MB/54/2015
Helsinki, 17.12.2015

ECHA's Approach on Avoiding Unnecessary Animal Testing

40th Meeting of the Management Board 16-17 December 2015

Item	13
Action	For information
Status	Final - Public

Proposal

This paper provides the Management Board with a status report on ECHA's approach to avoiding unnecessary testing on vertebrate animals, including a snapshot of the current external drivers which may result in changes to the operations of ECHA and the promotion of alternative methods and approaches to animal testing. Proposals are made to strengthen the position of ECHA over the next few years, including:

- Finalisation of the discussions and changes arising from the two cases by the European Ombudsman;
- Review of ECHA's relevant processes to see what more could be done to strengthen non-animal approaches;
- A status report on the validity and regulatory acceptability of alternative methods and approaches.

The Management Board is invited to take note of the proposed approach.

Background

At the EU level, ethical, scientific and economic drivers have been behind a continuous and intensive debate to reduce, replace and refine (the '3R' principle) vertebrate animal testing. At the same time the REACH Regulation requires registrants to collect and provide sufficient data on their substances to ensure they can be safely used and can be adequately classified and labelled.

For this reason, new studies on substances may have to be conducted, some of them using animals. To ensure registrants only carry out new animal tests when they have exhausted all other relevant and available data sources, REACH[1] places obligations on them particularly for human toxicity, to generate information by alternative means to vertebrate animal testing[2] where possible (testing as 'last resort'). The data sharing provisions[3] reiterate the same principle and also specify that measures should be taken to avoid the duplication of animal tests. Further clarification on how to avoid animal testing is given in REACH Annexes[4] and ECHA guidance.

Taken together, these elements of REACH are intended to apply the 3R principle. Nevertheless, according to EU legislation, the 3R principle must be applied without compromising a high level of human health and environmental protection. The same approach is also evident in other

[1] Article 13(1) of REACH
[2] In this paper hereafter, animal testing refers to vertebrate animal testing.
[3] Article 25 of REACH
[4] Annexes VI to XI which specify the standard information requirements for registration and evaluation purposes.

areas of ECHA's operations, for example in managing the Classification, Labelling and Packaging Regulation (CLP) and the Biocidal Products Regulation (BPR).

Placing animal testing in the wider context, it should also be recalled that animal testing for the purposes of toxicological and other safety evaluation of substances used by industry or by consumers is a small part of the total testing on animals carried out in the EU (approximately 1%[5]). The majority of animal testing is for biological and medical research (65%).

Rationale

Regulatory processes

Companies registering the same substance must work together and share the results of tests on vertebrate animals. Such tests must not be repeated when reliable and adequate studies are available. REACH and BPR also have specific mechanisms to allow ECHA to take decisions requiring companies to share animal test data on the same substance. The majority of REACH registrants submit data jointly[6]. ECHA also disseminates information on substances and the data obtained via testing. This, together with the OECD eChem Portal, developed in cooperation with ECHA, allows the registrants to verify whether information on animal tests is already available.

If companies need to do more tests for their higher tonnage substances[7] to gather the required information for registration, they must present plans for testing on animals to ECHA. The Agency and the MSCAs need to agree on the testing proposal before tests can be conducted, to verify that they are likely to produce reliable and adequate data. Testing proposals involving vertebrate animals are published on ECHA's website to invite third parties to provide scientifically valid information and studies on the substance that may help in avoiding the testing.

For the 2013 registration deadline, registrants submitted 701 testing proposals, which will be evaluated by 1 June 2016. Most proposals concern developmental toxicity and repeated dose toxicity studies. By the end of October 2015, over 470 public consultations on vertebrate testing proposals had been carried out. Most comments in the consultations address the use of alternative approaches. The input is sent to the registrant(s) for their consideration and is also assessed by ECHA in the decision-making process. In a limited number of cases, registrants have used the information from the public consultation to fulfil the information requirements by alternative approaches and have withdrawn their animal testing proposals.

In the compliance check process, ECHA verifies whether the data provided by the registrants meets the information requirements of REACH, and that the data can be used for the purposes risk assessment and for classification. Where testing has been waived, ECHA verifies whether the justifications for waiving fulfil these requirements. If not, ECHA requests the compliant information to be submitted.

Also substance evaluation can lead to a request for additional testing, to clarify a potential risk and to advise whether additional risk management measures may be needed. Information requested under substance evaluation can go beyond the standard information requirements in the REACH Annexes.

The use and development of alternative methods and approaches

[5] Seventh report by the European Commission on the statistics of the number of animals used for experimental and other scientific purposes (COM(2013)859 final of 5.12.2013)

[6] By end November 2015, there were approximately 4000 individual registrations out of a total of approximately 43,000. Most of the individual registrations were consistent with the requirements of REACH. A Commission implementing act in 2016 is expected which will strengthen ECHA's ability to require joint submissions.

[7] Standard information requirements for substances manufactured or imported at 100 or 1000 tonnes, respectively (Annexes IX and X of REACH).

