An answer to the EChA press release ECHA/PR/09/11, ALTEX 26, 3/09, 209-211:

That Which Must Not, Can Not Be... a Reply to the EChA and EDF Responses to the REACH Analysis of Animal Use and Costs

Thomas Hartung[1,2] *and Costanza Rovida*[2]
[1]Johns Hopkins University, Center for Alternatives to Animal Testing (CAAT), Baltimore, US and [2]CAAT-EU, University of Konstanz, Germany

For, he reasons pointedly,
That which must not, can not be.

(German: *Weil, so schließt er messerscharf,*
Nicht sein kann, was nicht sein darf.)

"The Impossible Fact"
("Die unmögliche Tatsache," 1910)
Christian Morgenstern

We appreciate the interest and discussion our study reassessing animal use and costs of REACH (Rovida and Hartung, 2009, Hartung and Rovida, 2009) has initiated. The issue has received serious press coverage in several countries. This reflects the extent of the REACH investment into consumer product safety, and it should stimulate further discussion regarding a revision of safety testing approaches, i.e. the transition toward a "Toxicology for the 21st Century." We believe that this continuing dialogue is essential to maximizing the public health protection that REACH can offer today and for future generations. Major disagreement came, however, from the European Chemical Agency (its statement was published back-to-back with our study in the last issue of *ALTEX*, EChA, 2009) and from the US Environmental Defense Fund blog (Denison, 2009). Unfortunately, both responses followed the reasoning process outlined in the Christian Morgenstern quote above, offering very little in the way of specific indications of errors in our estimates.

Neither response addressed the key questions, i.e. the impact of the larger EU and a continuously growing chemical industry, which was not reflected in previous estimates based on more than 15 year old figures, and where the testing facilities and toxicologists for the acknowledged or the even increased demand should come from. Going forward, however, we believe it makes most sense to look for areas of agreement and continue to discuss those topics upon which we do not yet agree. As a first step in that direction, we want to clarify several important points that we believe were not clear to some of the readers of our article.

1 We support REACH and want to make it feasible

Before addressing the EChA and EDF responses specifically, we feel it necessary to reiterate: we are in favor of REACH and similar programs to come. We broached the subject of potential implementation problems in order to make adaptations possible. REACH is an unprecedented program, and it is to be expected that we will learn "on the road". We have no interest in stopping reproductive toxicity testing—in fact, we at CAAT have been working for several years on Developmental Neurotoxicity Testing. REACH needs to be feasible, however, and worth the costs.

In short, the message of the article is: If we use 2-generation studies for screening large numbers of chemicals, we waste our resources on mostly innocuous substances. It may even endanger the feasibility of the whole program. The primary concerns involve throughput and the quality of results. The predictive capacities of animal tests are limited. If we carry out the same animal test in mice, rats, hamsters, rabbits etc., we get about 60% correlations. There is no reason to assume that we will do better with respect to humans in any of these species. It might be acceptable to put a lot of innocuous substances into the bin, if they have no commercial value as yet and one can choose another promising compound from many. But we now are applying this practice to our most valuable chemicals. Furthermore, the animal models were deliberately designed as precautionary. For example, we treat with maximum-tolerated doses (i.e. up to 10% of animals can die directly)—therefore, it's no wonder that many physiological functions are impaired. But can we afford to be precautionary with substances traded at volumes in thousands of tons and employed in complex use scenarios? This consideration was pointed out as prominently (Hartung, 2009) as the discussion of animal numbers (Hartung and Rovida, 2009), but it did not result in nearly as vehement a response. It appears that restricted use of high production volume chemicals may be as threatening as limiting laboratory capacities…

2 The discussion is not about costs but about testing capacities

Costs of testing are usually considered a major issue. We recently completed a study (Bottini and Hartung 2009), that put costs into perspective: the European chemical industry currently spends about 60 million € for toxicity testing per year. If our scenario holds true, the cost will be a billion euro per year, a twenty-fold increase. But the industry's turnover is 600 billion € per year in Europe. Toxicology is less than one thousandth of the turnover. And nobody has a competitive advantage, since all producers and vendors form a consortium to share the costs. The fear is more that they will be unable to comply with the legislation or that product withdrawals will occur, causing problems for downstream users. Costs and animal numbers indicate the dimension of the effort and the challenge it presents to testing capacities. We cannot quickly create the necessary test facilities; we simply do not have enough experts to do so. These costs would be justified, if the 2 gen tests could be done in a timely fashion and yielded information that was valuable to decision-making and for public health protection. But this reasoning does not give us in short-term the capacities, even if we agree that the two-generation study gets us what we need to better protect health.

