mentions being a developer. Unfortunately, *systematic* data on this point are not available for the first 24 respondents, and so these numbers may be incomplete. They suggest interestingly that **direct development of QSARs and other *in silico* tools can take place in each stakeholder context.**





more solid than anecdotal impressions. Finally, the interpretations offered here are **highly coherent with the actual professional experience of the authors as well as with the documented interview findings developed in other parts of the ORCHESTRA project**<sup>3</sup>.

Societal stakeholder categories (NGOs, citizens...) were not represented in the sample. This was not unexpected given the labelling of Questionnaire I as most appropriate for specialists.

Questionnaire II yielded **29** responses. No stakeholder category information was collected.

### 1.3 Data presentation

The report presents and discusses results by stakeholder category wherever possible. Because the sample is small, the authors judged that it might be misleading (over-interpretative) to cite percentages of response. Instead, a suggestive “colour/sized” system of representation is chosen:

- When more than 3/4 of the population within a given category chose the response option, that result is communicated by a large green square .
- When 1/2 to 3/4 of the population chose an option, this is communicated by a mid-sized orange lozenge .
- When 1/4 to 1/2 of the population chose an option, this is communicated by a small grey disc .
- When less than one quarter of the population chose an option, that is communicated by a tiny red dot .

Generally, options are arranged in tables by descending frequency of citation within the ACACON category, followed by REGUL frequencies.

All statements entered by respondents in the “free response” fields have been reproduced at the appropriate point in this report. These are identified by stakeholder group and marked by bullet points.

## 2 Findings on current awareness of, and interest in, *in silico* methods

This section reports findings from

- Questionnaire I – Q’s 1, 2, 3
- Questionnaire II.

Specialist stakeholders (academics or consultants, regulators, and industry users) were asked whether they use, or have used/tested the methods, under which conditions, and for which purposes.

They were asked to indicate the specific methods, models or software applications used or tested.

<sup>3</sup> See in particular the filmed interviews with stakeholders on the ORCHESTRA website.  
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The data give a picture of effective experience today with applying *in silico* methods, models and software. They also indicate stakeholders' vision of how these methods will be used tomorrow.

## 2.1 *In silico* methods: Used or not?

Among respondents to the detailed Questionnaire I, **the great majority states that they have used or tested QSAR or *in silico* methods**. In each stakeholder category (ACACON, N=13; REGUL, N=12; INDUS, N=8)<sup>4</sup>, a single subject stated that this use was carried out "*with expert help*" (suggesting that all others recorded as having used or tested *in silico* methods possess direct experience or expertise).

Of the 33 respondents in total, a single one (ACACON) claims to have used or tested *in silico* methods but that this was "*not successful*".

Only one respondent from this community (ACACON), and only two respondents from each of the other communities surveyed (REGUL, INDUS) state they have NOT at any time used the methods. To explain this, they usually state that they "*have not needed or wanted to so far*" (a single industry respondent mentions that s/he "wanted to use but no relevant model was available"). In contrast, no-one selected the more negative or even condemning options that were offered (e.g., "*not interested, satisfied with [currently used] methods*" or "*don't trust in silico methods*"). **ALL** persons responding to the detailed Questionnaire I indicate (see §2.4 below) that they **have some future plans to test or use QSAR methods**.

In the brief separate Questionnaire II:

- 20 persons stated they do use QSAR methods.
- 9 respondents said they do not (and gave reasons why not – these will be analysed under "barriers" below in §4).

## 2.2 Actual models, methods and software in use

Questionnaire I allowed respondents to freely enter text in response to the query "*Which models, methods and software have been used or tested?*" The quasi totality of respondents reply, citing in each case more than one model or software suite.

The methods cited are arranged below by descending frequency of citation among the academic or consultant respondents, followed by frequency of citation among REGUL, then among INDUS. When these frequencies are non discriminative, the methods are then listed in alphabetical order.













<sup>4</sup> See §1.2 for an explanation of these labels.

| Model, method, software that have been used or tested | Number of citations |                                       |                                      |                                    |
|---|---------------------|---------------------------------------|--------------------------------------|------------------------------------|
|   | $\Sigma$            | ACACON<br>(12 of 13 subjects replied) | REGUL<br>(10 of 12 subjects replied) | INDUS<br>(6 of 8 subjects replied) |
| OECD QSAR Toolbox                                     | 16                  | 7                                     | 6                                    | 3                                  |
| EPI, EPI Suite, EPI Win                               | 16                  | 7                                     | 5                                    | 4                                  |
| Caesar  | 7                   | 3                                     | 2                                    | 2                                  |
| Leadscope   | 4                   | 3                                     |                                      | 1                                  |
| ECOSAR  | 5                   | 2                                     | 3                                    |                                    |
| SPARC   | 5                   | 2                                     | 3                                    |                                    |
| ToxTree   | 5                   | 2                                     |                                      | 3                                  |
| Topkat  | 3                   | 1                                     | 2                                    |                                    |
| DEREK   | 4                   | 1                                     | 1                                    | 2                                  |
| ACD/Tox Suite   | 3                   | 1                                     | 1                                    | 1                                  |
| ToxBoxes  | 2                   | 1                                     | 1                                    |                                    |
| <i>EQUATIONS from LITERATURE</i>                      | 2                   | 1                                     | 1                                    |                                    |
| <i>OWN INTERNAL MODELS</i>                            | 2                   | 1                                     | 1                                    |                                    |
| Lazar   | 2                   | 1                                     |                                      | 1                                  |
| MultiCase   | 2                   | 1                                     |                                      | 1                                  |
| ChemAxon Marvin                                       | 1                   | 1                                     |                                      |                                    |
| Macromodel  | 1                   | 1                                     |                                      |                                    |
| Molcode Toolbox                                       | 1                   | 1                                     |                                      |                                    |
| OncoLogic   | 1                   | 1                                     |                                      |                                    |
| Sybyl   | 1                   | 1                                     |                                      |                                    |
| Danish EPA QSAR database                              | 3                   |                                       | 3                                    |                                    |
| LMC Oasis including CataLogic                         | 3                   |                                       | 3                                    |                                    |
| ChemCan   | 1                   |                                       | 1                                    |                                    |
| ChemSteer   | 1                   |                                       | 1                                    |                                    |
| EQC   | 1                   |                                       | 1                                    |                                    |
| PBKB (SimCYP & MCSim)                                 | 1                   |                                       | 1                                    |                                    |
| PBT Profiler  | 1                   |                                       | 1                                    |                                    |
| SoilFug   | 1                   |                                       | 1                                    |                                    |

**Twenty-eight models, methods or software suites are cited** by the population responding to the survey. **The two “top rated” or most frequently cited suites (OECD Toolbox; EPI)** are cited by a relatively large proportion of all three stakeholder communities (half of REGUL; about half of ACACON or of INDUS). **Caesar** is the only other suite that is cited by all three stakeholder communities. After this third line of the table, “shared” use drops. A rather large variety of models is cited; 11 different methods or suites in all are cited by a single user in each case (mostly REGUL or ACACON).

## 2.3 Domains of past application, and the endpoints investigated

Overall, **all categories of stakeholder respondents are simultaneously investigating different domains of application.** Among those who have used *in silico* methods, the proportion of actual application by area for the respective stakeholders is shown below (ordered by descending importance according to the expressed view by ACACON):

| Domains in which <i>in silico</i> methods are by now applied | ACACON  | REGUL   | INDUS   |
|--|---|---|---|
| Physico-chemical properties                                  |  |  |  |
| Human toxicology   |  |  |  |
| Environmental fate properties                                |  |  |  |
| Ecotoxicology  |  |  |  |

The ACACON community shows the highest rate of application in the area of physico-chemical properties of compounds. REGUL and INDUS appear at this time to be lending somewhat less attention to the assessment of physico-chemical properties through QSAR. INDUS also seems to “lag” behind the other categories in applications to human toxicology and environmental fate properties.

Looking at the within-subject results, ACACON respondents appear more apt to perform the full range of applications within a single organization. Some REGUL organizations also show the full range of experience but otherwise seem to have distinctive profiles (most cite just two areas of application, and this specific pairing of endpoints varies across authorities, perhaps reflecting priority domains chosen for assessment). The few INDUS organizations that have experimented with all four endpoints are those benefitting from expert help (as stated in Q1) or having a position of overview (regional chemical manufacturers’ association).

Those working most directly with QSAR, i.e. ACACON, are quite interested by physico-chemical properties. Physico-chemical properties are those which have historically attracted quite a lot of modelling activities and produced a stream of literature. Regulators’ interest in the application side of the model diversifies their attention to the range of endpoints.

