

*39th Joint Meeting of the Chemicals Committee and the Working Party on Chemicals,
Pesticides and Biotechnology
15-17 February 2006*

**Focus Session: Experiences using integrated approaches to fulfil information requirements
for Testing and Assessment**

**Contribution by European Commission
(Information Requirements in REACH: Approaches for both Industry and Authorities)**

Information Requirements in REACH

Approaches for both Industry and Authorities

1. INTRODUCTION

The REACH proposal was designed by the Commission to be a contribution towards achieving sustainable development in the chemicals sector. In doing so, the proposal represented what the Commission saw as a politically acceptable balance between the three pillars of sustainable development, represented by environmental, economic and social objectives. The Political Agreement achieved in Council on December 13, 2005 underlined this acceptance, illustrated by the Commissions statement at the Council meeting:

“The Commission supports the Political Agreement which is consistent with the Lisbon objectives on competitiveness and innovation while achieving a marked improvement in health and environment to the benefit of Europe’s citizens.”

From an environment and health perspective, REACH not only fulfils the requirements of maintaining a high level of health and environmental protection, laid down in the Treaty, it also represents a considerable improvement over the level of protection provided by the current chemicals legislation.

Whilst sustainable development and the thereby implied setting of a high level of protection, were the fundamental objectives of REACH, a number of other objectives were also sought to be addressed by the new legislation, in particular the promotion on non animal testing by avoiding animal testing whenever possible and by emphasising the principle of refinement, reduction and replacement in test method development.

The approach taken by the Commission in its original proposal and maintained in the European Parliaments position and the Political Agreement in trying to resolve the potential conflicts between a system designed to generate significantly more information on the properties of chemicals and the objective to promote non animal testing is:

- (1) To legislate that information needs are addressed by vertebrate testing only as a last resort;
- (2) To clearly define information requirements and identify the Test Methods and if relevant other conditions (e.g. GLP), which will generate results fulfilling the information requirements;
- (3) To legislate a far reaching obligation to share existing data and prevent duplicate testing;
- (4) To enable information needs to be met through a (combination of a) large variety of approaches not requiring vertebrate testing;
- (5) To oblige Manufactures and Importers to jointly develop testing proposals when an information requirement can only be met by specified vertebrate testing and submit them for examination by the Agency before testing can commence.

2. MEETING THE INFORMATION REQUIREMENTS

The high level of protection of human health and the environment is based on the establishment of the information requirements. In the REACH Regulation, these are set in Annexes IV through VIII. To give legal certainty and make the Regulation enforceable, the Regulation establishes the Test Methods which, when testing is needed, will fulfil the information requirements¹. These Test Methods need to generate information which can be used in a multiplicity of settings within REACH (e.g., for priority setting, classification and labelling and/or risk assessment), but also (e.g., based on the commitment to Mutual Acceptance of Data) in settings outside of REACH and even the EU. REACH therefore maintains the approach from current legislation that an information requirement can be met using internationally accepted test methods².

The European Parliament and the Council supported a more far-reaching obligation to share information than was in the original Commission proposal. The concept of One Substance – One Registration (OSOR) was introduced, creating an obligation on industry to share all studies. Currently Council and the European Parliament have developed different mechanisms for implementing of this obligation.

REACH lays down, in Article 23(1), a clear obligation to carry out vertebrate testing only as a last resort, thereby placing an obligation on industry and authorities alike to consider all other options before (requiring to) carry out testing. To create legal certainty and enforceability of this obligation, REACH establishes, in Annex IX, a legislative framework for industry and authorities to know when they have met this obligation.

In drafting Annex IX the Commission intended to create a broad legislative framework which could be applied to fulfil the information requirements while limiting vertebrate testing to the extent possible. In doing so the basic approach is that if a scientific justification can be given, demonstrating that the available information has the same information content as the internationally accepted test method, then the information requirement can be met using the available information. The Commission clearly acknowledges that the state of science today is not, and most likely will not be in the short term, one that all information requirements needed to maintain a high level of protection under REACH, can be met without vertebrate-animal testing³. Therefore Annex IX in effect establishes a broad legislative framework which can be applied as progress is made in the development of scientific methods designed to address information needs.

