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Companies must assess the toxicities of their products, but are there enough data in the pipeline?

TOXICOLOGY

# Data gaps threaten chemical safety law

*European companies are not providing robust information to regulators or alternatives to animal experiments.*

BY NATASHA GILBERT

Europe's sweeping chemicals law, sometimes described as its most complex piece of legislation, was meant to regulate thousands of common substances to protect people and the environment from harm. But four years after REACH (registration, evaluation, authorization and restriction of chemicals) came into force, the burdensome, costly law is beginning to look strangely toothless. Evidence seen exclusively by *Nature* shows that companies have failed to fill gaps in safety data — and European regulators have done little to pressure them.

REACH requires companies that produce or sell chemicals in the European Union to register toxicity data on the compounds and outline any new tests needed to clarify their biological effects, especially on reproduction and the development of offspring. Before REACH, these costly tests — multigenerational rat studies can cost up to €2 million (US$2.8 million) per chemical — were rarely performed in Europe because the previous law required them only for substances produced in very large quantities. Switching to the REACH system was predicted to trigger millions of extra animal tests (see *Nature* **460,** 1065; 2009), so companies were also expected to propose alternative methods wherever possible to minimize the use of animals.

The legislation requires companies to compile all safety information and planned tests into dossiers, one for each chemical, and submit them to REACH's regulator, the European Chemical Agency (ECHA), based in Helsinki. The ECHA has little power to enforce the regulations, however, leaving any penalties for non-compliance to individual governments.

Dossiers for more than 3,200 of the most ubiquitous chemicals have been filed with the agency, with more to come over the next seven years.

Costanza Rovida, a consultant chemist based in Varese, Italy, has now analysed summaries of 200 of these dossiers, chosen at random. She plans to analyse a further 800 summaries and present the findings at the 8th World Congress on Alternatives and Animal Use in the Life Sciences in Montreal, Canada, in August. But already, Rovida has uncovered a host of problems.

Commissioned by the European arm of the Center for Alternatives to Animal Testing (CAAT) at the University of Konstanz, Germany, her research shows that many dossiers rely heavily on old data and fail to suggest new tests, and that few include any mention of non-animal testing methods (see 'Mind the gap'). The ECHA acknowledges that there is room for improvement. "Industry has not taken full responsibility for the quality of data," says Jukka Malm, director of regulatory affairs at the ECHA.

The agency plans to check all dossiers that include proposals for new animal studies — but will look at only 5% of those that have no test proposals, a stipulation set out in the law. To some observers, this hands-off approach highlights a potential weakness in the system. "The purpose of REACH is to get data on many chemicals," says Thomas Hartung, director of the CAAT at its US headquarters in Baltimore, Maryland. "But it is clear that industry wants to avoid testing." If only 5% of dossiers that do not propose tests are checked, "we will not really get a lot of new information," he says.

## CREATIVE APPROACH

Rovida found that roughly one-third of the dossiers provide animal data on reproductive and developmental toxicity. But much of the information is from old studies — some more than 20 years old — "that don't meet today's testing standards", says Rovida.

Given the existing paucity of animal data on reproductive and developmental toxicity, toxicologists had expected many of the dossiers to propose new studies. However, Rovida says that her analysis shows that few new tests are being proposed to reproduce or challenge the findings. Some 36% of the dossiers she looked at fail to make conclusive judgements about the chemical's reproductive or developmental toxicity (see 'Chloroaniline') — but only 7% and 7.5%, respectively, propose new animal studies to clarify these effects.

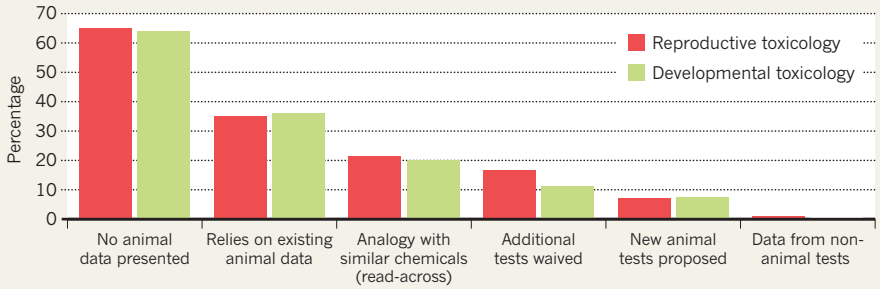
Sebastian Hoffmann, a toxicologist based in Cologne, Germany, who works as an industry consultant on REACH, says that companies seem to have been "creative" in interpreting REACH's demands for them to fill data gaps.

Rovida also found that of the 200 dossiers she examined, only two had provided data from non-animal tests. "This shows that they are not serious about alternative methods," she says.