Endpoints that have benefitted from actual *in silico* applications among our population are reported below. Because no ranking was requested from respondents, this table does indicate any hierarchy of endpoints. However, endpoints that were mentioned several times across subjects (within a single stakeholder family) are underlined.

| Sample endpoints mentioned from actual applications of <i>in silico</i> |   |   |  |  |
|---|---|---|--|--|
| Stakeholder group   | Physico-Chemical Properties   | Human Toxicity  | Ecotoxicity  | Environmental Properties   |
| <b>ACACON</b><br>(8 of 13 subjects replied)                             | Boiling point<br>Vapour pressure<br>Water solubility<br><u>Partition coefficients (LogP/LogD)</u> | Mutagenicity/genotoxicity (including Ames, micronucleus, mouse SCE, mouse COMET)<br><u>Carcinogenicity</u><br><u>Teratogenicity</u><br><u>Acute toxicity</u> (mammals)<br>Skin irritation, corrosion, or sensitization<br>Eye irritation<br>Endocrine disruption ( <u>estrogen binding</u> , antiadrogenic activity)<br>Reprotox<br>hERG inhibition | Acute aquatic invertebrate toxicity ( <u>Daphnia</u> )<br><u>Acute fish toxicity</u> ( <u>fathead minnow</u> , <u>trout</u> )<br><u>Algae Toxicity</u><br>Terrestrial<br>Ecotoxicology (bees)<br>Tetrahymena | <u>Bioaccumulation/BCF</u><br>Half-life in water/soil<br>Ready <u>biodegradability</u><br><u>Abiotic hydrolysis</u> /degradation<br><u>Koc/soil adsorption</u> |
| <b>REGUL</b><br>(6 of 12 subjects replied)                              | Partition coefficients (Pow)  | Carcinogenicity<br>Reproductive toxicity<br><u>Mutagenicity/genotoxicity</u> (also addressing metabolites)<br>Teratogenesis<br>Acute toxicity<br>Endocrine disruptions ( <u>estrogen</u> and androgen binding)<br>Skin sensitization<br>NOEC  | <u>Aquatic toxicity</u><br>Daphnia reproduction<br>All ecotox part of EPI Suite (Aquatic toxicity acute and chronic algae fish and daphnia)  | Bioaccumulation/ <u>BCF</u><br>Degradation (DT50)  |
| <b>INDUS</b><br>(3 of 8 subjects replied)                               | Partition coefficients (LogP)   | Mutagenicity<br>Genotoxicity<br>Carcinogenicity<br>Teratogenicity   | Acute aquatic invertebrate toxicity (Daphnia) (LC50 daphnia magna as supporting information)<br>Fish toxicity  |  |

The ACACON community displays somewhat larger panoply of endpoints, followed closely by REGUL. **Citations of Human Toxicity endpoints are most varied and numerous in all stakeholder groups.**













These free responses cannot be presented as proportions (unlike responses to other questions tabulated in this report) and one might surmise that INDUS lags behind predominantly because this group is less represented in the overall sample. Moreover, the INDUS subjects replied to this question proportionately less often. However, the sheer number of endpoints mentioned by any one

ACACON respondent indicates that this population is more deeply involved or more broadly exposed to *in silico* application opportunities. This breadth is comparable to that displayed by a REGUL respondent from a national institute of health (who cited the majority of the Human Toxicity endpoints listed).

One half the REGUL population mentions endpoints, and in several cases tie these explicitly to the *in silico* toolbox or suite they apply. Is regulators' use at this time of *in silico* methods driven by the endpoints best addressed by the operative suite of tools they have chosen (or find easiest to use), or, do they choose their tools to serve their endpoint analytic needs as these emerge? The frequent testing out by individuals of a model or method uncited by others – see §2.2 above, list of models currently in use - does suggest that **regulators may be exploring for tools that address their emergent need.**

### 2.4 Domains of future application, and the endpoints targeted

Stakeholders also rated the domains in which they would like to apply or test *in silico* methods in the future. **All respondents indicated that they have plans for future applications** (even if they have not yet tested *in silico* methods, and even, in the one case cited, despite finding that a first attempt was not satisfactory.) Below, anticipated enlargement or narrowing of future applications within the stakeholder group sampled is signalled by > or < respectively, while = indicates no change, taking as reference the table above in §2.3.

| Areas of application in which would like to use <i>in silico</i> methods in future | ACACON  | REGUL   | INDUS   |
|--|---|---|---|
| physico-chemical properties  |  < |  - |  > |
| human toxicology   |  > |  - |  > |
| environmental fate properties  |  > |  > |  > |
| ecotoxicology  |  > |  > |  = |

The overall “future” picture shows ACACON diminishing slightly the focus on historic physico-chemical properties to transfer some interest to human toxicology endpoints (thereby aligning somewhat better with current regulator practices, which may be interpreted as regulator demands). More subtly, within-subject data indicate that while half the ACACON subjects will continue at the same level to use or test methods in current areas, the other half might alter in some way their domains of application of *in silico* methods, enlarging, narrowing, or simply transferring the focus of their efforts. This pattern might reflect the periodicity of research programs or of client demands.

Regulators overall and within subjects indicated that there would be a slight tendency to transfer or add attention to environmental fate and ecotoxicology endpoints. Industry shows a firm tendency to continue applications for endpoints of current interest, as well as to diversify within subjects the range of endpoints. In particular, some will add a new focus on physico-chemical properties (contrary to the tendency seen in ACACON).

These data suggest overall that **all three stakeholder populations today are in a phase of experimentation with *in silico* methods.** Their practice and activity are not “set” at this time.




















Some sample endpoints for which future applications are planned are reported below. Because no ranking was requested from respondents, this table does indicate any hierarchy of endpoints. However, endpoints that were mentioned several times within stakeholder family are underlined.

| Stakeholder group                           | Sample endpoints mentioned for planned (future) applications of <i>in silico</i> |  |                    |   |
|---|--|--|--------------------|---|
|   | <i>Physico-Chemical Properties</i>   | <i>Human Toxicity</i>  | <i>Ecotoxicity</i> | <i>Environmental Properties</i>   |
| <b>ACACON</b><br>(5 of 13 subjects replied) | LogP/LogD/<br>Solubility   | Mutagenicity/<br><u>genotoxicity</u><br><u>carcinogenicity</u><br>teratogenicity<br>Developmental<br>Toxicity (e.g.<br>mothers' milk and<br>fetus penetration)<br><u>Toxicity after<br/>chronic exposure</u><br>Acute toxicity<br>Skin irritation,<br>corrosion, or<br>sensitization<br>Eye irritation<br>Human Organ<br>Toxicity (e.g., lung,<br><u>liver</u> and kidney) | aquatic toxicity   | bioaccumulation/<br>BCF<br>Ready<br>biodegradability<br>Abiotic hydrolysis        |
| <b>REGUL</b><br>(4 of 12 subjects replied)  | Partition coefficients<br>(Pow)  | Mutagenicity<br>carcinogenicity/<br>DT50<br>NOEC (screening<br>only)   | aquatic toxicity   | <u>Bioaccumulation/</u><br><u>BFC</u><br><u>persistence</u><br>Degradation (DT50) |
| <b>INDUS</b><br>(0 of 9 subjects replied)   | -  | -  | -                  | -   |

A steep drop in response rate to this “follow up – projective” question invites restraint in interpretation.

## 2.5 Functions addressed by past applications

The table below considers the uses to which QSAR methods have been put by the stakeholder categories. The data have been ordered according to descending order of importance, in the expressed view by ACACON.

| Functions addressed by actual (past) applications                  | ACACON  | REGUL   | INDUS   |
|--|---|---|---|
| Fast evaluation of the properties of chemicals of interest         |    |    |    |
| Research and development, for the evaluation of toxicity           |    |    |    |
| Regulatory requirements - as supporting information                |    |    |    |
| Regulatory requirements - as part of a weight-of-evidence approach |    |    |    |
| Prioritisation of compounds for further analysis                   |  |  |  |
| Regulatory requirements - as the key study                         |  |  | -   |
| None / not sure  | -   |  |  |

ACACON presently appear to prefer *in silico* tools as **time-saving devices** and **fundamental research devices**. They also acknowledge regulatory data demands.

Among REGUL, QSAR is principally applied to provide supporting information. Use for fast evaluation and as part of the weight-of-evidence approach are also acknowledged.

A non negligible proportion of REGUL states “none/not sure” about the pertinent functions – but checking into individual data, these respondents have already tried QSAR methods (generally the OECD Toolbox), and so this confessed ignorance by regulators regarding functions **may simply flag a need to develop their familiarity with the tools**<sup>5</sup>. (Indeed, anecdotally, one regulator chooses “none/not sure” to describe current functions of application, but also notes the organisation has used two tool suites and has purchased a third after expert demonstration; three future (§2.6) functions are then identified.)

**Among INDUS (like ACACON) fast triage applications are important** – more so than in the regulatory community, and the profile for prioritisation uses is similar if less pronounced. **INDUS and REGUL give similar importance to the use of *in silico* for providing supporting information.** INDUS match other stakeholders in their acknowledgement of weight-of-evidence uses, but differ by






















<sup>5</sup> Moreover, this confessed ignorance may reflect disciplinary gaps between toxicologists and physical chemists; such a gap is not necessarily reduced by the OECD Toolbox design itself, which explicitly attempts to fit the use of QSARS to a typical toxicologists’ workflow or cognitive approach. On this subject, view the ORCHESTRA interview performed with B. Diderich of the OECD (Paris, March 30, 2011; interview conducted without explicit consideration of the present survey findings).

appearing to leave aside key study applications. INDUS more than REGUL performs research and development via *in silico* for the evaluation of toxicity (this may permit INDUS in future to rise to meet the regulators' record of actual application in the toxicology domains; see findings above in §2.3).

## 2.6 Functions addressed in planned (future) applications

The table below shows the functions for which their own future applications of *in silico* could interest the stakeholder groups (percentages are rounded; mathematical symbols indicate direction of change from the past applications as reported above in §2.5). All respondents in the ACACON and INDUS categories (including those who have not yet applied QSAR) pointed to a range of future functions. As for REGUL, the respondent who had never applied *in silico* before was the only one to confess pure ignorance of the pertinent functions, while still planning to perform future applications. Another regulator also ticked "not sure" but had equally selected all the proposed functions, thereby suggesting that the future is wide open!

