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## REVIEW

# REACH and reproductive and developmental toxicology: still questions

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Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) is a new chemicals regulation law in the European Union (EU). The law is supplemented by tens of thousands of pages of guidance documents, and the implementation of REACH is still a work in progress. Requirements for chemical testing are based on the annual volume of a chemical or 'substance' that is produced or imported into the EU. These requirements include reproductive and developmental toxicity testing in experimental animals for an annual volume of 10 metric tonnes or more. However, under REACH, the testing in vertebrate animals may not be performed without permission, and the law encourages the use of alternative methods of filling data gaps on the toxicological properties of chemicals. These alternatives might include *in vitro* and structure-activity relationship studies, but the REACH technical guidance indicates that these kinds of studies are not adequate to replace reproductive and developmental toxicity testing in whole animals. The most practical opportunity for the avoidance of whole animal testing may be 'read-across,' a process in which gaps are filled using data from related compounds. A method called 'weight of evidence' under REACH may also be used to avoid whole animal reproductive and developmental toxicity testing based on existing data in regulation and non-regulation studies and based on factors such as chemical structure and anticipated exposure. It is also possible that thresholds of toxicological concerns will be accepted under REACH as a method to avoid vertebrate animal testing.

**Keywords** alternative toxicology tests, developmental toxicity testing, hazard assessment, REACH, reproductive toxicity testing, risk assessment

**Abbreviations** REACH: Registration, Evaluation, Authorization, and Restriction of Chemicals; EU: European Union; ECHA: European Chemicals Agency; EC: European Commission; CAS: Chemical Abstracts Service; UVCB: unknown or variable composition, complex reaction products or biological materials; SIEF: substance information exchange forum; EINECS: European Inventory of Existing Commercial chemical

Substances; OECD: Organisation for Economic Co-operation and Development; SVHC: substances of very high concern; NOAEL: No Observed Adverse Effect Level; EFSA: European Food Safety Authority; QSAR: Quantitative structure-activity relationship.

## Introduction

Although the European Union (EU) law known as REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) has been in force for nearly five years, there remain questions about how the requirements of the law will be implemented, particularly with respect to data requirements in reproductive and developmental toxicology. The 849-page law appears to be clear in its requirements, but the tens of thousands of pages of guidance documents that have been released by the European Chemicals Agency (ECHA) raise the possibility that some of the requirements specified by the law may be subject to modification.

## What is so special about REACH?

### Industry obligations

REACH is a chemicals regulation protocol that departs from the usual pattern of chemical regulation. Under REACH, the responsibility for chemical assessments is shifted to industry. REACH technical guidance documents make it clear that the assessment of chemical safety will be the responsibility of the companies that produce or import chemicals in the European Union and not the responsibility of ECHA or of the REACH competent authorities of the EU member states. According to the June, 2011 report of the agency, "Firstly at its core, REACH places the responsibility on industry. . . This change of mindset, shifting responsibility from regulators to industry, has been challenging for regulators and industry and is not yet fully implemented." [ECHA 2011a].

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What exactly must industry do? We have divided industry responsibilities into eight tasks.

