

# Can TTIP Improve Laboratory Animal Welfare in Safety Testing and 3Rs?

Francois Busquet, Joanne Zurlo, and Thomas Hartung

## Abstract

In the context of the current negotiations between the European Union (EU) and the United States under the Transatlantic Trade Investment Partnership (TTIP), there is the opportunity to look at both legislative frameworks to better pinpoint convergences, synergies, and gaps when it comes to use of laboratory animals for scientific purposes and bring together the best of both worlds. The objectives in this article are to indicate what are the current EU pieces of legislation that are relevant under TTIP regarding the uses of laboratory animals for scientific purposes under the regulations about cosmetics and chemicals, among others. The same approach will be taken to look at the relevant American legal frameworks, that is, the Food and Cosmetics Act and the Toxic Safety Control Act as well as its most recent reauthorization. In conclusion, the authors will identify future frameworks that can contribute to the harmonization of regulatory standards and further steps where TTIP negotiators should strengthen regulatory cooperation.

## Introduction

In the context of the current negotiations between the European Union and the United States under the Transatlantic Trade Investment Partnership (TTIP), there is the opportunity to look at both legislative frameworks to better pinpoint convergences, synergies, and gaps regarding the use of laboratory animals for scientific purposes and bring together the best of both worlds. The state of the 3Rs (replacement, reduction, refinement) is rather unbalanced, depending on whether the focus is on technology progress /methodologies or regulatory frameworks. One could simplify it the following way: "In the EU there are laws, in the US there are tools," or in other words: (1) the EU is more open

and advanced in the area of animal welfare and alternative methods (3Rs), including at a legal level; and (2) the United States is driving the development of new methodologies from the regulatory level and incorporates new types of data (i.e. in silico, in vitro, computer modeling, high-throughput methods). The Toxicology for the 21<sup>st</sup> Century (Tox21) program or the Environmental Protection Agency (EPA's) ToxCast are key examples for these developments.

TTIP is so far addressing very few of the issues of laboratory animal use and 3Rs. Nevertheless, there are opportunities to achieve coordinated progress on both sides of the Atlantic.

## The European Union 3Rs Policy Framework

When it comes to laws, the EU is spearheading efforts for the protection and recognition of laboratory animals used among the 28 different member states thanks to the multiple vertical legislative frameworks impacting on laboratory animals used for scientific purposes. However, the challenge for the EU lies in the implementation and enforcement of those laws within the EU member states. The EU texts listed in this chapter should not be considered as an exhaustive list, since food safety requirements are, for example, not included.

### TFEU (Treaty of the Functioning of the European Union)

Animal welfare is incorporated as a European value in Article 13 of the TFEU ([Treaty of the Functioning of the European Union, 2007](#)): “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.”

However, animal welfare is NOT officially an EU policy area, that is, animal welfare is not part of the agreed remit of joint legislation of the member states. However, as differences in animal welfare legislation affect the common market, since 1986 there has been European legislation on animal welfare. Furthermore, promotion and use of alternative test methods and the principle of the 3Rs are also anchored elsewhere within the EU legislation (see below for examples). EU agencies (e.g., the European Chemicals Agency, the European Medicines Agency, and the European Food Safety Authority) also contribute to fostering novel technologies such as *in silico* and *in vitro* methods.

In addition to the operational activities led by the commission services, the European Commission (EC) under President Barroso (2004–2014) also implemented two EU strategies for animal welfare. The last strategy ([European Commission, 2012](#)) ran from 2012 to 2015 and identified the next issues to be tackled. However, little is mentioned about laboratory animals.

### Directives and Regulations

It is important to understand the difference between an EU directive and an EU regulation. Directives are addressed to national authorities, who must then take action to make them part of national law. Regulations are the most direct form of EU law. As soon as they are passed, they have binding legal force throughout every member state. National governments do not have to take action to implement EU regulations ([Busquet et al. 2014](#)).

If a member state fails to pass the required national legislation, or if the national legislation does not adequately comply with the requirements of a directive or a regulation, the EC may initiate legal action against the member state in the European Court of Justice. EC releases a monthly infringement package ([European Commission, 2015](#)) for all the areas it is responsible for.

