Cruelty Free INTERNATIONAL

TSGE CONSULTING

How to avoid new animal tests in your 2018 REACH registration

A Cruelty Free International/TSGE Consulting report

Contents

Executive summary

Do you need to register your chemicals for REACH 2018? Are you assisting companies in their registrations? Are you looking at what information is required to fulfil REACH registration requirements? Might you be involved in commissioning new tests if they are required?

Then this guide is for you!

Since REACH was adopted in 2006 there have been some significant developments in alternative methods to animal testing. Several methods have now been approved that can fully replace some animal tests and there are new waiving approaches for others. There are changes to the REACH legal text as well as ECHA guidance that cover these new options.

In order to help companies avoid testing on animals we have produced this simple guide to signpost you to these recent changes. If you have any questions please don't hesitate to get in touch.

Cruelty Free International

Cruelty Free International is the leading organisation working to create a world where nobody wants or believes we need to experiment on animals. We are widely respected as an authority on animal testing issues and are frequently called on by governments, the media, corporations and official bodies for advice or expert opinion. We work professionally, building relationships with politicians, business leaders and officials, analysing legislation and challenging decision making panels around the globe to act as the voice for animals in laboratories.

Cruelty Free INTERNATIONAL

www.crueltyfreeinternational.org

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Introduction

REACH specifies strict data requirements that must be fulfilled when registering your substance. As a consequence, when compiling your registration dossier you may be faced with making a decision about the need to commission a new animal test.

The chemicals sector collectively managed to avoid a great number of new animal tests for the REACH deadlines in 2010 and 2013, through the use of the alternative method provisions in REACH. For the 2018 deadline we would like to keep it that way.

Under REACH, animal testing should be a last resort and alternative methods used wherever possible.

Furthermore, under the EU animal testing Directive (2010/63/EC) companies must not test on animals if an alternative method is accepted under EU legislation.

There are fewer requirements for vertebrate animal *(in vivo)* toxicity tests for substances being registered for the 2018 deadline (less than 100 tonnes production or import per year). These data requirements are listed in Annexes VII and VIII of REACH.

Happily, a number of new alternative methods for some of these data requirements have been accepted by the OECD since REACH was written in 2006. The OECD is the international harmonisation body to which the USA, Japan, Canada and Europe plus other countries belong to ensure that there is mutual acceptance of data. **Last year, REACH was updated to accommodate these new methods and some animal tests have even been deleted.** It is therefore important that registrants are familiar with these changes, and how alternative methods can now be used to avoid new animal tests.

It is important that companies registering their substances obtain the right technical expertise so that any testing needs can be minimised. TSGE Consulting Ltd. and animal protection organisation Cruelty Free International have jointly produced this guide to help update companies and their advisers on the opportunities to avoid unnecessary animal testing. We hope you find it helpful!

Source: Philippe Gotteland at EpiSkin

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.