To facilitate comparison the future functions are ordered below as per the table in §2.5 (functions addressed by past applications). Mathematical signs indicate the direction of change if any.

| Functions addressed by future (planned) applications of <i>in silico</i> | ACACON  | REGUL   | INDUS   |
|--|---|---|---|
| Fast evaluation of the properties of chemicals of interest               |  <  |  >  |  >  |
| Research and development, for the evaluation of toxicity                 |  = |  < |  > |
| Prioritisation of compounds for further analysis                         |  > |  > |  = |
| Regulatory requirements - as supporting information                      |  > |  > |  > |
| Regulatory requirements - as part of a weight-of-evidence approach       |  > |  > |  > |
| Regulatory requirements - as the key study                               |  > |  > |  > |
| None / not sure  |  = |  < |  < |

**ACACON respondents foresee a large extension of the functions for which they can apply *in silico* methods in the future.** In particular, the weight-of-evidence function promises to take on considerable importance in comparison to the situation today. The broader range of functions foreseen for future *in silico* applications may reflect the attitude of consultants looking forward to broadening their client services. Still however, ACACON **overall foresee the growing pertinence of QSAR methods to address a range of needs, and plan to apply, test or develop them with the regulatory uses also in mind.** (Among respondents, the consultant who has not applied QSAR, and who explains that it is not a priority for his organisation, still recognises the potential opening up of functionality by ticking all options.)

One scientist explained potential “other” target functions:

- E.g. as the basis for DK EPA advisory self-classifications for 34,292 substances for skin irritation, skin sensitization, acute oral toxicity, mutagenicity, cancer, reproductive toxicity (possible harm to the unborn child), and danger to the aquatic environment.

Regulators appear to anticipate a slight widening of functionality while they do not plan to abandon functionalities currently served by *in silico* applications. Only the applications in R&D regarding human toxicity appear to diminish slightly in this forecast. One REGUL pointed out that QSAR will support

- Research to be done by others because this [regulatory agency] is not a research institute.

The largest anticipated change will be in **more frequent application by regulators of *in silico* triage for the needs of prioritisation.**

The weight of evidence approach appears to be emphasized in this REGUL comment on potential “other” functions for *in silico*:

- Supplementary information to other information sources.

Among INDUS, some foresee little change in their practice; the majority of others, however, anticipate growing reliance on *in silico* tools to support regulatory dossiers. Anecdotally, the respondent who has not yet performed any applications, because “*there was no relevant model available*”, enthusiastically foresees that the full range of functions will be served by future applications. Only prioritisation diminishes slightly in the INDUS group; respondents are perhaps looking ahead to REACH tasks beyond prioritisation.

One industry user adds that a future functionality will be “*justification for grouping and read across*”, which may be interpreted as a need to take advantage of multiple possibilities within the same conceptual framework.






















**In sum, the respondents of every category appear to recognize that *in silico* methods will be applied more broadly in the future. Some stakeholders are gearing up to use, test or develop these methods themselves; but even those who today do not plan to use them clearly recognize their growing importance.**

### 3 Findings on perceived benefits and attractions of *in silico* methods

This section reports findings from Questionnaire I – Q 5.

In the context of the “Ways Forward” section of Questionnaire I scientists, regulators, and industry users were asked their view on the main reasons to use QSAR or *in silico* methods.

The data give a picture of the differential attractions and benefits of the methods in the perception of these specialist stakeholders. The data have been ordered according to descending order of importance, in the expressed view by ACACON.

| Main reasons to use <i>in silico</i> methods going forward   | ACACON  | REGUL   | INDUS   |
|--|---|---|---|
| To identify and prioritise substances of concern.  |    |    |    |
| To improve the response to regulatory requirements such as risk assessment and classification and labelling. |   |   |    |
| To reduce the use of vertebrates in experiments - to meet regulatory requirements.                           |  |  |  |
| To reduce the time and costs of experiments.   |  |  |  |
| To assess potentially thousands of chemicals simultaneously  |  |  |  |
| To reduce the use of vertebrates in experiments - to meet our own ethical policies.                          |  |  |  |
| To address endpoints for which animal models are not fully accepted.   |  |  |  |

There is a primary **consensus across stakeholders that going forward, *in silico* methods are very attractive for identifying and prioritising substances of concern.** For ACACON and REGUL in particular this perception is quite strong.

Also consensual across stakeholders, albeit at a lower level, is the view that these methods offer some attraction for assessing potentially thousands of chemicals simultaneously.

(Note some contrast with the findings in §2.5-6 where actual and planned functional applications by scientists highlighted the facility of fast evaluation of chemical properties. In this way, fast evaluation is the most frequent or common application of *in silico* methods, but prioritisation is regarded as a “better” reason to call on these techniques. Both aspects – fast evaluation and prioritisation – may be reflected in the assessment of reasons to use *in silico* emphasized by one ACACON respondent in comments to the present section of the questionnaire:

- “To overcome the challenge of assessing many thousands of chemicals in commerce which cannot all be tested in animal test batteries within a foreseeable future”.)

**ACACON and REGUL appear quite confident that risk assessment, classification and labelling will be well addressed by *in silico* methods**, whereas INDUS appear less convinced.

INDUS enthusiastically endorses *in silico* to **reduce the laboratory use of vertebrates to meet regulatory requirements**, an enthusiasm diminishing somewhat in the view of ACACON and quite middling in the view of REGUL. Less surprising is the smaller regard given by REGUL to the benefit of *in silico* methods to address in-house ethical requirements on animal use; this feature is most attractive to industry and ACACON.

ACACON is more sensitive to the cost-reducing qualities of QSAR for research than are REGUL and INDUS.

ACACON and INDUS stakeholders see less interest in *in silico* methods than do regulators to address endpoints for which animal models are not fully accepted.

One regulator explained:

- “Reduction of vertebrate testing is a major goal, however, **secondary to improved risk management** which is the reason why I didn't tick the two boxes [concerned]”.

ACACON responding to the questionnaire offered two further attractions of *in silico* methods:

- To supplement the information level for lower tonnage chemicals with limited test information requirements
- As a "glue" between in vitro data in ITS approaches.

Regulators emphasised in open comments that reasons to use *in silico* methods include:

- To get information on substances regardless of testing requirements.
- To help deriving mechanistic explanations for effects by extracting the common physico-chemical properties that index a specific effect.

## 4 Findings on current barriers to the use of *in silico* methods

This section reports findings from

- Questionnaire II
- Questionnaire I – Q 4 including sub questions.

Specialist stakeholders (consultants, academics, regulators, and industry users) were asked what prevents or limits their use of QSAR or *in silico* methods.

### 4.1 Findings on generic barriers

As described in §1.1, Questionnaire II was sent those stakeholder targets who had not responded to the detailed online Questionnaire I. The email asked if the recipient uses *in silico* methods, and contained two html links, allowing recipients to respond “yes” or “no” to the question. Those replying “no” were invited to reply to a complementary question, specifying why they don't use *in silico* methods. The results below (from just nine persons) give a quick view of barriers according to this special population.

| What are the main reasons you don't use computer-based methods in toxicology? (ie QSAR / <i>in silico</i> methods): | N/9 |
|---|-----|
| Not interested. I am satisfied with the methods I currently use.  | 0   |
| <i>Interested. But I have not needed (or wanted) to use these methods so far.</i>                                   | 7   |
| I don't know enough about these methods.  | 2   |
| I don't really trust these methods.   | 0   |
| We wanted to use these methods, but there was no relevant model available.  | 1   |
| We have tried to use these methods, but it was not successful.  | 0   |

The majority of this Questionnaire II sample thus responded that they were interested, but had not had the need or desire to use *in silico* methods up to now. This expressed interest might be expected from this population: if one is willing to take a few more seconds to attend to the email survey and online complementary question, this is probably due to pre-existing curiosity and openness to the *in silico* domain (after all, nothing required the email recipients to reply). However, the result remains striking. Only two persons also state that they “*don't know enough about the methods*” (and none mentions a lack of trust or a failure). It would seem that these 7 of 9 respondents are actually waiting for a chance to test the methods.

The other two persons (out of nine total) explained their non-use as follows:

- I work in a Government Department on general chemicals management, so we don't undertake any research ourselves. I do think, though, that computer based methods in (eco)toxicology offer many benefits, in collaboration with experimental approaches.
- As national Helpdesk we advise companies but usually do not get involved in tests or non-test methods such as QSAR etc.

These replies show that the major factor in the respondents' non-use of QSAR is their particular stakeholder role, and that they are by no means “hostile” to the methods.

Just one person, finally, claims that no relevant model was available to address a desired application. All in all, although this sample is tiny and it is probably biased toward persons interested by *in silico*, the **results suggest that persons already interested and whose role allows them to apply the methods, may be very open to opportunities to do so.**



















The following subsections all report findings from Questionnaire I.

## 4.2 Findings on the priority given to applying *in silico* methods

In the detailed Questionnaire I, Q4 asked respondents about what prevents or limits their use of *in silico* methods. Just 3 REGUL, and one ACACON or INDUS, agreed to the first sub question stating that *in silico* methods are “*not a priority for his/her organization*”, further indicating that “*other priorities are more important*”. Among these, the ACACON respondent went on to mention a preference to remain with traditional methods well-known by the organization, and, accepted by regulators. It is of interest that no other individual of 33 who replied to the questionnaire, chose to tick these latter options. It may be concluded that at least among persons who reply to such a questionnaire, **a preference for traditional, well-known and accepted methods is NOT a drag on application of *in silico* today.**

### 4.3 Findings on the need for information or guidance








This sub question allowed stakeholders to indicate areas in which more information or regulatory guidance might overcome barriers to the use of *in silico*. While all groupings called for more information or guidance, differential knowledge gaps are described by these specialist stakeholders. The data have been ordered according to descending order of importance, in the expressed view by ACACON.

| Main option/sub option<br><i>All proportions are calculated on <u>total</u> stakeholder subsample</i> | ACACON  | REGUL   | INDUS   |
|---|---|---|---|
| <b>We need more information and/or regulatory guidance ...</b>  |    |    |    |
|   |   |   |   |
| <i>to assess whether a model can be viewed as scientifically valid and adequately documented;</i>     |    |    |    |
| <i>to be able to use the technical software, and understand the outputs from it;</i>                  |    |    |    |
| <i>to know how to integrate different kinds of results from different methods into a submission;</i>  |    |    |    |
| <i>to know what QSAR models are available or appropriate for our work;</i>                            |   |   |   |
| <i>to know more about when and how QSAR / in silico methods can be used.</i>                          |  |  |  |

Across sectors the need is seen for “more information or regulatory guidance”. Academics and consultants showcase a predictable concern for information that will help to gauge the level of confidence that may be placed in a model. INDUS responses here seem to suggest that they feel they have scoped the technical requirements of *in silico* and need reassurance that the scientific quality of the tool is acceptable, and also, pointers to the best available QSAR models. REGUL answers suggest that their primary need is for good grasp of software outputs (the results of the model, and their meaning). To a lesser degree, they need information helping to assess the confidence they may place in QSAR tools, and identification of appropriate uses of the models.

