the (amended) draft decision to the Member State Competent Authorities (MSCAs) for review. The MSCAs have 30 days to indicate their disagreement with the content or wording of the decision via a "proposal for amendment" (PfA). Silence on the part of the MSCA is taken as endorsement of the draft decision. If there are no PfAs, the draft decision becomes the final decision and is sent to the registrant.

Draft decisions on testing proposals with PfAs are forwarded to the Member State Committee (MSC), which is made up of experts from each Member State, usually from the same MSCA. ECHA may have amended the draft decision based on the PfA and MSCAs vote on the final version of the decision letter either via a written procedure or during meetings held at the Agency six times a year. The registrant may be invited to the meeting to answer any questions related to the PfA. A unanimous decision is required within 60 days from when the (amended) draft decision was sent to the MSC, otherwise the European Commission become involved. A short period after the decision is agreed the final decision letter is sent to the registrant. Although not all stages in the decision making process have defined timescales in the legislation, ECHA had until December 1, 2012 to produce draft decisions on the substances registered under the first deadline.

1.3 ECEAE input in the process

The European Coalition to End Animal Experiments (ECEAE) is an umbrella organization now representing 24 animal protection organizations across 22 EU member and applicant states. They constitute Europe's leading alliance peacefully campaigning on behalf of animals in laboratories. The ECEAE have been very involved in REACH since its inception; lobbying for the animal protection measures that are now in the legislation and maintaining a strong interest in ensuring these are correctly implemented. The ECEAE is an accredited stakeholder at ECHA and a registered observer at the MSC meetings.

Since the animal protection movement argued in favor of the testing proposals system the ECEAE felt it was important to engage with it and have therefore provided toxicologists to systematically search for "*scientifically valid information and studies that address the relevant substance and hazard end-point*" (Article 40 (2)). These experts began by commenting on the first testing proposal published on August 10, 2009 and continue to date. This report summarizes the contribution the ECEAE's toxicologists have made in responding to the calls for available information on proposals to test substances registered for the first deadline on animals. Since ECHA had until December 1, 2012 to issue draft decisions on these substances, this "first deadline" period could reasonably include the first testing proposal published up to and including those published by July 31, 2012, a full three-year period.

The report discusses the problems the ECEAE have experienced with the consultation process itself and the success of the system in preventing the conduct of unnecessary animal tests. We conclude with recommendations for improvements to the system for the next REACH deadline and indeed for public comment systems of this kind in future. Throughout we draw not only on our own database of the comments but on the ECHA Evaluation reports[1] to provide official figures for numbers of concluded evaluation cases, as well as published decisions[2], public minutes of MSC meetings[3], and comments made by ECHA in their first Article 117.3 report on the use of alternative methods in REACH registrations (ECHA, 2011a).

2 Summary of testing proposals published for comment

2.1 The substances

Between August 1, 2009 and July 31, 2012 ECHA had published for comment 817 proposals for vertebrate tests on 480 substances. There were between 1-4 proposals per substance and 52% of substances had more than one testing proposal (average 1.7 testing proposals per substance).

Due to the delay with publication of information on the substances (see Section 3.3) it was not possible to obtain complete information on some of the substances at the time the testing proposal was published, therefore this is a summary of details on substances at the time of writing, unless otherwise stated.

406 (85%) were existing substances, registered for the first time (i.e., phase-in substances); the remaining 74 were non-phase-in substances (either new or so-called NONS substances that had been notified under the Dangerous Substances Directive).

355 (74%) substances were registered at Annex X, 74 (15%) at Annex IX, and 28 (6%) were at Annex VII or VIII (or appeared to be at the time of the proposed test). There were no details available for 23 substances.

5 substances were elements (cobalt, silver, bismuth, silicon, carbon (activated high density)), 3 were reported to be organometallics, 2 were reported to be inorganic/organic compounds, and 3 were unknown, 53 were inorganic but the vast majority, 414 (86%), were organic substances.

Substances were either mono constituent (223 substances, 46%) or UVCB (unknown or of variable composition, complex reaction products or biological materials) (221 substances, 46%). The rest were described as multi-constituent (32 substances) and 4 were of undisclosed composition.

Many of the substances had a primary use in the manufacture of other substances such as paints, resins, rubber, adhesives, industrial and household cleaning products, fertilizers, dyes, sealants, hydraulic fluids, lubricants, coating, and inks. Other substances were used in the production of glass, leather, plastics, and road and building materials. A proportion had direct use as fuels, flame retardants, fragrances and water treatment substances, amongst other uses.

A large proportion (approximately 25%) of substances appeared to be largely intermediates and/or used in closed sys-

[1] http://echa.europa.eu/regulations/reach/evaluation
[2] http://www.echa.europa.eu/web/guest/regulations/reach/evaluation/requests-for-further-information/evaluation-decisions
[3] http://www.echa.europa.eu/web/guest/about-us/who-we-are/member-state-committee/meetings-of-the-member-state-committee

tems, and about half of these (13%, 61 substances) appeared to be only used as an intermediate. Intermediates are substances whose only use is in the production of other substances; they have reduced data requirements if they are used in closed systems and there is no or very limited exposure to them. It is therefore a concern that a proportion of those with testing proposals could be classified as intermediates. It is not known whether the reason for testing proposals on these potential intermediates arises from ignorance of the legal requirements or that there is some human or environmental exposure and intermediate status cannot be claimed according to the definitions in Article 3 of the legal text, which have been interpreted quite strictly by ECHA in a recent update to guidance (ECHA, 2010a).

13 substances appeared from the dossier to have a predominant use in cosmetic products (They included fragrances, essential oils, lanolin and other cosmetic ingredients; EC numbers; 405-040-6, 639-566-4, 208-762-8, 906-125-5, 203-377-1, 270-302-7, 931-596-9, 931-291-0, 443-860-6, 232-430-1, 931-324-9, 923-835-0, 927-870-2).

For 197 substances (41%, 293 testing proposals) the test(s) proposed were not actually on the substance listed but on another substance with a similar chemical structure (which may or may not have also been registered with a testing proposal, not if it was produced at lower tonnage levels). These cases were so-called "read-across" cases whereby the registrant was proposing to test one (or more) substance(s) and use this information to "read across" to one (or more) other substance(s) expected to show similar physicochemical, toxicological, and ecotoxicological characteristics. For example, the registrant of a range of cobalt compounds proposed to test cobalt sulfate for 16 other cobalt compounds including cobalt itself, cobalt oxide, and cobalt carbonate. In cases such as these, from March 2011 ECHA indicated this by putting "testing proposed with (name of substance)" next to the substance with a testing proposal. Prior to this it was not always obvious that the registrant was proposing read-across. And, indeed, it is still not known if the registrant intends to read across to other, as yet unregistered substances, when proposing to test on the substance itself.

Tab. 2: The number of testing proposals per endpoint published during the 2010 deadline period and the estimated number of animals used within these, according to OECD Test Guidelines

Endpoint	OECD Test Guideline, animal	Number of proposals	Minimum number of vertebrate animals used per test*	Total number of animals
Two-generation reproductive toxicity	TG 416, rats	249	2,200	547,800
Pre-natal developmental toxicity	TG 414, assume rats	283	900	254,700
90-day repeated dose toxicity: oral	TG 408,rats	161	100	16,100
90-day repeated dose toxicity: inhalation	TG 413, rats	29	120	3,480
90-day repeated dose toxicity: dermal	TG 411, rats	5	120	600
Genotoxicity *in vivo*: Mammalian erythrocyte micronucleus test	TG 474, mice or rats	26	50	1,300
Genotoxicity *in vivo*: Mammalian bone marrow chromosome aberration test	TG 475, mice or rats	1	50	50
Genotoxicity *in vivo*: Unscheduled DNA Synthesis	TG 486, rats	1	12	12
Chronic toxicity/carcinogenicity	TG 453 or TG 451, rats	3	400	1,200
Long term fish toxicity: Prolonged Toxicity Test, 14-Day Study	TG 204, fish	1	70	70
Long term fish toxicity: Fish, Early-Life Stage Toxicity Test	TG 210, fish	33	420	13,860
Long term fish toxicity: Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stage	TG 212. fish fry	3	0	0
Long term fish toxicity: Fish, Juvenile Growth Test	TG 215, fish	2	96	192
Bioaccumulation in fish, aquatic (assume dietary test)	TG 305, fish	15	280	4,200
Bioaccumulation in Terrestrial Oligochaetes- erroneous	TG 317, earthworms	1	0	0
Long term or reproductive toxicity tests on birds	TG 206, assume quail	4	2,832	11,328
Total		**817**		**854,892**

*Animal numbers were estimated based on the protocols within the guideline for the minimum number of animals that would be used in the test (not including dose ranging or sighting studies for which the test guideline does not tend to give quantities).

2.2 The endpoints

The majority of testing proposals were for prenatal developmental toxicity (35% of tests proposed), two-generation reproductive toxicity (31%), and 90-day repeated dose toxicity (24%) endpoints, see Figure 2.

A relatively small number of genotoxicity, chronic/carcinogenicity, aquatic toxicity, and terrestrial toxicity tests were also proposed, in line with those tests listed in Annex IX and X. One proposed test on earthworms (OECD TG 317) was mistakenly published (only tests on vertebrate animals should be published for comment). There were three proposals for long term fish toxicity using Embryo and Sac-fry Stages (OECD TG 212), which would not be considered a vertebrate test under the EU Directive 2010/63 since the test ends before the fish fry are free-feeding. However, these were included in our analysis since this is a suitable test for long term fish toxicity, which can involve live adult fish.

In total it is estimated that if the testing proposals were all accepted and conducted, over 850,000 animals, mostly rats, would be used, see Table 2. It is possible that some of the prenatal developmental toxicity tests are actually for testing in a second species (usually rabbits); however this is not indicated on the consultation website.

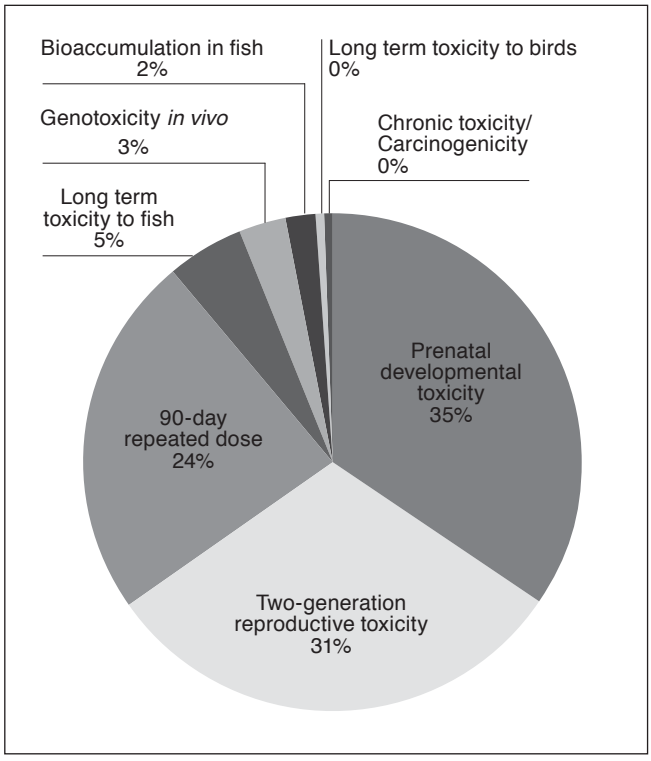

Fig. 2: The proportion of animal tests proposed for the first REACH deadline, N=817 tests on 480 substances

2.3 Comments by the ECEAE

Between August 1, 2009 and July 31, 2012, the ECEAE submitted comments on 391 proposals relating to 221 substances. The ECEAE therefore commented on 46% (221/480) of the substances with testing proposals. Comments were usually submitted in the form of a single document per substance covering the endpoints for which the testing was proposed. There was usually more than one comment per testing proposal (endpoint) within the submission (282 proposals, i.e., 72%, had more than one comment).

