Food for Thought ...

The Need for Strategic Development of Safety Sciences

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Summary

The practice of risk assessment and regulation of substances has largely developed as a patchwork of circumstantial additions to a nowadays more or less shared international toolbox. The dominant drivers from the US and Europe have pursued remarkably different approaches in the use of these tools for regulation, i.e., a more risk-based approach in the US and a more precautionary approach in Europe. We argue that there is need for scientific developments not only for the tools but also for their application, i.e., a need for Regulatory Science or, perhaps better, Safety Science. While some of this is emerging on the US side as strategic reports, e.g., from the National Academies, the NIH and the regulatory agencies, especially the EPA and the FDA, such strategic developments beyond technological developments are largely lacking in Europe or have started only recently at EFSA, ECHA or within the flagship project EU-ToxRisk.

This article provides a rationale for the creation of a European Safety Sciences Institute (ESSI) based on regulatory and scientific needs, political context and current EU missions. Moreover, the possible *modus operandi* of ESSI will be described along with possible working formats as well as anticipated main tasks and duties. This mirrors the triple alliance on the American side (US EPA, NIH and FDA) in revamping regulatory sciences. Moreover, this could fit the political agenda of the European Commission for better implementation of existing EU legislation rather than creating new laws.

Keywords: regulatory toxicology, testing strategies, scientific policy advice, alternative test methods

1 Introduction

For many, regulation has become a four-letter word, especially as it is perceived as a barrier to business. At the same time, everybody wants safety for consumers and patients, which is the aim of regulation. What is needed and desirable thus is efficient regulation. Current regulatory procedures do not always provide this – they use too many animals, are too costly, take too long, often lead to controversial results and are not based on human risk. No need to regurgitate all the arguments here (Hartung, 2017). The extent of the deficits can be argued, as can be the overall result of our regulatory processes, but it is clear that there is room for improvement. In fact, with rapidly changing products, markets – as demonstrated recently in this series of articles for the case of e-cigarettes (Hartung, 2016a) – and increasing knowledge on the effects of substances on humans and the environment, there is a continuous need for adaptation of regulation. Historically, a lot of this has been done by adding patches to the toolbox of toxicology – with the result of a regulatory patchwork, a crazy quilt (Fig. 1). And as any patchwork quilt, it is multilayered and interwoven, becoming rigid and losing flexibility.

This process of the development of regulatory practice seems to be evolutionary, but it is not. Simply adding species (or here tools) is not evolution. Evolution needs the predators, who create pressure under which only the fittest survive. There is no evolution in the zoo where the predators are separated from the prey. Validation could be the predator of the toxicological toolbox, but we keep it away from the established methods like in the allegory of the zoo, but unfairly throw the new arrivals into the cage of validation. We have argued elsewhere (Hartung, 2010a) that systematic review could be a milder predator (less lengthy and less costly) to be applied to the established methods. This process has started to gain traction (Stephens et al., 2016), but it is still rather applied to integrate information on a given substance than to evaluate our established methods.

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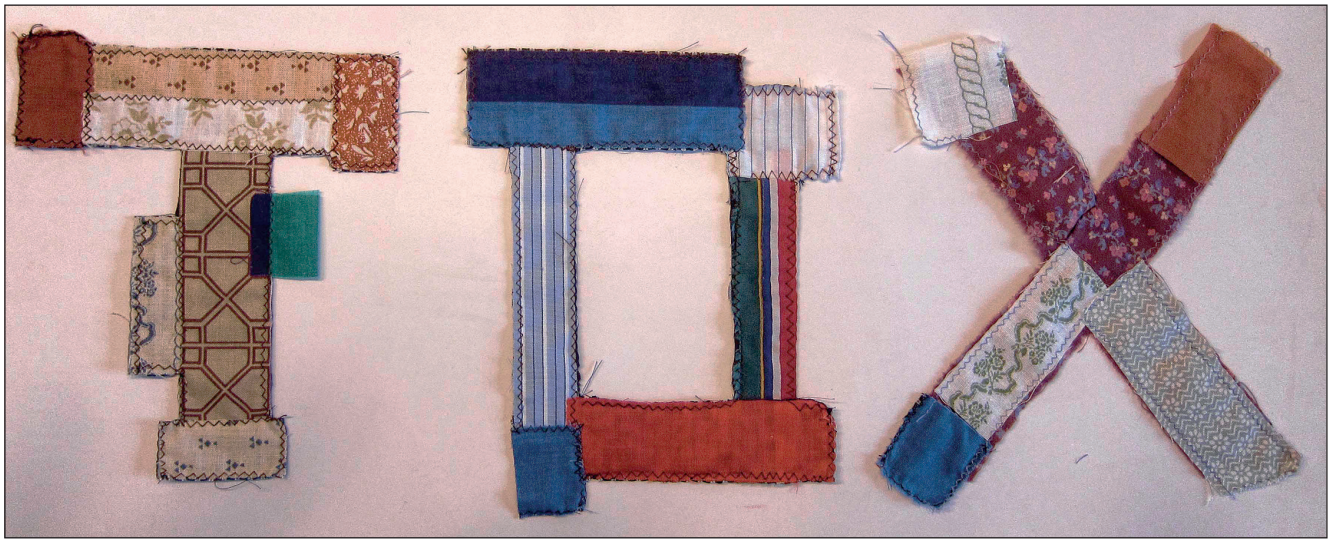

Fig. 1: The patchwork building of toxicology
(courtesy of Ingrid Hartung, Solingen, Germany)

If not evolution, what are the alternatives? Either revolution or intelligent design (to stay in the allegory of disputing evolution). It is appealing to think of the necessary changes as a scientific revolution, borrowing ideas from Thomas S. Kuhn (Hartung, 2008). However, the revolutionary change, the asteroid, which extinguishes large numbers of our species and lets us start from scratch, is not in sight. Kuhn also did not apply his concept to a science like toxicology as a whole, only to the exchange of individual ideas within the larger framework. So, intelligent design? While science can usually not be designed, and depends on the competition of ideas over time, the practical use of science can be designed, i.e., engineered. This is what is meant by "strategic development" in the title of this article. As much as we believe that sound science needs to be the basis of all these developments, we would prefer "intelligent engineering" over "intelligent design", which has more the connotation of art and beauty, not to belittle the role of design in serving function. The key element is "strategic", i.e., "carefully designed or planned to serve a particular purpose or advantage".

We will briefly review some of the strategic developments in the US with respect to regulatory processes. In Europe, we see some national equivalents, but only rudimentary developments on the transnational scale. The fundamental question of this article is, who should be in the driver seat to keep regulatory science up to date in Europe? In the US, as the most important trade partner, primarily the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) do this with support from the National Institutes of Health (NIH), especially via the National Toxicology Program (NTP). These agencies more recently have become very proactive and collaborative in fostering new approaches and technologies under the Tox21 program. Their approaches often cross industrial sectors, when for example high-throughput biological profiling programs include pesticides, pharmaceuticals (failed drug candidates), cosmetic ingredients and environmental toxicants. This has led to the use of new approaches for emergency risk assessments and is currently adapted to prioritize chemicals for the US endocrine disruptor screening program.

In Europe, activities to renovate regulatory tools are dispersed among many institutions, often in short-lived research programs without central steering or institutional memory. Statutes for executive agencies are laid down in EC regulation 58/2003[1]. In substance, they are more executive bodies implementing legislation and have specific mandates based on the European Commission's (EC) work plan but without capacity to steer new scientific developments. In effect, often there is no real partner to team up with as in the US developments. At the same time, the demanding EU legislations for chemicals, cosmetics, biocides, plant protection products and emerging legislations for medical devices and endocrine disruptors could benefit from a toolbox of 21st century science.