Article 25(1) of REACH

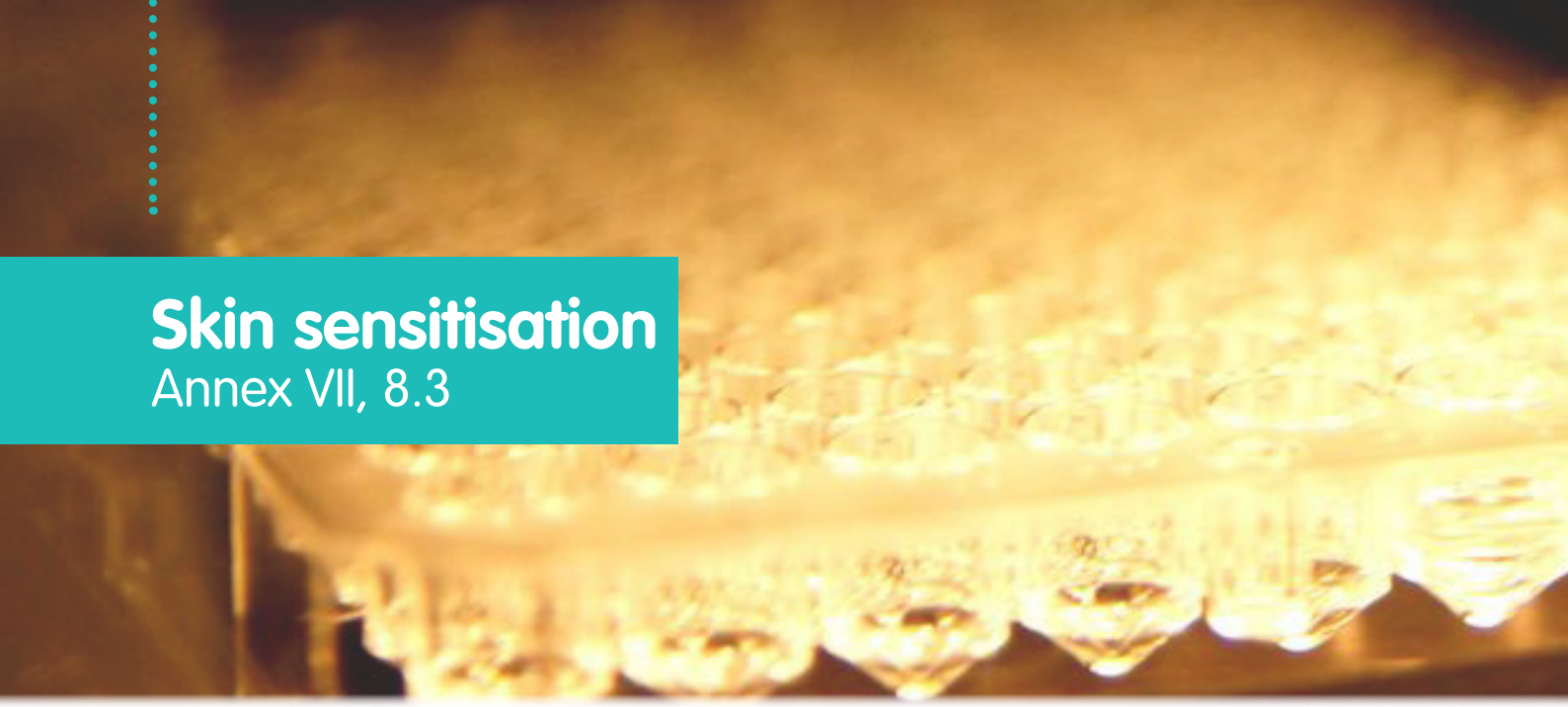
New possibilities to avoid animal testing

According to REACH, alternative methods should be used wherever possible.

> Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular for human toxicity, **information shall be generated whenever possible by means other than vertebrate animal tests**, through the use of alternative methods, for example...
>
> **Article 13(1) of REACH**

A number of cell-based *(in vitro)* approaches have now been validated and approved by international body the OECD.[1] Table 1. below highlights these new methods and when they have been added to ECHA guidance and the REACH legal text:

Animal test	New method	Update in ECHA guidance?	REACH text change?
Annex VII			
8.3 Skin sensitisation	Testing strategies that combine *in silico* (QSARs), *in chemico* (OECD TG 442c) and *in vitro* tests (e.g. OECD TG 442d and h-CLAT (approved 2016))	Updated December 2016	Use of in vitro methods first (Sept 2016)
8.5.1 Acute toxicity - Oral route	An *in vitro* assay can be used to demonstrate lack of oral toxicity (NRU3T3 test)	Updated December 2016	No change foreseen, use Annex XI weight of evidence
Annex VIII			
8.1.1 Skin corrosion/ irritation	*In vitro* reconstituted human skin methods (OECD TG 439 and 431, plus others)	Already included, further revision July 2015	*In vivo* requirement has been deleted (May 2016)
8.2.1 Serious eye damage/ irritation	Several *ex vivo* methods can now detect corrosive and non-irritant substances (OECD TG 437, 438, 491, 492, plus others)	Already included, further revision July 2015	*In vivo* requirement has been deleted (May 2016)
8.5.3 Acute toxicity - Dermal route	The dermal toxicity test can be waived if the substance is not classified by the oral route	Updated December 2016	Waiving dermal included (May 2016)
9.1.3 Acute fish toxicity	An acute fish test that does not use live fish has been approved and can be used to avoid adult fish testing (OECD TG 236) as part of the fish testing strategy	Already mentioned in existing guidance	No test method is specified