1. Identify the substance: The substance to be registered must be identified by name. In most cases, identification of the substance is straightforward: there is a unique chemical name, European Commission (EC) number, or Chemical Abstracts Service (CAS) registry number. In other cases, the substance is less clearly known, as in poorly defined reaction products or mixtures of related compounds with different side-chain lengths. The term UVCB substances has been introduced to refer to substances of 'unknown or variable composition, complex reaction products or biological materials.' ECHA has produced guidance on the substance identification issue [ECHA 2007].
2. Participate in the substance information exchange forum (SIEF): In the early years of REACH, producers and importers of existing European Inventory of Existing Commercial chemical Substances (EINECS) chemicals were required to pre-register these substances. Pre-registration of each chemical identified which companies had the intention of submitting registrations. All the companies that pre-registered the same substance were put in a SIEF for that substance. The SIEF is a group of companies that must submit a large portion of the registration data necessary for the registration dossier for that chemical as a common document. The purpose of the SIEF under REACH is to prevent the duplication of data, particularly data collected from the use of vertebrate animals. Within the SIEF, companies are obligated to share data on the substance. The owner of the data is expected to be compensated for sharing the data, but sharing is not optional. A company may opt out of SIEF participation if it meets certain requirements and pays a higher registration fee, but opting out is strongly discouraged.
3. Determine the production/import volume: As discussed below, the data requirements under REACH are determined by the volume of the substance to be produced or imported into the European Union annually. For mature product lines, this determination may be straightforward, but products in development may need to rely on best estimates. In addition, while not a legal requirement, practical implementation of the requirements within the SIEF working environment often compels companies to provide forecasts of future production expectations in order to comply with registration requirements.
4. Determine downstream use and fate: Under REACH, the producer or importer of a substance may need to describe what happens to the substance from the time it is placed into commerce until it is destroyed. This requirement calls for the sharing of information up and down the supply chain and may require a producer or importer to obtain confidential business information from its customers and from its customers' customers. This requirement necessitates care in avoiding violations of EU

antitrust measures when communicating sensitive information amongst competitors.

5. Identify data gaps: The SIEF must identify areas in which information is required but for which information of adequate quality may not be available. Working together with competitors on these types of tasks requires an entirely new framework for many organizations.
6. Apply to fill data gaps: In its registration dossier, the SIEF must indicate how it proposes to fill the data gaps that have been identified. If a vertebrate animal study is proposed to fill a data gap, the SIEF or its members must wait until the study is approved by ECHA before they proceed to fill the gap.
7. Notify on classification and labeling: Classification and labeling are activities that antedate REACH in the European Union and elsewhere. The classification and labeling initiative requires that the substance being registered fit into appropriate categories with respect to characteristics such as flammability and toxicity.
8. Submit technical dossier and chemical safety report: These reports are submitted online in the REACH-IT system, using a template developed by ECHA and disseminated via the International Uniform Chemical Information Database (IUCLID) software. These documents are electronically validated for completeness but may not be read by ECHA personnel. ECHA has announced that it plans to perform quality audits on 5 percent of submissions. Much of each submission will be viewable on a public web site.

## Definitions of substances, preparations, and articles

REACH uses the term substance for a chemical element and its compounds, what we might more informally call a chemical. The term preparation is used for a product containing two or more substances. The term article is used for a product if the physical form of the product is more important to the function of the product than is its chemical composition. For example, a toy car would be an article. A real car would also be an article.

There has been disagreement about how discrete an article must be to be considered one article. For example, if an importer brings laptop computers into the European Union, is the entire computer the article or is the computer a collection of individual articles (chips, drives, displays)? The answer to this question becomes important in calculating how much of an article by weight is made up of a particular substance of interest.

## Production and import volume as proxies for exposure

Under REACH, data requirements depend on the volume of a substance that will be produced or imported into the European Union, using annual tonnage as a proxy for the likelihood of or importance of human exposure. Substances produced or imported at less than 1 metric tonne (1,000 kg)

Table 1. REACH toxicology test requirements by tonnage band.

Test	Metric tonnes/year			
	1	10	100	1000
In vitro irritation/corrosion	×	×	×	×
In vitro eye irritation	×	×	×	×
In vivo skin sensitization	×	×	×	×
In vitro mutagenicity (Ames)	×	×	×	×
Acute oral toxicity	×	×	×	×
In vivo skin irritation		×	×	×
In vivo eye irritation		×	×	×
In vitro cytogenicity		×	×	×
Mutagenicity in mammalian cells		×	×	×
Acute inhalation toxicity		×	×	×
Acute dermal toxicity		×	×	×
28-Day repeat dose toxicity		×	×	×
Screening developmental toxicity		×	×	×
90-Day subchronic toxicity			×	×
Developmental toxicity			×	×
≥12-Month toxicity				×
2-Generation reproductive toxicity				×
Carcinogenicity				×

do not require registration under REACH. The registration begins at 1 tonne/year and the extent of toxicological information to be provided increases with tonnage in different tonnage bands as specified in REACH Annexes (Table 1).