Table 3 summarizes the broad categories of types of comments submitted by the ECEAE experts on the 391 testing proposals. The types of comments are categorized according to the sections under Annex XI of REACH: *General rules for adaptation of the standard testing regime set out in Annexes VII to X*. These include the use of existing data (section 1.1), information from a variety of sources (so-called "weight of evidence", section 1.2), data from (Q)SAR models (section 1.3), data from *in vitro* methods (section 1.4), read-across or grouping arguments (section 1.5), data suggesting that testing is not technically possible (section 2) and data suggesting that due to exposure considerations the testing is not required (section 3). "Other 3Rs comments" was a catch-all category to describe comments that

Tab. 3: Form of the comments submitted by ECEAE on 391 testing proposals (on 221 substances); most proposals had more than one comment

Annex XI section	Waiving option	Number of testing proposals used for
1.1	Existing data: on substance (16), on similar substance(s) (75), on category (75)	166
1.2	Weight of evidence	103
1.3	(Q)SARs	54
1.4	*In vitro* methods	67
1.5	Chemical grouping/read-across	151
2	Testing technically not possible	74
3	Exposure based waiving	128
	Other 3Rs comments (testing strategies, 3Rs considerations, column 2 adaptations)	178
	Total number of comments	**921**

argued that testing was not strictly required by the legislation, could be avoided through the use of other required tests, could be waived according to column 2 adaptations, or other 3Rs considerations.

2.4 Outcome of testing proposals evaluation

The decision making process, which includes the third party commenting period, is laborious and lengthy (Fig. 1). Final decisions typically took one year to be made from publication of the testing proposal (data not shown). ECHA reports the overall numbers of final decisions that have been made over the year in its annual Evaluation Reports. Table 4 summarizes the results of the first four ECHA Evaluation Reports on 2009-2012 inclusive (ECHA, 2010b, 2011b, 2012a, 2013). Decisions are made on the substance and may include one or more testing proposals, some of which may not be for tests on vertebrate animals (Tab. 1).

According to the 2012 Evaluation Report, a total of 715 testing proposals on 434 substances had been received by the ECHA by end of December 2012. Our figures do not quite match their figures, possibly due to withdrawals of testing proposals during the process. By the end of 2012, ECHA had only made final decisions on 198 of a reported 681 substances received with any kind of testing proposal. Some of these substances had their testing proposal withdrawn and therefore left the system. Indeed, according to an analysis of the ECHA Evaluation Reports some 145 substances (42%) had withdrawn testing proposals by the end of 2012. According to the 2012 report, 305 substances remain that had a draft decision that needed to be finalized by the MSC in 2013, with 26 yet to be processed. ECHA included in the "accepted or modified" category those substances for which the decision had been split to enable the decision on the need for the two-generation reproductive toxicity study versus the Extended One Generation Reproductive Toxicity Study (EOGRTS) to be made by the European Commission (see Section 4.8). According to ECHA, 2 cases were sent in 2011 and 24 cases were sent in 2012. According to the ECHA reports only one testing proposal has been rejected.

3 Experiences with the commenting process itself

3.1 Number of testing proposals

According to the Article 117(3) report (ECHA, 2011a), a total of 3,309 phase-in and 1,347 non phase-in substances were registered by February 2011. However, only 1,504 were Annex X phase-in registrations made for the 2010 deadline (and were the focus of the Article 117.3 report on the use of alternative methods). According to our database, only 321 substances with animal testing proposals were Annex X phase-in substances. Therefore, only 21% of the substances that would be expected to have had testing proposals for Annex X tests actually had them. It can therefore be assumed that the remaining substances either had existing data or the registrant used Annex XI or column 2 adaptations to waive the testing. ECHA noted in the Article 117(3) report that the number of testing proposals was less than anticipated and that they believed many of the adaptations were insufficiently justified.

According to the same Article 117(3) report, however, 107 animal tests had been conducted without a testing proposal. ECHA defined these as tests that were reported with study dates of 2009 or later, although, since REACH was agreed in 2006, the year 2008 should have arguably been included as well. In these cases the registrant should have known that the REACH requirement was for a testing proposal and not a test. The ECHA investigated a small number of these and concluded that the registrant often claimed "other legislative needs" as the reason for the test rather than REACH. Animal protection groups have complained that ECHA should have followed up all of these cases and, if the reason was not justified, initiated enforcement action. As a consequence of pressure from ourselves ECHA have conceded that they will investigate cases in the future and issue a letter that Member States can then follow up for enforcement, although our perception is that there is little interest by Member States in doing so.

According to the ECHA's 2011 Evaluation Report, non-governmental organizations were responsible for 293 out of 481 comments received in 2011. Based on the volume of com-

Tab. 4: Number of substances for which there has been a final decision made on the testing proposals for the substance or the case has been closed (includes testing proposals not on vertebrate animals), according to ECHA Evaluation Reports for 2009-2012

Year	Testing proposal accepted	Testing proposal modified	Testing proposal rejected	Testing proposal withdrawn by registrant before final decision (closed cases)	Total
2009	1	0	0	0	1
2010	3	1	0	3	7
2011	18	4	0	58	80
2012	130	40	1	84	255
Total	**152**	**45**	**1**	**145**	**343**

ments the ECEAE submitted in 2011 (Fig. 3), it is clear that our comments made up a significant proportion of this, and it is certainly our perception that we are the only organization commenting systematically. ECHA reported that industry (individual companies and trade associations) had provided 32% of the comments but that these seem to have been largely suggesting the use of commercially available QSAR models or giving support to read-across approaches, as opposed to data on the substance.

3.2 Publication rate of testing proposals

Figure 3 provides the number of substances with testing proposals published by the ECHA between August 2009 and July 2012 inclusive. It also shows the number of substances on which we commented. As can be seen from the graph, there was a very low publication rate of testing proposals until January 2011. This was largely due to companies not registering until near the deadline of December 2010.

Unfortunately for third parties wishing to comment, the Agency published the majority of substances with testing proposals in the six months between April 2011 and September 2011 inclusive (297, 62%). The proposals were published in two or three batches per month, not continuously. The significant increase in the publication rate of testing proposals, particularly during the summer months, made commenting on all proposals within the 45 day period completely unfeasible.

The ECEAE commented on the first 50 testing proposals and thereafter, as a result of the huge volume of testing proposals and early experiences in the response of ECHA to our comments (see Section 4), commented on only those substances for which we felt the case for waiving the test was particularly strong.

From October 2011, volumes of testing proposals returned to very low levels as ECHA had clearly processed the majority of the substances registered for the first deadline. There were a couple of spikes in publication as ECHA published testing proposals within categories of substances that had been proposed in a read-across approach or substances which they had initially struggled to identify.

ECHA had been under considerable pressure to publish testing proposals in time to enable them to meet their legal obligation to draft decisions by December 2012 (Article 43). However, they failed to give proper regard to ensuring that third parties could feasibly comment on the testing proposals published. Our ability to comment was severely impacted by the publication rate and the third party comment system was undermined as a result. Whilst some of the workload was an inevitable consequence of the deadlines within REACH both for registration (December 2010) and for processing (December 2012), not enough importance was given to the consultation aspect and therefore the need to stagger the publications as much as possible. Even though industry did not help by staggering their registrations, in theory it would have been possible to have the peak period between

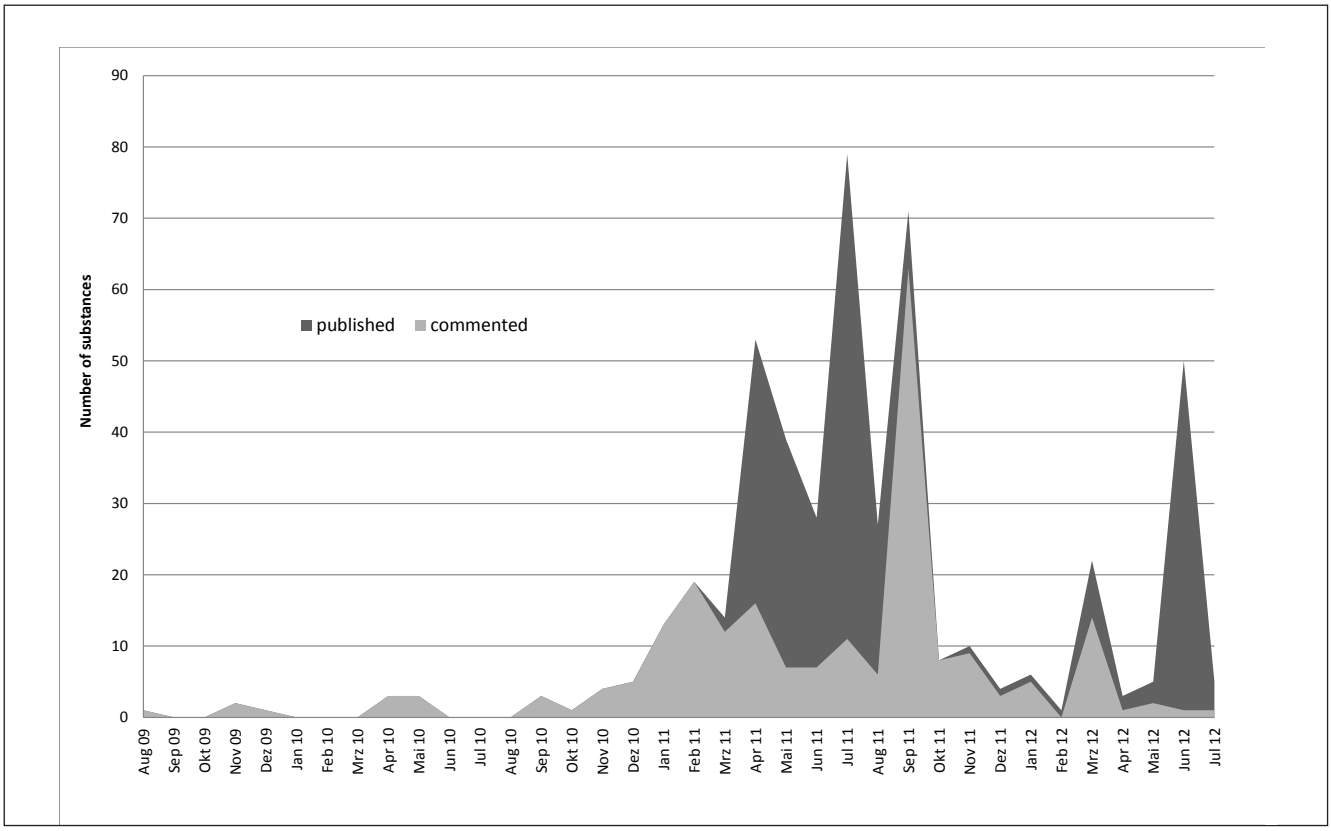

Fig. 3: Publication rate of testing proposals by the ECHA for the first deadline and the proportion on which the ECEAE commented

January 2011 and June 2012 (inclusive) – a period of 18 months instead of the six month period we experienced. ECHA also did not always publish proposals for all substances within a category together, making it difficult for us to construct category and read-across approaches. We have asked ECHA to consider this aspect and make more effort to spread the publications from the June 2013 deadline.

