Ten Years of REACH — An Animal Protection Perspective

Katy Taylor

European Coalition to End Animal Experiments (ECEAE) and Cruelty Free International Trust, London, UK

Summary — It has now been 11 years since the EU's new chemicals legislation (*Regulation No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals* [REACH]) came into force. Two important statements in the REACH Regulation in relation to animal testing and alternatives are: Article 1(1), which states that one of its purposes is to promote alternative methods; and Article 25(1), which states that animal testing should be used as a last resort. This review looks at the mechanisms that were put in place within REACH to achieve these aims and asks, not only if they are being implemented properly, but also if they have been sufficient. Whilst the chemical industry has heavily used data-sharing and read-across, this review concludes that nevertheless over 2.2 million animals have already been used in new tests for REACH registrations. This equates to an annual average of 275,000 animals; 58,000 more per year than the best-case estimate made by the European Commission in 2004. The use of *in vitro* and (Q)SAR approaches as standalone replacements for animal tests has been relatively low. The levels of funding for research into alternative methods remain low, and there are concerns over the speed of formal adoption of those that have been validated. In addition, there have been issues with the recognition that testing as a last resort and the promotion of alternative methods applies to all parties, including the Commission, Member States and the agency responsible, the European Chemicals Agency. This review provides ten recommendations for better implementation of these two key aspirations, as well as lessons to be learned for future similar legislation.

Key words: *alternative methods, animal protection, animal testing, EU legislation, REACH.*

Address for correspondence: *Katy Taylor, European Coalition to End Animal Experiments (ECEAE) and Cruelty Free International Trust, 16a Crane Grove, London N7 8NN, UK.*
E-mail: *katy.taylor@crueltyfreeinternational.org*

Introduction

It has now been 11 years since the EU's new chemicals legislation came into force on 1 June 2007, the *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)* (1). The main objective of REACH is: "the safe manufacture and use of chemicals so as to protect human health and the environment, at the same time as enhancing innovation and the competitiveness of EU industry" (2). One of the main mechanisms by which this is to be achieved is the requirement that all substances manufactured or imported into the EU are registered with all their relevant safety information, with the new European Chemicals Agency (ECHA; see *Glossary* for further details). This applies to all new and existing substances produced or imported at one tonne or more per producer or importer, per year. The registration information required includes physical chemical property information, (eco)toxicological information, and information on the use and the risk management measures taken to limit exposure of those substances considered to be harmful. Much of the toxicological information is addressed by tests on vertebrate animals.

As the scientific representative of Cruelty Free International and the European Coalition to End Animal Experiments (ECEAE), I have had direct experience of the REACH Regulation since its implementation. ECHA has just reached its 10-year anniversary, the second European Commission (Commission) review of REACH has just been published (3), and the final deadline for the registration of all remaining existing substances has also just passed (1 June 2018). As all these milestones have been reached, it feels pertinent to review REACH specifically from the perspective of animal welfare, which to my knowledge has not yet been done.

The ECEAE is an umbrella organisation, currently representing 24 animal protection organisations across 22 EU Member States. It constitutes Europe's leading alliance, peacefully campaigning on behalf of animals in laboratories, and is managed by Cruelty Free International, the UK member. The ECEAE was heavily involved in the negotiations during the drafting of the REACH Regulation, and has since closely followed the progress of its implementation. The ECEAE has had stakeholder observer status at ECHA since its establishment in 2008, an expert observer seat at the Member State (MSC) and Risk Assessment (RAC) Committees since stakeholders were first

permitted, and a seat on the Competent Authorities for REACH and CLP (Classification, Labelling and Packaging) expert advisory group to the Commission (CARACAL) since 2012. It has recruited toxicologists to comment on the testing proposal system, starting with the very first proposal published in 2009. It has submitted complaints to the European Ombudsman (the Ombudsman) and intervened in Board of Appeal (BoA) cases. It has produced its own reports and presentations on alternative methods, to assist registrants with avoiding animal testing. Therefore, ECEAE members are in a strong position to be able to review the implementation of REACH, and the extent to which animal welfare has been addressed.

The purpose of this review is to provide ECEAE's perspective on the extent to which the aims of REACH are being achieved, particularly with regard to: a) the promotion of alternative methods, and b) the use of animal testing as a last resort. It will look at the mechanisms within REACH that were put in place to achieve these aims, and ask if they are being implemented properly and if they are sufficient. Furthermore, it will consider the role that the animal protection movement has played in supporting these two aims, as well as the roles of the chemical industry, the Commission, the Member States and ECHA. The review draws upon previously published (and unpublished) evidence, as well as ECHA reports, which contain data from registrations on the use of alternatives and the extent of animal testing.

However, this review is not exhaustive. It does not cover the issue of whether the other aims of REACH — i.e. the protection of human health and the environment — are being achieved. It also does not cover transparency issues, such as access to information on substances, or other legal issues, such as the powers of the BoA or the relationship with the animal testing bans under *Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products* (the Cosmetics Regulation; recast; 4). It is *not*, in fact, a review of whether the improvements to human and environmental health as a result of REACH have outweighed the time, money and animal suffering that it has undoubtedly cost. That would be a much greater piece of work, hopefully to be attempted by the Commission in time.

Animal Testing Concerns during Negotiations on REACH

In 2001, the Commission published a White Paper outlining its plans for a new legislative scheme for industrial chemicals (5). The previous system was built on several pieces of law, including *Commission Directive 93/67/EEC* of 20 July 1993, which laid down the principles for assessment of risks to man and the environment of substances notified in accordance with *Council Directive 67/548/EEC* (6). This left a degree of discretion to Member States in its implementation, and was therefore causing disparities between Member States in their testing requirements and uncertainty for the industry. There was also consensus that the risks to human health and the environment of chemicals on the EU market were not being properly assessed and acted upon. The White Paper proposed that the industry should be required to ensure that all the "knowledge gaps" on the safety and use of chemicals were addressed, including for all substances already on the EU market (5).

A UK report that soon followed the White Paper estimated that 12.8 million animals could be needed to fill these data gaps (7). This caused a high level of concern in the animal protection movement. The environmental lobby accused the report of "scaremongering" (8), and an estimate from the Commission in 2004 suggested that overall "only" 2.6 million animals would be used (1.9 million and 3.9 million, in the best-case and worst-case scenarios, respectively; 9). In the same report, the Commission anticipated a high use of data waiving, Quantitative Structure–Activity Relationship models ([Q]SARs) and read-across, resulting in new tests only being required for an average of 7–35% of substances.

A report from the German Federal Institute for Risk Assessment was less optimistic about the potential for the use of *in silico* approaches and, along with counting the live pups used in reproductive tests that had not yet been considered, estimated that nine million animals could be used (10). In a now-buried briefing, the Commission's European Centre for the Validation of Alternative Methods (EURL ECVAM) estimated (with very little explanatory data) that total animal use could reach 18 million, even if (Q)SAR and read-across were employed, and 8–13 million if *in vitro* tests were employed to their maximum capability (11). This assessment returned the grounds of the debate to the original 2001 UK estimate (7). In 2009, Thomas Hartung, previously the head of EURL ECVAM, estimated that the number of animals could be much higher than these earlier estimates. His team estimated that 54 million animals might be used, largely on the basis that the number of pre-registrations indicated that there would be 68,000 substances registered in total, not 30,000 (12). ECHA disagreed; some companies, it said, had pre-registered every known chemical just in case, but, in reality, they would not actually register them (13).

The ECEAE, as well as other animal protection groups and the chemical industry, campaigned to ensure that any animal testing would be kept to a

minimum, and that alternatives would be used where possible. When REACH was finally agreed in 2006, some provisions were indeed built in to address these concerns, including the mandatory sharing of existing data and the promotion of alternative methods (14). Nonetheless, the resulting legal text was the usual political compromise. We were pleased with some of the aims to avoid animal testing, but were disappointed that the requirements for animal test data remained so extensive. One particular disappointment was that the testing proposal system did not extend to all the potential new animal tests, just to sub-sets of them.

Animal Testing Provisions in the Final REACH Regulation

Two important declarations found themselves in the final REACH Regulation in relation to animal testing and alternatives. These aims, and the mechanisms built into the legislation to achieve them, are presented in Table 1 and summarised below:

Promotion of alternative methods

The first point in Article 1: Aim and scope, states that:

The purpose of this Regulation is to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market, while enhancing competitiveness and innovation.

This aim has two main mechanisms embedded in the Regulation to achieve it (see Table 1). Article 13(1) requires that information "shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods". Details on the types of alternatives, including (Q)SARs, *in vitro* methods, read-across, weight-of-evidence approaches, and how they can be used to replace the standard information requirements, are given in Annex XI. Article 13(2) mandates the Commission to amend *Council 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)* (the Test Methods Regulation [TMR]; 15), "as soon as possible"… "so as to replace, reduce or refine animal testing".

Measures of success for the promotion of alternative methods therefore include the extent of use of alternative methods by registrants, the acceptance of the use of alternatives by ECHA, and the number of alternative methods that have been adopted.

Animal testing as a last resort

The first point in Article 25: Objectives and general rules, states that:

In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort. It is also necessary to take measures limiting duplication of other tests.

The Regulation contains three mechanisms that can serve to ensure that animal testing is a last resort. This includes the mandatory sharing of vertebrate animal data between registrants of the same substance, the testing proposal system that provides third parties the possibility to provide additional information to help avoid the testing proposed, and options within the legal text to avoid (waive) animal testing, if certain circumstances are met.

Various articles in REACH describe the data sharing and testing proposal systems (see Table 1). Column 2 within each of the Annexes VII to X sometimes includes options to avoid testing, particularly in instances where testing would be duplicative or not lead to greater risk management measures. Annex XI also gives options to use existing data, as well as to avoid testing, where it is technically not possible, e.g. for very volatile, highly reactive or unstable substances, or where the exposure to the substance is insignificant, so called "substance-tailored exposure-driven testing" (commonly referred to as "exposure-based waiving").

Measures of success for the aim of testing as a last resort include: the numbers of animals that have been used in new testing for REACH registrations, the extent of data sharing by registrants, the number of testing proposals that were submitted, and the success of third party comments on these proposals and ECHA decisions on them. The extent to which new animal tests are 'waived' by exploiting the options in Column 2 and Annex XI, and the acceptance of these waiving arguments by ECHA, are also measures of the success of this mechanism to keep animal testing to a minimum.

What follows is an analysis of the evidence of the success of these mechanisms, and recommendations for steps to strengthen their impact.

Table 1: The principles on animal testing in REACH and the mechanisms provided to achieve them

Principle in REACH	Mechanisms in legislation	Related articles	Measures of success
Promotion of alternative methods [Article 1(1)]	Use of alternative methods	— *Article 13(1)* General requirements for generation of information on intrinsic properties of substances, referring to the use of Annex XI. — *Annex XI* General rules for adaptation of the standard testing regime set out in Annexes VII to X, including: 1. Testing does not appear scientifically necessary 1.2. Weight-of-evidence 1.3. Quantitative Structure–Activity Relationship ([Q]SAR) 1.4. *In vitro* methods 1.5. Grouping of substances and read-across approach	— Use of alternatives by registrants — ECHA decisions on use of alternatives
	The ongoing adoption of alternative methods	— *Article 13(2)* General requirements for generation of information on intrinsic properties of substances, requiring timely update of TMR and REACH Annexes	— Number of new or revised alternative methods adopted
Animal testing as a last resort [Article 25(1)]	Data-sharing	— *Article 11* Joint submission of data by multiple registrants — *Article 27* Sharing of existing data in the case of registered substances — *Article 28* Duty to pre-register for phase-in substances — *Article 29* Substance Information Exchange Forums — *Article 30* Sharing of data involving tests	— Numbers of animals used — Extent of data sharing by registrants
	Testing proposal system	— *Article 10(a) (ix)* Information to be submitted for general registration purposes, stating that tests for Annex IX and X had to be proposed — *Article 12(1) (d) and (e)* Information to be submitted depending on tonnage, stating that tests for Annex IX and X had to be proposed — *Article 40* Examination of testing proposals	— Number of testing proposals submitted — Success of third party comments — ECHA decisions on testing proposals
	Options to avoid testing	— *Annex VI* Information requirements referred to in Article 10: Guidance note on fulfilling the requirements of annexes VI to XI — *Annexes VII to X* Column 2 specific rules for adaptation from Column 1 — *Annexes XI* General rules for adaptation of the standard testing regime set out in Annexes VII to X, including: 1. Testing does not appear scientifically necessary 1.1. Use of existing data 2. Testing is technically not possible 3. Substance-tailored exposure-driven testing	— Use of waiving arguments by registrants — ECHA decisions on waiving arguments

Success in Achieving the Two Aims Related to Animal Testing and Alternatives

Promotion of alternative methods

The use of alternative methods by registrants

In their latest report on the use of alternatives to testing on animals for the REACH Regulation (16), ECHA claimed that registrants had made "extensive use" of alternatives, noting that:

— 89% of registrations contained at least one adaptation instead of a study result;

— 63% of registrations contained at least one read-across adaptation;

— 43% of registrations contained at least one weight-of-evidence argument; and

— 34% of registrations contained at least one (Q)SAR prediction.

