3 The REACH regulation

3.1 REACH in general

REACH is a new European Community Regulation on chemicals and their safe use. It entered into force on June 1st 2007 and introduced an integrated system for Registration, Evaluation, Authorisation and Restriction of Chemical substances [25].

REACH replaces about 40 pieces of legislation with a streamlined and improved regulation, aiming at filling the gaps and solving some problems linked to the current system.

The aims of REACH are to:

- improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances;
- maintain and enhance innovative capability and competitiveness of the EU chemicals industry (the current 10 kg threshold for registration discouraged research and invention on new substances and favoured the development and use of existing substances over new ones);
- prevent fragmentation and ensure the free circulation of substances on the internal market of the European Union;
- promote alternative methods for the assessment of hazards of substances;
- facilitate data sharing in order to reduce tests on vertebrate animals and to reduce costs to industry. In fact, new tests are only required when it is not possible to provide information in any other permitted way and data gained by vertebrate animal testing are to be shared, in exchange for payment. Information not involving tests on vertebrates animals (e.g. in vitro studies or QSARs) must be shared on the request of a potential registrant.

The new law imposes the general obligation for manufacturers and importers of substances to submit a registration to the ECHA for each substance manufactured or imported to the European Countries in quantities of 1 tonne or above per year. ECHA is the European Chemical Agency in Helsinki and it will manage and in some cases carry out the technical, scientific and administrative aspects of the REACH system at Community level, aiming to ensure that REACH functions well and has credibility with all stakeholders.

REACH covers all substances whether manufactured, imported, used as intermediates or placed on the market, either on their own, in preparations or in articles, unless they are radioactive, subject to customs supervision, or are non-isolated intermediates. Waste is specifically excepted. Food is not subject to REACH as it is not a substance, preparation or article. Member States may exempt substances used in the interest of defence. Other substances are exempted from parts of REACH, where other equivalent legislation applies.

A single regulatory system will be created that divides substances into two different categories: non-phase-in substances, i.e. those not produced or marketed prior to the entry into force of REACH, and phase-in substances that are those substances listed in the EINECS, or those that have been manufactured in the Community, but not placed on the Community market, in the last 15 years or the so-called “no longer polymers” of Directive 67/548.

As the acronym REACH indicates, the basic elements of the new regulation are four, Registration, Evaluation, Authorisation and Restriction of Chemical substances.

3.1.1 Registration

As mentioned above, there is the general obligation for manufacturers and importers to submit a registration to the European Chemical Agency for each substance manufactured or imported in quantities of 1 tonne or above per year. Failure to register means that the substance is not allowed to be manufactured or imported. Registrants have to submit a technical dossier, which contains some general information about both the substance (i.e. identity, information about the manufacture and the uses, classification and labelling, etc.) and the manufacturer or importer. In addition, registrants have to submit a chemical safety report (CSR) for the registration of substances that are produced or imported in quantities of 10 or more tonnes per year, where risks measures are defined. This report contains information on the different exposure scenarios linked to the different uses of the substance and it needs to point out the adequate measures for the risk assessment focused on the substance.

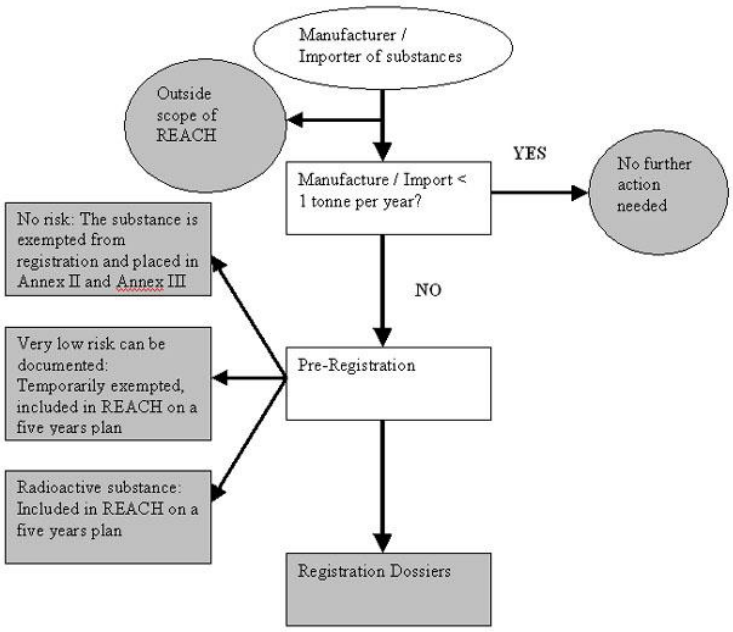

Figura 17: Scheme of the REACH registration process.