3.3 Publication of information on substances

For some time the only information accessible on the testing proposal and the substance was the minimum required by the legislation relating to the publication of testing proposals, i.e., the name of the substance, the hazard end-point for which vertebrate testing is proposed, and the date by which any third party information is required. We soon found that in order to comment effectively we would require:

- *Information on the toxicological tests already conducted for all endpoints*, not just those associated with the testing proposal. This was so that we could determine what existing information the registrant had already relied on (so not to duplicate efforts) and also to determine if column 2 waivers could apply, such as that the substance was already considered harmful to human health.
- *Information on physicochemical properties*, which can provide information on the likely route(s) of exposure, the extent of systemic absorption, and stability in the gastro-intestinal tract.
- *The Annex for which the substance is registered*. This was useful as the legal requirement for some tests, e.g., the two-generation reproductive toxicity test, differs between Annexes VIII, IX, and X. Some proposals were issued for substances for which the endpoint was not a standard information requirement and therefore this was potentially an easy "mistake" to spot.
- More information on the test proposed, *including justification for the test proposed, route of administration proposed, whether testing is for a second species, and the species on which testing is proposed*. For example, for 11-aminoundecanoic acid (EC 219-417-6) the testing proposal was for a prenatal developmental toxicity study on rabbits as a second species, but this was not indicated on the website and we realized this only after receiving the registration dossier (see below). This kind of information would have aided prioritization of our commenting as well as the content of the comments themselves, since tests on second species need extra justification.
- *The identity of the lead registrant*. This information would help us evaluate the likelihood that the registrant has any existing information that we might uncover (if it is linked to them for example) and would have enabled us to provide the registrant directly with our suggestions for testing strategies, rather than doing this formally through ECHA. This could have given the registrant more time to consider our suggestions and enable us to explain them if needed.
- *Information on the use of the substance*. Exposure scenarios can help with data waiving arguments if the substance is used under strictly controlled conditions, for example.

According to Article 119, however, the Agency is supposed to publish information on the substances being registered. Separately to the testing proposal consultation information, ECHA therefore did begin publishing parts of registration (IUCLID) dossiers on the ECHA website: http://apps.echa.europa.eu/registered/registered-sub.aspx (so called dissemination website) at the very end of 2009 (ECHA, 2009). Initially, however, the website was not populated with many substances and the information on the substance rarely was uploaded at the same time as the testing proposal was published. This was because there were confidentiality claims to evaluate and many of the early testing proposals were on newer substances (non-phase-in) for which confidentiality tends to be more important to the registrants. In June 2010 ECHA released an IT tool to enable registrants to see what parts of their dossiers would be published to help speed up the process (ECHA, 2010c).

Initially, we therefore had to submit Access to Document requests (EC Regulation 1049/2001) for the full dossiers, which were provided with the exception of the Chemical Safety Report (CSR) that provides information on uses and exposure and which was claimed confidential. Unfortunately, these dossiers often arrived too late to help us with the 45 day commenting period. As a result of our requests however, we believe ECHA realized that they needed to speed up dissemination (since the information would be requested anyway) and efforts were made to publish the registration dossier at the same time as the testing proposal. However, it was not until April 2011 that this situation was almost completely resolved. In May 2011 ECHA confirmed, following challenges by the environmental NGOs (Client Earth, 2012), that they would publish the names of the companies registering substances (ECHA, 2011c). However, this did not start to actually happen until November 2012, to enable registrants to first claim confidentiality, and coincided with also publishing the Annex (tonnage band) under which the substance was registered (ECHA, 2012b).

However, more detail on the testing proposal itself is still not proactively disseminated by ECHA on the consultation or dissemination websites. Our understanding is that justifications for the test proposed may lie in the CSR, which tends to be treated as confidential and is not currently disseminated. Justifications for new testing may also be discussed in the overall endpoint summaries in IUCLID, which are not disseminated. It is therefore still difficult to assess the extent to which the registrant has considered all options before proposing the test and therefore whether it is worthwhile making various suggestions.

3.4 Publication of outcome

Initially, the decisions on testing proposals were indicated via an ECHA press release following the MSC meeting at which the decision was made. The first decision was made in June 2010 for a substance identified only as "Hydrogenated oligomerisation product, including dimers and trimers, of tetradec-1-ene and alkene", which was also the first testing proposal issued in August 2009 (ECHA, 2010d). However, as the number of decisions made by the MSC increased, these informative press releases soon ceased.

As an accredited stakeholder observer to the MSC it is possible for us to monitor some of the decisions made at the meetings, but this is limited to only some decisions and is not entirely transparent. Firstly, the MSC only decides in the meeting itself those decisions that are particularly contentious, i.e., those where a PfA has been made by a MSCA and this has not been resolved in a written procedure prior to the meeting that is closed to stakeholders. About 50% of decisions have PfAs but about 50% of these will be resolved in the written procedure. Therefore, the meeting typically discusses less than 25% of the decisions actually being taken by ECHA (data not shown). Secondly, stakeholders at the meeting are prevented under confidentiality rules from disclosing details of the meeting. Public minutes typically cryptically state that "there was agreement with the draft decision", with no details of what this was. The draft decision may have been to reject, modify, or accept the testing proposal. No details are given in the minutes for decisions made by written procedure.

The annual Evaluation Reports produced by ECHA give an overall summary of the number of decisions made. However, they do not provide details by substance or the reason for rejection, acceptance, modification, or withdrawal of the testing proposal. After requests from us, ECHA agreed on January 31, 2011 that they would publish the "response to third party comments" for each substance, as they realized that some feedback on the third party consultation was needed (ECHA, 2011d). These were an excerpt from the final decision letter and give a sense of whether comments were considered useful (see Section 3.6). However, they were not a substitute for the final decision, which outlines the actual decision and may include more information on the justification for the test. Only a limited number of these "response to third party comments" was ever published.

We had been asking for full decision letters to be published on the website since 2010 and in December 2012 ECHA agreed (ECHA, 2012c). They now have a policy of publishing these letters after the three month appeal window has passed and the registrant has had a chance to claim confidentiality. By July 1, 2013 however, only 150 decisions (150 substances) had been published out of the 198 decisions made by the end of 2012 according to the Evaluation Reports. It is still not clear which substances have had their testing proposals withdrawn by the registrant.

3.5 ECHA role in evaluation – Rejection of proposals

The fact that only one testing proposal has reportedly been rejected by ECHA should raise questions about their role in the evaluation of testing proposals. We were, as perhaps were many, under the impression that ECHA would evaluate each proposal and come to a judgment as to whether the test was required and that this decision would be informed by third party comments.

Strictly speaking, in cases where the information is a standard information requirement ECHA's role is limited. We understand that ECHA do not consider that they have a role in constructing weight of evidence or read-across arguments themselves. However, there was still an expectation that they would evaluate whether column 2 or certain Annex XI adaptations could be used, where that information was easily accessible to them. Indeed this is what is described in the REACH guidance (ECHA, 2007), which was drafted following the agreement of REACH but prior to the formation of the agency. Since Article 40(2) on the testing proposals system states that "All such scientifically valid information and studies received *shall be taken into account by the Agency* in preparing its decision in accordance with paragraph 3", we believed that the Agency had a role in evaluating the need for the proposed test and we directed our comments at them with this is mind.

ECHA's current position is that it can only reject testing proposals where the data that would be generated is already available or it is not required at the tonnage at which the substance is produced or imported. This has been elucidated from correspondence with us and is the subject of a maladministration complaint to the EU ombudsman submitted in June 2013. The basis for their position is the view that REACH imposes responsibility (for registration and safe use) on the registrant and not the Agency. We are frequently told that the agency "*cannot do the registrant's job for them*." The passive nature of evaluation is clear from this statement regarding the utility of third party comments in the 2012 Evaluation report (ECHA, 2012a, page 19):

> "*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*."

ECHA believes it is the responsibility of the registrant to propose or waive testing and also to withdraw the testing proposal. In most cases ECHA will accept the testing proposal. Third party comments are therefore only in theory useful to ECHA if they provide existing information or remind the agency of the legal text. Indeed it is not even clear if the agency would reject a testing proposal in the situation where a third party had found existing data but the registrant had not yet obtained a letter of access for it. If the registrant is not persuaded by the third party comments then, even if the agency is, the agency cannot act on them. Through its legal approach to testing proposal evaluation the agency has rendered the system almost completely useless – at least as far as its own role is concerned.

The third party commenting process can be useful however if directed at the registrant, who could take into account the comments received and modify or even withdraw the testing proposal. The agency has further undermined this possibility, however, by sending third party comments to the registrant with the draft decision for the 30-day comment period. This is hardly enough time for the registrant to deal with the decision let alone consider and obtain the data suggested by any third party comments. Given that the comments come with a draft decision, which in most cases requests the test and rejects the third party comments (see Section 3.6), registrants are further dissuaded from investigating other ways to obtain the information. We are therefore in the rather farcical situation whereby the agency processes and comments on third party comments but believes that it cannot act on them and the registrant, who can act on them, is not given

access to them until almost too late. We are working with ECHA to see if they can – at least – get our comments to the registrant much earlier in the process.

The statement by ECHA, above, that none of the third party information has given grounds for ECHA to reject a testing proposal is therefore rather unfair given that ECHA do not believe they could act on third party comments anyway, save in very limited circumstances. It also seems unfounded since, based on published decisions, the agency has actually rejected at least six testing proposals to date and in two of these cases our comments were credited. ECHA have rejected four two-generation reproductive toxicity tests because the substance was registered at Annex IX (substances EC 480-370-1, EC 700-427-9, EC 423-340-5, EC 249-204-3). According to column one of Annex XI 8.7.3, the two-generation study is not needed unless effects on reproductive tissues have been seen in the 28 or 90-day repeated dose tests. In all four cases the 90-day test had not yet been conducted. Therefore, ECHA rejected the testing proposal for the two-generation study but asked for a new testing proposal to be submitted if effects were seen in the 90-day study, for which the testing proposal was granted. We made this comment in two of the four cases and were credited with this in the decision letters.

In another case ECHA rejected a testing proposal for a reproductive toxicity screening study but asked the registrant to submit testing proposals for prenatal developmental toxicity and 90-day tests as these were the standard requirements at their tonnage level (EC 915-673-4). For another substance ECHA rejected the testing proposal for a two-generation test as the data was already available from another registrant who had been requested to do the tests under the previous legislation (EC 425-220-8); confusingly, in an earlier decision on a testing proposal for a 90-day test for the same substance, ECHA had technically accepted the testing proposal but insisted in the letter that the data be obtained through the same data-share.

3.6 ECHA response to comments

We have been told anecdotally that third party comments do serve a function in encouraging Member States to look at draft decision letters. This may encourage Member States to investigate the need for the proposed test and issue PfAs, even if they suggest different approaches to the third party comments.

This is illustrated in the decision letters for substances for which no third party comments were received. In these cases ECHA's "statement of reasons" is notably brief. For example, the decision on 101 triallyl cyanurate (EC 202-936-7) simply states; "*A prenatal developmental toxicity study is a standard information requirements as laid down in Annexes IX, section 8.7.2 of the REACH regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to generate the data for this endpoint*."