If the manufacturers and importers of a substance deem that the only way to address an information requirement listed in Annexes VII or VIII is through vertebrate testing, then they must agree on the test(s) needed and submit (a) proposal(s) for doing the test to the Agency. The Agency examines the proposal(s) before the test can be carried out.

¹ As these Test Methods are mostly equivalent to OECD Test Guidelines, this requirement simultaneously preserves the Mutual Acceptance of Data regime beyond the EU borders.

² The EU is committed to support research and validation work of Alternative Methods which reduce, refine and replace the use of vertebrates, in particular work leading to revisions of these internationally accepted test methods.

³ This follows for example from [CSTEE and other References]

3. ANNEX IX OF REACH

Annex IX of the REACH Regulation (the full text of Annex IX is given as the Annex to this document) contains three basic approaches to fulfilling the information requirements in REACH:

- Testing does not Appear Scientifically Necessary;
- Testing is Technically not Possible;
- Substance-Tailored Exposure Driven Testing.

Generally the technical applicability of a test is covered within the test guideline itself and the latter bullet is very dependent of the legislative framework within which exposure is defined and applied. These two points are not covered in any further detail in this paper.

It is very challenging to develop the concepts lying behind “Testing does not Appear Scientifically Necessary”. The next sub-sections present the methods developed in Annex IX for doing so.

3.1. The current legislative approach

The approaches used under the current chemicals legislation for evaluating whether available information which has not been generated by applying internationally accepted test methods under GLP can be used for a specific purpose, are

- Use of Existing Data;
- Weight of Evidence.

The first bullet for example enables the use of non-GLP non-Guideline information and historic human data, under the condition that it can be demonstrated that the information content of the information covers the elements of the internationally accepted test method. The second bullet is used for example when evaluating several studies, where no one study is “equivalent” to the internationally accepted test method under GLP, but it can be demonstrated that the collection of studies are or when evaluating several well conducted guideline, GLP compliant, studies having differing or conflicting results.

These approaches are used to a large extent for filling information requirements under the Existing Chemicals Regulation (Reg. 793/93). They are also used extensively when classifying and labelling existing substances under the Dangerous Substance Directive (Dir. 67/548). Whilst the criteria for classification in that Directive are based on test results generated by applying internationally accepted test methods under GLP, data for existing substances is often available for studies carried out before these internationally accepted methods were adopted, and, as a result, an element of scientific judgement is needed in evaluating these non-standard data.

These examples above fall under the traditional application of these approaches under current EU legislation, but other examples have been applied successfully, for example:

- The use of “QSAR” for environmental hazard assessment for classification and risk assessment purposes;

- The use of “grouping” in the classification of petroleum products and other, mainly inorganic, groups of compounds;
- The use of “read across” for both classification and risk assessment purposes and notification of new substances;
- The use of “non validated in-vitro” test results for risk assessment purposes.
- The use of log Pow⁴ as a surrogate for the fish bio-concentration factor for classification and risk assessment purposes.

OECD has also gained relevant experience in grouping of substances under the OECDs High Volume Programme.

3.2. The REACH Approach

The “new” approaches explicitly mentioned in Annex IX of REACH which can be used to fulfil information requirements are:

- In vitro Methods
- Grouping of Substances and Read-across Approach
- Structure Activity Relationships (SARs)

From Section 3.1 it is clear that in fact these approaches are not “new”. The novelty is that they have been explicitly included in the REACH Regulation and that the way in which these approaches are expected to be applied may differ from current day applications.

3.2.1. In-vitro information

In-vitro methods which have not undergone a scientific validation process according to international standards can be used directly to fulfil an information requirement if the method fulfils (for example) the ECVAM criteria for the entry of the method into the pre-validation phase. However, if the result is negative, then confirmatory testing will be needed at the appropriate tonnage level and if it is positive it may be necessary to carry out further studies to identify the hazard in greater detail This is applicable when the in vitro test is being used as a direct replacement of a traditional test

These conditions for direct use of “non validated” in-vitro information of course do not in anyway preclude the use of this type of information in the more traditional “weight of evidence” approach.