#### Directive 2010/63/EU

On January 1, 2013, EU Directive 2010/63/EU on the protection of animals used for scientific purposes ([European Union, 2010](#)) entered into force for the 28 EU member states. It repealed the

previous Directive 86/609/EEC ([Hartung, 2010](#)). Since it is a directive, it allows member states certain flexibility in its transposition into national laws. Among the purposes of this directive are to (1) harmonize the current EU understanding of what defines a laboratory animal; (2) map the resources; (3) include “...competent people and authorities, and establishments...”; (4) establish a common framework; (5) detail duties and tasks of European Union Reference Laboratory for Alternatives to Animal Testing (formerly the European Centre for the Validation of Alternative Methods); (6) promote collaboration of the member states with the EC to disseminate animal welfare in the EU; and (7) request the member states to assist the EC in identifying and nominating suitable specialized and qualified laboratories to carry out validation studies of alternative methods via the European Union Network of Laboratories for the Validation of Alternative Methods.

It should also be noted that this is the first time EU legislation spells out the principle of the 3Rs and makes it a firm legal requirement (see [Table 1](#) for relevant articles stating or implying 3Rs).

#### Cosmetics

The Cosmetics Directive (7th amendment to 76/768/EEC) provided the regulatory framework for phasing out animal testing for cosmetics purposes ([Hartung, 2008](#)). It established a testing ban on finished cosmetic products and cosmetic ingredients on animals as well as a marketing ban of finished cosmetic products and ingredients included in cosmetic products that were tested on animals for cosmetics purposes in the EU. The same provisions are contained in the Cosmetics Regulation ([European Union, 2009](#)), which replaced the Cosmetics Directive from July 11, 2013.

More than 3 years after the full ban entered into force, the interpretation of the ban on animal testing for cosmetics is once again questioned. One can see, for example, the court case C-244/03 put forward at the European Court of Justice (2005). In 2013, the European Federation for Cosmetic Ingredients asked the high court in London to clarify whether the cosmetics industry is legally allowed to sell “on the Community market cosmetic products containing ingredients, or a combination of ingredients, which have been the subject of animal testing where that testing was performed outside the European Union to meet the legislative or regulatory requirements of third countries in order to market cosmetic products containing those ingredients in those countries” in court case C-592/14 ([European Court of Justice, 2015](#)). The European Court of Justice’s advocate general gave his opinion on the case on March 17, 2016. The main conclusion was “Only the reliance on the results of animal testing conducted after the relevant cut-off dates will trigger the ban.” The authors refer the reader directly to the conclusion of the Advocate General to avoid misinterpretation ([European Court of Justice, 2016](#)). To our understanding, it confirms that testing outside of the EU after the deadline triggers a marketing ban only if this information is used to satisfy the legal requirements in the EU.

#### REACH (Registration, Evaluation and Authorisation of Chemicals)

In 2007, REACH legislation ([European Commission, 2006](#)) entered into force. This regulation relates to chemicals and their safe use ([Hartung, 2010](#)). The aim of REACH is to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. It promotes the use of alternative methods for

**Table 1.** Elements of 3Rs within the EU directive 2010/63/EU

Directive 2010/63/eu	
Article	Content
1	Subject matter and scope: directive lays down rules for 3Rs
4	Principle of 3Rs
13	Choice of methods: consider 3Rs first hand
23 and 24	Competence and specific requirements for personnel: animal welfare
26 and 27	Animal-welfare bodies: advise on 3Rs
33	Care and accommodation of animals: refinement
38	Project evaluation: project must be in compliance with the 3Rs
39	Retrospective assessment: evaluate elements contributing to the 3Rs
43	Nontechnical project summaries: demonstration of compliance with the 3Rs
47	Alternative approaches: EC and member states shall contribute to the development and validation of alternative approaches
48	The European Union Reference Laboratory for Alternatives to Animal Testing : coordinating and promoting alternatives as well as the validation
49	National committees for the protection of animals used for scientific purposes: advise animal welfare bodies on the latest information on the 3Rs or dissemination of information on the 3Rs to enable others to comply with their obligations.
54	Reporting: member states are to report on aspects related to 3Rs
57	Commission report: implementation of the directive
58	Review: the directive shall take into account advancements in development of alternatives
58	Review: EC to carry out periodic thematic reviews on the 3Rs related to the use of animals in procedures.