However, a closer look at the data in the report shows that the use of alternatives is not as significant as these figures might suggest. According to Figure 2 in the ECHA report (16), for each of the standard human health tests, approximately 30–40% of the registrations used existing data, 20% used new tests, 20% used read-across, 10% used a weight-of-evidence approach, less than 10% used waiving arguments, and less than 5% used (Q)SARs. This suggests that the use of weight-of-evidence approaches, waiving and (Q)SARs was actually relatively low, and the use of *in vitro* tests was so low that it was not even included in this statistic.

In the pre-REACH reports on data requirements, it was anticipated that (Q)SARs would be used heavily. Based on the experience with the US HPV Challenge Program — a voluntary scheme predating REACH, which attempted to obtain more data on high production volume chemicals in the USA — the Commission estimated that the optimal use of (Q)SARs (albeit including read-across) could be between 10% (e.g. for reproductive toxicity) and 92% (e.g. for 28-day repeated-dose) (9). The Commission estimated that, for the REACH endpoints that had been covered in the HPV programme, 60%, 30% and 0% of the test needs could be covered by (Q)SARs, etc. (given high, average and low acceptance levels, respectively). For the endpoints that had not been covered by the HPV programme, it was assumed that 80%, 40% and 10%, respectively, of the test needs could be covered by (Q)SARs (9). It certainly looks as if the best-case scenario was not realised.

The low level of use of *in vitro* tests as complete replacements should be a concern, especially as so much recent effort has gone into their validation. According to the latest ECHA report on the use of alternatives (16), dossiers included 1,418 new *in vitro* skin irritation tests compared to 502 new tests on rabbits, and 1,088 new *in vitro* eye irritation tests compared to 734 new eye irritation tests on rabbits. In just 11% of cases for skin irritation and 7% for eye irritation were the *in vitro* test data the only data submitted for that endpoint. For skin sensitisation, only 102 new *in vitro*/*in chemico* studies were submitted (see shaded rows in Table 2). The fish embryo test (FET) is a potential replacement for the live fish test for short-term toxicity testing. However, just four new FETs were submitted, according to the ECHA report (Table 2).

The reasons for the relatively low use of (Q)SARs and *in vitro* tests as standalone replacements has been discussed by others (17–19), and appears to be a combination of acceptance issues (see *ECHA decisions on the use of alternatives*) and other practical reasons. Unfortunately, the second review of REACH (20) did not seem particularly concerned about the lack of uptake, although it did make the following observation:

The experience from recent modifications of standard information requirements in Annexes VII–X to REACH have also highlighted a number of challenges for regulatory acceptance of new methods. This can significantly influence the time needed to complete the process of gaining acceptance, in particular related to concerns raised in relation to assessing the equivalence of information generated via in vitro *or* in vivo *testing, maintaining the previous level of protection for human health and the environment, addressing flexibility in test guidelines as well as testing costs and availability of test laboratories able to perform new tests.*

ECHA decisions on the use of alternatives

It is hard to provide evidence of ECHA's and MSC's views on the acceptability of *in vitro* (Q)SAR approaches, because most evaluation decisions to date have focused on the higher tier tests for which these types of alternatives are rarely used in isolation. I have noticed, however, that *positive* results from (Q)SARs are being used by some Member States to justify the need for *additional* animal tests (minutes of MSC 53: CCH-003/2017, dimethyl ether [EC No. 204-065-8]). Skin sensitisation has only come up recently in a substance evaluation case at the MSC, where a Local Lymph Node Assay (LLNA) in mice was requested to be conducted (minutes of MSC 52: SEV-IE-023/2015, 3-trimethoxysilylpropyl methacrylate [EC No. 219-785-8]). This decision was made after the update of Annexes VII to X in September 2016, which require the consideration of three key events by using *in vitro*/*in chemico* tests before conducting

Table 2: The numbers of new animal tests for REACH for 6,290 substances registered by March 2016

2017 Report	OECD TG[a]	Description	Minimal no. of animals per test	New tests	Total no. of new animals used
Bioaccumulation, fish	305[a]		280	59	16,520
Short-term toxicity, fish	203[a]		42	1,031	43,302
	204	TG deleted 2014	70	25	1,750
	236	FET	n/a	4	—
Long-term toxicity, fish	210[a]	FELS	420	105	44,100
	212	Short-term embryo	n/a	25	—
	215	Juvenile	96	14	1,344
Toxicity to birds	205	Dietary, LC50	150	3	450
	206	Reproduction	2,832	6	16,992
	223	LD50	45	2	90
Skin irritation, in rabbits	404		3	502	1,506
Skin irritation, *in vitro*	Various		n/a	1,418	—
Eye irritation, in rabbits	405		3	734	2,202
Eye irritation, *in vitro*	Various		n/a	1,088	—
Skin sensitisation, guinea-pig	406	GPMT, Buehler	33	166	5,478
Skin sensitisation, mice	429[a]	LLNA	25	1,351	33,775
Skin sensitisation, *in vitro*	Various		n/a	102	—
Acute toxicity, oral	401	LD50 deleted 2002	15	19	285
	420	Fixed dose	24	50	1,200
	423	ATC	24	306	7,344
	425	Up & Down	15	52	780
	Other		24	585	14,040
Acute toxicity, inhalation	403	LC50	46	144	6,624
	436	ATC	24	88	2,112
	Other		46	80	3,680
Acute toxicity, dermal	402	LC50	20	496	9,920
	434	Fixed dose	24	5	120
	Other		24	242	5,808
Repeated-dose toxicity, oral	407	28-day	60	347	20,820
	408	90-day, rodent	100	204	20,400
	409	90-day, non-rodent	48	7	336
	Other		100	35	3,500
Repeated-dose toxicity, inhalation	412	28-day	60	79	4,740
	413[a]	90-day	120	52	6,240
Repeated-dose toxicity, dermal	410	28-day	60	16	960
	411	90-day	120	5	600
	Other		120	5	600
Chronic toxicity	452		160	5	800
	453[a]	combined	400	18	7,200
Neurotoxicity	424		80	2	160
Genotoxicity, *in vivo*	Various		50	297	14,850
Carcinogenicity	451[a]		400	15	6,000

Table 2: continued

2017 Report	OECD TG[a]	Description	Minimal no. of animals per test	New tests	Total no. of new animals used
Reproductive toxicity	415	One generation	720	19	13,680
	416	Two generations	2,200	23	50,600
	421[a]	Screening study	400	388	155,200
	422	Combined	500	587	293,500
	443	EOGRTS	960	0	—
Developmental toxicity	414[a]	PNDT	900	367	330,300
	426	Neurotoxicity	820	2	1,640

[a]*Denotes that very similar other tests are included.*
*Where 'Other' (*in vivo *method) is given, the worst-case scenario for that test was chosen to represent the number of animals used.*
The maximum number of animals described in the TG is given, but this does not include animals used in sighting studies.
This Table was adapted from Table 8.1 in Ref. 16. Some in vitro *tests are included for illustrative purposes, and shaded rows indicate* in vitro *methods. The total number of new animals used was 1,151,548. n/a = not applicable; TG = Test Guideline.*

the LLNA (21). The need to be able to sub-classify strong sensitisers (see *The ongoing adoption of alternative methods*), and the physical–chemical properties of the substance, were the reasons given for nevertheless requesting the LLNA.

ECHA's view of the industry's use of alternatives, particularly read-across, is that it has been too cavalier. It has said that, "In particular, adaptations based on read-across and weight-of-evidence are often poorly documented and justified, and are not acceptable" (2). In its latest report on alternatives, ECHA stated that, "We are concerned that, in many cases, the quality of information on alternatives in the submitted dossiers is not robust enough to replace animal tests and therefore we urge registrants to update their dossiers accordingly before evaluation" (16). Clearly, without adequate information, ECHA evaluators may not be able to tell if the read-across is scientifically sound, but that does not mean that, in principle, it might not be. Unfortunately, under the REACH system, decisions are only issued if registrations are considered to *not* be compliant; registrants are not told if their registrations *are* compliant. This may give a false sense about ECHA's overall acceptance of alternative approaches such as read-across, fuelling concerns from industry and academia (22–24).

In response to calls for more guidance, ECHA produced its Read-Across Assessment Framework (RAAF) document in 2015 (updated in 2017; 25), which outlines how they would like to see a read-across approach constructed. The document does give the impression that the hurdle for demonstrating a sound read-across is very high. ECHA appears to expect evidence, not only that the substances are structurally similar, but also that their toxicological properties are similar, even to the extent of indicating their preference for toxicokinetic test data and bridging studies to support the hypothesis. Registrants are also required to consider the effects of any remaining parent compounds, intermediate compounds and constituents (16, 25). This can be very challenging, if not impossible, for biological or variable, complex chemicals.

However, it is common for testing proposals to suggest testing on a few substances that are considered representative of a larger 'category' or group of very similar chemicals. In their latest report on alternatives (16), ECHA described several cases where it has considered this kind of read-across approach acceptable. For example, ECHA agreed with the registrant's category approach for cobalt salts, requiring tests on two substances to represent approximately 12 compounds (minutes of MSC 30: TPE [various] cobalt category), and for petroleum substances by requiring tests on six substances to represent 22 (minutes of MSC 32: TPE [various] petroleum category).

However, the acceptance of a read-across approach appears more problematic for analogue approaches, where read-across is relevant between just a few, often two or three, substances. In this case, it is harder to establish whether the substances "follow a regular pattern of toxicity". For example, a read-across from propylidynetrimethanol to three other substances for prenatal developmental toxicity was rejected, and testing was requested on all three substances (minutes of MSC 25: TPE 104/2012 propylidynetrimethanol [EC No. 201-074-9]). ECHA and Member State Competent Authorities (MSCAs) appear particularly cautious in cases where the read-across hypothesis indicates essentially 'no toxicity' or that one of the substances converts into the other, i.e. by hydrolysis or

metabolism. ECHA guidance is unclear on how rapid the conversion in the body needs to be, although the evidence from recent BoA cases (Dow A-001-2012, see 26; and Huntsman Holland A-012-2014) suggests that ECHA would require it to be "very rapid". Unfortunately, the BoA have deferred to ECHA on science matters, and have left it to "balance the objectives of the read-across provisions in the REACH Regulation, with that inherent uncertainty" (27).