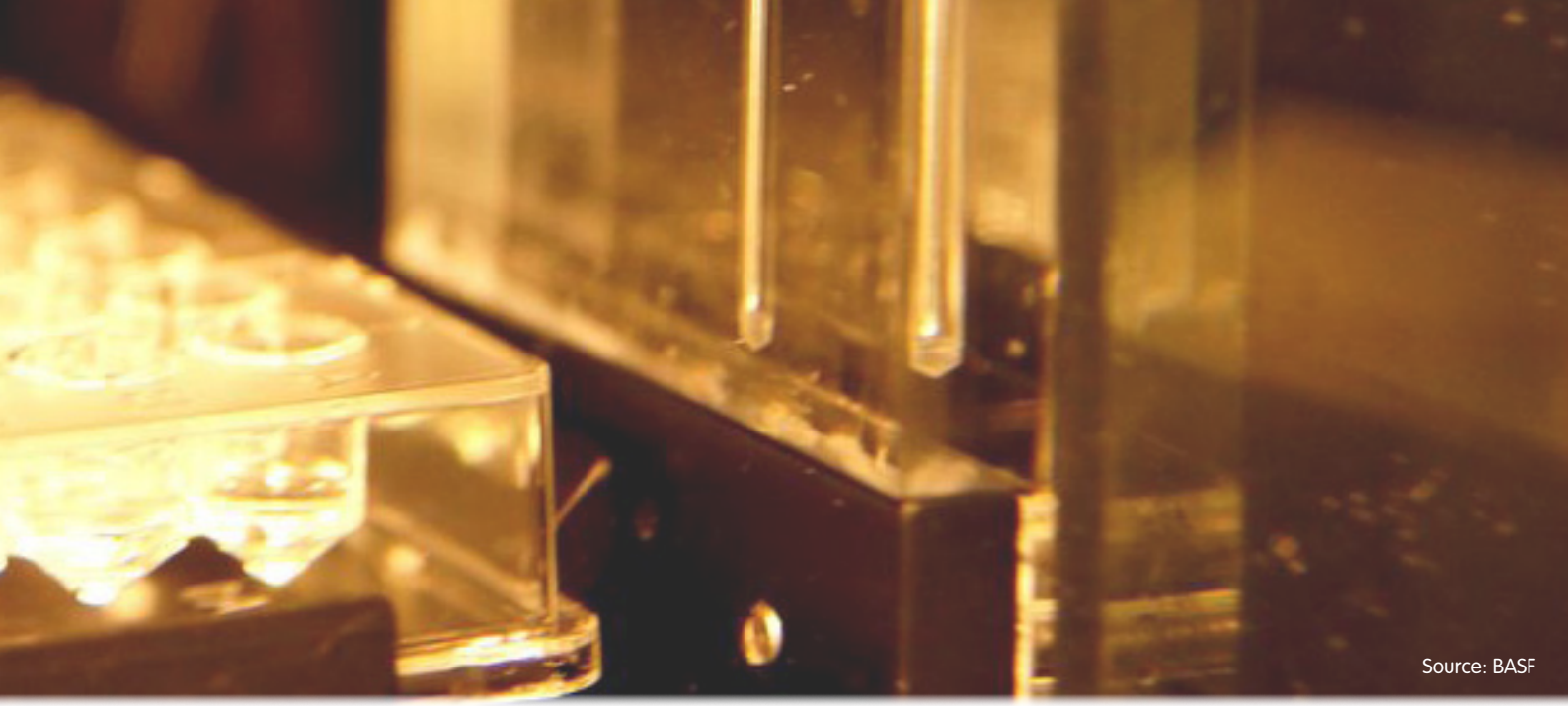
Skin sensitisation
Annex VII, 8.3

Introduction

There are several testing strategies that combine *in silico* (QSARs), *in chemico* (OECD TG 442c) and *in vitro* tests (e.g. OECD TG 442d) to distinguish skin sensitisers from non-sensitisers, avoiding the conduct of the current standard test method the Local Lymph Node Assay (LLNA), that uses live mice.