animal testing but can only encourage the test performer to do so: “In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort. It is also necessary to take measures limiting duplication of other tests.” Notably, article 1 of the regulation states: “Aim and scope 1. The purpose of this Regulation is to ensure a high level of protection of human health and the environment, including the *promotion of alternative methods for assessment of hazards of substances*, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation.” [emphasis added]

The ban on animal testing for cosmetics obliged the EC and the European Chemical Agency to clarify the interface (ECHA, 2014) between REACH and the cosmetics regulation, since a dedicated molecule can have multiple applications falling under different legal frameworks. In brief, registrants are allowed to perform animal testing when the substances have dual uses, that is, cosmetics *and* other purposes (e.g. painting etc.). Nevertheless, it is important to note the opinion drafted by the ECHA is not legally binding and only their interpretation. Lastly, registrants may perform testing also for environmental safety and worker safety, as these are not for the purposes of cosmetics regulation.

#### Test Methods Regulation

In parallel to the adoption of REACH, the EC published standardized and accepted methods for testing hazardous properties of chemicals. These were written into the Test Methods Regulation (European Commission, 2008), which came into force on May 30, 2008. “The European Union is committed to promoting the development and validation of alternative techniques which can provide the same level of information as current animal tests, but which use fewer animals, cause less suffering or avoid the use of animals completely. Such methods, as they become available, must be considered wherever possible for hazard characterisation and consequent classification and labelling for intrinsic hazards and chemical safety assessment.”

In practice, this document is irregularly updated, but an increasing backlog of validated nonanimal testing methods has

not yet been inserted. Formal complaints submitted to the European Ombudsman by the PETA foundation have been made to speed up the process (European Ombudsman, 2014).

#### Pharmaceuticals

The current legislative frameworks for medicinal products for human use are laid down in Directive 2001/83/EC (European Commission, 2001). This fairly old directive was supplemented thereafter by Regulation 726/2004/EC (European Commission, 2004), which focuses on manufacturing, distribution, and marketing of medicinal products and contains many more directives and regulations (such as pediatrics, pharmacovigilance, orphan drugs, etc., all listed in Eudralex Vol 1), which need to be addressed in conjunction with the Directive 2001/83/EC (European Commission, 2001).

Directive 2001/83/EC (European Commission, 2001) states that “(10) Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes.” This is now updated as Directive 2010/63/EU (European Union, 2013). Therefore, the directive ensures that the 3Rs are considered before animal testing. Furthermore, the European Medicine Agency has its specific group with specific guidance on use of 3Rs in medicines development.

#### Plant Protection Product

This regulation (European Commission, 2009) included strong impact of the 3Rs following the intensive work performed for REACH. Here are some elements, which imply 3Rs considerations for the registrants:

- Development of nonanimal test methods should be promoted
- Use of nonanimal test methods and other risk assessment strategies should be promoted
- Animal testing should be minimized and tests on vertebrates shall be taken as a last resort

- Commission work program to include measures to minimize animal testing
- Applicants shall make every effort to ensure they share animal test data

#### **Biocidal Products Regulation**

In the same manner, the biocide regulation (European Union, 2012) also has strong provisions to reduce animal testing by encouraging data sharing and alternative approaches; the contents relevant to the 3Rs are briefly listed below.

- Data requirements include good 3Rs focus (12-month dog study removed);
- Lethal-dose skin, inhalation, and injection tests on rabbits and other animals are no longer a strict requirement;
- First-in-the-world legal acceptance of test methods/strategies that reduce animal use by 40% to 70% for skin allergy, fertility, and birth defects and other health concerns;
- Systematic move away from testing that uses more than one animal species and/or route of exposure;
- New legal text encouraging companies to combine two or more toxicity evaluations into a single test instead of conducting separate animal tests

#### **7th Environmental Action Plan**

This piece of EU legislation (European Commission, 2013) is rather a roadmap and is totally dependent of the full commitment of the member states and the relevant EU institutions as well as the willingness to take responsibility for the delivery of the program's intended benefits. There are nevertheless two priorities that are worth being mentioned:

**Priority objective 3:** To safeguard the Union's citizens from environment-related pressures and risks to health and well-being: "(iv) developing a comprehensive chemical exposure and toxicity knowledge base which draws on data generated without animal testing where possible."