Testing for reproductive and developmental toxicity begins at 10 tonnes/year. A screening reproductive/developmental test (Organisation for Economic Co-operation and Development (OECD) Test Guideline 421 or 422) is required at 10 tonnes/year and above. A prenatal (embryo-fetal) toxicology test (OECD Test Guideline 414) is required at 100 tonnes/year and above. A two-generation reproductive test (OECD Test Guideline 416) is required at 1,000 tonnes/year. Although the requirement for the two-generation test is written into the law, it appears likely that an extended one-generation reproductive test (OECD Test Guideline 443) will come to be accepted to meet this requirement.

The timetable for registration is also dependent on the tonnage band. For substances produced or imported at ≥1,000 tonnes/year, the registration deadline was November 30, 2010. Substances that are carcinogenic, mutagenic, or toxic to reproduction (defined below) also had a registration deadline of November 30, 2010 as long as they were produced or imported at ≥1 tonne/year. The deadlines for substances produced or imported at ≥100 tonnes/year is May 31, 2013, and the deadline for substances produced or imported at ≥1 tonne/year is May 31, 2018.

### The SIEF experience in 2010

The first round of registrations were due at the end of 2010, and ECHA produced a report in June, 2011 describing certain aspects of the process. Table 2 shows the distribution of SIEF size, based on preregistration data. For several thousand substances, SIEFs were constituted of more than 100 member companies, and for tens of thousands of substances, SIEFs contained 10 or more members. These figures suggest that considerable difficulties in organization needed to be

Table 2. Size distribution of SIEFs.

SIEF size (no of companies)	Substances	% total (of substances)
5000 +	2	0.0
1000–4999	146	0.1
500–999	290	0.2
200–499	1 115	0.8
100–199	1 946	1.3
75–99	1 241	0.8
50–74	2 539	1.7
25–49	8 542	5.8
10–24	28 973	19.7
4–9	60 647	41.3
3	4 023	2.7
2	5 108	3.5
1	32 207	21.9
<b>Total number</b>	<b>146 779</b>	<b>100.0</b>

Source: from [ECHA 2011a].

overcome and that an unusual degree of cooperation among competitors was required. At this writing, there are no official accounts of how successful the SIEF process was in producing joint submissions of adequate quality. There are, however, anecdotal accounts suggesting that the process did not work smoothly in all instances.

### The Questions

We have formulated three interrelated questions that are relevant to reproductive and developmental toxicity testing and, indeed, all toxicity testing under REACH. We do not propose to have answers to these questions, although we will offer speculations about the answers.

#### Will hazard always trump risk assessment?

Hazard refers to a presumed innate toxicity of a substance. Simply put, hazard identification asks the question: “Is this chemical toxic?” Risk, on the other hand, recognizes that toxicity depends on characteristics of the exposure, including the exposure level and assumes that under some exposure levels, all chemicals can produce toxicity. Risk assessment asks the question, “Under what exposure conditions is this chemical toxic and how close are those conditions to human exposure?” US regulatory agencies (e.g., the Environmental Protection Agency, the Occupational Safety and Health Administration) regulate based on risk.

REACH is fundamentally based on hazard identification. Although REACH provides for the assessment of exposure and the characterization of risk, hazard assessment comes first and can drive regulation independent of exposure. Under REACH, there is a category of substances called substances of very high concern (SVHC). These substances are characterized as: i) carcinogenic, ii) mutagenic, iii) toxic to reproduction, iv) persistent, bioaccumulative, and toxic, v) very persistent and very bioaccumulative, and vi) endocrine disruptors for which there is scientific evidence of probable serious effects to human health or the environment.

The delineation of SVHCs is set forward in Article 57 of REACH, the exact text of which is reproduced in Table 3.