3.1.2 Evaluation

The Agency is responsible for performing the evaluation procedure. There are two types of evaluation with different aims: the dossier evaluation, on the one hand, and the substance evaluation, on the other hand. In the first case, the Agency checks the compliance of the registration dossier with the registration requirements and evaluate testing proposals made by industry, in order to prevent unnecessary animal testing, i.e. the repetition of existing tests and poor quality tests. In the second case, substances will be evaluated on the basis of considerations about risks, exposure and tonnage.

The Agency in co-ordination with the Competent Authorities of Member States may clarify suspicions of risks to human health or the environment by requesting further information from industry.

Evaluation may lead authorities to the conclusion that action needs to be taken under the restrictions or authorisation procedures in REACH, or that information needs to be passed on to other authorities responsible for relevant legislation. The evaluation process will ensure that reliable and useful data is provided and made available to the relevant bodies by the Agency.

3.1.3 Authorization

For substances of very high concern, an authorisation is required for their use and their placing on the market. This procedure aims at substituting the most dangerous substances and better managing risks coming from or linked to specific uses.

The substances required to be authorised are CMR substances (Carcinogenic, Mutagenic or toxic to Reproduction), PBT substances (Persistent, Bioaccumulative and Toxic), vPvBs (very Persistent, very Bioaccumulative substance), and substances identified from scientific evidence as causing probable serious and normally irreversible effects to humans or the environment, equivalent to the previous ones, on a case-by-case basis, as endocrine disrupters.

The authorization application is to be submitted to the Agency, by manufacturers, importers and/or downstream users of a specific substance.

The Commission is responsible for the granting and the rejection of the authorization. Authorization is granted if the risks for human health and the environment coming from the use of a specific substance is adequately controlled. If the risks cannot be controlled, the authorization would be granted if the socio-economic benefits of their use outweigh the risks for human health and the environment and if there are not any safer suitable alternative substances or technologies. If there are, the applicants must prepare substitution plans, if not, they should provide information on research and development activities, if appropriate. The Commission may amend or withdraw any authorisation on review if suitable substitutes become available.

3.1.4 Restrictions

The restriction provisions act as the safety net for the system because they are applied to any substance on its own, in a preparation or in an article where there is an acceptable risk to health or the environment. This procedure regulates Community conditions for the manufacture, placing on the market or use of such substances and eventually forbids any of these activities if necessary.

Proposals for restrictions will be prepared by Member States or by the Agency on behalf of the Commission in the form of a structured dossier.

Reporting a brief cost and benefit analysis of REACH, it is possible to claim that the introduction of the new regulation would have some relevant benefits, such as:

- positive occupational impact;
- positive public health impact: a deeper knowledge about chemicals, hazards and more controls will help better implementation on existing legislation. According to World Bank estimates, diseases caused by chemicals were assumed to account for some 1% of the overall burden of all types of disease in the EU. Assuming a 10% reduction in these diseases

as a result of REACH would result in a 0.1% reduction in the overall burden of disease in the EU. This would be equivalent to around 4,500 deaths due to cancer being avoided every year;

- positive environment impact: thanks to REACH, current chemical releases to the environment and exposure of humans via the environment can be reduced. A recent study commissioned by DG Environment illustrated that the long-term benefits of REACH would be significant, because its introduction will contribute to reduce pollution of air, water and soil as well as to reduce pressure on biodiversity.

However, the new regulation will introduce also additional costs, as explained in the Extended Impact Assessment of the Commission's proposal. The direct costs of REACH to the chemicals industry were estimated at a total of € 2.3 billion over the first 11 years after the entry into force of the Regulation.