**Priority objective 5:** To improve the knowledge and evidence base for Union environment policy: "50. Horizontal chemicals legislation (REACH) and the Classification, Labelling and Packaging Regulations, as well as legislation on biocidal products and plant protection products, provides baseline protection for human health and the environment, ensures stability and predictability for economic operators, and promotes the uptake of evolving non-animal testing methods."

The text foresees and claims, "Long-term actions with a view to reaching the objective of a non-toxic environment will be identified." Until now, only Sweden has officially endorsed this objective under the operations by its chemical agency (KEMI).

In conclusion, the EU legislation incorporates directly (3Rs spelled out) or indirectly (data sharing, reference to Directive 2010/63/EU) laboratory animal welfare wherever and whenever possible. Their correct application and implementation by the member states may, however, be a different story.

## **The US 3Rs Policy Framework**

### **Animal Welfare Act**

Public Law 89-544, commonly referred to as The Animal Welfare Act (AWA) (1966), is the primary US regulation that governs laboratory animals and is overseen by the United States Department of Agriculture (USDA). Since its initial enactment in 1966, the AWA has been amended seven times.

Significant changes and improvements for laboratory animal welfare were enacted in the 1985 amendment to the AWA, which also saw the establishment of Institutional Animal Care and Use Committees (IACUCs) to oversee research at every institution using USDA-covered species. The AWA provides guidance and standards for laboratory animals, but since 2002 has specifically excluded birds, rats from the genus *Rattus*, and mice from the genus *Mus* bred for research. The AWA provides engineering standards for animals in research, including housing conditions and temperature control, but also allows for performance standards that can be overseen by the IACUC, the institutional official, and attending veterinarian. The USDA allows for achieving compliance with some flexibility, reflecting a sense of performance standards rather than strictly engineering standards (National Academies of Science, Engineering and Medicine, 2015).

The USDA also issues policies to clarify the regulations by which regulated institutions must abide (United States Department of Agriculture, 2016). Included within these policies is Policy 12, which requires investigators to consider alternatives to painful/distressful procedures. This policy specifically refers to the 3Rs. Through this policy, an investigator must document that s/he has performed an acceptable literature search and/or consulted with experts and demonstrate that there are no alternatives to the proposed experiment.

### **US Public Health Service Policy**

Any institution that receives funding from any of the agencies of the Public Health Service (National Institutes of Health, Food and Drug Administration (FDA), Centers for Disease Control and Prevention among others) is required to hold file an Animal Welfare Assurance Statement with the Office of Laboratory Animal Welfare at the National Institutes of Health (NIH). Public Health Service (PHS) policy is mandated by the Public Health Extension Act, passed in 1985, and covers all vertebrate animals (National Institutes of Health, 2015). The Animal Welfare Assurance Statement assures that the institution will abide by the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training (National Research Council, 2011). Guidelines for PHS policy are presented in the *Guide for the Care and Use of Laboratory Animals* (the Guide) (National Research Council, 2011). Both the US Government Principles and the Guide contain explicit reference to the 3Rs. The Guide is primarily considered a performance standard but contains some mandates noted in the text as practices that "must" be done. Other practices are indicated by "should" and are strongly encouraged. The IACUC, which is also mandated by PHS Policy, has the responsibility of oversight into how the 3Rs and the Guide are implemented.

Both the EU directive and US laws and policies specifically incorporate the 3Rs into practices for laboratory animal care and use. The difference lies in how this is done. Cultural differences between Europe and the United States dictate that the implementation of the 3Rs will also differ. PHS policy supports a primarily self-regulated system, putting the onus of compliance on the individual institutions through the Institutional Official and the IACUC. The USDA relies on the IACUC for compliance, but also conducts unannounced annual inspections of licensed institutions, during which the inspector may review IACUC protocols for the quality of compliance with Policy 12. Insufficient compliance may result in a citation. On the other hand, European guidelines for implementation of the 3Rs are more prescribed than those in the United States. As shown in

Table 1, the EU directive goes much further in mandating that all activities related to laboratory animal care and use comply with the 3Rs principles.

