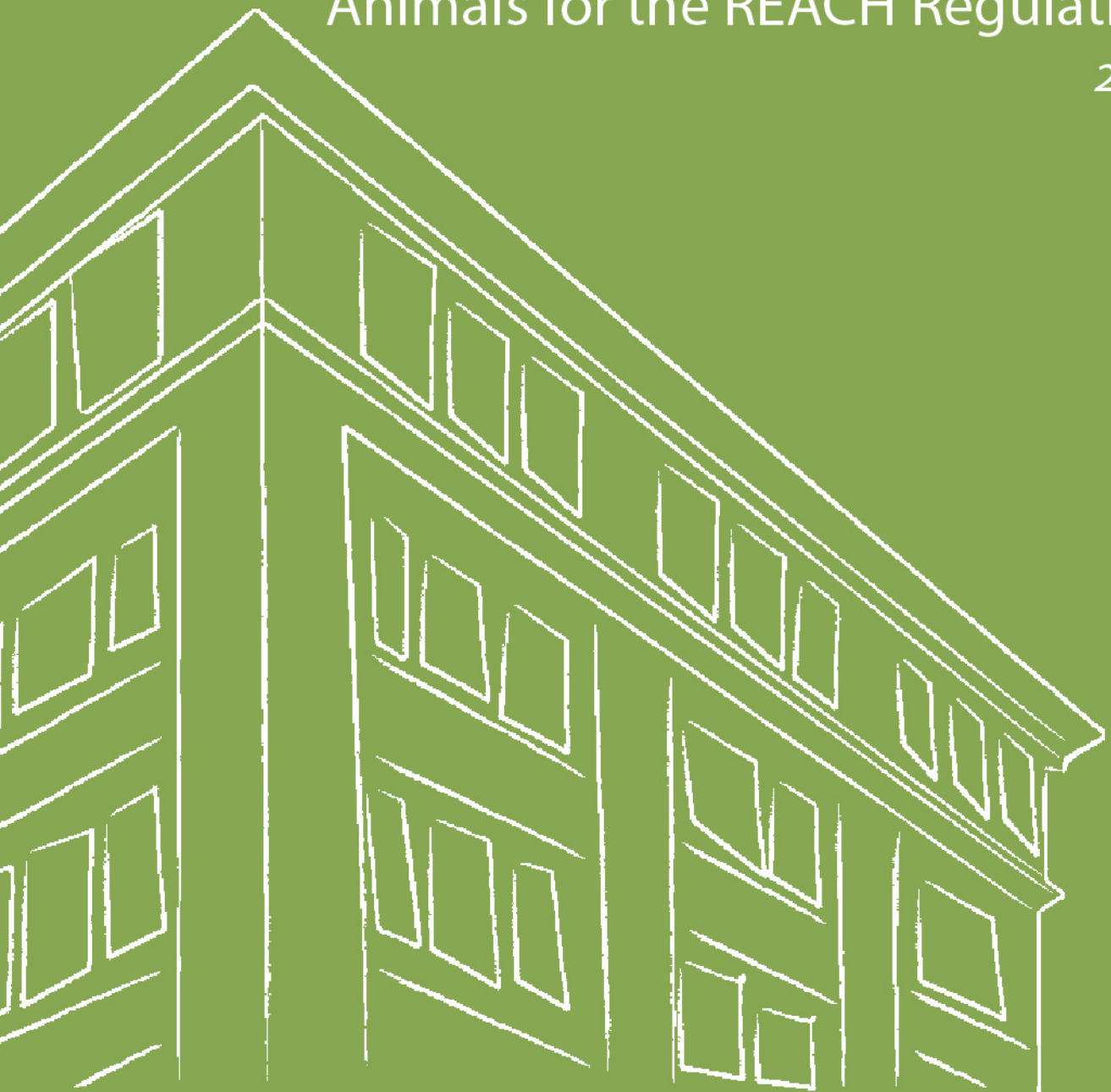
ECHA
European Chemicals Agency

The Use of Alternatives to Testing on Animals for the REACH Regulation

2011



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Corrigenda

Figure 7 (page 31); Table 6 (page 63); Figure 14 (page 42) have been amended.

The Use of Alternatives to Testing on Animals for the REACH Regulation 2011

Reference: ECHA-11-R-004.2-EN
ISBN-13: 978-92-95035-96-6
Publ.date: 29/07/2011
Language: EN

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Foreword by the Executive Director

One of the fundamental aims of the REACH Regulation – the most ambitious chemicals legislation in the world – was to understand better and more thoroughly, the impact of chemicals on human health and the environment. That in turn means that industry can make decisions in order to manage the risks posed more effectively and that we all, as workers and consumers, can make more informed decisions about the chemicals that we use daily.

To understand the impact of chemicals better, we need reliable hazard and exposure information which demonstrates that they can be used safely. The hazard data has been traditionally generated through experimental animal testing but there are a number of other ways – by comparing substances with similar ones; by grouping them together into logical categories; by doing specialised computer modelling; by using weight of evidence; by using a validated alternative test; and, therefore, testing them on live animals should be seen as a last resort.

The REACH Regulation is clear that every effort must be made so that testing chemicals on animals is truly a last resort – when there is no other scientifically reliable way of showing the impact on humans or the environment. REACH also demands that companies in possession of data on a chemical must share it (and share the cost) with any other companies making the same substance, thereby removing the potential for duplicate testing.

This report is a legal requirement of REACH – ECHA needs to report to the European Commission every three years on how companies are using alternatives to testing on animals to provide the information demanded by the Regulation on the chemical substances that they produce or import. I am conscious that, although this report is formally addressed to the European Commission, it is of interest and will be read by many others. In order to make what is essentially a very technical subject accessible to a wider audience, we have also produced a short summary which is available in 22 EU languages.

This is the first such report and demonstrates the Agency's experience based largely on registration dossiers that were submitted for the first deadline in 2010. In many ways it is too early to give an accurate picture because, as yet, relatively few dossiers have been evaluated by our in-house scientists. Nevertheless, this report clearly shows that companies have shared data or made extensive use of the alternative methods available so as to avoid the need to test chemicals on animals, which is positive. The report provides detailed information on the methods they have chosen to generate the data for the so-called "endpoints" – the intrinsic properties of chemicals for which traditionally tests on animals were used such as: effects on the developing foetus; acute toxicity (the impact of a single high dose); chronic toxicity (the impact of a low level but longer term exposure); and the bioaccumulation of substances in aquatic animals like fish.

The use of alternative methods is a work in progress. I take this opportunity to thank companies for taking this aspect of REACH so seriously – and urge them to reflect on the justifications that they have provided for using alternative methods and to improve them where they can. Companies - the registration dossiers you submitted are yours and you can and indeed must update them at any time if you have new information to give.

I welcome the continued work of the European Commission and others to introduce a pragmatic approach to reducing experimentation on live animals and on the introduction of validated alternatives. Although REACH is European legislation, the work to have safer chemicals and find alternatives to testing on animals is truly international and we in ECHA are proud to play our part in that.

Thank you and I hope that you will find the report of interest.

Geert Dancet, Executive Director

Executive Summary

One of the objectives of the REACH Regulation is to promote non-animal test methods. This is the first report written by the European Chemicals Agency (ECHA) to the European Commission since REACH came into effect which provides the latest information on the status of non-animal test methods and alternative testing strategies used to generate information for registration purposes. The aim of this report is to describe to the extent to which registrants used non-animal test methods within their registration dossiers to fulfil the information requirements stated in Annexes VII to VIII of the legislation and to what extent they have proposed to use such approaches for the higher-tier studies of Annexes IX and X. The Agency will prepare such a report every three years.

The 24 560 registration dossiers successfully submitted by registrants from 1 June 2008 until 28 February 2011 have been used as the source of data for this report. The relevant information in the registration dossiers has been identified, extracted and analysed using specifically-developed data extraction tools which have been applied to data stored in ECHA's IUCLID database. The data-sharing mechanism has been analysed using both information from the inquiry process and by analysing the data in the dossiers of Lead Registrants versus that in dossiers submitted jointly (i.e. where there is more than one registrant per substance). Data extraction tools were also used to analyse how registrants applied *adaptations of the standard information requirements* that are used to account for the use of non-standard information on the properties of their substances. The focus is on those dossiers with the greatest amount of data, i.e. substances imported or manufactured in volumes at or above 100 tonnes per year. In line with the purpose of the report, only hazard endpoints that may require testing on vertebrate animals were investigated. The number and content of testing proposals in registration dossiers have also been analysed for all tonnage levels.

Data sharing is a core principle of REACH and one of its aims is to require that testing in vertebrate animals is not repeated. Registrants use the data sharing mechanism to avoid unnecessary animal testing. The legislation provides several mechanisms to ensure the sharing of data: companies may need to inquire if data has already been submitted on their substance; share information from animal studies and, with some exceptions, submit joint registration dossiers with other registrants for the same substance.

Potential registrants of so called non-phase-in substances or of phase-in substances not pre-registered must inquire of ECHA whether a registration has been made for the same substance, with a view to sharing data. The inquiry process ensures the sharing of existing data between registrants of the same substance. For non-phase-in substances and for phase-in substances not pre-registered, the inquiry process ensures the sharing of existing data between registrants of the same substance. The Agency has successfully processed almost 1 500 inquiries made by potential registrants, and of these, about 50 % have led to registration afterwards.

For phase-in substances, each legal entity that has pre-registered on time and wishes to then register the substance does so by submitting a dossier to ECHA. If there is more than one registrant for the same substance, the registrants must form a substance information exchange forum (SIEF), to collect and share data. The Lead Registrant submits a dossier with the joint information, describing properties and hazards of the substance, and other SIEF participants submit member dossiers with their company-specific information.

The joint submission of information worked well in general as shown by the proportion of total registrations submitted jointly: nearly 90% of the total number, the remaining part also covering individual submissions of non-phase-in substances. From nearly 3000 joint submissions containing almost 20 000 member dossiers, there were only 135 member dossiers with opt-outs for one or more end-points as described in Articles 11(3) and 19(2) of

REACH. An overview of the main reasons for opt-outs is provided in the report 'The Operation of REACH and CLP 2011' provided in accordance with Article 117 (2) of REACH.

However, a more detailed analysis reveals that in some cases the registrants, instead of opting out, within the joint submission, instead submitted separate registration dossiers. For about 250 substances, ECHA received either multiple joint submissions or, in addition to the joint submissions, one or more individual submissions on the same substance. ECHA is currently examining the explanations for these situations.

The sharing and joint submission of information generally worked and the registrants used it to fulfil the information requirements and to avoid unnecessary animal testing. However, the number of separate registration dossiers for the same substances indicate that the sharing and joint submission of information still needs further improvement.

Registrants also made full use of the adaptation possibilities provided by the legislation. The standard information required for registration comprises a number of hazard endpoints (such as repeat-dose toxicity and irritation effects) which are usually based on information from standard experimental studies with vertebrate animals. The standard data requirements are linked to the tonnage of the substance and are listed in Annexes VII to X of the legislation. *Core data* are those specified in Annexes VII and VIII and higher-tier data, as specified in Annexes IX and X. If data gaps have been identified and cannot be filled otherwise, studies may need to be conducted. In the case of missing *higher-tier data,* a testing proposal has to be submitted by the Lead Registrant. This report focuses on 15 endpoints that may require studies on vertebrate animals.

Information on each endpoint for a substance is included in an endpoint study record (ESR) within the registration dossier. Data from ESRs available in ECHA´s database have been analysed in two ways for this report. The first is to sum the total number of endpoint study records in Lead Registrant and stand-alone dossiers (i.e. summing up all available information over all dossiers and substances within the scope of this report). A second type of analysis gives an insight to the relative proportions of either experimental studies, testing proposals or alternative methods used by the registrants when fulfilling the information requirements for substances at or above 1 000 tonnes per year. When considering these two ways of presenting the findings, it is important to understand that the ESRs are provided by registrants and the quality of the contents of these ESRs were not scrutinised by the Agency.

Any deficiencies identified during the compliance checks that are part of dossier evaluation and could result in the Agency requesting further studies on vertebrate animals are not included in this report.

For substances at or above 100 tonnes per annum, the ESR data show that registrants used data from studies conducted prior to the entry into force of REACH as the main source of information to meet both the core and higher tier information requirements. Especially for longer-term animal studies, the second most common means of fulfilling the information requirements was predicting substance properties by *read-across*. Other adaptations of the standard testing requirements were also used to justify omitting studies. The use of these options varied between endpoints. When assessing the available information for all relevant substances it became clear that a higher proportion of substances had experimental studies for acute toxicity than were available for higher-tier toxicological endpoints (e.g. reproduction toxicity and repeat-dose toxicity). For a number of toxicological endpoints required by REACH there are accepted *in vitro* tests that can be used instead of the corresponding animal study. Hence, for these endpoints the *in vitro* studies are presented separately to the data on animal studies.

Annexes IX and X include those information requirements that involve testing on a large number of vertebrate animals and that are also the most expensive. Before embarking on such testing, registrants have to submit a testing proposal to ECHA. When a testing proposal concerns a study involving vertebrate animals, ECHA publishes the name of the substance

and the hazard endpoint for which testing is proposed on its website and invites third parties to submit existing scientifically valid information, with a view to avoid the need for conducting a new study. The Agency has to examine and decide on all testing proposals before registrants can initiate such studies on vertebrate animals.

Fewer testing proposals for the higher-tier endpoints have been submitted than had been anticipated based on previous estimates from the European Commission or from interested scientists. This lower number of testing proposals is due, at least in part, to registrants using the *read across* or *category approach* to fill data gaps for these higher-tier studies, i.e. a study on one substance to cover information requirements for another, or multiple substances. Between 2008 and February 2011, the Agency received registration for 3 308 phase-in and 1 347 non-phase-in substances (at all tonnages). Testing proposals were made in 574 dossiers covering a total of 1 175 tests, of which 711 were vertebrate animal studies. The totals include 78 substances that were submitted as category dossiers, covering 17 chemical categories and testing proposals for 104 animal studies.

It seems reasonable to conclude that in general registrants have first considered other options to meet the higher-tier data requirements, before resorting to a testing proposal.

Based on the data with a reference year of 2009 or later, the dossiers analysed demonstrate that companies carried out relatively few new studies for their registration dossiers. In total, 3 340 such studies have been conducted, of which 1 849 involved tests on vertebrate animals. In total 107 higher tier studies appeared to be conducted in the absence of testing proposals. This information will be further analysed in future compliance checks.

Results from dossier evaluation conducted as part of compliance checks show that the use of read-across and category prediction methods are often not well-justified. In addition, the experimental data provided in the dossiers are in some cases also not sufficient to meet information requirements under REACH. Further analysis of the submitted data and the outcomes of compliance checks in the future will enable ECHA and stakeholders to develop a better understanding of the reliability of animal and non-animal test methods used by registrants so far. Currently it is expected that more animal testing will need to be requested by ECHA to ensure the safe use of chemical substances.

The Agency has disseminated the endpoint information from the registrations and will continue to do so whenever registrants submit new data either spontaneously or after the evaluation decisions. This will assist future registrants as they may be able to predict the properties of their substance by read-across to existing data on analogus substances. The amount and quality of disseminated information will increase as more substances are registered and registrants undertake the higher-tier studies after testing proposals are approved and occasional extra studies on registered substances are conducted as an outcome of compliance checks or other REACH processes such as substance evaluation.

This report provides, for the first time, an overall insight into the options the registrants followed to meet the information requirements under REACH. Based on these findings, ECHA will continue with efforts to facilitate the use of non-animal test methods by actively informing registrants about alternatives for animal testing and their use via guidance documents, awareness raising campaigns, events, the Helpdesk, special services for Lead Registrants, and through the dissemination website.

Preface

This report is intended to meet ECHA's legal obligation under Article 117(3) of the REACH Regulation which states that: "Pursuant to Article 117(3) of the REACH Regulation, every three years the Agency, in accordance with the objective of promoting non-animal test methods, shall submit to the Commission a report on the status of implementation and use of non-animal test methods and testing strategies used to generate information on intrinsic properties and for risk assessment to meet the requirements of this Regulation." The primary source of information for this report is that available to ECHA in the registration dossiers submitted by manufacturers and importers. The results of ECHA's dossier evaluations (compliance checks and examinations of testing proposals) is another source of information but relates only to a fraction of the dossiers submitted.

This report analyses the data submitted by registrants with a view to describing the extent to which alternative test methods and test strategies have been used. This analysis is complemented by the observations obtained from dossier evaluation. Such findings are also reported by ECHA in its annual evaluation progress report. Pursuant to Article 54 of the REACH Regulation, an evaluation progress report is published in February each year.

This report was submitted to the Commission in parallel with the first report by ECHA on the operation of the REACH Regulation in accordance with Article 117(2) thereof.

These reports contribute to the monitoring of the implementation of the REACH Regulation and are intended to provide useful information for the Commission when reviewing the legislation.

List of abbreviations

CASPER IT	Characterisation Application for Selection, Prioritisation, Evaluation
CLP	Classification, Labelling and Packaging
CMR	Carcinogenic, Mutagenic, Reprotoxic
Commission	European Commission
DG JRC	Directorate General Joint Research Centre
DSD	Dangerous Substances Directive
ECHA	European Chemicals Agency
ECVAM	European Centre for the Validation of Alternative Methods
EFSA	European Food Safety Authority
EINECS	European Inventory of Existing Commercial Chemical Substances
EMA	European Medicines Agency
ESR	Endpoint Study Record
EU	European Union
GLP	Good Laboratory Practice
ICAPO	International Council on Animal Protection
IUCLID	International Uniform Chemical Information Database
MS	Member State
MSC	Member State Committee
MSCA	Member State Competent Authority
NONS	Notified Substances (substances already notified in accordance with Directive 67/548/EEC that are considered as registered according to Art. 24 of REACH)
OECD	Organisation for Economic Cooperation and Development
PARERE	Preliminary Analysis of Regulatory Relevance
PPORD	Product and Process Oriented Research and Development
QSAR	Quantitative Structure-Activity Relationships
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
REACH-IT	REACH-IT is the central IT system providing support for REACH
SIEF	Substance Information Exchange Forum
TCC	Technical Completeness Check
TG	Test guideline
TMR	Test Methods Regulation
TSAR	Tracking System for Alternative test methods Review, Validation and Approval in the Context of EU Regulations on Chemicals

List of the terms (glossary)

Alternative test: alternative techniques that can provide the same level of information as current animal tests, but which use fewer animals, cause less suffering or avoid the use of animals completely. Such methods, as they become available, must be considered wherever possible for hazard characterisation and consequent classification and labelling for intrinsic hazards and chemical safety assessment.

Endpoint study record: IUCLID format of the technical dossier used to report study summaries and robust study summaries of the information derived for the specific endpoint according to Annexes VII to XI of the REACH Regulation.

Endpoint: an observable or measurable inherent property/data point of a chemical substance. It can for example refer to a physical-chemical property like vapour pressure or to degradability or to a biological effect that a given substance has on human health or the environment, e.g. carcinogenicity, irritation, aquatic toxicity.

Hazard: a property or set of properties of the chemical substance that may cause an adverse health or ecological effect provided if there is an exposure at a sufficient level.

***In vitro* test:** literally stands for “in glass” or “in tube”, refers to the test taking place outside of the body of an organism, usually involving isolated organs, tissues, cells, or biochemical systems.

***In vivo* test:** a test conducted within a living organism.

IUCLID flag: an option used in the IUCLID software to indicate submitted data type (e.g. experimental data) or their use for regulatory purposes (e.g. confidentiality).

Prediction model: a theoretical formula, algorithm or program used to convert the experimental results obtained by using a test method into a prediction of the toxic property/effect of the chemical substance.

QSARs and SARs (Q(SAR)): theoretical models that can be used to predict in a quantitative or qualitative manner the physicochemical, biological (e.g. (eco)toxicological) and environmental fate properties of compounds from knowledge of their chemical structure. A SAR is a qualitative relationship that relates a (sub)structure to the presence or absence of a property or activity of interest. A QSAR is a mathematical model relating one or more quantitative parameters, which are derived from the chemical structure, to a quantitative measure of a property or activity.

Test (or assay): an experimental system set up to obtain information on the intrinsic properties or adverse effects of a chemical substance.

Validated test: a test for which its performance characteristics, advantages, and limitations have been adequately determined for a specific purpose.

Validation: the process by which the reliability and relevance of a test method are evaluated for the purpose of supporting a specific use.

Vertebrate animal: animals that belong to the subphylum *Vertebrata*, chordates with backbones and spinal columns.

List of legislation

CLP Regulation	Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures
DSD	Dangerous Substances Directive; Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances
Existing Substances Regulation	Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances
Good Laboratory Practice	Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (codified version)
Protection of animals	Directive 2010/63/EU of the European Parliament and of The Council of 22 September 2010 on the protection of animals used for scientific purposes
	Council Directive of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86/609/EEC)
REACH Regulation	Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC
Test Methods Regulation	Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

1 General

1.1 Background

One of the main reasons for developing and adopting the REACH Regulation was that a large number of substances have been manufactured and placed on the market in Europe for many years, sometimes in very high amounts, and yet there has been limited information on the hazards that they might pose to human health and the environment. It was considered that there is a need to fill these information gaps which would help to ensure that industry is able to assess hazards and risks, and to identify and implement the necessary risk management measures in order to protect human health and the environment.

It has been known and accepted since the drafting of the REACH Regulation that the need to fill the data gaps would result in an increased use of laboratory animals for the next ten years until that goal has been reached. Nevertheless, in order to avoid unnecessary animal tests, the REACH Regulation provides mechanisms to share data and to adapt the standard information requirements and use existing data and alternative data generation approaches instead.