Where there are third party comments, the decision letter deals with these. Initially, quite extensive comments on our proposed approach (e.g., read-across or QSAR model) were given. For example, for 3-amino-4-octanol (EC 482-070-6) ECHA gave a point-by-point explanation of our comments that was three and a half pages long. However, perhaps when the agency came to the position that they could only consider actual data on the substance (see Section 3.5), it was easier to dismiss our comments as not complying with this. For example, for reaction products of benzeneamine, N-phenyl- with nonene (branched) (EC 253-249-4) they state:

> "*The third party has proposed five testing strategies for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40 (2) to submit 'scientifically valid information and studies that address the relevant substance and hazard endpoint, addressed by the testing proposal'. As the proposal for a strategy cannot be regarded as such information or studies, ECHA concludes that this is not a sufficient basis for rejecting the Testing Proposal*."

A newsletter piece in April 2011 (ECHA, 2011e) sent a pointed message, contained also in the Evaluation Report for 2010, that comments had to be equivalent to the information required in the dossier:

- *In order to be relevant, the information submitted during the public consultation should fulfill REACH information requirements specified for the endpoint under examination*
- *Test data submitted should contain sufficient level of detail in order to allow an independent assessment*
- *If non-test data is provided, e.g. read-across, QSAR, etc they should fulfill the same requirements as the data submitted by the registrants and specified in REACH*

We have worked since then to provide comments that are closer to actual data rather than theoretical suggestions for approaches or tests that could be done. Even in these cases, however, ECHA have said that it is up to the registrant to accept the proposed read-across, for example, rather than ECHA, so the level of detail provided to ECHA is actually irrelevant. For example, for 3-hydroxy-2,2-dimethylpropyl 3-hydroxy-2,2-dimethylpropionate (EC 214-222-2), the letter said:

> "*ECHA acknowledges the information provided by the third party but notes that it is the responsibility of the registrant to use read across. Furthermore the registrant has to justify that the criteria set out in Annex XI 1.5 of the REACH regulation are met and that the information provides a sufficient basis to fulfil the data/information requirement(s)*."

Rather than being concerned that ECHA have interpreted their evaluation role so narrowly, the European Commission in their review of REACH (EC, 2013a) have supported their concern that dealing with third party comments is laborious. Recommendation 6.2 states: "*ECHA is invited to re-examine and streamline the third-party consultation process, for example through standardised replies and further guidance to focus these contributions to further increase efficiency of the dossier evaluation*." We therefore anticipate even less recognition of third party comments in final decision letters in the future.

3.7 Withdrawal of testing proposals

It was a surprise to us that the main mechanism for avoidance of the animal test appears to be withdrawal of the testing proposal by the registrant and not rejection by the agency. In fact, a large

number of testing proposals have been withdrawn, 42% overall for the first REACH deadline (Tab. 4).

Withdrawal or rejection could be considered equal from our perspective – either way the animal test is not performed. However, the reasons for withdrawal are not usually transparent and can raise suspicions that it was not appropriate. ECHA could still issue a compliance check and conclude that the test is necessary. According to the Evaluation Report 2011, reasons for withdrawal can include ceasing import or manufacture completely or downgrading use to below the tonnage band to avoid the need for testing. Sometimes ECHA gives the term "inadmissible" to tests proposed that are withdrawn because they were made in error, i.e., proposals for tests for Annex VII or VIII or where the testing had in fact already started (see Section 3.7).

The reason for most withdrawals however is not always known and indeed ECHA claim that they do not know it either (ECHA, 2012a). We suspect that there are a proportion of registrants that withdraw their testing proposal when they receive the draft decision and our comments. ECHA describe two such cases in their Evaluation Report 2012 (see Section 4.5). Until very recently we did not know the identity of the lead registrant and therefore could not ask. For a period ECHA offered informal discussions with the registrant after they received the draft decision and we think it is likely that this also facilitated the appropriate withdrawal of unnecessary animal tests.

Registrants can withdraw their testing proposal any time up to the point at which the draft decision goes to the MSCAs, i.e., soon after the 30-day commenting period for the registrant. After this, it is ECHA policy to process the testing proposal regardless of the registrant's wishes. Indeed, the minutes of the MSC meetings include several cases where the testing proposal was accepted even though the registrant no longer wanted to conduct the test and had provided justification (e.g., EC 251-090-5, MSC-22).

One such case was subject to a complaint to the Board of Appeal, which reviews ECHA decisions (http://www.echa.europa.eu/documents/10162/13571/a_002_2012_announcement_en.pdf). In this case the registrant (BASF) no longer felt a long term fish toxicity test was necessary but at the MSC meeting the decision had been made to accept the test. BASF withdrew their appeal after the final decision was amended to make it clear that updates to the dossier beyond a certain point had not been taken into account in the decision. Indeed the minutes of the meeting in which the BASF case was discussed show that ECHA got round their inflexible approach by indicating that "*The registrant can update the dossier at any point in time e.g. he can also waive a test with adequate justification but these updates/ waivers will be examined only when the deadline to fulfil the information requirements set in the final decision expires*" (MSC-21, p7). What ECHA are effectively saying is that, although the decision letter technically asks for the test, the registrant can still, up to the deadline for submitting the information, use other methods to supply the required information. Registrants run the risk, however, that when the agency reviews whether the registrant has complied (Article 42) they could be found to be in breach. ECHA may indicate in final decision letters or in the MSC meeting that there remains a possibility to avoid the test, even though the final decision letter technically asks for it, but this relies on registrants "reading between the lines" that they can still yet avoid the test. This contorted approach appears to enable ECHA to feel better about accepting testing proposals when they know the test is not scientifically necessary without them having to "take the registrants responsibility from them" by actively rejecting the testing proposal.

4 Lessons learned from commenting

4.1 Existing data

Under Annex XI (section 1.1) existing data can be used even if it is old or not conducted according to the OECD principles of Good Laboratory Practice (GLP), as long as the data is suitable for classification and labelling and/or risk assessment.

Additional relevant data on the substance itself or similar substances that had not been reported (as far as we are aware) in the registration dossier was found in 166 cases, see Table 3. In 16 cases data on the substance itself was found that had not been reported by the registrant, i.e., 4% of testing proposals. Sometimes the data did not match exactly to the test proposed, but would have been sufficient, i.e., was on the same endpoint and was of the same or longer duration.

For example, a six-month rat inhalation study was found in a publically available IUCLID dossier (via the European Chemicals Bureau website) for pentasodium triphosphate (EC 231-838-7). This was included in our comments on a testing proposal for a 90-day inhalation rat study. The study was assessed by the registrants, and the testing proposal was subsequently withdrawn.

Several reproductive toxicity studies were found on the HPVIS and Toxnet websites for N-(cyclohexylthio)phthalimide (EC 241-774-1) and were included in comments on a proposed prenatal developmental toxicity study. The testing proposal was withdrawn, and the registration dossier was amended with the study from HPVIS as a key study for this endpoint.

An actual experimental value for fish bioaccumulation factor was found in a CAESAR training data set for isodecyl diphenyl phosphate (EC 249-828-6) and was included in our comments on a testing proposal for the same endpoint. The testing proposal was withdrawn, and the existing experimental data were included as key study in the dossier.

In many of these cases the actual data were not submitted by the ECEAE but the source was identified. Apart from the case mentioned in Section 3.5, we are not aware of any cases where the agency – in their final decision letter – insisted the company pay for and use the data identified by us; indeed we are not sure that legally they feel they would be able to do this unless the data is found within another registration dossier for the same substance.

The vast majority of the information we found, however, was not on the substance itself but was on analogues, components, hydrolysis products or on members of the category to which the substance belonged (or could belong) and therefore formed part of a read-across approach (see Section 4.4). Sources of this data included mainly EPA reports and OECD SIDS dossiers and less commonly data from other programs including Health Canada,

Tab. 5: Sources of existing data

OECD eChemPortal	http://www.echemportal.org
US EPA ACTOR	http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=F41F6F578E0F80580281D65180C7D9FD
OECD SIDS	http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html
IPSC INCHEM	http://www.inchem.org/
ToxNet	http://toxnet.nlm.nih.gov/
US NIH National Toxicology Program	http://ntp.niehs.nih.gov/
US EPA High Production Volume Challenge	http://www.epa.gov/HPV/pubs/general/hpvchemdata.htm
US EPA HPV Chemical Hazard Characterizations	http://iaspub.epa.gov/oppthpv/hpv_hc_characterization.get_report_by_cas?doctype=2
US EPA TSCA New Chemicals Program	http://www.epa.gov/oppt/newchems/
US EPA High Production Volume Information System	http://www.epa.gov/hpvis/
ESovTox (Database of Russian language studies, abstracts in English, registration required, data for weight-of-evidence)	http://kbfi-databases.eu/database/
BIBRA	http://www.bibra-information.co.uk/toxicity_profiles_overview.html
COSing EU cosmetics database	http://ec.europa.eu/consumers/cosmetics/cosing/
NICNAS Australia National Industrial Chemicals Notification and Assessment Scheme	http://www.nicnas.gov.au/
Canada Challenge program	http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/list-eng.php

NRC Canada, IPCS, NTP, the Russian database eSov Tox and published scientific papers (Tab. 5).

The perception was that we would be unlikely to find existing data on the substance that has not already been considered by the registrant but, although rare, it is surprising how many cases there have been. Given that this is one of the only reasons that ECHA will reject a testing proposal it is worth continuing to look for existing data or data on similar substances to support read-across.

4.2 Weight of evidence

103 comments comprised a "weight of evidence approach." Weight of evidence arguments can be used according to REACH Annex XI, section 1.2. This is defined as data "*from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion*."

Although we could not see what considerations the registrant had made in their dossier that led them to submit a testing proposal, we did not want to assume that all options to reasonably avoid testing had been made. Our weight of evidence comments therefore usually constituted a descriptive argument for why no further testing should be required based on a combination of the presence of existing data on the substance already within the dossier, additional data found during the commenting process (see Section 4.1), and the results (real or hypothetical) from tests that could be relatively easily obtained or performed such as from QSAR models and *in vitro* assays (see Sections 4.3 and 4.4).

Often these arguments centered on the likely low sub-chronic or reproductive toxicity of the substance based on the results of existing sub-acute or screening test results. This was sometimes supported by statements from other testing programs, such as the US EPA HPV, that the substance was not of concern or evidence that the substance already is used safely in food or medical products.

For example, our comments on a proposal to test slimes and sludges, blast furnace and steelmaking (EC 266-006-2) for prenatal developmental toxicity summarized the general low toxicity of the substance, the fact that it is made up of iron oxides and that iron is given as a supplement to pregnant women. The test proposed was withdrawn. The registrant confirmed that our comments were used to prepare a data waiver.

In general, however, our "weight of evidence" comments were not taken up by ECHA or the registrants. On ECHA's part this was due to their position that they cannot do the registrant's job for them (see Section 3.5). For example, their final decision on cyclohexane-1,4-diyldimethanol (EC 203-268-9) said, "*Considering the possibility of establishing a weight of evidence approach on the basis of such tests and existing in vivo data, which could fulfil the information requirements of REACH, is the registrants responsibility and cannot be requested by ECHA*." As a consequence, the hurdle for weight of evidence was much higher; we had to not only provide all the data, but we had to construct the approach, and, crucially, the registrant had to accept it and insert it into their dossier (within 30 days).