Currently, for some lower tier toxicological end points[8] alternative test methods are either available, or will become available in the near future. However, no alternative test methods are available to replace the 28 day and reproductive toxicity screening studies[9]. For higher tier toxicological testing[10] more scientific development will be needed before these can be replaced by alternative test methods. The Commission's Joint Research Centre carried out a review in 2014 of the state-of-the-art of alternative methods which was co-produced with ECHA[11].

By 2014 almost 20% of analysed registration dossiers contained *in vitro* studies, either alone or combined with other information. For example, *in vitro* methods are available to fulfil the skin corrosion/irritation and partly serious eye damage/eye irritation end points. In some cases registrants also use alternative test methods for meeting the skin sensitisation end point, even though these are still in the early stages of development.

In addition to alternative test methods, registrants also make use of other alternative approaches ('non-test methods'). The most widely used approach is 'read-across', which means filling data gaps either by reference to a group of substances or substance with properties that are likely to be similar or follow a regular pattern as a result of structural similarity. In 2014 the read-across approach was used to fulfil at least one endpoint in 75% of the dossiers assessed. Grouping, read-across and weight of evidence approaches can also be used for long-term endpoints, but require robust scientific justification and enough experimental data to form the basis for waiving the testing.

To assist registrants with the read-across approach, ECHA has developed and published this year a read-across assessment framework (RAAF)[12]. RAAF is intended to make read-across assessment more transparent and consistent. The published version covers human health and a version covering the environment is under preparation.

In cooperation with the OECD, ECHA has developed the qualitative/quantitative structural-activity relationship (QSAR) Toolbox, a software application which helps companies to group chemicals into categories and fill data gaps in (eco)toxicity data. The OECD QSAR Toolbox is the most comprehensive, widely recognised and freely available platform for filling data gaps in regulatory hazard assessment, while avoiding tests. For complex human health endpoints however these methods and QSARs cannot yet provide reliable predictions that are fit for the purpose of classification, labelling and risk assessment.

ECHA promotes the use of alternative methods via publications, its website, guidance, and events. For example, ECHA regularly publishes on its website how new or alternative test methods can be used in the REACH context.

European Ombudsman cases and other drivers for change

The first European Ombudsman case was opened on 19 September 2012 and concluded on 11 December 2014[13]. The complainant, the PETA[14] Foundation, considered that ECHA does not do enough to ensure that registrants refrain from performing unnecessary animal tests in order to demonstrate their substances' safety. The Ombudsman found that ECHA's interpretation of its obligations was excessively restrictive, particularly in relation to using compliance checks to verify if the last resort principle has been applied. The Ombudsman thus made a 'friendly solution' proposal to ECHA concerning its own role as well as the co-operation it should

[8] Tests specified in Annexes VI and VIII REACH for lower tonnage chemicals.
[9] Annex VIII of REACH standard information requirements for substances manufactured or imported in quantities of 10 tonnes or more.
[10] See footnote 7.
[11] http://publications.jrc.ec.europa.eu/repository/bitstream/JRC91361/echa_jrc_sla_report_public_05-09-14_withcover%20ipo.pdf
[12] http://echa.europa.eu/documents/10162/13628/raaf_en.pdf
[13] Decision of the European Ombudsman closing the inquiry into complaint 1568/2012/(FOR)AN against the European Chemicals Agency (ECHA).
[14] People for the ethical treatment of animals (PETA).

establish with MSCAs who are responsible for enforcing the legislation and was satisfied with ECHA's reply and closed the case.

ECHA also responded[15] to PETA directly to explain the action it is taking as a result of the case. Appropriate dossiers for compliance check are being identified to verify why animal tests were conducted when non-animal methods seemed possible. On the basis of the first experience of doing this, it will be decided whether compliance check proves to be an effective way of checking that animal testing is conducted only as a last resort. ECHA also continues to inform the Member States of possible breaches of the registrants' obligations to consider alternatives before conducting tests on animals, because it is their responsibility to initiate enforcement actions where appropriate.

The second Ombudsman case was opened on 20 November 2013 and an Ombudsman decision published on 11 September 2015[16]. The case was triggered by a group of NGOs which challenged ECHA's position that it could not reject testing proposals involving animals on the grounds that the data could be generated by an alternative method, not involving animal tests.

The Ombudsman concluded that ECHA's interpretation of its role was too strict and did not take into account the fact that the avoidance of animal testing is, together with the protection of human health and the environment, one of the guiding principles of the Regulation. The Ombudsman recognised that although the objective of human health (and the environment) is the most important[17], this does not mean that the objective of the avoidance of animal testing can be disregarded. The Ombudsman thus proposed to ECHA: (i) that it requires all registrants to show that they have tried to avoid animal testing and (ii) that it provides registrants with all the information at its disposal which could allow them to avoid animal testing. ECHA accepted the proposal, but has indicated that further discussions with the Commission and the MSCAs will be needed, as well as possible additional measures, particularly to implement the first aspect.