It is difficult to assess ECHA's view on weight-of-evidence approaches, for the same transparency reasons as for read-across. My impression from cases discussed at MSC meetings and ECHA responses to third party comments on testing proposals (see section on *The success of third party comments on the testing proposals*) is that there is also a high bar for the acceptance of a weight-of-evidence approach. In one case, unsuccessfully brought before the BoA in 2012, ECHA had requested a 90-day repeated-dose study on triphenyl phosphate, even though the dossier already included 13 existing repeated-dose studies of varying lengths and quality (minutes of MSC 22: CCH-042/2011 triphenyl phosphate [EC 204-112-2]; the minutes say "many", I said 13). In the second review of REACH (20), the Commission acknowledged that: "Respondents from almost all stakeholder groups agreed that the principle of 'animal testing as a last resort' is not yet fully implemented. Respondents explain this problem by strict information requirements coupled with a low acceptance of alternative methods."

— ***Recommendation 1:*** Reasons for the low uptake of *in vitro, in chemico* and *in silico* methodologies in REACH registrations should be thoroughly investigated, and recommendations should be made to the appropriate bodies for steps that they can take to increase their use.

The ongoing adoption of alternative methods

According to Article 13(2) of REACH, the Commission has a duty to review regularly the TMR and Annexes VII to X, and update them "as soon as possible", in order to replace, reduce or refine animal testing. Timely update is important, because under Article 13(1) of *Directive 2010/63/EU* (28), an animal test may not be carried out in the EU where there is a replacement method or approach recognised under EU legislation, which in this case would be the TMR or REACH. The Commission has taken the view that, in order to promote international harmonisation, it is better to seek the adoption of methods at the OECD first, rather than at the European level (29). However, REACH does not specifically require this; Recital 47 makes it clear that the TMR should be updated as soon as the Commission or ECHA considers a method "appropriate".

When the TMR to support REACH was first created in May 2008 (15) from the previous list of Test Methods (contained in Annex V to *Directive 67/548/EEC* [30]), there was political uproar as the new, *in vitro* skin irritation tests approved by EURL ECVAM in 2007 had not been included (31). The Commission promised to add them to the first review of the TMR (called "adaptation to technical progress" [ATP]), and instigated a "streamlined procedure" whereby methods could be submitted to the TMR process, if there was "undue delay" at the OECD (29). The *in vitro* skin irritation tests were indeed included in the first ATP in 2009 (32), one year prior to their final OECD adoption. However, the streamlined procedure has not been used for any other method since then.

Table 3 provides an analysis of the timescales, from validation to acceptance, for key alternative methods for skin irritation/corrosion, eye irritation, skin sensitisation, acute fish toxicity, and reproductive toxicity. These are the tests for which there has been most progress in replacing, refining and reducing animal tests since REACH was implemented. Table 3 shows the 'typical' time to publication of the method at each of the relevant stages (OECD, TMR, ECHA guidance and Annexes VII to X). It appears that it is normal for a method to take two years to be approved at the OECD, and then a further two years to be published in the TMR. For example, the *In Chemico* Skin Sensitisation: Direct Peptide Reactivity Assay (DPRA), a partial replacement of the LLNA, was endorsed by EURL ECVAM in 2012 (33), adopted at the OECD in 2015 (34), but not published in the TMR until 2017 (35), a total of five years since its validation.

Oddly, the *revision* of existing methods appears to be taking an additional year at both the OECD and TMR stage. For example, the Bovine Corneal Opacity and Permeability (BCOP) test method for identifying ocular corrosives and severe irritants was re-evaluated by the US Interagency Coordinating Committee on the Validation of Alternative Methods in 2010 (36). It was decided that the method could also predict lack of irritancy potential. A revision of the Test Guideline (TG) to take this into account was not adopted at the OECD until 2013 (37), and it was not published in the TMR until 2017 (35), a total of seven years since its validation.

Cruelty Free International has launched a complaint with the Ombudsman about the slow pace of adoption and questioning whether deferring to the OECD process is lawful (38). Our argument is that EU acceptance could be done in parallel with the OECD process, as the Commission agreed when implementing the streamlined procedure, so as not to cause undue delay. The TMR stage also needs to

be speeded up; several bureaucratic steps that must be followed could be unnecessary, particularly as much of the scientific debate over the methods has already occurred at the OECD stage, of which most EU Member States are also members. ECHA appears to agree with us: "In many cases, recognising a new method requires action by the Commission and amendment of both REACH annexes and the Test Methods Regulation, which may take a considerable time and could be accelerated" (2). It has recommended that: "The Commission should accelerate the inclusion of new alternative Test Methods and integrated testing strategies in the REACH annexes to avoid unnecessary animal testing" (2). Furthermore, in the Commission's latest review of REACH (20), it is admitted that the process is "taking considerable time", with a pledge that "further effort will be made to speed up the process".

Delay has not just been seen in the update of the TMR. There have also been delays to the revision of Annexes VII–X, to allow for the use of alternative approaches. The *in vitro* skin irritation methods were added to the TMR in 2009 (32), effectively replacing the need to use rabbits for this endpoint. However, a revision of the Annexes VII to X, which, until then had specified the conduct of the rabbit test, was not published until July 2016, seven years later (39). This is likely to have contributed to the number of new *in vivo* skin irritation tests that feature in REACH registrations (see section on *The use of alternative methods by registrants*). Confusingly for registrants, ECHA guidance updates have often preceded TMR updates, but nevertheless with some delay after validation and OECD acceptance (see Table 3). For example, an update to the ECHA guidance to reflect the revision of the BCOP method (see above) was not made until July 2015 (two years after the publication of the revised OECD TG [37], although two years before its publication in the TMR [35]).

In my opinion, ECHA has taken an overly cautious view of some of the recent alternative methods, delaying or failing to recognise them as complete replacements. The FET was validated by the OECD in 2012 (40), and published as a TG in 2013 (41). It was widely anticipated to be a replacement for the acute fish toxicity study, although the OECD TG stopped short of saying as much. However, it was not until September 2016 that ECHA concluded, following expert advice, that the study could not be used as a complete replacement of the adult fish test (42). Validation studies have continued, and it is still possible that, in the future, the FET will be accepted as a standalone replacement (43). Similarly, the adoption of the *in vitro/in chemico* test methods for skin sensitisation was widely anticipated to completely replace the LLNA. However, late on in the process of updating the ECHA guidance and Annexes VII to X, some Member States and ECHA took up the position that sub-classification of strong sensitisers was needed, which the alternative methods could not provide at that time (44). The resulting update to Annexes VII to X (21) was a messy compromise that appears to require registrants to use the alternative methods first, but then ultimately conduct the LLNA if the result is positive, in order to sub-classify.

— ***Recommendation 2:*** The procedure for the update of the Test Methods Regulation (and associated guidance) to include alternative methods should be expedited.

Animal testing as a last resort

Data-sharing: The numbers of animals used

The actual numbers of animals that have been used for the entire REACH registration process of all existing substances will not be known for a few years after the 2018 deadline. Furthermore, the numbers will continue to rise, as new tests under dossier and substance evaluation are requested. The final numbers will depend on how many substances are ultimately registered, how much existing data were available, and the extent to which alternatives are used. However, due to the detail in the ECHA reports on alternatives to animal testing under REACH, we can estimate the numbers used to date. According to its latest report, the number of new animal tests conducted in registrations received up to March 2016 was 9,287 (16). An analysis of the numbers of animals used in these tests is shown in Table 2, and totals 1,151,548 animals.

The number of animals used, based on ECHA's data, is likely to be an underestimate. Firstly, ECHA took study report dates of 2009, or later, as evidence that the tests had been performed for REACH, despite the fact that REACH entered into force in 2007. Secondly, in all its reports, ECHA has disregarded substances, such as intermediates, that have no, or less, information requirements. In fact, the number of substances that ECHA analysed (16) is less than half of those actually registered by April 2016 — 6,290 and 14,000, respectively (2). Thirdly, the number does not include all the animals that will be used in tests that were proposed before being conducted (see section on *The testing proposal system*). ECEAE records (see *Success of third party comments on the testing proposals*) show that for the first two registration deadlines, there were 1,557 testing proposals published for commenting. An analysis of the number of animals that would be used, if all these tests were permitted, is given in Table 4, and totals

Table 3: The speed of update of the OECD and EU test methods regulations for key alternatives methods validated since REACH came into force

Alternative test method	Summary	Date of validation	Date of OECD adoption (delay from validation)	Date of TMR (delay from OECD adoption)	Change to relevant REACH annexes (VII–X)	ECHA R7a guidance updated
Section 8.1: Skin irritation/corrosion						
EU B.46 *In vitro* skin irritation: Reconstructed Human Epidermis Test Method (RHE)	New *in vitro* test, partial replacement for the *in vivo* EU B.4 test (irritation)	27.04.07 (ESAC)	TG 439, 23.07.10 (three years, three months)	24.08.09 (preceded)	31.05.16 *in vivo* deleted	Included in the 1st edition of the testing strategy (May 2008); updated July 2015
	Revision, new test method added	08.07.09 (ESAC)	TG 439 (R1), 26.07.13 (four years), one subsequent revision	20.07.12 (preceded)	n/a	July 2015
Section 8.2: Eye irritation						
EU B.47 Bovine Corneal Opacity and Permeability Test Method for identifying ocular corrosives and severe irritants	New *ex vivo* test, partial replacement for *in vivo* EU B.5 test (corrosion)	27.04.07 (ESAC)	TG 437, 08.09.09 (two years, four months)	09.12.10 (one year, three months)	n/a	Included in the 1st edition of the testing strategy (May 2008)
	Revision, scope expanded	2010 (ICCVAM)	TG 437 (R1), 26.07.13 (three years)	28.04.17 (three years, nine months)	31.05.16, *in vivo* deleted	July 2015
EU B.48 Isolated Chicken Eye Test Method for identifying ocular corrosives and severe irritants	New *ex vivo* test, partial replacement for *in vivo* EU B.5 test (corrosion)	27.04.07 (ESAC)	TG 438, 08.09.09 (two years, four months)	09.12.10 (one year, three months)	n/a	Included in the 1st edition of the testing strategy (May 2008)
	Revision, scope expanded	2010 (ICCVAM)	TG 438 (R1), 26.07.13 (three years)	28.04.17 (three years, nine months)	31.05.16, *in vivo* test deleted	July 2015
EU B.61 Fluorescein Leakage Test method for identifying ocular corrosives and severe irritants	New *in vitro* test, partial replacement for *in vivo* EU B.5 (corrosion)	08.07.09 (ESAC)	TG 460, 02.10.12 (three years, three months)	28.04.17 (four years, seven months)	n/a	Mentioned only in 2008, included fully in July 2015
Short time exposure *in vitro* test method for identifying i) chemicals inducing serious eye damage and ii) chemicals not requiring classification for eye irritation or serious eye damage	New *in vitro* test, partial replacement for *in vivo* EU B.5 (corrosion) by using rabbit cells	2013 (ICCVAM/ ICEATM/ JaCVAM)	TG 491, 28.07.15 (two years)	Pending (in 8th ATP) (two years, six months, to date)	31.05.16, *in vivo* test deleted	Mentioned only in 2008, included fully in July 2015

Table 3: continued

Alternative test method	Summary	Date of validation	Date of OECD adoption (delay from validation)	Date of TMR (delay from OECD adoption)	Change to relevant REACH annexes (VII–X)	ECHA R7a guidance updated
Reconstructed human Cornea-like Epithelium (RhCE) Test Method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage	New *in vitro* test, partial replacement for *in vivo* EU B.5 (irritation)	17.11.14 (ESAC)	TG 492, 28.07.15 (eight months)	Pending (in 8th ATP) (two years, six months, to date)	31.05.16, *in vivo* test deleted	Mentioned only in 2008, included fully in July 2015
Section 8.3: Skin sensitisation						
EU B.59 *In chemico* skin sensitisation: Direct Peptide Reactivity Assay (DPRA)	New *in vitro* test, for partial replacement of *in vivo* EU B.42	17.12.12 (ESAC)	TG 442C, 05.02.15 (two years, two months)	28.04.17 (two years, three months)	20.09.16, to be used in advance of *in vivo*	December 2016
EU B.60 *In vitro* skin sensitisation: ARE-Nrf2 Luciferase Test Method (Keratinosens™)	New *in vitro* test, for partial replacement of *in vivo* EU B.42	17.12.12 (ESAC)	TG 442D, 05.02.15 (two years, two months)	28.04.17 (two years, three months)		
In vitro skin sensitisation: h-CLAT	New *in vitro* test, for partial replacement of *in vivo* B.42	11.03.14 (ESAC)	TG 442E, 29.07.16 (two years, four months)	Pending (8th ATP) (one year, six months, to date)		
EU B.42 Skin sensitisation: Local Lymph Node Assay	Revision to *in vivo* test, reduction in the number of animals	27.04.07 (ESAC)	TG 429, 23.07.10 (three years, three months)	20.07.12 (two years)	None made	Included in the 1st edition of the testing strategy (May 2008)
Section 9.1.3: Short-term toxicity testing on fish						
EU C.49 Fish Embryo Acute Toxicity (FET) Test	New *in vivo* (sub-threshold) test, for potential replacement of C.1 acute fish toxicity	July 2012 (OECD)	TG 236 26.07.13 (one year)	28.04.17 (three years, nine months)	None made; Annex VIII, Section 9.1.3 does not specify the test	Indicated that it was going to be included in the 1st edition (May 2008) but no update yet
Section 8.7.3: Two-generation reproductive toxicity study						
EU B.56 Extended one-generation reproductive toxicity study	New animal test for reproductive toxicity. Reduction compared to EU B.35	January 2006 (US EPA)	TG 443, 28.07.11 (five years, six months)	21.08.14 (three years, one month)	21.02.15	July 2015

1,372,648 animals. Testing proposals do not tend to be rejected (see *ECHA decisions on testing proposals*), but approximately 25% have been withdrawn by the registrants before decisions were made (16). Reducing the total by this value of 25% would give an estimate of 1,028,787 animals.