In the "low toxicity" cases we often used the data from tests of shorter duration than the test proposed, e.g., acute tests and 28-day tests in place of the 90-day test. The position of the Agency however is that results of screening studies or sub-acute tests are not considered suitable to waive testing for longer term studies unless they indicate severe toxicity. For example, in response to a comment regarding low toxicity of 1,5-bis[1,2-bis(ethoxycarbonyl) ethylamino]-2-methylpentane (EC 433-260-2) in the 28-day study plus other information, the final decision letter stated,

> "*ECHA generally refers to Annex XI, 3.2 according to which, without prejudice to column 2 of section 8.6 of Annexes IX and X, a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study*."

This "footnote" to Annex XI, 3.2 was added later to REACH and, whilst it strictly speaking only relates to options to waive data requirements based on exposure, it does indicate the prevailing view that studies of shorter duration cannot be used to waive studies of longer duration.

For the 90-day repeated dose toxicity endpoint there is a column 2 adaptation allowing waiving based on the 28-day study but the requirements are very strict: "*8.6.2 The sub-chronic toxicity study (90 days) does not need to be conducted if…the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test', particularly if such a pattern is coupled with limited human exposure*." A similar waiver exists for reproductive toxicity (8.7) but the preconditions are even stricter: "*if the substance is of low toxicological activity (no evidence of toxicity seen in any of the test available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure…and there is no or no significant human exposure*."

However, a new argument has come to light from one MSCA who has shown that in all cases where the 28-day study was "negative", i.e., a NOAEL equal to or greater than 1,000 mg/kg bw/d, the 90-day was also of this magnitude (see Taylor et al., in press). They propose that low toxicity based on a weight of evidence argument could be used in these (limited) cases, but it is not clear if ECHA will accept this.

Interestingly, the "weight of evidence" option within Annex XI (section 1.2) does not require that the information has to be equivalent to the test prescribed in the Annex or indeed suitable for classification and labelling, and/or risk assessment, which is a requirement for the other options in Annex XI, such as existing data (1.2), QSARs (1.3), and *in vitro* methods (1.4). Given this inconsistency it is not clear whether a registrant could in practice use a weight of evidence argument. We have no knowledge where a weight of evidence approach has been used to reject a testing proposal and no knowledge of where it was accepted under a compliance check. We have in general abandoned giving weight of evidence arguments.

4.3 (Q)SARs

(Q)SARs are defined as (qualitative or quantitative) structure activity relationship models which are computer models that utilize the existing data from a group of substances to predict the likely toxicity of other substances based on similar structural features. According to Annex XI (section 1.3) these models can be used instead of testing in their own right but the model must be validated, the substance must be within the applicability domain of the model, and the results must be adequate for classification and labelling and/or risk assessment.

54 comments related to the use of (Q)SARs. These included the results from primarily CAESAR (free), T.E.S.T. (free), EPI Suite (free), OECD toolbox (free), Toxtree (free) and MolCode Ltd. (proprietary) models. The endpoints these were used for were mainly prenatal developmental toxicity (all models), genotoxicity (CAESAR, T.E.S.T., and OECD Toolbox) and bioaccumulation factor (CAESAR, T.E.S.T., EPI Suite). The ANTARES project lists a range of QSAR models for REACH http://www.antares-life.eu/.

As far as we are aware, the results of QSARs were not used to withdraw or reject testing proposals. There appeared to be a lack of willingness on the part of both the registrants and ECHA to accept QSAR test results on their own to waive testing. For example, for phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide (EC 423-340-5) a positive result was obtained for prenatal developmental toxicity using a MolCode Ltd. model but the testing proposal was not withdrawn and the test was agreed by the agency.

Due to the slow rate of feedback on the utility of some of our suggested approaches it was some time before we realized that, as with all approaches, ECHA would not consider the information useful unless it was presented in the form of information that a registrant would provide in their dossier. We therefore needed to provide both a (Q)SAR Model Reporting Format (QMRF) and (Q)SAR Prediction Reporting Format (QPRF) demonstrating not only the results but evidence that the model is valid and the substance falls within its applicability domain (ECHA, 2010e). For example, with regard to a suggestion to use a QSAR model (for which the results were provided) for the substance 2,2-bis(hydroxymethyl) propionic acid (EC 225-306-3) ECHA said:

> "*In accordance with Annex XI, section 1.3, results of QSAR may be used instead of testing when the following conditions are met:*
> – *results are derived from a QSAR model whose scientific validity has been established,*
> – *the substance falls within the applicability domain of the QSAR model*
> – *results are adequate for the purpose of classification and labelling and/or risk assessment and*
> – *adequate and reliable documentation of the applied method is provided*
>
> *As such the results provided cannot be utilised or extrapolated directly to fulfil these information requirements. ECHA therefore concludes that this is an insufficient basis for rejecting testing which has been proposed for these endpoints*."

Even so, our submissions were not considered useful. In one case a registrant of diethylmethylbenzenediamine (EC 270-877-4) did try to incorporate the result from a QSAR model we suggested to waive a proposed prenatal developmental toxicity test. Unfortunately, although the QSAR reported the substance likely to be a developmental toxicant, the registrant did not classify it as such. Therefore, although we have some sympathy with ECHA in that regard, the position of ECHA in their decision on

the utility of the QSAR data itself was worrying and seems to run counter to what Annex XI, 1.3 says:

> "*Based on this model it can only be assumed that the chemical may have a developmental toxicity effect, but this information alone cannot be used to conclude that the substance is a developmental toxicant*."

Crucially, ECHA will not run a QSAR themselves and use the results to waive testing and do not feel they are able to ask a registrant to do so either. There appeared to be an additional difficulty with recommending the use of proprietary models since the registrant would need to pay the (Q)SAR company to use the results. In response to third party comments to use a proprietary model to waive a prenatal developmental toxicity test for 3-amino-4-octanol (EC 482-070-6) ECHA said;

> "*However, its goes beyond ECHA's mandate regarding the examination of testing proposals, as described in Article 40 of the REACH regulation, to impose on registrant to seek approval from a legal entity doing business with QSAR to use its proprietary models in order to meet a data requirement*."

As a result we have tended to stop suggesting the use of QSAR models, particularly as standalone replacements.

4.4 *In vitro* tests

In vitro test results can be used in place of *in vivo* tests as standalone replacements under Annex XI, section 1.4 (*in vitro* tests) or in combination with other information under Annex XI, section 1.2 (weight of evidence). According to section 1.4 of Annex XI, *in vitro* tests that are at the stage of ECVAM pre-validation (or equivalent) can be used alone to waive testing if the result is positive, i.e., indicative of a hazardous property. However, if the test has been validated "according to internationally agreed validation principles", and can be used for classification and labelling and/or risk assessment then negative results can also be accepted. There are no such restrictions on the use of *in vitro* (or other) test methods when used in combination with other information under Annex XI, section 1.2 (weight of evidence).

There are actually a limited number of *in vitro* tests that could be suggested under Annex XI section 1.2 to waive the tests under Annex IX and X. This is partly because the endpoints to which testing proposals apply are those more complex, long term tests for which the *in vitro* tests are at a development stage only or only measure one aspect of the pathway of toxicity. The requirements of section 1.4 are also rather strict, requiring validation to international principles and suitability for classification. Methods adhering to these requirements would be likely to be in the EU Test Methods Regulation or OECD process already, so section 1.2 in theory could only be invoked for a limited period before such a method could be used anyway under Article 13 (3). Article 13(3) states that "*Where tests on substances are required to generate information on intrinsic properties of substances, they shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the Agency as being appropriate*." However, there are some methods that are "stuck" in the regulatory process and where section 1.2 could apply to their use.

In 67 cases we suggested *in vitro* tests that could be used (but we could not provide this service and therefore the results). The majority of these cases (54) related to the use of the validated embryonic stem cell test (Genschow et al., 2004), limb bud micromass test (Spielmann et al., 2004), or the rat whole embryo culture test (Piersma et al., 2004) as a positive screen for prenatal developmental toxicity. In a few limited cases we also suggested use of the endocrine receptor assays as a positive screen to waive the need for the two-generation reproductive toxicity study. Two estrogen receptor and androgen receptor gene reporter assays have been pre-validated by ECVAM (Freyberger et al., 2010; Witters et al., 2010, respectively). Other suggestions included the use of the Fish Embryo Test, currently going through the OECD process, to demonstrate long term fish toxicity (Embry et al., 2010).

Conservatively, even though the *in vitro* developmental toxicity tests are ECVAM validated (and therefore conforming to internationally agreed validation principles), we only recommended them to be used as standalone if the results were positive. However, the agency's approach to their use (irrespective of the fact that we did not provide actual test results) showed a worrying failure to accept what Annex XI, section 1.2 says. For example, in a decision on 3-amino-4-octanol (EC 482-070-6) requiring a prenatal developmental toxicity test, ECHA state:

> "*However, the REACH Guidance R.7a (R.7.6 Reproductive and developmental toxicity) also states that there are a number of weaknesses in the design of both the validation study and of the in vitro tests that have been identified, such as the limited number and range of the substances tested, and absence of a biotransformation system, which have led to the conclusion that the tests currently have limited value in a regulatory context. Regarding the adequacy of the data for the purpose of classification and labelling and/or risk assessment it is stated that while a positive result in an in vitro tests could provide justification for further testing, such a result in isolation would not be adequate to support hazard classification*."

Furthermore, in a decision on 3-[(diisoalkyloxyphosphorothioyl) thio]-2-methylalkanoic acid (EC 434-070-2) they go on to say that such tests cannot be used as standalone replacements and ECHA cannot request that they are conducted:

> "*Concerning scientifically validated in vitro methods such as the embryonic stem cell test, the limb bud micromass culture and the whole embryo cultures such methods may provide additional information which can be assessed together with existing in vivo data in a weight of evidence approach. However, ECHA notes that the mentioned in vitro tests only cover some of the reproductive toxicity endpoints, modes of action and mechanisms covered by the in vivo pre-natal developmental toxicity tests and therefore cannot be used as standalone replacement tests. Furthermore these alternative methods are not part of the information requirements laid down in Annex VII to X of REACH and can therefore not be requested by ECHA in the context of a testing proposal examination*."

We suggested the use of these tests to remind registrants that they could, under section 1.2, use them if they were positive. These

tests are significantly cheaper and quicker than the *in vivo* reproductive toxicity tests. However, no company seems to have taken these comments on board, perhaps as there is a tendency to not want to classify a substance as harmful on the basis of an unrecognized *in vitro* test. Others reviewing the use of *in vitro* methods for REACH endpoints have made a similar observation (Rovida, 2010; Scialli and Guikema, 2012). Section 1.2 therefore appears to be redundant within the testing proposal context and we have now ceased recommending the use of *in vitro* tests such as these.

Another suggestion related to the use of *in vitro* tests involved recommending that the *in vitro* test battery for genotoxicity is completed before conducting the *in vivo* genotoxicity study (usually by completion of OECD TG 473 or 476). Although the *in vivo* genotoxicity study was usually proposed when there had been a positive result in one of the three *in vitro* tests required by the legal text (the correct legal approach), we found evidence in some cases that this positive could have been a "false positive", explained by cytotoxicity, for example. We therefore recommended investigating this in addition to completing the final *in vitro* test before (re) considering the *in vivo* test. Our suggestions in this regard appeared to have been ignored by both ECHA and the registrants.

4.5 Chemical grouping/read-across

Annex XI (section 1.5) relates to the use of grouping or read-across and states that, "*Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances*." In this case, tests on one (or more) members of the group can be used to provide data for the other members.