3 What is the background?

REACH expected that 27,000 companies would submit 180,000 pre-registrations on 30,000 chemicals. The actual outcome surprised everyone: by the end of December 2008, 65,000 companies had submitted 2.7 million pre-registrations on 143,000 chemicals. Presumably, companies know their chemicals and production volumes on the market. We tried to correct this number downwards with some assumptions, arriving at 101,000. But we still consider this a worst-case scenario, which we did not pursue further.

We then started analyzing the reasons for higher numbers and identified the following:

- All previous studies were based on figures from 1991-1994 for chemical numbers and production volumes. At that time, the EU had only 12 member states; the number is now 27, plus 3 EFTA countries that also adhere to REACH. Furthermore, chemical production has grown by about 5% per year. This is like the interest rate on your bank account—15 years later your savings have doubled.
- At the last minute, REACH included "intermediates," which have lower test requirements.
- Due to reclassification, at least 700 substances called "no-longer-polymer," probably with high production volumes, have to be added. The number 700 is an underestimate, as their earlier registration was on a voluntary basis only.
- Estimates so far do not include the additional testing requirements for problem substances, i.e., carcinogenic, mutagenic, or reproductive toxicants (CMR), and bioaccumulating substances.
- Estimates so far do not consider that the "new chemicals" notified over the last thirty years are now produced and/or imported in volumes larger than at original notification, thus requiring additional testing.

In addition to the increase in number of substances (the 68,000 reflect only the first bullet point), the following factors had a strong impact on animal numbers:

- At the last minute, REACH included the request to consider a second species for the two-generation study, which the EChA guidance document now transformed to a one-generation study in a second species.
- The former official study did not count the offspring (pups) for the two-generation study; pups are included, however, in EU statistics.
- Assumptions regarding the use of computational methods and the existence of data, especially for reproductive toxicity, had to be corrected downwards. especially for this most demanding area.

We identified the two-generation study as the bottleneck responsible for limiting testing capacities. In Europe, two or three industrial chemicals have been tested per year over the last 28 years. Overall capacity (block-booked for drugs and pesticides) is about 50-60 chemicals per year. By our calculations, several thousand such studies would be necessary if we follow current guidance and our estimate on chemical numbers. One can now start assuming the possible increase in test capacities... This is not a study to be set up in a lab next door: it would cost more than 300,000 euro and last two years. Eighty endpoints are assessed, among them complex histopathology.

4 Response to the European Chemical Agency (EChA)

EChA's press release in response to our study suggests that only about 34,000 substances will fall under REACH, requiring just nine million animals at a cost of 1.5 billion euro. Additional information is provided only on the 2010 deadline, where 8,700-9,000 registration submissions are expected (we calculated 6,300). According to EChA, 3,500 of these submissions will be more than 1,000 tons, but an unknown number of chemicals of very high concern with similar data requirements will have to be added.

EChA notes that it "was estimated during the negotiation of the REACH legislation that nine million laboratory animals were involved." It is true that from a footnote in the assessment, the number of nine million animals can be deduced. Officially, however, the number 2.6 million, from the summary of this study, has been used throughout. It was by no mean public knowledge at the time of REACH completion that most optimistic calculations indicated a 10% increase in all animal use in Europe (or a tenfold increase of testing for chemicals) for one decade.

As we indicated, previous estimates were based on the 12-member EU of 1991-1994. EChA "concludes that the original numbers of the estimates still hold" but does not explain how that could be so, given an estimate based on figures more than 15 years old without correction for EU expansion in the interim. The original estimate does not include the increase in EU membership from 12 countries to the current 27, plus 3 of the

EFTA countries and the accession countries applying REACH. In addition, industrial growth over 20 years has doubled this industries' production (figures 1 and 2) (Eurofund, 2005). EChA also does not explain how the numbers can hold when additional substance groups ("no longer polymers" and "intermediates") and test requirements (second species for reproductive toxicity) were only added two years later at the finalization of legislation. Furthermore, we have analyzed the sources for "existing data" referred to in the original estimate and found them much more limited than had been thought. We have also analyzed the current guidance of EChA regarding the waiving of testing, finding very few such options as compared to the assumptions in the official estimate. Again, it is not clear why this does not require a correction of the estimates. EChA states that for the 2010 deadline "*slightly over 9,000*" substances are expected, including 3,500 of the most demanding class: >1,000 ton. How can the old estimates still hold, when they foresaw only 2,704 registrations for this tonnage class but neglected problem substances and intermediates, as well as at least 700 no-longer-polymers? Assuming only these 3,500 chemicals and addressing only reproductive toxicity testing, we can easily calculate that: each substance requires tests according to TG 414 (784 animals and 63k €) and 416 (3,200 animals and 328k €), adding up to 13 million animals and 1.4 billion €. We have shown that such studies are not available (confirmed by industry: "Nobody carries out such studies without regulatory requirement"). We also demonstrated that the guidance gives essentially no opportunity to waive testing, and alternative approaches in this field do not exist. This alone exceeds the estimations of EChA for all animal use and represents the cost estimates suggested by EChA for the whole program. More than 30,000 other substances and 17 animal tests still have to be included.