2 Strategic planning in toxicology

What is Strategic Planning? The website of the Balanced Scoreboard Institute[2] and Strategy Management Group[3], two consultancies for organizations in strategic planning, define: "*Strategic planning is an organizational management activity that is used to set priorities, focus energy and resources, strengthen*

[1] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003R0058&from=EN

[2] http://balancedscorecard.org/Resources/Strategic-Planning-Basics

[3] http://www.strategymanage.com/strategic-planning-basics/

operations, ensure that employees and other stakeholders are working toward common goals, establish agreement around intended outcomes/results, and assess and adjust the organization's direction in response to a changing environment. It is a disciplined effort that produces fundamental decisions and actions that shape and guide what an organization is, who it serves, what it does, and why it does it, with a focus on the future. Effective strategic planning articulates not only where an organization is going and the actions needed to make progress, but also how it will know if it is successful." In short, strategic planning means to identify needs, find the solution, define the roadmap and resources as well as the measures of success. As we will see below, in toxicology we have hardly achieved agreement on the needs…

Where does such strategic discussion take place in toxicology? A few prominent examples include:

– The *US Environmental Protection Agency* (EPA), especially out of their Office of Research and Development (ORD) with the National Center for Computational Toxicology (*NCCT*)[4]. Their programs *ExpoCast* (Wetmore et al., 2015; Wambaugh et al., 2015), *ToxCast* (Richard et al., 2016), the *Tox 21* collaboration with the NIH and the FDA, the *Virtual Tissues*[5] and computation toxicology in general (Patlewicz and Fitzpatrick, 2016) are systematically developing new approaches to chemical safety assessment. By commissioning the National Research Council report on *Toxicity Testing for the 21st Century* (NRC, 2007), the EPA started one of the most prolific debates on how to modernize risk assessment.
– The *US FDA* has with its report *Advancing Regulatory Science at FDA: A Strategic Plan*[6] of 2011 identified eight priority areas of which four are most relevant to modernize safety sciences: (1) Modernize toxicology to enhance product safety, (4) Ensure FDA readiness to evaluate innovative emerging technologies, (6) Implement a new prevention-focused food safety system to protect public health, (7) Facilitate development of medical countermeasures to protect against threats to U.S. and global health and security. Notably, in 2013, FDA added a ninth strategic priority: (9) Strengthening the global product safety net. Earlier, FDA promoted the application of emerging science to drug safety as one of the goals of the FDA's *Critical Path Initiative*[7] based on the 2004 FDA white paper *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*[8]. The role of the US FDA is especially key for safety assessments of pharmaceuticals – they dominate the international discussion, though harmonized via the International Conference on Harmonization[9], as the US, which has 6% of the world population, consumes about 60% of drugs under patent, which gives them a lighthouse function for the pharmaceutical industry (Rovida et al., 2015a).
– The *US NIH National Institute for Environmental Health Sciences (NIEHS)* cohosts the *National Toxicology Program (NTP),* which has developed its own strategic plan[10], last updated 2014. Already a decade earlier, this plan spearheaded some of the high-throughput testing and big data approaches to toxicology, which are now implemented within the Tox 21 alliance with EPA, FDA and NIH NCATS. Within NIEHS, the *NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)* is currently developing into an engine of change in toxicology. A key example is the current development of a roadmap for replacing rodents in acute toxicity tests[11]. In 2015, this already impacted on EPA's endocrine disruptor screening program[12], for the first time replacing animal screening tests with assays from the EPA ToxCast program.
– *The US National Academies of Sciences, Engineering and Medicine (NAS)* and their *National Research Council (NRC)* have made several contributions (all freely available on the NAS website https://www.nap.edu/) to revamping safety sciences, including *Risk Assessment/Safety Evaluation of Food Chemicals* (1980), *Risk Assessment in the Federal Government: Managing the Process* (1983), *Monitoring Human Tissues for Toxic Substances* (1991), *Science and Judgment in Risk Assessment* (1994), *Human Biomonitoring for Environmental Chemicals* (2006), *Toxicity Testing in the 21st Century: A Vision and a Strategy* (2007), *Science and Decisions: Advancing Risk Assessment* (2009), *Animal Models for Assessing Countermeasures to Bioterrorism Agents* (2011), *Science for Environmental Protection: The Road Ahead* (2012), *Exposure Science in the 21st Century: A Vision and a Strategy* (2012), *Research Progress on Environmental, Health, and Safety Aspects of Engineered Nanomaterials* (2013), *Review of EPA's Integrated Risk Information System (IRIS) Proces*s (2014) *Application of Modern Toxicology Approaches for Predicting Acute Toxicity for Chemical Defense* (2015) and *Using 21st Century Science to Improve Risk-Related Evaluations* (2016). This is a remarkable series of high-quality contributions to explore in a consensus process new opportunities in risk assessment of substances, to which a number of workshops (reports available from the same site) contributed.
– In recent years, especially the *NRC report on Toxicity Testing*

[4] https://www.epa.gov/aboutepa/about-national-center-computational-toxicology-ncct

[5] https://www.epa.gov/chemical-research/virtual-tissue-models-predicting-how-chemicals-impact-development

[6] http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm

[7] http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm

[8] http://bit.ly/2iImua7

[9] http://www.ich.org/home.html

[10] https://ntp.niehs.nih.gov/ntp/pubs/currentdirections2014_508.pdf

[11] https://www.niehs.nih.gov/news/newsletter/2015/11/spotlight-toxicity/index.htm

[12] https://www.niehs.nih.gov/news/newsletter/2015/8/spotlight-replaceanimal/index.htm

in the 21st Century: A Vision and a Strategy (NRC, 2007; Krewski et al., 2010) led to a number of follow-up activities for implementation. Especially, Mel Andersen and the *Hamner Institute* pursued important implementation activities for pathway-based case studies in risk assessment (Andersen et al., 2011, 2015). It is most unfortunate that the Hamner Institute ceased to exist a year ago, and we will have to wait and see how much of this work can be sustained in another form. Dan Krewski and coworkers at the University of Ottawa and *Risk Sciences International* pursued their steering work in implementing this vision also by developing overarching new frameworks for risk assessment and management (Krewski et al., 2014).

– *The Adverse Outcome Pathway (AOP)* concept (Ankley et al., 2010) was developed to meet the needs for translation questions through the identification and depiction of causal linkages between mechanistic *in vitro* or *in vivo* data and biological endpoints meaningful to risk assessment (Ankley et al., 2016). The AOP concept promoted by *OECD*[13] has received considerable interest and support as a communication and organizational tool by research toxicologists and risk assessors throughout the world. Dozens of AOPs have been proposed thus far and scores are being developed collaboratively by the toxicology community[14]. Noteworthy, while originally developed in the context of environmental chemical safety, the concept increasingly impacts on drug safety testing (Hartung, 2016b).
– The *Human Toxome Project*[15] (Bouhifd et al., 2015) aims primarily to support the evolution of toxicology towards a mechanism-based science. *CAAT*, with one of the authors (TH) as principal investigator, promotes the use of advanced-omics and high-throughput technologies and supports the implementation of knowledge-based frameworks such as Pathways of Toxicity and Adverse Outcome Pathways (Hartung and McBride, 2011) and thus plays a key role in implementing the NAS Tox21 vision. A key goal of the Human Toxome Project is the development of tools for identification of pathways of toxicity (Kleensang et al., 2014) from multi-omics technologies (Maertens et al. 2015, 2016; Pendse et al., 2016) to feed into a systems toxicology approach (Hartung et al., 2012). The combination of orthogonal omics technologies has the advantage that the tremendous signal/noise problem of any omics technology is overcome. Simply said, a pathway perturbation, which is visible in several technologies, strongly corroborates a biologically meaningful pattern. The respective approaches developed in the Human Toxome Project are currently being published (Fasani et al., 2016; Rosenberg et al., unpublished). The workflow involves corroboration of mechanism by linguistic search engines and mechanistic validation (Hartung et al., 2013a). These bioinformatics approaches can be applied to any (multi-)omics dataset of projects, and pilot projects have expanded them to proteomics and RNASeq data. At the moment, the program is mainly driven by two funded projects: The NIH Transformative Research Grant "Mapping the Human Toxome by Systems Toxicology" and the *EU-ToxRisk* project[16]. Starting in January 2016, EU-ToxRisk received €30 million in the EU Horizon 2020 initiative and includes 36 European organizations and CAAT from the US. EU-ToxRisk aims to develop a new way of risk assessment. It promotes mechanism-based toxicity testing and risk assessment according to the principles laid down for toxicology for Tox21. The project will integrate advances in *in vitro* and *in silico* toxicology, read-across methods, and adverse outcome pathways. EU-ToxRisk will continue to make use of the case study strategy deployed in SEURAT-1[17], a FP7 initiative that ended in December 2015. Even though the development of new non-animal methods is one target of EU-ToxRisk, the project puts special emphasis on their acceptance and implementation in regulatory contexts (Daneshian et al., 2016).
– The Johns Hopkins Center for Alternatives to Animal Testing (*CAAT*) aims, outside of the pressures of regulating or being regulated, to be an engine of change in the safety sciences and other areas of animal use, overcoming the limitations of animal-based approaches and accelerating the uptake of new technologies by collaboration with all stakeholder groups. CAAT has started a number of collaborative programs to advance safety sciences, which include the Human Toxome Collaboration (see above), the Evidence-based Toxicology Collaboration (see below), the Good Cell Culture Practice Collaboration (Pamies et al., 2017) building on earlier work steered by ECVAM (Coecke et al., 2005), the Good Read-Across Practice Collaboration (Patlewicz et al., 2014, Ball et al., 2016; Zhu et al., 2016), the Refinement Collaboration (Zurlo and Hutchinson, 2014) and others. CAAT's *transatlantic think tank for toxicology (t^4)* has organized more than 30 workshops to advance concepts of toxicology such as integrated testing strategies (Hartung et al., 2013b; Rovida et al., 2015b), epithelial barrier models (Gordon et al., 2015), 3D cell cultures (Alépée et al., 2014), microphysiological systems (Marx et al., 2016), high-content imaging (van Vliet et al., 2014), and has commissioned a number of white papers.
– The Health and Environmental Sciences Institute *(HESI)* is a global branch of the International Life Sciences Institute *(ILSI),* which aims to provide an international forum to advance the understanding of scientific issues related to human health, toxicology, risk assessment, and the environment. HESI is funded and driven by industry. HESI recently managed the development of the *RISK21* framework[18], aimed at