### Cosmetics

In the United States, the federal Food and Drug Cosmetics Act is the piece of legislation covering the authorization process of cosmetics products and is supervised by the FDA. Although it is not stated that the FDA specifically requests animal testing, the companies should take any necessary steps to make sure that their products meet the safety requirements. Therefore, safety assessment data are not restricted to nonanimal testing methods (as it is the case in the EU) and allow any kind of data set to be accepted. However, the law may change with the following bill ([Humane Cosmetics Act, 2015](#)), whose objective is to phase out cosmetic animal testing and the sale of cosmetics tested on animals and for other purposes ([Knight and Rovida, 2014](#)). The draft text is similar to some extent to the EU ban. It was introduced at the House of Representatives in June 2015. It is worth being mentioned that it is not the first attempt to pass such kind of bill (e.g., H.R. 4148 or H.R. 1385).

### Toxic Safety Control Act (TSCA)

TSCA was enacted in 1976 and is the equivalent of REACH for the United States. There are multiples differences when it comes to the assessment of chemicals on both sides of the Atlantic. In the United States, the TSCA requires premarketing notification for any substance without data, and typically 1500–2000 substances are notified per year; only 15% of these contain toxicity testing data. The EPA then has 90 days to request testing. This prompted a culture of structure/activity relationship-based assessments, which were the only way to respond quickly to the notification.

However, in only about 200 cases of 26,000 notifications were actual testing demands the result. Reassessments around the turn of the century, however, showed that new chemicals represent a tiny proportion of chemical commerce (1–3%) and indicated a dramatic gap in knowledge with regard to the existing “old” chemicals. The resulting decade-long attempts to reauthorize TSCA were finally completed in spring 2016.

The US House of Representatives and the Senate passed H.R. 2576, the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which strengthens federal oversight for the use of tens of thousands of chemicals in commercial use and contains provisions to minimize and in some cases replace animal testing to evaluate chemical safety. The legislation is summarized on the EPA website ([United States Environmental Protection Agency, 2016](#)). It now includes a provision discouraging the use of chemical testing on vertebrate animals and requiring the EPA to create and promote a database of alternative testing methods within two years.

### TTIP

This potential trade agreement between the EU and the United States started in June 2013 under President Obama’s administration when the 28 EU member states gave a mandate to the ex-president of the Commission Barroso to lead and deal with the negotiations on their behalf. If a final agreement is found, the draft text will be submitted to the 28 EU member states and the European Parliament for adoption.

The final agreement should contain 24 chapters grouped together in 3 parts such as market access, regulatory cooperation, and rules. In our context, the regulatory cooperation is the most interesting to look at the future impact of the TTIP and in particular three specific sectors among others: cosmetics, chemicals, and pharmaceuticals. Nevertheless, pesticides and medical devices are also part of the sectors where a trade agreement is foreseen.

The agreement can take three different formats: mutual recognition, full harmonization, or regulatory cooperation. The authors have summarized in Table 2 a comparison of the EU and US legislation and federal programs with regard to laboratory animal welfare clauses.

**Disclaimer:** Since negotiations are still ongoing, the EU positions presented below are still subject to change. It is worth mentioning that only the EU is periodically releasing the status of negotiations for the sake of transparency to EU citizens. The United States, however, is not releasing any documents until Greenpeace published on their website the US position in May 2016 ([Greenpeace, 2016](#)). The authors will refer in this section to the US position based on the publically available “Tactical State of Play of the TTIP Negotiations” dated March 2016.

Lastly, the EU negotiators are inviting regularly the EU stakeholders to round-table discussions and giving them opportunities to make presentations and express their views.

### Cosmetics

As stated previously, in the EU, any new ingredient and product that has been tested on animals even outside the EU may not be marketed in the EU.

Regarding the TTIP, the EU latest public position ([European Commission, 2015](#)) states the following: “Both Parties could agree on further fostering the development of alternative methods to replace animal testing. The overall objective is to promote the use of validated and OECD accepted alternative test methods for regulatory purposes for cosmetics. Both sides could share scientific knowledge on the matter including existing technical assessments and guidance documents, and could collaborate in the development and implementation of the ‘read across data approach and integrated testing strategies’ that use all available information and data.”