If an in-vitro method is or becomes formally validated, then it can be used in addition directly to replace information requirements if it is included in the formal list of recognised Test Methods or as a component of a strategy intended to do so.

⁴ The Annex V of Dir. 67/548 test method on LogP even allows calculation methods to be used as a surrogate for experimental derivation

3.2.2. *Grouping of Substances*

Grouping can be seen as the generic concept drawing a conclusion about the likely property of one substance based on the knowledge of the properties of one or more similar substances. In this context grouping can be seen as a broadening of the traditional expert judgement approach to include information from similar substances in drawing conclusions regarding the properties of the substance. Its validity clearly has to be judged on a case by case basis and within the context that the result is used. In particular, Annex IX stipulates that grouping can be used if it can be demonstrated that the substance in fact is a member of the group and:

- (1) the reliability of the approach can be established;
- (2) the results are adequate for the purpose used;
- (3) adequate and reliable documentation is provided.

REACH will facilitate read-across as during pre-registration of a substance, companies can also indicate other substances to which the data is relevant.

The concept of “grouping” includes both “read-across” and the related “categories” approach. These approaches may or may not involve formal calculation methods and/or computer modelling (e.g., QSARs).

3.2.3. *Read-across Approach*

In “read-across” information for one chemical is used to make a prediction for one or more chemicals, which are considered to be "similar" in some way. When “read across” is used under current EU legislation, it is often used in the context of an assessment of a substance where information is lacking for a property under investigation. The assessor then seeks to identify “similar” substances which have information for the property and where that information can be used to deduce that the substance under investigation has the same property. The reverse approach has been applied successfully under the EU classification system, where all “similar” substances (sometimes identifying all the substances, sometimes leaving them as a generic group) are expected to have the same property as the substance. In this context the read-across is a simple form of a structure activity relationship (SAR), with the property (or activity) as the starting point for finding “similar” substances and the “structure” being the substructure (or set of fragments) that associates all members of the group.

3.2.4. *Categories*

Chemical categories are groups of chemicals which follow a regular pattern as a result of structural similarity. As a result, their properties are likely to be similar or follow a certain pattern. In many cases it is possible to model these similarities or patterns mathematically (e.g. Quantitative structure activity relationships (QSARs) and activity-activity relationships (AARs)).

The category approach, applied in its fullest extent, should enable the establishment of categories covering all possible chemicals (across company portfolios, across production volume bands, across legislative scopes and even covering substances which are not anymore produced or have not (yet) been produced) and establishing through the category approach what the relationships are between the category members and their properties. The biggest challenge in this approach lays in defining the category itself and in particular its boundaries.

In contrast to the potential of the category approach, the “read across” approach would be a more limited ad-hoc way of looking at predicting the property of one chemical from the property of one or more others.

As with the non-validated in-vitro methods, grouping approaches can be used in REACH directly to fulfil information requirements, provided a number of conditions are met, including a scientific justification.

3.2.5. *Quantitative Structure Activity Relationship (QSAR)*

In addition to the SAR approaches described in Section 3.2.3, computer models are available to predict the properties of individual chemicals. The scope of application of these models (their “domain”) and the accuracy of their predictions need to be assessed before these methods are used.

QSARs may also be applied directly to individual compounds to predict their properties and thereby replace the need for a test, under the condition that the relevant QSAR is shown to be valid for the effect and the type of compound being studied. Annex IX stipulates that the validity of a QSAR can be established if:

- (1) the scientific validity of the (Q)SAR model can be established;
- (2) the substance falls within the domain of the model;
- (3) the results are adequate for the purpose used;
- (4) adequate and reliable documentation is provided.

The further elaboration of guidance on establishing the validity of QSARs will be based on the OECD criteria and further elaboration on documenting transparently the results of the application of these criteria.

The next section examines some of the challenges faced by the Commission in developing guidance for implementing Annex IX in REACH.