[13] http://bit.ly/1Av6cj0
[14] https://aopwiki.org/aops/1
[15] http://humantoxome.com
[16] http://www.eu-toxrisk.eu
[17] http://www.seurat-1.eu
[18] http://www.risk21.org

developing a scientific, transparent, and efficient approach to the evolving world of human health risk assessment, bringing together international stakeholders from government, academia, industry, and some NGOs. Over 120 participants from 12 countries, 15 government institutions, 20 universities, 2 non-governmental organizations, and 12 corporations contributed. This process was created to address a needed transition in toxicology, exposure, and risk assessment methodology and communication to develop a cohesive framework that is practicable for risk assessment. A number of papers (Embry et al., 2014; Pastoor et al., 2014; Simon et al., 2014; Moretto et al., 2016; Solomon et al., 2016) and a web-based tool[19] have been published. The most distinctive aspect of RISK21 is that exposure drives the data acquisition. RISK21 principles include focusing on problem formulation, utilizing existing information, starting with exposure assessment (rather than toxicity), and using a tiered process for data development. Bringing estimates of exposure and toxicity together in a two-dimensional matrix provides a clear rendition of human safety and risk. Addressing the combined exposure to different chemicals as part of the problem formulation process, the RISK21 framework allows the identification of the circumstances in which it is appropriate to conduct a cumulative risk assessment for a group of compounds. A tiered approach has been proposed in which additional chemical stressors and/or non-chemical modulating factors (ModFs) are considered sequentially.

– The accurate assessment of environmental exposures remains an outstanding and largely unmet challenge. The *Human Exposome* is the environmental equivalent of the human genome, representing the complex exposures throughout life, including diet, lifestyle factors, and social influences (Smith and Rappaport, 2009; Rappaport, 2011; Escher et al., 2016). It also incorporates how the body responds to these exposures, encompassing much of what we refer to as "nurture". While the exposome concept has been established for human health, its principles can be extended to include broader ecological issues. The term exposome was coined by Wild (2005) at the International Agency for Research on Cancer (IARC), World Health Organization (WHO). A number of organizations are active in this field, including the NIEHS and the NAS[20]; the Human Exposome Project[21] brings together several academic and government laboratories across the world, collecting data that can contribute to our understanding of the exposome. The goal is to bring these investigators together to formulate a plan to define the exposome. Although at this stage it may not be possible to measure or model the full exposome, some recent European projects such as HELIX (The Human Early-Life Exposome)[22] (Vrijheid et al., 2014), EXPOsOMICS[23] (Callaway, 2012; Vineis et al., 2016) and HEALS (Health and Environment-wide Associations based on Large population Surveys)[24] and the American initiative HERCULES (Health and Exposome Research Center: Understanding Lifetime Exposures)[25] have started to make first attempts. A recent workshop at the Helmholtz Centre for Environmental Research (UFZ), Leipzig, Germany, explored if mechanistic understanding of the causal links between exposure and adverse effects on human health and the environment can be improved by integrating the exposome approach with the adverse outcome pathway (AOP) concept (Escher et al., 2016).
– The *Evidence-based Toxicology Collaboration (EBTC)*[26], with a secretariat at CAAT, has evolved over the last decade and promoted the use of tools from Evidence-based Medicine, such as systematic reviews. EBTC aims to foster the development of systematic, objective, and transparent test method assessment and decision-making based on test results. With agencies like EFSA, the EPA and the US NTP increasingly embracing systematic reviews (Stephens et al., 2016) and collaborating in EBTC, these approaches are gaining traction as a new paradigm of how to handle existing data in safety assessments. Noteworthy, EBT approaches cross-fertilize with the various quality assurance approaches: only evidence of high-quality sources can be used (requiring quality scoring (Samuel et al., 2016)) and this teaches the scientific community how to produce and report properly, as discussed recently for *in vitro* work (Pamies and Hartung, 2016).

Taken together, these different approaches have in common that they use modern technologies for data generation, including high-throughput and high-content methods, that they rely much less on animal models but combine *in vitro* and *in silico* tools, aim for quality assurance in data generation / integration and often make use of exposure information.

The most advanced strategic discussion is probably what is often called Toxicity Testing for the 21st Century (TT21c), Tox21 program[27] or Toxicology for the 21st Century (Tox-21c) (Hartung, 2009a). The tremendous efforts to promote the TT21c report of the NRC over the last decade as an anchor for change as well as the buying power of the agencies setting this into practice within the Tox 21 program have made a strong impact. This is not a single program, but a largely US-centered discussion with overlapping and collaborating players. The authors have been intimately involved with these activities and especial-

19 http://www.risk21.org/?page_id=11840

20 https://www.nap.edu/read/23414/chapter/1

21 http://humanexposomeproject.com

22 http://www.projecthelix.eu

23 http://www.exposomicsproject.eu

24 http://www.heals-eu.eu

25 http://emoryhercules.com

26 http://www.ebtox.org

27 https://ncats.nih.gov/tox21/about

ly aimed to bridge this to the European discussion by creating CAAT-Europe, a European policy program informing policy-makers in Brussels, and the transatlantic think tank for toxicology (t[4]). Already at the time of transitioning from the European Commission to the US in early 2009, strategic planning on how to contribute to Tox-21c started (Hartung, 2009b). This paper already identified a number of challenges for the implementation of Tox-21c: "*The landmark publication ...toxicology for the 21st century in 2007 has created an atmosphere of departure in our field. The alliances formed, symposia and meetings held and the articles following are remarkable, indicating that this is an idea whose time has come. Most of the discussion centers on the technical opportunities to map pathways of toxicity and the financing of the program. Here, the other part of the work ahead shall be discussed, that is, the focus is on regulatory implementation once the technological challenges are managed, but we are well aware that the technical aspects of what the National Academy of Science report suggests still need to be addressed: A series of challenges are put forward which we will face in addition to finding a technical solution (and its funding) to set this vision into practice*." This is the first time, to the best of our knowledge, that the term pathways of toxicity (PoT) was used, a concept which we later expanded (Kleensang et al., 2014) to describe "*A molecular definition of cellular processes shown to mediate adverse outcomes of toxicants*", which is the basis of the Human Toxome Project. The ten challenges put forward at the time were:

1. *Testing strategies instead of individual tests* – A toxicology based on pathways is one that is likely based on various tests; we therefore need other ways to combine tests for the different pathways in a different way, but we have neither a terminology for test strategies nor tools to compose or validate them.
2. *Statistics and multiple testing* – When testing for multiple pathways, we will need to correct our statistics for multiple testing. We have to lower significance levels accordingly or we will run increasingly into false-positive findings.
3. *Threshold setting* – Where does a relevant effect start? Certainly not where we can measure a significant change. What is measurable depends only on our detection limits, and in the case of multi-endpoint methods a lot on signal/noise relation and the inevitable number of false-positive results. What does it mean if a pathway is triggered but is accompanied by some compensatory ones as well? We definitively have to overcome the mentality of "we see an effect, this is an effect level."
4. *What to validate against?* – The first problem is that the choice of the point of reference determines where we will arrive. If the new toxicology is based on animal tests as the reference, we can only approach this "gold standard" but will not be able to overcome its shortcomings. The second problem is that it is unlikely that we will be able to evaluate the entire pathway-based test strategy in one step. So, the question becomes what to validate against, if we have only partial substitutes? As a way forward we have proposed a "mechanistic" validation (Coecke et al., 2007), where it is shown that the prototypic agents affecting a pathway are picked up while others not expected to do so are not.
5. *How to open regulators for change?* – Change requires giving up on something not adding to it. As long as most new approaches are considered "valuable additional information", the incentive to drive new approaches through technical development, validation and acceptance is rather low, given 10-12 years of work of large teams and costs of several hundred thousand dollars. The process is so demanding because regulatory requirements often mandate virtually absolute proof that a new method is equal to or better than traditional approaches. Most importantly, to let go of tradition requires seeing the limitations of what is done today. This discourse was too long dominated by animal welfare considerations. This has been convincing for parts of the general public, but the scientific and regulatory arena is much less impressed by this argument. We (Hoffmann and Hartung, 2006) and others (Guzelian et al., 2005) have put forward the idea to initiate … Evidence-based Toxicology (EBT). Three main areas of interest emerged (1) a systematic review of methods (similar to the review of diagnostic methods in EBM), (2) the development of tools to quantitatively combine results from different studies on the same or similar substances (analogous to meta-analyses); and (3) the objective assessment of causation of health or environmental effects. With regard to the novel toxicological approaches, however, most important will be that existing and new ways are assessed with the same scrutiny. Sound science is the best basis for the selection of tools. Validating against methods believed to do a proper job is only betting and will always introduce uncertainty about the compromise made while forgetting about the compromise represented by the traditional method.
6. *The global dimension* – A central obstacle for the introduction of new approaches is globalization of markets. Globally acting companies want to use internationally harmonized approaches. This means that change to new approaches, if not forced by legislation, will occur only when the last major economic region has agreed on the new one.
7. *Quality assurance for the new approach* – For the global use of methods, it does not suffice to agree on how to test. If we want to accept approaches executed at other places, challengeable quality standards for performance and documentation of tests must exist, as they have been developed as OECD Good Laboratory Practice (GLP) or various ISO standards. … A key problem will be the fluid nature of the new methodologies: standardization and validation requires freezing things in time, every change of method requires re-evaluation not possible for the complex methodologies. On the contrary, we see continuous amendments of *in silico* models or new technologies (e.g., gene chips). Shall we validate and implement a certain stage of development and close the door for further developments?
8. *How to change with step by step developments now becoming available?* – Things would be easy if a new regulatory toxicology would become available at once – we might then compare old and new and decide to change. But we will continue to receive bits and pieces as we have already experienced for a while. When should we make a major change and not just add or replace patches?

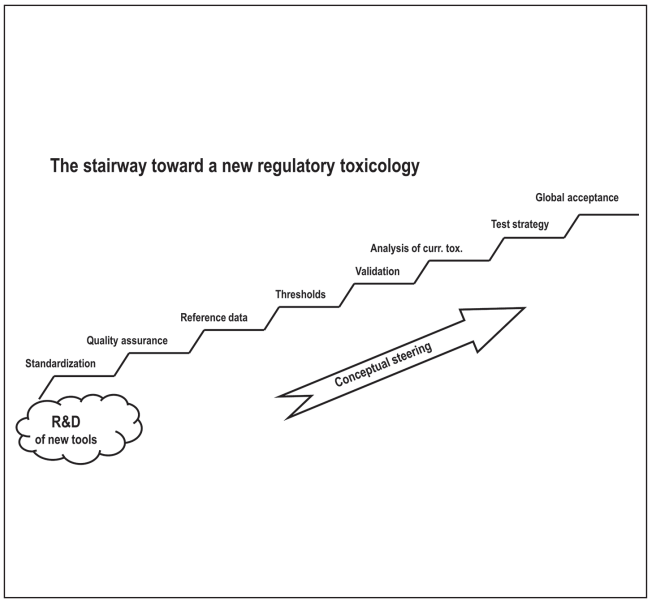

Fig. 2: Conceptual steering through the ten challenges identified for implementing Tox-21c
(modified from Hartung, 2009b)

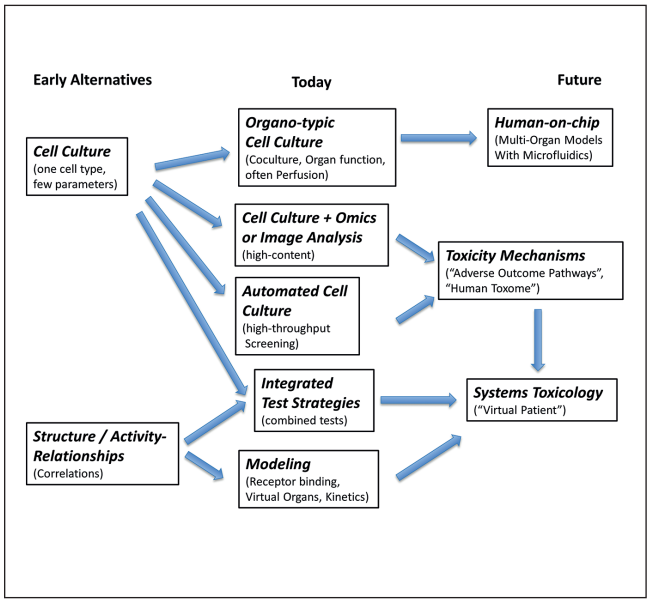

Fig. 3: The technological developments in support of new approaches in safety testing

9. *How to organize transition?* – Beside the technological challenge, we have identified the need for systematic combination of approaches (integrated testing), and a program to objectively assess current approaches, to validate them and to implement them. This program requires out-of-the-box thinking, that is, intellectual steering (Fig. 2).
10. *Making it a win/win/win situation* – Three major stakeholders will have to collaborate to create the new toxicology, that is, the academia, regulators and the regulated communities in industry. … The shear dimensions of the tasks ahead will require a trans-disciplinary, trans-national, trans-stakeholder and trans-industrial sectors approach. … There is gain for all players including the following: the challenge of the development of new approaches; the better understanding of limitations of our assessments; the likely development of safer products with new test approaches; and the international harmonization prompted by a major joint effort.

Over the last eight years, we have been mainly addressing the challenges 1-7 with CAAT's work plan. With the limited resources of an academic center, progress where achieved was only possible in collaborations and this is why we have recently renamed our different programs as collaborations. We have seen remarkable technological developments in this period (Fig. 3). We have accompanied this with some strategic discussions such as the development of a roadmap for systemic toxicity testing (Basketter et al., 2012; Leist et al., 2014). Our policy program and the discussion with policy-makers often leads to activities such as written questions to the European Commission as shown for example in Box 1. With the development of CAAT's new strategic plan we are now starting to tackle challenges 8-10 more directly. This article is part of wrapping our mind around these issues.

Box 1
Question for written answer E-001165/13 to the Commission
Christel Schaldemose (S&D) (4 February 2013)

Subject: Testing strategies for endocrine disrupters in Europe

Parliament's own-initiative report entitled 'Protection of public health from endocrine disrupters' (2012/2066 (INI)) discussed the criteria for assessing putative substances, but did not sufficiently address the underlying issue of testing strategies.

A European research centre focusing on endocrine disrupters and other regulatory scientific advances would strengthen the EU's strategy for better policy research on endocrine disrupters and facilitate the development of EU tools by looking at pathways of toxicity through, *inter alia*, *in vitro* testing methods. Ultimately, this would be a very effective way to help assess endocrine disrupters with a view to protecting the environment and consumers.

I would therefore like to ask the following questions:

1. What is the Commission's approach to the development of testing strategies for endocrine active substances?
2. Does the Commission plan to take advantage of US developments such as the Endocrine Disrupter Screening Program 21 (EDSP21) and the National Institutes of Health Human Toxome Project?
3. Is the Commission considering establishing a European research centre focusing on regulatory sciences?
4. Is the Commission considering approaches involving evidence-based toxicology?

Answer given by Mr Potočnik on behalf of the Commission (22 April 2013)

1. Testing strategies for regulatory purposes are developed by the Commission and relevant Agencies in consultation with Member States and stakeholders through the procedures foreseen in specific legislation. The Commission has however recognised the need to fill knowledge gaps to further improve the application of testing strategies in legislation. The Commission in its proposal for 'a General Union Environment Action Programme to 2020' and in its 2012 Communication to the Council on the combination effects of chemicals recognised the need to develop a comprehensive toxicity knowledge base to better understand how chemicals interact with organisms. This will also include improved understanding of endocrine disruptors. The Commission is currently assessing how such a comprehensive knowledge base can best be established and managed. Such an effort would require support for research projects under the next Horizon 2020 Research and Innovation Framework.
2. The Commission in its Community Strategy for Endocrine Disruptors [COM(1999) 706] recognised the need for information exchange and international coordination and is following closely the international developments in the field including those in the US.
3. The Commission is currently reviewing its Community Strategy for Endocrine Disruptors to reflect the progress achieved in science and changes in legislation. The Commission will consider the idea of a virtual European research centre in the review process.
4. The development of a comprehensive toxicity knowledge base to better understand how chemical interact with organisms referred to in paragraph 1 above includes approaches involving evidence-based toxicology.