The United States stated the following: “All in all, discussions on cosmetics remain very difficult and the scope of common objectives fairly limited. The United States confirmed that in the United States, UV filters (which are used in many cosmetic products) will continue to be subject to safety assessment based on animal carcinogenic studies that EU enterprises cannot provide due to the EU ban on animal testing. The EU and US approaches remain irreconcilable and EU market access problems will therefore remain. Although it would be important to enhance scientific cooperation on the safety assessment of cosmetic ingredients, there was no agreement on the modalities to be established.”

More interesting, this US analysis confirms the EC position on cosmetics described above: “On alternatives to animal testing (ATMs), the FDA is willing to accept TPP language (recommendation to use ATMs when available) but that would not apply in any case of any cosmetic product containing a sun-screen ingredient.”

The current EU position pushes for more collaboration, which adds to existing forum such as the International Cooperation on Cosmetics Regulation or International Cooperation on Alternative Test Methods since 2009.

Table 2. Comparison of the EU and the US legislations and federal programs with regard to laboratory animal welfare clauses

	EU legislation	3Rs provisions or elements under EU legislation	US legislation	3Rs provisions or elements under US legislation	Regulatory cooperation under TTIP	3Rs provisions or elements under TTIP
Chemicals	EC 1907/2006	Yes	TSCA	No	Yes	NO
Cosmetics	EU 1223/2009	Yes	Food and Drug Cosmetics Act	No	Yes	YES
Pharmaceuticals <sup>a</sup>	2001/83/EC Associated with regulation 726/2004/EC. This includes having regard to Directive 2010/63/EU and European Medicine Agency <sup>b</sup>	Yes	Food and Drugs Act (1906) and more than 200 laws since <sup>c</sup>	No	Yes	NO
Plant protection products or pesticides	EC 1107/2009	Yes	FIFRA <sup>d</sup>	No	Yes	NO EU position paper available (only factsheet with NO 3Rs provisions or elements). Industry position <sup>e</sup> (ECPA & Croplife America) available but NO 3Rs provisions or elements
Medical devices <sup>f</sup>	93/42/EEC <sup>g</sup>	Yes This revision foresees reference to include having regard to Directive 2010/63/EU	Food and Drug Cosmetics Act	No	Yes	NO
Biocides <sup>h</sup>	EU 528/2012	Yes	FIFRA	No	No	Not applicable
Protection of animals used for scientific purposes	2010/63/EU	Yes	AWA	Yes	No	Not applicable
HORIZON 2020 research funding <sup>i</sup>	EU 1291/2013	Yes	NIH extramural program	Yes also via IACUC guidelines	No	Not applicable

<sup>a</sup><http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF><sup>b</sup>[http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CVMP/people\\_listing\\_000094.jsp&mid=Wc0b01ac05803a9d6d](http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CVMP/people_listing_000094.jsp&mid=Wc0b01ac05803a9d6d)<sup>c</sup><http://www.fda.gov/RegulatoryInformation/Legislation/><sup>d</sup><http://www.epa.gov/enforcement/federal-insecticide-fungicide-and-rodenticide-act-fifra-and-federal-facilities><sup>e</sup><http://www.ecpa.eu/files/attachments/ECPA-CLIA%20TTIP%20Position%20-%20Paper%2010-03-14.pdf><sup>f</sup><http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:01993L0042-20071011&from=EN><sup>g</sup>Currently in revision<sup>h</sup><http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02012R0528-20140425&from=EN><sup>i</sup><http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:347:0104:0173:EN:PDF>

## Chemicals

From the EU position paper (European Commission, 2014) and as far as the negotiation goes, the EU side is outlining the most probable solution for the chemical sector that is: “A right to regulate from each side” (Transatlantic Consumer Dialogue, 2016). The EU is so far not considering any mutual recognition or regulatory cooperation. Nevertheless, the two sides have launched pilot studies based on the EU community roll action plan under REACH and the chemical work plan from the US EPA in order to understand the obstacles with their respective regulatory bodies (Chemical Watch, 2015) regarding hazard/risk assessment. Some substances were overlapping, and it was decided to share and compare assessment practices. Unfortunately, the two case studies' compounds contain no data from ToxCast and do not provide an angle to disseminate data-rich substances based on the use of alternative methods or new methodologies for regulatory requirements. Nevertheless, it could be a good starting point, since the United States indicated that these efforts were found “useful” by multiple competent authorities (i.e., EU member states) and that “all competent authorities confirmed that the cooperation with the US had not led to additional work nor to any delays in the planning and execution of its own activities.”