#### 4.4 Findings on the costs anticipated in the case of using *in silico* methods

This sub question collected views on economic barriers to the use of QSAR. Data below are ordered by descending order of importance in the expressed view by ACACON.

















| Main option/sub option, if any<br><i>All proportions are calculated on <u>total</u> stakeholder subsample</i>                                      | ACACON   | REGUL   | INDUS   |
|--|--|---|---|
| <b>We are concerned about the potential costs or delays if we use <i>in silico</i> methods</b>   |   |  |  |
|  |  |   |   |
| <i>that the models (or our use of them) may not be accepted by the regulator, and so create additional costs for us in delay and resubmission;</i> |   | -   |  |
| <i>that we need to invest in technical training and/or consultancy;</i>  |   | -   | -   |
| <i>that using QSAR models might commit us to using expensive commercial software in future.</i>  |  | -   | -   |

Few replies to this sub question were obtained. Thus **costs do not seem a barrier to the implementation of *in silico***, compared to other aspects measured by Q4 and reported in the present §4. Understandably, regulators are not too much involved in the user economic considerations surveyed here, although we notice that the sole regulator responding to this mentioned:

- Regrettably, we no longer have money for continuing our CATABOL license.

#### 4.5 Findings on the perceived insufficiency of (current) QSAR models

This sub question investigated perceived lacks in the current QSAR models. Replies are ordered in the table by descending order of importance according to expressed views by ACACON.

| Main option/sub option, if any<br><i>All percentages are calculated on total stakeholder subsample</i>   | ACACON  | REGUL   | INDUS   |
|--|---|---|---|
| <b>The current QSAR models don't yet provide what we need</b>  |    |    |    |
| <i>current models often do not provide what the toxicologist needs for making decisions on toxicity;</i>   |    |    |    |
| <i>models do not (yet) evaluate chemicals in combination, or adequately evaluate chronic toxicity;</i>   |    |    | -   |
| <i>models can be a 'black box', lacking the documentation we need to check their quality and their applicability to our work, and/or lacking the transparency that is required in REACH submissions;</i> |    |    |    |
| <i>the range of models is currently too limited for us to start using these methods regularly;</i>   |  | -   |  |
| <i>we fear the models may not be reliable, and require support from other models and/or tests.</i>   |  |  |  |

Responses to this sub question remain limited. ACACON have the most to say here and perceive to some degree that the approach to decision by toxicologists are not served (INDUS agree), or that QSAR models have a limited applicability domain in that they do not yet facilitate current challenges like evaluating real-world mixtures of compounds.

In the free input field of this sub question, an academic commented:

- QSAR scientists are chasing their tail - shuffling algorithms with use of the same datasets and approaches won't allow making substantial change in the quality and usability of models. [As sole explanatory sub option, this individual ticked that "current models often do not provide what the toxicologist needs for making decisions..."]

Only two persons responded to the final open question associated with Q4: "QSAR / *in silico* methods will not / cannot provide what we need". The following remarks were collected from these members of the academic or consulting community:

- Human endpoints suffer from the lack of intra- and inter-individual variability assessment.
- The predictability of current QSAR models appears limited and restricted to few toxicological endpoints. Most current models apparently focus on the properties of the chemicals and do not sufficiently consider the relevant biological structures that get in contact with the chemicals. [This comment was made by a subject who stated s/he has not to date used *in silico* methods. Note that the other comments cited above come from members of the scientific community who state they do have direct experience with QSAR.]

## 5 Opening the way forward to increased use of *in silico* methods

























This section reports findings from Questionnaire I, Q6 and Q7.

Specialist stakeholders (scientists, regulators, and industry users) were asked what would help them to use QSAR or *in silico* methods, and what in their view will have most impact on the wider acceptance and use of *in silico* methods.

More responses were obtained than for Q4 on barriers ( §4 above), suggesting a proactive attitude.

### 5.1 Findings on what would help to use QSAR/*in silico* methods

In this question stakeholders reported items that could favour more use of *in silico* methods. Responses are heterogeneous according to stakeholder affiliation. Data in the table below are ordered in descending order of importance according to the expressed view by ACACON.

| What would help you to use QSAR/ <i>in silico</i> methods?   | ACACON  | REGUL   | INDUS   |
|--|---|---|---|
| Seeing good examples of industry using <i>in silico</i> methods successfully (in documentary video, industry events, online reports and trade magazines).                      |    |    |    |
| Lists and reviews of the available models, with information on where to access them.   |  |  |  |
| Examples from the regulators about acceptance of / enthusiasm for <i>in silico</i> methods   |  |  |  |
| Seeing more peer-reviewed journal articles about the practical applications of <i>in silico</i> methods, illustrated by case studies.  |  |  |  |
| Clear guidelines for reporting toxicity results from <i>in silico</i> methods (maybe as an automatic report generator within the software that matches the submission format). |  |  |  |
| Clear standardisation of the ways in which individual QSAR models and their appropriate uses are described, and their applicability domains are defined.                       |  |  |  |
| Support and guidance from laboratories with expertise in the uses of QSARs.  |  |  |  |
| Examples of the reasoning and transparent documentation required for submissions.  |  |  |  |

The regulators clearly place emphasis on aspects that are less outstanding to ACACON or industry. Regulators' answers point to a desire for a documented, reasoned, exemplified and standardized approach. This is coherent with results seen in §4.3 on knowledge needs, as are the findings here

from the ACACON sector. The latter scientists portray themselves as focussed on diverse signals of validity, availability and uptake of *in silico* methods.

INDUS' few replies to these questions seem to align more with ACACON than with REGUL. However, INDUS leave aside suggestions for more peer reviewed articles, case studies, examples of applications and expert guidance, and thereby seem here to be most attracted by a kind of automated, standardized and simplified process. (Note however that in §6, in contrast, an industry subset refers to scientific literature as their primary source of information on *in silico* methods in toxicology.)

In response to the invitation to give further suggestions, a regulator commented with enthusiasm:




- Many good suggestions above! [meaning, the proposed survey options] [I] don't think standard use can be fully described but [I] support the use of QMRFs and QPRFs [and] have made own ad hoc list on important QSAR models and other NTA, exposure models and databases on chemicals.

Industry users made detailed suggestions that highlight the potential value of networking, mutuality of expertise, and cooperation:

- Better databases for mining particularly repeat dose endpoints - need agreement on common format - way to deal with proprietary information - resources to shred data and get it entered - broad agreement to collaborate and enter data.
- Definition of expert network in QSAR/*in silico* methods.

## 5.2 Findings on views of what will have the most impact on acceptance of *in silico* methods

In this section, stakeholders ranked measures that could have impact on the acceptance of *in silico* methods. The data in the table below are ordered according to descending importance in the expressed view of ACACON.

| What will have the most impact on the wider acceptance of QSAR/ <i>in silico</i> methods? | ACACON  | REGUL   | INDUS   |
|---|---|---|---|
| Industry using <i>in silico</i> methods more, and producing high quality results.         |  |  |  |
| Case study research evidence of the quality and reliability of <i>in silico</i> methods.  |  |  |  |
| Use by high-profile companies / organisations, and in cases with high visibility.         |  |  |  |
| The monitoring, review and updating of models by specialist QSAR laboratories.            |  |  |  |
| The trademarking of models by trusted software companies or organisations.                |  |  | -   |

There is consensus across sectors that **in order to foster use, industry must demonstrate successful actual applications**; ACACON is particularly convinced of this pragmatic assertion. All sectors also affirm that case study evidence of the quality and reliability of *in silico* methods will foster their greater use. In this way, a “democratic”, evidence-based demonstration, with expert

quality assurance in the background, emerges as perhaps the best way to trigger greater use, rather than reliance on high-profile leadership or on trademarking.

In response to the invitation to explain “other” options, scientists highlighted the importance of regulatory acceptance:

- Regulators understanding and accepting the results
- Acceptance by regulators
- The wide acceptance of *in silico* methods and results from the regulators.

One industry respondent reinforced the comment of scientists:

- Regulatory acceptance.

A regulator’s advice seems to suggest that a “super regulator” would be an appreciable role model:

- Most important: use by international regulatory bodies (under e.g. OECD SIAM, EU REACH).

One scientist detailed advice on confidence building:

- An important factor in the confidence building is to simply start using the tools, both industry and regulatory bodies, to see themselves how they work. Look at the predictions also when you have experimental data and see how they fit. A strength with the models is that once they are made they are cheap to use; look at the results from many different models when possible in overall weight-of-evidence. Better awareness that experimental data are not 100% correct either. Good case studies are also fine.

Finally, one other scientist commented:

- Access to the data used for models development.


















## 6 Findings on stakeholders’ current and desired sources of information on *in silico* methods in toxicology

This section reports Questionnaire I, Q8 (two sub questions).

Specialist stakeholders were asked about the media and networks by which they hear about developments relevant to regulatory toxicology, and by which they would like to hear about *in silico* methods. These were open questions with a field for entering free-form answers.