Assuming that the market behaves as expected with only 1-2% of substances withdrawn because their continued production would not be profitable, the additional costs to downstream users of chemicals were estimated at €0.5 – 1.3 billion in a "normal expectation" case and €1.7 – 2.9 billion in a scenario with higher substitution costs assumed.

Combining the estimates of the direct and indirect costs, the overall costs were estimated to fall in the range of €2.8 - 5.2 billion. These costs will be incurred over a period of 11 to 15 years. Therefore, from a macroeconomic perspective, the overall impact in terms of the reduction in the EU's Gross Domestic Product (GDP) is expected to be very limited.

Finally, a further work on the REACH Impact Assessment together with industry and monitored by all stakeholders was conducted by the Commission and some relevant conclusions have been drawn:

- There is limited evidence that higher volume substances are vulnerable to withdrawal following the REACH registration requirements. However, lower volume substances under 100 tonnes are most vulnerable to being made less or non profitable by the REACH requirements.
- There is limited evidence that downstream users will be faced with a withdrawal of substances of greatest technical importance to them.
- SMEs can be particularly affected by REACH having regard to their more limited financial capacity and lower market power in terms of passing on costs.
- Companies have recognised some business benefits from REACH [9].

3.2 REACH focusing on QSARs

In the ideal situation, QSAR results can be used on their own for regulatory purposes if they are considered relevant, reliable and adequate for the purpose, and if they are documented in an appropriate manner. In practice, there may be uncertainty in one or more of these aspects, but this does not preclude the use of QSAR estimate in the context of a Weight of Evidence approach, in which additional information compensates for uncertainties resulting from the lack of information on the QSAR [7].

A number of conditions need to be met in order for QSAR results to provide an acceptable alternative to experimental data.

There is widespread agreement that models should be scientifically valid if they are to be used in the regulatory assessment of chemicals; since the concept of validation is incorporated into legal texts and regulatory guidelines, it is important to clearly define what it means, and to describe what the validation process might entail.

For the purposes of REACH, an assessment of QSAR model validity should be performed by reference to the internationally agreed OECD principles for the validation of QSARs.

The validation exercise itself may be carried out by any person or organization, but it will be the industry registrant of the chemical who needs to argue the case for using the QSAR data in the context of the Registration process. This is consistent with a key principle of REACH that the responsibility for demonstrating the safe use of chemicals lies with industry.

The principles for QSAR validation identify the types of information that are considered useful for the assessment of QSARs for regulatory purposes; however, fixed criteria will be difficult, if not impossible, to define in a pragmatic way, given the highly context-dependent framework in which non-testing data will be used. Instead, experience and common understanding should be gained by learning-by-doing approach, and by documenting the learning.

Under REACH, there will be no formal adoption process for QSARs; the information generated on the characteristics of a QSAR model will be used as the basis for deciding whether the information on the substance, taken as a whole, is adequate for the regulatory purpose. This process will therefore involve an initial acceptance of the data (including non-testing data) by the industry registrant and the subsequent evaluation, on a case-by-case basis, by the authorities.

The OECD Principles for QSAR validation state that in order "to facilitate the consideration of a QSAR model for regulatory purposes, it should be associated with the following information:

1. A defined endpoint;
2. An unambiguous algorithm;
3. A defined domain of applicability;
4. Appropriate measures of goodness-of-fit robustness and predictivity;
5. A mechanistic interpretation, if possible."

3.2.1 Validity of QSAR model

According to the OECD Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment, the term validation is defined as "…the process by which the reliability and relevance of a particular approach, method, process or assessment is established for a defined purpose".

In the context of QSARs, this definition is rather abstract and difficult to interpret in relation to the OECD validation principles; thus, for the practical validation of QSAR models intended for use in the regulatory assessment of chemicals, the following operational definition has been proposed: "the validation of a QSAR is the process by which the performance and mechanistic interpretation of a model are assessed for a particular purpose."