In particular tests on vertebrate animals may only be carried out as last resort and studies involving vertebrate animals shall not be repeated. The current scientific status still is that for some hazard endpoints, such as repeated dose toxicity or reproductive toxicity, results from animal tests will be needed although there is still the possibility to use 'read-across' study results from a tested source substance to structurally-related analogue target substance(s). This is counterbalanced by the obligation on the participants in the Substance Information Exchange Fora (SIEFs) to share available information from vertebrate tests on phase-in substances and for corresponding data sharing obligations for non-phase-in substances. The REACH Regulation also provides specific rules in Annexes VII to X (column 2) to omit animal studies in certain circumstances and general rules in Annex XI on how to adapt the standard information requirements to enable alternative methods to be used for the endpoint. In any case, it is up to the registrant to justify that alternative data are sufficient for the purpose of classification and labelling and/or risk assessment.

1.2 Standard information requirements in the REACH Regulation and the safe use of chemical substances

The principal objective of assessing the risks from the use of chemical substances is to provide a reliable basis for deciding on adequate safety measures (risk management). Any risk assessment on chemical substances comprises two distinct elements: an evaluation of the properties which are intrinsic to the substance, called hazard assessment, and an estimation of the exposure which depends on the use of the substance.

The hazard assessment identifies the hazardous intrinsic properties (e.g. sensitising, carcinogenic, toxic for the aquatic environment) and determines the potency of the chemical substance with respect to these hazardous properties. The exposure assessment identifies the sources of the substance which leads to exposure and calculates the amount taken up by an exposed organism or estimates the release of the substance into a particular compartment of the environment.

Since one of the most important measures for ensuring safe use of substances is that sufficient information on the hazardous properties is available to the manufacturers,

importers and users, REACH specifies the standard information that is required. The standard data requirements, which are linked to the tonnage of the substance, are listed in Annexes VII to X of the REACH Regulation, with core data (as required in Annexes VII and VIII) to be included in the registration at submission. If data gaps have been identified and cannot be filled otherwise, registrants will have to conduct higher-tier studies to fulfil the requirements of Annexes IX and X and only after the approval of their testing proposals by ECHA. The information requirements increase with increasing volume of the substance manufactured or imported. A higher volume of a substance is regarded as an indicator of a higher potential to cause damage to human health and/or the environment and therefore needs to be investigated more thoroughly than lower volumes. Therefore, the standard information requirements are highest for substances at or above 1 000 tonnes per annum (tpa).

1.3 The sharing and joint submission of information

The principle of 'one substance one registration' set by REACH requires that cooperation between potential registrants must be established and data must be shared and submitted jointly. This is a core principle within REACH intended to prevent duplicated testing in vertebrate animals.

According to Article 11 and Article 19 of the REACH Regulation, when a substance is intended to be registered by more than one legal entity, the information for the classification and labelling of the substance, study summaries, robust study summaries and testing proposals shall be submitted by one registrant (the Lead Registrant) acting with the agreement of the other assenting registrants. That is to say, a joint submission shall be created.

REACH distinguishes between so called non-phase-in substances and phase-in substances. In the case of non-phase-in substances, potential registrants are obliged to ascertain the availability of information they may require from any registrants of the same substance using an inquiry process operated by ECHA. For phase-in substances, the Substance Information Exchange Fora (SIEFs) should have been set up, where potential registrants of the same substance collaborate on obtaining and sharing the necessary information.

In either case outlined above, potential registrants have an obligation to request that studies involving vertebrate animals are shared. This principle applies to both phase-in and non-phase-in substances. Studies, involving testing on vertebrate animals, can only be conducted if the necessary data cannot be obtained from a registrant or potential registrant of the same substance. The test may sometimes actually be conducted at a later date, if REACH stipulates that a testing proposal shall first be submitted to ECHA.

ECHA is only obliged to step in, if an owner of a study is not willing to share the study, if the SIEF members cannot agree on sharing the costs, or if the SIEF members cannot agree on who should carry out a new study for filling data gaps.

1.4 Principal possibilities for registrants to avoid unnecessary animal tests

The REACH Regulation also provides registrants with the possibility to adapt the standard information requirements based on the specific conditions listed in column 2 of Annexes VII to X and more general conditions given in Annex XI of the Regulation. Appropriate use of these options allows registrants to avoid unnecessary testing, including vertebrate animal testing. Column 2 of the Annexes VII-X of the REACH Regulation provides endpoint specific conditions under which a test does not need to be conducted. In addition, Annex XI specifies several other options for possibilities to omit animal testing. These are when testing does not

appear to be scientifically necessary, it is technically not possible or when substance-tailored exposure-driven testing may be applied. In addition, before any new tests are carried out, all available *in vitro* data, *in vivo* data, historical human data, data from valid quantitative structure-activity relationships ((Q)SAR)s and predictions from structurally related substances (read-across of intrinsic hazard properties within groups or categories of substances) shall be assessed first by the registrant. Such alternative methods can be applied if they are scientifically valid and provide results that are adequate for classification and labelling and/or risk assessment.

However, every adaptation to the standard information requirements in column 1 of Annexes VII to X needs a valid justification based on the provisions in column 2 of the Annexes or on the provisions in Annex XI. Detailed explanations for registrants on possibilities to adapt information requirements are provided in ECHA's Practical Guide 10 *How to avoid unnecessary testing on animals*, available on ECHA's website.

Before embarking on testing for fulfilling the data requirements specified in Annexes IX and X (which include those tests requiring the largest number of vertebrate animals and which are the most expensive), the registrants have to submit a testing proposal to ECHA (see 3.7.2).

1.5 Implementation and use of non-animal testing methods: responsibilities and roles

This section describes the roles and responsibilities of different involved parties in the context of the REACH Regulation. It does not cover all other activities of national or international bodies concerned with the development, validation and assessment of alternative methods.

1.5.1 Registrants

One of the main obligations of registrants is to share data on animal tests. This has been earlier described in section 1.3. A further obligation for the registrants is to obtain data on their substances as specified in Annexes VI to X of REACH. Annex VI of REACH provides a basic four-steps procedure for fulfilling the information requirements. The procedure comprises the following steps: (i) Gather and share existing information; (ii) Consider information needs; (iii) Identify information gaps; and (iv) Generate new data/Propose testing strategy. Furthermore, testing on vertebrate animals should only be undertaken as a last resort. The principal possibilities for registrants to avoid unnecessary testing on animals have been described in section 1.4. Before embarking on testing for fulfilling the data requirements in Annexes IX and X, registrants have to submit testing proposals to ECHA. This process is further described in section 3.4.2.

It should be noted that registrants are fully responsible for the content and data quality of their registration dossiers, including the choices they make for fulfilling the standard information requirements.

Detailed explanations on duties and responsibilities of registrants are provided in *Guidance on Registration* and in Practical Guide 10 *How to avoid unnecessary testing on animals,* available on ECHA's website. This Guide brings together in one place information from a number of ECHA guidance documents.

1.5.2 ECHA

The principle of animal testing as the last resort is implemented in the REACH Annexes as described above. ECHA's role is to help registrants to implement these provisions and to promote alternative methods to animals testing. ECHA has a role to play in facilitating the

duties of the various actors in meeting the legislative requirements which balance the need to assess the risks of substances to human health and the environment and to avoid unnecessary animal testing. ECHA fulfils this role by a number of means:

- ECHA has developed a series of Guidance documents, among them, e.g. Guidance on Registration, Guidance on Information Requirements and Chemical Safety Assessment, Guidance on Data Sharing and a range of Practical Guides supporting the registrants in all their tasks.
- From June 2007 to December 2010 the ECHA Helpdesk dealt with more than 570 enquiries on information requirements, (Q)SARs, read-across, adaptation rules and testing proposals. In 2010 the ECHA Helpdesk also advised on data sharing issues in more than 150 cases. During the six months prior to the first registration deadline, the ECHA Helpdesk dealt with in excess of 5500 enquiries from companies and proactively contacted almost 500 companies.
- ECHA facilitates and promotes the formation of SIEFs to allow better data sharing for phase-in substances and runs the inquiry process for non-phase-in substances.
- ECHA organises targeted awareness raising and stakeholder support activities, including workshops, Stakeholder Days, webinars and other web-based information and tools.
- ECHA publishes the Annual Progress Reports on Evaluation, describing the progress the Agency has made in evaluating registration dossiers and provides recommendations for the registrants to improve the quality of future registrations. The first report has been published in 2009. In these reports the results of the examination of testing proposals are described in detail. ECHA has an obligation to examine all testing proposals, including the running of third party consultations for tests involving vertebrate animals. More information is provided in the section 3.4.2. Furthermore, in compliance checks, ECHA verifies whether the registration dossier is compliant with the information requirements of the REACH Regulation. This includes the evaluation of whether alternative methods or approaches used are adequate for the purpose of classification and labelling and/or risk assessment. When information is missing or not adequate, ECHA may require the registrant to submit any information needed to bring the registration into compliance with the relevant information requirements. See the section below on the role of the Member States.
- At the end of 2009, ECHA has started to publish on its website hazard and safe-use information on chemical substances that have been registered. This disseminated information allows other registrants and stakeholders the access to information formerly not available to the public. It may help future registrants to fill data gaps in their registration dossiers and may facilitate further developments of prediction methods. The number of substances for which information is available in the database will increase considerably over time as more registrations are received by ECHA. Currently the database contains more than 4000 disseminated data sets.
- Since June 2007, ECHA has published eleven News Alerts and nine Press Releases addressing questions on animal testing issues, on its website. Of particular relevance to avoid unnecessary animal testing, in 2009 ECHA has informed registrants of the possibilities to omit short-term repeated dose toxicity or screening for repeated dose/reproductive toxicity studies if they provide either the results or testing proposals for long term tests (ECHA/PR/09/13) to achieve a technically complete registration dossier.
- Internationally-agreed test methods are especially important for avoiding unnecessary animal testing, since they standardise the study protocols. These standardised protocols can be used in regulatory contexts worldwide and the results are generally accepted by different regulatory agencies. Further development of test methods, in terms of refining, reducing or replacing animal tests (so called 3Rs principle), has to be assessed in the context of the REACH requirements. Therefore ECHA contributes to such developments

by participating in EU and OECD working groups, and maintaining links with other important actors, such as the Member States as well as with the Directorate Generals (e.g. DG JRC) and agencies (e.g. EFSA, EMA) of the European Commission.

1.5.3 Member States

As explained above, ECHA checks whether the information requirements of the REACH Annexes are met (in compliance checks) and examines testing proposals. In both cases, the result may be a draft decision requesting further information including results from tests on animals. The Member States Competent Authorities review draft decisions and may propose amendments, and if so, the case is referred to the Member State Committee. The representatives of the Member States seek agreement on the draft evaluation decisions in that committee. These decisions have to be unanimously agreed ensuring a broad consensus on the need for further animal testing. If no agreement can be reached, the European Commission will decide.

In the European Union, enforcement is a task of the Member States.

1.5.4 Third parties

“Third parties”, such as Non-governmental organisations (NGOs) or research institutes, may play a role in ensuring that best use is made of existing information, and thereby, contribute to ensuring that testing in vertebrate animals is performed as a last resort. On its website, ECHA publishes all testing proposals involving vertebrate animals, for endpoints specified in Annexes IX and X under REACH. These are the costly tests for complex endpoints which require most animals. Third parties then have 45 days to submit scientifically valid information and studies that address the relevant substance and hazard end-point, relating to the testing proposal. All scientific information thus collected is taken into account by ECHA during preparation of the final decision on the testing proposal, which, as stated above, also includes representatives of the Member States.

1.5.5 European Commission

The protection and welfare of animals is an area covered by a wide range of EU legislation. The conduct of studies on animals, whether it is for the development or production of new medicines, for studying physiological or environmental effects, or for the testing of chemical substances or new food additives, have to be carried out in compliance with EU legislation.

On 22 September 2010 the EU adopted Directive 2010/63/EC to update the 1986 Directive 86/609/EEC on the protection of animals used for scientific purposes. The aim of the new Directive is to strengthen the legislation, and improve the welfare of those animals use of which in experimental procedures is still necessary and to firmly anchor the principle of the 3Rs in EU legislation.

Duplication of testing may be avoided if tests are conducted according to GLP. The purpose of the principles of good laboratory practice is to promote the development of good quality test data such that individual countries can confidently rely on test data developed in other countries. The REACH Regulation requires new (eco)toxicological tests and analyses shall be carried out in compliance with the principles of GLP provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency. Annex XI of REACH provides for some exemptions for existing data in case that testing does not appear scientifically necessary.

The Test Methods Regulation (Commission Regulation (EC) No 440/2008) governs the conduct of testing for the REACH Regulation. Prior to changes in the Test Method

Regulation, the regulatory acceptance of a method in the EU has to be ensured. The Commission has a responsibility, having consulted stakeholders, to propose changes to the Test Methods Regulation. It was recognised that there was a need to streamline the procedures relating to the regulatory acceptance of validated alternatives to animal testing. The Commission committed itself to improve the acceptance process by introducing a mechanism of "preliminary analysis of regulatory relevance" (PARERE) to be established. The consultation networks involve EU Member State contact points and relevant agencies and committees including ECHA.

The Commission also collects and publishes statistics on the use of animals used for experimental procedures. The latest report (2010) provides statistics from 2008 (available at http://ec.europa.eu/environment/chemicals/lab_animals/statistics_en.htm).

Newly-developed alternative methods have to be validated in order to assess their relevance and reliability. In 1991, the Commission set up the European Centre for the Validation of Alternative Methods, ECVAM, to promote the validation of alternative methods. ECVAM is part of the Institute for Health and Consumer Protection (IHCP) of Directorate General Joint Research Centre (DG JRC) of the European Commission. One of the main tasks of ECVAM is to validate alternative methods that replace, reduce and refine the use of animals in scientific procedures. The work carried out by ECVAM is essential to reduce animal experiments in the EU.

The new Directive 2010/63/EU has further developed the role of ECVAM (referred to therein as the Union Reference Laboratory), and its duties and tasks are defined as follows:

- Coordinating and promoting the development and use of alternatives to procedures including in the areas of basic and applied research and regulatory testing;
- Coordinating the validation of alternative approaches at Union level;
- Acting as a focal point for the exchange of information on the development of alternative approaches;
- Setting up, maintaining and managing public databases and information systems on alternative approaches and their state of development;
- Promoting dialogue between legislators, regulators, and all relevant stakeholders, in particular, industry, biomedical scientists, consumer organisations and animal-welfare groups, with a view to the development, validation, regulatory acceptance, international recognition, and application of alternative approaches;
- It is intended that ECVAM will coordinate requests and input from the PARERE networks.

ECVAM thus seeks to promote the scientific and regulatory acceptance of alternative methods through research, new test development and validation, and the establishment of specialised databases, with the aim of contributing to the replacement, reduction and refinement of laboratory animal procedures (in accordance with the 3Rs concept).

1.6 Progress in the development of alternatives to animal testing

This section provides an overview on the development of alternative methods to animal testing. It is not meant to give a comprehensive review of all activities of this area, but only addresses REACH relevant approaches.

1.6.1 Development of alternative methods

There are many research projects ongoing within and beyond the EU that focus on replacement, reduction or refinement of animal testing. Important examples within the EU are research initiatives that have been launched in recent last years. These include the development and optimisation of reproductive toxicology (Re-Pro-Tect; 2004-2009), acute

toxicity (A-Cute-Tox; 2004-2009), skin and respiratory sensitisation (sens-it-iv; 2005-2010), carcinogenicity (Carcinogenomics; 2006-2011), chronic toxicity (Predict-iv; 2008-2013) and repeated dose toxicity (COLIPA-DG RTD Joint Research Initiative; 2009). In the future, these research projects may deliver in the future new approaches to combine different tests in the most optimal way (testing strategies) for these endpoints. For more details, please visit the ECVAM website.

It has to be noted that the results of research projects and new or refined methods based on those results can be used for regulatory purposes once they are validated and adopted. In the area of alternative methods to animal testing, such validations are conducted according to internationally agreed principles. In Europe, ECVAM is the responsible body for the validation of these methods, and more internationally, the OECD plays a role. This process is rather time consuming and may take years for a specific method to be internationally validated and accepted for regulatory purposes.

1.6.2 Progress in validation and adoption of in vitro test methods

This section refers to the test methods performed *in vitro*. These tests are performed in a controlled environment, such as a test tube or Petri dish, and usually involve the use of isolated organs, tissues, cells, or biochemical systems.

The ECVAM technical report (Zuang *et al*., 2010) and the recent overview paper of Adler *et al* (2011) both describe the current status of *in vitro* methods.

Currently, there are *in vitro* test methods under validation for assessing potential skin sensitisation, severe ocular irritants and non-irritants. The methods listed here have the potential to be used under the REACH Regulation (Annex XI 1.4.). A test battery consisting of three tests (Direct peptide reactivity assay, the Myeloid U397 Skin Sensitisation Test (MUSST), and the human cell line activation test (h-CLAT)) for detecting potential skin sensitisers has entered the ECVAM pre-validation process in 2009. In the area of ocular irritation, tests assessing irritant potential of substances such as the SkinEthic™ HCE test and the EpiOcular assay, are also under validation.

In the past three years a number of *in vitro* test methods that are suitable for REACH purposes have been adopted and incorporated into the Test Methods Regulation. These methods are:

in vitro skin irritation test, B.46 (2009)/OECD TG 439 (2010); bovine corneal opacity and permeability test method for identifying ocular corrosives and severe irritants (BCOP) B.47 (2010)/OECD TG 438 (2009); isolated chicken eye test method for identifying ocular corrosives and severe irritants (ICE) B.48 (2010)/OECD TG 438 (2009); and skin absorption *in vitro* B.45 (2008)/OECD TG 428, 2008).

More information on other test methods that have been validated by ECVAM and adopted by OECD can be found on the respective websites as well as on the TSAR database provided by the Institute for Health and Consumer Protection, a scientific institute of the Joint Research Centre (JRC).

1.6.3 Progress in concepts for read across, categories, (Q)SARs and new approaches

Substances with physicochemical, toxicological and ecotoxicological properties that 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. Applying the group concept means that the physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data available for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). This

avoids the need to test every substance in the group for every hazard endpoint. Preferably, a category should include all similar substances. REACH Annex XI, section 1.5 sets out the requirements for the application of this strategy.

The original concept for the read-across approach and category building was implemented at OECD level. The REACH Regulation and the ECHA Guidance on Information Requirements and Chemical Safety Assessment developed such concepts further. Therefore, ECHA has an in-house team of experts on non-test method approaches and the supporting specialist software. This team exploits the information available since the first registration deadline to facilitate future assessments of chemical properties.

Animal tests can be avoided if the hazardous properties of a substance can be predicted using computer models, sometimes referred to as "*in-silico*" methods. The (Q)SAR [(quantitative) structure-activity relationship] approach seeks to predict the intrinsic properties of chemicals by using various databases and theoretical models, instead of conducting tests. Based on knowledge of chemical structure, QSAR quantitatively relates characteristics of the chemical to a measure of a particular activity. QSAR should be distinguished from SAR, which makes qualitative conclusions about the presence or absence of a property of a substance, based on a structural feature of the substance.

The OECD QSAR Toolbox is an important tool for supporting and enabling category building. ECHA actively contributes to the further development of this Toolbox. This freely available software is useful to group chemicals and apply read-across techniques for assessing the (eco)toxicity hazards of chemical substances under REACH.

ECHA is collaborating with the JRC Computational Toxicology Group in its mission to promote the availability for regulatory use of valid computer-based methods, for example, QSARs, used for assessing the intrinsic properties of chemical substances. More information, including structured and peer-reviewed documentation of (Q)SAR models and free access to JRC QSAR Model Database is available from the JRC website.

In September 2010, ECHA held a first workshop on dealing with uncertainty related to the application of non-test methods under REACH. This workshop concentrated on how to deal with scientific uncertainties when non-test methods are used for predicting intrinsic properties within the context of the regulatory decision making process.

1.6.4 OECD

The Organisation for Economic Cooperation and Development (OECD) is the main organisation for developing and validating both conventional and alternative test methods. The adoption of valid test guidelines by OECD gives them international recognition and a possibility for regulatory use. More information on the recent activities is available from the OECD website. The regulatory use of OECD test methods in the EU may require changes to the legislation which applies to a number of different industry sectors.

1.6.5 Promotion platforms and other organisations

There are a number of promotion platforms and organisations which actively contribute to the promotion and/or development of alternative methods, e.g. the European Partnership for Alternative Approaches to Animal Testing (EPAA), European Consensus-Platform for Alternatives (ECOPA), and many others.

The International Council on Animal Protection in OECD Programmes, ICAPO is an international organisation that develops guidelines and programmes for the testing of chemicals. ICAPO is currently working with the Working Group of National Co-ordinators of the Test Guideline Program, Task Forces on Endocrine Disruptor Testing and Assessment

and Existing Chemicals, including (Q)SAR, and in the Validation Management Groups for Non-Animal testing and for Mammalian testing.

For the up-to-date progress in the development of alternatives to animal testing the reader is referred to the above listed organisations and their websites, which provide useful information.

2 Data Analysis

The main data set used for analysis in this report is based on the available endpoint study records in the registration dossiers submitted for phase-in substances at or above 1 000 tpa. In addition, also the available dossiers for phase-in substances at or above 100 tpa have been analysed and dossiers for non-phase-in substances at or above 100 tpa were also analysed. Dossiers may be updated by registrants after submission and so for this analysis, the data that were available up to a cut-off date of 28 February 2011 were used.