It is striking that most of the strategic discussions listed above are centered in the US. Sure, there are also a number of workshops and smaller projects on national (e.g., in the Netherlands, Germany and the U.K.) and European Union level in Europe but, with no offense intended, they are typically not long-lasting and often address only smaller aspects of the safety science paradigms. We have earlier identified that this is in part due to the bottom-up approach in the EU compared to the US, where especially strong agencies manage change top-down (Hartung, 2010b). European agencies in comparison are more executive and, with the notable exception of European Food Safety Authority (EFSA) (Benfenati et al., 2016) and more recently the European Chemicals Agency (ECHA) (see below), do not embark on strategic planning. There is simply no institution in Europe empowered to strategically develop safety testing approaches and keep track of the different contributions over time. This is not saying that the discussion, competence and contribution from European scientists and regulators is by any means less than from the US, but their impact is reduced as it is less organized or takes place via the US and international activities. Other parts of the world beside Canada are not very prominent in the discussion to renovate safety sciences.

3 The EU paradox with respect to safety sciences

With the tremendous available sources of information and constant issues on safety science to be solved for consumer protection, the environment as well as for industry, communication of safety science by scientists to policy-makers and legislators (e.g., the European Commission and Members of the European Parliament (MEP)) is of particular importance. In this respect, one of the most challenging aspects is to provide evidence-based arguments that are understandable to the national and EU legislators, to the diversity of stakeholders and EU bodies. Paradoxically, the abundance of technical information undermines its intelligibility and use for policy purposes, because of a lack of coordination and steering to guide its production.

Safety sciences in Europe already started in 1957 with the creation of the European Commission Joint Research Center (JRC), at the time EURATOM, as the scientific arm for policy-making with a scope restricted to the nuclear energy field. With the creation of an Institute for the Environment and one for Health and Consumer Protection in the JRC, this scientific support was expanded to support, among others, safety-relevant legislations. However, such support is only occasionally meant to drive new technological developments in safety sciences. Almost forty years later in 1995, the first EU executive agency for product safety, i.e., the European Medicines Agency (EMA), which deals with authorization of some drug categories for the EU market, was created.

Since then, the numbers of EU bodies, agencies and committees have strongly increased, causing a thorny issue in 2010-2012 in Europe and a big fight in the European Parliament: At the last count i) there were 34 decentralized EU agencies for the different EU policies far beyond safety considerations installed in 24 out of 28 EU member states[28] (Tab. 1), ii) in the last twenty years, the European Commission (EC) established more than 10 scientific committees[29,30] advising different Directorates General (DG) when external expertise was required, iii) in 2012 the President of the European Commission created a Chief Scientific Adviser (CSA)[31], who was under the recent Commission replaced by an advisory group, iv) the EU execu-

[28] http://europa.eu/about-eu/agencies/index_en.htm

[29] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004D0210&qid=1483543839910&from=en

[30] http://ec.europa.eu/health/scientific_committees/about/index_en.htm

[31] http://ec.europa.eu/archives/commission_2010-2014/president/chief-scientific-adviser/index_en.htm

Tab. 1: List of EU countries hosting decentralized EU agencies (in bold those with obvious overlap with the suggested ESSI)

European Banking Authority (EBA)	United Kingdom
European Medicines Agency (EMA)	United Kingdom
European Police College (CEPOL)	United Kingdom
European Police Office (EUROPOL)	The Netherlands
The European Union's Judicial Cooperation Unit (EUROJUST)	The Netherlands
European Centre for Disease Prevention and Control (ECDC)	Sweden
European Agency for Safety and Health at Work (EU-OSHA)	Spain
European Fisheries Control Agency (EFCA)	Spain
Office for Harmonisation in the Internal Market (OHIM)	Spain
Agency for the Cooperation of Energy Regulators (ACER)	Slovenia
European Maritime Safety Agency (EMSA)	Portugal
European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)	Portugal
European Agency for the Management of Operational Cooperation at the External Borders (FRONTEX)	Poland
European Asylum Support Office (EASO)	Malta
Translation Centre for the Bodies of the European Union (CdT)	Luxembourg
European Institute for Gender Equality (EIGE)	Lithuania
Body of European Regulators for Electronic Communications (BEREC)	Latvia
European Food Safety Authority (EFSA)	Italy
European Training Foundation (ETF)	Italy
European Foundation for the Improvement of Living and Working Conditions (EUROFOUND)	Ireland
European Centre for the Development of Vocational Training (Cedefop)	Greece
European Network and Information Security Agency (ENISA)	Greece
European Aviation Safety Agency (EASA)	Germany
European Insurance and Occupational Pensions Authority (EIOPA)	Germany
Community Plant Variety Office (CPVO)	France
European Railway Agency (ERA)	France
European Securities and Markets Authority (ESMA)	France
European Chemicals Agency (ECHA)	Finland
European Agency for the operational management of large-scale IT systems in the area of freedom, security and justice (eu-LISA)	Estonia
European Environment Agency (EEA)	Denmark
European GNSS Agency (GSA)	Czech Republic
Single Resolution Board (in preparation) (SRB)	Belgium
European Union Agency for Fundamental Rights (FRA)	Austria
European Public Prosecutor's Office (EPPO) (in preparation)	To be determined

tive receives *ad hoc* advice for risk management from a number of "comitology" committees regarding the implementation of EU legislation in national administrations.

The numerous structures currently existing in addition to a high turn-over and short shelf-life of experts or *ad hoc* advisory committees illustrates the complexity of safety sciences' landscape in the EU. Indeed, in the EU member states (MS) and therefore in the EU, the knowledge and concerns of the public regarding consumer protection and the environment is extremely high[32]. Apparently, this level of awareness seems to have triggered unilateral (i.e., MS vs. EU) actions in risk management rather than collective (i.e., MS + EU) steering at the EU level. Indeed, multiple disagreements on safety assessment and management arose between MS and EU bodies, e.g., regarding the tolerable daily intake of bisphenol A (BPA), where France's legislation banning BPA from 2012 conflicted with EFSA's risk assessment and was repealed in 2015 by France's highest court, or restriction of phthalate uses, where Denmark did not

[32] http://europa.eu/rapid/press-release_IP-14-976_en.htm

Tab. 2: Competences of current safety science structures in the EU and internationally in 2015[a]

	European Commission Directorate Generals	EC Scientific Committees	EU Agencies	International Bodies
Biocides	SANTE	–	ECHA	
Chemicals including nanoparticles	GROW	–	ECHA	OECD
Cosmetics	GROW	SCCS	–	ICCR
Endocrine Disrupting Chemicals	SANTE (lead) GROW ENV JRC	SCCS SCENIHR	EEA EFSA ECHA	WHO
Food	SANTE		EFSA	FAO, Codex alimentarius
Genetically Modified Organisms (GMOs)	SANTE		EFSA	
Medical devices	SANTE*	SCENIHR	–	ISO
***In vitro* diagnostics**	GROW		–	
Pharmaceuticals Veterinary pharmaceuticals	SANTE*		EMA	ICH, VICH
Plant Protection Products	SANTE		–	OECD
Others		SCENIHR		
Environment	ENV	SCHER	EEA	

Abbreviations: European Commission (EC) Directorates General: SANTE (Health and Food Safety), GROW (Internal Market, Industry, Entrepreneurship and SMEs), ENV (Environment), JRC (Joint Research Centre); EC Scientific Committees: SCCS (Consumer Safety), SCHER (Health and Environmental Risks), SCENIHR (Emerging and Newly Identified Health Risks); EC agencies: ECHA (European Chemicals Agency), EEA (European Environment Agency), EFSA (European Food Safety Authority), EMA (European Medicine Agency); International: OECD (Organisation for Economic Co-operation and Development), ICCR (International Cooperation on Cosmetics Regulation), WHO (World Health Organization), FAO (Food and Agriculture Organization of the United Nations), ISO (International Organization for Standardization), ICH (International Conference on Harmonisation), VICH (Veterinary International Conference on Harmonisation).

[a] http://europa.eu/rapid/press-release_IP-14-984_en.htm

agree with ECHA's position[33]. These cases are clear examples of vertical disagreement. Another example to illustrate horizontal divergences pertains to endocrine disrupters, where multiple DGs, agencies and scientific committees started to work on the subject with different expert groups.

These examples illustrate how EC complexity works in an *ad hoc* situation: by creating groups, committees, and separate steering. However, lack of persistence of such steering structures prevents building up experience for possible future problems. Indeed, the safety sciences landscape is fragmented and none of the EU bodies have so far entirely embraced safety sciences as an umbrella *per se*. Instead this always falls to a subsection within the agencies or the DGs (see Tab. 2) that are most relevant in the field of hazard/risk assessment, i.e., European Food Safety Agency (EFSA; Parma, Italy), European Center for Disease Prevention and Control (ECDC; Solna, Sweden), European Environmental Agency (EEA; Copenhagen, Denmark) or EMA (European Medicine Agency; London, United Kingdom).