Alternative methods

- Direct Peptide Reactivity Assay (DPRA) (OECD TG 442c, adopted 2015)
    - An *in chemico* method that measures depletion of cysteine- or lysine-based peptides following 24 hours incubation with the test substance. Assesses the key step in the mechanism of skin sensitisation; protein reactivity
- ARE-Nrf2 Luciferase Test Method (Keratinosens™) (OECD TG 442d, adopted 2015)
    - An *in vitro* test that uses a human cell line to measure the activation of genes known to be involved in triggering the immune response to contact allergens
- h-Clat (draft OECD guideline, OECD TG 442e, adopted 2016)
    - An *in vitro* test that uses a human cell line that addresses the third key event in skin sensitisation, activation of the dendritic cells
- QSAR models
    - Quantitative Structure-Activity Relationship (QSAR) computer models have particularly strong predictive strength for skin sensitisation because reactivity can be predicted based on chemical structure alone. The reactivity of a chemical structure can be predicted based on its structural similarity to other chemicals in the database with known properties. See www.antares-life.eu for models



Source: BASF

How good are they?

Several organisations have successfully assessed the use of the tests in various combinations, usually using two or three of the tests above to predict whether the substance is a sensitiser or not.

BASF use an in-house version of Keratinosens, the DPRA and h-Clat/mMUSST test and a two out of three rule; any two assays must be positive to rate the substance as a skin sensitiser and any two assays must be negative to rate the substance as a non-sensitiser.[2] A large study by BASF showed that their two out of three test strategy accurately distinguished human sensitisers from non-sensitisers 94% of the time.[3]

The Dutch authorities use a slightly different testing strategy comprising of QSAR models and the DPRA followed by the Keratinosens and the h-Clat for equivocal results.[4] Their strategy was found to be accurate 95% of the time just using the DPRA and QSARs and 100% accurate using all three *in vitro* tests.[5]

The new test methods and QSAR models on their own are very predictive, for example, the QSAR model CAESAR is 90% predictive alone.[6] The original LLNA mouse test however is only 72%[7] - 82%[8] predictive of human allergic reactions and has been shown to place nearly half of known human strong sensitisers in the wrong sub category.[9]

How can they be used?

The new ECHA OECD and EU test guidelines update pages acknowledges the new tests and agrees they can be used within a weight of evidence assessment. A revision of Annex VII of REACH was published at the end of 2016. The text permits the use of *in vitro/in silico* methods in place of the LLNA if adequate for classification and labelling. An OECD guidance document was also published in 2016 which gives examples of the various testing strategies. A revision of the ECHA R7a guidance on skin sensitisation to explain these options was also published in December 2016.

Skin corrosion/irritation
Annex VIII, 8.1.1

Introduction

The existing skin *in vitro* methods have been improved and can be used in combination to demonstrate a lack of irritation (not classified) as well as irritation and corrosion. The testing strategy has been formalised and accepted by the OECD and ECHA. The rabbit *in vivo* test originally specified in Annex VIII has been deleted from column 1 (May 2016).

Alternative methods

In vitro models based on reconstituted human epithelium (RhE) comprise of small discs of cells from human skin donated as waste from cosmetic surgery, grown into an epidermal layer. The tests can be used to classify substances as corrosive (UN GHS/EU CLP category 1; some tests can be used for sub classifications of this category), irritating (UN GHS/EU CLP category 2) and not irritating (not classified).

Skin corrosion:

- *In Vitro* Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method (OECD TG 431, updated 2016)
    - Models include: Episkin™, Epiderm™, Skin Ethic™, epiCS®. They can predict category 1A from 1B/C and non-corrosive
- *In Vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test Method (TER) (OECD TG 430, updated 2015)
    - Based on rat skin, this test detects corrosive chemicals (category 1)
- *In Vitro* Membrane Barrier Test Method for Skin Corrosion (OECD TG 435, updated 2015)

Source: Philippe Gotteland at EpiSkin

- Sold as Corrositex™, this *in vitro* synthetic membrane based test predicts category 1A, 1B, 1C from non-corrosive

Skin irritation:

- *In Vitro* Skin Irritation - Reconstructed Human Epidermis Test Method OECD 439, updated 2015
    - Models include: Episkin™, Epiderm™, Skin Ethic™, LabCYTE EPI model. They can predict irritants (category 2) from non-irritants

How good are they?

There have now been several large-scale studies of the RhE models. They have consistently shown to be reliable and predictive. For example in a study of tests on 184 cosmetic ingredients EpiSkin® demonstrated 86% accuracy.[10] Another study found that Epiderm® was found to be 76% accurate at predicting human skin patch test results whereas the rabbit test was only correct 60% of the time.[11]

How can they be used?