## 6.1 Current sources of information

The authors grouped citations of current information sources into five sets, assigning responses to exclusive categories. Data are reported below in descending order of prominence according to the expressed view of ACACON. Proportions (rounded upwards) are calculated on the subset of stakeholders who provided replies to this question.

| What are the main sources of information about methods for toxicity assessment for regulatory purposes?   | ACACON  | REGUL   | INDUS   |
|---|---|---|---|
| Proportion of overall sample that replied to question:  |    |    |    |
| <i>Communication and guidance by international organizations, e.g. OECD and OECD toolbox, REACH guidance, ECVAM, EPA, other international organizations</i> |    |    |    |
| <i>Scientific literature</i>  |    |    |    |
| <i>Face to face organized learning &amp; exchange: Conferences, workshops, international regulatory meetings</i>  |  |  |  |
| <i>Proximity to development process: Experimental data, industry test results, contact with regulators and with software developers</i>                     |  |  | -   |
| <i>Internet resources: group lists following meetings; online databases; other search opportunities</i>   |  |  |  |

Note that when respondent mentioned online databases or simply ‘Internet’ without other specification, the category “Internet resources” was assigned.

Overall, according to this subset, **international organisms provide the principal actual source of information**, through their published guidance and also their online offerings of tools and data. For INDUS replying to this question, scientific literature is the major actual source; in this way, they attribute more value to scientific literature than did the full INDUS sample above in §5.1 (“What would help you to use QSAR/*in silico* methods?”). ACACON also rely on the literature. Those REGUL who reply here appear in contrast *not* to be reading the literature.

For REGUL and INDUS, information is currently gathered in face-to-face dialogue and learning. Industry responses indicate that a scientific context to this exchange may make it more pertinent.

## 6.2 Desired (future or supplementary) sources of information

Regarding desired (future or supplementary) sources, few replies were gathered.

ACACON mention regulators as informers:

- Some more compact information from regulators would be OK

REGUL point to the ECHA website, and one states:

- For practical reasons, I think it should be only one or maximum two internet pages which gather the information about the QSAR / *In silico* methods and their possible use for regulatory purposes.

INDUS ask for more information from all the sources cited in §6.1, with particular emphasis on guidelines coming from the authorities. For instance:

- Official channel from Institution when a new (and validated) tool is developed.

Interactivity (workshops) and mutualisation of knowledge appear important as well:

- Associations could be useful for detailed information.

All sectors thus seem to have a particular demand upon authority to provide guidance and information.

## 7 Summary, discussion and tentative conclusions

The ORCHESTRA “technical” questionnaire on “benefits and barriers to the use of QSAR methods” addressed the academic, consultant, regulatory and industry communities potentially interested by *in silico* methods in the context of REACH.

This section summarizes results, in counterpoint with discussion meant to place the results in context. The contextual discussion will consider four linked themes:

- What is offered: the design and functionality of *in silico* models in relation to the regulatory demands;
- How it is offered: the clarity and simplicity of *in silico* models for the various users;
- Access to *in silico* models;
- Agreement between developers, regulators and users on the ways forward.

### 7.1 Reminder of method and sample

The questionnaire was administered online over the period Sept. 2010 to April 2011 to a self-selected sample of specialists. Three spaced e-mail invitations were sent to a large roster of specialists, based on mailing lists compiled in the first part of the project. Response rate was never more than 10%: these invitations yielded 33 replies to the detailed Questionnaire I. A second type of reminder yielded 29 responses to an ultra short form (Questionnaire II).

Caution has thus been employed in reporting and interpreting results above. It is expected that a larger response rate could change the complexion of trends and findings. The following discussion places the results in context without attempting to draw firm conclusions. It is hoped that the report may foster reflection and discussion among stakeholders in the REACH process.

The specialists responding arose in majority from a large scientific community, while displaying different roles, duties and activities<sup>6</sup> - in a manner cutting across institutional lines. The sample was grouped by the authors into three *stakeholder* categories, designated as **ACACON** (academics and/or consultants, i.e. having no direct stake in chemical manufacturing, nor a mission to protect and regulate public health); **REGUL** (having a regulatory mission); **INDUS** (chemical manufacturers or their organizations, having a direct stake in the outcome of specific REACH dossiers). The categorized populations numbered respectively: **13**, **12**, and **8**. Results were presented as proportions of each population and all open comments entered by the respondents were cited. (See §1 of this report.)

## 7.2 Benefits: Actual and planned use of QSAR / *in silico* methods

Respondents state in great majority that they have used QSAR/ *in silico* methods. All have some future plans to test or use QSAR methods. (§2.1) Interested persons who have not applied these methods, and whose role allows them to do so, appear very open to future opportunities. (§4.1)

The stakeholder respondents cited a total of 28 models, methods or software that they have actually applied. The two most frequently cited suites (OECD Toolbox; EPIsuite) are cited by a relatively large proportion of all three stakeholder communities. Caesar is the only other suite of models that is cited by all three stakeholder communities. Other methods cited more than once by two stakeholder categories were ECOSAR, SPARC, and TOXTREE. The remainder of citations indicate great dispersion in use of models, within and across stakeholder groupings. (§2.2)

All categories of stakeholder respondents are simultaneously investigating different domains of application. All stakeholder groups name a large variety of Human Toxicity endpoints in their current application of *in silico*.

ACACON show the highest rate of application in the area of physico-chemical properties of compounds. There may be different reasons for this, but in principle it could reflect a certain degree of inertia. Physico-chemical properties are those which have historically attracted quite a lot of modelling activities and produced a stream of literature. Scientific innovation has consisted of introducing improvements to these historic approaches but has not shifted the target of application.

REGUL and INDUS are lending somewhat less attention to the assessment of physico-chemical properties through QSAR. Regulators' interest in the application side of the model diversifies their attention to the range of endpoints, and this broad need should be kept in consideration.

ACACON may move in the direction of regulator interests; planned future applications will transfer attention to human toxicity. The gap will close also from the other side: REGUL overall and within subjects plan to transfer or add attention to environmental fate and ecotoxicology endpoints. (§2.4)

INDUS today seem to "lag" behind the other categories in applications to human toxicology and environmental fate properties. (§2.3) They plan to continue applications for endpoints of current interest, as well as to diversify the range of endpoints. (§2.4)

Regarding the functions to which QSAR models are applied, ACACON presently appear to prefer *in silico* tools as time-saving devices and fundamental research devices. For INDUS as well, fast triage

<sup>6</sup> Note that actual developers of QSAR models were seen across institution types and categories, such that this criterion did not discriminate.

applications are important – more so than in the regulatory community. INDUS and REGUL are alike in the level of importance they attribute to the use of *in silico* for providing supporting information. (§2.5)

Unlike the other two categories, REGUL have not often used QSAR models for prioritisation. (§2.5) This may translate a sceptical attitude, or that this is not their specific duty at this time in the REACH calendar. However, they foresee augmenting this type of application. (§2.6) There is consensus across stakeholders that going forward, *in silico* methods will be very attractive for identifying and prioritising substances of concern. Also consensual across stakeholders is the view that these methods offer some attraction for assessing potentially thousands of chemicals simultaneously. (§3)

ACACON and REGUL see particular potential for *in silico* methods to improve response to risk assessment, classification and labelling, and other regulatory requirements; industry users appear less convinced. (§3) Specific information actions may be justified towards industry, which is requested to classify chemicals for several purposes, such as CLP and REACH. Currently the situation is quite fuzzy, since several thresholds and rules apply, and the scenarios are changing depending on the fact that some criteria will be enforced in different years.

Respondents of every category acknowledge in their future plans that *in silico* methods will be of much broader applicability in the future. Some stakeholders are gearing up to use, test or develop these methods themselves; but even those who today do not plan to use them clearly recognize their growing importance. (§2.6)

Today, international organisms provide the principal actual source of information about *in silico*, through their published guidance and also their online offerings of tools and data. INDUS and ACACON may look into the scientific literature more than REGUL. Information is also currently gathered in face-to-face dialogue and learning, according to REGUL and INDUS. A scientific context (conferences, workshops) makes this exchange more pertinent for INDUS. (§6.1)

### 7.3 Barriers to the use of *in silico* methods

Stereotyped assumptions about the barriers to application of *in silico* may be incorrect. At least among persons who reply to such a questionnaire, a preference for traditional, well-known and accepted toxicological assessment methods is NOT a drag on application of *in silico* today. (§4.2) Nor are economic costs (including potential delays) a major barrier in the view of ACACON or INDUS (§4.4). Little input was offered regarding perceived limitations of QSAR models today, although ACACON and INDUS both suggest that toxicologists may not find what they need for decision making, and academics or consultants also comment on the current inability of *in silico* to address the challenges of cocktail compounds or chronic toxicity. (§4.5)

Information barriers to *in silico* application are more salient. Across sectors, a considerable need is expressed for “more information or regulatory guidance”. But varying demands are then made by the different stakeholders. ACACON are interested in both technical and scientific aspects of *in silico* applications, but they particularly want information that will help to gauge the level of confidence that may be placed in a model. INDUS also want reassurance that the scientific quality of a given tool is acceptable; next they want pointers to the best available QSAR models. They do not ask for technical information about software, nor for guidance about when and how QSAR can be used. REGUL on the other hand are seeking a good grasp of software outputs (the results of the model,

and their meaning). To a lesser degree, they need information helping to assess the confidence they may place in QSAR tools, and identification of appropriate uses of the models. (§4.3)

On the basis of these answers, and given the fact that regulators are the primary actors in acceptance of QSAR models, initiatives should address regulatory information needs as a main target. A good model and its suite of tools are not sufficient, if the model is not described and if output components are not transparent. Regulators, compared to other sectors, assign slightly less concern to the scientific validity of models, but they require relatively more understanding of the correct applications for REACH.