The expertise on the safety of products and substances available in Europe has never been so abundant, and yet it has also never been so fragmented. The result of this fragmentation is frequent vertical and horizontal divergence of opinions.

4 Current mechanisms of scientific advice on safety assessments at EU level

EU scientific advice is introduced and described in a chronological manner in this section and most scientific structures relevant to this article are presented. Historically, expertise was built to answer specific DG's needs or so to say "in silos". Any form of steering was only considered approximately 10 years ago. With the many agencies and committees that were established in the EU in the past decades, a sufficient amount of expertise is available. However, the coordination and optimal use of this expertise should now be improved. This cannot be done by the EC itself. It is worth keeping in mind that there are more than 30 DGs that employ 33,000 people (excluding agencies) to

[33] http://www.euractiv.com/consumers/danish-minister-bans-endocrine-d-news-514424

serve 510 million citizens, i.e., 0.006% of the population works for the EC[43]. In comparison, the US EPA alone has 15,400 employees (2014) and 14,600 work at the US FDA (2014), not even including the many contractors. This means that the two major US regulatory agencies employ as many people as the entire European Commission with all of its duties. The respective agencies in Europe have about 300 (EFSA), 600 (ECHA) and 900 (EMA) employees. Naturally, the EC has to draw on the competent authorities in the member states and on individual experts in various committees.

4.1 Commission Expert Groups on Safety Sciences

4.1.1 DG Joint Research Center (JRC)

The JRC is the DG in charge of science for EU policy support. Its first site was inaugurated in 1961. The JRC was originally created to fulfill requirements under the Euratom Treaty of Rome (1957). During the past century, the JRC has extended its expertise to other fields important to policy making, such as life sciences, energy, security and consumer protection. It is now composed of seven scientific institutes and located in five different countries across Europe, i.e., in Ispra (Italy), Geel (Belgium), Petten (The Netherlands), Karlsruhe (Germany) and Seville (Spain). Each site has its own specialty with Ispra, Italy, being the largest, with three institutes, and the oldest.

Especially relevant in the context of this article is the European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM)[35] hosted by the JRC in Ispra, which recently was made an EU reference laboratory following Directive EU/2010/63 (Hartung, 2010c). The assessment of the validity of new approaches (Hartung et al., 2004), with a strong focus of EURL-ECVAM's work on regulatory methods, is a key step in the introduction of new methods into regulatory practice. On this level, intense collaboration takes place with the respective international organizations. EURL-ECVAM also acts as a method and data repository. The mandate of EURL-ECVAM, however, does not really include the steering of a scientific strategy for safety sciences though its work often impacts here.

4.1.2 European Commission Scientific Committees

Scientific advice to policy-making in the EC has gradually become more formal and institutional. Scientific committees were often established without much publicity to respond to the needs of policy makers, in particular DGs. Most of the time, external scientists were individually invited directly by DGs to join the committee. The scientific committee for food and many other similar committees (e.g., the committee for proprietary medicinal products, now the CHMP managed by the EMA) were established in this manner in the 1970s. Consumer health concerns have led to beefing-up and formalizing the system of scientific advice. More committees were created at the end of the 1990s under DG SANCO (a scientific steering committee, a scientific committee on plants, a scientific committee on animal nutrition…). Many of these were transferred to the EFSA when the latter was created in 2002.

Currently, DG SANTE (formerly DG-SANCO) relies on only three independent scientific committees to provide scientific advice and draw its attention to new and emerging problems when preparing its policy and proposals relating to consumer safety, public health and the environment. Since March 2004, three non-food scientific committees[36] formed by a panel of experts, renewed every 5 years, meet 2 to 6 times a year (see Tab. 2 for more details). The scientific committees cover:

– Consumer Safety (SCCS)
– Health and Environmental Risks (SCHER)
– Emerging and Newly Identified Health Risks (SCENIHR)

DG SANTE also set up the Inter-Committee Coordination Group (ICCG)[37], composed of the chairs and vice-chairs of the three scientific committees, to help coordinate the committees and deal with:

– matters relating to harmonization of risk assessment
– questions common to more than one committee
– diverging scientific opinions
– exchange of information on the activities of the committees

The scientific committees were hosted in Brussels until 2012. They were then moved to Luxemburg[38] for reasons that are not entirely clear: It is said that the work would be more efficient since DG SANTE's headquarters are in Luxemburg. However, it is more difficult for experts to commute but also protects the panel members from being lobbied too actively.

DG EMPL (Employment, Social Affairs and Inclusion) steers the Scientific Committee on Occupational Exposure Limit Values (SCOEL)[39] set up in 1995 with the mandate to advise the EC on occupational exposure limits for chemicals at the workplace.

4.1.3 EU Scientific Positions and Advisory Groups under President Barroso and under President Juncker

Under the previous EC (2009-2014), the post of Chief Scientific Adviser (CSA) was created by President Barroso's office in January 2012 and held by Scottish scientist Prof. Anne Glover. During three years in function with limited staff and budget, the CSA gave scientific evidence-based opinions in safety sciences on GMOs[40], organized face-to-face meetings between the different parties after a heated debate on endocrine disrupt-

34 http://frdocs.com/doc/217860/key-figures-2014-jaune-2.indd---european-commission

35 https://eurl-ecvam.jrc.ec.europa.eu

36 European Commission scientific committees; http://ec.europa.eu/health/scientific_committees/index_en.htm

37 European political strategy centre (EPSC): http://ec.europa.eu/epsc/pdf/epsc-organisation-chart.pdf

38 26/03/2013; european voice; Luxembourg move 'sidelines' scientific committees: http://www.europeanvoice.com/article/luxembourg-move-sidelines-scientific-committees/

39 http://ec.europa.eu/social/main.jsp?catId=148&intPageId=684&langId=en

40 26/09/2013; euractiv; EU chief scientist: "It is unethical not to use GM technology"; http://www.euractiv.com/science-policymaking/eu-chief-scientist-unethical-use-interview-530692

ers in Europe to discuss the threshold vs. non-threshold approach[41], and commented on how science shapes EU policy or *vice versa*[42]. Although the reasons remain unclear, President Juncker eliminated the position: "*Since the mandate of the CSA was linked to the mandate of the previous Commission it therefore automatically came to an end on 31/10/2014*". It is worth mentioning that NGOs such as Greenpeace campaigned actively in favor of axing the job, arguing that the position concentrated too much power under only one person[43]. However, other stakeholders (scientists, industry, and institutions, e.g., the WHO scientific adviser) supported the idea to maintain the position. The CSA position was replaced by the Scientific Advice Mechanism (SAM)[44], a group of seven experts, who published first reports on light-duty vehicle CO_2 emissions and glyphosate. Interestingly, they give expertise based only on publicly available documents.

The Bureau of Economic Policy Advisers (BEPA) was converted into the European Political Strategy Centre (EPSC)[45] headed by Ms. Ann Mettler. The EPSC is organized around 6 teams: an Economic Team, a Social Affairs Team, a Sustainable Development Team, a Foreign Affairs Team, an Institutional Team and an Outreach and Communication Team. The European Group on Ethics in Science and New Technologies (EGE)[46] was maintained while the Science and Technology Advisory Council[47] was terminated. Scientific policy advice is currently a matter of intense debate, e.g., in a recent conference "Science and Policy Making: towards a new dialogue", i.e., the 2nd International Network for Government Science Advice Conference[48]. One of the authors (TH) is engaged with this process *Science, Society & Policy-Making: A New Blueprint of Ethics & Principles*[49].

4.2 Relevant EU agencies (EFSA and ECHA)

As mentioned above, EFSA and ECHA as well as others provide input and steer actions in the field. EFSA was created in 2002 and absorbed most of the EC scientific committees at that time. EFSA is regularly in the center of the debate in the national and EU media, mainly because it tackles sensitive topics such as GMO safety, aspartame, bisphenol A, neonicotinoides, and has developed its own definition of endocrine active substances. The agency's opinion is regularly disputed by NGOs and/or member states. EFSA has most recently developed a strategic plan for 2020[50] (Box 2).

Box 2
EFSA Strategy 2020 -Trusted science for safe food
(excerpt from the 2016 plan, ISBN 978-92-9199-847-0, https://doi.org/10.2805/397609, numbering changed)

EFSA has formulated five strategic objectives that "will enable us to progress our main areas of work while addressing the challenges and opportunities".