So, by early 2016, an estimated 2.2 million animals in total will have been used in new tests. This equates to approximately 275,000 animals per year (2009–2016 inclusive). The Commission's 'best-case' scenario estimate of 2.6 million animals in total (9) equates to 217,000 animals per year over the whole period of registration (2007–2018, inclusive). The actual annual rate is greater than this, and it is therefore extremely likely that the 'best-case' total estimate will be exceeded by 2018.

Unfortunately, the second review of REACH did not cover the use of animals in any detail. A cursory analysis of the number of new tests and testing proposals (but not the number of animals this would correspond to) from ECHA reports led the Commission to conclude that: "On the one hand this means that less vertebrate animals than initially predicted have been used for testing, but on the other hand, hazard information has not been generated to the extent predicted either" (20).

— ***Recommendation 3:*** Greater acknowledgement by the Commission of the total number of animals used for REACH purposes should be made, especially in the context of reviewing the success of REACH.

The extent of data-sharing by registrants

The formation of substance information exchange forums (SIEFs) required a huge effort from companies and a great deal of outreach by industry organisations, ECHA and MSCAs (45). Nonetheless, by April 2016, only 2% of the registrations had not been submitted jointly (2), and existing data appear to have been used for between 30–40% of substances (see Figure 2 in 16). This means that the aim of reducing animal testing — by ensuring that all existing data were shared and that any new tests were done only once — appears to have been largely realised (20). This is a great achievement.

There have been complaints that the larger companies have dominated decision-making, and demanded unreasonably high fees for the cost of the registration package (45, 46). The Commission responded in 2016, by issuing an implementing regulation *(Commission Implementing* Regulation (EU) 2016/9 *of 5 January 2016 on joint submission of data and data-sharing in accordance with* Regulation (EC) No 1907/2006 *of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) [47]).* This gave clearer instructions on how registrants should interact, and insisted on a transparent breakdown of the costs related to tests and SIEF administration. Complaints about the cost of data do not, in fact, seem to have led to duplicative animal testing (as evidenced by a lack of duplicate registrations), but it may explain data gaps in some registrations.

One outstanding issue, however, is that the data-sharing requirements do not appear to extend to substances other than the one being jointly registered. As a result, registrants have struggled to access data that they wish to rely on to support a read-across approach (46). I have seen cases discussed at the MSC, where it seemed possible to read-across from another substance not being registered by the registrant, but the ECHA/MSCAs felt powerless to insist that this must be done. ECHA is now recommending to the Commission that it should consider provisions for obligatory data-sharing between analogue substances for read-across and category purposes (2). They say that: "The fact that there is no obligatory data-sharing between structurally similar substances is hampering registrants' possibilities to make full use of scientifically robust read across or category approaches" (2). The second REACH review acknowledged that, "further data-sharing could be enhanced by accommodating data-sharing for structurally similar substances to allow better read-across" (20).

— ***Recommendation 4:*** Data-sharing should be mandatory in scenarios where read-across from substances in other registrations could be used to help avoid animal testing.

The testing proposal system

The testing proposal system was a new addition to the EU chemicals regulation, whereby any tests required to satisfy the information requirements listed under Annex IX and X (only) have to be proposed. An ECHA decision then notifies the registrant that they need to conduct the test by a certain deadline to remain compliant. The aim was to help ensure that the costlier, time-consuming tests were necessary and could not be avoided. Only those proposals involving vertebrate animals went through the third party consultation aspect of the process. To determine the effect of this system on the second aim of the REACH legislation (animals being used as a last resort), the following points were evaluated:

1. *The number of testing proposals submitted:* By the second registration deadline in 2013, only about 10% of Annex IX and X substances registered had a testing proposal (905 out of 8,729 substances). The Commission report in 2004 did

suggest that existing data, read-across and (Q)SARs could potentially avoid a large proportion of new testing (see *The use of alternatives by registrants*; 9). However, in the second review of REACH, the Commission felt that the number was "lower than expected", and that the use of adaptations to avoid proposing testing was potentially inadequate (20; see *ECHA decisions on the use of alternatives*).

Furthermore, according to the ECHA reports, approximately 25% of these proposals were subsequently withdrawn by the registrants before ECHA had reached a decision (2, 16). It is permitted to withdraw a testing proposal prior to the receipt of a draft decision. It seems that a high proportion of registrants did so, possibly following the third party comments (see *The success of third party comments on the testing proposals*). Unfortunately, it is often hard to determine from the disseminated dossier, why the testing proposal was withdrawn, particularly if the information submitted in its place is not an existing animal study or read-across approach.

2. *The success of third party comments on the testing proposals:* The testing proposal system was a measure particularly encouraged by the animal protection groups, so the ECEAE felt obliged to support it. A review of the ECEAE members' experiences from the proposals submitted in the first registration deadline was published by Taylor *et al.* (48), and an update is provided here. Overall, the ECEAE submitted comments on 35% of the 1,557 testing proposals published between 10 August 2009 (the very first testing proposal) and 16 March 2015 (by which time most of the proposals from the second registration deadline had been published), see Table 4.

So far, only 50 (10%) comments appear to have been influential in changing ECHA's draft decision or the withdrawal of a proposal by a registrant. Nonetheless, this has saved an estimated minimum of 35,752 animals (the analysis is available upon request). There were only six cases in which ECHA agreed with our submission, and formally rejected the testing proposal; in one case, they altered the route of administration to refine and reduce the animal test. In all these cases, our comment had simply been that the test was not legally required according to the data requirements in the relevant Annex, i.e. the testing proposal was made in error. This type of comment also led to a further 14 withdrawals by the registrants. On occasion, we found existing data that the registrant had not yet found, but these data were only used to withdraw the testing proposal in five cases. However, existing data on similar substances to support a read-across approach were used in a further 12 withdrawals. Our arguments, that testing was scientifically unjustified due to the physical/chemical properties of the substance, were used by registrants in a further eight withdrawals.

The low success rate of our comments can be explained by a number of factors. Firstly, it appears that registrants had already tried to use all existing information, to avoid having to propose new tests. The relatively low number of testing proposals (see *Number of testing proposals submitted*) supports this assumption. Secondly, ECHA unhelpfully published the majority of the testing proposals in very large batches over a six-month period for each deadline (see 48). Only having 45 days to comment is already a short period, but when there are over 50 substances in each batch, then the task becomes impossible for only one or two people. Thirdly, ECHA did not begin to publish even basic information on the substances until April 2011, and did not start publishing the outcome of testing proposal decisions until December 2012 (see 48). This information would have helped our toxicologists improve the quality of their comments, by enabling us to understand the information that the registrants had already used, and to assess how our comments were being received. Importantly, this also meant that some time had passed before we realised that ECHA was taking a narrow interpretation of its role in assessing the comments (see *ECHA decisions on testing proposals*). The legal text says that the comment period was to enable third parties to provide "scientifically valid information and studies". ECHA considered that this meant information equivalent to the information requirement, rather than suggestions about approaches that could be used, such as read-across or weight-of-evidence (49). Therefore, registrants were typically faced with a draft decision requesting that the test be conducted, which included a statement that the third party comments were "not adequate". Given that the legal text only gives registrants 30 days to respond to the draft decision and update their dossier, they were not really predisposed to take these comments on board.

There is no publicly-available analysis of who else commented on testing proposals and the extent to which their comments resulted in withdrawal or rejection of the testing proposed. ECHA has noted that non-governmental organisations (including the ECEAE) were responsible for 61% of the comments, and that very few comments from industry constituted the provision of existing data (49). It seems that the chemical industry either did not possess data on the substances that they were not registering themselves, or they did not see the commercial

Table 4: The numbers of published animal testing proposals for the first two deadlines (August 2009 to March 2015)

Type of test	Typical OECD TGs	No. of animals per test	No. of tests with ECEAE comments	% of total	Total no. of tests	Potential total number of animals
Sub-chronic toxicity (90-day) oral, rat	TG 408	100	142	37%	380	38,000
Sub-chronic toxicity (90-day) dermal or inhalation, rat	TG 411/413	120	26	40%	65	7,800
Chronic toxicity/carcinogenicity, rat	TG 451/453	400	1	33%	3	1,200
Genotoxicity *in vivo*, mouse or rat	TG 474/475	50	21	27%	78	3,900
Prenatal developmental toxicity, rat or rabbit	TG 414	900[a]	207	34%	601	540,900
Two-generation reproductive toxicity, rat	TG 416	2,200	126	38%	334	734,800
Long-term toxicity to birds, quail	TG 206	2,832	1	25%	4	11,328
Long-term toxicity to fish	TG 210	420	7	11%	64	26,880
Bioaccumulation in fish	TG 305	280[b]	9	32%	28	7,840
Total		—	**540**	**35%**	**1,557**	**1,372,648**

[a]*Testing as a second species (rabbit) was not usually identified in the proposal but was of course possible, which would instead involve 580 rabbits.*
[b]*Route not usually specified, decisions often asked for the dietary route, so assuming number for dietary study.*
TG = Test Guideline.
The testing proposals were for 905 substances, and our data were used to estimate the numbers of animals.

advantage in offering it to others through the comment system. This meant that those third parties using the commenting system were largely outsiders with access only to public databases of substances. As a result, they were often unable to find existing data that the registrant had not already found.

3. *ECHA decisions on testing proposals:* ECHA guidance (50) claimed that it could reject testing proposals. However, it was not until 2013 that ECHA admitted, in correspondence with the ECEAE, that it believed itself to have no legal basis to reject any testing proposal, except in very limited circumstances. Indeed, by the end of 2015, ECHA had only rejected nine testing proposals (2), including the six for which we claim some credit (see *Success of third party comments on the testing proposals*). ECHA's position was that it could only reject a proposal, if the data were already available, or if the information was not required at the tonnage at which the substance was marketed. Its basis for this belief was the view that REACH imposes responsibility for registration and safe use of chemicals on the registrant. We are frequently told that ECHA "cannot do the registrant's job for them". The passive nature of the evaluation is clear from ECHA's statement, in the 2012 Evaluation report (51), regarding the utility of third party comments:

   So far, none of the third party information received has given grounds for ECHA itself to reject a testing proposal directly. It is the registrant who, after obtaining the relevant information, determines if the suggested approach can be scientifically justified and whether the information requirements can be met by such an approach.