Skin corrosion can be assessed using RhE skin *corrosion* model OECD TG 431 or other *in vitro* models, TG 430 (TER) or TG 435 (Corrositex®). If the test is negative, the RhE skin *irritation* models (OECD TG 439) should then be used to assess whether or not the substance is irritating. Although the two RhE tests are similar, they have different exposure times. A testing strategy is given in OECD guidance document No 203.[12] ECHA OECD and EU test guidelines update pages reiterates how the tests can be used and the ECHA R7a guidance on skin corrosion/irritation has just been updated. Deletion of the *in vivo* requirement in column 1 of AnnexVIII was published in May 2016.

Serious eye damage/irritation
Annex VIII, 8.2.1

Introduction

Ex vivo eye corrosion methods can be used to demonstrate a lack of irritation (no classification) as well as whether a substance is likely to be severely irritating (corrosive). *In vivo* testing can therefore be avoided in many cases. Other *in vitro* eye irritation methods are now available (EpiOcular™) and a complete testing strategy is being drafted. The rabbit *in vivo* test originally specified in Annex VIII has been deleted from column 1 (May 2016).

Alternative methods

Serious eye damage/no classification:

Isolated eyes from cattle or chickens killed for food purposes can now be used to detect both severely irritating/corrosive (UN GHS/EU CLP category 1) and non-irritating substances (not classified).

- Isolated Chicken Eye Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (OECD TG 438, updated 2013)

- 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 Bovine Corneal Opacity and Permeability test (OECD TG 437, updated 2013).

Other methods using animal cell lines can be used if the methods above are not available or suitable:

- Short-Time Exposure for the detection of chemicals causing Serious Eye Damage and chemicals Not Requiring Classification for Serious Eye Damage or Eye Irritation (OECD TG 491, adopted 2015)

Source: MatTek Corporation

- Fluorescein Leakage Test Method for Identifying Ocular Corrosives and Severe Irritants (OECD TG 460, adopted 2012)

No classification:

A new *in vitro* test based on reconstituted human cells, has now been approved, initially as EpiOcular™ although others are available (SkinEthic HCE™). It can currently be used to identify substances not requiring classification for irritation or serious eye damage.

- Reconstructed Human Corneal Epidermis for the Detection of Chemicals Not Requiring Classification and Labelling for Eye Irritation or Serious Eye Damage (OECD TG 492, adopted 2015).

How good are they?

The rabbit test is known to be unreliable, with laboratories often giving very different results and with only low to moderate correlation with human responses as rabbits tend to experience more severe effects than humans.[13] The validation of EpiOcular™ showed it to be 85% predictive of human eye irritants.[14]

How can they be used?

Two *in vitro* tests can be used in combination in a Top Down/Bottom up approach.[15] An OECD guidance document is in preparation - expected 2017. In the meantime, ECHA OECD and EU test guidelines update pages confirm that the ICE and BCOP can be used to demonstrate serious eye damage (corrosives) or no classification (negatives) in a weight of evidence assessment. Furthermore, the ECHA R7a guidance on serious eye damage/irritation has been updated to permit the use of these methods. Deletion of the *in vivo* requirement in column 1 of Annex VIII was published in May 2016.

Acute toxicity

Annex VII, 8.5.1 (oral), Annex VIII, 8.5.3 (dermal)

Introduction

The acute dermal toxicity test (OECD TG 402) normally required at Annex VIII can now be waived if the substance is not classified by the oral route. An *in vitro* assay has been validated and can be used together with other information to demonstrate a lack of oral toxicity (NRU3T3 test).

Alternative methods

Gases need only be tested by the inhalation route for acute toxicity. However, for non-gases, Annex VIII of REACH calls for an acute test by the dermal route in additional to the oral route. However, retrospective analysis has shown that the dermal route adds nothing to the risk assessment (see below).

The 3T3NRU test[16] can be used together with other information to demonstrate lack of toxicity by the oral route. The test is based on an animal cell line and has been shown to predict non-toxic substances with 95% sensitivity.

How good are they?

