Inconsistencies in data requirements of EU legislation involving tests on animals

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Outline

- Introduction
- Problem
- Project

  → Project stages
  → Results
  → Outlook

Animal testing in the EU – statistics

EU 2008:
12 million vertebrates

Toxicological and other safety evaluations represented 8.7% of the total number of animals used for experimental purposes.

with an upward trend

EU legislation that involves animal testing

- REACH
- Plant protection products regulation
- Biocidal products regulation
- Novel Foods regulation
- Food safety (marine biotoxins, etc.)
- Cloning, GMO foods
- Pharmaceuticals

Protection of animals in the EU

Animal Welfare:

- Treaty on the Functioning of the European Union (TFEU), amended 2009:
  *"**In formulating and implementing the Union's** agriculture, fisheries, transport, internal market, research and technological development and space **policies, the Union and the Member States shall, since animals are sentient beings, pay full regard to the welfare requirements of animals**, while respecting the legislative or administrative provisions and customs of the Member States relating in particular to religious rites, cultural traditions and regional heritage."*

Animal experiments - legal situation

- Directives 86/609/EEC and 2010/63/EU
- European Convention ETS 123
- Animal Welfare Acts of the EU Member States

Common basic principles:

- Each experiment has to be essential for a given purpose
- The number of animals as well as pain, suffering and harm have to be reduced to a minimum
- Pain, suffering and harm caused to the animals have to be ethically justifiable

Directive 86/609/EWG

Recitals:

*[…] whereas such harmonization should ensure that **the number of animals used for experimental or other scientific purposes is reduced to a minimum**, that such **animals are adequately cared for**, that **no pain, suffering, distress or lasting harm are inflicted unnecessarily** and ensure that, **where unavoidable, these shall be kept to the minimum**; Whereas, in particular, **unnecessary duplication of experiments should be avoided**, […]*

Article 7

2. ***An experiment shall not be performed if another scientifically satisfactory method** of obtaining the result sought, **not entailing the use of an animal, is reasonably and practicably available.***

4. ***All experiments shall be designed to avoid distress and unnecessary pain and suffering to the experimental animals.***

Directive 2010/63/EU

Recital 11:

*[…] When choosing methods, **the principles of replacement, reduction and refinement should be implemented through a strict hierarchy of the requirement to use alternative methods.** Where no alternative method is recognised by the legislation of the Union, **the numbers of animals used may be reduced by resorting to other methods and by implementing testing strategies**, such as the use of in vitro and other methods that would reduce and refine the use of animals.*

Recital 12:

*[…] **The use of animals** for scientific or educational purposes **should therefore only be considered where a non-animal alternative is unavailable**. […]*

Recital 42:

*[…] **It is necessary to introduce specific measures in order to increase the use of alternative approaches and to eliminate unnecessary duplication of regulatory testing.** […)*

Article 4 'Principle of replacement, reduction and refinement'

*1. Member States shall ensure that, **wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure.***

Article 13 'Choice of methods'

*1. […] **Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union**.*

*2. **In choosing between procedures, those** which to the greatest extent meet the following requirements **shall be selected: (a) use the minimum number of animals; (b) involve animals with the lowest capacity to experience pain, suffering, distress or lasting harm; (c) cause the least pain, suffering, distress or lasting harm;***

Problem

- Various requirements in EU legislation to consider animal welfare and to use alternative methods and reduce and replace testing on animals
- More than 40 alternative methods that are internationally accepted are available
- Even so, animal testing is still required in data requirements/EU legislation

→ Detailed analysis necessary!

Analysis of EU legislation – work stages

1. Identification of data requirements that involve testing on animals within EU legislation. Collection of available data, literature research
2. Analysis and comparison of data requirements in the different regulations
3. Identification of inconsistencies + other problems
4. Drafting of recommendations to resolve the problems that were identified and to facilitate and improve the design of future data requirements

Analysis of EU legislation – what did we look for?

- Analysis of data requirements of EU legislation that involves testing on animals:
  - Are accepted alternatives considered/included/referred to?
  - How are data requirements structured?
  - Waiving criteria?
  - Rules for adaptation?
  - Consistency of legislation/data requirements?

Analysis of EU legislation – what did find?

- Some of the accepted alternative methods that are available are not considered in the data requirements we analyzed
- Structure of data requirements is non-uniform from legislation to legislation
- Considerable disparities were also identified in wording, terminology and references to waiving criteria and rules for adaptation

→ **Lacking consistency of legislation/data requirements!**
→ **May lead to unnecessary tests on animals**

Example 1: eye irritation

- Internationally accepted AMs available since 2009 (OECD, TGs 437 + 438, can partly replace *in vivo* test)
- Adaptation to Technical Progress: AMs were updated in TMR (440/2008/EC) via Amending Regulation (EC) No. 1152/2010 in 2010

BUT:

→ Biocidal Products Regulation + Plant Protection Products Regulation still lack an update or inclusion of AMs in respective data requirements

- PPPR: *in vivo* test (B.5., TMR) required exclusively (!), no reference to AMs
- BPR: reference to "Sequential Testing Strategy for Eye Irritation and Corrosion" (appendix to *in vivo* eye irritation and corrosion test method (B.5.) in TMR)

→ Testing strategy (in appendix to B.5., TMR) **"not an integral part of testing method B.5."**, was developed by the OECD in 1996, therefore does not mention specific AMs (just mentions "validated and accepted *in vitro* or *ex vivo* tests").