As in other findings, we observe a role-related gap. The primary demand by ACACON concerns scientific aspects of the *in silico* approach. INDUS want to know which models to choose with confidence. In contrast, a key issue for regulators is a better grasp of the possible application for the specific use: REACH. To close this gap demands more detailed attention by developers and consultants to the REACH requirements.

#### 7.4 Way forward to increased use of *in silico*

What could help to generalize and augment use of QSAR for toxicology applications? REGUL call for a documented, reasoned, exemplified and standardized approach. ACACON focus instead on demonstrations of validity, availability and actual uptake of *in silico* methods. INDUS seem here to be most attracted by a kind of automated, standardized and simplified process of application. They recommend networking, cooperation and mutualisation of expertise. (§5.1)

There is consensus across sectors that industry demonstrating successful actual applications will have a large impact. Regulatory acceptance too is highlighted by comments. All sectors also affirm that case study evidence of the quality and reliability of *in silico* methods will foster greater use. In this way, a “democratic”, evidence-based demonstration, with expert quality assurance in the background, emerges as perhaps the best way to trigger broader use, rather than reliance on high-profile leadership or on trademarking. “*An important factor in the confidence building is to simply start using the tools, both industry and regulatory bodies, to see for themselves how they work.*” (§5.2) Cross-sector initiatives (demonstrations, training workshops, case study exercises) could be valuable here for familiarizing stakeholders with the tools and their outcomes.

#### 7.5 What is offered: design and functionality to meet regulatory demands

All three stakeholder groups today are in a phase of experimentation with *in silico* methods. (§2.3, 2.4) REGUL in particular appear to be exploring for tools that may address their emergent need. (§2.3)

The *in silico* models currently available are not yet sophisticated enough to address all the requirements of regulators and potential industry users. (§4.5) This is a priority for development, and where possible the ORCHESTRA project aims to inform that development.

Regulators require a significant level of detail in the documentation of an *in silico* model and transparency in results (§5.1; §4.3). *In silico* methods therefore need to be developed so that they meet the regulatory requirements in terms of documentation and clearly defined areas of

applicability, and also adapt the outputs in accordance with the specific inputs and requests of the user.

Some issues are formal: different format of the output, immediate use for the IUCLID scheme, reference to the QMRF, etc. Compatibility with IEUCLID is essential:

“Without an appropriate IT tool, it would be extremely difficult for industry, especially for small and medium enterprises, to comply with the REACH data requirements. In order to structure these requirements, REACH requires a specific reporting format, namely the IUCLID 5 format. The European Commission has therefore since 2004 managed - as part of the REACH implementation strategy - the analysis, design and build of the IUCLID 5 software...”

*IEUCLID: Overview*

*[www.iuclid.eu/index.php?fuseaction=home.project](http://www.iuclid.eu/index.php?fuseaction=home.project)*

Other issues are substantial: what kind of information should be presented in order to provide all elements for regulatory acceptance? (§6.1) While stakeholders claim no attachment to traditional methods (§4.2), it is a fact that the requested elements for acceptability imply a cultural shift, a move from one paradigm to another, and this is necessarily related to revision of knowledge and conceptualization. Currently, decision is taken on the basis of experimental data, and inherent uncertainties there are discounted<sup>7</sup>.

The new paradigm is to use a virtual case: not real (even if surrogate) data, but “probable” data. Any predictive model can by definition offer only predicted data, not real data. To support the predicted data, regulators, in particular, request more information about the reasoning behind the model, the role of its components, assurance that a certain model can be used for a certain compound. (§4.3, §5.1) Documentation is very important; outputs in themselves are not sufficient.

## 7.6 How it is offered: the clarity and simplicity of *in silico* models for the user

Overall, REGUL have clearly in mind some important needs they have for regulation duties. (§2.5, §2.6, §3, §4.2, §5.3) Patterns of difference seen with other stakeholder groupings can be interpreted as a lack of knowledge by developers of the needs identified by regulatory community. Thus, we may be observing mutual gaps in knowledge or culture: the academic and consulting community may not know exactly what regulators ask for, and regulators may not be fully aware of the possibilities offered by the models and the basis on which they offer them.

Models have been developed for different targets. Legislative requirements are very specific. Typically, the user for regulatory purposes is not a developer, and has limited knowledge on the *in silico* models and formats. There may be problems in using the models, because these are not simple, and also in extracting information from the results.

Most of the models have been developed by scientists, and are not optimized for a specific use, such as REACH. Furthermore, in many cases it is likely that a certain experience is needed to correctly interpret the results. Research scientists are surely more familiar with these methods, but if these methods are to be accepted, and used, much more documentation is necessary, and also training on the new conceptual approach. Documentation is recurrently present in the answers from regulators. This shows that more efforts have to be addressed in this direction.

<sup>7</sup> ORCHESTRA filmed interview with B. Diderich, OECD (March 2011).  
© 2011 ORCHESTRA project

It may be that some models in the literature are quite simple, just a linear equation. However, typically they need inputs which have to be obtained through other sources, for instance calculating chemical descriptors. In many cases this operation brings variability, related to how these descriptors are calculated. A limited number of models exist which are ready to be used. Some are commercial, some are freely available. These are the most mature examples, and are probably of first choice for regulatory purposes. They provide in many cases a certain basis of the reasoning done, and of the model basis. However, more will have to be done to provide satisfaction and confidence.

### **7.7 Access to *in silico* models: cost, required expertise, knowledge and training**

Accessibility depends on the clarity of the model, but it also refers to the degree of experience which may be needed to use the model in the correct way. This depends on the model, in many cases. Some models are quite simple, and ideally the commercial and the free internet models should aim at the greatest clarity in this way. However, certain models are quite complex, in view of the plurality of options, and the appropriate choice requires experience and training.

While cost is little cited as a barrier, it may represent an issue for regulators. (§4.4) Freely available models will surely facilitate their access and use by national competent authorities whose budget is limited.

### **7.8 Agreement between developers, regulators and users on the issues and ways forward**

All stakeholder sectors are interested by the QSAR models, and willing to better explore the approach. However, this process should proceed along an agreed process, without excluding industry and regulators. The pure availability of a model is not enough; the evaluation has to be done in common, in appropriate ways. This means increasing information, detailing possibilities, uncovering pros and cons, and preferably, in interactive scientific contexts: meetings, conferences, and workshops. (§5, §6)

\* \* \*

—

## **Annex I: Questionnaire I**

### Invitation and content of “technical” questionnaire



Recipient address (?)

...  
...  
...

Dear ...

## **Survey of the benefits and barriers to the use of quantitative structure-activity relationships (QSAR) / *In Silico* methods in toxicology**

In recent years the EU have funded research into developing QSAR / *In Silico* (i.e. computer-based) methods for the evaluation of chemical toxicity. This project is intended to communicate those findings so that the research is used more widely. This survey will help us to find out what information is needed and how we should communicate it.

We would therefore like to ask for your thoughts about the use of QSAR / *In Silico* methods in toxicology, based on your experience of using them – or not using them.

The results will guide our work over the next two years to disseminate and exploit this recent research on QSAR / *In Silico* methods.

**We really hope you can take a few minutes to complete it.**

***Please also copy this to other colleagues who you think could also offer useful insight.***

You can complete it online at [www.in-silico-methods.eu](http://www.in-silico-methods.eu)

or send the PDF to (*a dedicated email should be added here*)

or fax it to Dr. Emilio Benfenati, 0039-02-39014735

or post it to Dr. Emilio Benfenati, Mario Negri Institute, Via Giuseppe La Masa 19, 20156, Milano, Italy

If you complete it online you can also see the results as they develop.

Thank you.

Yours sincerely,

Dr Emilio Benfenati

*Head, Laboratory of Environmental Chemistry and Toxicology*

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*I CONTRIBUTI PER LA RICERCA VERSATI ALL'ISTITUTO SONO FISCALMENTE DEDUCIBILI DAL REDDITO (Gazzetta Uff. N.135 del 13/6/2007)*

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## Online Questionnaire: "Benefits and barriers to the use of QSAR methods"

### Your use of QSAR / In Silico methods

#### Q1 Have you used or tested QSAR / In Silico methods?

|   |
|---|
| <input type="checkbox"/> Yes<br><input type="checkbox"/> Yes, with expert support<br><input type="checkbox"/> No  |
| <p><i>If 'Yes', which In Silico models / methods / software have you used / tested?<br/>Please indicate the name of the software, or indicate if the source is internal</i></p><br><br><br>   |
| <p><b>If no:</b> <input type="checkbox"/> We wanted to use <i>In Silico</i> methods, but there was no relevant model available.<br/> <input type="checkbox"/> We have tried to use <i>In Silico</i> methods, but it was not successful<br/> <input type="checkbox"/> We have not needed (or wanted) to use <i>In Silico</i> methods so far.</p> |

#### Q2 Domains for using QSAR / In Silico methods *Please tick all which apply to you.*

|  |  |
|--|--|
| <p><b>We have used<br/>In Silico methods for:</b></p> <p style="text-align: center;">↘</p> <p><input type="checkbox"/> Physico-chemical properties .....</p> <p><input type="checkbox"/> Human toxicology .....</p> <p><input type="checkbox"/> Environmental fate properties .....</p> <p><input type="checkbox"/> Ecotoxicology .....</p> <p><input type="checkbox"/> None .....</p> | <p style="text-align: right;"><b>We want to use<br/>In Silico methods for:</b></p> <p style="text-align: right;">↙</p> <p><input type="checkbox"/> Physico-chemical properties .....</p> <p><input type="checkbox"/> Human toxicology .....</p> <p><input type="checkbox"/> Environmental fate properties .....</p> <p><input type="checkbox"/> Ecotoxicology .....</p> <p><input type="checkbox"/> None .....</p> |
| <p><i>Please identify some example endpoints:</i></p><br><br>  |  |