   Therefore, third party comments were for the registrants to use and not ECHA. Under ECHA's approach, if the registrant was not persuaded by the third party comments, then, even if ECHA was, it could not act on this. In 2013, the ECEAE complained to the Ombudsman about ECHA's view of its role in evaluating testing proposals, but the Ombudsman did not make a decision until 2015 (52). The Ombudsman agreed that "ECHA's interpretation of its role was too strict and did not take into account the fact that the avoidance of animal testing was, together with the protection of human health and the environment, one of the guiding principles of the Regulation". A 'friendly solution' was agreed between them, in which ECHA offered to impose a requirement for registrants to 'justify' their testing proposals by using a new online form (53). In our view, this was still delegating responsibility to the registrant to avoid animal testing. The case was only finally settled in June 2017, when, in correspondence, ECHA acknowledged that it would reject a testing proposal, if, on the basis of the consideration of alternatives, testing was not necessary, even if the registrant disagreed.

— ***Recommendation 5:*** Future schemes involving third party consultation should ensure that the scheme supports the submission of comments, and that there are appropriate mechanisms to take these comments on board.

Options to avoid testing

Waiving arguments are commonly used to justify the avoidance of animal testing. Two relevant aspects of waiving arguments are considered here:

1. *The use of waiving arguments by the industry:* Despite ECHA's repeated complaints that there are serious data gaps in many registrations (20, 45, 54), only about 10% of the substances on average had an argument waiving one or more of the endpoints required (see Figure 2 in the ECHA report [16]). Waiving was more likely to be used to avoid new testing for the environmental endpoints, which often have Column 2 options permitting this, such as toxicity to birds (85% of all substances), long-term toxicity to fish (65%), bioaccumulation (50%), and some of the non-standard human health endpoints, such as carcinogenicity (33%). According to Figure 4.6 of the same ECHA report (16), the majority of the waiving arguments were these Column 2 adaptations, or that testing is scientifically unjustified according to Annex XI (which could be for a range of reasons). Out of all waiving arguments, exposure-based waiving, another option given in Annex XI, was used less than 10% of the time for each endpoint.

   Exposure-based waiving was anticipated to be possible, to help keep the REACH regulation focused on obtaining data for substances to which humans or the environment are genuinely exposed (55). However, a last-minute amendment to the legal text, at the insistence of some Member States, emasculated the option to waive testing based on low exposure of the substances to humans or the environment (56). The amendment inserted a footnote to Section 3 of Annex XI that prevented the waiving of long-term studies based on the information from shorter-term studies. It also only permitted waiving for substances that are used under "strictly controlled conditions" — i.e. substances only ever kept in sealed units. Companies no longer had the option to waive on the basis of little or low exposure, something that is still causing consternation. For example, the low

human or environmental exposure to the substance was one of the arguments that the registrants used to argue against the need for additional animal testing in the BoA case Honeywell A-005-2011 (57).

2. *ECHA decisions on waiving arguments:* Initially, it appeared that ECHA was sensitive to the need to avoid duplicative animal tests. In 2009, it issued a statement, following pressure from animal protection groups, to clarify two scenarios in which new animal tests could be waived according to the REACH Regulation (58). The statement said that 28-day repeated-dose studies did not need to be conducted, if there was a testing proposal for a 90-day test, and screening tests for reproductive toxicity did not need to be conducted, if testing proposals for the prenatal developmental toxicity or the two-generation reproductive toxicity study had been submitted (58). The first scenario was already permissible according to Annex IX, and the second, if data were 'available'. The point was that to insist on a screening study in the short time period before a higher-tier reproductive toxicity test was completed would be contrary to the last resort principle. The industry was also complaining about lack of laboratory space to conduct the screening study in time for the first registration deadline. If every company had followed the press statement, it was estimated at the time that 4.5 million animals would have been spared (59).

   It is not known how many registrants took up this option, but the ECEAE became aware, in 2011, that the MSC appeared to be overturning the policy, and had begun requesting the screening study *along with* a prenatal developmental toxicity test in compliance checks, and strongly recommending a screening study when approving testing proposals for the same (Notification of decision on TPE-D-0000001417-76-06/F dated 24 October 2011, and Decision CCH-D-0000001752-76-06/F dated 28 February 2012). The ECEAE complained to the Ombudsman in 2013, who in 2014 ruled that ECHA's original press statement only related to the technical registration stage, and that "available" meant "already performed" (60). So, the press statement had only delayed the conduct of the screening test until such time as a testing proposal was agreed or a compliance check conducted.

   A BoA case (Lanxess A-004-2012) sought to change ECHA's similarly rigid position on the need for prenatal developmental toxicity tests in two species. Lanxess, supported by the ECEAE, argued that testing on a second species was not a default at Annex X, but rather depended "on the outcome of the first test and all other relevant available data" (as stated in Column 2 of Annex IX). Unfortunately, the BoA ruled that ECHA was correct to assume that a test on a second species was a default requirement according to Annex X (61).

   On balance, it seems that the use of Column 2 rules to avoid testing is not so straightforward. In those cases where Column 2 states that further testing can be avoided if the substance is 'known to be' a carcinogen, mutagen or reproductive toxicant, ECHA seems to have difficulty in accepting waivers. There have been cases at the MSC, where testing proposals submitted in error, and which the registrant seeks to waive on the basis of Column 2 rules, are nevertheless demanded. The scenarios are often where the registrant is either not prepared to give their substance the most severe classification (minutes of MSC-27: TPE-172/2012 phenol, isopropylated, phosphate), or the most severe classification is not 'harmonised' among all registrants of the substance (minutes of MSC-28: TPE-182/2012 shale oils, heavy). The concern from the perspective of the MSC is that the RAC is the committee tasked with harmonising classification, following a request from a registrant or Member State. Even if the MSC could formally request a RAC opinion to harmonise a classification, some MSC members have raised concerns that the process would take longer than conducting a new animal test, and that the outcome would be uncertain. In their view, it is preferable to impose higher tier animal tests that are likely to indicate adverse effects that the registrant(s) cannot continue to ignore.

— ***Recommendation 6:*** A thorough review of the use and acceptance of waiving arguments should be made, in order to inform an EU discussion on whether the language in REACH is unintentionally leading to unnecessary animal tests in some circumstances.

What Is Missing?

Promotion of alternative methods

Who takes responsibility?

The mechanisms in REACH to ensure promotion of alternative methods relate to their adoption by ECHA and the Commission, and their use by registrants. The 'promotion' of alternatives *per se*, written into Article 1(1), is not directed at any one party.

ECHA was initially very slow to actively promote the use of alternative methods, save the creation of a practical guide on *How to Avoid*

Unnecessary Testing on Animals (62), following a meeting between ECHA and animal protection groups in 2009. It was not until 2015, following the recommendations of the Ombudsman and the BoA about the last resort principle, that ECHA entered a period of proactive communication. In addition to various webinars and news alerts, a dedicated webpage outlining ECHA's position on the acceptance of new OECD TGs was created (63), a revised practical guide on how to avoid unnecessary testing on animals (64) was published, and specific guidance for registrants under the 2018 deadline that included a lot of detail on alternative methods was issued (65). ECHA has also invested in OECD activities related to alternatives — supporting the QSAR toolbox and eChemportal projects, which rely heavily on the ECHACHEM database of registrations — as well as supporting the Commission during the revision of specific OECD TGs (20).

Much of this activity has, in my view, come too late to have been able to influence registrants in time for the 2018 registration deadline. The message is also often tempered with warnings about the inadequacy of current read-across and waiving arguments, which can serve to dampen any confidence a company has in the use of alternatives. Aside from the provision of funding (see *Funding*), and support of the European Partnership on Alternative Approaches to Animal Testing (EPAA), the Commission do not appear to have 'promoted' the use of alternatives to any discernible extent.

— ***Recommendation 7:*** Care should be taken when drafting legislation to ensure that any requirement to promote alternatives is clearly directed at the relevant bodies, and that the mechanisms to achieve this requirement are clear.

Funding

One possible mechanism to promote alternative methods is to provide dedicated funding for their development and validation. Recital 40 states that: "The Commission, Member States, industry and other stakeholders should continue to *contribute* to the promotion of alternative Test Methods on an international and national level…", but what 'contribute' means is not defined, and the recital is not reflected by a specific action required in the Articles.

However, there is a requirement for the Commission to report on the "amount and distribution of funding made available by the Commission for the development and evaluation of alternative Test Methods" every five years, under the review required in Article 117(4). According to the first review (45), 287 million Euros had been spent on projects related to alternative methods under the Framework 6 and 7 science funding programmes in the years 2004 to 2011. The Commission had also granted EURL ECVAM 40 million Euros during the same time period. According to the second review of REACH, in 2018 (20), during the period 2012–2016, the Commission had provided 350 million Euros for projects on alternatives. In addition, in the period 2012–2016, about 36 million Euros were given to EURL ECVAM, whose current annual budget is 6.5 million Euros. The Commission states that funding in the field of research into alternatives has remained stable over the last decade, with an average of 35 million Euros awarded to new research projects per year (20). However, given that the total budget of Framework 7 was 55 billion Euros (from 2007 to 2013; see 66), an average of 35 million Euros per year for alternative methods is only approximately 0.4% of the Commission's annual science budget.

Member States are also required to report on their levels of funding of alternatives to animal testing for REACH purposes, under the five-year reports required under Article 117(1) (see 67). An analysis of the individual reports for 2015 shows that only 10 out of 28 EU countries reported funding of alternative methods, to a total amount of just over seven million Euros annually. This represents an overall decrease of one million Euros from 2010. Two-thirds of Member States stated that they had "no information" on the amount of funding. In 2013, the ECEAE conducted a survey to try to obtain more information on the direct funding by Member States, of all alternative methods for all purposes (68). The total reported was only 18.7 million Euros for the year 2013, from seven Member States. For the Member State providing the largest annual amount (the UK, with approximately 11 million Euros), this amount still only constituted 0.04% of its national science research and development expenditure for that year (68).

The level of financial support given by industry is much harder to establish, as this often stems from contributions by individual companies, which they may or may not make public. Clearly, many of the alternatives now in use were developed, or commercialised, by the industry. The European Chemical Industry Council (CEFIC) funds some alternative method development through its Long-Range Research Initiative programme. The SEURAT-1 project (www.seurat-1.eu/) was highly relevant to chemicals, as a joint venture between the Commission (with funding from Framework 7) and the European Cosmetics Association (COLIPA), each contributing 25 million Euro. This has developed into the EuToxRisk project (www.eutoxrisk.eu/), but the investment by industry is less transparent in this particular case.

Member State direct contribution to alternative methods appears to be proportionately ten times

lower than that of the Commission. Nevertheless, the amount dedicated by the Commission to the development of alternatives is only a fraction of the EU's science budget. Even ECHA has recently said that: "Greater investment of time and money into the identification, development and especially the regulatory acceptance of alternatives would be extremely welcome to all" (2).

— ***Recommendation 8:*** A greater commitment toward direct funding of the development of alternative methods by Member States and the Commission needs to be made, either through political commitments or legislative means.

Animal testing as a last resort

Who takes responsibility?

As with the promotion of alternative methods, the aim that animal testing be conducted as "a last resort" was not directed at any one party. Until recently, ECHA believed that the last resort principle did not apply to it (see BoA case Dow A-001-2012). To some extent, this has been reflected in a number of decisions that have been brought by registrants to the BoA.