151 comments related to read-across or grouping. In some cases the read-across was in support of a category approach (possibly already identified by the OECD), in others it was that data existed on structurally similar, related substances, in others it was that information was known on the precursors or breakdown products or, for multi-constituent substances, on the components.

For example a prenatal developmental and a 90-day study were proposed for aluminum triformate (EC 230-898-1). However, the dossier itself (which we obtained from ECHA under Access to Document legislation, see Section 3.3) stated that the substance dissociates at any pH to aluminium salts and formic acid. We suggested that data from these compounds should be used instead. Since the substance dissociates to formic acid we also argued that the substance would be corrosive to the animals and testing should not be performed (see Section 4.8). The testing proposal was withdrawn with the justification that testing was scientifically unjustified. ECHA referred to this example in their Evaluation Report 2012.

For sodium permanganate (EC 233-251-1) we suggested that the data for potassium permanganate (EC 231-760-3) could be used. A one-generation (OECD TG415) and a prenatal developmental toxicity study (OECD TG 414) were available and indicated both developmental effects and effects on fertility. We also noted that sodium permanganate is classified as corrosive and therefore tests on animals should not be performed (see Section 4.8). The registrant agreed with the approach, but too late for the ECHA decision. In their decision letter ECHA indicated that the read-across was plausible, but still requested the test anyway because the read-across approach had, at the time of the decision, not been formally added to the dossier (see Section 3.7). The dossier for sodium permanganate now refers to a read-across approach and it does not appear that testing has been done. ECHA also referred to this example in their Evaluation Report 2012, indicating that the read-across approach would be acceptable.

In 51 cases the comments supported a read-across strategy already proposed by the registrant. From March 15, 2011, ECHA indicated these cases by putting "testing proposed with (name of substance)" next to the substance with a testing proposal. Prior to this it was not always obvious that the registrant was proposing read- across. We were surprised that registrants were proposing read-across as technically this should not require a testing proposal, i.e., it should just be included in the dossier as a read-across case and only the test on the substances should be proposed. This was the feeling also of one Member State who thought that testing proposals not on the substance should be formally rejected (MSC-25 minutes, page 32). We suspect companies are using the testing proposal system to avoid a compliance check whilst gaining assurance from ECHA that their approach is sound. In doing so they may avoid doing unnecessary animal testing but they also run the risk that the approach in general is rejected and they have to do many more tests than they were proposing.

The strategy agreed by ECHA and MSCAs is to accept the testing proposed (whether it is on the substance or not), indicating that they feel the approach is "plausible" but in cases where they think the approach is not plausible they will ask for the test to be done on the substance itself (MSC-24 minutes, page 2-3). Indication about the acceptance of read-across approaches by the agency is currently mixed, some have been rejected with tests on all the substances required and not many have been accepted as proposed by the registrant. However, many of the categories of substances with large, complex read-across cases have however not yet been finalized by the agency.

For example, we provided supporting comments regarding the read-across strategy proposed by the registrant to read across to 2-ethyl-2-(hydroxymethyl)propane-1,3-diol (propylidynetrimethanol) (EC 201-074-9) for three other substances (EC 245-509-0; 204-794-1; EC 204-104-9) for prenatal developmental toxicity. This was based on the structural similarity (same functional hydroxy groups) and the fact that the substance to be tested is likely to be the more toxicologically active of the four, based on its smaller size and existing toxicological data including reproductive toxicity screening studies (although these indicated that the substance was in fact not toxic to reproduction; it was systemically more toxic than the others). The MSC, however, did not think the approach, as it stood, was plausible and rejected the proposed read-across by instead insisting that the testing was conducted on all three substances (MSC-25 minutes, page 7-8).

However, for one substance, acetalization products between glucose and C20-22(even numbered)- alcohol (EC 923-835-0), ECHA did accept the read-across to its analogue "acetalization products between glucose and C16/18(even numbered)-alcohol" (EC 927-870-2), which was supported by us, as plausible and in the decision letter asked that the testing was done on the analogue.

Read-across or substance based grouping have been heavily used by the industry. The Article 117(3) report indicates that it was used for 24% of information requirements (ECHA, 2011a). However, ECHA complained in that report that the justifications for read-across are not often well described and this is likely to affect their approach to testing proposals (and compliance checks). Following their request for better third party comments (see Section 3.6), we have also sought to improve the quality of our read-across arguments, trying to construct the read-across hypothesis and demonstrate the likely similar structure, physico-chemical properties, and toxicity using a data matrix for the substances included in the hypothesis. In cases where the registrant has clearly already proposed read-across, given that we do not have access to the CSR in which the strategy would be presented, it is not always worthwhile commenting as we do not know if we can improve on their approach.

4.6 Testing technically not possible

According to section 2 of Annex XI, testing can be waived if it is technically not possible. This section relates more to the physical impossibility to test the substance due to volatility, reactivity, or instability. However, we included in our comments other physico-chemical properties that could seriously affect the ability to test the substance or interpret the results, which are mentioned in other parts of the Annexes (mainly column 2 adaptations), such as flammability, solubility, pH, etc. A limited number of comments also related to solubility/stability issues relevant for fish toxicity and bioaccumulation in fish.

74 comments related to the feasibility of testing, but the vast majority of these (68%) referred to the fact that the substance was classified as corrosive (GHS hazard code 05) and/or signs of corrosivity/severe irritation had been seen in the existing studies. The preamble to Annex VII to X states that "*in vivo testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided*." This is largely for animal welfare reasons but feasibility could come into play when the dose levels have to be so low to avoid corrosive effects that systemic toxicity will unlikely be seen.

For example, a prenatal developmental and a 90-day oral toxicity study were proposed to be conducted on 4-nitrotoluene-2-sulphonic acid (EC 204-445-3). We argued that the substance was classified as corrosive and moderate to severe erosions in the glandular stomach had been found in some animals in the reproductive toxicity screening study. The testing proposals were withdrawn, a read-across (also suggested by us) was used and the study was reported to be "scientifically unjustified."

Unfortunately, ECHA are currently paying little regard to our concerns about corrosive effects in the animals. Even when substances are known to be corrosive, ECHA are assuming that registrants will know not to test at levels that will cause corrosion and are not reminding them of their obligation to avoid this in the decision letter.

4.7 Exposure based waiving

According to section 2 of Annex XI "Substance tailored exposure-driven testing" – commonly referred to as exposure based waiving – testing for repeated dose toxicity and reproductive toxicity can be omitted based on the exposure scenario provided in the CSR. However, the requirements are very strict and require that there is "no or no significant exposure" throughout the lifecycle of the substance. Specific endpoints, for example, reproductive toxicity tests, can also be waived under column 2 if there is "no or no significant exposure", and other conditions are met.

We made exposure-based comments for 128 testing proposals. The majority of these (89; 70%) were to remind the registrant about the concept of the Threshold of Toxicological Concern (TTC). This is a concept not included in the REACH legal text but is increasingly being applied to food and cosmetic risk assessment. The TTC approach is based on the concept that for all substances there is a level of exposure below which there is hardly any risk to human health, regardless of the toxicity of the substance. The level of exposure depends on very broad classes of likely toxicity; those chemicals not at all likely to be toxic can have higher exposure levels. Using papers by Bernauer et al. (2008) and Kroes et al. (2004) we provided values for reproductive toxicity and repeated dose toxicity, respectively, and if exposure is less than this then testing is not considered scientifically necessary. Depending on the use of the substance it was possible that the TTC approach could be used. However, in all these cases the suggestion was hypothetical since we did not have the exposure scenarios for the substances (found in the CSR) in order to determine that the TTC approach could indeed be applied. We do not know if any registrant tried to apply the TTC approach. In response to our suggestion in comments, ECHA largely dismissed it on the grounds that the registrant had not used the approach, not that it looked plausible (or not):

> "*The registrant did not use substance-tailored exposure-driven testing according to Annex XI*." (final decision on phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide (EC 423-340-5)).

In 11 cases we were able to infer from the disseminated dossier that the substance was predominantly used as an intermediate in closed systems and therefore most testing could be avoided (under Articles 17 and 18). ECHA have not however rejected any testing proposals on the grounds of exposure. They came close in one case. For 3,4,5,6,7,8,9,10,11,12,13,14-dodecahydro-2H-cyclododeca[b]pyran (EC 251-090-5) we argued that it appeared that the substance was used as a transported, isolated intermediate. The registrant agreed and wanted to withdraw the testing proposal on this basis, but ECHA still requested an *in vivo* genotoxicity study. Under Article 18 (3) transported isolated intermediates must still comply with Annex VII (the minimum data requirements). Under Annex VII "further mutagenicity studies shall be considered in case of a positive result", so it seems that in this specific case testing may have been justified, although ECHA failed to explain this in their decision letter.

We have ceased recommending the TTC approach because substances are usually used in a wide variety of scenarios such that it may be difficult to determine accurate exposure levels for all uses let alone demonstrate that they are below the threshold. We will continue to flag substances for which the "no or no significant exposure" waiver could apply, because there have been some occasions where it seems that it could be applied if registrants tightened up their use scenarios.

4.8 Other 3Rs comments

In 178 cases we provided comments that did not easily fall into an Annex XI "waiver", but included comments that argued that testing was not strictly required by the legislation, could be avoided through the use of other required tests, could be waived according to column 2 adaptations, or other 3Rs considerations.

4.8.1 Testing not justified

Initially, we were not aware if the substance was actually registered as an Annex IX substance. We assumed most substances would be Annex X given the deadline, although non-phase-in substances could have been Annex IX. If the substance is Annex IX, a two-generation reproductive toxicity test is only needed if signs of toxicity to reproductive organs are seen in the 28 or 90-day repeated dose tests. In this case it is important that the 28 or 90-day test is conducted first, enabling the two-generation test to be avoided unless signs are seen. We therefore highlighted this possibility in cases where we were not sure of the tonnage band of the substance. This was successful in at least two cases and in total ECHA have rejected the two-generation test on this ground in four cases (see Section 3.5).

Once the tonnage levels were published on the website (see Section 3.3) we were able to identify those substances for which testing did not seem to be legally required. For example, for 2-{N-[2,6-Diamino-4-oxo-4H-pyrimidin-(5Z)-ylidene]-hydrazino}-5-methyl-benzenesulfonic acid (EC 700-002-8) the registrant proposed a prenatal developmental toxicity study even though the substance was only registered at Annex VIII. We commented to this effect and at MSC-30 it was decided to reject the test as it is not required at this tonnage and there did not seem to be strong justification for the test. In fact ECHA's position seems to be that they *will* accept a testing proposal even if the tonnage band means it is not legally necessary, as long as the testing appears justified.

In a limited number of cases where the use of the substance appeared to be predominantly in cosmetics (see Section 2.1) we made a legal statement that the test should not be performed since the Cosmetic Directive has testing bans on cosmetic ingredients and Article 4(b) of Reach provides:

> "*This regulation shall apply without prejudice to … Directive 76/768/EEC as regards testing involving vertebrate animals within the scope of that Directive*."

The legal consequences of asking for animal testing on substances that are essentially cosmetic ingredients have not been seriously considered by ECHA. In response to this issue at a MSC meeting ECHA merely said that "*the EU legislation on cosmetics has no direct link to REACH" and that "it is up to the registrant to decide how to comply with ECHA's decision taking into account his other legislative obligations as well*." (MSC-16 minutes, page 5). The European Commission have only recently made a statement indicating the position that the testing bans only apply to ingredients whose sole use is in cosmetics (EC, 2013b). Aside from the fact that this statement is not legally binding and could be challenged, this could still apply to some of the substances being tested for REACH.