Although the latest EU position paper (European Commission, 2014) on chemicals does not provide direct references to alternatives to animal testing, the EU is suggesting in section 2.4 that: “In addition, several animal welfare organisations have called on the authorities to increase data exchange between regulators to avoid duplication of tests involving animals.” This is the most used mechanism in EU legislation (e.g., REACH, plant protection products...) to limit animal testing. Data sharing on the US side indicates that there is common ground for such an option, but the handling of confidential business information still needs to be addressed.

There is another reference in section 3.1 from the EU position paper (European Commission, 2014) that states “A mechanism for mutual consultation on prioritisation of chemicals for assessment/risk management and for cooperation in the development of assessment methodologies would be set up. Both sides would also inform each other about activities at sub-federal level in the US and Member State activities in the EU, respectively.” The United States did not address this position.

The Tox21 and ToxCast programs of the US federal agencies (US EPA, 2008), which have started to deliver the first regulatory tools relying solely on computational methods and high-throughput screening (United States Federal Register, 2015), could be an excellent showcase and venue for the United States to promote nonanimal testing methods in the case of compounds with endocrine-disrupting properties. Last but not least, it is the understanding of the authors that the recent US TSCA reauthorization will not be included in the current TTIP negotiations. It is a tremendous missed opportunity to fuel in TTIP the Tox21 tools.

## Pharmaceuticals

Based on the last EU position document on TTIP (European Commission, 2014), the EU and the United States have already strong regulatory cooperation under the International Conference on Harmonisation. Nevertheless, some areas could fit further collaboration but none of them strictly or directly refer explicitly to the use of laboratory animals nor the test methods or guidelines although they consider “fostering additional

harmonization of technical requirements in new areas or in areas where the need to improve harmonization at bilateral or international level has been identified (e.g. biosimilars, paediatrics, generics, terminology).” This might be an opportunity to further push computer modeling (i.e., in silico), read-across, organs-on-a-chip, or in vitro testing methods.

However, the United States indicates, “Considerations that scientific work should be excluded from TTIP were also put forward. However, the EU insisted on the need to work under TTIP to promote regulatory and scientific collaboration in areas such as biosimilars, generics and pediatrics.” It seems that there is still some latitude for improvement for the US position.

## The Position of the European Parliament

The European Parliament drafted and adopted an initiative report (EP, 2014/2228(INI)) in January 2015 that draws the lines to accept the deal if an agreement will be found between the parties. Within the document, there is one reference to alternatives to animal testing: “Calls on the Commission to ensure that a common approach, regulatory cooperation or mutual recognition, as appropriate, is reached in the following areas, provided the level of EU standards is not compromised (...) on alternative methods to animal testing.”

Based on the latest EU Parliament positions published, one could say that the EC is not really listening to this specific request.

## Existing Collaborations outside the TTIP Negotiations

Transatlantic cooperation has already taken place in many 3Rs topics for many years. The two validation counterpart bodies, the Interagency Coordinating Committee on the Validation of Alternative Methods/National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods and the European Union Reference Laboratory for Alternatives to Animal Testing Evaluation of Alternative Toxicological Methods both collaborate and signed a memorandum of cooperation establishing International Cooperation on Alternative Test Methods (International Cooperation on Alternative Test Methods, 2009) in order to facilitate recognition of validated test methods since 2009. Moreover, when it comes to research, the following four examples can be pointed out.

### Endocrine Disrupters

Since 1999 and the EU-US Science and Technology Agreement, common research priorities were identified and, subsequently, funding for research was made available by the EC and the US EPA.

