OPINION

Chemical regulators have overreached

The costs — both in animal lives and euros — of the European REACH legislation on chemical testing are escalating. **Thomas Hartung** and **Costanza Rovida** argue for a suspension of certain toxicity tests.

SUMMARY

- Complying with REACH may use 20 times more animals and cost 6 times as much as previously estimated.
- Regulatory toxicology has neither the high-throughput methods nor alternatives to animal testing to cope.
- A moratorium on reproductive toxicology tests would be wise, until alternatives are approved.

More than 100,000 synthetic chemicals are used in consumer products. In 1981, both the United States and the European Union (EU) introduced comprehensive safety evaluations for novel chemicals coming on to the market. However, existing chemicals represent about 97% of those in use today and 99% of the production volume. Safety testing data are needed for most of these 'old' chemicals. Over the next decade, the EU's 2006 Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation aims to assess the toxicity of all chemicals sold in Europe in quantities of more than one tonne per year.

As toxicologists, we support the aims of REACH — it is the biggest investment into consumer safety ever. However, we feel that legislators have underestimated the scale of the challenge. Our report[1], released today by the Trans-Atlantic Think Tank for Toxicology at John Hopkins University in Baltimore, Maryland, is the first analysis of REACH costs to be published in 5 years. It is based, among other things, on the pre-registration of chemicals, which ended in 2008. It was expected that 27,000 companies would submit 180,000 pre-registrations on 29,000 substances. Instead, some 65,000 companies made more than 2.7 million pre-registrations for in excess of 140,000 substances. REACH aims to complete data collection on these substances by 2018. In recent decades Europe has tested some 200–300 new chemicals each year, making REACH an unprecedented challenge. Toxicologists do not have the appropriate tools — whether high-throughput methods or acceptable alternatives to animal testing — to meet these expectations.

Official estimates

When REACH was negotiated, between 2001 and 2005, several attempts were made to estimate the costs of the regulation, both financially and in terms of the number of animals used for toxicity testing. Officially, the EU is relying on estimates suggesting probable costs[2] of €1.6 billion (US$2.3 billion) — range of estimate €1.2 billion–€2.4 billion — and 2.6 million animals[3] (range of estimate 2.1 million–3.9 million). These estimates are based on data on chemical production from 1991 to 1994.

Our report relies on several new public sources of information that allow these estimates to be reassessed. Among the factors that have increased costs and animal numbers are changes to the final legislation, such as the inclusion of reaction intermediates, and changes to the guidance for industry on how to test. The EU also now contains 27 members (plus three non-EU countries that adhere to REACH), compared with the 12 members on which the 1994 data were based. Factors that could, in principle, reduce the costs of REACH include progress in the availability of alternative methods to animal testing and availability of safety data from other sources, such as voluntary industry databases.

The latest published list of REACH chemicals contains 143,835 substances that are supposed to be fully registered, each requiring a chemical-safety report. However, this figure is likely to be an overestimate because of redundancies or mistakes made in deposition. The final number will be somewhere between 143,835 and the official estimate of 29,342 substances[2]. We have re-evaluated the estimates for the number of *in vivo* tests required by REACH. The plausibility of our assumptions and calculations was checked by eight experts from industry, academia and regulatory authorities[1].

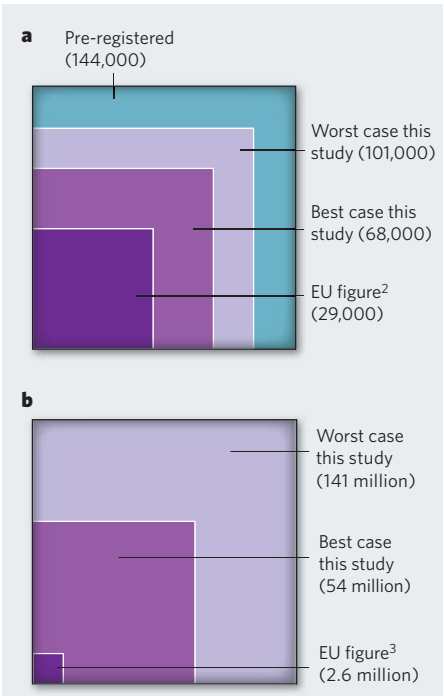

Figure 1 | Numbers too large to handle. Estimates for the numbers of chemicals (**a**) and of animals (**b**) expected to be needed for compliance with REACH legislation. Our best-case estimates[1] of 68,000 substances and 54 million animals are far above the official EU estimates.

We focused on the expansion of the EU and how that affects chemical production. Since 1994, the chemical industry in Europe has grown by about 5% per year, almost doubling its production and sales size by 2008, and the expansion of the EU further increases chemical production volume by 18%. This growth leads to an estimate of 68,000 chemicals falling under REACH, and this is the lower (optimistic) estimate in our study (see Fig. 1).

Optimistic assumptions

These 68,000 chemicals were then modelled under REACH testing requirements. Total chemical production or marketing volume in Europe determines the testing requirements, which are then modified by the specific toxicity and usage profiles of the substances. In all cases, our modelling used the most optimistic assumptions (minimal animal numbers per test and neglecting the triggering of additional tests). We ignored the need for confirmatory retesting as well as tests that have not yet been defined for endocrine disruption, respiratory irritation, respiratory sensitization and developmental neurotoxicity. We also considered alternative approaches (including computational toxicology) far enough along in the validation and acceptance process to have an impact on the execution of REACH.