Endpoint study records are specific entries filled by registrants for the hazard endpoints in the IUCLID dossiers. It is important to note that there may be more than one or even many endpoint study records submitted per endpoint.

In section 2.1, the scope of this analysis, in terms of dossier types, is further described in details.

In sections 2.2 to 2.4, the statistical analysis of endpoint information from three perspectives is described:

(1) from the endpoint study record perspective (further called in this report “ESR approach”), which analyses the overall quantitative picture of options used by registrants for dossiers within the scope of this analysis (see section 2.1, Table 1)

(2) from the substance perspective (registered phase-in substances at or above 1 000 tpa, excluding category dossiers and dossiers for only intermediates), further called “substance approach”. This analyses the strategic choices the registrants have made to fulfil the information requirements, and

(3) from the perspective of new vertebrate animal testing for REACH purposes to evaluate how many studies have been performed for REACH or are planned to be performed for REACH (across all dossiers and all substances, excluding category dossiers and dossiers for only intermediates).

2.1 Analysis of endpoint data in the registration dossiers

By the first registration deadline for phase-in substances of 30 November 2010, ECHA received registration dossiers for phase-in substances manufactured or imported in quantities of 1 000 tonnes or more per year, phase-in substances classified as R50/53 in accordance with Directive 67/548/EEC and manufactured or imported in quantities of 100 tonnes or more per year and phase-in substances classified as CMR, category 1 or 2, in accordance with Directive 67/548/EEC and manufactured or imported in quantities of 1 or more tonne per year. In addition, other registrations were made for non-phase-in substances and early registrations of phase-in substances with later deadlines. The total number of registration dossiers received by the said deadline was 24 560.

The in-depth analysis of registration data for this report is on registrations received by at the 30 November 2010 deadline for substances at or above 100 tonnes per annum, both phase-in and non-phase-in substances. These dossiers should contain the core data of Annex VII and VIII in order to be accepted for registration (and pass the Technical Completeness Check). If data gaps have been identified by the registrants, that could not be filled otherwise, where appropriate they should contain testing proposals for the necessary higher-tier studies of Annex IX (for substances at or above 100 tpa) and Annex X (for substances above 1 000 tpa). Hence, these dossiers allow an assessment of the use of non-animal data

used to meet the core data registration needs and also to investigate how registrants plan to use non-test data for higher-tier endpoints, i.e. analysis of these dossiers provides a good source of data to examine the use of alternative methods and options chosen by the registrants to fulfil information requirements under REACH.

Certain submissions were excluded from the scope of this analysis: substances manufactured or imported only for use as intermediates under strictly controlled conditions, substances notified for use in process-orientated research and development (so-called 'PPORD's') and notified substances under the former regulatory scheme (so-called 'NONS' substances) for which no update in respect of a tonnage band increase had been received.

On-site isolated (Article 17) and transported (Article 18) intermediates can benefit from reduced information requirements provided they are used under strictly controlled conditions. Studies on properties are not needed for these registrations, except for transported isolated intermediates at or above 1 000 tpa for which only Annex VII data are needed. For all other intermediates, registrants submit only the existing information on properties. Therefore, intermediates are not considered in this analysis. From 1 June 2008 to 28 February 2011 ECHA received 5 079 dossiers on intermediates covering 2 231 unique substances.

According to Article 3 (22) of the REACH Regulation product and process oriented research and development (PPORD) is defined as "any scientific development related to product development or the further development of a substance, on its own, in mixtures or in articles in the course of which pilot plant or production trials are used to develop the production process and/or to test the fields of application of the substance". In order to promote innovation, Article 9 of the REACH Regulation specifies that substances manufactured or imported on their own or in mixtures, as well as substances incorporated in articles or imported in articles for the purpose of PPORD can be exempted from the duty to register for a period of five years. Studies on the properties of PPORD substances are not mandatory for a PPORD notification, therefore, PPORDs are not considered in this analysis. From 1 June 2008 to 28 February 2011 ECHA has received 679 PPORD notifications.

So called 'NONS' substances' are those which were placed on the European Community market after September 1981 i.e. substances that were not included in the inventory of substances on the Community market (EINECS-list). Such substances had to be notified according to Council Directive 67/548/EEC to the Member States Competent Authorities. As with the REACH Regulation, the information requirements were also tonnage dependant for such notified substances, however, the information requirements were not the same as for the REACH Regulation. Such notified substances are regarded as registered substances according to Article 24 of the REACH Regulation. The IUCLID database contains migrated files from the old data base, but this migration does not produce fully completed records and so these were not suitable for analysis using the tools developed for the purposes of this report.

From the original number of 24 560 registration dossiers, 17 062 dossiers were identified to be registration dossiers with a tonnage band at or above 100 tpa. It was necessary to exclude dossiers for 'chemical categories' (i.e. IUCLID category dossiers) from the in-depth analysis due to the complex endpoint interrelationship between dossiers that currently did not allow a reliable data analysis to be performed. At or above 100 tpa, there were 568 IUCLID category dossiers (i.e. 2.3% of the total number of dossiers) covering 85 substances, so the overall findings of this report are not unduly affected, because 16 494 dossiers remained in the data set for analysis.

From the remaining 16 494 dossiers, only the lead registrant's dossiers, dossiers submitted under the opt-out provisions from joint submissions and dossiers for individual registrations contained endpoint information for the registered substances. Thus, the total number of dossiers to be considered for the in-depth analyses was reduced to 1 862.

These dossiers were analysed within three groups: dossiers for phase-in substance at or above 1 000 tpa, phase-in substance dossiers at between 100 and 1 000 tpa and non-phase-in dossiers with a tonnage band of 100 tpa or more (see Table 1)

Table 1: Registration dossiers within the scope of in-depth analysis of this report

Tonnage band	Phase-in	Non phase-in	Total
All	22 995 (3 308 substances)	1 565 (1 347 substances)	24 560 (4 599* substances)
Registration dossiers with tonnage band > 100 tpa			
≥ 1 000 tpa	15 421	172	17 062 (2 219 substances)
100 - <1 000 tpa	1 469		
Registration dossiers excluding category dossiers			
≥ 1 000 tpa	14 875	171	16 494 (2 134 substances)
100 - <1 000 tpa	1 448		
Lead and individual dossiers			
≥ 1 000 tpa	1 504	140	1 862 (1 789 substances)
100 - <1 000 tpa	218		

**56 substances were classified as phase-in by some registrants and non-phase-in by other registrants, so they count as both. Therefore, whilst the sum of 3 308 and 1 347 is 4 655, this is actually 4 599 unique substances.*

In order to analyse data submitted by registrants in the registration procedure to ECHA, the Agency has developed an IT application allowing identification of substances fulfilling pre-defined criteria. These selection criteria were designed to find and extract information on the number and type of different options used by the registrant in order to meet the information requirements under REACH.

Further information on the selection criteria applied in data analysis for the individual endpoints is presented in Figure 1.

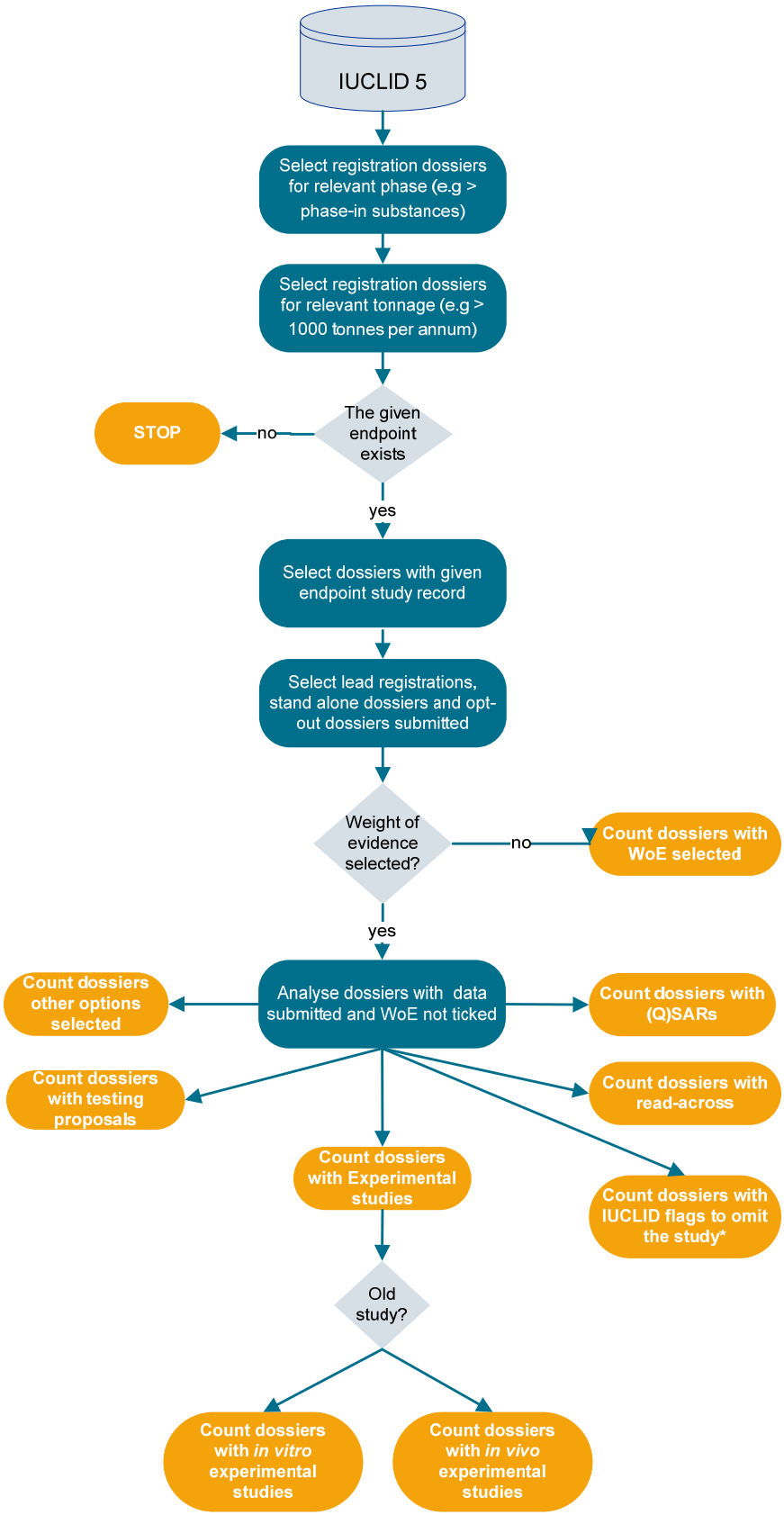


Figure 1: Schematic of data analysis for individual endpoints

**IUCLID flags to omit the study are set by the registrant to omit the submission of the required data filling the "data waiving" pick-list. These are used when testing does not appear to be: scientifically necessary; technically not possible; or not necessary based on low exposure considerations*

2.2 Endpoint Study Record (ESR) approach

The ESR approach consists of the analysis of all endpoint study records submitted for the 1 862 dossiers for a given endpoint. For each endpoint, more than one or even many endpoint study records are possible and were summarised for these dossiers (see below). The ESR approach provides the overall quantitative picture of options used by registrants for dossiers within the scope of this analysis (see section 3.2). .

The results of this approach show what information has been submitted for a given endpoint cumulatively in all dossiers. This analysis provides an overall data availability for endpoints. However, it does not cover which of these data have been used as key data to fulfil the information requirements and it does not allow assessing the degree to which data redundancy is involved per substance.

2.3 Substance approach

Whereas the ESR approach is based on dossiers collectively, it is of further interest to analyse at substance level, how the registrants used alternative approaches. Such an analysis provides the relative proportions of the principal options used by registrants to fill the information requirements per endpoint. These options have been categorised as testing proposals, experimental studies and alternative methods.

- If there was a testing proposal included this was taken as evidence that the endpoint was supposed to be filled by future testing;
- If there was one ESR entry referring to an experimental study, this was taken as evidence that the endpoint on the substance level was filled with experimental data (including a weight of evidence approach also using experimental data); and
- If there was no ESR entry referring to an experimental study but listing either a possibility to omit the information or to fill the information requirements using alternative approaches, it was counted as evidence that the endpoint on the substance level was filled with alternative method.

Each of these options has been only counted once per endpoint at substance level. Therefore this way of analysing the data does not provide a frequency distribution on how many experimental or alternative studies have been entered per endpoint at substance level. Such a frequency distribution will be different between individual substances, depending on their extent and history of use.

2.4 Studies conducted or proposed for the purpose of REACH

Beside the cumulative analysis of endpoint data from the selected registration dossiers (see section 2.1 for dossier inclusion criteria) , the ESR approach has also been used to perform a complete statistical analysis of these registration dossiers to assess what new studies had been conducted in order to complete the core data requirements and what testing proposals had been made, which may ultimately require the conduct of new studies using vertebrate animals to fulfil the higher-tier information requirements.

In this analysis all vertebrate animal testing proposals and experimental studies performed in 2009 or later have been counted for all tonnage bands for both phase-in and non-phase-in dossiers. For this analysis an assumption was made that studies described in the IUCLID dossier with a reference date of 2009 or later had been conducted for REACH. It should be noted that this assumption will overestimate the number of new animal studies for two reasons. Firstly some studies may have been conducted for purposes other than REACH, e.g. for other non-EU chemical control schemes. Secondly the study may have commenced earlier but the date of the study report was 2009 or later.

In this analysis all reproduction toxicity screening studies (performed according to OECD test guideline 422 or 421 or the equivalent US EPA guidelines) have been counted and presented separately as they can be used to fulfil information requirements for Annex VII core data for one or more different endpoints (i.e. repeated dose toxicity and reproductive toxicity). Hence, counting them at the endpoint level could lead to double-counting (e.g. a single test could be counted once for repeated dose toxicity and counted again for reproductive toxicity), therefore potentially overestimating the overall number of tests conducted. Furthermore, some registrants have argued in their dossiers that this screening reproduction toxicity study can be used to meet the higher-tier Annex IX and X data requirements of developmental toxicity and fertility studies instead of making testing proposals. This practice results in an incorrect impression that higher-tier two-generation fertility studies or prenatal developmental toxicity studies have been conducted without the submission of a testing proposal. In order to analyse the use of these reproduction toxicity screening studies, all the respective dossiers had to be checked manually.

It is important to add some explanations on the numbers of testing proposals provided in different results sections of this report. The reference numbers of testing proposals for all dossiers are provided in section 3.4. The different scope of the dossiers within the analyses explains differences in the numbers of testing proposals in other sections.

3 Results

3.1 The sharing and joint submission of information

The joint submission of information worked well in general as shown by the proportion of total registrations submitted jointly: nearly 90% of the total number, the remaining part also covering individual submissions of non-phase-in substances. From nearly 3000 joint submissions containing almost 20 000 member dossiers, there were only 135 member dossiers with opt-outs for one or more end-points as described in Articles 11(3) and 19(2) of REACH. An overview of the main reasons for opt-outs is provided in the report 'The Operation of REACH and CLP 2011' produced in accordance with Article 117 (2) of REACH.

However, a more detailed analysis reveals that in some cases the registrants, instead of opting out, within the joint submission, instead submitted separate registration dossiers. For about 250 substances, ECHA received either multiple joint submissions or, in addition to the joint submissions, one or more individual submissions on the same substance. ECHA is currently examining the explanations for these situations. The joint submission of information generally worked well in general as shown by the proportion of total registrations submitted jointly: 90% of the total number of dossiers, the remaining part also covering individual submissions of non-phase-in substances. From nearly 3 000 joint submissions covering almost 20 000registrations, there were only 135 member dossiers with opt-outs for one or more end-points in accordance with Articles 11(3) and 19(2) of REACH. An overview of the opt-out reasons given per end-point type is provided in the Article 117 (2) report.

More specifically, for the registration dossiers in the focus of this report (phase-in substances with a tonnage band of at or above 1 000 tpa (excluding categories)), 82 dossiers covering 60 substances have been flagged by the registrants for opting out from a joint submission. Of these, 19 "opt-outs" concerned endpoints which required testing on animals

For non-phase-in substances and for phase-in substances not pre-registered, the inquiry process ensures the sharing of existing data between registrants of the same substance. The Agency has successfully processed almost 1 500 inquiries made by potential registrants, and of these, about 50 % have led to registration afterwards.

In conclusion, these numbers demonstrate that generally the sharing and joint submission of information worked and that the registrants used them to fulfil the information requirements. However, the number of separate registration dossiers for the same substances indicate that the sharing and joint submission of information still needs further improvement.

3.2 Endpoint analysis

The results of the ESR approach are presented for each endpoint of concern in the endpoint sections below. In addition, Tables 4 to 6 in Appendix I provide detailed data from the ESR perspective. During the creation of the study records in IUCLID5, the registrant can select from a number of pre-defined options depending on the purpose of that study record. For the purpose of this analysis, the following groups of options have been used:

- "Experimental studies: classified by the registrant as "experimental result" from the pick-list of options in the field "Study result type" (abbreviation: ES; *in vitro* and *in vivo* studies are treated separately if applicable)

- "Testing proposal": classified by the registrant as "experimental study planned" from the pick-list of options in the field called "Study result type" (abbreviation TP).
- "Read-across": classified by the registrant as read-across from the pick-list of options in the field called "Study result type" (abbreviation RA).
- "IUCLID flags to omit the study": selected by the registrant to omit the submission of the required data by choosing the appropriate option from those available in the pick-list in the field called "data waiving". These options are to be used to indicate when testing does not appear to be: scientifically necessary; technically not possible; or not necessary based on low exposure considerations (abbreviation FO).
- "Weight of Evidence[1]": classified by the registrant as weight of evidence in the "purpose flag" pick-list (abbreviation WE).
- "(Q)SAR studies": classified by the registrant as "(Q)SAR studies" in the pick-list called "Study result type" (abbreviation QS).
- "Miscellaneous": classified by the registrant as "other" in the pick-list called "Study result type"; their content cannot be further verified without detailed examination (abbreviation MS).

In the endpoint charts, the above described options have been used to graphically represent the findings for registration dossiers for phase-in substances at or above 1 000 tpa.

The results from the substance perspective have been presented in the form of bar charts for all relevant endpoints and described in the section 3.3.

The results of a separate cumulative analysis of the studies conducted or proposed for the purpose of REACH are presented in the section 3.4.

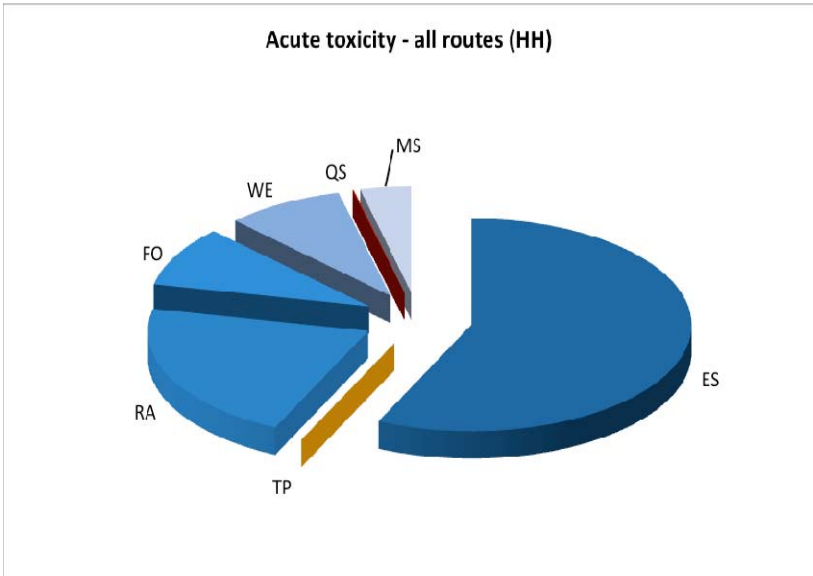
It is important when considering these findings to understand that the ESRs are provided by the registrants and the contents of the ESRs were not scrutinised by ECHA, and there will certainly be some errors in the dossiers. Nevertheless it is possible to get a general picture of the animal studies submitted in registrations and how non-animal data were used instead.

It is possible to get insight into the quality of the information in registration dossiers from the compliance checks which are conducted on some registrations in accordance with the REACH Regulation. The results of the compliance checks performed up to December 2010 are contained in the Article 54 reports on Evaluation published in February each year by ECHA. When interpreting the findings of the ESR analysis, it should be noted that in principle there may be deficiencies discovered in the compliance check dossier evaluation work that results in further animal studies being requested if the quality of the non-standard data in the dossier is discovered to be inadequate (see section 4).

[1] Weight of evidence option covers various combinations of old experimental data, literature information and read-across possibilities and it is assumed that it does not contain new animal tests performed for the registered substance. In order to avoid double counting whenever the study was classified by the registrant as weight of evidence, it was counted and excluded from the further analysis of the other options.

3.2.1 Acute toxicity

The information requirement for an acute toxicity study conducted using the oral route applies at or above 1 tpa (Annex VII) and is therefore part of the core data for all the registrations. The requirement for such a study can be adapted, for example if the substance is corrosive. Acute toxicity by either dermal or inhalation exposure, or in some cases both routes, is needed for all substances (except gases) at or above 10 tpa (Annex VIII), depending on the likely human exposure, and is therefore also part of the core data for the registrations in this study. The purpose is to have information on the toxicity of a chemical substance. The standard laboratory animal species used for this purpose is the rat, but the mouse is also used. The effects of the administered dose(s) are monitored and reported according to EU TMR/OECD TG standard protocols ensuring that the results can be used worldwide. *In vitro* approaches for this endpoint have not been validated yet. Available alternative approaches are therefore mainly prediction methods (read-across and grouping) or Weight of Evidence using experimental methods in combination with prediction methods. In analysing this endpoint, records were observed addressing the oral, dermal, or inhalation route only, or all possible combinations.