Studies of 2,350 substances showed that the dermal route gave a more severe classification in only 6 cases (three of which could have been foreseen based on the physiochemical properties of the substance)[17]. Since most substances are non-toxic[18] the use of the waiver can avoid further dermal testing in many cases.

A NICEATM/ECVAM validation of the NRU3T3 has shown it predicts non-toxic substances with 95% sensitivity. ECVAM has recently concluded in a large scale analysis that the test can be safely used to detect non-toxic, non-classified substances (LD50 values greater than 2,000 mg/kg bw/d). Only two substances (plant toxins) that were classified for acute toxicity were not identified by the test, therefore if the test result is negative it can be trusted.[19]

How can they be used?

Annex VIII of the REACH legal text has been revised (May 2016) to make it clear that the dermal route can be waived if the substance is not classified via the oral route (LD50=>2,000mg kg bw/d). A revision of ECHA R7a guidance on acute toxicity was published in December 2016.

Despite the evidence for its reliability the NRU3T3 test is only likely to be accepted by ECHA when used in a weight of evidence approach with other information such as other test results, QSARs or physical chemical properties. Registrants will need to argue for non classification using Annex XI (weight of evidence) adaptations to waive the *in vivo* study according to the revised ECHA R7a guidance on acute toxicity which was published in December 2016.

Short term toxicity in fish
Annex VIII, 9.1.3

Introduction

An acute fish test that uses fish embryos has been approved (OECD TG 236) and can be used to avoid adult fish testing as part of the fish testing strategy.

Alternative methods

The Fish Embryo Acute Toxicity (FET) Test (OECD TG 236, adopted 2013) uses newly fertilised zebrafish eggs which are incubated with the test substance for 96 hours only. The test does not use live animals (as defined by EU Directive 2010/63) and can therefore be seen as a refinement of existing acute toxicity tests that use live fish. An ECVAM recommendation in 2014 supported its use to replace acute fish toxicity.[20]

There are also some reliable QSAR models for acute fish toxicity, see www.antares-life.eu for models.

How good are they?

Validation of the FET in hundreds of chemicals demonstrated extremely strong (r=0.95) correlation between embryo toxicity and adult fish toxicity LC50 values.[21]

How can they be used?

ECHA guidance on acute aquatic toxicity R7b already outlines a testing strategy, which includes a placeholder for validated alternative methods to the acute fish toxicity test. The ZFET is specifically mentioned as a possible alternative provided that it is fully validated and available as a standardised method (e.g. OECD test guideline), a requirement now met by the availability of OECD TG 236 Fish Embryo acute Toxicity (FET) test.

Furthermore, the OECD recommends the 'threshold approach'[22] in which only a single concentration is tested based on results from algae and daphnia tests. Registrants are also recommended to follow the OECD fish testing framework to avoid unnecessary fish testing.[23]

It is important to note that a specific test method for 9.1.3 (Short-term toxicity testing on fish) is not specified in the REACH legislation, but ECHA's acceptance of the FET as a standalone test for this information requirment is not yet clear.

Key points to avoid unnecessary animal testing

Consult your SIEF before commissioning new animal tests

Commissioning a test, before consulting with your SIEF, even if you think it is needed, could prevent the use of all opportunities to avoid testing through the use of existing data and read across. It is also unlawful; under Article 30.1 companies should to make enquiries within their SIEF before conducting testing.

Maximise the use of existing data

Always check that a thorough review of the literature on your substance has been made including published databases such as TOXNET, PubMed, OECD databases (see www.echemportal.org), and other national regulatory schemes.

Existing data can be used even though it may be old and not performed under GLP. It is important however that the studies are comparable to their modern equivalents in terms of key parameters covered, species and duration of the testing and that the results are suitable for classification and labelling purposes, even if the decision is that the substance does not need to be classified.

Maximise the use of read-across, category approaches and (Q)SARs

- The opportunity to avoid new animal tests by using existing data is a universal strategy.
- Existing data for read-across purposes can also be used even if it is old or not generated according to GLP. The data must be adequate for classification and labelling, cover the same key parameters and be of comparable or longer duration to the test you are seeking to avoid. You need to have access to the data you are using to read-across from.
- (Q)SARs (Quantitative) Structure Activity Relationship models can be used also but the results must be adequate for classification and labelling and the model itself should have been validated. The ANTARES project lists some good models for REACH purposes (see Further Information). You should show that the substance falls within the model's applicability domain and provide proper documentation of both the model (using the (Q)SAR Model Reporting Form (QMRF) and the result (using the (Q)SAR Prediction Reporting Format (QPRF), see JRC (Q)SAR Model Inventory in Futher Information.
- It is vital that the read across or category approach is properly described and fully justified. ECHA have recently published their internal Read-Across Assessment Framework[24] that outlines the components of a read-across argument that need to be considered in order to be accepted.