Our results suggest that generating data to comply with REACH will require 54 million vertebrate animals and cost €9.5 billion over the next 10 years. This is 20 times more animals and 6 times the costs of the official estimates. By comparison, some 90,000 animals are currently used every year for testing

new chemicals in Europe, costing the industry some €60 million per year. Without a major investment into high-throughput methodologies, the feasibility of the programme is under threat — especially given that our calculations represent a best-case scenario. In 15 months' time, industry has to submit existing toxicity data and animal-testing plans for the first of three groups of old chemicals.

Disaster prevention

Our modelling shows that the studies contributing most to animal use and costs are from reproductive-toxicity testing — the effects of the chemicals on reproductive functions — representing about 90% of projected animal use and 70% of projected costs (see Fig. 2).

In the short term, we recommend that testing requirements for reproductive toxicity are urgently reviewed with the goal of prioritizing the most suspicious chemicals, reviewing test strategies and allowing more time to carry out the programme.

Much of the projected increase in animal use is the result of the two-generation study for reproductive toxicity, in which toxic effects are studied in the offspring of exposed rats and then in a second generation. The EU animal estimate[3] did not include offspring (despite their inclusion in EU animal-use statistics). This method consumes an average of 3,200 rats per chemical compared with 784 animals for a one-generation study with costs increasing five-fold. Moreover, changes to REACH introduced the unusual requirement of repeating the two-generation study in a second species, further increasing animal use and costs.

There are many limitations associated with the two-generation study in a second species (not least an increase in false positives) despite marginal gains in safety information[4]. A high number of false positives (perhaps as much as 40–60%) after REACH testing might lead to the expensive withdrawal of widely used chemicals, and cause unnecessary fears in consumers[5]. Over the past 25 years, only 2–3 industrial chemicals a year have been tested in two-generation studies — with REACH the challenge will be to test several hundred chemicals per year. We urgently need alternatives.

Despite concerted efforts, no acceptable alternatives to reproductive-toxicity testing have emerged, or are likely to be validated by 2018. Computational approaches are also limited by the complexity of reproductive toxicity and because half of the REACH chemicals are mixtures, inorganic, salts or contain metal atoms, rendering toxicity less predictable.

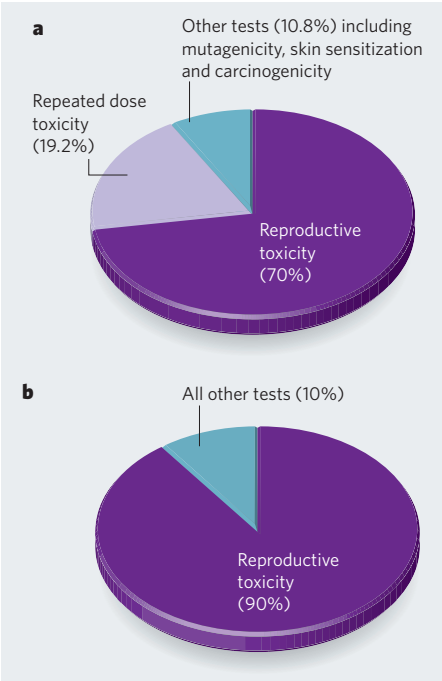

Figure 2 | The biggest piece of pie. Reproductive-toxicity testing makes a huge contribution to the estimated costs (**a**) and the number of animals used (**b**) for compliance with REACH legislation.

The only real alternative is an extended one-generation study, guidelines for which are under development by the Organisation for Economic Co-operation and Development (OECD). This approach extends the observation period for the first-generation offspring with additional testing on developmental neuro- and immunotoxicity if triggered by test results.

We favour replacing the two-generation study with the OECD test, which would, in our estimation, reduce animal use for this test by 40–60% and overall animal use by REACH by 15%. We recommend a moratorium on reproductive-toxicity testing, or at least limiting testing to the most suspicious substances, until the OECD guidelines are completed and alternative strategies for screening lots of chemicals are available. There are political as well as technical barriers to overcome, however — two EU member states are against the extended one-generation study unless the additional testing is mandatory, which would eliminate any cost or animal saving.

> "Regulatory toxicology needs to move into the twenty-first century."

In the medium term, a different approach is needed. An initiative similar to the €50-million partnership between the European Commission and the cosmetic industry (Colipa), for research into alternatives for systemic toxicity, is needed for reproductive toxicity. Colipa includes trans-Atlantic partners and the strong integration of computational and high-throughput approaches. The only serious EU investment into reproductive toxicity is the ReProTect project, which ends this year and should be continued.

In the longer term, regulatory toxicology needs to move into the twenty-first century[5] — many core methods have remained largely unchanged for 40 years. The US Environmental Protection Agency understands this need. It introduced a new toxicity-testing strategy in March. The aim is to move to high-throughput methods based on identified pathways of toxicity with human cells, fish eggs, invertebrate species and computational methods. Instead of exposing animals to high doses and observing a multitude of possible effects, precise questions can be asked about whether sensitive physiological processes are disturbed.

REACH is not the only chemical testing programme coming online — others are planned in the United States, Japan and Canada — but it is the biggest and the first to come into effect. Lessons learned from REACH should be heeded by the others. Our report might be bad news for REACH as currently imagined, but it is also an opportunity. Given the EU's expansion, the growth in financial costs and animal use was inevitable — and would have been revealed in time as indicated by the pre-registration data. We are showing the challenges that lie ahead. Armed with this knowledge of the shortcomings of the current approach, regulators and industry can work together to protect consumer safety without using an excessive number of animals for toxicity testing. ■

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