Acute toxicity - all (HH)		
	No. ESR	% ESR
ES	7 328	56.9
TP	0	0.0
RA	2 756	21.4
FO	1 184	9.2
WE	1 116	8.7
QS	11	0.1
MS	479	3.7
Total	12 874	100

Figure 2: Acute Toxicity (all routes, 1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESR may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

In the dossiers for phase-in substances at or above 1 000 tpa, 12 874 entries (100 %) have been counted in total. A Weight of Evidence approach was flagged by the registrant in 1 116 (8.7 %) of these entries, thereby indicating that in these cases several independent sources of information, including animal studies had been used to cover this endpoint. Experimental studies have been used for 7 328 (56.9%) of the ESRs.

The IUCLID flags to omit the information have been used in 1 184 (9.2 %) of all ESRs and read-across approaches have been flagged in 2 756 (21.4 %) of ESRs. In 479 (3.7 %) of ESR, the registrant flagged other information sources for covering this endpoint. In 11 cases (0.1 %) QSAR was used as the ESR. The percentages of different ESR types for phase-in substances in the 100 to 1 000 tpa range did not vary significantly from those of phase-in substances at or above 1 000 tpa. For non-phase-in substances at or above 100 tpa the total percentage of entries for experimental studies was 38.9 % of the total. Analyses which separated the acute toxicity endpoint by route of administration did not provide significantly different results (see rows 1.0, 1.1, 1.2 and 1.3 in Table 4).

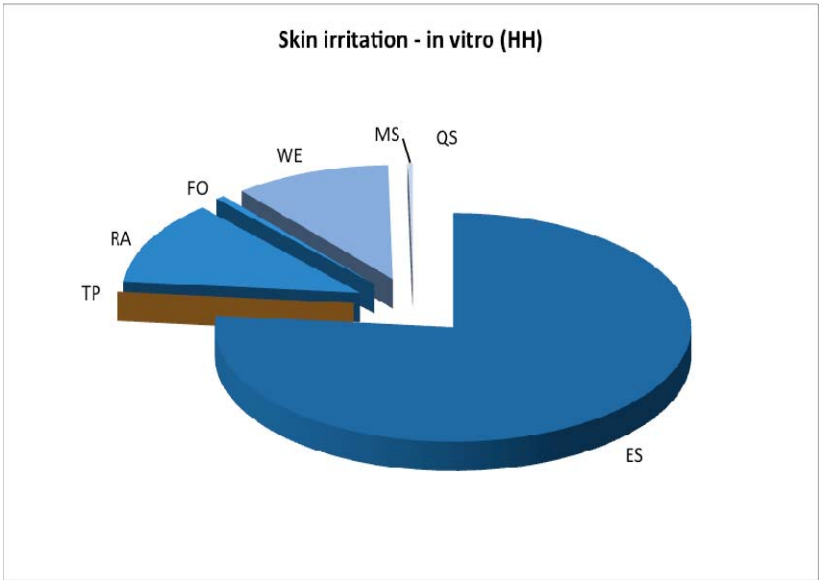
3.2.2 Skin irritation/corrosion

The studies used to investigate this endpoint predict the local effects of the test substance on humans at the site of first contact (skin, eye, mucous membrane of respiratory or gastrointestinal tract) after a single exposure. Observed local effects can be further differentiated as either irritant or corrosive effects, depending on their severity, reversibility or irreversibility. For *in vivo* studies, the substance to be tested is applied in a single dose to the skin of an experimental animal, the preferred species being the albino rabbit, for four hours; untreated skin areas of the test animal serve as the control.

The standard information requirements for this endpoint are provided in Annexes VII to X of the REACH Regulation and differ depending on the tonnage band. Annex VII (1 to 10 tpa) requires only *in vitro* studies, while Annex VIII (10 – 100 tpa) requires a confirmatory additional *in vivo* test, unless the substance is classified as an irritant or corrosive, and hence should be included in all the registrations for this study. Alternative options to fulfill standard information requirements for this endpoint under REACH include prediction methods, weight of evidence approach and possibilities to adapt information requirements according to column 2 of Annexes VII to X. The potential to cause irritation or corrosion can be also predicted based on physicochemical properties of the chemical (e.g. the substance is a strong acid/base or is spontaneously flammable). According to Annex XI 1.4, the registrant can also adapt the standard information requirements based on the results of *in vitro* studies.

There are validated *in vitro* methods available for this endpoint that can be used by the registrants in a tiered testing strategy within a weight of evidence approach to fully replace testing on animals. For studying skin corrosion/severe irritation, these methods include, for example, EU TMR/OECD TG standard protocols such as the transcutaneous electrical resistance (TER) test, human skin model test and 3T3 NRU phototoxicity test. For skin irritation, a reconstructed human epidermis test method is available.

In Table 4 the endpoint study records for *in vitro* and *in vivo* studies on skin irritation/corrosion for non-phase-in and phase-in substances manufactured or imported at or above 100 tpa are summarized in rows 2.1 and 2.2.

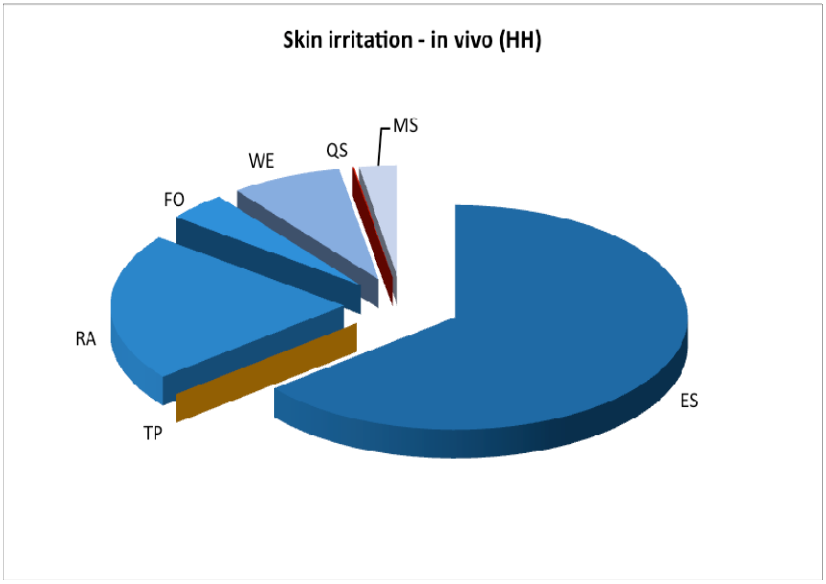


Skin irritation – in vitro (HH)		
	No. ESR	% ESR
ES	252	76.6
TP	0	0.0
RA	39	11.9
FO	2	0.6
WE	35	10.6
QS	0	0.0
MS	1	0.3
Total	329	100

Figure 3: Skin irritation *in vitro* (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESR may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

As presented in Figure 3, for dossiers of phase-in substances at or above 1 000 tpa, there were 329 (100 %) ESRs in total. Experimental studies have been used for 252 (76.6 %) of all ESRs submitted for this endpoint. In 35 (10.6 %) of the entries Weight of Evidence approach was flagged by the registrant. Two registrants have used IUCLID flags to omit the information and read-across approaches have been flagged in 39 (11.9 %) of ESRs.

For the dossiers of phase-in substances manufactured or imported at 100 – 1 000 tpa only 24 ESRs for skin irritation *in vitro* have been found, while for the non-phase-in substances produced at or above 100 tpa only one old study has been submitted.



Skin irritation – in vivo (HH)		
	No. ESR	% ESR
ES	3 343	64.1
TP	0	0.0
RA	1 113	21.3
FO	216	4.1
WE	402	7.7
QS	5	0.1
MS	137	2.6
Total	5 216	100

Figure 4: Skin irritation *in vivo* (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

The registrants submitted in total 5 216 ESRs of skin irritation *in vivo* to fulfil the information requirements for the phase-in substances at or above 1 000 tpa. In comparison with the skin irritation *in vitro* endpoint, significant differences in the strategy used by registrants to fulfil the information requirements were noted. Experimental studies have been used for 3 343 (64.1 %) of all ESRs. In 402 (7.7 %) of these entries, a Weight of Evidence approach was flagged by the registrant.

The IUCLID flags to omit the information have been used in 216 (4.1 %) of all ESR and read-across approaches have been flagged in 1 113 (21.3 %) cases. Registrants have used five (Q)SAR predictions for this endpoint, and other information has been flagged in 137 (2.6 %) of ESR.

For the dossiers of phase-in substances produced at 100 to 1 000 tpa the total number of ESRs was almost nine times less (600 ESR entries) when compared with the substances produced at or above 1 000 tpa, but no significant differences in the proportional distribution of various options of ESR were observed.

For non-phase-in substances at or above 100 tpa, 157 ESRs have been submitted for this endpoint. In 45.9 % of cases, the registrants have provided experimental data, other information has been chosen in 26 % of ESRs, read-across approach has been selected in 14.6 % of cases and 8.9 % of ESRs have been flagged in IUCLID to omit the study.

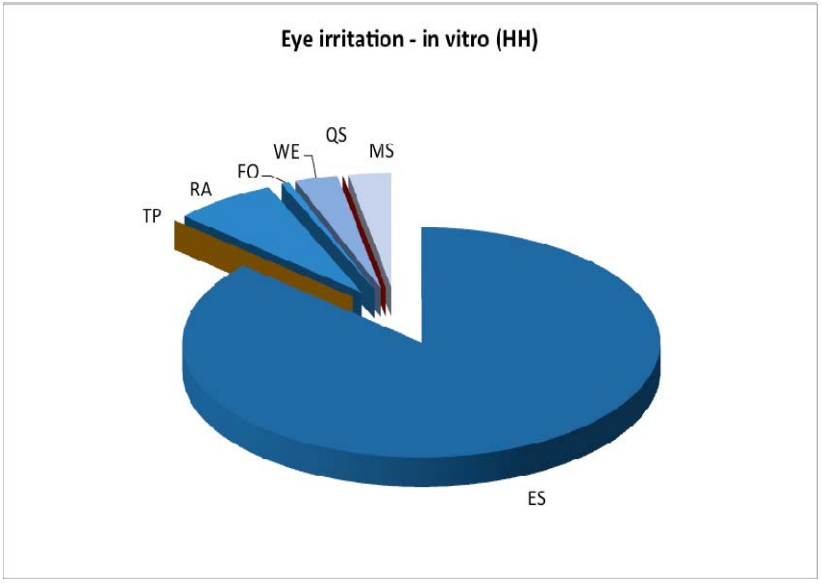
3.2.3 Eye irritation

As with the skin irritation/corrosion endpoint, studies on eye irritation are used to predict the local effects of the test substance on human eyes following a single exposure. For *in vivo* studies conducted according to EU TMR/OECD TG standard protocols, the substance to be tested is applied in a single dose to the eye of an experimental animal, usually the albino rabbit, for 24 hours; the untreated eye of the test animal serves as the control. The effects of the substance on the exposed animals are usually monitored for 72 hours and reported in a standardised format.

The potential of a substance to cause eye irritation can be assessed using an *in vitro* test for registration(s) at less than 10 tpa (Annex VII) and with an *in vivo* study at or above 10 tpa (Annex VIII) unless the substance is already classified as an eye irritant or corrosive, is a strong acid or base, or is flammable in air at room temperature. The standard information requirements, and the possibilities to adapt them according to column 2 of Annexes VII to X for eye irritation under REACH, are similar to those for skin irritation/corrosion.

There are *in vitro* methods that have undergone a validation process that could be used by the registrants to fulfill information requirements for this endpoint. A positive outcome from *in-vitro* assays such as the bovine corneal opacity and permeability (BCOP) or isolated chicken eye (ICE) tests is sufficient to classify severe eye irritants under Annex VII and Annex VIII using adaptations of the standard testing regime specified in Annex XI.

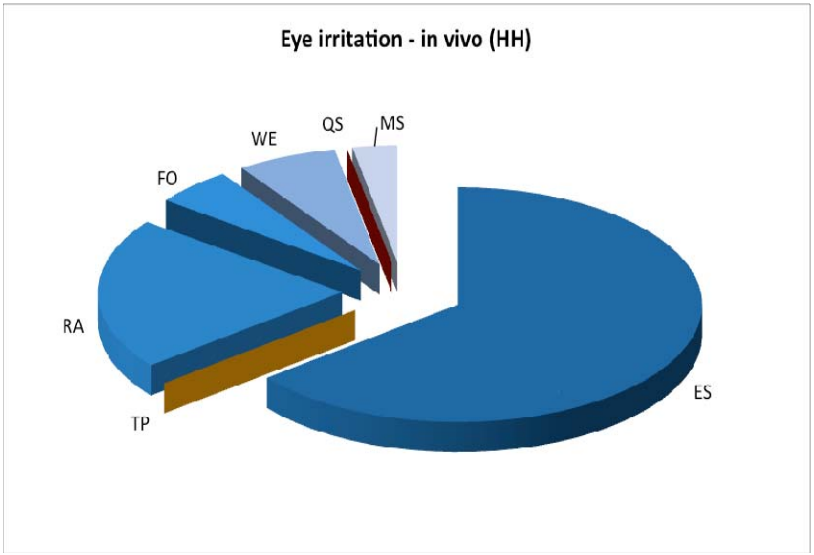
In Table 4, the endpoint study records for *in vitro* and *in vivo* studies on eye irritation/corrosion for non-phase-in and phase-in substances manufactured or imported at or above 100 tpa are summarised in rows 3.1 and 3.2.



Eye irritation – in vitro (HH)		
	No. ESR	% ESR
ES	149	86.6
TP	0	0.0
RA	12	7.0
FO	1	0.6
WE	5	2.9
QS	0	0.0
MS	5	2.9
Total	172	100

Figure 5: Eye irritation *in vitro* (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

For the dossiers for phase-in substances at or above 1 000 tpa, a total of 172 ESRs have been counted. Experimental studies have been used for 149 (86.6 %) of all ESRs for this endpoint. In five (2.9 %) of the entries, a Weight of Evidence approach was flagged by the registrant and the same number of ESRs have been flagged as other information. In 12 cases (7.0%) registrants have used read-across approaches.



Eye irritation – in vivo (HH)		
	No. ESR	% ESR
ES	2 714	64.3
TP	0	0.0
RA	884	20.9
FO	219	5.2
WE	279	6.6
QS	0	0.0
MS	125	3.0
Total	4 221	100

Figure 6: Eye irritation *in vivo* (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

For the dossiers of phase-in substances manufactured or imported at 100 – 1 000 tpa only 27 ESRs for eye irritation *in vivo* have been found; from those, 19 ESRs (70.4 %) have been filled with experimental data. For the non-phase-in substances produced at or above 100 tpa only one old study has been submitted.

The registrants submitted in total 4 221 ESRs of eye irritation *in vivo* to fulfil the information requirements for the phase-in substances at or above 1 000 tpa. Experimental studies have been used for 2 714 (64.3 %) of the ESRs. In 884 (20.9 %) of theses entries, a read-across approach was flagged by the registrant.

The IUCLID flags to omit the information have been used in 219 (5.2 %) of all ESRs and Weight of Evidence approaches have been flagged in 279 (6.6 %) cases. Registrants have flagged “other information” in IUCLID in 125 (3.0 %) of the cases.

For the dossiers of phase-in substances produced at 100 – 1 000 tpa total number of ESRs was 8 times less (524 ESR entries) when compared to the those available for substances produced at or above 1 000 tpa, but no significant differences in the proportional distribution of various options of ESR were observed (ref. Table 4 row 3.1).

For non-phase-in substances at or above 100 tpa 140 ESR have been submitted for this endpoint. In 45 % of cases registrants have provided experimental data, other information has been chosen in 27.9 % of ESRs, a read-across approach has been selected in 11.4 % of cases and 10.7 % of ESRs have been flagged in IUCLID to omit the study.

3.2.4 Skin sensitisation

Skin sensitisation is the toxicological endpoint associated with chemical substances that have the intrinsic property to cause skin sensitisation and allergic contact dermatitis in humans following repeated exposures to a substance.

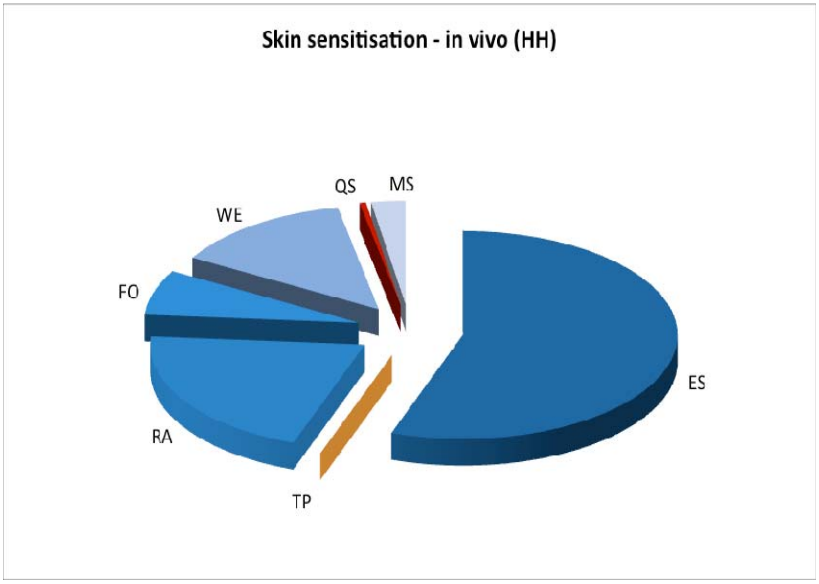
The standard skin sensitisation test methods, for which EU TMR/OECD TG are available, include the guinea pig maximisation test (GPMT), the occluded patch test of Buehler and the

murine local lymph node assay (LLNA). In the GPMT, guinea pigs are exposed to the test substance by intradermal injection and topical application by occlusion. Following a rest period of ten to fourteen days, the challenge dose is introduced dermally. The extent and degree of skin reactions to this challenge exposure are then compared with control animals. In the Buehler test, guinea pigs are repeatedly exposed to the test substance by topical application under occlusion. Following a rest period of twelve days, a dermal challenge treatment is performed under occlusive conditions. In the LLNA, the test substance is applied to the ears of mice for three days and later tritiated radioactive thymidine is introduced to measure cell proliferation in auricular lymph nodes. An increase in lymph node cell proliferation compared to control animals indicates sensitisation. There are currently no validated non-animal alternative methods to identify skin sensitisation hazard potential.

The information requirements for skin sensitisation are described in REACH Annex VII. Data on skin sensitisation are required for substances produced or imported at or above 1 tpa, and hence should be in all the registrations for this study. *In vivo* studies do not need to be conducted, if there is enough evidence that the substance should be classified or based on physicochemical properties of the test substance (strong acid or base or flammable in air at room temperature). The murine local lymph node assay (LLNA) is the first choice method for *in vivo* testing and another test should only be chosen in exceptional circumstances that have to be correctly justified. The LLNA is regarded as being more capable of predicting the relative potency of skin sensitising chemicals, i.e. the chemical's relative power/strength to induce skin sensitisation.

In Table 4, the endpoint study records for *in vitro* and *in vivo* studies on skin sensitisation for non-phase-in and phase-in substances manufactured or imported at or above 100 tpa are summarised in rows 4.1 and 4.2.

For dossiers for phase-in substances at or above 1 000 tpa, there were 21 entries for *in vitro* skin sensitisation studies. Further analysis revealed that in most cases, these entries were (*in vivo*) LLNA tests that were misclassified by registrants as *in vitro* tests.



Skin sensitisation – in vivo (HH)		
	No. ESR	% ESR
ES	2 080	55.4
TP	0	0.0
RA	782	20.8
FO	264	7.0
WE	513	13.7
QS	18	0.5
MS	97	2.6
Total	3 754	100

Figure 7: Skin sensitisation *in vivo* (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

For the skin sensitisation *in vivo* endpoint many more ESR entries have been filled.

For phase-in substances at or above 1 000 tpa 3 754 ESRs have been counted. In 2 080 (55.4 %) of theses entries registrants have used experimental data. The IUCLID flags to omit the information has been used in 264 (7.0 %) of all ESR and read-across approaches have been flagged in 782 (20.8 %) of ESRs. Weight of Evidence has been used in 513 (13.7 %) ESRs and other information has been flagged in 97 (2.6 %) cases. Comparison of the phase-in dossiers at 100 – 1 000 tpa with the results described above (see Table 4 row 4.2) did not result in the observation of significant differences.

For the non-phase-in substances only 176 ESRs have been created by the registrants. The percentage of experimental studies in total reached 41.5 %, other information has been chosen in 21.0 % of cases and the read-across approaches have been flagged in 15.3 % of the ESRs. The number of selected IUCLID flags to omit the study was 19.9%.