Analytical and *in vitro/in silico* toxicokinetic tests can help

You may have reason to believe that due to its physical/chemical properties your substance would be inaccessible to the human body or aquatic environment, cannot be tested appropriately in an animal test or would be corrosive at relevant dose levels. In these cases, rather than attempting tests that may cause animal welfare issues and be inconclusive, ensure that you have exhausted all other analytical techniques first.

Some animal tests can be avoided based on physiochemical properties (see column 2 of Annexes VII-X). Relatively simple tests can show the substance is flammable at room temperature, explosive, very reactive, unstable, hydrolyses in air or bodily fluids or is corrosive. In addition, *in vitro* toxicokinetics tests such as *in vitro* dermal or gastrointestinal absorption tests could help indicate that the substance is not accessible to the internal tissues of the body and could be used to support a read across argument or in a weight of evidence approach.[25] Absence of absorption can also be predicted for some substances based on physicochemical properties. Toxicokinetic information could improve a read-across case, especially if it is based on the fact that the substance breaks down into other substances for which there is data. ECHA will need to see evidence that the hydrolysis is rapid and complete. Standard hydrolysis studies that look at chemical hydrolysis as a function of pH will look at conditions relevant to the gastrointestinal tract, for example.

Avoid testing corrosive substances

Testing of substances that are likely to cause severe irritation to the animals should be avoided. **According to column 2 of the Annexes VII and VIII, tests for skin irritation, eye irritation, skin sensitisation and acute toxicity do not need to be conducted if the substance is classified as corrosive to the skin.**

In addition, according to the preamble at the start of each of the Annexes VII to X; '*In vivo* testing with substances at concentration/dose levels causing corrosivity shall be avoided'. Furthermore, many OECD Test Guidelines request that testing is not done at levels that will cause corrosivity.

Consider the irritation potential of your substance based on pH and existing data before commissioning any further animal studies. If the level at which severe irritation will not occur cannot be determined or is lower than necessary to render the test feasible or useful (based on a limited range-finding study) then provide this argumentation in your registration dossier under 'study scientifically unjustified'.

If animal testing cannot be avoided

Use animal tests that cause least suffering

According to EU Directive 2010/63, where there is a choice between test methods, companies should perform the animal test that causes the least suffering to the least number of animals.

- For acute oral toxicity, the Fixed Dose Procedure (OECD TG 420, adopted 2002) is preferable since it avoids mortality, starts at low rather than high doses and uses a minimum number of animals.
- For acute inhalation toxicity, the acute toxic class (OECD TG 436, revised 2009) is preferable to the classic LC50 method (OECD TG 403, revised 2009) as it uses fewer animals.
- If skin sensitisation cannot be assessed *in vitro* the local lymph node assay (LLNA OECD TG429, revised 2010) is the preferred method according to the REACH text over the guinea pig maximisation test (OECD TG406, adopted 1992). However, the guinea pig test can be relied on if existing data are available. The LLNA uses fewer animals, does not involve the use of Freud's Complete Adjuvant which causes pain and irritation and is of shorter duration.

Combine tests to reduce animal numbers

Evaluating more than one endpoint in a single animal test is a cost-effective way to maximise the information as well as saving some animals. Examples relevant to Annex VIII include:

- Using a combined repeat dose/reproductive toxicity screening test (OECD TG 422) to cover the 28 day repeated dose (OECD TG 407) and a separate reproductive toxicity screening test (OECD TG 421) - saving at least 60 animals.
- It is possible to assess mutagenicity (*in vivo* micronucleus assay, comet assay) within a 28-day repeated dose test.[26] The updated ECHA R7a guidance on mutagenicity mentions this.