The very first animal testing-related BoA case was Honeywell, in 2011 (Honeywell A-005-2011). Under a compliance check, ECHA had requested a rabbit 90-day repeated-dose toxicity test, via the inhalation route. This is an almost unprecedented test that the ECEAE (in their intervention) and the registrant both argued would cause very high suffering to the rabbits. ECHA relied on a Column 2 option in section 8.6.4 of Annex X, to request further studies to investigate "toxicity of particular concern". The BoA ruled that ECHA nevertheless had breached the 'last resort principle' (69). A *Chemical Watch* article, published at the time, summarised the BoA decision succinctly (70):

The BoA criticised ECHA's decision on a number of fronts. It said the decision: was disproportionate; failed to identify properly what the aim of the study was or account for its unprecedented nature; did not consider whether rabbits were the appropriate species or consider whether the results would be at all useful, or if the study would be permitted in the EU. The BoA said ECHA should have adopted a 'stepwise' approach, looking first at whether non-animal approaches could allay the identified concern.

The BoA ruled similarly in one of the first cases brought against a substance evaluation decision requesting new animal testing (Akzo Nobel A-005-2014), in which the ECEAE also intervened. The BoA agreed with the registrant that ECHA had breached the 'last resort principle' (57). Furthermore, they instructed ECHA that future substance evaluation decisions must be able to demonstrate that:

a) there is a potential risk to human health or the environment;

b) the potential risk identified needs to be clarified (data gaps cannot on their own justify a request for that information); and

c) the information requested has a realistic possibility of leading to improved risk management measures.

The Member States represented by the MSCAs, particularly when it concerns substance evaluation, also have a role to play in ensuring that animal testing is used as a last resort. In my view, the balance between the need for more information and the need for testing to be used as a last resort is currently weighted toward the former. I have seen requests for higher-tier animal tests on substances to which workers or consumers were not exposed (minutes of MSC 41: SEV-SE-029/2013, butyl acrylate), or where there was little evidence pointing toward a real health concern (minutes of MSC 41: SEV-IT-022/2013, octabenzone). There have also been examples of where existing older studies or weight-of-evidence arguments were dismissed in preference for a new animal test (minutes of MSC 41: SEV-IT-022/2013, octabenzone), and where the results of higher-tier animal tests, normally considered definitive for classification and labelling, were ignored, and animal tests potentially providing mechanistic information were requested to investigate concerns (minutes of MSC 41: SEV-SE-029/2013, butyl acrylate; the results of two negative carcinogenicity studies were considered of limited value and an *in vivo* genotoxicity study was requested). There is also a tendency for some MSCAs to request the testing of corrosive substances, particularly via the inhalation route, with the main purpose of detecting 'local' effects on respiratory tissues that could be underestimated in oral studies (minutes of MSC 29: TPE 029B/2013, 2-piperazin-1-ylethylamine). However, the preamble to Annexes VII to X states: "*In vivo* testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided". ECHA and MSC appear to have interpreted the wording (wrongly in my view) to mean that an animal test is permitted, even on a substance classified as corrosive, as long as the dose levels do not cause corrosivity. The problem with that approach is that: a) one does not know whether corrosivity is caused, until *after* the test has been conducted; b) there are no safeguards to ensure that the levels of the test substance are sufficiently low; and c) corrosivity is a particularly severe endpoint.

Clearly, there has been an issue with ECHA and Member States not considering that testing as a 'last resort' applied to their decision-making. Registrants and animal protection groups have had to resort to the Ombudsman and BoA cases to resolve this. Whilst ECHA appear to have now accepted their responsibility in upholding animal testing as a last resort, it is not yet evident, in my experience, that Member States have done so.

— ***Recommendation 9:*** Care should be taken when drafting legislation that any requirement to avoid animal testing is clearly directed at the relevant bodies, and that the mechanisms to achieve this requirement are clear.

Enforcement

Enforcement of the 'last resort principle' outlined in Article 25(1) has proved difficult, partly because the Regulation is not clear on who has the responsibility for this, in what circumstances, and, importantly, what the penalties should be. There are two scenarios where the 'last resort principle' could be breached by registrants: a) where they have conducted an animal test without first going through the testing proposal system; and b) where they have conducted an animal test, but an alternative approach could have been used instead.

In the first report on the use of alternatives under REACH (71), ECHA proactively identified 107 new animal tests that appeared to have been done prior to a decision on a testing proposal. It agreed to investigate further. However, by the time of their second report, in 2014, the number of tests conducted without a testing proposal had risen to 293 (later amended to 295; 72). ECHA released a report in 2015 summarising the reasons that the registrants had given for bypassing the system, and asked MSCAs to investigate (73). In 2017, ECHA presented the findings from the MSCAs, which were disappointing, to say the least (74). Less than half of the relevant Member States had bothered to investigate, and overall only 20% of the 295 substances were actually investigated. In the majority of cases, the MSCA decided that there had been no breach of REACH rules, but little information is given in the report as to the basis for that conclusion. Nonetheless, ECHA is still monitoring this issue, and, following requests by animal protection groups, the ECHA forum on enforcement has taken it up (75).

According to data within the third ECHA report (see Table 2 in 16), there have been a number of new *in vivo* tests for endpoints for which there are recognised alternatives, such as skin irritation. In addition, a number of the *in vivo* tests conducted were not the most-refined tests available. For example, there were: 25 acute toxicity fish tests based on OECD TG204, which was deleted in 2014 and uses 75% more fish than the standard test; 19 LD50 tests, a notorious test that was deleted by the OECD in 2002; and 166 skin sensitisation tests with guinea-pigs, even though Annexes VII to X say that the LLNA is the preferred method for this endpoint. There were also 496 acute dermal studies, which is a test that can be waived in most cases; a revision to the Annexes VII to X, in July 2016, made this much clearer (39). There might, of course, be sound scientific reasons as to why these tests were considered necessary, but the ECEAE is concerned that not enough is being done to ensure that this is the only reason that they are still being conducted (76).

In 2012, the PETA Foundation set out their argument to the Ombudsman — that compliance checks should cover Article 25(1), and therefore ECHA should be rejecting registrations that include a recently-conducted animal test for which an alternative method is widely accepted (77). ECHA claimed, as it had in the BoA case Dow A-001-2012, that testing as a last resort was a principle directed (only) at registrants (77). The Ombudsman agreed with PETA that ECHA has a role to play in ensuring animal testing is used as a last resort, but that there is no legal basis for ECHA to reject a registration when an animal test is performed in violation of the REACH Regulation (77). The problem is that the registrant would still have satisfied their REACH obligations by providing (presumably) adequate animal test data. The current preference of ECHA (78), in both testing proposals and compliance check cases, is to notify MSCAs of a potential violation, who then investigate and enforce under *Directive 2010/63/EU* (28). Unfortunately, MSCAs do not seem motivated to investigate, and are content with the excuse that the testing was required by a third country.

— ***Recommendation 10:*** Specific sanctions for the breach of the 'last resort principle' should be included in any revised legislation. In the meantime, Member States should be reminded that they can and should enforce under *Directive 2010/63*.

Conclusions

This review is the first to estimate that 2.2 million animals are likely to have been used to date in new tests for REACH. The fact that the number does not include those substances that will be registered by 2018, and yet, it is already close to the Commission's 'best case' scenario, should be of grave concern to all. That said, the industry has done well to share data and avoid proposing new animal tests. The numbers of animals used so far

may be lower than more-extreme estimates, but this appears to have less to do with the use of (Q)SARs and *in vitro* methods than was anticipated, and more to do with the use of read-across and, according to ECHA, incomplete documentation.

Some progress on the development and use of alternative methods has also undoubtedly been made during the first ten years of REACH — the Annexes VII to X have been updated to remove some animal tests, and to further encourage the use of alternatives for others. There is also unmeasurably greater awareness of alternative methods. However, much of this progress had already been instigated *before* the REACH Regulation was implemented, possibly more because of the animal testing bans in the Cosmetics Regulation (4) or *in preparation* for REACH, than as a result of any activity under it. Significant problems remain with the use of alternatives to actually replace animal tests, their availability and their formal acceptance (17–19, 22–24, 26).

There is, in my view, an unacceptable malaise within the regulatory system to formally adopt alternative methods, even those developed and validated within the EU. It commonly takes four to six years from successful scientific validation to publication of the method in the TMR. I believe that the overly bureaucratic, two-step, OECD–EU process is partly to blame. The situation is not helped by the apparent requirement for the Annexes VII to X, ECHA guidance and the TMR to be updated before all the boxes are ticked in terms of formal acceptance. Furthermore, in my view, there does not appear to be a clear order in which these three documents should be updated, and which one takes precedence.

Part of the responsibility for the promotion of alternative methods lies with individual Member States, who, out of all the actors, have probably contributed least as a group. This is shown by the levels of national funding, proportionately tenfold lower than the Commission's, and the low level of awareness among many Member States of whether they contribute at all. It is also clear, from observing decision-making at the MSC, that the Member States have not considered themselves particularly bound to the 'last resort principle'. Several cases at the BoA have been overturned on the grounds that the MSC had an unnecessarily rigid adherence to procedure and/or lack of proportionality in their decision-making, that has led on occasion to requests for unnecessary animal tests. Furthermore, Member States seem reluctant to enforce nationally, when the principle of animal testing as a last resort appears to have been breached by registrants, even when encouraged by ECHA.

The weakness in the REACH Regulation with regard to testing as a last resort is, in my opinion, that the requirement to avoid testing was not clearly directed at anyone. The statement has become a rather hollow phrase. For a long time, ECHA's view was that it was directed solely at the registrants. As a result, in my experience, ECHA has adopted a tick-box approach and does little actual evaluation itself, as to whether an alternative approach could be used instead of an animal test. This is profoundly disappointing for those of us who thought that the agency responsible for REACH would ensure that animal testing was a last resort. Our view — and that of the Ombudsman and the BoA — is that animal testing as a last resort also applies to ECHA. As a result of these cases, minor improvements have been made to ECHA's approach, but arguably these have come too late to change an approach that is now ten years in the making. The testing proposal system has been a particular disappointment, largely caused by unavoidable procedural and legal restrictions that serve to limit its utility, but also by a lack of inclination on the part of ECHA to properly, in my view, support it.

There is nothing in the legal text to require specific funding for the development of alternatives, or other mechanisms that might help increase their availability to chemical companies. In hindsight, REACH should have included additional mechanisms to ensure that alternatives were more quickly developed. Hopefully, developments in alternatives will continue, and more animal tests will be replaced as REACH continues. Unfortunately, even if the tools arrive and the process is improved for their acceptance, this will come too late to save the majority of the animals used for the existing substances registered by 2018.

To ensure that the aims professed within a piece of legislation can be met, in the future, legislators should ensure that the legal text includes mechanisms to achieve these aims, and they should clearly be directed at a body. The documentation required to be produced by the ECHA according to the legislation has been incredibly informative in the area of animal testing. However, the Commission's reviews of REACH have not properly examined the data therein or focused sufficiently on this important aspect. Greater acknowledgement by the Commission of the total number of animals used for REACH purposes should be made, especially in the context of reviewing the success of REACH. Furthermore, examining the reasons why alternative methods are not being used — and addressing them — should also help avoid a great deal of animal suffering in the future.

Acknowledgements

I would like to thank Cruelty Free International Trust for funding my work during the last 11

years. I would like to thank the ECEAE for funding much of my travel over this period, for funding the testing proposal project and the toxicologists who assisted with this. I would also like to thank David Thomas for his advice over the years, and for his comments on this review.