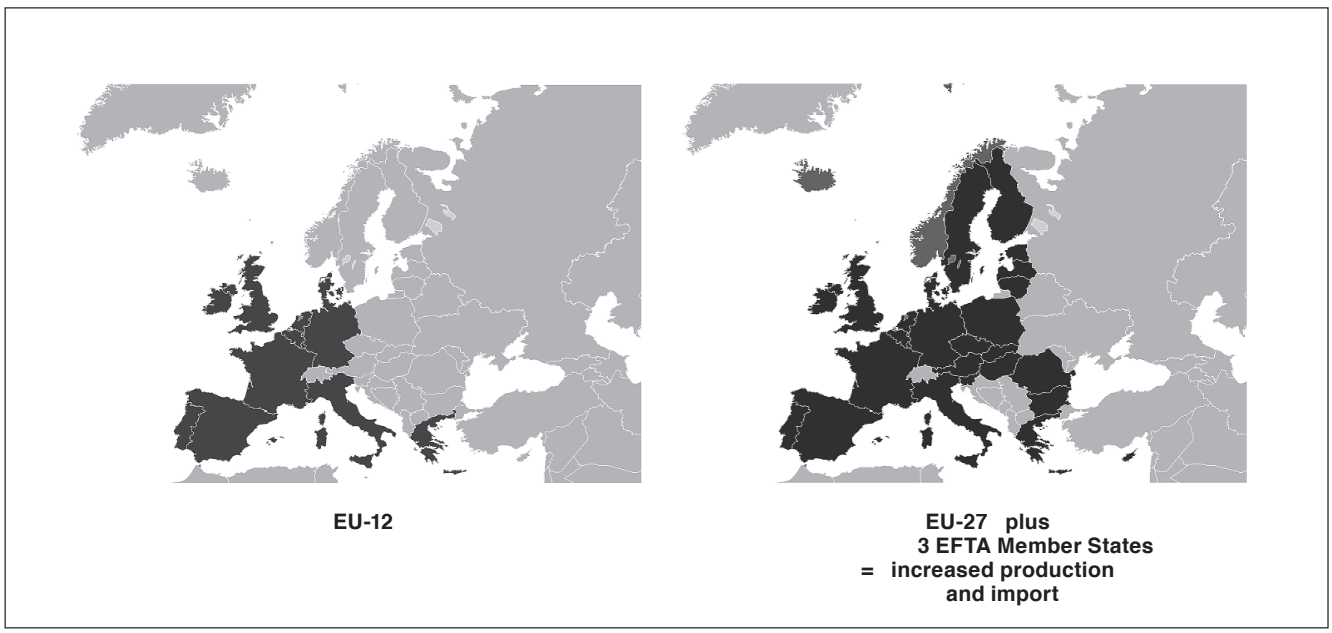
EChA states that we "*suggest that industry is almost starting from scratch, i.e. that hardly any data is available at all… This is of course not correct*." We have analyzed this in depth for the most relevant area in our study, reproductive toxicity (which involves more than 70% of the costs and 90% of the animals). We have very clearly shown that, for precisely this testing, no data exist, and no alternative methods – be they (Q)SAR, read-across, or *in vitro* – exist. The published EChA test guidance for industry does not foresee relevant waiving opportunities. Thus, unfortunately, at this stage, the argument is correct that data are not available and cannot be made available by other means than animal tests in the only relevant area.

4 Response to the US Environmental Defense Fund (EDF)

We appreciate the attention our study received from Dr. Denison in his blog on the EDF website and are impressed by how quickly (one day after our publication) this response was posted given the complex situation. We referred like him to the "toxicological ignorance" toward old chemicals and the need to address this. We are personally devoted to the implementation of the Toxicity in the 21st Century approach, which from our point of view provides an answer to the problems raised by REACH. We agree with Dr. Denison's initial statement, that "*during the nearly decade-long debate over the final text of REACH, animal welfare advocates extracted major concessions from the EU*." He is incorrect, however, in asserting that chemicals in REACH below 10 tons are not tested in animals: both acute toxicity and sensitization tests are required by Annex VII of the legislation for substances between 1 and 10 tons.