Table 3. The text of Article 57.

## Substances to be included in Annex XIV

The following substances may be included in Annex XIV in accordance with the procedure laid down in Article 58:

- (a) substances meeting the criteria for classification as carcinogenic category 1 or 2 in accordance with Directive 67/548/EEC;
- (b) substances meeting the criteria for classification as mutagenic category 1 or 2 in accordance with Directive 67/548/EEC;
- (c) substances meeting the criteria for classification as toxic for reproduction category 1 or 2 in accordance with Directive 67/548/EEC;
- (d) substances which are persistent, bioaccumulative and toxic in accordance with the criteria set out in Annex XIII of this Regulation;
- (e) substances which are very persistent and very bioaccumulative in accordance with the criteria set out in Annex XIII of this Regulation;
- (f) substances - such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties, which do not fulfil the criteria of points (d) or (e) - for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59.

Source: REACH

The definition of toxic to reproduction includes impairment of fertility or development or should be regarded as impairing fertility or development in humans based on epidemiology studies or based on well conducted experimental animal studies in which the reproductive effects are not due to generalized toxicity, poor animal husbandry, infection, or malnutrition. The toxic to reproduction category is a feature of the classification and labeling system in use in Europe and elsewhere prior to the REACH legislation. The new element in REACH is an incorporation of this labeling system into the definition of SVHC, which is a creation of REACH.

The endocrine disruptor criterion for an SVHC raises another hazard question. Endocrine disruption is a term denoting a mechanism, actually several mechanisms, rather than a toxic endpoint. For a substance to be placed on the SVHC list specifically for this criterion would imply that the substance interferes with endocrine activity but does not interfere with reproduction. Given the current conception of endocrine disruption as involving estrogenic, androgenic, or thyroid endpoints, a scenario in which there is interference with endocrine activity without an interference with reproduction appears unlikely. It is possible that ECHA intends to extend the endocrine disruption idea to other hormone systems or that ECHA intends to consider substances for SVHC status based on screening tests for endocrine activity rather than based on the apical endpoints that come from standard whole animal studies.

The SVHC list was updated in June, 2011 and appears in Table 4. This list is modified periodically based on dossiers submitted by European Union member states and by ECHA at the direction of the EU itself. Substances on the SVHC list will require authorization prior to production or import into the European Union. Authorization, which may be conditional, requires showing that there is no less toxic substance that can be substituted and that marketing

Table 4. Substances of Very High Concern, including candidates added August 29, 2011.

Acrylamide	Diisobutyl phthalate
Alkanes, C10-13, chloro (short chain chlorinated paraffins)	N,N-dimethylacetamide (DMAC)
Aluminosilicate refractory ceramic fibers	2,4-Dinitrotoluene
Ammonium dichromate	Disodium tetraborate, anhydrous
Anthracene	2-Ethoxyethylacetate
Anthracene oil	2-Ethoxyethanol
Anthracene oil, anthracene paste	Formaldehyde, oligomeric reaction products with aniline (technical MDA)
Anthracene oil, anthracene paste, anthracene fraction	Hexabromocyclododecane (HBCDD) and all major diastereoisomers
Anthracene oil, anthracene paste, distn. lights	Hydrazine
Anthracene oil, anthracene-low	Lead azide
Arsenic acid	Lead chromate
1,2-Benzenedicarboxylic acid	Lead chromate molybdate sulphate red (C.I. Pigment Red 104)
Benzyl butyl phthalate (BBP)	Lead diazide
5-tert-Butyl-2,4,6-trinitro-m-xylene (musk xylene)	Lead dipicrate
Bis (2-ethylhexyl)phthalate (DEHP)	Lead hydrogen arsenate
Bis(2-methoxyethyl) ether	Lead styphnate
Bis(2-methoxyethyl) phthalate	Lead sulfochromate yellow (C.I. Pigment Yellow 34)
Bis(tributyltin)oxide (TBTO)	2-Methoxyaniline; o-Anisidine
Calcium arsenate	2-Methoxyethanol
Chromic acid	1-Methyl-2-pyrrolidone
Oligomers of chromic acid and dichromic acid	Pentazinc chromate octahydroxide
Dichromic acid	Phenolphthalein
Chromium trioxide	Pitch, coal tar, high temp
Cobalt dichloride	Potassium chromate
Cobalt(II) carbonate	Potassium hydroxyoctaoxodizincatedichromate
Cobalt(II) diacetate	Potassium dichromate
Cobalt(II) dinitrate	Sodium dichromate
Cobalt(II) sulphate	Strontium chromate
DHNUP (di-C7-11 branched and linear alkyl esters)	Tetraboron disodium heptaoxide, hydrate
4,4'-Diaminodiphenylmethane (MDA)	4-(1,1,3,3-Tetramethylbutyl) phenol, (4-tert-Octylphenol)
Diarsenic pentaoxide	Trichloroethylene
Diarsenic trioxide	1,2,3-Trichloropropane
Dibutyl phthalate (DBP)	Triethyl arsenate
1,2-Dichloroethane	Trilead diarsenate
2,2'-dichloro-4,4'-methylenedianiline (MOCA)	Tris(2-chloroethyl)phosphate
Dichromium tris(chromate)	Zirconia aluminosilicate refractory ceramic fibers
DIHP (di-C6-8-branched alkyl esters, C7-rich)	