#### Q3 Functions of QSAR / In Silico methods *Please tick or rank 1, 2... all which apply to you.*

|   |   |
|---|---|
| <p><b>We have used<br/>In Silico methods for:</b></p> <p style="text-align: center;">↘</p> <p><input type="checkbox"/> Prioritisation of compounds for further analysis .....</p> <p><input type="checkbox"/> Fast evaluation of the properties of chemicals of interest .....</p> <p><input type="checkbox"/> Research and development, for the evaluation of toxicity .....</p> <p><input type="checkbox"/> Regulatory requirements - as supporting information .....</p> <p><input type="checkbox"/> Regulatory requirements - as part of a weight-of-evidence approach .....</p> <p><input type="checkbox"/> Regulatory requirements - as the key study .....</p> <p><input type="checkbox"/> None / not sure .....</p> | <p style="text-align: right;"><b>We want to use<br/>In Silico methods for:</b></p> <p style="text-align: right;">↙</p> <p><input type="checkbox"/> Prioritisation of compounds for further analysis .....</p> <p><input type="checkbox"/> Fast evaluation of the properties of chemicals of interest .....</p> <p><input type="checkbox"/> Research and development, for the evaluation of toxicity .....</p> <p><input type="checkbox"/> Regulatory requirements - as supporting information .....</p> <p><input type="checkbox"/> Regulatory requirements - as part of a weight-of-evidence approach .....</p> <p><input type="checkbox"/> Regulatory requirements - as the key study .....</p> <p><input type="checkbox"/> None / not sure .....</p> |
| <p><input type="checkbox"/> Other functions (please explain):</p><br><br>   |   |

## The challenges / barriers to using *In Silico* methods

### Q4 What prevents or limits your use of QSAR / *In Silico* methods?

Please tick or rank 1, 2... all which apply to you. (If a set of issues is not significant, leave it blank.)

↓ You can select just the headings - the detailed responses are optional.

***In Silico* methods are not a priority for us**

- other priorities are more important at this time;
- we want to focus on using traditional methods, where our expertise is strong;
- we want to focus on using traditional methods which we know have been accepted in the past.

Other (please explain):

**We need more information and/or regulatory guidance**

- to know more about when and how QSAR *In Silico* methods can be used;
- to know what QSAR models are available or appropriate for our work;
- to assess whether a model can be viewed as scientifically valid and adequately documented;
- to be able to use the technical software, and understand the outputs from it;
- to know how to integrate different kinds of results from different methods into a submission.

Other (please explain):

**We are concerned about the potential costs or delays if we use *In Silico* methods**

- that the models (or our use of them) may not be accepted by the regulator, and so create additional costs for us in delay and resubmission;
- that we need to invest in technical training and/or consultancy;
- that using QSAR models might commit us to using expensive commercial software in future.

Other (please explain):

**The current QSAR models don't yet provide what we need**

- the range of models is currently too limited for us to start using these methods regularly;
- we fear the models may not be reliable, and require support from other models and/or tests;
- current models often do not provide what the toxicologist needs for making decisions on toxicity;
- models can be a 'black box', lacking the documentation we need to check their quality and their applicability to our work, and/or lacking the transparency that is required in REACH submissions;
- models do not (yet) evaluate chemicals in combination, or adequately evaluate chronic toxicity.

Other (please explain):

**QSAR / *In Silico* methods will not / cannot provide what we need**

Please explain:

## Ways forward

Please tick or rank 1, 2, 3... all which apply to you.

### Q5 What are the *main* reasons to use QSAR / *In Silico* methods, in your view?

|  |
|--|
| <input type="checkbox"/> To assess potentially thousands of chemicals simultaneously<br><input type="checkbox"/> To identify and prioritise substances of concern.<br><input type="checkbox"/> To improve the response to regulatory requirements such as risk assessment and classification and labelling.<br><input type="checkbox"/> To address endpoints for which animal models are not fully accepted.<br><input type="checkbox"/> To reduce the time and costs of experiments.<br><input type="checkbox"/> To reduce the use of vertebrates in experiments - to meet regulatory requirements.<br><input type="checkbox"/> To reduce the use of vertebrates in experiments - to meet our own ethical policies. |
| <input type="checkbox"/> Other reasons (please explain):   |

### Q6 What would help you to use QSAR / *In Silico* methods?

|   |
|---|
| <input type="checkbox"/> Lists and reviews of the available models, with information on where to access them.<br><input type="checkbox"/> Seeing good examples of industry using <i>In Silico</i> methods successfully (in documentary video, industry events, online reports and trade magazines).<br><input type="checkbox"/> Seeing more peer-reviewed journal articles about the practical applications of <i>In Silico</i> methods, illustrated by case studies.<br><input type="checkbox"/> Examples from the regulators about acceptance of / enthusiasm for <i>In Silico</i> methods.<br><input type="checkbox"/> Clear standardisation of the ways in which individual QSAR models and their appropriate uses are described, and their applicability domains are defined.<br><input type="checkbox"/> Clear guidelines for reporting toxicity results from <i>In Silico</i> methods (maybe as an automatic report generator within the software that matches the submission format).<br><input type="checkbox"/> Examples of the reasoning and transparent documentation required for submissions.<br><input type="checkbox"/> Support and guidance from laboratories with expertise in the uses of QSARs. |
| <input type="checkbox"/> Other (please explain):  |

### Q7 What will have most impact on the wider acceptance and use of *In Silico* methods?

|   |
|---|
| <input type="checkbox"/> Industry using <i>In Silico</i> methods more, and producing high quality results.<br><input type="checkbox"/> Use by high-profile companies / organisations, and in cases with high visibility.<br><input type="checkbox"/> The trademarking of models by trusted software companies or organisations.<br><input type="checkbox"/> The monitoring, review and updating of models by specialist QSAR laboratories.<br><input type="checkbox"/> Case study research evidence of the quality and reliability of <i>In Silico</i> methods. |
| <input type="checkbox"/> Other:   |

**Finally...****Q8 What are your main sources of information about methods for toxicity assessment for regulatory purposes?**

|  |
|--|
|  |
|--|

And where else would you like to see or hear information about QSAR / *In Silico* methods?

|  |
|--|
|  |
|--|

**Would you like to be notified of events and information about QSAR / *In Silico* methods?**

- Yes (*Please include some contact details below*)  No

**Can you offer an example or experience of using *In Silico* methods?**

Would you be willing to say more (perhaps by phone) about one experience of using *In Silico* methods? This will help us to ensure the information and guidance we produce is informed by experience and by real examples, and so can inform future use.

- Yes (*If yes, please include your email and phone below*)  No

**Thank you.****With which major stakeholder group do you identify yourself most closely?:**

|  |  |
|--|--|
| <input type="checkbox"/> Academic Community<br><input type="checkbox"/> Consultant (including advisors and independent QSAR developers)<br><input type="checkbox"/> Industry (including chemicals research, evaluation, distribution, associations, investment, services and trade unions)<br><input type="checkbox"/> Regulator or national competent authority | <input type="checkbox"/> Other Governmental Organisation<br><input type="checkbox"/> Non-Governmental Organisation<br><input type="checkbox"/> Media & communication<br><input type="checkbox"/> Citizen<br><input type="checkbox"/> Other |
|--|--|

**If you are directly involved with QSAR / *in silico* methods, ..please help us by identifying your main activity. (If you also have a significant secondary activity, please identify this as well):**

|  |  |
|--|--|
| My main involvement with QSAR / <i>in silico</i> is: | <input type="checkbox"/> DEVELOPING QSAR/ <i>in silico</i> models<br><input type="checkbox"/> PREPARING chemical registration dossiers<br><input type="checkbox"/> ADVISING / HELPING other organisations to prepare chemical registration dossiers<br><input type="checkbox"/> EVALUATING chemical registration dossiers as a regulator<br><input type="checkbox"/> None, I'm not directly involved |
| I am also involved secondarily with:                 | <input type="checkbox"/> DEVELOPING QSAR/ <i>in silico</i> models<br><input type="checkbox"/> PREPARING chemical registration dossiers<br><input type="checkbox"/> ADVISING / HELPING other organisations to prepare chemical registration dossiers<br><input type="checkbox"/> EVALUATING chemical registration dossiers as a regulator<br><input type="checkbox"/> None                            |

**Anything else you wish to state about your role:**

|  |
|--|
|  |
|--|

**Optional personal details:**

|   |             |            |
|---|-------------|------------|
| Title:  | First name: | Last name: |
| Organisation:   |             |            |
| Position:   | Department: |            |
| Email:  | Website:    |            |
| Phone:  | Country:    |            |
| Address:  |             |            |
| <input type="checkbox"/> I have given my contact details but I want my responses to be used anonymously.            |             |            |
| <input type="checkbox"/> I would be willing to offer comments or advice to the dissemination project in the future. |             |            |

## Annex II: Questionnaire II

An email was circulated to all persons who had received the invitation to fill out Questionnaire I, but who did not respond. The email contained two url labelled “yes” or “no”.

This email asked the recipient if s/he uses/has used QSAR/*in silico* methods.

If the recipient clicked on “yes”, a webpage opened thanking the participant and highlighting the slogan:

"DO YOU KNOW THAT *IN SILICO* METHODS, ACCORDING TO REACH, CAN BE USED FOR DOSSIER COMPILATION, CLASSIFICATION & LABELLING AND PRIORITIZATION?"

If the url “no” was selected, a webpage opened with the following questionnaire.

## Online Survey - Use of QSAR / In-silico methods

Thank you for your collaboration!