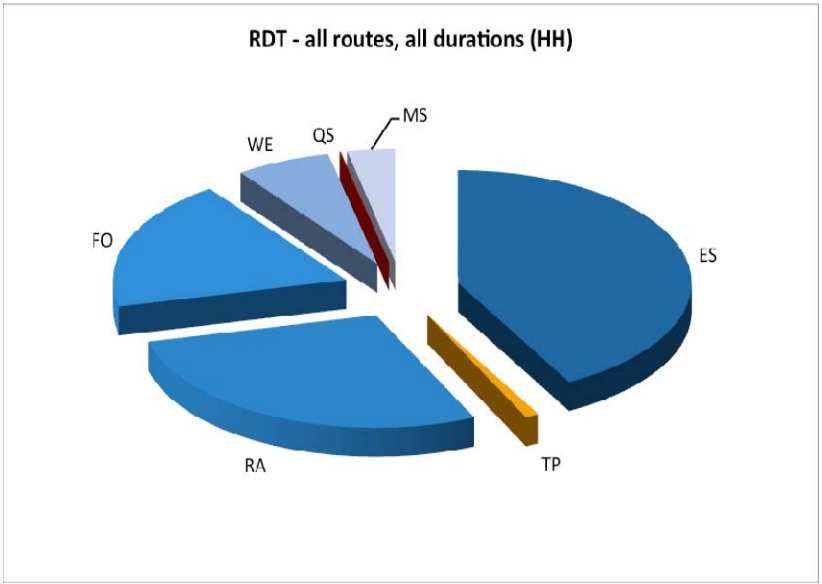
3.2.5 Repeated dose toxicity

Information on repeated dose toxicity is used to predict the effects of longer term exposure of chemical substances to humans. During the study, purpose-bred animals such as the rat or mouse receive repeated doses of a substance via oral, dermal or inhalation routes of exposure. In Annex VIII, a study with a duration of 28 days (sub-acute) is the standard information requirement, but note as described below that there was the possibility to omit this study from the core data set at the time of registration to achieve a technically complete dossier by making a testing proposal for a 90-day study if adequate risk management measures are in place. At Annex IX additionally a study with 90-days duration (sub-chronic) is the standard information requirement. The oral route in many cases is the default, but depending on the relevant exposure route for humans also dermal application or inhalation may be needed. At Annex X long term studies with duration up to two years (chronic) can be proposed by the registrant or can be used to fill the endpoint.

In vitro methods have not been validated for repeated dose toxicity and cannot be predicted by QSAR. Alternative methods are therefore mainly other prediction methods (read-across and grouping), Weight of Evidence approaches and the possibilities to omit the studies in accordance with the requirements in column 2 of Annexes VII to X and in Annex XI.

In IUCLID the repeated dose endpoint is one of the most complicated ones. It can have entries for studies with different durations and for different routes and for all combinations of these. In addition, a so-called combined screening study, combining studies of repeated dose toxicity with reproductive toxicity, may have been used by the registrant to meet the core data requirements (Annex VIII) for this endpoint. For all types of studies, the effects of the substance on the test animals are monitored and reported according to EU TMR/OECD TG standard protocols thereby ensuring that the results can be used worldwide. *In vitro* methods have not been validated for this endpoint. The alternative methods used are therefore mainly prediction methods (read-across and grouping), Weight of Evidence approaches and the possibilities to omit the studies provided by column 2 of Annexes VII to X and in Annex XI.

In Table 5 summarising ESRs for repeated dose toxicity the total number of entries for this endpoint separated by route and duration is collected.



RDT – all routes, all study durations (HH)		
	No. ESR	% ESR
ES	4 546	42.1
TP	104	1.0
RA	3 032	28.1
FO	2 033	18.8
WE	709	6.6
QS	9	0.1
MS	357	3.3
Total	10 790	100

Figure 8: Repeated dose toxicity – all routes, all study durations (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

In Figure 8 for the dossiers for phase-in substances at or above 1 000 tpa, 10 790 entries (100 %) have been counted in total as ESRs. In 4 546 cases (42.1 %) registrants used experimental data for these endpoints. In 104 (1 %) ESRs, testing proposals have been submitted for these phase-in substances at or above 1 000 tpa. Read-across approaches have been used in 3 032 (28.1 %) of the ESRs. Weight of evidence was flagged by the registrants in 709 entries (6.6 %). Flags to omit the information have been set by the registrants in 2 032 cases (18.8 %). QSAR predictions are not very relevant to these endpoints and correspondingly have been used only in 9 cases (0.1 %). Other information has been flagged in 357 cases (3.3 %). It should be noted that this analysis covers all routes and all study durations. More detailed information is provided in Table 5.

With the aim of helping the companies to meet the first registration deadline and to avoid unnecessary vertebrate animal testing, in 2009 ECHA issued a dedicated press release and a related fact sheet elaborating on the information requirements for substances manufactured or imported at or above 100 tpa. ECHA stated that registration dossiers for substances at or above 100 tpa will be considered as technically complete even if they do not contain the results of a 28-day repeated dose toxicity study, if instead a testing proposal for a 90-day repeat-dose toxicity study is submitted in the registration and appropriate risk management measures are in place. Among Annex IX dossiers, submitted to ECHA by the first deadline, 55 dossiers did not contain a sub-acute (28-day) repeated dose toxicity study, but did contain a testing proposal for sub-chronic, 90-day study. This analysis was performed assuming that the missing 28-day study and TP for a 90-day study was for the same route.

3.2.6 Genetic toxicity

The aims of testing for genetic toxicity (genotoxicity) are to assess the mutagenic potential of substances, i.e. their ability to induce genotoxic effects which may lead to cancer or cause heritable damage in humans. Information is required on the capability of substances capability to induce gene mutations, structural chromosome aberrations (clastogenicity) and numerical chromosome aberrations (aneugenicity). To obtain such information, many *in vitro* and in *vivo* test methods officially adopted by the EU or the OECD are available. Non-testing options, for example (Q)SAR and the use of read-across approaches, may also provide information on the mutagenic potential of chemical substances.

Standard information requirements on mutagenicity under REACH are described in the Annexes VI to XI and the specific rules to omit, replace, and adapt the required standard data or to use alternative options are listed in column 2 of the Annexes VII-X.

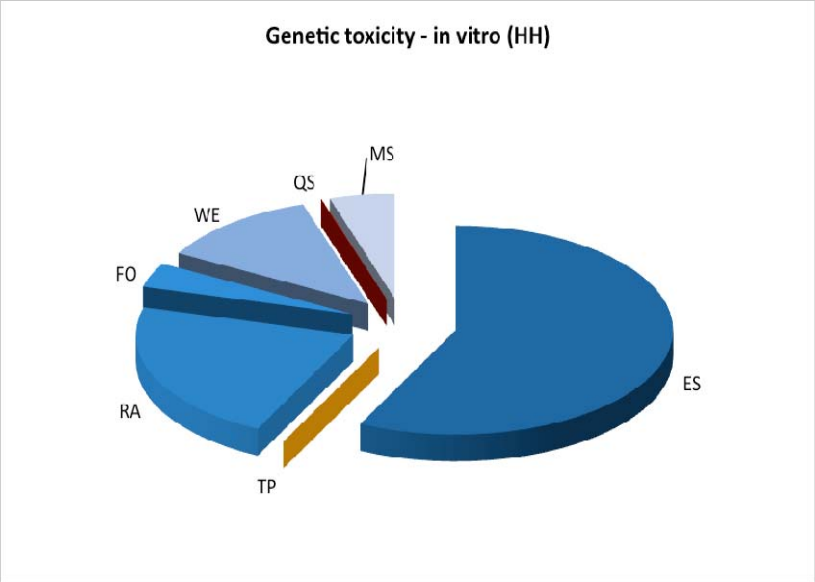
For substances manufactured or imported at the lower tonnage (1-10 tpa), only an *in vitro* gene mutation study in bacteria is required (Annex VII). No further studies at this tonnage level are required if the result is negative (i.e. no signs of adverse effects).

For substances falling under the Annex VIII information requirements of REACH, additional *in vitro* tests are required. An *in vitro* cytogenicity study or an *in vitro* micronucleus study in mammalian cells needs to be conducted but may be omitted if reliable data from an *in vivo* mammalian cell gene mutation test are available or if the substance is already classified as a carcinogen or mutagen. If both the *in vitro* gene mutation study in bacteria and the cytogenicity study in mammalian cells are negative, another *in vitro* study – gene mutation in mammalian cells – is required, unless reliable *in vivo* mammalian gene mutation data are available. At this tonnage level, *in vivo* mutagenicity studies shall only be considered in cases of a positive (i.e. signs of an adverse effect) result in any of the required *in vitro* tests.

For substances manufactured or imported between at 100-1 000 tpa, if there is a positive result in any of the *in vitro* genotoxicity studies and no reliable *in vivo* data available, registrants have to submit testing proposal for an *in vivo* somatic cell genotoxicity study. For substances falling under the Annex X requirements of REACH, a positive result in any *in vitro* studies may additionally trigger a need for a second *in vivo* somatic cell test. For all substances manufactured at 100 tpa or more, a positive outcome from *in vivo* somatic cells test should lead to considerations on the potential for germ cell mutagenicity.

In summary, generally only *in vitro* mutagenicity tests are needed for the core data, and some *in vivo* confirmatory mutagenicity studies may be necessary as higher-tier studies to be conducted after the testing proposals have been approved.

In Table 4 on the ESRs for genetic toxicity the total number of entries for this endpoint separated by *in vitro* and *in vivo* test is summarised in the rows 5.1 and 5.2



Genetic toxicity - in vitro (HH)		
	No. ESR	% ESR
ES	5 908	57.2
TP	0	0.0
RA	2 272	22.0
FO	394	3.8
WE	1 245	12.1
QS	5	0.0
MS	498	4.8
Total	10 322	100

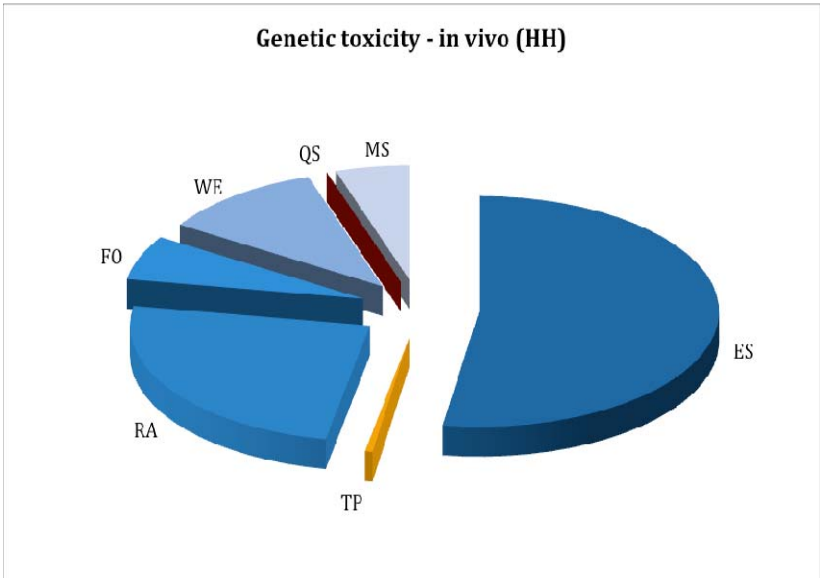
Figure 9: Genetic toxicity *in vitro* (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

As presented in Figure 9, for the dossiers for phase-in substances at or above 1 000 tpa, 10 322 entries (100 %) have been counted in total as ESRs. Experimental studies have been used for 5 908 (57.2 %) of all ESRs for this endpoint. In 1 245 (12.1 %) of theses entries Weight of Evidence approach was flagged by the registrant.

The IUCLID flags to omit the information have been used in 394 (3.8 %) of all ESRs and read-across approaches have been flagged in 2 272 (22.0 %) of ESRs. QSAR was used in 5 ESRs, and other information has been flagged in 498 (4.8 %) ESRs.

For the dossiers of phase-in substances produced at 100 – 1 000 tpa, a total number of ESRs was almost six times less (1 745 ESR entries) than at the higher tonnage described above. Comparison of the distribution of options to fulfil information requirements among ESRs with the results for dossiers at or above 1 000 tpa described above (see Table 4 row 5.1) did not result in the observation of significant differences.

For the non-phase-in substances produced at or above 100 tpa, the results were slightly different. The percentage of experimental studies in total reached only 51.3 % and the read-across approaches have been flagged in only 10.3 % of the ESRs. Weight of Evidence has been only flagged in 2.8 % of all ESRs, while the flags to omit the study have been chosen in 9.1 % of the cases. For non-phase-in substances the registrants have used many more other options to fulfil information requirements (26 % of the ESRs).



Genetic toxicity – in vivo (HH)		
	No. ESR	% ESR
ES	1 852	52.4
TP	18	0.5
RA	875	24.8
FO	221	6.3
WE	389	11.0
QS	0	0.0
MS	177	5.0
Total	3 533	100

Figure 10: Genetic toxicity *in vivo* (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

The registrants submitted in total 3 533 ESRs (100 %) of genetic toxicity *in vivo* studies to fulfil the information requirements for the phase-in substances manufactured or imported at or above 1 000 tpa. The distribution among the different options to fulfil the information requirements under REACH seemed to be similar to the genetic toxicity *in vitro* endpoint. Experimental studies have been used for 1 852 (52.4 %) of all ESRs for this endpoint. In 389 (11.0 %) of these entries a Weight of Evidence approach was flagged by the registrant.

The IUCLID flags to omit the information have been used in 221 (6.3 %) of all ESRs and read-across approaches have been flagged in 875 (24.8 %) cases. Registrants have not used QSAR predictions for this endpoint, and other information has been flagged in 177 (5.0 %) ESRs.

For the dossiers of phase-in substances produced at 100 – 1 000 tpa, the total number of ESRs was again almost six times smaller (596 ESR entries) when compared with the substances produced at or above 1 000 tpa, but no significant differences in the proportional distribution of various options of ESRs were observed (ref. Table 4 row 5.2).

For the non-phase-in substances at or above 100 tpa, almost 50 % of ESRs have been filled with experimental studies data, and the other options have been chosen in 36.2 % of the cases. Read-across approaches have been flagged in only 5.3 % of the ESRs and only one ESR has been flagged as Weight of Evidence.

3.2.7 Toxicity to reproduction

The aims of testing for reproductive toxicity are focused on two related endpoints which are usually tested separately: a prenatal developmental toxicity study analysing possible damaging effects on the developing organism and a reproduction toxicity study covering one or more generations and analysing possible damaging effects on the ability to breed or on the development of the offspring. Both study types are essential for discovering hazards to reproduction and therefore evaluate potentially very serious consequences for human

reproduction as well as foetal and child development. The standard laboratory animals used for these study types are rat, rabbit or mouse for the developmental tests or rat and mouse for the reproduction studies. Alternative *in vitro* tests or stand alone computational prediction methods are currently not able to predict the impact that disturbing single or multiples of these mechanisms could have on the entire reproductive process including the normal postnatal development. Therefore, read-across and grouping or weight of evidence can be used if scientifically justified as possibilities to omit the testing for these endpoints

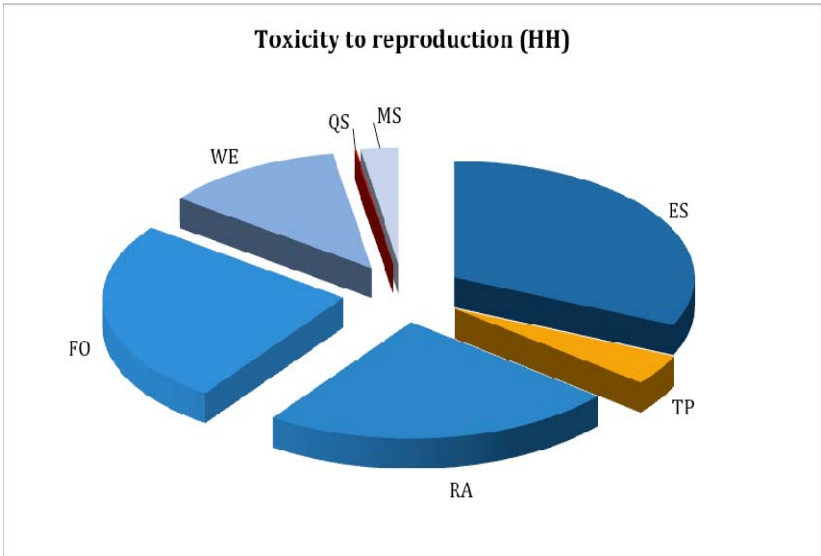
Standard information requirements on toxicity to reproduction under REACH apply for the substances manufactured on imported at or above 10 tpa (Annex VIII-X substances). Possibilities for the registrants to adapt these requirements are addressed in column 2 of relevant Annexes as well as in Annex XI.

For the substances of 10-100 tpa, a reproduction/developmental toxicity screening test (ref. OECD TG 421 or 422) is usually required to meet the core data requirements. There was the possibility to omit this study from the core data set at the time of registration to achieve a technically complete dossier by making testing proposals for higher-tier studies and providing that there were adequate risk management measures. This screening test cannot be used as an alternative or replacement for the higher-tier studies on reproductive toxicity. However, should the screening study show clear adverse effects on reproduction functions or reproductive organs and provided that these screening results are sufficient for classification and risk assessment, there may be no need for further testing.

For substances manufactured or imported between 100-1 000 tpa, in addition to the screening study, a prenatal developmental toxicity study (ref. OECD 414, EU B.31) is usually required. Annex IX provides that this study has to be performed in one species. It is noteworthy that, since the information for developmental toxicity in one species is required by both Annexes IX and X and the requirements are additive, the information requirements from these two Annexes comprise pre-natal developmental toxicity tests in two species. However, according to column 2 of Annex IX, 8.7.2, the decision on the need for performing the test in a second species should be based on the outcome of the study on the first species and all other relevant data.

For substances falling under Annex X requirements of REACH, in addition to the lower tier tests, a two-generation reproduction toxicity study (ref. OECD TG 416, EU B.35) is required.

In Table 4 on endpoint study records (ESR) for reproductive toxicity the total number of entries for this endpoint (toxicity to reproduction, developmental toxicity, and toxicity to reproduction – other studies) is summarised in the rows 6.0, 7.0 and 8.0.



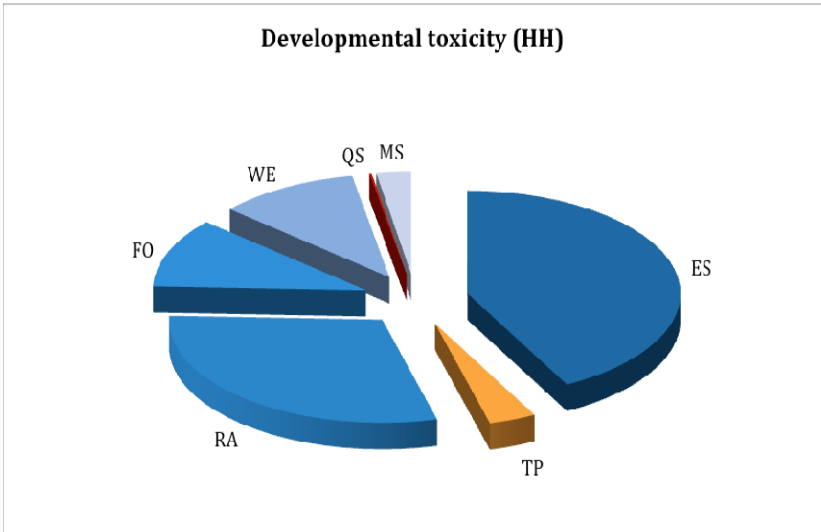
Toxicity to reproduction (HH)		
	No. ESR	% ESR
ES	1 121	31.7
TP	150	4.2
RA	840	23.8
FO	904	25.6
WE	428	12.1
QS	4	0.1
MS	88	2.5
Total	3 535	100

Figure 11: Toxicity to reproduction (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

For the dossiers for phase-in substances at or above 1 000 tpa, registrants submitted 3 535 entries as ESRs. Experimental data have been used for 1 121 (31.7 %) of the ESRs. The IUCLID flags to omit the information have been used in 904 (25.6 %) of these entries, and a read-across approach was selected in 840 ESRs (23.8 %). Registrants also submitted 150 testing proposals to fulfil information requirements for this endpoint – the second highest number of testing proposals among all analysed endpoints and ESRs (Table 4 row 6.0). QSAR predictions were used in 4 ESRs, and miscellaneous studies were submitted in 88 (2.5 %) of the cases.

For the dossiers of phase-in substances produced at 100 – 1 000 tpa, the total number of ESRs was more than seven times less (487 ESR entries) than at the higher tonnage. No significant percentage differences among selected options to fulfil information requirements with the results for dossiers at or above 1 000 tpa described above (see Table 4 row 6.0) were noted. However, only nine testing proposals have been submitted (1.8% of all cases).

For the non-phase-in substances produced at or above 100 tpa, the registrants submitted only 156 ESRs and the chosen options varied from the ones used for phase-in substances. The percentage of experimental studies in total reached only 26.3 % and the read-across approaches have been flagged in only 7.1 % of the ESRs. In contrast to phase-in substances, the flags to omit the study have been chosen in 41 % of the cases. The registrants have also used many more other options to fulfil information requirements (17.3 % of the ESRs).



Development toxicity (HH)		
	No. ESR	% ESR
ES	1 783	42.3
TP	151	3.6
RA	1 254	29.7
FO	460	10.9
WE	451	10.7
QS	7	0.2
MS	111	2.6
Total	4 217	100

Figure 12: Developmental toxicity (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

For the prenatal developmental toxicity, registrants have submitted 4 217 entries for phase-in substances at or above 1 000 tpa. 1 783 ESRs were filled by experimental data (42.3 % of the entries). Registrants submitted the highest number - 151 testing proposals for prenatal developmental toxicity, corresponding to 3.6 % of the ESRs. In 1 254 (29.7 %) of these entries registrants flagged read-across approach. IUCLID flags to omit the study and to use Weight of Evidence have been selected in 10.9 % and 10.7 % of ESRs, respectively.

Only seven entries were filled by the QSAR predictions, while 111 ESRs referred to miscellaneous information (2.6 %).