### Innovative Medicine Initiative (IMI) and the Critical Path Institute (CPI)

IMI is a public-private partnership between the EC and European Federation of Pharmaceutical Industries and Associations. This joint initiative started in 2009 and renewed in 2015 is now worth almost 4 billion Euros. All funded projects have the objectives to solve a practical dead-end faced by the pharmaceutical industries or develop technologies that they do not have the capacity to develop as individual companies. The latest results are directly feeding the EU regulatory framework, and for this reason the IMI board has from the inception decided to inform the

United States (via the CPI) on the outcomes of the projects to strengthen novel technology acceptance. CPI, founded in 2005 in Tucson, Arizona, is an independent, nonprofit organization dedicated to bringing scientists from the FDA, industry, and academia together to collaborate and improve the drug development and regulatory process for medical products.

### Tox21

Tox21 is a federal collaboration initiated by the US EPA, which includes the NIH, the National Toxicology Program, National Center for Advancing Translational Sciences Chemical Genomics Center and the FDA that work together to reframe, update, rethink, and transform how safety assessment is currently performed by embracing all the cutting-edge technologies for that purposes. One of the key strategies of Tox21 is to establish collaboration with as many stakeholders as possible. In this context, a material transfer agreement was signed with the EC Joint Research Center in 2010. The close collaboration with EU officials has continued since then. For example, in 2013, Tox21 met the largest EU research consortium on alternatives to animal testing, Safety Evaluation Ultimately Replacing Animal Testing, and a similar collaboration is foreseen with its successor, the new flagship EU-ToxRisk (see below).

### Horizon2020

Horizon2020 is the ongoing EU framework research program with 80 billion Euros as the total foreseen budget. This amount is almost exclusively dedicated to EU member states only. Participating countries outside the EU including the United States are welcome to join. Those countries are not necessarily funded by H2020, except under the health section, in which US tenants can be funded if they are part of the winning consortium, based on a memorandum of understanding with NIH. One of the most relevant EU calls so far is phc-33, which is meant to develop new tools to improve predictive human safety thanks to alternative test methods. The project funded in 2015 was the EU-ToxRisk consortium also involving Johns Hopkins Center for Alternatives to Animal Testing as the only US partner with a share of a total budget of 30 million Euros over the next 6 years. Such access of US partners to EU research consortia is reciprocal, since NIH can fund European partners.

### Conclusions

Overall, the opportunities to make progress in 3Rs practices under TTIP are rather scarce and thin considering the current negotiation texts. The different EU flagships sectors (cosmetics, chemicals, and pharmaceuticals) are so far not including strong 3Rs provisions in this draft trade agreement, although opportunities to harmonize 3Rs framework and testing requirements exist. The exceptional disclosed "Tactical State of Play of the TTIP Negotiations" from the United States allowed the authors a primary analysis on possible 3Rs intention from the American side. Some genuine recommendations can be made under TTIP regulatory cooperation:

1. Data-sharing seems the way forward for the chemicals sector to reduce animal testing and should be extended to the other sectors whenever possible.
2. Moreover, the integration of the dataset generated under ToxCast and SEURAT-1 when pilot studies are performed between the two task forces (i.e., chemicals) should be emphasized. One could also extend this working format to

other flagship sectors, for example, plant protection products, pharmaceuticals, or cosmetics.

3. In the absence of strong 3Rs anchoring in US legislation, best practices from the EU could be considered by the US regulatory agencies. They should encourage the use of alternative test methods by educating US applicants (who in general opt for the most conservative testing approaches, i.e., in vivo) when preparing their toxicological dossiers and use knowledge from the EU regulatory context, which is more 3Rs friendly.

Last but not least, one reason to explain this low enthusiasm for incorporating more 3Rs under TTIP may be that close cooperation has already existed for many years between the scientific and regulatory community on both sides of the Atlantic. Eventually, other frameworks or new negotiations should be started to strengthen best practices regarding 3Rs. Two future tracks could be:

1. The development of a harmonized definition of animals used for scientific purposes by the United States, best based on the EU definition in order to similarly report animal studies and therefore facilitate efforts to implement 3Rs.
2. The research and development within academia and industry is the area that consumes by far the largest number of laboratory animals rather than safety testing (in the EU, roughly 1 million for safety versus 7 million for basic research per year (European Commission, 2013)). Initiatives to develop and spread the use of alternatives in this global scientific community are urgently needed.

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