4. THE CHALLENGE OF “INTEGRATED TESTING STRATEGIES”

REACH therefore emphasises a holistic integrated approach to the use of all available information. Therefore REACH would generally promote the usage of several methods simultaneously, rather than concentrate on one method alone. For example, the use of (Q)SAR methods could take place in the context of having established the membership of a category, having considered the existing available data of other category members and evaluated the available non validated in-vitro information to draw a conclusion using a weight of evidence approach. In such cases, the use of QSAR or in vitro data does not depend solely on the validity of these data in isolation, but also on the validity of the overall weight-of-evidence.

Some of the main challenges which Annex IX of REACH poses for the next years are:

- Challenge 1. Defining and giving (detailed) guidance on how to integrate information;

Challenge 2. Defining and giving (detailed) guidance on when information can be used for which purpose;

Challenge 3. Determining and developing which (additional or new) tools are needed to support the integration.

Annex IX and the guidance documents for implementing current legislation present (very) generic approaches which in essence state that the assessor should “use expert judgement” and apply the weight of evidence. From current legislation and OECD work a number of examples have also been worked out.

Along side a number of projects intended to develop guidance for implementing the whole of REACH, the Commission has already started the development of a guidance document for addressing the information requirements in REACH, including the application of Annex IX (called REACH Implementation Project 3.3). The work from the implementation of current legislation and OECD has thereby been used by the Commission and the many stakeholders, coming from industry, authorities, consultancies and academia, involved in the project.

A scoping study was conducted in 2005 which developed a general framework and specific approaches for 4 end-points (the results are available from: <http://ecb.jrc.it/REACH/>). The work will be continued in 2006 with the objective to develop a draft guidance document by the end of the year.

The expectations are that the RIP 3.3 will (attempt to) develop more detailed guidance filling the void between the all encompassing guidance of “use expert judgement” and the available examples.

ANNEX IX

GENERAL RULES FOR ADAPTATION OF THE STANDARD TESTING REGIME SET OUT IN ANNEXES V TO VIII

Annexes V to VIII set out the information requirements for all substances manufactured or imported in quantities of:

- 1 tonne or more in accordance with Article 11 (1) (a),
- 10 tonnes or more in accordance with Article 11 (1) (b),
- 100 tonnes or more in accordance with Article 11 (1) (c), and
- 1000 tonnes or more in accordance with Article 11 (1) (d).

In addition to the specific rules set out in Column 2 of Annexes V to VIII, a registrant may adapt the standard testing regime in accordance with the general rules set out in Section 1 of this Annex. Under evaluation competent authorities of evaluating Member States may assess these adaptations to the standard testing regime.

1. TESTING DOES NOT APPEAR SCIENTIFICALLY NECESSARY

1.1. Use of existing data

1.1.1. Data on physical-chemical properties from experiments not carried out according to GLP or the test methods referred to in Article 12(2)

Data shall be considered to be equivalent to data generated by the corresponding test methods referred to in Article 12(2) if the following conditions are met:

- (1) adequacy for the purpose of classification and labelling and/or risk assessment,
- (2) sufficient documentation is provided to assess the adequacy of the study and
- (3) the data are valid for the endpoint being investigated and the study is performed using an acceptable level of quality assurance.

1.1.2. Data on human health and environmental properties from experiments not carried out according to GLP or the test methods referred to in Article 12(2)

Data shall be considered to be equivalent to data generated by the corresponding test methods referred to in Article 12(2) if the following conditions are met:

- (1) adequacy for the purpose of classification and labelling and/or risk assessment,
- (2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 12(2),
- (3) exposure duration comparable to or longer than the corresponding test methods referred to in Article 12(2) if exposure duration is a relevant parameter, and

- (4) adequate and reliable documentation of the study is provided

1.1.3. Historical human data

Historical human data, such as epidemiological studies on exposed populations, accidental or occupational exposure data and clinical studies, shall be considered.

The strength of the data for a specific health effect depends, among other things, on the type of analysis and on the parameters covered and on the magnitude and specificity of the response and consequently the predictability of the effect. Criteria for assessing the adequacy of the data include:

- (1) the proper selection and characterisation of the exposed and control groups,
- (2) adequate characterisation of exposure,
- (3) sufficient length of follow-up for disease occurrence,
- (4) valid method for observing an effect,
- (5) proper consideration of bias and confounding factors, and
- (6) a reasonable statistical reliability to justify the conclusion.