For the dossiers of phase-in substances produced at 100 – 1 000 tpa, 589 ESR entries were extracted from the IUCLID database. In 260 (44.1 %) of the cases, registrants referred to the experimental studies and submitted 34 testing proposals. A read-across approach has been flagged in 29.5 % of ESRs.

The percentage of experimental studies for the non-phase-in substances at or above 100 tpa reached only 29.8 % and the read-across approaches have been flagged in 9.9 % of the ESRs. IUCLID flags to omit the study have been chosen in 33.1 % of the cases.

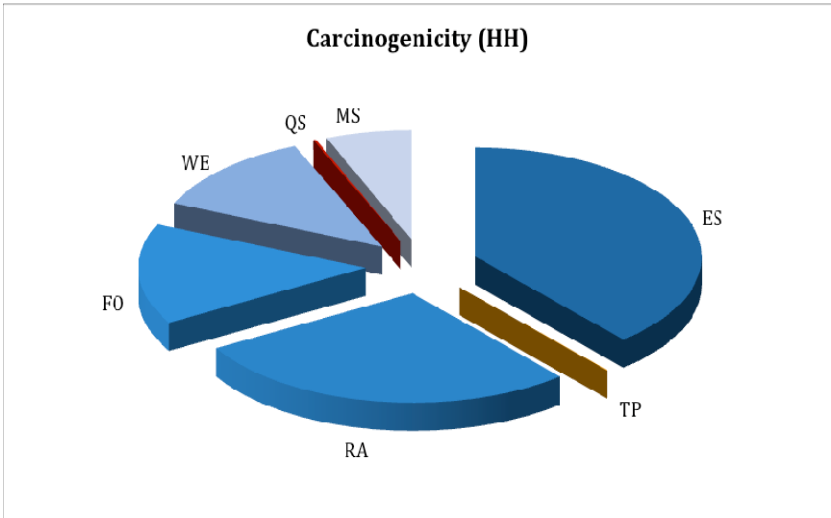
In the above mentioned press release, ECHA has also highlighted that registration dossiers submitted for substances at or above 100 tpa will be considered as technically complete even if they do not contain the results of a screening study for reproductive/developmental study if instead a testing proposal for the higher-tier developmental toxicity study and two-generation study (if applicable for the tonnage) are submitted in the registration and appropriate risk management measures are in place. Among Annex IX dossiers, submitted to ECHA by the first deadline, 175 dossiers did not contain screening for reproductive/developmental toxicity study, but testing proposal for pre-natal developmental toxicity. When screening the Annex X dossiers, ECHA has obtained 61 cases where the approach of registrant was consistent with the conditions above (dossiers did not contain screening study but testing proposals for both prenatal developmental and two-generation reproductive toxicity).

3.2.8 Carcinogenicity

The objective of carcinogenicity studies on chemical substances is to identify potential human carcinogens, their mode(s) of action and their potency. Human data are available for only a few substances; therefore animal tests are generally used for detecting such a property.

Once a substance has been identified as a carcinogen, the next step is to assess whether a known carcinogen is directly genotoxic or not. Exposure conditions are utmost important as the hazard and a mode of action of a carcinogen may be highly dependent on, for example, the route of exposure.

Based on the complexity and length of the process of carcinogenesis, complex biological interactions and many different modes of action involved, even for the same substance, it is not possible to date to get a full understanding and complete mimicking by the use of alternative, non-animal tests. The 2-year cancer assay in rodents, usually the rat or mouse, is typically conducted to evaluate the cancer hazard and potency of a substance. Standard information requirements for carcinogenicity endpoint under REACH are laid down in Annex X, thus they are applicable for the highest tonnage substances (at 1 000 tpa or above). However, the information needs will vary from substance to substance, based on its toxicological properties, use and potential exposure(s). The specific rules and conditions to omit, replace or adapt standard information requirements are provided in column 2 of Annex X, 8.9.1.



Carcinogenicity (HH)		
	No. ESR	% ESR
ES	1 377	38.7
TP	2	0.1
RA	992	27.9
FO	530	14.9
WE	434	12.2
QS	7	0.2
MS	217	6.1
Total	3 559	100

Figure 13: Carcinogenicity (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) ***- Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

For the Annex X phase-in substances, 3 559 ESRs have been submitted on carcinogenicity. 38.7 % of them were experimental studies, in 27.9 % registrants chose read-across approach, 14.9 % of ESRs were flagged as studies to be omitted and in 12.2 % of the entries, a Weight of Evidence approach was flagged by the registrant. Two testing proposals on carcinogenicity have been submitted. QSAR predictions have been proposed seven times.

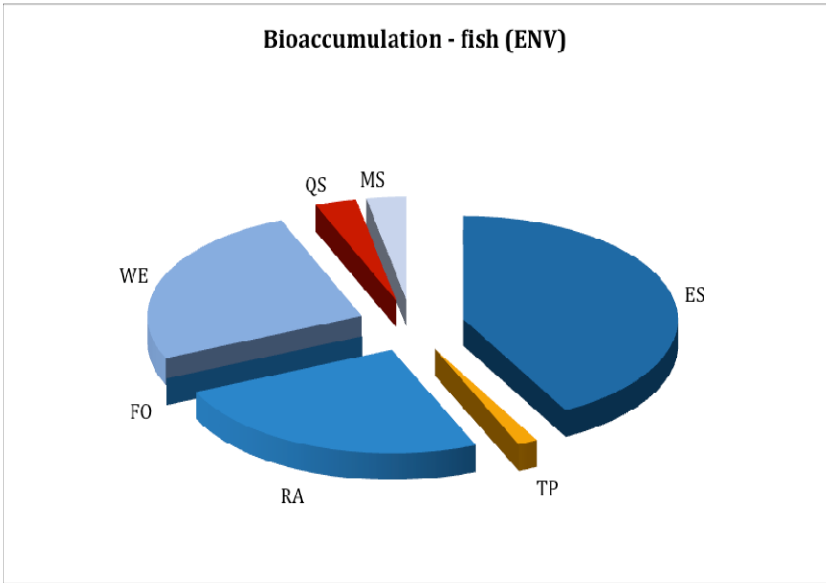
For the dossiers of phase-in substances produced at 100 – 1 000 tpa, in total 451 ESR entries were extracted from the IUCLID database. For this tonnage level, more experimental data were used to cover the endpoint (56.3 % of ESRs). A read-across approach was

selected in 22.2 % of the cases and IUCLID flags to omit the studies have been selected in 13.1 % of the entries. Only 29 ESRs for non-phase-in substances at or above 100 tpa have been found.

3.2.9 Bioaccumulation in fish

Information on accumulation in aquatic organisms is a vital part to understand the environmental fate and behaviour of a substance. This information is used for hazard classification and PBT assessment as well as wildlife and human food chain exposure modelling for the chemical safety assessment. It is also a factor in deciding whether long-term ecotoxicity testing might be necessary. This is because the accumulation of a chemical substance following long-term exposures, even when external concentrations are very low, may result in internal concentrations of a substance which causes toxicity to the organism. Highly bioaccumulative chemical substances may also be transferred through the food web, which in some cases may lead to biomagnification.

Under REACH, standard information requirements on bioaccumulation in aquatic organisms, preferably fish, are included in Annex IX, thus are applicable to substances manufactured or imported at or above 100 tpa. Reliable measured data are preferred if available, but the study needs not to be conducted if the substance has low potential for bioaccumulation or direct and indirect exposure of the aquatic compartment is unlikely. REACH Annex XI also applies, encouraging the use of alternative information at all supply levels before a new test on fish is conducted. Prediction techniques are well developed for many classes of organic substances, and surrogate information (e.g. the octanol-water partition coefficient or Kow) as well as invertebrate tests may sometimes suffice on its own or as part of a weight of evidence approach. For this analysis, as it was focussed only on the use of vertebrates, only those records in which registrants declared the use of fish as the test species were counted i.e.ESRs where either the test species was declared as a species other than fish or was not specified were not counted. Therefore, ESR in which the species related to invertebrates were not analysed for the purposes of this report. The number of testing proposals was confirmed manually.



Bioaccumulation – fish (ENV)		
	No. ESR	% ESR
ES	336	42.1
TP	12	1.5
RA	197	24.7
FO	0	0.0
WE	204	25.6
QS	25	3.1
MS	24	3.0
Total	798	100

Figure 14: Bioaccumulation in fish (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

For the phase-in substances at or above 1 000 tpa, registrants have submitted 798 ESRs related to the fish bioaccumulation study in the IUCLID database. Of these ESRs, 336 (42.1 %) were filled by experimental data. In 197 (24.7 %) of "fish" ESR entries for this endpoint registrants flagged read-across approach. Weight of Evidence option had been selected in 25.6 % of ESRs, and 25 ESRs were filled by QSAR predictions where the fish species was declared. Twelve testing proposals were submitted for the highest tonnage band.

For the selected dossiers of phase-in substances produced at 100 – 1 000 tpa, 278 ESR entries were identified in the IUCLID database. In 59 (21.2 %) of the cases, registrants referred to the experimental studies and submitted 103 (37.1%) ESRs on read-across results. Weight of evidence was flagged in 38.5 % of ESRs. 5 testing proposals have been submitted for this tonnage band.

Twenty ESRs were found for non-phase-in substances at or above 100 tpa and mainly referred to experimental data (70 %), read across (15 %) and other studies (10 %).

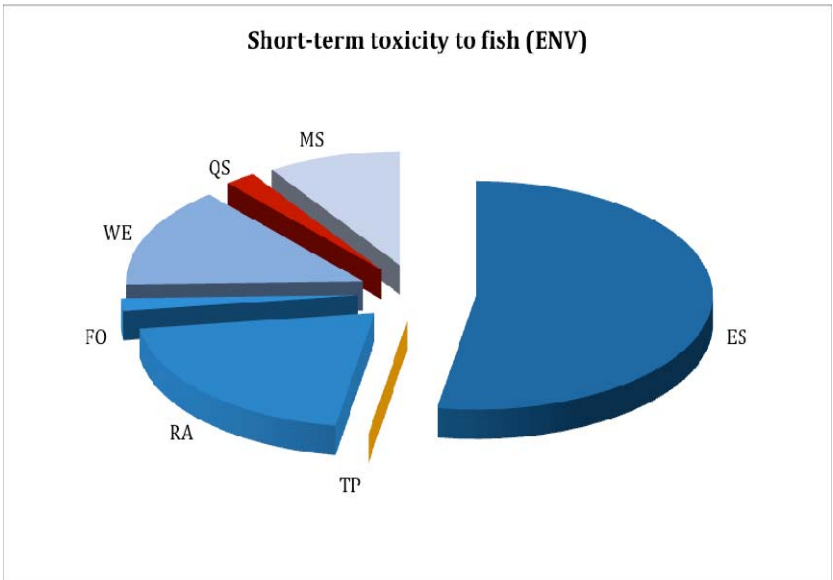
3.2.10 Toxicity to fish

Information on aquatic toxicity is used to assess the hazards and risks of a test substance to freshwater and marine organisms living in the water column. In addition, the data obtained from testing on aquatic species may also serve as a basis for extrapolation of the effects to other compartments such as sediment and soil. Data on fish toxicity are generated for environmental hazard assessment of substances (i.e. classification and derivation of PNEC) and the estimation of toxicity in the PBT assessment.

Short-term toxicity testing on fish is required for substances covered by Annex VIII of REACH (produced or imported in a quantity of at least 10 tpa). However this test does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur (e.g. the substance is highly insoluble in water or the substance is unlikely to cross biological membranes). However, if the chemical safety assessment according to Annex I indicates the need to investigate further effects on aquatic organisms, long-term testing as described in Annex IX shall be considered. Long-term testing should also be considered if the substance is poorly water soluble. Hence, in general acute fish toxicity is part of the core data for all the

registered substances in this study whereas long-term fish toxicity is a higher-tier study to be covered in a testing proposal.

Regarding acceptance of the use of alternative methods covering this endpoint, at present, there are no EU or OECD guidelines for *in vitro* tests of relevance to aquatic toxicity. Regarding the (Q)SAR predictions for aquatic toxicity, the validity of applied models should be assessed according to the OECD validation principles for QSARs (and the criteria mentioned in Annex XI) and the results of the analysis should be reported in detail in a transparent way in the form of a template so called: QSAR model reporting formats (QMRFs) and QSAR prediction reporting formats (QPRFs). In addition there is the possibility to assess toxicity to fish using read-across approaches if scientifically justified.



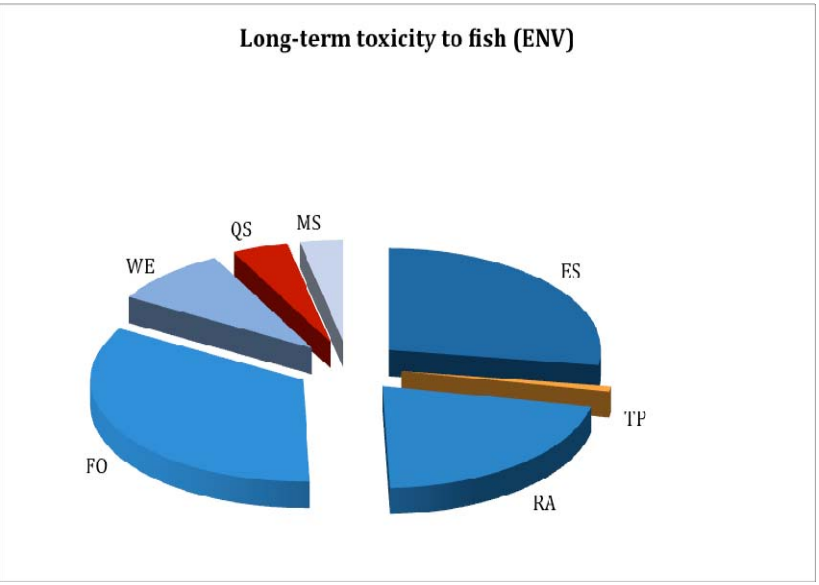
Short-term toxicity to fish (ENV)		
	No. ESR	% ESR
ES	3 653	52.6
TP	0	0.0
RA	1 400	20.2
FO	124	1.8
WE	983	14.2
QS	147	2.1
MS	635	9.1
Total	6 942	100

Figure 15: Short-term toxicity (fish) (1 504 dossiers covering phase–in substances at or above 1 000 tpa, one or more ESRs may be present per dossier) **-** *Legend: (ES) - Experimental studies; (TP) - Testing proposal; (RA) - Read-across; (FO) - IUCLID flags to omit the study ; (WE) - Weight of Evidence; (QS) - (Q)SAR studies; (MS) - Miscellaneous.*

For the short-term toxicity to fish, registrants have submitted 6 942 ESR entries for phase-in substances at or above 1 000 tpa (Annex X). Experimental data were indicated in 3 653 ESRs (52.6 % of the entries). Registrants flagged 1 400 entries as a read-across approach, covering 20.2 % of all ESRs submitted for this endpoint. In 983 (14.2 %) of these entries registrants chose to use Weight of Evidence approach. In 635 cases (9.1% of the ESRs) registrants filled the endpoint by submitting other information. For this endpoint and this tonnage, however, the highest number of QSAR predictions has been found – 147 ESRs, even though, this corresponds to only 2.1% of all extracted entries.

For Annex IX dossiers, 1 405 ESR entries were filled by the registrants. The distribution of the options chosen by the registrants to fulfil information requirements for this tonnage did not differ from the Annex X dossiers (ref. Table 6 row 12.0). However, slightly more read-across approaches (27.3 %) and substantially less QSAR studies (18 ESRs) were submitted.

For non-phase-in substances at or above 100 tpa, in total 143 ESRs have been identified in the IUCLID database (see table 6 row 12.0). The difference between the selected strategies to fulfil information requirements for phase-in and non-phase-in substances was mainly noticeable in the number of miscellaneous studies that reached 28.0 % of the submitted ESRs for analysed dossiers of non-phase–in substances.



Long-term toxicity to fish (ENV)		
	No. ESR	% ESR
ES	899	27.4
TP	27	0.8
RA	697	21.2
FO	1 113	33.9
WE	296	9.0
QS	141	4.3
MS	108	3.3
Total	3 281	100

Figure 16: Long-term toxicity (fish) (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) ***- Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

Registrants have submitted 3 281 ESR entries for long-term toxicity to fish for phase-in substances at or above 1 000 tpa. A total of 899 ESRs were filled by experimental data (27.4 % of the entries) and 27 ESRs – by testing proposals (0.8 % of all entries). IUCLID flags to omit the study and the use of read-across approaches have been selected in 33.9 % and 21.2 % of ESRs, respectively. In 296 (9.0 %) of the ESRs registrants flagged Weight of Evidence. QSAR predictions were reported in 141 ESRs which is a similar amount to those QSAR predicitions found in the short-term toxicity to fish entries.

For the Annex IX dossiers, 812 ESR entries were identified. In 288 (35.5 %) of cases, registrants used experimental data and submitted ten testing proposals. A read-across approach was flagged in 34.7 % of ESRs. Registrants chose to omit studies in 17.1% of submitted entries and in 67 cases a Weight of Evidence approach was taken. Ten ESRs contained QSAR predictions.

In contrast with phase-in, the percentage of experimental studies for the non-phase-in substances at or above 100 tpa reached was 13.9 % while the most frequent option chosen by registrants was to select IUCLID flags to omit the study (65.3 % of the cases).

3.2.11 Long-term or reproductive toxicity to birds

Information on long-term or reproductive avian toxicity needs to be considered only for substances manufactured or imported in quantities of at least 1 000 tpa (i.e. an Annex X requirement).

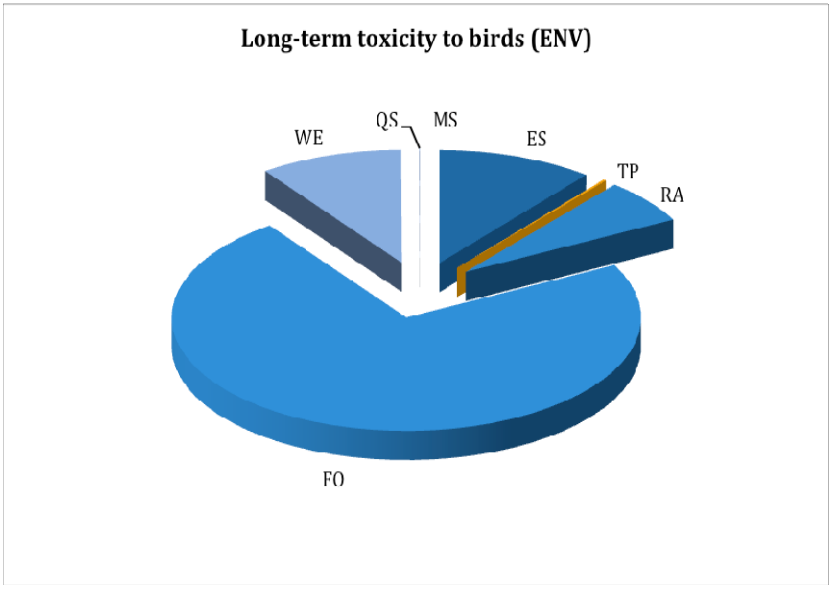
The data may be needed to assess the secondary poisoning risks to predators following chronic exposure to a substance via the fish and earthworm food chains. Given that mammalian toxicity is considered in detail for human health protection, the need for additional data for birds must be considered very carefully – new tests are a last resort in the data collection process. However, birds are fundamentally different from mammals in certain aspects of their physiology (e.g. the control of sexual differentiation, egg laying, etc.), and so mammalian toxicity data are of limited predictive value for birds.

The need to conduct a secondary poisoning assessment is triggered by a number of factors. If these criteria are not met, then further investigation of chronic avian toxicity is

unnecessary. However, if the substance has a bioaccumulation potential and a low degradability (e.g. not readily biodegradable or not hydrolysable) and has also a potential to cause toxic effects if accumulated in higher organisms, a detailed assessment of secondary poisoning should be conducted.

Avian toxicity tests are often carried out for substances with intentional biological activity as a result of other regulatory approval requirements (especially active substances used in plant protection products, veterinary medicines and in biocides). They are rarely performed for most other substances. When available from other regulatory approval requirements such data are relevant for REACH purposes as a source of analogue data or when the substance also has other uses which need to be registered under REACH. In addition avian toxicity data may be considered on a case-by-case basis in the assessment of toxicity for PBT assessment but avian toxicity data will not only be necessary for this purpose alone.

No specific avian *in vitro* methods are currently available or under development.



Long-term toxicity to birds (ENV)		
	No. ESR	% ESR
ES	216	10.8
TP	4	0.2
RA	128	6.4
FO	1 460	72.7
WE	198	9.9
QS	1	0.0
MS	0	0.0
Total	2 007	100

Figure 17: Long-term toxicity (birds) (1 504 dossiers covering phase–in substances > 1 000 tpa, one or more ESRs may be present per dossier) - ***Legend:*** *ES - Experimental studies; TP - Testing proposal; RA - Read-across; FO - IUCLID flags to omit the study; WE - Weight of Evidence; QS - (Q)SAR studies; MS - Miscellaneous.*

For phase-in substances at or above 1 000 tpa for this endpoint ECHA has found 2 007 ESR entries. Only 216 of ESRs contained experimental studies (10.8 % of all ESR entries for this endpoint) and four testing proposals were submitted. In most of the cases (72.7 %), registrants chose to select IUCLID flags to omit the study and to use a weight of evidence approach (9.9 % of ESRs). 128 entries contained data on read-across.

For the Annex IX dossiers, 350 ESR entries were identified. Slightly fewer registrants used experimental data (16.3 % of the cases), yet 41.4 % of the ESRs there was a flag to omit the study. Weight of Evidence approach was chosen in 28.9 % of the entries.