Anticipate testing demands to reduce duplicative testing

If you think it is likely that an Annex IX test (e.g. prenatal developmental toxicity study, 90 day repeated dose toxicity or long term fish toxicity study) is going to be required (for example due to an imminent tonnage band upgrade or specific concerns about the substance) then propose the 'higher tier' test and do not conduct the 'lower tier' test. REACH allows for this by waiving the 'lower tier' test in place of the 'higher tier test' but not vice versa. And, in 2009 ECHA produced a clarification, which they still stand by, that states that proposals for these tests can be made in lieu of testing if certain circumstances are fulfilled.[27] If submitting an animal-based testing proposal, under a new process, registrants now need to provide their considerations of alternative methods in a form in IUCLID for ECHA to also evaluate.

Dealing with compliance checks

The process of Evaluation at ECHA may seem daunting but it is relatively straightforward and well organised. Once you have registered, however, do not expect immediate feedback about read-across approaches or an alternative testing strategy. Unless your substance comes up for a compliance check you will not be told that your approach is acceptable and your dossier is 'compliant'. Registrants with dossiers that are found to be inadequate, however, will be given time to bring them into compliance and conduct any testing if necessary.

Here are three key points based on our experience so far. For more information see ECHA guidance (see Further Information) and also read the annual ECHA Evaluation Reports which give important general feedback to registrants.

1. Use the 30-day period after you receive a draft decision

You only have 30 days to strengthen your arguments about the lack of need for the animal test after you receive your draft decision. Ensure you take every opportunity to interact with the ECHA at this stage to ensure you understand their approach and they understand yours. Talk to them during this period if you feel that you are able to add more data within a relatively short period to strengthen your approach.

2. Deal with proposals for amendments to the draft decision by Member States

If Member States wish to alter a draft decision made by the ECHA they will issue a 'proposal for amendment' (PfA). This will be sent to you and you will have a further 30 days to comment on it. At this stage, your comments can only address the specific issue raised in the PfA. This may require additional scientific explanation. Be clear about what you think is the right approach and make sure this is reflected in the information already in your registration dossier. If your substance is discussed in the Member State Committee, do take every opportunity to attend, but do not expect to be able to bring in new information at this stage or to address anything not related to the outstanding issue (the PfA).

3. Read your final decision letter carefully

If you receive a final decision after a compliance check read it carefully as it may signpost you to possibilities to still yet avoid the animal test. If you can adequately satisfy the information requirements through other means then you can still do this. After the deadline given in your decision letter the ECHA will review your dossier to see if you have provided the information. If they are satisfied that you have then the case will be closed and no further action will be taken.

Further information

Information on alternative approaches	
Updates to REACH and the Test Methods Regulation	www.ec.europa.eu/growth/sectors/chemicals/legislation/index_en.htm
OECD Test Guidelines	www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788
JRC (Q)SAR Model Inventory	http://ihcp.jrc.ec.europa.eu/our_databases/jrc-qsar-inventory
OECD QSAR toolbox	www.qsartoolbox.org
ANTARES: QSAR models for REACH	www.antares-life.eu
OSIRIS ITS web tool	http://osiris.simpple.com/OSIRIS-ITS

ECHA guidance	
ECHA OECD and EU test guidelines update pages - provides updates on ECHA's opinion on the new tests available	http://echa.europa.eu/support/oecd-eu-test-guidelines
Information requirements - links to official ECHA guidance on testing and assessment	http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
Practical guides - on topics such as how to use alternatives and how to report (Q)SARs	http://echa.europa.eu/web/guest/practical-guides
ECHA evaluation reports - helps update registrants on ECHA experience with evaluating new tests	http://echa.europa.eu/eu/regulations/reach/evaluation
Information toolkit - links to various information sources within ECHA website	http://echa.europa.eu/web/guest/support/information-toolkit
What about animal testing? - links to other ECHA reports related to animal testing and alternatives	http://echa.europa.eu/web/guest/chemicals-in-our-life/animal-testing-under-reach

References

1. Note: Currently, entry of OECD approved tests to the EU Test Methods Regulation (TMR; 440/2008) is lagging about 2 years behind. However, tests approved by the OECD can be used within a weight of evidence assessment following ECHA guidance- there is no requirement for them to have to be published in the TMR before they can be used, see http://echa.europa.eu/support/oecd-eu-test-guidelines

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5. Ibid.

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