I Prioritise public and stakeholder engagement in the process of scientific assessment.
  1. Promote enhanced dialogue with stakeholders on mandates in collaboration with risk managers
  2. Make documentation on information gathering and the evaluation process available
  3. Foster engagement throughout the development of scientific assessments
  4. Ensure clarity and accessibility/usability in the communication of findings

II Widen EFSA's evidence base and optimise access to its data.
  5. Adopt an Open Data approach
  6. Improve data interoperability to facilitate data exchange
  7. Migrate towards structured scientific data

III Build the EU's scientific assessment capacity and knowledge community.
  8. Strengthen capacity building and capacity sharing with Member States, in collaboration with the European Commission's Directorate-General for Research and Innovation and its Joint Research Centre, EU agencies, international organisations
  9. Foster the growth of the EU risk assessment community in collaboration with international organisations
  10. Review and further develop EFSA's scientific assessment model

IV Prepare for future risk assessment challenges.
  11. Strengthen EFSA's resilience and ability to anticipate and respond effectively to food safety risks in coop-

41 12/2013-01/2014; chemical watch; Global Business Briefing; Bridging the EDC divide; http://chemicalwatch.com/17736/bridging-the-edc-divide?q=glover

42 27/05/2014, euractiv; EU twisting facts to fit political agenda, chief scientist says: http://www.euractiv.com/sections/eu-priorities-2020/eu-twisting-facts-fit-political-agenda-chief-scientist-says-302399

43 19/08/2014; euractiv; NGO backlash to Chief Scientific Advisor position grows; http://www.euractiv.com/sections/science-policymaking/ngo-backlash-chief-scientific-advisor-position-grows-307823

44 https://ec.europa.eu/research/sam/index.cfm

45 https://ec.europa.eu/epsc/home_en

46 https://ec.europa.eu/research/ege/index.cfm

47 http://ec.europa.eu/archives/commission_2010-2014/president/advisory-council/index_en.htm

48 http://ec.europa.eu/research/conferences/2016/ingsa2016/index.cfm

49 http://www.sci-com.eu/main/

50 https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/strategy2020.pdf

eration with EU and international partners
12. Develop and implement harmonised methodologies and guidance documents for risk assessment across the EU and internationally
13. Become a hub in methodologies, tools and guidance documents for risk assessment

V Create an environment and culture that reflects EFSA's values.
14. People: build a culture that puts EFSA's values into practice
15. Organisation and processes: develop an environment focused on improving organisational performance and capabilities

The document has an implementation plan annexed.

REACH (EC1907/2006)[51] and in consequence the creation of ECHA in 2008 has resulted in a booming and blooming of the EU safety sciences panorama. The EU faced new challenges such as i) harmonization of safety testing and principles (EU 440/2008)[52] among all the EU member states by writing them into stone, ii) communication platforms with MS committees and a stakeholder forum and iii) developing a regulatory science strategy[53]. There is a clear wish of ECHA to become more central in the debate of safety sciences, at least for the chemical and biocides' sector. Box 3 shows ECHA's priorities.

Box 3
ECHA's priority regulatory science areas
(excerpt from ECHA's Regulatory Science Strategy, ECHA-15-A-03-EN February 2015)

The selection of areas of regulatory science of importance to ECHA is primarily driven by their relevance to ECHA's work, taking into account the current and emerging scientific needs within REACH, CLP and BPR implementation. In addition, the following elements are considered:
– Important developing areas of regulatory science
– EU-wide policy need
– New and emerging scientific issues that have potential regulatory relevance.
– New areas of focus which emerge during ECHA's operational work.

Based on the above, the following list outlines the current priority areas for ECHA's regulatory science activities:
- Improved methodologies for risk assessment:
- For 'difficult' scenarios: e.g. substances with complex composition, substances that undergo transformation and naturally-occurring entities.
- For 'difficult' types of substance: e.g. metals, petroleum chemicals.
- Release from articles.
- Non-animal alternative methods and new approaches to hazard assessment, in particular rational integration of different lines of evidence (ITSs, IATAs, AOPs; with links to the QSAR Toolbox, omics and high-throughput screening methodologies) and other means of reduction or refinement when non-animal approaches are not yet available.
- Exposure assessment, in particular, quality and interpretation of exposure models, and the assessment of the presence and release of chemicals from articles.
- Tools and methods for identifying and assessing endocrine disrupting substances, and effects of exposure during sensitive life stages.
- Improved tools and methods for assessing persistence and bioaccumulation.
- Characterisation, hazard and exposure assessment, risk assessment and risk management of nanomaterials.
- Approaches to screening and priority setting of substances.
- Methods for combining evidence and integrating assessment methods, such as Weight-of-Evidence approaches.
- Assessing, describing and communicating uncertainty and incomplete knowledge (both classical randomness, i.e. statistical, and unforeseeable chaotic 'unknown unknowns'), including the impact on the conclusions. This should include qualitative and preparatory examination of the a priori, explicit or implicit hypotheses used in the assessment.
- Health and environmental impact, socio economic analysis and risk-benefit approaches (including social science approaches).

Abbreviations: REACH – Regulation (EC) No 1907/2006; CLP – CLP Regulation (EC) No 1272/2008; BPR – Biocidal Products Regulation (EU) No 528/2012; ITS – integrated testing strategy; IATA – integrated approach for testing and assessment; AOP – adverse outcome pathway; QSAR – quantitative structure-activity relationship

Noteworthy, both European agencies most recently have started a discussion toward strategic planning including the tools and ways safety assessments should be done. This represents a major change from their former more receiving and executing roles. It is not clear how much of this change is harmonized and coordinated, e.g., by the *Agency Network Scientific Advice (ANSA),* but they appear rather independent. ANSA is a recently established structure that organizes face-to-face

51 http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1907-20140410&from=EN

52 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:142:0001:0739:en:PDF

53 https://echa.europa.eu/documents/10162/13609/echa_science_strategy_final_web_en.pdf

meetings that take place once a year at rotating locations. It was initiated by the CSA in order to share "good practices" and harmonize working vocabulary such as "independent", etc. The network has survived the CSA's termination and was renamed *The EU Agency Network*[54]. It is worth mentioning that such steering already existed from 2006 to 2011 but was terminated by the EC.

In conclusion, EFSA and ECHA have started to fill the void of strategic discussion on the future of safety assessments. Given their rather slim resources, enormous workloads, the absence of an intramural scientific program and lack of history in advancing regulatory science and engagement in the respective discussions, it will have to be discussed whether this is the most effective approach. At the moment, the strategic planning appears more as a shopping list, lacking both an implementation plan and the performance indicators to measure success.

4.3 STOA – Science and Technology Option Assessment at the European Parliament

Increasingly, political issues at the European Parliament are closely linked with scientific progress or need scientific expertise (e.g., new regulations on *in vitro* medical devices, clinical trials, Horizon2020, etc.) in order for the Members of the European Parliament (MEPs) to legislate based on the scientific state-of-the-art. It is the role of STOA to coordinate the requests from the MEPs and more generally from the Parliament committees (e.g., ITRE or ENVI[55]), which are seeking an overview as well as accurate information for ongoing legislative processes. Furthermore, it is the function of STOA to get together experts on an *ad hoc* basis as a scientific panel to reply to Parliament's needs. STOA also interacts with its counterparts in some of the EU national parliaments.

Raising awareness on new trends and/or disrupting technologies is also part of their remits. As an example, in 2013, more than 17 workshops were held at the EP to discuss issues such as "Risk and innovation: balancing benefits and hazards" or "How to feed the world in 2050".

4.4 International developments impacting on the EU safety science landscape

Since the early 1980's the *Organisation for Economic Co-operation and Development (OECD)* has strongly shaped the current framework of chemical and pesticide safety assessment with its test guideline program via dedicated working groups. These methods are applied in all industry sectors and the parallel Good Laboratory Practice (GLP) framework and auditing allows the Mutual Acceptance of Data (MAD). With 35 countries covering 4 out of 5 continents and the major G8 and G20 countries on board, OECD plays a key role in terms of production of technical guidance for hazard and risk assessment. However, OECD has mostly not driven new approaches but has served their standardization and international harmonization. Remarkably different in approach, however, were the more recent OECD activities toward a (Q)SAR tool box and Adverse Outcome Pathways, which spearhead some innovative changes to safety sciences.

The most common international bodies dealing with safety sciences are compiled in Table 2, last column. In the scope of this article, only TTIP will be discussed below (see also Busquet et al., 2017). Under the TTIP agreement, the EC is negotiating with the United States on behalf of the EU member states. Obviously, every EU industrial sector is concerned with this bilateral discussion, since it will define the standards of practice on both sides of the Atlantic. Ironically, it seems that it is only on the EU side that strong fears are emerging regarding lowering those standards when it comes to safety, knowing that EU national regulatory agencies still rely heavily on animal test methods rather than human-based models as put forward under Tox21. The incoming new US administration has expressed concerns about pursuing TTIP, thus the following considerations might soon be void.