The Ombudsman asked ECHA to report on how it has implemented the decision within six months. This work is on-going, but a key point here is that ECHA does not itself build or improve a waiving statement on behalf of registrants (e.g. read-across, or weight of evidence), as ECHA's role is to validate the information submitted by industry. This principle has been also confirmed by the Ombudsman and via decisions of the Board of Appeal (see below).

As an element of implementing the conclusion of the second European Ombudsman case, ECHA now requests registrants to accompany the testing proposal with its considerations on why alternative methods could not be used to fulfil the particular information requirement. The justification will be published as part of the public consultation[18] on the testing proposal.

ECHA's Board of Appeal has examined the scope of REACH in relation to avoiding unnecessary animal testing[19] in its decisions. It has recognised that in principle the duty is on registrants to perform testing as a last resort. Thus, where a registrant provides a read-across adaptation for a standard information requirement, REACH does not impose any additional duties on the Agency beyond evaluating the read-across proposals. But if the Agency imposes a non-standard test, the obligation to ensure that vertebrate animal testing is only undertaken as a last resort also applies to the Agency, i.e. in such cases ECHA should examine the possibility of the existence of alternatives.

Judgments of the European Court of Justice have emphasised that the main objective of the REACH Regulation is to ensure a high level of protection of human health and the

[15] Letter of 12 June 2015 from ECHA published on ECHA website.
[16] Decision of the European Ombudsman in case 1606/2013/AN on how the European Chemicals Agency applies rules concerning animal testing.
[17] Decision referred to in footnote 16, paragraph 23.
[18] The first such justification has been received and will be published shortly.
[19] Article 25 of REACH.

environment[20]. Most recently the Court indicated that REACH places the responsibility for the identification of hazardous properties and demonstrating safe use of chemical substances clearly with industry[21].

Actions to strengthen ECHA's operations and activities to promote alternatives

1) ECHA will, together with the Commission and the MSCAs, finalise agreement of the specific changes needed to respond to the Ombudsman recommendations. Discussions in this respect are already well underway and some agreed changes have already been implemented. ECHA aims to conclude these discussions by the end of Q1 2016.

2) ECHA will review its relevant operations, by end of 2017, to determine what further steps may be taken to implement the 3R principle. The review may include, *inter alia*:

- A review of ECHA's evaluation practice, including the role of the ECHA Committees;
- Further clarification of the use of data generated via alternative methods in the application of classification and labelling criteria under the CLP Regulation;
- Explore the potential to enhance alternative methods and approaches by data mining.

3) It has become apparent[22] that there is not a common understanding amongst authorities, registrants and stakeholders about what alternative methods and approaches are scientifically possible and, in turn, acceptable from a regulatory perspective. An on-going project by ECHA to support SMEs in the context of the 2018 registration deadline will give an overview of alternative approaches and methods for different endpoints in a readily accessible format by Q2 2016.

4) ECHA is also planning to compile a more comprehensive status report on the validity and regulatory acceptability of alternative methods and approaches by the end of 2017. The report will update the one carried out by JRC in 2014 (see above) and could also help to manage expectations of the opportunities and limitations of alternatives. As this report is relevant for many other actors, the ECHA Secretariat will engage with other relevant bodies such as JRC, EFSA[23], EPAA[24], MSCA's and ECHA Committees. This longer term status report will i.a. examine innovative ways of combining evidence to address complex toxicological endpoints.

5) The following additional activities are proposed starting from Q4 2016 onwards:

- Internal capacity building to consistently apply the 3R principle in the regulatory processes ECHA manages, including with ECHA Committee members;
- A joint communication project with stakeholders to bring together and promote information and sources of advice to companies on the use of non-animal approaches;
- Advise those working with registrants e.g. contract research organisations (CROs) on non-animal approaches and their role in avoiding unnecessary animal testing.

A room document provides a summary of ECHA's planned activities on animal testing methods and their alternatives.

Alternative options

An alternative option considered in the preparation of this paper is the do nothing option and maintain business as usual. However, with the drivers described above, this is not considered a realistic option, and would create negative impacts on ECHA's credibility and reputation.

---

[20]See for example the judgment of the Court of 7 July 2009 in S.P.C.M. and Others, C-558/07, ECR, EU:C:2009:430, paragraph 45 and the judgment of 30 April 2015 in Polynt and Sitre v. ECHA ECLI:EU:T:2015:254, paragraphs 46 and 106.
[21]See judgment of 10 September 2015 in FCD and FMB, Case C-106/14) ECLI:EU:C:2015:576, paragraph 33.
[22] Most recently at the Stakeholder Workshop held in Brussels 9 October, see proceedings published here.
[23] European Food Safety Authority.
[24] European Partnership for Alternative Approaches to Animal Testing.

Drawbacks

The potential drawbacks are twofold: firstly that the pressure for ECHA to do more to avoid animal testing may confuse the division of responsibilities between ECHA and industry; and second that ECHA may need to invest more resources to this work. However, it is intended that the proposed approach will be sufficiently flexible to optimise the proposed actions to be fit-for-purpose.