Adapted from: [http://echa.europa.eu/chem\\_data/authorisation\\_process/candidate\\_list\\_table\\_en.asp](http://echa.europa.eu/chem_data/authorisation_process/candidate_list_table_en.asp) as modified by [http://echa.europa.eu/news/pr/201108/pr\\_11\\_20\\_svhc\\_consultation\\_20110829\\_en.asp](http://echa.europa.eu/news/pr/201108/pr_11_20_svhc_consultation_20110829_en.asp)

of the SVHC chemical entails a benefit to the public that offsets the risk. The marketing or import of a SVHC will require submission of a risk management plan that indicates, among other things, how danger to human beings will be monitored and controlled.

The presence of a SVHC must be reported to recipients of that article if the SVHC constitutes more than 0.1% by weight of the article. The reporting requirement may change if the definition of an article changes. For example,



a SVHC in a computer chip will represent a higher percentage by weight if the article is considered the chip than if the article is considered the computer in which the chip is located or the automobile in which the computer is located. In June 2011, France announced that it considers the article to be the smaller functional unit even though ECHA guidance indicates that the article is the larger unit [Bureau Veritas 2011].

In addition to the list of SVHCs, which has been constructed only since REACH was enacted, the law includes a listing in Annex XVII of restricted substances, preparations, and articles. This list includes the name of the substance or category of substances and the specific restrictions for each substance. REACH also includes a listing of carcinogens. Exposure is not entirely neglected under REACH; it enters into the risk characterization step and, as we will see, very low exposures might have an impact on the way testing requirements are interpreted.

### Can exposure level be used to modify requirements?

If a chemical does not appear in Annex XVII, there is no automatic restriction, and the chemical needs to be evaluated for toxicity. As we have discussed, the number of studies required to characterize the potential toxicity of a chemical depends on its tonnage band. In some instances, it may be reasonable to modify the requirement for testing based on low anticipated human exposure.

REACH recognizes that toxicity is a function of exposure level, and the description of anticipated human exposure enters into the REACH process in the preparation of the Chemical Safety Report, which is a document required for substances at the 10 tonne and above bands. The Chemical Safety Report is written, in theory, after the toxicology data are accumulated and includes presentation of those data. Would it be possible when data are missing to assert that the data are not necessary based on low anticipated exposure? A related question is whether low human exposure can be used to justify authorization for an SVHC and, if so, how low the exposure would have to be in comparison to exposure levels shown to produce adverse effects in experimental studies.