Example 2: skin irritation

- Internationally accepted AM for skin irritation available since 2010 (OECD, TGs 439, can partly or fully replace *in vivo* test)
- Adaptation to Technical Progress: AM were updated in TMR (440/2008/EC) via Amending Regulation (EC) No 761/2009 in 2009

BUT:

→ Biocidal Products Regulation + Plant Protection Products Regulation still lack an update or inclusion of AM in respective data requirements

- PPPR: *in vivo* test (B.4., TMR) required exclusively (!), no reference to AM
- BPR: reference to "Sequential Testing Strategy for Skin Irritation and Corrosion" (appendix to *in vivo* eye irritation and corrosion test method (B.4.) in TMR)

→ Testing strategy (in appendix to B.4., TMR) **"not an integral part of testing method B.4."**, was developed by the OECD in 1996, accepted AM only mentioned under "References" in description of testing strategy

Results – analysis of data requirements 1

- No binding procedure for inclusion of newly adopted OECD TGs in the TMR
- Confusion about status of inclusion of newly accepted AMs because of separate Amending Regulations for Adaptation to Technical Progress
- Lacking Adaptation to Technical Progress of the TMR:
  → *In Vitro* Mammalian Cell Micronucleus Test (OECD TG 487)
  → Acute Toxic Class Method for Acute Inhalation Toxicity (OECD TG 436)
  → EOGRTS (OECD TG 443)
  → OECD GD No. 129 on using cytotoxicity tests to estimate starting doses for acute oral systemic toxicity tests
- Listing of outdated or unnecessary animal test methods for reproductive toxicity and skin sensitization (One generation reproductive toxicity study, Guinea Pig Maximization Test / Buehler-Test) (TMR)
- Reference to corresponding OECD TG missing (TMR)
- Issues concerning unclear, inconsistent or confusing structure of the TMR and its register of test methods

Results – analysis of data requirements 2

- Lacking reference to accepted alternative methods for skin irritation (BPR, PPPR)
- Lacking reference to accepted alternative methods for eye irritation (BPR, PPPR)
- Lacking reference to accepted alternative methods for skin sensitization (PPPR)
- Lacking reference to accepted alternative methods for reproductive toxicity (PPPR)
- Requirement of unnecessary 12-month toxicity study in dogs (PPPR)
- Inconsistencies in terminology, design of data requirements, and rules for adaptation to technical progress (PPPR)
- Introduction of endpoints that still lack standard testing methods (respiratory sensitization, BPR)

Further inconsistencies

- Lacking or insufficient instructions how testing on animals can be replaced, reduced or refined in BPR (partly) und PPPR (continuously)
- "Waiving" criteria and rules for adaptation differ from legislation to legislation
- Structure, terminology and wording of data requirements inconsistent and often confusing

Recommendations

To reduce and replace testing on animals for regulatory toxicity testing and to improve consumer protection in the EU:

- The European Commission has to act immediately to eliminate those animal tests from the data requirements that can be replaced by accepted alternative methods
- Setting up a central organ or institution that is responsible for the design and update of data requirements
- Strategy for design, compilation and update of data requirements needs to be revised and harmonized (harmonized structure, harmonized terminology, harmonized wording, "Waiving" criteria and rules for adaptation)
- Lay down best practice rules for EU acceptance of an AM after its adoption of an alternative method as an OECD TG (do all OECD TGs have to be accepted? Timeline?)

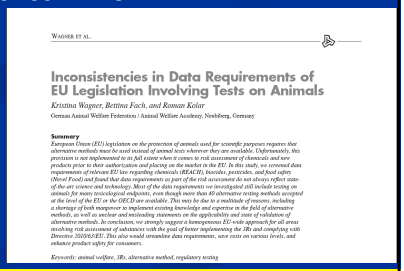
Summary + outlook

- Poster about project was presented at WC8 in Montréal, 2011
- Final project report was just published in ALTEX 29 3/12
- Publication in other relevant journals possible (Regulatory Toxicology, Critical Reviews in Toxicology, ATLA)
- Results will be presented to European Commission and affiliated DGs
  Still to be discussed: Presentation done by SET or ecopa?
  Forward results to EPAA? ECHA? EFSA?
  Forward results to involved MEPs?

Prospect:

→ Immediate action by the EC, spreading of information and discussion about results

→ **Ultimately: Replacement and reduction of testing on animals!**



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Inconsistencies in Data Requirements of EU Legislation Involving Tests on Animals

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Summary

European Union (EU) legislation on the protection of animals used for scientific purposes requires that alternative methods must be used instead of animal tests wherever they are available. Unfortunately, this provision is not implemented to its full extent when it comes to risk assessment of chemicals and new products prior to their authorization and placing on the market in the EU. In this study, we screened data requirements of relevant EU law regarding chemicals (REACH), biocides, pesticides, and food safety (Novel Food) and found that data requirements as part of the risk assessment do not always reflect state-of-the-art science and technology. Most of the data requirements we investigated still include testing on animals for many toxicological endpoints, even though more than 40 alternative testing methods accepted at the level of the EU or the OECD are available. This may be due to a multitude of reasons, including a shortage of both manpower to implement existing knowledge and expertise in the field of alternative methods, as well as unclear and misleading statements on the applicability and state of validation of alternative methods. In conclusion, we strongly suggest a homogeneous EU-wide approach for all areas involving risk assessment of substances with the goal of better implementing the 3Rs and complying with Directive 2010/63/EU. This also would streamline data requirements, save costs on various levels, and enhance product safety for consumers.

Keywords: animal welfare, 3Rs, alternative method, regulatory testing

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Research Team

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Thank you for your attention!

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Project summary:

http://www.stiftung-set.de/projects/projectlist.html?L=1