4.8.2 Testing strategies

When there was more than one test proposed for a substance we suggested strategies to order the testing. This was done with the view that the results from the first test could mean that the second, or third, test is no longer necessary. In cases where both a two-generation and a prenatal developmental toxicity study were proposed, we recommended beginning with the two-generation test (or better still, an EOGRTS, see Section 4.8.4). The OECD test guideline on the two-generation study (TG 416) also says that it can be extended to include prenatal parameters. However, aside from the fact that ECHA rejected comments like this since they were not "information", in a decision on 2-hydroxy-2-methylpropiophenone (EC 231-272-0) they said that "*Additionally, the availability of a two-generation study is not, in itself, a basis for adaptation of the information requirement for Annex IX, 8.7.2 [prenatal developmental toxicity study] according to column 1 or 2, or Annex XI*." This is not very helpful; ECHA could instruct registrants to consider including prenatal parameters in the two-generation (or EOGRTS) tests, described in the OECD guidelines, to reduce animal numbers.

ECHA's statement is also not entirely true; one MSCA has recommended a testing strategy recently based on a similar premise to ours. In cases where a prenatal developmental study in a second species is likely to be required they suggested that the first test should be done in rabbits. That way, they argued, the two-generation reproductive toxicity test, which is conducted in rats, could be used to waive the second prenatal developmental toxicity test, since both rats and rabbits have been evaluated. ECHA supported the idea but only went so far as to say that in future they would not specify the species required for the prenatal developmental toxicity test, again leaving these kinds of 3Rs strategies up to the registrant (MSC-25 minutes, page 4-5 pages).

In fact both strategies have been hampered by the situation that, since September 2011, all decisions on two-generation reproductive studies have been sent to the European Commission because of the EOGRTS issue (see Section 4.8.4). In these cases, the decision is "split" to remove the two-generation reproductive toxicity test and a decision is made on all the other tests. The implication of delaying decisions on the two-generation reproductive toxicity test on the number of animals that will ultimately be used in unnecessary prenatal developmental toxicity studies has not been appreciated to date.

4.8.3 Column 2 waivers

Column 2 of Annexes VII to X lists specific rules for adaptation of the test required in column 1. In some cases, based on our knowledge of the toxicity data already in the dossier, we suggested that the testing could be waived according to column 2. One of the most common column 2 waivers we suggested was in relation to reproductive toxicity studies (8.7) in which column 2 says testing does not need to be conducted if the substance is known to be a genotoxic carcinogen or a germ cell mutagen and appropriate risk management measures are implemented. This was a pragmatic measure put in the legislation since substances with these properties are already considered very hazardous and will already have appropriate controls on their use.

Unfortunately, ECHA seem to be reluctant to "do the registrants' job for them" and reject testing proposals in these instances. For 4,4'-methylenebis[N,N-bis(2,3-epoxypropyl)aniline] (EC 249-204-3) we found it was already classified as a germ cell mutagen GHS cat 2, supported by positive *in vitro* and *in vivo* genotoxicity studies. A MSCA also agreed with this analysis but it was overlooked during the discussion, the registrant unfortunately did not object and the test was requested (MSC-20 minutes, page 8-9).

Following discussion of a similar case, sodium hydroxymethanesulphinate (EC 205-739-4) at MSC-23, ECHA concluded in a presentation at MSC-25 that adaptation possibilities and their justification should be left to the registrant and as a default, ECHA will not reject testing proposals on the basis of classification-related adaptations. ECHA are interpreting "known to be" to mean "classified as" and are requiring classification of the substance for the waiver to apply. However, since the MSC cannot impose classification on the registrant – this is a separate process done by another ECHA committee – they feel they cannot accept the waiver.

If the registrant agrees with our approach and updates their dossier then column 2 waivers are still useful to suggest. For example for potassium permanganate (EC 231-760-3) (also used in a read-across case described in Section 4.5) we suggested that existing prenatal developmental, one-generation, and sub-acute toxicity studies indicated that it could already be classified as a reproductive toxicant (effects on fertility (male) and on the unborn child) and further testing in the two-generation study could therefore be waived according to column 2 for this endpoint. The registrant withdrew the testing proposal.

4.8.4 Other 3Rs considerations

The extended one-generation reproductive toxicity study (EOGRTS) was approved by the OECD as TG443 on July 28, 2011. It is seen by many as a replacement of the two-generation reproductive toxicity study that has the potential to reduce the number of animals used in the test by 40%. Since this date we recommended in our comments that the EOGRTS was used, as a last resort, instead of the two-generation reproductive toxicity study. Some Member States also began to suggest this and this has caused decisions on the issue to be sent to the European Commission to decide, since there remains disagreement within the MSC as to whether the EOGRTS can and should be used. Decisions have been further delayed by the European Commission and ECHA position that the method needs to be published in the EU Test Methods Regulation and the annexes updated to remove the specific requirement for a "two-generation study" (8.7.3) before it can be considered mandatory. We believe this approach is overly conservative, since REACH requires testing to be a last resort and Annex XI allows adaptations to be used.

We also initially suggested that the EOGRTS could even waive the need for the 90-day test and also the prenatal developmental toxicity test. This is because the EOGRTS provides a thorough evaluation of systemic toxicity in young and adult animals for a minimum of 70 days and also looks at the health, growth, development, and function of the offspring. However, in a decision on substance (EC 203-920-2), ECHA indicated that the EOGRTS could not replace the prenatal developmental toxicity test because it does not investigate skeletal and visceral malformation in the unborn pups. Presumably also, testing for 70 days will not suffice to replace the 90-day study.

Most OECD guidelines, including the 90-day and EOGRTS, permit a reduced test design in which only the highest dose is tested, i.e.,1,000 mg/kg bw/d, for those substances for which no toxicity is expected. This can reduce animal numbers by at least 50%. This recommendation has been ignored in ECHA's response to third party comments and ECHA have not put this reminder in their decision letters to registrants, missing an opportunity to help reduce unnecessary testing.

Any one of three fish tests can be conducted to satisfy the requirement for long term fish testing under Annex IX (9.1.6). OECD TG212 (Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages) is the most animal welfare friendly of the three because if the test ends before the fish are free-feeding, as it should, then it is not considered an animal experiment under the new EU Directive 2010/63. We therefore recommended that this test was used for testing proposals on long term fish toxicity. However, ECHA's position is that the preferred method for long term fish toxicity is actually the OECD TG210 (Fish early life stage, FELS, test). In the decision on sodium hydroxymethanesulphinate (EC 205-739-4) they claim that the TG210 method is the most sensitive, covering the most critical life stages, is the most widely used, and is preferred by the OECD. They have even overturned registrants that wanted to do the TG212 (e.g., BASF appeal case on aziridine EC 205-793-9) for these reasons, adding that, "*In addition, in the technical dossier there is no available information on the mode of action of the substance. Therefore, it is difficult to establish whether the OECD 212 test method is sufficiently sensitive to determine the chronic effect on fish for this substance*."

We will continue to make some of these 3Rs comments such as testing is not legally justified or where column 2 waivers could apply. However, we remain disappointed that ECHA are failing to remind registrants of any relevant, reasonable steps to reduce animal numbers in their final decision letters.

5 Recommendations for the second deadline

2,923 substances manufactured or imported by registrants in quantities of more than 100 tons per year were registered for the second deadline of June 1, 2013. Since these substances are Annex IX substances, there will be another batch of testing proposals, largely for 90-day repeated dose toxicity tests, pre-natal developmental toxicity tests, long term fish, bioaccumulation, genotoxicity as well as some two-generation reproductive toxicity tests. The ECEAE have committed funds to continuing the process of commenting and we will take the lessons learned from our experiences with the first deadline. It is important, however, that the agency continues to improve the commenting process. Here we list our recommendations to ECHA, to registrants and to agencies considering consultations of this kind in future.

Recommendations to ECHA, to registrants, and to agencies considering consultations of this kind in the future

Recommendations to ECHA

1. Publish proposals at a rate that is a reasonable for third parties to comment

Over 60% of the testing proposals were published over a six month period over the summer of 2011. A period of 18 months was theoretically feasible. Although the deadline for 2013 is longer, three years for ECHA to draft decisions, consideration should be made to ensure that third parties are also able to appreciate the longer timeframe.

2. Send third party comments to the registrant

Since ECHA's position on testing proposals is that they cannot do the registrant's job for them, it is imperative that registrants, who have the power to change their testing proposals, benefit from third party comments as soon as possible. Registrants should receive third party comments, without any qualification from ECHA, as soon as the deadline for commenting is over.

3. Make 3Rs recommendations in decision letters and be consistent in this

There are some established 3Rs principles that it is easy for ECHA to insert into decisions, such as the need to consider the fish testing strategy (which recommends starting with a daphnia test before long term fish testing, see REACH guidance R7.8.5), the use of the limit test, avoidance of testing at corrosive levels, and opportunities to order testing or chose species carefully to avoid further testing in future. These should be agreed in the Manual of Decisions, which records ECHA positions on issues, and clear, standard text should be applied.

Recommendations to Registrants

1. Do not submit a testing proposal unless you genuinely feel there is no other way to avoid the animal test

ECHA's current position is that they cannot do the registrant's job for them. If a test is proposed, then the assumption made by ECHA is that the registrant feels such a test is justified and it is very likely to be ordered. Registrants are unlikely to receive recommendations about possible alternative approaches or rejection of their proposals on that basis unless the registrant has already included them.

2. Be prepared to offer classification to avoid testing

Some of the more expensive, long term animal tests can be waived if the substance is already known to be hazardous. For example, according to Annex IX and X (8.7), the reproductive toxicity tests can be waived if the substance is known to be a genotoxic carcinogen or germ cell mutagen. Appropriate risk management measures need to be in place and the substance appropriately classified by all registrants. Similarly, if the substance is already classified it is unlikely that a negative result in a new test will improve this classification and therefore registrants should avoid proposing new animal tests purely for this purpose.

3. Continue to look for alternative ways to satisfy the endpoint even after submitting a testing proposal

Testing proposals can be withdrawn at any point up until the ECHA have notified the Member States of their draft decision. Registrants should ask ECHA for any third party comments they have received as soon as the deadline is over. The 30-day comment period is really the last chance to consider other information and should be used. Registrants should ensure their dossier is updated with all appropriate information at this point, if not before, for example by performing extensive literature searches for published data from peer reviewed sources or grey literature. Even after a final decision letter has been issued it may still be possible to avoid the testing if new information becomes available.

4. Help others avoid testing

According to the Evaluation Report for 2011 industry only provided 32% of the third party comments. Companies are not therefore using the system to share data on chemicals that they no longer wish to register. This is a shame as NGOs generally only have access to the same public information that the registrants can access. Companies can claim costs to share existing old data if useful and therefore it is in the interest of those with large data sets to proactively review the consultation website to see if they have any relevant data to offer.

Recommendations for future consultations

1. Do not ask for public comments unless there is an adequate mechanism for the information to be utilized

The ECEAE, and possibly others, have been working on the assumption that third party comments could be accepted by ECHA and used to reject testing proposals. It appears that except in very limited scenarios this is not the case. The narrow approach of the Agency is that comments would only be useful in cases where 1) There is existing data and 2) The testing is not required by the legal text. As a result, the testing proposal system is currently a very limited mechanism to try to assist companies in reducing animal tests.