References

1. Anon. (2006). *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 ECHA, 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*. *Official Journal of the European Union* **L396**, 30.12.2006, 1–849.
2. ECHA (2016). *Report on the Operation of REACH and CLP 2016*, *ECHA-16-R-08-EN*, 155pp. Helsinki, Finland: European Chemicals Agency.
3. European Commission (2018). *Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee. Commission General Report on the Operation of REACH and Review of Certain Elements. Conclusions and Actions*, *COM/2018/ 0116 Final*. Brussels, Belgium: European Commission.
4. Anon. (2009). *Regulation (EC) No 1223/2009* of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast). *Official Journal of the European Union* **L342**, 22.12.2009, 59–209.
5. European Commission (2001). *White Paper: Strategy for a Future Chemicals Policy, 27.2.2001, COM(2001) 88 Final*. Brussels, Belgium: European Commission.
6. Anon. (1993). *Commission Directive 93/67/EEC* of 20 July 1993 laying down the principles for assessment of risks to man and the environment of substances notified in accordance with *Council Directive 67/548/EEC*. *Official Journal of the European Union* **L227**, 08.09.1993, 9–18.
7. IEH (2001). *Testing Requirements for Proposals Under the EC White Paper 'Strategy for a Future Chemicals Policy', Web Report W6*, 23pp. Leicester, UK: Institute for Environment and Health.
8. Friends of the Earth (2002). *Safety Testing of Chemicals and the New EU Chemicals Policy*, 12pp. Amsterdam, The Netherlands: Friends of the Earth International. Available at: https://www.foe.co.uk/sites/default/files/downloads/safety_test_new_eu_chems.pdf (Accessed 11.12.18).
9. van der Jagt, K., Munn, S., Tørsløv, J. & de Bruijn, J. (2004). *Alternative Approaches Can Reduce the Use of Test Animals Under REACH*, 27pp. Ispra, Italy: Institute for Health and Consumer Protection.
10. Höfer, T., Gerner, I., Gundert-Remy, U., Liebsch, M., Schulte, A., Spielmann, H., Vogel, R. & Wettig, K. (2004). Animal testing and alternative approaches for the human health risk assessment under the proposed new European chemicals regulation. *Archives of Toxicology* **78**, 549–564.
11. Anon. (2006). *Briefing Note on Number of Animals Expected to be Used Under REACH: Summary of Re-Assessment Performed by the JRC*. Ispra, Italy: Institute for Health and Consumer Protection.
12. Rovida, C. & Hartung, T. (2009). Re-evaluation of animal numbers and costs for *in vivo* tests to accomplish REACH legislation requirements for chemicals — A Report by the Transatlantic Think Tank for Toxicology (t4). *ALTEX* **26**, 1–22.
13. ECHA (2009). *New Study Inaccurate on the Number of Test Animals for REACH, ECHA/PR/09/11*, 5pp. Helsinki, Finland: European Chemicals Agency.
14. Science and Technology Committee (2004). *Within REACH: The EU's New Chemicals Strategy. Sixth Report of Session 2003–04. Volume I: Report, HC 172-I*, 67pp. London, UK: The Stationery Office.
15. Anon. (2008). *Council 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). *Official Journal of the European Union* **L142**, 31.5.2008, 1–739.
16. ECHA (2017). *The Use of Alternatives to Testing on Animals for the REACH Regulation, ECHA-17-R-02-EN*, 101pp. Helsinki, Finland: European Chemicals Agency.
17. Ramirez, T., Beken, S., Chlebus, M., Ellis, G., Griesinger, C., De Jonghe, S., Manou, I., Mehling, A., Reisinger, K., Rossi, L.H., van Benthem, J., van der Laan, J.W., Weissenhorn, R. & Sauer, U.G. (2015). Knowledge sharing to facilitate regulatory decision-making in regard to alternatives to animal testing: Report of an EPAA workshop. *Regulatory Toxicology & Pharmacology* **73**, 210–226.
18. Rovida, C. (2010). Food for Thought… Why no new *in vitro* tests will be done for REACH by registrants. *ALTEX* **27**, 175–183.
19. Sauer, U.G., Hill, E.H., Curren, R.D., Kolle, S.N., Teubner, W., Mehling, A. & Landsiedel, R. (2016). Local tolerance testing under REACH: Accepted non-animal methods are not on equal footing with animal tests. *ATLA* **44**, 281–299.
20. European Commission (2018). *Commission Staff Working Document Accompanying the document Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee. Commission General Report on the Operation of REACH and Review of Certain Elements. Brussels, 5.3.2018. SWD(2018) 58 final. PART 1/7 (Conclusions and Actions)*. Brussels, Belgium: European Commission.
21. Anon. (2016). *Commission Regulation (EU) 2016/1688* of 20 September 2016 amending Annex VII to *Regulation (EC) No 1907/2006* of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards skin sensitisation. *Official Journal of the European Union* **L255**, 21.9.2016. 14–16.
22. Patlewicz, G., Roberts, D.W., Aptula, A., Blackburn, K. & Hubesch, B. (2013). Workshop: Use of "read-across" for chemical safety assessment under REACH. *Regulatory Toxicology & Pharmacology* **65**, 226–228.
23. Patlewicz, G., Ball, N., Boogaard, P.J., Becker, R.A. & Hubesch, B. (2015). Building scientific confidence in the development and evaluation of read-across. *Regulatory Toxicology & Pharmacology* **72**, 117–

133.
24. Patlewicz, G., Ball, N., Becker, R.A., Booth, E.D., Cronin, M.T., Kroese, D., Steup, D., van Ravenzwaay, B. & Hartung, T. (2014). Read-across approaches — Misconceptions, promises and challenges ahead. *ALTEX* **31**, 387–396.
25. ECHA (2017). *ECHA Read across Assessment Framework (RAAF), ECHA-17-R-01-EN*. Helsinki, Finland: European Chemicals Agency.
26. Ball, N., Bartels, M., Budinsky, R., Klapacz, J., Hays, S., Kirman, C. & Patlewicz, G. (2014). The challenge of using read across within the EU REACH regulatory framework; how much uncertainty is too much? Dipropylene glycol methyl ether acetate, an exemplary case study. *Regulatory Toxicology & Pharmacology* **68**, 212–221.
27. Anon. (2014). *Decision of the Board of Appeal of the European Chemicals Agency, 13 February 2014, A-006-2012*, 25pp. Helsinki, Finland: European Chemicals Agency.
28. Anon. (2010). *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. *Official Journal of the European Union* **L276**, 20.10.2010, 33–79.
29. European Commission (2009). *Process to be Followed prior to Inclusion of Test Methods in the Test Methods Regulation, 20 May 2009, Doc. CA/33/2009*. Brussels, Belgium: European Commission.
30. Anon. (1967). *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. *Official Journal of the European Union* **196**, 16.8.1967, 1–98.
31. Anon. (2008). REACH (Draft Test Methods Regulation) European Parliament resolution of 22 May 2008 on the draft Commission Regulation 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). *Official Journal of the European Union* **C279**, 19.11.2009, 85–89.
32. Anon. (2009). *Commission Regulation (EC) No 761/2009* of 23 July 2009 amending, for the purpose of its adaptation to technical progress, *Regulation (EC) No 440/2008* 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). *Official Journal of the European Union* **L220**, 24.8.2009, 1–94.
33. JRC (2013). *EURL ECVAM Recommendation on the Direct Peptide Reactivity Assay (DPRA) for Skin Sensitisation Testing*, 36pp. Ispra, Italy: EU Reference Laboratory for Alternatives to Animal Testing.
34. OECD (2015). *Test No 442C:* In Chemico *Skin Sensitisation: Direct Peptide Reactivity Assay (DPRA), OECD Guidelines for the Testing of Chemicals, Section 4*, 19pp. Paris, France: Organisation for Economic Co-operation and Development.
35. Anon. (2017). *Commission Regulation (EU) 2017/735* of 14 February 2017 amending, for the purpose of its adaptation to technical progress, the Annex to *Regulation (EC) No 440/2008* 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). *Official Journal of the European Union* **L112**, 28.4.2017, 1–402.
36. ICCVAM (2010). *ICCVAM Test Method Evaluation Report: Current Validation Status of* In Vitro *Test Methods Proposed for Identifying Eye Injury Hazard Potential of Chemicals and Products. NIH Publication No. 10-7553*. Research Triangle Park, NC, USA: National Institute of Environmental Health Sciences.
37. OECD (2017). *Test No. 437: Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage, OECD Guidelines for the Testing of Chemicals, Section 4*, 27pp. Paris, France: Organisation for Economic Co-operation and Development.
38. European Ombudsman (2018). *The European Commission's Failure to Handle Properly the Updating of the TMR Regulation with New Alternatives to Animal Testing*. Available at: https://www.ombudsman.europa.eu/en/case/en/51637 (Accessed 10.12.18).
39. Anon. (2016). *Commission Regulation (EU) 2016/863* of 31 May 2016 amending Annexes VII and VIII to *Regulation (EC) No 1907/2006* of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards skin corrosion/irritation, serious eye damage/eye irritation and acute toxicity. *Official Journal of the European Union* **L144**, 1.6.2016, 27–31.
40. Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology (2012). *Validation Report (Phase 2) for the Zebrafish Embryo Toxicity Test, No 179, Series on Testing and Assessment*, 57pp. Paris, France: Organisation for Economic Co-operation and Development.
41. OECD (2013) *Test No. 236: Fish Embryo Acute Toxicity (FET) Test, OECD Guidelines for the Testing of Chemicals, Section 2,* 22pp. Paris, France: Organisation for Economic Co-operation and Development.
42. ECHA (2016). *Aquatic*. Helsinki, Finland: European Chemicals Agency. Available at: https://www.echa.europa.eu/documents/10162/21650280/oecd_test_guidelines_aquatic_en.pdf/2548af92-ffe1-4e38-a42a-463103b1586f (Accessed 10.12.18).
43. ECHA & UBA (2018). *Expert Workshop on the Potential Regulatory Application of the Fish Embryo Acute Toxicity (FET) Test under REACH, CLP and the BPR, 3–4 May 2017, Helsinki, Finland*. Helsinki, Finland: European Chemicals Agency. Available at: https://www.echa.europa.eu/documents/10162/13630/fet_workshop_proceedings_en.pdf/a987ccab-5d4a-a226-2a73-994be484ca8d (Accessed 10.12.18).
44. Anon. (2016). *Summary Record. 19th Meeting of Competent Authorities for REACH and CLP (CARACAL), 12–13 November 2015, Doc. CA/108/2015 rev.1*. [Incorrectly titled 18th.] Brussels, Belgium: European Commission.
45. Anon. (2013). *Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions in accordance with Article 117(4) REACH and Article 46(2) CLP, and a review of certain elements of REACH in line with Articles 75(2),*