For the non-phase-in substances at or above 100 tpa, only 36 ESRs have been submitted and almost all of them contained IUCLID flags to omit the study (91.7 %).

3.3 Substance approach

This analysis provides the relative proportions of the principal options used by registrants to fill the information requirements by endpoint. These options have been categorised as testing proposals, experimental studies and alternative methods (see section 2.3. for more details).

For some endpoints, the need to address an information requirement is conditioned on findings from other endpoints. For example, if the results of the required *in vitro* tests for mutagenicity are negative, *in vivo* testing may not be required. In such cases there is no obligation for the registrant to enter information. Such situations are characterised by "no data" (ND).

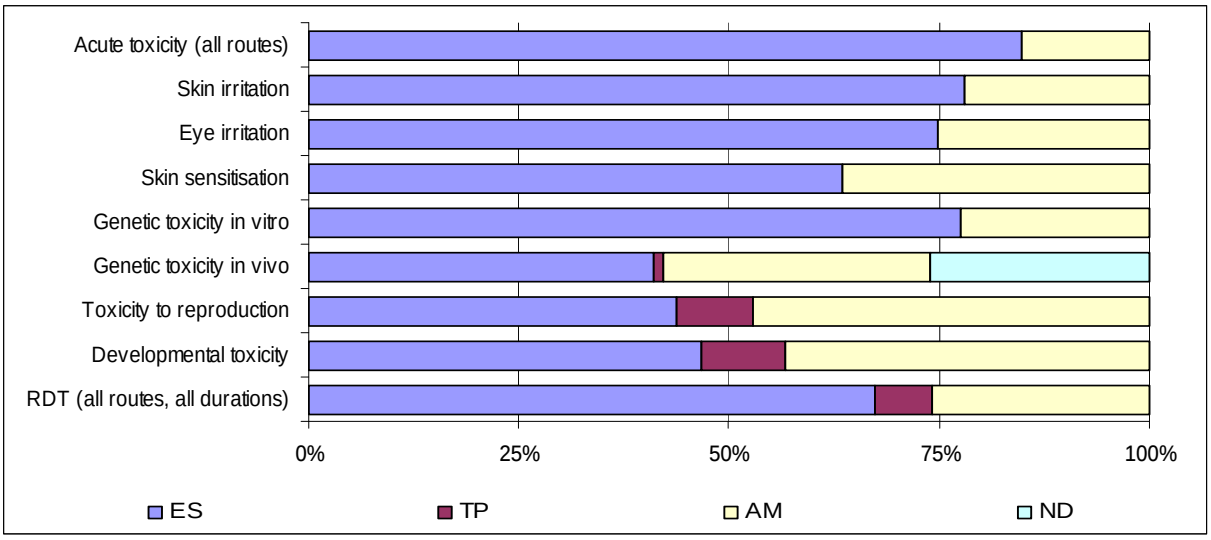


Figure 18: Relative proportions of the principal options to fulfil information requirements for human health endpoints for the substances (phase-in, at or above 1 000 tpa, 1 453 substances) - *Legend; ES - Experimental studies; TP- Testing proposal; AM - Alternative methods; ND - No data .*

This analysis provides an overall relation between experimental studies and alternative options for the REACH relevant endpoints. The experimental studies have been counted per substance without checking the study type or the quality of the information for the endpoints. Therefore, it is important to note that an entry as experimental study under an endpoint does not mean that the information requirement is filled according to the requirements in the REACH Annexes. This is specifically relevant for repeated dose toxicity, toxicity to reproduction and developmental toxicity. The percentages shown in the bar chart represent an upper boundary for experimental data availability for the endpoints. Further analysis, focusing on study types on the basis of the test guideline number only, provides much lower numbers for experimental data availability for these endpoints.

For instance, further analysis at the substance level for repeated dose toxicity, extracting only study types clearly related to 90-day study (Annex IX requirement) or chronic studies, revealed that 465 substances had studies covering such tests, representing about 32 % of 1 453 substances. The gap between the upper and lower boundaries on experimental data availability for this endpoint is mainly due to the presence of 28-day and screening studies.

Further analysis at the substance level for toxicity to reproduction, extracting only study types clearly related to one or more generation studies, revealed that 182 substances had studies covering such tests, representing about 12 % of 1 453 substances. Further analysis for the prenatal developmental toxicity endpoint, extracting only study types clearly related to prenatal developmental toxicity studies, revealed that 425 substances had studies covering such tests, representing about 30 % of 1 453 substances. The gap between the upper and lower boundaries on experimental data availability is mainly due to the screening studies. For example, registrants may report these data in repeated dose toxicity and reproductive toxicity endpoints. They may also refer to screening studies as "other studies" in developmental toxicity endpoint. One reason is that there is no option to report screening studies in the developmental toxicity endpoint in IUCLID separately.

Acute toxicity

For acute toxicity, in 85 % of cases the endpoint was filled with experimental data, the rest was filled with information using only alternative options. Testing proposals are not used for this endpoint since it is not an Annex IX or X requirement.

Skin irritation

In Figure 18, the combined results used to fill the endpoint of skin irritation per analysed substance are shown. In 78 % of the cases the endpoint was filled with experimental data, while in 22 % of the cases registrants chose only alternative options. As for acute toxicity, testing proposals are not used for this endpoint since it is an Annex VII standard information requirement.

Eye irritation

Similarly, as with skin irritation, the eye irritation endpoint was covered by experimental data in 75 % of the cases. No testing proposals are submitted as information requirements for eye irritation also fall under Annex VII of the REACH Regulation.

Skin sensitisation

For this Annex VII endpoint 63 % of data submitted referred to the experimental studies and 37 % of cases were covered by alternative options.

Repeated dose toxicity

Around 67 % of the submitted data were experimental studies. In 7 % of the cases, registrants submitted testing proposals for this endpoint and the remaining 26 % of the entries chosen were covered by alternative options.

Genetic toxicity

The genetic toxicity *in vitro* endpoint was covered by experimental data in more than 77 % of the cases while for the remaining cases alternative options were used. In contrast to the *in vitro* studies, experimental data were only available to cover 41 % of the cases of genetic toxicity *in vivo*. In 32 % of the cases, alternative options to fulfil standard information requirements were chosen, while there were no completed endpoint study records for 26 % of the cases. This is due to the fact that *in vivo* tests may not need to be conducted for this endpoint, depending on the results of the *in vitro* studies.

Toxicity to reproduction and pre-natal developmental toxicity

Specifically for these endpoints, as already explained above, experimental data availability does not mean that the information requirements are filled according to the requirements in the REACH Annexes.

As presented in Figure 18, almost 42 % of the analysed phase-in substances at or above 1 000 tpa already had experimental data on toxicity to reproduction, while in 48 % of the cases registrants used alternative options to cover the endpoint. In 10 % of the cases, registrants have submitted testing proposals.

Experimental pre-natal developmental toxicity studies were available for 47 % of substances, while in 43 % of the cases registrants used alternative options to make their dossiers complete. As for toxicity to reproduction, in 10 % of cases testing proposals were submitted.

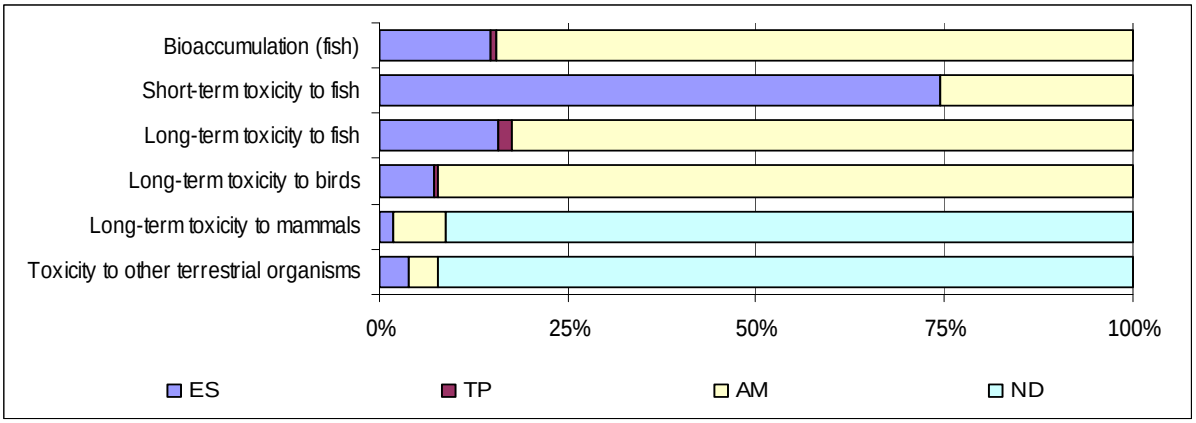


Figure 19: Relative proportions of the principal options to fulfil information requirements on environmental endpoints for the substances (phase-in, at or above 1 000 tpa, 1 453 substances) - ***Legend:*** *ES - Experimental studies; TP- Testing proposal: AM - Alternative methods; ND - No data*

Bioaccumulation (fish)

Experimental data on bioaccumulation in fish were available for only 14.8 % of the analysed substances. For 0.8% of the substances, testing proposals were submitted and for 84.4 % of the substances registrants used alternative options (in most cases, read-across approaches or weight of evidence) to cover this endpoint. Please note that experimental data on invertebrates have been counted as alternative methods for the purpose of this report.

Toxicity to fish

With regard to this endpoint, experimental studies were available for almost 75 % of the cases. Registrants used various alternative options to cover the remaining 25 % of the entries.

For the long-term toxicity to fish, registrants submitted experimental data for only less then 16 % of the covered substances while in 82 % of the cases they used alternative options (justifications to omit the study).

Long-term toxicity to birds

For this endpoint information might be required under Annex X. Experimental data covered only 7 % of the selected substances while in 92 % of the cases registrants chose alternative options (in most cases, justifications to omit the study) to cover this endpoint.

Long-term toxicity to mammals

The availability of experimental data was indicated for 1.8 % of the analysed substances while for 91 % of the substances, registrants reported that no data were available. The remaining 7 % were filled by alternative options.

Toxicity to other terrestrial organisms

The results on data availability for this endpoint were similar those presented for long-term toxicity to mammals. Registrants provided experimental studies for 4 % of the selected substances, while in 92 % of the cases, no data were available.

3.4 Studies conducted or proposed for the purpose of REACH

3.4.1 Studies conducted for the purpose of REACH

For this analysis an assumption was made that studies described in the IUCLID dossier as of 2009 or later had been conducted for the purpose of fulfilling the REACH requirements. It should be noted that this assumption will overestimate the number of new animal studies for two reasons. Firstly some studies may have been conducted for other reasons, e.g. for other non-EU chemical substance control schemes. Secondly the study may have begun earlier but the date of the study report was 2009 or later.

The basis for the year identification is an entry in the IUCLID reference fields. Whenever different dates were indicated for the same study, the oldest date was taken for further analysis assuming that all later dates refer to the literature publications or quotations of the older study. In such a way, double counting of the studies was avoided.

As shown in Table 2, most of the new studies have been conducted on genetic toxicity *in vitro*, thus without involving of vertebrate animals. A substantial number of new studies were also submitted to fill the data gaps for the Annex VII and VIII endpoints (acute toxicity, eye and skin irritation, skin sensitisation, sub-acute repeated dose toxicity, repeated dose/reproductive toxicity screening study, short-term toxicity on fish) that do not require testing proposals *a priori*.

Regarding the performance of new studies on vertebrate animals required for Annexes IX and X after REACH entered into force, new tests were carried out for bioaccumulation in fish, repeated dose toxicity (sub-chronic and chronic duration, all routes), pre-natal developmental toxicity, and reproductive toxicity (one- and two-generation studies). However, in the context of the overall number of all ESRs extracted from registration dossiers of all tonnage bands, and both phase-in and non-phase-in substances, new studies represented less than 1% of the total ESRs extracted for these endpoints (total ESRs are presented in Tables 4 to 6 of Appendix I). Therefore, it can be concluded that registrants mainly used old experimental data as well as the options for the adaptation of the standard information requirements and other alternatives before electing to conduct new studies to meet their obligations and make their registration dossiers compliant under REACH.

Table 2: Studies with the reference date of 2009 or later (all tonnages, phase-in and non-phase-in substances, excluding IUCLID category dossiers and dossiers covering only intermediates). Annex IX and X endpoints counts were manually verified.

Endpoint name	Species usually tested	New experimental study
Skin irritation	*In Vitro*	301
Eye irritation	*In Vitro*	206
Genetic toxicity	*In Vitro*	984
Total number of "new" experimental studies *in vitro*		1 491
Acute toxicity (oral)	Rat or mouse	211
Acute toxicity (inhalation)	Rat or mouse	114
Acute toxicity (dermal)	Rat or mouse	161
Skin irritation	Rabbit	135
Eye irritation	Rabbit	188
Skin sensitisation	Guinea pig or mouse	336
Repeated dose toxicity (oral)	Rat or mouse, subacute	79
	Rat or mouse, subchronic	16
	Rat or mouse, chronic	1
Repeated dose toxicity (dermal)	Rat or mouse, subacute	7
	Rat or mouse, subchronic	1
	Rat or mouse, chronic	0
Repeated dose toxicity (inhalation)	Rat or mouse, subacute	23
	Rat or mouse, subchronic	2
	Rat or mouse, chronic	0
Genetic toxicity	Rat or mouse	33
Carcinogenicity	Rat or mouse	0
Screening studies (OECD TG 422 Or 421 Or EPA Guidelines)	Rat	234
Toxicity to reproduction (One (1) And Two (9) Generation Studies)	Rat or mouse	10
Prenatal developmental toxicity	Rat or rabbit	24
Bioaccumulation: aquatic / sediment	Fish	7
Short-term toxicity to fish	Fish	254
Long-term toxicity to fish	Fish	13
Long-term toxicity to birds	Bird	0
Toxicity to other above-ground organisms		0
Additional ecotoxicological information		0
Total number of "new" experimental studies *in vivo*		1 849
Total number of "new" experimental studies		3 340

For the purposes of generating data for this table, a number of ESRs had a test type assigned by the registrant as "other", which when manually checked were found to be incorrect and reassigned as either in vitro or in vivo, as appropriate.

Acute toxicity

Registrants conducted 211 oral, 114 inhalation and 161 dermal acute toxicity studies with the date of 2009 or later.

Skin irritation

For skin irritation, 301 *in vitro* studies and 135 *in vivo* studies dated at 2009 or later were identified. These numbers demonstrate an increasing use of *in vitro* studies for this endpoint.

Eye irritation

Regarding the new studies conducted for this endpoint (see Table 2), registrants performed almost the same number of *in vitro* and *in vivo* tests dated at 2009 or later (206 and 188 studies, respectively).

Skin sensitisation

For this Annex VII endpoint, as provided in Table 2, 336 *in vivo* studies were dated at 2009 or later.

Repeated dose toxicity

Registrants have conducted 109 28-day repeated dose toxicity studies (all routes), 19 new studies on 90-day repeated dose toxicity (all routes) and one chronic study (oral route) dated 2009 or later.

Genetic toxicity

The registrants conducted 984 *in vitro* studies on genetic toxicity. Regarding *in vivo* tests, 33 studies were dated 2009 or later.

Toxicity to reproduction/prenatal developmental toxicity

In this analysis all reproduction toxicity screening studies dated 2009 or later (performed according to OECD test guideline number 422 or 421, as well as according to the various equivalent US EPA guidelines) have been counted and presented separately as they can be used to fulfil information requirements for Annex VII core data under different endpoints (i.e. repeated dose toxicity and reproductive toxicity). Hence counting them at the endpoint level could lead to double counting, therefore potentially overestimatng the number of tests conducted. Furthermore, some registrants have stated in their dossiers that this screening reproduction toxicity study can be used to meet the higher-tier Annex IX and X data requirements of developmental toxicity and fertility studies instead of making testing proposals. This inappropriate practice results in an incorrect impression that higher-tier two-generation fertility studies or prenatal developmental toxicity studies have been conducted without the submission of a testing proposal. In order to interpret the dossiers with these reproduction toxicity screening studies, all the dossiers had to be checked manually.

After subtracting the screening studies from the total number of studies entered for reproductive toxicity, registrants conducted 10 new one or two-generation reproductive toxicity studies.

After subtracting the screening studies from the total number of studies entered for pre-natal developmental toxicity, 24 studies dated from 2009 or later were detected in the data base.

Bioaccumulation (fish)

Registrants conducted seven studies in 2009 or later. However, as already explained above, the purpose to perform new studies on vertebrate animals without submitting a testing proposal to ECHA cannot be clarified unless a compliance check is opened.

Toxicity to fish

254 new studies were conducted to investigate short-term toxicity to fish. 13 new experimental studies on long-term toxicity to fish were dated from 2009 or later.

The new studies were largely for the core Annex VII and VIII data obligatory for registration, as would be expected, because higher-tier Annex IX and X studies require approval of testing proposals before being conducted. The dossiers analysed demonstrate that companies carried out relatively few new studies for their registration dossiers. In total, 3 340 such studies have been conducted, of which 1 849 involved tests on vertebrate animals. In total 107 Annex IX and X studies appeared to be conducted in the absence of testing proposals. If tests have been conducted without submitting a testing proposal for higher tier tests, the registrant has to justify them. Examples for justifications determined by ECHA so far include testing triggered by non-EU legislation or testing required by a MSCA decision for notified or existing substances (Dangerous Substances Directive 67/548 EEC, and Existing Substances Regulation 793/93 EEC). If ECHA observes that a test was performed for an endpoint, for which a testing proposal is required under REACH, the Member States are informed by ECHA and are responsible for taking, if relevant, enforcement actions.

3.4.2 Studies proposed for the purpose of the REACH Regulation

Registrants have to fulfil the higher-tier data requirements as specified in Annexes IX and X either by providing available data or by submitting a testing proposal intended to obtain the information. They should not undertake new Annex IX or Annex X studies until the decision taking process has been completed and ECHA issues a decision requiring the registrant to carry out a proposed test. When a testing proposal concerns a study involving vertebrate animals, ECHA publishes the name of the substance and the hazard endpoints for which testing is proposed. Third parties are invited to submit scientifically valid information and reports of studies that address the hazard endpoint. This consultation is in essence a call for data to identify specific studies on the substance that might already have been conducted but not available to the registrant, or relevant information on close chemical analogues that can be used for read-across.

Following the end of the consultation period, ECHA will draft one of the following decisions: a decision accepting the testing proposal, a decision accepting the testing proposal with modified conditions, a decision rejecting the testing proposal, or a decision accepting or rejecting the testing proposal but requiring one or more additional tests to be carried out. These draft decisions can also be made if several registrants or downstream users have submitted proposals for the same test. In preparing the draft decision ECHA will take into account all information contained in the registration dossier as well any scientifically-valid information obtained from the public call for data. It may be that ECHA has to add extra vertebrate animal studies to the testing proposal if the registrant has omitted Annex IX or X endpoints without fulfilling the specific rules for adaptation including an adequate scientific justification.

The decision of ECHA involves the consultation of the registrant who submitted the testing proposal, the Member State competent authorities and, if necessary, ECHA's Member State Committee (MSC). Although yet to happen, if the MSC were not able to reach a unanimous agreement, ECHA would refer the draft decision to the European Commission which would take the final decision after further consultation with the Member States. This procedure was established to ensure that the best possible use is made of existing information, and that animal testing is required only when the necessary information is unavailable.

As of February 2011 ECHA now publishes brief conclusions of third parties' comments and information provided during consultations.

Table 3: Testing proposals submitted to ECHA (all tonnages, phase-in and non-phase-in substances, including IUCLID category dossiers)

Endpoint Name	Number
Repeated dose toxicity (oral)	121
Repeated dose toxicity (dermal)	6
Repeated dose toxicity (inhalation)	27
Genetic toxicity (*in vivo*)	25
Carcinogenicity	3
Toxicity to reproduction	231
Developmental toxicity	239
Bioaccumulation: aquatic / sediment	17
Long-term toxicity to fish	38
Long-term toxicity to birds	4
Total	711*

*In addition, two testing proposals have been received for a dermal absorption endpoint. However, this endpoint is not a standard information requirement under Annex IX or X of the REACH Regulation

Between 2008 and February 2011, the Agency received registration for 3 308 phase-in and 1 347 non-phase-in substances (at all tonnages). Testing proposals were made in 574 dossiers covering a total of 1 175 tests, of which 711 were vertebrate animal studies. The totals include 78 substances that were submitted as category dossiers, covering 17 chemical substance categories and testing proposals for 104 animal studies.

The total number of testing proposals submitted to ECHA appears to be at the low end of the range that might have been expected. This is confirmed by the results of compliance checks (see section 4). These results seem to indicate that adaptations to the standard information requirements for higher tier testing are often insufficiently justified and testing proposals should have been submitted for some cases instead. In addition, experimental data provided for the higher tier endpoints, often do not meet the information requirements under the REACH Regulation and testing proposals should also have been submitted in those cases.

4 ECHA evaluation of the use of adaptations to standard information requirement by registrants

It is possible to get an insight into the quality of the information in registration dossiers from the compliance checks which are conducted on some registrations in accordance with the REACH Regulation. The results of such compliance checks performed up to December 2010 are contained in the Article 54 reports on Evaluation published in February each year by ECHA. The latest report covered findings of 2010 and reported results from only a limited number of final decisions. The following conclusions therefore also take into account findings from dossiers still in the decision making process and therefore lacking confirmation by the Member States Competent Authorities.