The EDF blog questions whether *more than 100,000 synthetic chemicals are used in consumer products*. Later, however, they correctly refer to registers with 84,000 and 100,000 substances, but simply miss the fact that many substances with

Fig. 1: All previous estimates based on a database from 1991-1994



production volumes below that required to enter into these registries are nonetheless commercialized and in present in consumer products. The EPA alone receives about 2,000 TSCA premarketing notifications and requests for exemption per year, adding considerably e.g. to the EU 1981 inventory of 100,000 over three decades.

A repeated allegation in the EDF blog is that we base our analysis on the preregistration data, which do not allow such analysis. Indeed, the preregistration surprise (180,000 preregistrations were expected from 27,000 companies on 30,000 chemicals; in reality, 2.7 million preregistrations were received from 65,000 companies on 143,000 substances) prompted our reanalysis. We concluded, similar to the European Chemical Agency in their response, that this forms no solid basis for estimates. In effect, we do not understand Mr. Denison's allegation, as the study comes to exactly the same conclusion: that, after analysis, the preregistration does not allow the estimate we aim for. We made some effort to bring this number to more realistic lower figures, but that left us with 101,000 substances (which would roughly correspond to animal use in the order of 141 million). We did not pursue this. We analyzed the hard facts, however, which explain the higher numbers (see above). This shifts old and new (post-1981) chemicals to higher production volume groups. Our scenario also sees two-thirds of chemicals below 10 tons, so it is not clear what Dr. Denison opposes.

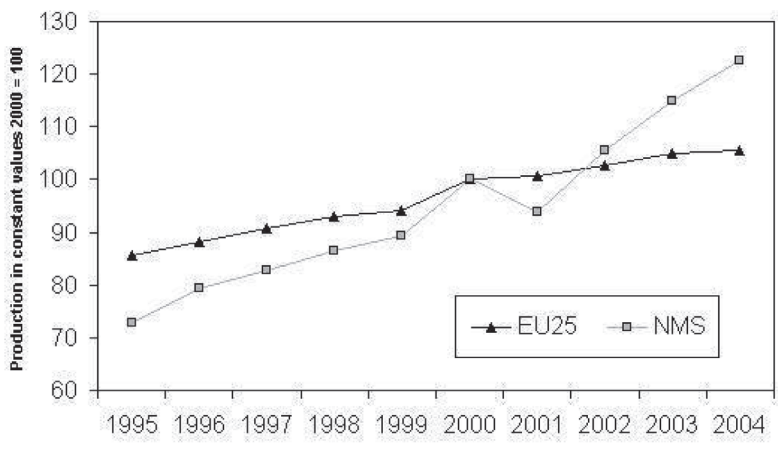
The statement "*The authors characterize the estimate they derived from pre-registration lists as 'worst-case,' yet they use it as the primary basis for their analysis*" is wrong. As explained above, the evaluation is based on the 1991-1994 figures (not disputed by anyone) corrected for growth of EU and chemical industry. Dr. Denison appears to understand and accept this. However, he states further: "*The notion that recent growth in the sales and volumes of chemicals in the EU was derived entirely by introduction of new chemicals, and not primarily by increases in production of existing chemicals, is contradicted by all empirical evidence*." There is no such assumption in our study. About 5,000 new chemicals were registered in the EU in the last 28 years, mostly specialty chemicals, and they cannot account for the recent growth rates. Dr. Denison is correct in stating the increase results primarily from an increase in production of existing ("old") chemicals. This was exactly our assumption.

The blog also questions the number of 3,200 animals per chemical in a two-generation study. We have used this animal number, suggested by the German Federal Institute for Risk Assessment, but we expressed some doubt here ourselves as correctly cited by the blog. The impact on the final result is less than 12%.

Dr. Denison concludes: "As noted at the start, this study has used numerous *demonstrably false or highly questionable assumptions, one piled on another, to grossly inflate the number of chemicals requiring testing under REACH, and the number of animals involved*." Given our replies above, this statement is difficult to understand. The lion's share of test demands comes from HPV chemicals and reproductive toxicity testing. We assume 6,286 substances, OECD lists more than 5,000, and EChA expects 8,730-9,000. Even though the latter figure includes isolated intermediates, where is the inflation? The notorious test for animal use was calculated according to German BfR with 3,200 animals; even the quoted 2,600 would bring numbers down by only 12%. Again, where is the inflation?