ECHA considers human exposure in evaluating whether to waive requirements for testing. The guidance on information requirements and chemical safety assessment contains a chapter on adaptation of requirements that indicates that testing might be waived if there is, variously, no exposure, no relevant exposure, or no significant exposure [ECHA 2010]. The criteria for these categories of no/low exposure were not given, but a paper from the German Federal Institute for Risk Assessment suggests that significant/relevant exposure could be defined by endpoint-specific thresholds of toxicological concern [Bernauer et al. 2008].

Thresholds of toxicological concern are exposure levels that have been empirically determined to be without the likelihood of harm based on data from other chemicals rather than from the chemical under question. Based on structural characteristics, chemicals are divided into one of three classes. For each class, a large number of experimental animal studies have been reviewed and no observed adverse effect levels (NOAELs) determined.

The distribution of NOAELs from these studies is examined and a point at the low end of the distribution (10<sup>th</sup> or 5<sup>th</sup> percentile) selected. Cumulative uncertainty factors of 100, 500, or 1,000 have been applied to derive the threshold of toxicological concern for that class. This method has been adopted by the US Food and Drug Administration for food contact materials and by the European Food Safety Authority (EFSA) for flavorings. EFSA is currently considering using this method for other chemicals in food [EFSA 2011].

### Can experimental animal studies be avoided?

Although REACH requires data from large numbers of toxicology studies for registration of high production-volume compounds (Table 1), the law also includes a prohibition against the performance of studies in vertebrate animals to provide those data. Article 13 of REACH states, "In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests..." and Article 25 states, "In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort." Registrants that have identified a data gap for which vertebrate animal testing is proposed must obtain permission from ECHA prior to conducting that testing.

REACH requires that alternatives to vertebrate animal testing be considered, and there is information in a Guidance document about these alternatives [ECHA 2008a]. *In vitro* testing and use of quantitative structure-activity relationships (QSAR) are considered as possible alternatives to vertebrate animal testing. The Guidance document makes clear, however, that with respect to reproductive and developmental toxicity, the available *in vitro* tests and QSAR methods are not adequate substitutes for whole-animal tests, although they may provide alerts that prompt additional testing.

The Guidance document suggests that a method called 'read-across' may provide adequate information for the avoidance of vertebrate animal testing. Read-across refers to inferences made from data on related compounds. For example, a phthalate diester with a side-chain length six carbons in length might be considered likely to cause male reproductive toxicity, because other phthalate diesters with six-carbon side chains have been shown to do so. There are no specific rules for how closely substances must be related to one another in order to take advantage of read-across opportunities, but ECHA provides information on general principles for the use of read-across methods [ECHA 2008b]. It is likely that the acceptability of read-across efforts will be decided on a case-by-case basis.

There is also a method that ECHA calls a weight of evidence approach that integrates available information from guideline tests, non-guideline tests, and other types of information. This weight of evidence approach can be used to justify the waiving of vertebrate animal testing requirements. Exposure can be a part of the weight of evidence argument if it can be shown to be sufficiently low. As discussed above, in Can exposure level be used to modify requirements?, the use of toxicological thresholds of concern may be one route to the waiving of testing requirements using the weight of