138(3) and 138(6) of REACH, SWD(2013) 25 Final. Brussels, Belgium: European Commission.
46. CSES (2012). *Interim Evaluation: Impact of the REACH Regulation on the Innovativeness of the EU Chemical Industry*, 101pp. Sevenoaks, UK: Centre for Strategy & Evaluation Services. Available at: http://ec.europa.eu/environment/chemicals/reach/pdf/studies_review2012/report_study5.pdf (Accessed 10.12.18).
47. Anon. (2016). Commission implementing *Regulation (EU) 2016/9* of 5 January 2016 on joint submission of data and data sharing in accordance with *Regulation (EC) No 1907/2006* of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). *Official Journal of the European Union* **L3**, 6.1.2016, 41–45.
48. Taylor, K., Stengel, W., Casalegno, C. & Andrew, D. (2014). Food for Thought: Experiences of the REACH testing proposals system to reduce animal testing. *ALTEX* **31**, 107–128.
49. ECHA (2012). *Evaluation Under REACH, Progress Report 2011, ECHA-12-R-02-EN*, 53pp. Helsinki, Finland: European Chemicals Agency.
50. ECHA (2007). *Guidance on Dossier and Substance Evaluation*. Helsinki, Finland: European Chemicals Agency.
51. ECHA (2013). *Evaluation under REACH, Progress Report 2012, ECHA-13-A-01-EN*, 45pp. Helsinki, Finland: European Chemicals Agency.
52. European Ombudsman (2015). *Decision in Case 1606/2013/AN on How the European Chemicals ECHA Applies Rules Concerning Animal Testing*. Available at: https://www.ombudsman.europa.eu/en/cases/decision.faces/en/60909/html.bookmark (Accessed 10.12.18).
53. ECHA (2015). *ECHA Asks Registrants to Show How they Considered Alternative Methods Before Consulting on Testing Proposals, ECHA/PR/15/13*. Helsinki, Finland: European Chemicals Agency.
54. ECHA (2017). *Important Safety Information on Chemicals Still Missing, ECHA/PR/17/03*. Helsinki, Finland: European Chemicals Agency.
55. Vermeire, T., de Bovenkamp, M., Bruinende Bruin, Y., Delmaar, C., van Engelen, J., Escher, S., Marquart, H. & Meijster, T. (2010). Exposure-based waiving under REACH. *Regulatory Toxicology & Pharmacology* **58**, 408–420.
56. Anon. (2009). *Commission Regulation (EC) No 134/2009* of 16 February 2009 amending *Regulation (EC) No 1907/2006* of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annex XI. *Official Journal of the European Union* **L46**, 17.2.2009, 3–5.
57. Anon. (2015). *Decision of the Board of Appeal of The European Chemicals ECHA, 23 September 2015, A-005-2014*, 18pp. Helsinki, Finland: European Chemicals Agency.
58. ECHA (2009). *Clarification Will Avoid Unnecessary Animal Tests, 15 September 2009*. Helsinki, Finland: European Chemicals Agency.
59. PETA (2009). *Victory! 4.5 Million Animals to Be Spared From Toxicity Tests*. Norfolk, VA, USA: People for the Ethical Treatment of Animals. Available at: https://www.peta.org/blog/victory-45-million-animals-spared-toxicity-tests/ (Accessed 10.12.18).
60. European Ombudsman (2014). *Decision of the European Ombudsman Closing the Inquiry into Complaint 1301/2013/(FOR)AN Against the European Chemicals Agency (ECHA)*. Available at: https://www.ombudsman.europa.eu/et/decision/en/54578 (Accessed 10.12.18).
61. Anon. (2013). *Decision of the Board of Appeal of the European Chemicals Agency, 10 October 2013, Case A-004-2012*, 33pp. Helsinki, Finland: European Chemicals Agency.
62. ECHA (2010). *Practical Guide 10: How to Avoid Unnecessary Testing on Animals. ECHA-10-B-17-EN*. Helsinki, Finland: European Chemicals Agency.
63. ECHA (undated). *OECD and EU Test Guidelines*. Helsinki, Finland: European Chemicals Agency. Available at: https://echa.europa.eu/support/oecd-eu-test-guidelines (Accessed 10.12.18).
64. ECHA (2016). *Practical Guide, How to Use Alternatives to Animal Testing to Fulfil your Information Requirements for REACH Registration, version 2.0 — July 2016, ECHA-16-B-25-EN*, 41pp. Helsinki, Finland: European Chemicals Agency.
65. ECHA (2016). *Practical Guide for SME Managers and REACH Coordinators, How to Fulfil your Information Requirements at Tonnages 1–10 and 10–100 tonnes per Year, version 1.0 — July 2016, ECHA-16-B-24-EN*, 130pp. Helsinki, Finland: European Chemicals Agency.
66. Anon. (2013). *Factsheet: Horizon 2020 Budget*, 4pp. Brussels, Belgium: European Commission.
67. Anon. (2016). *Member States Reports on the Operation of REACH (Art.117)*. Available at: http://ec.europa.eu/environment/chemicals/reach/reports_en.htm (Accessed 10.12.18).
68. Taylor, K. (2014). EU Member State government contribution to alternative methods. *ALTEX* **31**, 215–218.
69. Anon. (2013). *Decision of the Board of Appeal of the European Chemicals Agency, 29 April 2013, Case A-005-2011*. Helsinki, Finland: European Chemicals Agency.
70. Jones, P. (2013). *ECHA Board of Appeal Annuls Animal Testing Decision*. 29 April 2013. Available at: https://chemicalwatch.com/14659/echa-board-of-appeal-annuls-animal-testing-decision?q=board+of+appeal+honeywell (Accessed 10.12.18).
71. ECHA (2011). *The Use of Alternatives to Testing on Animals for the REACH Regulation, ECHA-11-R-004.2-EN*, 64pp. Helsinki, Finland: European Chemicals Agency.
72. ECHA (2014). *The Use of Alternatives to Testing on Animals for the REACH Regulation, Second Report Under Article 117(3) of the REACH Regulation, ECHA-14-A-07-EN*, 129pp. Helsinki, Finland: European Chemicals Agency.
73. ECHA (2015). *Survey Results — Analysis of Higher Tier Studies Submitted Without Testing Proposals, ECHA-15-R-13-EN*, 21pp. Helsinki, Finland: European Chemicals Agency.
74. ECHA (2017). *Reports from Member State Investigations Concerning the Obligation to Submit Testing Proposals for Vertebrate Animal Tests Under REACH, ECHA-17-R-05-EN*. Helsinki, Finland: European Chemicals Agency.
75. ECHA (2017). *10th Meeting of the NGO–ECHA Discussion Platform, Meeting Note 25 April 2017*, 6pp. Available at: https://www.echa.europa.eu/about-us/partners-and-networks/stakeholders/cooperation-with-accredited-stakeholders/ngo-echa-

discussion-platform (Accessed 10.12.18).
76. Anon. (2011). *Welfare Group Reviews ECHA Report on Animal Testing, 4 July 2011*. Available at: https://chemicalwatch.com/7854/welfare-group-reviews-echa-report-on-animal-testing (Accessed 10.12.18).
77. European Ombudsman (2014). *Decision of the European Ombudsman Closing the Inquiry into Complaint 1568/2012/(FOR)AN Against the European Chemicals Agency (ECHA)*. Available at: https://www.ombudsman.europa.eu/en/decision/en/58549 (Accessed 10.12.18).
78. ECHA (2017). *Use of Compliance Check to Verify Compliance with Article 13(1) of REACH. Helsinki, 14.06.2017, Doc. CA/42/2017*. [Presented at 24th Meeting of Competent Authorities for REACH and CLP, 28–29 June 2017, Brussels, Belgium.] Helsinki, Finland: European Chemicals Agency.

Glossary

Bodies with a role in REACH

Abbreviation/ acronym	Description
BoA	Board of Appeal. An independent body, based within ECHA, responsible for deciding on appeals lodged against ECHA decisions.
CARACAL	Competent Authorities for REACH and CLP expert advisory group to the Commission. CARACAL is an expert group, formed of representatives of MSCAs and observer organisations that advises the Commission and ECHA on questions related to REACH and CLP.
ECHA	European Chemicals Agency. Formed in 2008 to process and evaluate the registration dossiers submitted according to REACH.
EURL ECVAM	European Union Reference Laboratory, European Centre for the Validation of Alternative Methods. Part of the Commission's Joint Research Centre, the centre coordinates the validation of alternative methods and produces recommendations on the applicability of new test methods following advice from its Scientific Advisory Committee.
European Commission (Commission)	The EU's politically independent executive arm, responsible for drawing up and implementing European legislation.
European Ombudsman (Ombudsman)	An elected individual (currently Emily O'Reilly), who deals with complaints about malpractice in the bodies of the European Union.
Member States	Member countries of the European Union (EU), bound by REACH.
MSC	Member State Committee. An ECHA committee formed of Member State representatives (usually from the MSCA), who make the final decision on testing proposals, compliance checks and substance evaluation cases.
MSCA	Member State Competent Authority. The designated authority responsible for REACH within each Member State, usually a government ministry or agency.
OECD	Organisation for Economic Cooperation and Development. An international organisation made up of Member Countries from around the world. Among other tasks, it produces harmonised Test Guidelines for the testing of chemicals.
RAC	Committee for Risk Assessment. An ECHA committee formed of representatives nominated by the Member States that makes decisions on harmonised classification and labelling, restriction and authorisation of substances identified as of very high concern.
Registrant	An importing or manufacturing company that registers their substance under REACH.

REACH Processes

Abbreviation/ acronym	Description
ATP	Adaptation to Technical Progress. The process by which the TMR is updated to include new or revised Test Methods, in practice those from the OECD Test Guidelines programme.
Classification and Labelling Regulation (CLP)	The *Regulation EC No 1272/2008* is based on the United Nations' Globally Harmonised System (GHS), and requires manufacturers, importers or downstream users of substances or mixtures to classify, label and package their hazardous chemicals appropriately before placing them on the market.
Compliance check	The process by which ECHA reviews registration dossiers to ensure compliance with the REACH regulation. There are minimum targets in REACH that ECHA must meet for checking registrations.
Data-sharing	Registrants of the same substance have a duty to share their vertebrate animal test data, reimbursing the data owner. Registrants of pre-existing substances can join together in Substance Information Exchange Forums (SIEFs) to facilitate this.
Dossier evaluation	The ECHA process for drafting and finalising decisions on the need for new tests, following a compliance check, or a testing proposal submission.
ECHA decision	A decision letter sent to the registrant outlining the requirements to bring the registration dossier into compliance. The decision is a formal ECHA decision, even though the MSC is the body that approves the final decision based on an ECHA draft decision.
ECHA Guidance	Guidance produced by ECHA on how to register a substance. Guidance R7 outlines the appropriate information requirements for registrants, including alternative methods for human and environmental health endpoints. The creation and revisions of these documents is done in consultation with Member States and external experts. See https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
Endpoint	A toxicological outcome (e.g. carcinogenicity, repeated-dose toxicity) that can be addressed by single or multiple *in vivo* or alternative test methods.
Information requirements	Hazard information required for registration, outlined in Annexes VII to X. Requirements are cumulative across the Annexes: Annex VII are the requirements for substances produced or imported in quantities per company of one tonne or more per year; Annex VIII, the requirements for substances in quantities of 10 tonnes or more per year; Annex IX in quantities of 100 tonnes or more per year; and Annex X in quantities of 1,000 tonnes or more per year.
Pre-registration	Preliminary registration of substances by an importer or manufacturer, expressing their intent to submit a full registration dossier by the respective deadline.
Registration deadline	Deadlines imposed by REACH for the submission of registrations; 2010 for substances falling under Annex X, 2013 for substances falling under Annex IX and 2018 for substances falling under Annexes VII and VIII.
Registration dossier	The documents detailing the composition, uses, health and environmental hazards, and the chemical safety assessment of a substance that are submitted to ECHA upon registration.
SIEF	Substance Information Exchange Forums. A grouping of all pre-registrants of the same chemical substance with the aim to facilitate the exchange of information to avoid duplication of animal tests, to prepare a joint lead registration dossier of the substance; and to agree, if possible, the classification and labelling of the substance.
Substance	Chemical elements and their compounds in the natural state or obtained by any production process that are required to be registered under REACH.
Substance evaluation	A process led by Member States to evaluate certain substances to clarify whether their use poses a risk to human health or the environment. The objective is to request further information from the registrants of the substance to verify the suspected concern, if necessary.
Test Guidelines/ Test Methods TMR	OECD Test Guidelines for human and environmental health endpoints are used internationally; within the EU these are transposed into the Test Methods Regulation (*No. 1907/2006 [TMR]*).
Testing proposal	Registrants of substances falling under Annex IX or X must submit proposals for any tests required in these Annexes that have not yet been conducted. ECHA then publishes the proposals relating to tests on vertebrate animals, giving third parties 45 days to submit 'scientifically valid information and studies'. ECHA had until 1 December 2012 to issue draft decisions on the testing proposals submitted for the 2010 registration deadline, and until 1 June 2016 for the 2013 registration deadline.

Alternative Methods

Abbreviation/ acronym	Description
Alternative methods	Methods that replace, reduce or refine tests on live, vertebrate animals.
Data waiving	Arguments put forward by registrants that the requested data requirement does not need to be fulfilled.
(Q)SARs	Quantitative structure–activity relationship models; computer models that predict the (eco)toxicological properties and/or environmental fate properties of one or more substances based on their structural similarity to other substances for which these properties are known.
Read-across	A technique that uses the results of data for one or more substances to predict the (eco)toxicological properties and/or environmental fate properties of one or more other substances, usually based on a hypothesis that their structures are similar or follow a regular pattern.
Weight-of-evidence approach	The combination of several pieces of information, including the results of existing experimental data and *in silico* approaches, to satisfy the information requirement for an endpoint, which on their own might be considered insufficient.