Furthermore, throughout this study we have used optimistic assumptions for the 68,000 chemical (6,286 HPV) scenario. Thus, we do not understand the fierce comments. We share the desire to assess as many environmental chemicals as reasonably possible. Animal use is only one of many considerations here. Our numbers, however, address feasibility, testing capacities, throughput, etc. This is not meant to let "industry off the hook." We want to identify the bottlenecks that must be amended. Our comments are intended to offer some realistic opportunities.

Fig. 2: Annual average growth of chemical industry in Europe: 5%



Doubling since 1991-1994 plus ongoing growth…
(figure reproduced from Eurofund 2005 with permission, http://www.eurofound.europa.eu/emcc/content/source/eu05021a.htm?p1=sectorfutures&p2=eu05020a&p3=Chemicals)
NMS = new member states; EU-25 = EU member states before Romania and Bulgaria joining

Conclusions

We hope that EChA is right, because we very much want REACH to succeed. We believe, however, that we have identified an important bottleneck in the execution of REACH, which could have been addressed some years earlier. We propose a consensus meeting with EChA to evaluate the actual numbers and the possible conclusions to be drawn.

We hope that our study helps build momentum for a revision of current practices in regulatory toxicology. Europe needs to develop a program similar to the new US EPA toxicity testing strategy from March 2009 adopting the 2007 NAS report. We appreciate the interest and discussion our study has generated, which reflects the broad scope of this investment into consumer product safety. This will stimulate further discussion regarding a revision of safety testing approaches, i.e. the transition toward a "Toxicology for the 21st Century." Apparently, EChA has paid increased attention to alternative approaches since our publication. This is more than overdue, as increased use of alternatives is a key goal of REACH (see article 1). In practice, however, this does not always hold. For example, both the possibility of using existing data and the possibility of doing *in vitro* tests are seriously hampered by the design of IUCLID 5 (the software used for submitting registration dossiers).

We need to change our approach. This could be done with reasonable investment in a decade; then we could start with high-throughput testing. This would not prevent all other parts of REACH from proceeding apace. It was essential to demonstrate the impact of current test approaches. This theoretical scenario will not happen because it cannot happen. Then start us on a new path.

The question is, how to get information that regulators can use to make good decisions – i.e. eliminating the bottleneck. REACH is advancing this by shifting the burden - compounds have to make their case for safety before they are widely used. For those already in the market, there cannot be a free pass just because they have not yet been directly implicated in harming humans and the environment. Lack of knowledge is not a substitute for proof of safety.

What alternatives are there to reproductive toxicity testing? The options include:

- Testing only suspicious chemicals first. Currently the main trigger is production volume; We should at least prioritize the suspicious substances and leave the others for later, when high-throughput strategies are developed.
- Using an extended one-generation study. It has been shown that very little additional information comes from studying the grandchildren of the exposed animals; the respective OECD test guideline is close to finalization, though some European (!) member states still block it. Even worse, EChA representatives at the respective OECD meeting in October 2009 declared that this study would not be applicable (Gilbert, 2010).
- Changing the guidance to make the test in a second species less frequent. Developing *in vitro* approaches—e.g. 80-90% of the classifications of chemicals in two-generation studies are based on testis toxicity, for which promising tests exist.

Regulators need to understand that the issue is not only animal numbers; feasibility is even more important. The requisite test facilities are not available, and it is not possible to create them in time. About 70 two-generation studies in one species have been carried out for industrial chemicals over the last 28 years; the overall capacity in Europe is 50-60 substances per year, required almost completely for drugs and pesticides. Our analysis showed several thousand such studies currently requested for REACH.

Nor do we have the toxicologists. Our analysis should not be misread as driven by purely ethical or financial concerns—we are concerned about a serious bottleneck that could block the progress of a program we want to see happen. The need to address all these chemicals is clearly warranted, as has been put forward by REACH. Implementation of this program, however, will require more activity in Europe. The most relevant developments are actually occurring in the US, with the Toxicology in the 21st Century activities. We will not arrive at our scenario, however, because it simply is not feasible. We only show where the current guidance arrives for the minimum number of substances, i.e. non-feasibility. We pinpointed a single animal test as the bottleneck for REACH. This can be taken as a starting point for amending the strategy.

Regardless of the numbers or other differences, there is obviously an enormous amount of testing to carry out. We must have a system in place that can deliver high quality toxicity testing data so that we can make decisions that protect public health. We continue to believe that the best and fastest way to carry out such testing is in a high throughput, *in vitro* approach with minimum confirmatory testing *in vivo*. But this will not work if relatively simple feasibility calculations to demonstrate reality are simply dismissed.

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