2. Publish enough information so that commenting is possible

We experienced difficulties in the first 18 months as the registration dossiers were not published on the ECHA website. It was only recently that information on the identity of the registrant and the tonnage band were made available. The information publically available in dossiers assists third parties as it allows them to assess, 1) what information already exists to the knowledge of the registrant, thereby avoiding pointless submission of data and 2) what opportunities based on physical-chemical properties or the results of existing data there are to avoid testing. We are still not given access to the Chemical Safety Report in which the risk assessment of the substance is found along with justifications for tests proposed.

3. Publish proposals at a rate that is a reasonable for third parties to comment

Public consultation processes can be completely undermined if the volume of documents is too large and/or the time scales for commenting are too short. Already a 45-day comment period is quite short but if this is coupled with many consultations during this time frame, third parties may not be able to cope and may not be able to provide useful comments.

4. Report back on the results transparently

If the public are being consulted on something it is important to not only report what the final outcome was but whether their comments were taken into account. This gives transparency to decision making and also enables third parties to assess if they are performing a useful role.

6 Conclusion

The ECEAE provided a significant proportion of the third party comments on the first deadline testing proposals. We have been successful in influencing Member State comments on testing proposals and actual rejections in three cases. It is likely that we were much more successful in encouraging registrants to withdraw unnecessary testing proposals, of which there have been 145 to date.

Our ability to comment has been seriously limited by lack of information on the substances up to April 2011 and then from April 2011 to September 2011 by the high publication rate of testing proposals. The third party consultation is currently not taken seriously by the agency. This is partly due to their belief that they cannot do the registrant's job for them, i.e., they cannot reject testing proposals except in very limited circumstances. The way the legislation is interpreted, i.e., that it is the registrant's responsibility to waive tests and the agency's responsibility to accept tests, undermines the utility of the comment period and steers the direction away from the animals' favor. This approach is currently being investigated in a case we have brought to the EU ombudsman. The process does seem to be useful however, just not in the manner envisaged; companies are withdrawing testing proposals as a result of third party comments. Only over time, as compliance is assessed, will we know the extent to which withdrawals were adequately justified.

Initially our comments were directed at ECHA as we were under the mistaken impression that they may trigger ECHA to investigate a potential waiver. We are now striving to simulate actual data requirements to help the registrants. A number of suggestions and strategies have been rejected by ECHA, such as the use of *in vitro* methods, QSARs, the TTC approach, testing strategies, and weight of evidence. We remain extremely concerned about the Agency's conservative approach and apparent dismissal of the legal text in this regard. Others also looking at the operation of REACH in practice also are concerned about apparent inconsistencies with the legal text and a failure to promote alternative methods (Rovida, 2010; Rovida et al., 2011, Wagner et al., 2012).

References

Bernauer, U., Heinemeyer, G., Heinrich-Hirsch, B., et al. (2008). Exposure-triggered reproductive toxicity testing under the REACH legislation: A proposal to define significant/relevant exposure. *Toxicol Lett 176*, 68-76. http://dx.doi.org/10.1016/j.toxlet.2007.10.008

Client Earth (2012). ECHA names chemical producers following lawsuit from ClientEarth and ChemSec. 29 November 2012. http://www.clientearth.org/201211292067/news/press-releases/echa-names-chemical-producers-following-lawsuit-from-clientearth-and-chemsec-2067

ECHA (2007). ECHA Guidance on Dossier and Substance Evaluation (June 2007). http://echa.europa.eu/documents/10162/13628/evaluation_en.pdf

ECHA (2009). ECHA starts to publish information on safe use of chemicals for citizens – Press release ECHA/PR/09/17, Helsinki, 18 December 2009. http://apps.echa.europa.eu/legacy/doc/press/pr_09_17_dissemination%20_information_20091218.pdf

ECHA (2010a) Guidance on intermediates, version 2. December 2010. ECHA-2010-G-17-EN. http://echa.europa.eu/documents/10162/13632/intermediates_en.pdf

ECHA (2010b). Evaluation under REACH Progress Report 2009. 25 February 2010. ECHA-10-R-001-EN. http://echa.europa.eu/documents/10162/13628/progress_report_2009_en.pdf

ECHA (2010c). Companies can now check what will be published on ECHA's website from their dossiers. News Alert ECHA/NA/10/36. Helsinki, 30 June 2010. http://echa.europa.eu/view-article/-/journal_content/title/companies-can-now-check-what-will-be-published-on-echas-website-from-their-dossiers

ECHA (2010d). Member State Committee agreed on three draft decisions resulting from dossier evaluation and on the identification of eight substances of very high concern. News Alert. ECHA/NA/10/32. Helsinki, 11 June 2010. http://echa.europa.eu/view-article/-/journal_content/title/echa-member-state-committee-agreed-on-three-draft-decisions-resulting-from-dossier-evaluation-and-on-the-identification-of-eight-substances-of-very-hi

ECHA (2010e). Practical guide 5: How to report (Q)SARs. Reference: ECHA-10-B-11.1-EN. http://echa.europa.eu/documents/10162/13655/pg_report_readacross_en.pdf

ECHA (2011a). The use of Alternatives to Testing on Animals for the REACH Regulation. ECHA-11-R-004.2-EN. 29 July 2011. http://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2011_en.pdf

ECHA (2011b). Evaluation under REACH Progress Report 2010. ECHA-11-R-001-EN. 28 February 2011. http://echa.europa.eu/documents/10162/13628/evaluation_under_reach_progress_report_2010_en.pdf

ECHA (2011c) ECHA to publish more information on chemical substances. Press Release. ECHA/PR/11/09. Helsinki, 11 May 2011 http://echa.europa.eu/view-article/-/journal_content/title/echa-to-publish-more-information-on-chemical-substances

ECHA (2011d). ECHA improves transparency of dossier evaluation. News Alert. ECHA/NA/11/03 Helsinki, 31 January 2011 http://echa.europa.eu/view-article/-/journal_content/title/echa-improves-transparency-of-dossier-evaluation

ECHA (2011e). Comments from interested parties on animal testing should fulfil the information requirements of REACH. ECHA Newsletter No. 2, April 2011. http://echa.europa.eu/documents/10162/13584/echa_newsletter_2011_2_en.pdf

ECHA (2012a). Evaluation under REACH Progress Report 2011. ECHA-12-R-02-EN. 27 February 2012. http://echa.europa.eu/documents/10162/13628/evaluation_report_en.pdf

ECHA (2012b). Company names and registration numbers now published. ECHA/PR/12/31. Press release. Helsinki, 28 November 2012. http://echa.europa.eu/view-article/-/journal_content/title/company-names-and-registration-numbers-now-published

ECHA (2012c). ECHA starts publishing dossier evaluation decisions. ECHA/PR/12/35. Press release. Helsinki, 13 December 2012. http://echa.europa.eu/view-article/-/journal_content/title/echa-starts-publishing-dossier-evaluation-decisions

ECHA (2013). Evaluation under REACH Progress Report 2012. ECHA-13-A-01-EN. 27 February 2013. http://echa.europa.eu/documents/10162/13628/evaluation_report_2012_en.pdf

Embry, M. R., Belanger, S. E., Braunbeck, T. A., et al. (2010). The fish embryo toxicity test as an animal alternative method in hazard and risk assessment and scientific research. *Aquatic Toxicol 97*, 79-87. http://dx.doi.org/10.1016/j.aquatox.2009.12.008

EC – European Commission (2013a). Commission Staff Working Document: General Report on REACH accompanying the document "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. COM(2013) 49 final, Brussels, 5.2.2013, SWD(2013) 25 final.

EC (2013b). Communication from the Commission to the European Parliament and the Council on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics. Brussels, 11.3.2013, COM(2013) 135 final.

Freyberger, A., Wilson, V., Weimer, M., et al. (2010). Assessment of a robust model protocol with accelerated throughput for a human recombinant full length estrogen receptor- binding assay: Protocol optimization and intralaboratory assay performance as initial steps towards validation. *Reprod Toxicol 30*, 50-59. http://dx.doi.org/10.1016/j.reprotox.2010.01.001

Genschow, E., Spielmann, H., Scholz, G., et al. (2004). Validation of the embryonic stem cell test in the international ECVAM validation study on three in vitro embryotoxicity tests. *Altern Lab Anim 32*, 209-244.

Kroes, R., Renwick, A.G., Cheeseman, M., et al. (2004). Structure-based thresholds of toxicological concern – guidance for application to substances present at low levels in the diet. *Food Chem Toxicol 42*, 65-83. http://dx.doi.org/10.1016/j.fct.2003.08.006

Piersma, A. H., Genschow, E., Verhoef, A., et al. (2004). Validation of the postimplantation rat whole-embryo culture test in the international ECVAM validation study on three in vitro embryotoxicity tests. *Altern Lab Anim 32*, 275-307.

Rovida, C. (2010). Food for thought … Why no new in vitro tests will be done for REACH by registrants. *ALTEX 27*, 175-183. http://www.altex.ch/All-issues/Issue.50.html?iid=117&aid=1

Rovida, C., Longo, F., and Rabbit, R. R. (2011). How are reproductive toxicity and developmental toxicity addressed in REACH dossiers? *ALTEX 28*, 273-294. http://www.altex.ch/All-issues/Issue.50.html?iid=128&aid=2

Scialli, A. R. and Guikema, A. J. (2012). REACH and reproductive and developmental toxicology: still questions. *Syst Biol Reprod Med 58, 63-69*. http://dx.doi.org/10.3109/19396368.2011.648301

Spielmann, H., Genschow, E., Brown, N. A., et al. (2004). Validation of the rat limb bud micromass test in the international ECVAM validation study on three in vitro embryotoxicity tests. *Altern Lab Anim 32*, 245-274.

Taylor, K., Andrew, D., and Rego, L. (2013). The added value of the 90-day repeated dose oral toxicity test for industrial chemicals with a low toxicity profile in a high quality dataset. *Regul Toxicol Pharmacol*, in press.

van der Jagt, K., Munn, S., Tørsløv, J., et al. (2004). Alternative approaches can reduce the use of test animals under REACH. European Commission Joint Research Centre. November 2004, EUR 21405 EN.

Wagner, K., Fach, B., and Kolar, R. (2012). Inconsistencies in data requirements of EU legislation involving tests on animals. *ALTEX 29*, 302-332. http://www.altex.ch/All-issues/Issue.50.html?iid=133&aid=5

Witters, H., Freyberger, A., Smits, K., et al. (2010). The assessment of estrogenic or anti-estrogenic activity of chemicals by the human stably transfected estrogen sensitive MELN cell line: Results of test performance and transferability. *Reprod Toxicol 30*, 60-72. http://dx.doi.org/10.1016/j.reprotox.2010.02.008

Acknowledgements

Grateful thanks go to various animal protection organizations; Animal 2000, the BUAV, the BUAV Charitable Trust, Doctors Against Animal Experiments, and other members of the European Coalition to End Animal Experiments (ECEAE) for funding the authors and additional experts who assisted the authors with commenting on the proposals. Grateful thanks also are given to those additional anonymous experts who assisted with the commenting during this period.

Correspondence to

Katy Taylor, PhD
ECEAE
16a Crane Grove
London, N7 8NN, UK
Phone: +44 207 619 6979
e-mail: katy.taylor@buav.org