In all cases adequate and reliable documentation shall be provided.

1.2. Weight of evidence

There may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion.

There may be sufficient weight of evidence from the use of newly developed test methods, not yet included in the test methods referred to in Article 12(2) or from an international test method recognised by the Commission or the Agency as being equivalent, leading to the conclusion that a substance has or has not a particular dangerous property.

Where sufficient weight of evidence for the presence or absence of a particular dangerous property is available:

- further testing on vertebrate animals for that property shall be omitted,
- further testing not involving vertebrate animals may be omitted.

In all cases adequate and reliable documentation shall be provided.

1.3. Structure-activity relationship (SAR)

Results obtained from valid qualitative or quantitative structure-activity relationship models ((Q)SARs) may indicate the presence or absence of a certain dangerous property. Results of (Q)SARs may be used instead of testing when the following conditions are met:

- results are derived from a (Q)SAR model whose scientific validity has been established,
- the substance falls within the applicability domain of the (Q)SAR model,
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied method is provided.

The Agency in collaboration with the Commission, Member States and interested parties shall develop and provide guidance in assessing which (Q)SARs will meet these conditions and provide examples.

1.4. In vitro methods

Results obtained from suitable *in vitro* methods may indicate the presence of a certain dangerous property or may be important in relation to a mechanistic understanding, which may be important for the assessment. In this context, "suitable" means sufficiently well developed according to internationally agreed test development criteria (e.g. the ECVAM criteria for the entry of a test into the prevalidation process). Depending on the potential risk, immediate confirmation requiring testing beyond the information foreseen in Annex V or VI or proposed confirmation requiring testing beyond the information foreseen in Annex VII or VIII for the respective tonnage level may be necessary.

If the results obtained from the use of such *in vitro* methods do not indicate a certain dangerous property, the relevant test shall nevertheless be carried out at the appropriate tonnage level to confirm the negative result, unless testing is not required in accordance with Annexes V to VIII or the other rules in Annex IX.

Such confirmation may be waived, if the following conditions are met:

- (1) results are derived from an *in vitro* method whose scientific validity has been established by a validation study, according to internationally agreed validation principles,
- (2) results are adequate for the purpose of classification and labelling and/or risk assessment, and
- (3) adequate and reliable documentation of the applied method is provided.

1.5. Grouping of substances and read-across approach

Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or "category" of substances. Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for a reference substance within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint.

The similarities may be based on:

- (1) a common functional group,
- (2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals, or

- (3) a constant pattern in the changing of the potency of the properties across the category.

If the group concept is applied, substances shall be classified and labelled on this basis.

In all cases results should:

- be adequate for the purpose of classification and labelling and/or risk assessment,
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 12(2)
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 12(2) if exposure duration is a relevant parameter, and
- adequate and reliable documentation of the applied method shall be provided.

2. TESTING IS TECHNICALLY NOT POSSIBLE

Testing for a specific endpoint may be omitted, if it is technically not possible to conduct the study as a consequence of the properties of the substance: e.g. very volatile, highly reactive or unstable substances cannot be used, mixing of the substance with water may cause danger of fire or explosion or the radio-labelling of the substance required in certain studies may not be possible. The guidance given in the test methods referred to in Article 12(2), more specifically on the technical limitations of a specific method, shall always be respected.

3. SUBSTANCE-TAILORED EXPOSURE-DRIVEN TESTING

- 3.1 Testing in accordance with Annex VI, section 6.6 and 6.7, Annexes VII and VIII may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report.
- 3.2 In all cases, adequate justification and documentation shall be provided. The justification shall be based on an exposure assessment in accordance with Annex I, section 5, and be consistent with the criteria adopted pursuant to paragraph 3.2bis, and the specific conditions of use must be communicated through the chemical supply chain in accordance with Articles 29 or 30.
- 3.2bis. The Commission shall adopt criteria defining what constitutes adequate justification under Section 2 in accordance with Article 130(3) within 18 months of entry into force of this Regulation.