SOURCE: C. ROVIDA

## MIND THE GAP

About two-thirds of the 200 REACH chemical-safety information dossiers examined do not contain data from animal tests of the chemical in question, but even fewer propose tests to fill that data gap.




"This is not what I hear from our companies," counters Erwin Annys, director of REACH and chemicals policy for the European Chemical Industry Council (CEFIC) in Brussels. "We are not sure that the findings on this small sample are representative," he says. "We remain active in promoting non-alternative testing methods and are looking to get a better understanding by more companies on this issue."

Robert Kavlock, director of the National Center for Computational Toxicology at the US Environmental Protection Agency, says that companies are in a bind because few non-animal testing methods are "scientifically acceptable or ready for regulatory use".

***"Industry has not taken full responsibility for the quality of data."***

Rovida also found that companies are relying heavily on a technique known as read-across, in which the effects of a substance on human health are predicted by considering the effects of structurally similar chemicals. The REACH legislation, and guidance from the ECHA, is generally supportive of this, as long as it provides sufficiently convincing conclusions.

For around 21% of the dossiers studied by Rovida, reproductive toxicity was judged solely using read-across methods. Although read-across may be appropriate for simple chemical and physical properties, toxicologists are far less positive about its validity for assessing reproductive and developmental toxicity, especially in the absence of other animal test data on the substance. "Whether read-across will prove to be robust is an open question," says Alan Boobis, a toxicologist at Imperial College London. "It will come down to companies proposing good arguments for why read-across is sufficient to make a judgement. But if there are no animal data, I don't know how they can make a case."

The legislation does allow companies to suggest waiving reproductive and developmental toxicity tests, but only if people are unlikely to be significantly exposed to the substance, or if it is already known to damage DNA or gametes. In the dossiers studied by Rovida, companies suggested waiving these tests for 16.5% and 11% of substances, respectively. "Waiving is quite broadly applied, even though the guidance is extremely strict about when its use is valid," says Hartung.

REACH is far from being useless, emphasizes Rovida. It has forced companies to collate a great deal of existing information about the chemicals they handle, which is an improvement on the situation before REACH. But as a mechanism for collecting and generating data on reproductive and developmental toxicity, it is "a complete failure", she says. What's more, "there is no effort to promote alternative methods. Very little is done to avoid some animal tests," Rovida says.

Hartung hopes that the revelations will build momentum to develop alternative non-animal tests. But Boobis predicts that many more *in vivo* toxicity tests are inevitable. "We have seen this in other areas, where, despite a commitment to reduce animal use where possible, the need to protect public health overrides the lag in scientific development of credible alternatives," he says.

On 30 June, the ECHA published a progress report on REACH that echoes some of Rovida's findings. "The quality of many of the chemical safety assessments is of concern," the report says. In particular, it notes that the quality of the scientific arguments put forward by industry to justify using read-across, and to waive additional safety tests, is "not high enough".

The European Commission, which was involved in drawing up the REACH policy, says that the overall message of the ECHA's report is that the system is working well. "Most of the issues raised in the report can be improved by more efficient implementation," a spokesperson told *Nature*.

Although the ECHA lacks enforcement powers, it can ask companies to provide more toxicity data and request new studies if it judges dossiers to be incomplete. If companies don't comply, the agency can report them to national authorities. "Companies are now waiting to see if the ECHA tells them to do extra studies," says Hartung. He argues that the ECHA should check all the dossiers it has received. But Malm says that the ECHA does not have enough resources to check more than 5% of dossiers without test proposals — and even that will be a challenge. Instead, the ECHA will ask industry to "take a serious look back at the quality and improve it proactively rather than wait for us to do compliance checks".

"It is not a failure of REACH," Malm adds. Because this is the first phase of REACH's implementation, and companies are still learning the system, "we should have expected a lower quality of dossier to start with." ■

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## CASE STUDY

### *Chloroaniline*

The summary dossier on 2-chloroaniline, an aromatic amine used to manufacture pesticides and pharmaceuticals, reports toxicity data that it describes as "conclusive", but says that they are "not sufficient" to classify the substance as toxic to reproduction. It also says that data are "lacking" on whether toxic effects can be passed on to offspring through the mother's milk.

Yet the summary suggests that children of fathers exposed to aromatic amines before conception are at higher risk of brain tumours (J. R. Wilkins and T. Sinks *Am. J. Epidemiol.* **132,** 275–292; 1990). It also cites what Costanza Rovida, a consultant chemist in Varese, Italy, describes as a "robust" (but unpublished) study showing that the substance caused malformations in rats.

The summary dossier does not suggest new tests to investigate 2-chloroaniline. **N.G.**

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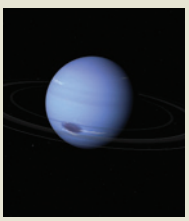

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