



Minimising animal use in the implementation of REACH

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The European regulation relating to the safe use of chemicals - REACH (the Registration, Evaluation, Authorisation and Restriction of Chemicals) entered force on 1st June 2007, after six years of negotiation. A total of 146,000 chemicals have been pre-registered with the European Chemicals Agency as of May 2009, although ultimately only 30,000 of these may require full registration dossiers (Pedersen et al. 2003). The numbers of animals estimated to be required under REACH for these chemicals at the last assessment by the European Commission was 8-13 million (Anon 2006), taking into account existing data and use of QSARs, read across and non-animal methods.

There has been increased research into alternative methods for the toxicological endpoints required under REACH but now there are immediate deadlines for registration, beginning with 2010 for chemicals produced in excess of 1,000 tonnes. It is therefore imperative to disseminate the practical, common-sense, but nonetheless scientifically sound steps that can be made to reduce animal use today, irrespective of the presence of any alternatives that may or may not become validated over this time.

Here we list some of the most significant animal reduction strategies that can be employed now based on avoidance of duplicative testing and utilisation of alternatives that have been most recently validated. The figures are maximum animal savings that could be achieved, including foetuses and under the assumption that there is no existing data, read across or exposure based waiving, which is unlikely. There have been estimates of the percentage of chemicals that already have full data sets; ranging from 14% (Allanou et al. 1999) to 50% (Bradbury et al. 2004) for High Production Volume (HPV) chemicals and 17-22% for lower production chemicals (see Pedersen et al. 2003), however, the true extent will not be known until REACH phase-in registration is complete. Following pre-registration, there are also concerns that the number of chemicals requiring full registration is likely to be significantly higher than the estimates used here, which are rounded up from Pedersen et al. (2003): Annex VII= 20,000, Annex VIII= 5,000, Annex IX= 3,000 and Annex X=3,000.

Smart testing includes:

- Testing requirements are cumulative across the Annexes. In the absence of existing data and adaptations for testing, avoid duplicative testing by not conducting the less comprehensive/shorter term test if the more comprehensive/longer term test is required or proposed
- Utilise all validated alternatives even if they do not appear in the Test Methods Regulation or the Annexes
- Maximise the use of adaptations under Column 2 of the Annexes, e.g. testing not possible, or scientifically not necessary. E.g. do not further test volatile, corrosive or mutagenic chemicals, do not test the aquatic toxicity of insoluble chemicals or those that hydrolyse to known chemicals
- Maximise the use of adaptations under Annex XI including use of existing data, *in vitro* and *in silico* tests within a weight of evidence approach, and exposure-based arguments
- Care should be taken when choosing the route of exposure (having regard to the likely route of human exposure) to avoid studies on multiple routes
- Use intelligent testing strategies (see REACH Guidance and EU FP projects such as OSIRIS)



References

- Allanou et al. 1999. Public availability of data on EU HPV chemicals. JRC, European Commission Report. EUR18996.
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- Bremer et al. 2007. The development of new concepts for assessing reproductive toxicity applicable to large scale toxicological programmes. Current Pharmaceutical Design 13(29): 3047-58
- Hoffmann et al. 2005. Skin irritation: prevalence, variability, and regulatory classification of existing *in vivo* data from industrial chemicals. Regulatory Toxicology and Pharmacology 41(3):159-66.
- Pedersen et al. 2003 Assessment of additional testing needs under REACH: Effects of (Q)SARS, risk based testing and voluntary industry initiatives. JRC, European Commission EUR 20863.
- Sandusky et al. 2006. Strategies to reduce animal testing in US EPA's HPV Programme. Altex 23, World Congress special Issue, 117-9.

Strategy	Maximum animal saving within Annex
Annex VII (1-10 tonnes)	
Skin sensitization: Perform reduced Local Lymph Node Assay (rLLNA) (max 12 animals) instead of original LLNA (max 20 animals)	Annex VII, VIII, IX and X 248,000
Annex VIII (10-100 tonnes)	
Skin irritation: Use <i>in vitro</i> skin models for skin irritation (Test method B46-Aug 2009) instead of <i>in vivo</i> skin irritation method (max 3 animals)	Annex VIII, IX and X 33,000
Eye irritation: Test for skin irritation first using <i>in vitro</i> method and do not test for eye irritation if identified as an irritant (likely 10% chemicals) (Hoffman et al. 2005) Use <i>in vitro</i> method (Annex VII) and do not progress to <i>in vivo</i> method if test is positive (likely 20% remaining chemicals) (Hartung pers comm) (max 3 animals)	Annex VIII, IX and X 2,640
Acute toxicity: Derive an LD50 from the repeat dose study (if already conducted) (Bulgheroni et al. 2009) or use MTD within a repeat dose study if this has to be conducted (max 20 animals)	Annex VIII, IX and X 220,000
Repeat dose, screening for reproductive/developmental toxicity: use a combined study (OECDTG422, max 675 animals) instead of separate reproductive screening (OECDTG421, max 675 animals) and repeat dose (OECDTG407, max 60 animals) studies	Annex VIII only 300,000
Acute aquatic toxicity: Perform Upper Threshold Concentration (UTC) step-down approach acute fish toxicity testing strategy (saving 70% of max 49 animals)	Annex VIII, IX and X 377,300
Annex IX (100-1000 tonnes)	
Repeat dose toxicity: If proposing a 90-day study (OECDTG408, max 100 animals) do not also conduct the 28-day (OECDTG407, max 60 animals) study	Annex IX and X 360,000
Developmental and reproductive toxicity: If proposing a pre-natal development study (OECDTG414, max 880) or a 2-gen reproductive study (OECDTG416, max animals 1680), do not also do the reproductive screening study or the combined study above (max 675 animals)	Annex IX and X 4,050,000
Consider the evaluation of effects on reproductive organs during the proposed 90 day study (OECDTG408, max 100 animals) to omit the need for a 2-generation study (OECDTG416, max 1680 animals), not needed if no effects are seen (likely 95% chemicals, see Bremer et al. 2007)	Annex IX only 4,788,000

Action required:

It is imperative that industry and regulators appreciate the steps that can be taken now to mitigate animal use. Promotion of these ideas is required; the experience under the HPV programme was that animal protection groups were able to facilitate significant animal savings based on such common sense strategies (Sandusky et al. 2006). Savings of animals are greatest if care is taken over the order of the conduct of developmental and reproductive toxicity tests. The omission of the screening test if the more comprehensive tests are proposed has the potential to save over 4 million animals. Not conducting the 2-generation study unless alerts are found within a repeat dose study (as recommended in Annex IX 8.7.3) could save a further 5 million animals.

ECHA and Competent authorities need to send out a clear message that these strategies are acceptable and must be used for REACH registration dossiers.