When interpreting the findings of the ESR analysis, it should be noted that in principle there may be deficiencies discovered in the compliance check dossier evaluation work that result in further animal studies being requested if the quality of either the experimental data or the justifications for the adaptations in the dossiers is discovered to be inadequate. This was found for read-across approaches as well as for the options to omit the study. These two approaches are identified in the current report as the main options used by the registrants for higher tier tests if they did not use experimental data or submitted a testing proposal. It was also noted that for some higher tier test requirements, screening studies had been submitted in place of the actual test(s) specified in REACH. If such results are found under compliance checks, ECHA may be obliged to ask the registrant for the missing information. This may result in additional, new animal testing compared with the results provided in this report.

Another option is that registrants may voluntarily update their dossiers either providing better justifications for adapting standard information requirements or submitting new testing proposals, if the latter is not possible.

ECHA will continue using all available tools to promote a better quality of the dossiers. This will include further efforts to educate registrants in a compliant use of adaptation possibilities, communication efforts to increase voluntary actions and compliance checks to ask for missing information.

5 Conclusions

The principle in REACH of 'one substance one registration' requires that cooperation between potential registrants must be established and that data must be shared and submitted jointly. In general, the sharing and joint submission of information worked and the registrants used it to fulfil the information requirements and to avoid unnecessary animal testing. However, the number of separate registration dossiers for the same substances indicate that the sharing and joint submission of information still needs further improvement.

The REACH Annexes VII-X and XI provide a number of adaptation possibilities allowing registrants to avoid unnecessary animal testing. Registrants made full use of these adaptation options. The data in this report showed that registrants mainly used the results of animal studies conducted prior to the entry into force of REACH. Predicting substance properties by 'read-across' was the second most common means of fulfilling the information requirements, followed by other alternative options.

Registrants submitted testing proposals for the higher-tier studies specified in Annexes IX and X testing before conducting such tests. Fewer testing proposals have been submitted than had been anticipated based on previous estimations made taking into account the estimates of experimental data availability for the higher-tier endpoints. One reason for this appears to be that registrants used other adaptation possibilities before resorting to making a testing proposal. Another reason is that, at least in part, registrants used the 'category' or 'read-across' approach to fill data gaps for these higher-tier studies, i.e. proposing to conduct one study to cover more than one substance.

The report also provides the number of studies that appear to have been conducted for the purpose of the REACH Regulation. Such new studies were largely for the core Annex VII and VIII data obligatory for registration, as would be expected, because higher-tier Annex IX and X studies require the approval of testing proposals before being conducted. In total 107 Annex IX and X studies appeared to be conducted in the absence of testing proposals. This will be further analysed in future compliance checks.

The number of studies using animals conducted or proposed for the purpose of REACH are lower than expected in previous publications predicting animal tests to be performed for REACH Regulation. The reasons are that the number of high tonnage level (Annex X) substances is considered somewhat lower than expected, data sharing was working well between the registrants, and the adaptation possibilities have been fully used by the registrants.

It is possible to get insight into the quality of the information in registration dossiers from the compliance checks which are conducted on some registrations in accordance with the REACH Regulation. When interpreting the findings in this report, it should be noted that in principle there may be deficiencies discovered in the compliance check dossier evaluation work that result in further animal studies being requested if the quality of either the experimental data or alternative approaches in the dossier are discovered to be inadequate.

In the future, ECHA will use all available tools to promote a better quality of the dossiers. This will include further efforts to educate registrants in a compliant use of adaptation possibilities, communication efforts to increase voluntary actions and compliance checks to ask for missing information.

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Appendix I

Table 4 to Table 6 present the available data from endpoint study record (ESR) perspective in detail. It shows the number of ESRs available in the registration dossiers to fulfil a specific endpoint (column 1) for phase-in or non-phase-in substances (Column 2) in a given tonnage band (Column 3). During the creation of study records in IUCLID5, the registrant can classify them according to the purpose of that study record. Column 4 “Total ESR” shows the total number of study records in the IUCLID 5 dossiers. The rest of the columns contain the number of study records according to the classification assigned by the registrant:

- Column 5 “Experimental studies” contains the number of ESRs classified as “experimental result” from the pick-list in the field “Study result type” (abbreviation: ES)
- Column 6 “Testing proposal” shows the number of ESRs employed by the registrant for the testing proposals. These are classified by the registrant as “experimental study planned” from the pick-list of options in the field “Study result type” (abbreviation TP).
- Column 7 “Read-across” contains the number of ESRs classified by the registrant as read-across from the pick-list of options in the field “Study result type” (abbreviation RA).
- Column 8 “IUCLID flags to omit the study”: selected by the registrant to omit the submission of the required data by choosing the appropriate option from those available in the pick-list in the field called “data waiving”. These options are to be used to indicate when testing does not appear to be: scientifically necessary; technically not possible; or not necessary based on low exposure considerations (abbreviation FO).
- Column 9 “Weight of Evidence” consists of the number of ESRs classified by the registrant as weight of evidence in the “purpose flag” pick-list. All cases selected as Weight of Evidence, were counted and not taken into account in more detailed analysis (abbreviation WE).
- Column 10 “QSAR studies” has the number of ESRs classified by the registrant as “(Q)SAR studies” from the pick-list of options in the field “Study result type” (abbreviation QS).
- Column 11 “Miscellaneous” shows the number of ESRs classified by the registrant as “other” from the pick-list of options in the field “Study result type” (abbreviation MS).

Table 4: HH Endpoint Study Records (1 of 2)

1. Test type	2. Phase	3. Tonnage band	4. Total ESR	5. Experimental Studies (ES)	%	6. Testing Proposals (TP)	%	7. Read-across (RA)	%	8. IUCLID flags to omit the study (FO)	%	9. Weight of Evidence (WE)	%	10. QSAR Studies (QS)	%	11. Miscellaneous Studies (MS)	%
1.0 Acute toxicity (all routes)	Phase-In	>1000	12874	7328	56.9	0	0.0	2756	21.4	1184	9.2	1116	8.7	11	0.1	479	3.7
	Phase-In	100to1000	1649	988	59.9	0	0.0	342	20.7	178	10.8	113	6.9	3	0.2	25	1.5
	Non-Phase-In	>100	396	154	38.6	0	0.0	51	12.9	80	20.2	20	5.1	0	0.0	91	23.0
1.1 Acute toxicity (oral)	Phase-In	>1000	5864	3724	63.5	0	0.0	1241	21.2	143	2.4	502	8.6	4	0.1	250	4.3
	Phase-In	100to1000	797	560	70.3	0	0.0	164	20.6	17	2.1	43	5.4	1	0.1	12	1.5
	Non-Phase-In	>100	156	71	45.5	0	0.0	23	14.7	8	5.1	13	8.3	0	0	41	26.3
1.2 Acute toxicity (inhalation)	Phase-In	>1000	3990	2000	50.1	0	0.0	818	20.5	633	15.9	383	9.6	7	0.2	149	3.7
	Phase-In	100to1000	433	207	47.8	0	0.0	94	21.7	97	22.4	26	6.0	2	0.5	7	1.6
	Non-Phase-In	>100	112	26	23.2	0	0.0	13	11.6	53	47.3	5	4.5	0	0	15	13.4
1.3 Acute toxicity (dermal)	Phase-In	>1000	3020	1604	53.1	0	0.0	697	23.1	408	13.5	231	7.6	0	0.0	80	2.6
	Phase-In	100to1000	419	221	52.7	0	0.0	84	20.0	64	15.3	44	10.5	0	0.0	6	1.4
	Non-Phase-In	>100	128	57	44.5	0	0	15	11.7	19	14.8	2	1.6	0	0.0	35	27.3
2.1 Skin irritation (in vitro)	Phase-In	>1000	329	252	76.6	0	0.0	39	11.9	2	0.6	35	10.6	0	0.0	1	0.3
	Phase-In	100to1000	24	20	83.3	0	0.0	2	8.3	0	0.0	2	8.3	0	0.0	0	0.0
	Non-Phase-In	>100	1	1	100.0	0	0.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0
2.2 Skin irritation (in vivo)	Phase-In	>1000	5216	3343	64.1	0	0.0	1113	21.3	216	4.1	402	7.7	5	0.1	137	2.6
	Phase-In	100to1000	600	402	67.0	0	0.0	131	21.8	28	4.7	31	5.2	1	0.2	7	1.2
	Non-Phase-In	>100	157	72	45.9	0	0.0	23	14.6	14	8.9	7	4.5	0	0.0	41	26.1
3.1 Eye irritation (in vitro)	Phase-In	>1000	172	149	86.6	0	0.0	12	7.0	1	0.6	5	2.9	0	0.0	5	2.9
	Phase-In	100to1000	27	19	70.4	0	0.0	6	22.2	0	0.0	2	7.4	0	0.0	0	0.0
	Non-Phase-In	>100	1	1	100.0	0	0.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0
3.2 Eye irritation (in vivo)	Phase-In	>1000	4221	2714	64.3	0	0.0	884	20.9	219	5.2	279	6.6	0	0.0	125	3.0
	Phase-In	100to1000	524	343	65.5	0	0.0	102	19.5	53	10.1	19	3.6	0	0.0	7	1.3
	Non-Phase-In	>100	140	63	45.0	0	0.0	16	11.4	15	10.7	7	5	0	0.0	39	27.9
4.1 Skin sensitisation (in vitro)	Phase-In	>1000	21	10	47.6	0	0.0	6	28.6	0	0.0	5	23.8	0	0.0	0	0.0
	Phase-In	100to1000	4	4	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Non-Phase-In	>100	3	0	0.0	0	0.0	0	0.0	0	0.0	2	66.6	0	0.0	1	33.3
4.2 Skin sensitisation (in vivo)	Phase-In	>1000	3754	2080	55.4	0	0.0	782	20.8	264	7.0	513	13.7	18	0.5	97	2.6
	Phase-In	100to1000	488	283	58.0	0	0.0	119	24.4	0	0.0	72	14.8	3	0.6	11	2.3
	Non-Phase-In	>100	176	73	41.5	0	0.0	27	15.3	35	19.9	4	2.3	0	0.0	37	21.0
5.1 Genetic toxicity (in vitro)	Phase-In	>1000	10322	5908	57.2	0	0.0	2272	22.0	394	3.8	1245	12.1	5	0.05	498	4.8
	Phase-In	100to1000	1745	1128	64.6	0	0.0	308	17.7	53	3.0	206	11.8	0	0.0	50	2.9
	Non-Phase-In	>100	351	180	51.3	0	0.0	36	10.3	32	9.1	10	2.8	1	0.3	92	26.2
5.2 Genetic toxicity (in vivo)	Phase-In	>1000	3533	1852	52.4	18	0.5	875	24.8	221	6.3	389	11.0	0	0.0	177	5.0
	Phase-In	100to1000	596	366	61.4	2	0.3	128	21.5	26	4.4	60	10.1	0	0.0	14	2.3
	Non-Phase-In	>100	94	47	50.0	0	0.0	5	5.3	7	7.4	1	1.1	0	0.0	34	36.2
6.0 Toxicity to reproduction	Phase-In	>1000	3535	1121	31.7	150	4.2	840	23.8	904	25.6	428	12.1	4	0.1	88	2.5
	Phase-In	100to1000	487	146	30.0	9	1.8	118	24.2	138	28.3	47	9.7	0	0.0	29	6.0
	Non-Phase-In	>100	156	41	26.3	7	4.5	11	7.1	64	41.0	6	3.8	0	0.0	27	17.3
7.0 Developmental toxicity	Phase-In	>1000	4217	1783	42.3	151	3.6	1254	29.7	460	10.9	451	10.7	7	0.2	111	2.6
	Phase-In	100to1000	589	260	44.1	34	5.8	174	29.5	71	12.1	32	5.4	2	0.3	16	2.7
	Non-Phase-In	>100	121	36	29.8	13	10.7	12	9.9	40	33.1	4	3.3	0	0.0	16	13.2
8.0 Toxicity to reproduction - other studies	Phase-In	>1000	390	293	75.1	0	0.0	37	9.5	22	5.6	8	2.1	0	0.0	30	7.7
	Phase-In	100to1000	41	22	53.7	0	0.0	2	4.9	10	24.4	7	17.1	0	0.0	0	0.0
	Non-Phase-In	>100	3	2	66.7	0	0.0	0	0.0	1	33.3	0	0	0	0.0	0	0.0
9.0 Carcinogenicity	Phase-In	>1000	3559	1377	38.7	2	0.1	992	27.9	530	14.9	434	12.2	7	0.2	217	6.1
	Phase-In	100to1000	451	254	56.3	1	0.2	100	22.2	59	13.1	26	5.8	0	0.0	11	2.4
	Non-Phase-In	>100	29	4	13.8	0	0.0	7	24.1	14	48.3	0	0.0	0	0.0	4	13.8

Table 5: HH Endpoint Study Records (2 of 2)

1. Test type	2. Phase	3. Tonnage band	4. Total ESR	5. Experimental Studies (ES)	%	6. Testing Proposals (TP)	%	7. Read-across (RA)	%	8. IUCLID flags to omit the study (FO)	%	9. Weight of Evidence (WE)	%	10. QSAR Studies (QS)	%	11. Miscellaneous Studies (MS)	%
10.0 RDT (all routes, all durations)	Phase-In	>1000	10790	4546	42.1	104	1.0	3032	28.1	2033	18.8	709	6.6	9	0.1	357	3.3
	Phase-In	100to1000	1333	538	40.4	32	2.4	355	26.6	262	19.7	101	7.6	0	0.0	45.0	3.376
	Non-Phase-In	>100	359	105	29.2	8	2.2	30	8.4	162	45.1	3	0.8	0	0.0	51	14.2
10.1.1 RDT subacute+screening (oral)	Phase-In	>1000	1704	989	58.0	1	0.1	490	28.8	24	1.4	178	10.4	0	0.0	22	1.3
	Phase-In	100to1000	266	152	57.1	1	0.4	79	29.7	2	0.8	32	12.0	0	0.0	0	0
	Non-Phase-In	>100	60	52	86.7	0	0.0	7	11.7	0	0	0	0	0	0.0	1	1.7
10.1.2 RDT subacute+screening (dermal)	Phase-In	>1000	296	198	66.9	0	0.0	53	17.9	27	9.1	17	5.7	0	0	1	0.3
	Phase-In	100to1000	28	16	57.1	0	0.0	9	32.1	2	7.1	1	3.6	0	0	0	0.0
	Non-Phase-In	>100	9	4	44.4	0	0.0	4	44.4	1	11.1	0	0.0	0	0	0	0.0
10.1.3 RDT subacute+screening (inhalation)	Phase-In	>1000	997	610	61.2	2	0.2	284	28.5	16	1.6	57	5.7	2	0.2	26	2.6
	Phase-In	100to1000	84	64	76.2	0	0.0	18	21.4	0	0.0	2	2.4	0	0.0	0	0.0
	Non-Phase-In	>100	8	5	62.5	1	12.5	1	12.5	1	12.5	0	0.0	0	0.0	0	0.0
10.2.1 RDT subchronic (oral)	Phase-In	>1000	2365	1025	43.3	28	1.2	1072	45.3	38	1.6	184	7.8	0	0.0	18	0.8
	Phase-In	100to1000	303	136	44.9	15	5.0	129	42.6	4	1.3	14	4.6	0	0.0	5	1.7
	Non-Phase-In	>100	37	28	75.7	1	2.7	5	13.5	3	8.1	0	0	0	0.0	0	0
10.2.2 RDT subchronic (dermal)	Phase-In	>1000	276	129	46.7	2	0.7	103	37.3	28	10.1	12	4.3	0	0	2	0.7
	Phase-In	100to1000	26	6	23.1	0	0.0	15	57.7	3	11.5	2	7.7	0	0	0	0.0
	Non-Phase-In	>100	3	0	0.0	0	0.0	3	100	0	0.0	0	0.0	0	0	0	0.0
10.2.3 RDT subchronic (inhalation)	Phase-In	>1000	1366	682	49.9	8	0.7	541	39.6	27	2.0	77	5.6	0	0.0	31	2.3
	Phase-In	100to1000	125	66	52.8	0	0.0	49	39.2	1	0.8	8	6.4	0	0.0	1	0.8
	Non-Phase-In	>100	8	7	87.5	0	0.0	1	12.5	0	0.0	0	0.0	0	0.0	0	0.0
10.3.1 RDT chronic (oral)	Phase-In	>1000	574	266	46.3	0	0.6	189	32.9	19	3.3	85	14.8	3	0.5	12	2.1
	Phase-In	100to1000	94	42	44.7	0	0.0	31	33.0	1	1.1	15	16.0	0	0.0	5	5.3
	Non-Phase-In	>100	8	3	37.5	0	0.0	5	62.5	0	0	0	0	0	0.0	0	0
10.3.2 RDT chronic (dermal)	Phase-In	>1000	40	20	50	0	0.0	7	17.5	13	32.5	0	0.0	0	0	0	0
	Phase-In	100to1000	4	2	50	0	0.0	1	25	1	25	0	0.0	0	0	0	0.0
	Non-Phase-In	>100	0	0	0.0	0	0.0	0	0	0	0.0	0	0.0	0	0	0	0.0
10.3.3 RDT chronic (inhalation)	Phase-In	>1000	340	157	46.2	0	0.0	117	34.4	11	3.2	36	10.6	0	0.0	19	5.6
	Phase-In	100to1000	39	16	41.0	0	0.0	13	33.3	1	2.6	9	23.1	0	0.0	0	0.0
	Non-Phase-In	>100	1	1	100	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
10.4.1 RDT other (oral)	Phase-In	>1000	966	225	23.3	47	4.9	127	13.1	418	43.3	30	3.1	2	0.2	117	12.1
	Phase-In	100to1000	154	29	18.8	14	9.1	11	7.1	59	38.3	9	5.8	0	0.0	32	20.8
	Non-Phase-In	>100	92	3	3.3	6	6.5	1	1.1	36	39.1	1	1.1	0	0.0	45	48.9
10.4.2 RDT other (dermal)	Phase-In	>1000	893	47	5.3	3	0.3	4	0.4	810	90.7	11	1.2	0	0	18	2.0
	Phase-In	100to1000	118	4	3.4	1	0.8	0	0	107	90.7	6	5.1	0	0	0	0.0
	Non-Phase-In	>100	66	0	0.0	0	0.0	3	4.5	61	92.4	1	1.5	0	0	1	1.5
10.4.3 RDT other (inhalation)	Phase-In	>1000	973	198	20.3	13	1.3	45	4.6	602	61.9	22	2.3	2	0.2	91	9.4
	Phase-In	100to1000	92	5	5.4	1	1.1	0	0.0	81	88.0	3	3.3	0	0.0	2	2.2
	Non-Phase-In	>100	67	2	3.0	0	0.0	0	0.0	60	89.6	1	1.5	0	0.0	4	6.0

Table 6: ENV Endpoint Study Records

1. Test type	2. Phase	3. Tonnage band	4. Total ESR	5. Experimental Studies (ES)	%	6. Testing Proposals (TP)	%	7. Read-across (RA)	%	8. IUCLID flags to omit the study (FO)	%	9. Weight of Evidence (WE)	%	10. QSAR Studies (QS)	%	11. Miscellaneous Studies (MS)	%
11.0 Bioaccumulation (fish)	Phase-In	>1000	798	336	42.1	12	1.5	197	24.7	0	0.0	204	25.6	25	3.1	24	3.0
	Phase-In	100to1000	278	59	21.2	5	1.8	103	37.1	0	0.0	107	38.5	0	0.0	3	1.1
	Non-Phase-In	>100	20	14	70.0	0	0.0	3	15.0	0	0.0	1	5.0	0	0.0	2	10.0
12.0 Short-term toxicity to fish	Phase-In	>1000	6942	3653	52.6	0	0.0	1400	20.2	124	1.8	983	14.2	147	2.1	635	9.1
	Phase-In	100to1000	1405	684	48.7	0	0.0	384	27.3	12	0.9	227	16.2	18	1.3	80	5.7
	Non-Phase-In	>100	143	76	53.1	0	0.0	12	8.4	6	4.2	6	4.2	3	2.1	40	28.0
13.0 Long term toxicity to fish	Phase-In	>1000	3281	899	27.4	27	0.8	697	21.2	1113	33.9	296	9.0	141	4.3	108	3.3
	Phase-In	100to1000	812	288	35.5	10	1.2	282	34.7	139	17.1	67	8.3	10	1.2	16	2.0
	Non-Phase-In	>100	101	14	13.9	0	0.0	3	3.0	66	65.3	6	5.9	2	2.0	10	9.9
14.0 Long term toxicity to birds	Phase-In	>1000	2007	216	10.8	4	0.2	128	6.4	1460	72.7	198	9.9	1	0.0	0	0.0
	Phase-In	100to1000	350	57	16.3	0	0.0	36	10.3	145	41.4	101	28.9	0	0.0	11	3.1
	Non-Phase-In	>100	36	0	0.0	0	0.0	0	0.0	33	91.7	1	2.8	0	0.0	2	5.6
15.0 Toxicity to other above-ground organisms	Phase-In	>1000	495	129	26.1	0	0.0	16	3.2	84	17.0	212	42.8	0	0.0	54	10.9
	Phase-In	100to1000	254	84	33.1	0	0.0	2	0.8	7	2.8	131	51.6	0	0.0	30	11.8
	Non-Phase-In	>100	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
16.0 Additional ecotoxicological information	Phase-In	>1000	644	244	37.9	0	0.0	143	22.2	7	1.1	27	4.2	3	0.5	220	34.2
	Phase-In	100to1000	129	18	14.0	0	0.0	26	20.2	1	0.8	7	5.4	3	2.3	74	57.4
	Non-Phase-In	>100	12	2	16.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	10	83.3

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