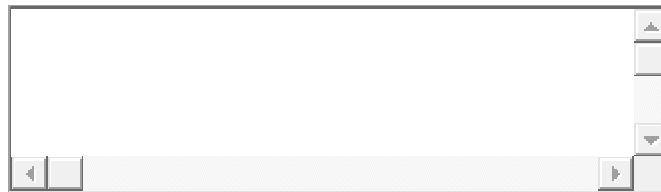
**Please answer just one question to explain your response.**

What are the main reasons you don't use computer-based methods in toxicology? (ie QSAR / *in silico* methods):

- Not interested. I am satisfied with the methods I currently use.
- Interested. But I have not needed (or wanted) to use these methods so far.
- I don't know enough about these methods.
- I don't really trust these methods.
- We wanted to use these methods, but there was no relevant model available.
- We have tried to use these methods, but it was not successful.

**Click all which apply to you. Thank you.**

Other reasons (please explain):



### **Annex III. Policy Issues Questionnaire**

Invitation and Questionnaire on Policy issues around '*in silico*' methods as alternatives to animal testing.

Results not reported in the present document.

Dear Sir or Madam

## The need for information on '*In Silico* methods' – an alternative to animal testing

In recent years the EU has funded research into developing computer-based methods for evaluating the toxicity of chemicals, called '*in silico* methods'. These are potentially important in making it possible to test large numbers of chemicals (as required by the EU REACH legislation) while also reducing the numbers of tests on animals.

The ORCHESTRA project is funded by the EU to communicate some of those research findings. Our intention is to raise understanding of these alternative methods among potential users, decision-makers and others. This survey will help us to find out what information is needed by whom, and how and where we should communicate it.

- The short questionnaire on the following pages is our invitation to **policy makers, industry managers, educators, political leaders, NGOs, investors, citizens and all others who are not specialists** in toxicology to comment on some of the issues that are raised and/or addressed by *in silico* methods.
- Online we are offering a parallel questionnaire specifically for regulators, industry specialists, toxicologists, QSAR developers, scientists and any others with specialist knowledge or experience. If you would like to complete that questionnaire, please do so. ([www.in-silico-methods.eu](http://www.in-silico-methods.eu))

We really hope you can take a few minutes to complete the questionnaire with this letter. Please also copy it to others who are interested in this topic and issue.

You can send the completed form by fax to Dr. Emilio Benfenati, 0039-02-39014735

or by post to Dr. Emilio Benfenati, Mario Negri Institute, Via Giuseppe La Masa 19, 20156, Milano, Italy

Thank you.

Yours sincerely

Dr Emilio Benfenati  
*Head, Laboratory of Environmental Chemistry and Toxicology*

**Online Questionnaire:**  
**A questionnaire for policy makers, industry managers, educators ... and citizens.**

You may find the introductory leaflet on *in silico* methods useful: [www.in-silico-methods.eu](http://www.in-silico-methods.eu)

**Q1 The 2007 REACH legislation on industrial chemicals has four aims.**

**In your view, what is their relative importance?** 0 = not important; 10 = extremely important

|  | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|--|---|---|---|---|---|---|---|---|---|---|----|
| Example  |   |   |   |   |   |   | X |   |   |   |    |
| 1. 'Improve the protection of human health and the environment from the risks that can be posed by chemicals'      |   |   |   |   |   |   |   |   |   |   |    |
| 2. 'Enhance the competitiveness of the EU chemicals industry, a key sector for the economy of the EU'              |   |   |   |   |   |   |   |   |   |   |    |
| 3. 'Promote alternative methods for the assessment of hazards of substances' (i.e. alternatives to animal testing) |   |   |   |   |   |   |   |   |   |   |    |
| 4. 'Ensure the free circulation of substances on the internal market of the European Union'                        |   |   |   |   |   |   |   |   |   |   |    |

**Q2 The following are some of the ways in which the REACH aims can be achieved.**

**In your view, what is their relative importance?**

|   | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|----|
| <p><b>Testing new chemicals</b></p> <p>Obtaining scientifically sound information on the potential hazards to human health and the environment of <i>new</i> chemical substances produced or imported into the EU.</p>  |   |   |   |   |   |   |   |   |   |   |    |
| <p><b>Testing existing chemicals</b></p> <p>Obtaining scientifically sound information on the large number of <i>substances already in use</i> where there is inadequate information.</p>   |   |   |   |   |   |   |   |   |   |   |    |
| <p><b>Placing the responsibility and costs onto industry</b></p> <p>Placing the responsibility on industry to provide the evidence (i.e. propose, carry out and report tests), and assess and manage the risks, so that industry bears these costs rather than the taxpayer. (Regulators review test proposals and results, do spot checks and focus on problem areas.)</p> |   |   |   |   |   |   |   |   |   |   |    |

|   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| <p><b>Prudence towards alternative methods</b></p> <p>Before accepting each use of non-animal methods, judging whether this will best protect human health and the environment.</p>   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <p><b>Sharing test data</b></p> <p>Requiring industry to share test results with other companies, to avoid repeating animal experiments.</p>  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <p><b>Animal testing as a last resort</b></p> <p>Approving further animal tests only in cases where other methods are not available.</p>  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <p><b>Public investment in developing alternative methods</b></p> <p>Investing in both <i>in vitro</i> and <i>in silico</i> methods, and in the information available about these alternative methods.</p>  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <p><b>Ensuring access to data to develop <i>in silico</i> models:</b> requiring companies to make the results from animal tests accessible at low cost to the developers of <i>in silico</i> models, so that <i>in silico</i> models can develop to replace animal tests.</p> |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <p><b>Ensuring <i>in silico</i> models remain accessible,</b> either at low cost or freely available online.</p>  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

**Q3 The following are some of the advantages of *in silico* methods.**

**From your perspective, which are most important?**

(Please number them 1-6. **1 = most important.** You can show equal priority, e.g. 1, 2, 2, 2, 5, 6.)

|   |  |
|---|--|
| <p><b>Enabling the testing of large numbers of chemicals:</b> <i>in silico</i> methods make it possible to assess large numbers of chemicals and/or prioritise their testing. (There are many thousands of chemicals being used in the EU which need to be tested under REACH.)</p>   |  |
| <p><b>Providing regulators with the information they need:</b> <i>in silico</i> methods can integrate the findings from different kinds of experiments to generate an understanding of the toxicity of a chemical; the quantitative results can be used directly in risk assessment.</p>  |  |
| <p><b>Reducing costs and delays:</b> the additional tests required by REACH will cost industry billions of Euros in animal experiments. Those costs could be reduced by using <i>in silico</i> methods. Animal tests also take time, and laboratories are limited, causing expensive delays for industry, whereas <i>in silico</i> methods can assess thousands of chemicals quickly.</p> |  |

|   |  |
|---|--|
| <b>Reducing testing on animals:</b> reducing the numbers of animals and fish (vertebrates) used in tests for toxicity. (This is an aim of the REACH legislation.)                               |  |
| <b>Reducing testing on invertebrates:</b> reducing the numbers of invertebrates, such as worms, used in tests for toxicity. (This is <i>not</i> an aim of the REACH legislation.)               |  |
| <b>Pro-active planning:</b> until now, chemicals were developed before testing their toxicity. <i>In silico</i> methods can predict toxicity, so safer chemicals can be planned from the start. |  |

#### Q4 Is animal testing a significant issue in your life or work?

'Animal testing' here refers to the use of around a million live animals and fish every year in Europe in laboratory tests to assess chemical toxicity. (Greater numbers are used in pharmaceutical and other research.)

- Animal testing is not an issue that usually concerns me** personally or professionally.
- or  **Animal testing concerns me** and I wish I could do something about it, but in reality it does not affect what I do in my life or work.
- or  **Animal testing concerns me, and it does affect what I do** (choose any or all):
- at work, it affects my professional or commercial decisions (please explain below);
  - as a consumer, when possible I will select products which display a statement that they have not been tested on animals;
  - as a citizen, I support or would support campaigns against animal testing;
  - as a voter, these issues concern me and could affect my vote.

*Please explain if necessary*

#### Q5 After reading the introductory leaflet, what further information about *in silico* methods would be useful to you? (The leaflet is at [www.in-silico-methods.eu](http://www.in-silico-methods.eu) in four languages)

#### Q6 In what media and publications would you like to see or hear information about developments in alternative (non-animal) methods?

## Finally...

How did you hear about this questionnaire or the ORCHESTRA website?

What is your role in relation to issues in chemical evaluation?

(Please tick, or rank 1, 2, 3... if more than one applies.)

|  |   |
|--|---|
| <input type="checkbox"/> Citizen, inc. citizen groups and online communities.    | <input type="checkbox"/> Regulator or national competent authority            |
| <input type="checkbox"/> Media, online communicator or journalist                | <input type="checkbox"/> Industry user / association / trade union, inc. SMEs |
| <input type="checkbox"/> Non-governmental organisations (NGO)                    | <input type="checkbox"/> Distributor / retailer                               |
| <input type="checkbox"/> Governmental organisation; local / national / internat. | <input type="checkbox"/> Consultant   |
| <input type="checkbox"/> Non-university researcher                               | <input type="checkbox"/> Association for alternative methods                  |
| <input type="checkbox"/> University researcher                                   | <input type="checkbox"/> Information technology user or evaluator             |
| <input type="checkbox"/> Scientist or science associations                       | <input type="checkbox"/> QSAR / <i>In Silico</i> methods developer            |

Would you like to be notified of events and information about *in silico* methods?

Yes (Please include some contact details below)

No

## Thank you

### Optional personal details:

|   |             |             |
|---|-------------|-------------|
| Title:  | First name: | Last name:  |
| Organisation:   |             |             |
| Position:   |             | Department: |
| Email:  |             | Website:    |
| Phone:  |             | Country:    |
| Address:  |             |             |
| <input type="checkbox"/> I have given my contact details but I want my responses to be used anonymously.            |             |             |
| <input type="checkbox"/> I would be willing to offer comments or advice to the dissemination project in the future. |             |             |