In this definition, the performance of a model refers to its goodness-of-fit, robustness and predictive ability, whereas purpose refers to the scientific purpose of the QSAR, as expressed by the defined endpoint and applicability domain. So a QSAR can be valid, because the model has a scientific relevance, without being relevant for a given regulatory purpose: in fact, the regulatory relevance of the model expresses the usefulness of the predicted endpoint in relation to the information needed for the regulatory purpose.

3.2.2 Reliability of QSAR prediction

A valid QSAR will be associated with at least one defined applicability domain in which the model makes estimations with a defined level of accuracy (reliability): when applied to chemicals within its applicability domain, the model is considered to give reliable results. There is no unique measure of model reliability, in fact it should be regarded as a relative concept, depending on the context in which the model is applied.

However, it is always important to wonder if a specific QSAR is appropriate for the compound of interest. This means firstly to consider if the chemical of interest is within the scope of the model, according to the defined applicability domain. Clearly, the more explicit the definition of the model domain, the easier it will be to answer. The second consideration consists in evaluating the suitability of the defined applicability domain for the regulatory purpose. This question arises because most currently available models were not tailor-made for current regulatory needs and inevitably incorporate biases which may or may not be useful, depending on the context of prediction. Such biases do not affect the validity of the model, but they affect its applicability for specific purposes. The third aspect to be considered is how well the model predicts chemicals that are similar to the substance of interest. This question provides a simple way of checking whether a model is appropriate by checking its predictive capability for one or more analogous compounds that are similar to the one of interest and for which measured values exist. Finally, it is important to assess if the model estimate is reasonable, taking into account other information. This inevitably implies an expert judgment, which should be clearly rationalized.

3.2.3 Adequacy of QSAR prediction

In order for a QSAR result to be adequate for a given regulatory purpose, the following conditions must be fulfilled:

- the estimate should be generated by a valid (relevant and reliable) model;
- the model should be applicable to the chemical of interest with the necessary level of reliability;
- the model endpoint should be relevant for the regulatory purpose.

When applying these conditions in the context of a chemical assessment, it is also necessary to consider the completeness of the overall information.

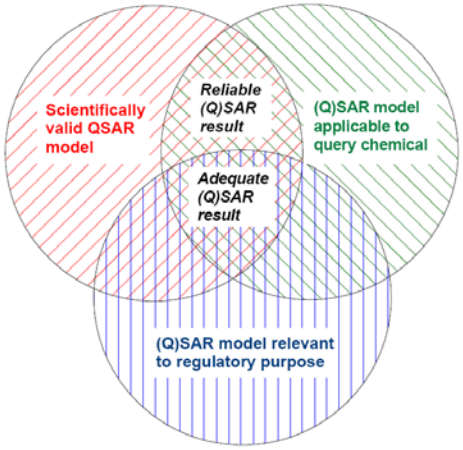

Figure 18: Interrelated concepts of QSAR validity, reliability, applicability, adequacy, regulatory relevance. The circles refer to (Q)SAR models whereas the intersections refer to (Q)SAR results with certain features. In order for a (Q)SAR result to be reliable for a given chemical, it should be generated by a scientifically valid (Q)SAR that is also applicable to the chemical of interest. This (Q)SAR estimate may or may not be adequate (fit for purpose), depending on whether the endpoint predicted is relevant to the particular regulatory purpose, and whether the estimate is sufficiently reliable for that purpose.

Finally, if a registrant intend to use QSAR data instead of experimental data, the adequacy of the QSAR result should be documented by using the appropriate QSAR Reporting Formats. Different types of QSAR Reporting Formats (QRFs) are being developed to provide a standard framework for summarizing and structuring key information about QSAR models and their predictions. In the first one, the QSAR Model Reporting Format (QMRF), it is stored the description of a particular QSAR model (i.e. description of the algorithm, of its development and validation based on the OECD principles). The second one, the QSAR Prediction Reporting Format (QPRF) explains how an estimate has been derived by applying a specific model or method to a specific substance (i.e. information on the endpoint, identities of close analogues, etc.). The last one, Totality of Evidence Reporting Format (TERF) or Weight of Evidence Reporting Format (WERF), has not been developed yet, but it will be useful to integrate the QSAR estimates with other sources of information based on Weight of Evidence considerations.