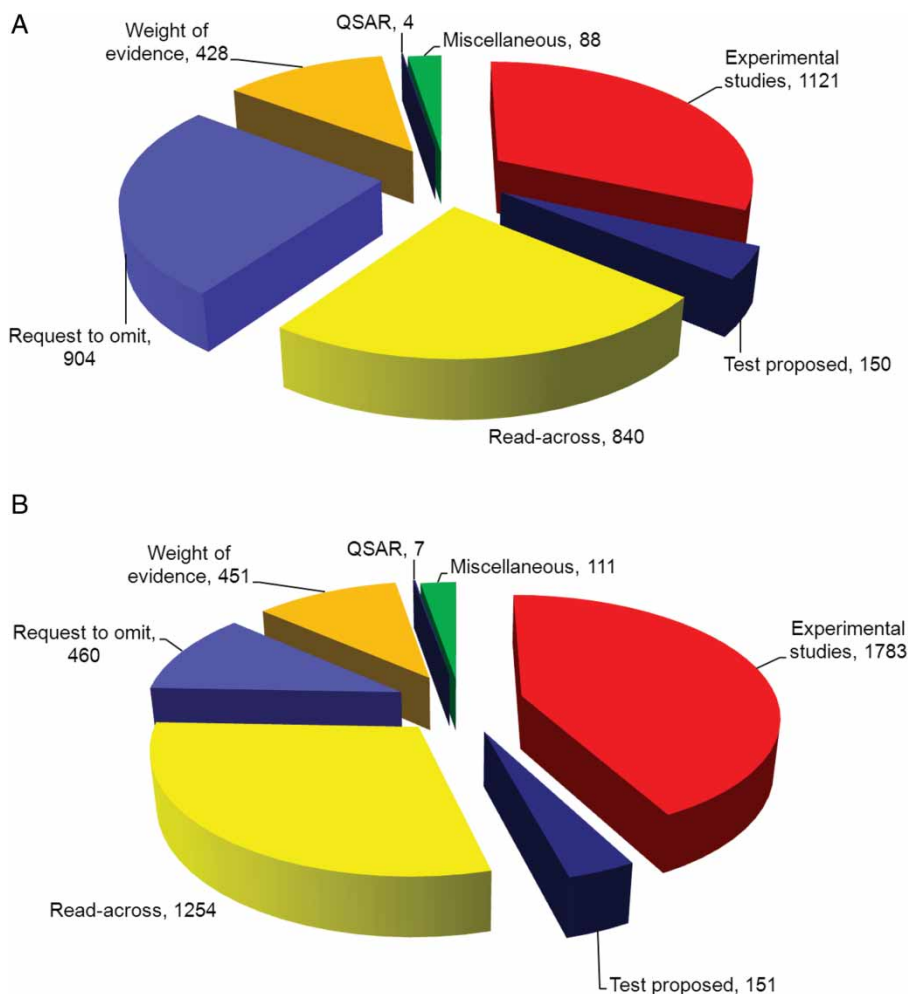


Figure 1. Distribution of requested actions in response to data gaps in reproductive toxicity testing. A)  $n = 3,535$  submissions and developmental toxicity testing; B)  $n = 4,217$  submissions. QSAR: qualitative structure-activity relationships. Redrawn from ECHA [2011b].

evidence approach. Weight of evidence applications also have included the use of QSAR modeling and data from sub-chronic toxicity and genotoxicity testing to assert that a given substance is of very low toxicity and should be exempted from whole-animal reproductive toxicity testing.

ECHA released a report in June 2011 on the proposed use of alternatives to vertebrate animal testing to fill data gaps. Figure 1 shows the distributions of samples of applications for the waiving or meeting of requirements in reproductive and developmental toxicology. Requests to perform vertebrate animal testing occurred in about one-third of samples, and two-thirds of samples proposed alternative methods for satisfying or waiving the requirements. At this writing, it is too early to report how ECHA will respond to these requests. The implementation of REACH in this regard is still a work in progress.

## Conclusions

REACH is a new kind of chemical regulation in which the responsibility for chemical assessment is placed on the importer or producer of a substance. Testing requirements are triggered by the annual tonnage. REACH specifies the whole-animal

reproductive and developmental toxicity testing required for each tonnage band but at the same time prohibits new vertebrate animal testing without permission. The use of methods of filling data gaps other than vertebrate animal testing is encouraged. Although ECHA recognizes the existence of *in vitro* and QSAR methods, it does not consider these methods adequate to replace whole-animal testing. Rather, the use of read-across appears to be the preferred method of filling data gaps. Weight of evidence approaches in which the toxicity of a compound is characterized with available information from guideline and non-guideline studies can be used to request that testing requirements be waived. The extent to which such approaches will succeed under REACH is not known at the present time.

**Declaration of interest:** The authors report no conflicts of interest.

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