Since negotiations are still ongoing, the EU positions presented below are still subject to change. It is worth mentioning that only the EU periodically releases a status of negotiations for the sake of transparency to the EU citizens. The EU negotiators also regularly invite the EU stakeholders to round-table discussions and give them the opportunity to make presentations and express their views. The US, however, had not released any documents until Greenpeace published the US position on their website in May 2016[56]. We refer thus to the US position based on the publicly available "Tactical State of Play of the TTIP Negotiations" dated March 2016.

It is of particular importance for cosmetics since the EU has banned the use of laboratory animals for safety testing since 2013 (Hartung, 2008). The EU was asking its US counterpart to "formally accept validated test methods for regulatory purposes" in its position paper in May 2014. This is watered down in the latest EC position paper released in March 2015 and considers instead "fostering the development of alternative methods to replace animal testing" and the development of read-across[57]. The latest EU public position on TTIP[58] states: "*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*

[54] https://euagencies.eu

[55] ITRE deals with Industry, Research and Energy files such as Horizon2020; ENVI works on Environment, Public Health and Food Safety and is the parliament contact point with EFSA, ECHA as well as EMA among other agencies.

[56] https://www.ttip-leaks.org/

[57] see section 2.3 in http://bit.ly/2iPogDO

[58] http://trade.ec.europa.eu/doclib/docs/2014/may/tradoc_152470.pdf

across data approach and integrated testing strategies' that use all available information and data".

The US position reads: "*All in all, discussions on cosmetics remain very difficult and the scope of common objectives fairly limited. The US confirmed that in the US, 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*." Interestingly, the US analysis confirms "*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 sunscreen ingredient*."

The field of industrial chemicals is also controversial (Hartung, 2010d). The EU has made clear that neither full harmonization nor mutual recognition are feasible on the basis of the existing framework legislations in the US (Toxic Substances Control Act, TSCA, recently reauthorized as H.R. 2576, the Frank R. Lautenberg Chemical Safety for the 21st Century Act[59]) and the EU (REACH)[60]. From the EU position paper[61] and as far as the negotiation goes, the EU side is outlining the most probable solution for the chemical sector, which is: "*A right to regulate from each side*". The EU is so far not considering any mutual recognition, nor regulatory cooperation. Nevertheless, the two sides have launched pilot studies with their respective regulatory bodies based on the EU community roll action plan (corap) under REACH and the chemical work plan from the US EPA in order to understand the obstacles when it comes to hazard/risk assessment. Ten substances were overlapping and it has been decided to share and compare assessment practices[62]. Unfortunately, the case-study 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 US indicated that these efforts were found "useful" by multiple competent authorities (i.e., EU MS) 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*".

The positions on plant protection products, pharmaceuticals and food safety are less detailed so far. Altogether, the opportunities to make progress via TTIP with respect to new regulatory approaches are rather scarce and thin considering the current negotiation texts. For this reason, we have to expect a longer process of harmonization, which will require collaboration in these strategic developments. However, there is, as laid out above, no European institution, which would naturally serve such purpose.

5 Possible format and function of a European Safety Sciences Institute (ESSI)

The central proposal of this article is to institutionalize the steering toward new and advanced methods and approaches in the safety sciences on a European level. We use the working title of European Safety Sciences Institute (ESSI). This is first of all to stress that this is a scientific exercise as indicated by the term *Safety Sciences* or *Regulatory Sciences*. This is why institutes like the European Molecular Biology Laboratory (EMBL)[63] or the associated European Bioinformatics Institute (EBI)[64] come to mind as role models. These are flagship laboratories for the life sciences – an intergovernmental organization with more than 80 independent research groups. They are funded by public research monies from more than 20 member states, including much of Europe and Israel, and two associate members, Argentina and Australia. The organization is governed by a Council comprised of representatives of all member and associate member states.

ESSI should take into consideration scientific evidence about the current methods, assessment of technological opportunities, the societal regulatory needs and the development of roadmaps (gap analysis, mapping of emerging approaches, development, funding and validation / quality assurance needs) and facilitating measures such as data sharing, depositories, consensus processes, strategy papers, international dialogue, etc. An important role should be the continuity of activities, as a lot of energy is wasted with short-term financing of projects in Europe toward new regulatory methods after which most capacity built, knowledge and data is lost. By networking different national, EU and international programs and increasing transparency and exchange of information, synergies in research funding can be developed. Especially, ESSI would have to address the gap between research funding and practical application of methods. This phase, which includes performance assessment, standardization, possible commercialization, validation and implementation of test methods, is notoriously underappreciated with respect to funding.

ESSI by itself or in collaborations should serve as a repository of data and reference materials. Increasingly, methods and protocols are being amended and it will be necessary to track different versions and their validity status. ESSI could be a single go-to-point for high-quality guidance.

59 https://www.epa.gov/laws-regulations/summary-toxic-substances-control-act

60 http://trade.ec.europa.eu/doclib/docs/2014/november/tradoc_152914.pdf

61 http://trade.ec.europa.eu/doclib/docs/2014/may/tradoc_152468.pdf

62 https://chemicalwatch.com/22031/ttip-pilot-projects-move-forward

63 https://www.embl.de

64 http://www.ebi.ac.uk

Tab. 3: Possible formats for ESSI

Criteria	New entity	Existing entity with additional function	Virtual entity
Operational costs	High	Low	Minimum
Manpower	New manpower required	Low manpower added	Secretariat only
Location	Location within one of the EU member states, e.g., not yet hosting an EU agency as mentioned in the treaty of the functioning of the EU	Best candidates to host are: • DG JRC, e.g., Institute for Health and Consumer Protection with EURL-ECVAM • ECHA • EFSA	Not applicable
Budget	high	middle	low
Tasks	• Steer strategic discussions, shape research agendas, coordinate collaborations • Act as repository for EU funded research via subsection from CORDIS, including methods, data, reference materials, validity status • Act similarly as repository for national developments and accessible international results • Act as a hub for international exchanges, e.g., as partner to the US Tox21 activities, foster harmonization • Top-down: Dissemination of regulatory safety sciences progress at the European level • Collect data requirements from the relevant EU agencies • Bottom-up: organization of regular meeting with rotating places with the EU regulatory agencies		
Audience	Member states? Journalists? Public? Scientific Peers?		
Major challenge	Finances, governance and empowerment	Bias towards one sector	Actual impact

Developing strategies in the absence of practical experience is dangerous as the realistic view of what science can deliver is quickly lost. Ideally, ESSI will include active researchers, either in an intra-mural program or including them into the respective networks and groups.

How to create ESSI? If not as part of the EC itself, e.g., as part of the JRC as an extended ECVAM, the construct of an agency represents an opportunity. Statutes for executive agencies are laid down in EC regulation 58/2003[2]. Article 3 in particular describes the prerequisite for establishing a new entity, which is a cost-benefit analysis. An intergovernmental institute as discussed above represents another possibility. Lastly, a public-private partnership such as the Innovative Medicines Initiative (IMI)[65] represents a further opportunity to create such a structure, though the clear role of academic science has to be safeguarded.

Three different models to establish ESSI come to mind (Tab. 3): Obviously, it would be ideal to create a new entity, but the required resources might be prohibitive. At the same time, the monetary and societal advantage of improved safety assessments should outweigh this. The second model, to task an existing institution, has the disadvantage of a possible predominance of the respective sector and the traditional approaches taken by the institution. More promising is the emerging collaboration of EU agencies, especially between EFSA and ECHA. A purely virtual network is the least desirable scenario, and would at least require a secretariat associated with an existing institution.

Possible functions would include:

Implementation and monitoring of EU laws

– Update of 2008/440/EC Test Method Regulation following OECD Test Guideline approval as well as International Cooperation on Alternative Test Methods (ICATM)[66]/ EURL-ECVAM validation; input as to priorities for the methods validation pipeline

Filling institutional gaps

– Inclusion of a system of cross-sector data-sharing to avoid duplication of animal experiments echoing the new memorandum of understanding to Access Confidential Business Information by the Food and Drug Administration, Office of Foods and Veterinary Medicine[67].
– Mapping risk management practices and monitoring implementation of EU laws in harmonization with EU safety requirements at the member states level; Watchdog?
– Steering public–private efforts for efficiency and to avoid work duplication
– Harmonization of technical terminology

Providing roadmaps and timelines linked to EC mandate

– Setting-up Good Regulatory Practice for safety testing to echo Good Laboratory Practice and Good Manufacturing Practice
– Fostering evidence-based approaches

[65] https://euagencies.eu

[66] https://www.ttip-leaks.org/

[67] see section 2.3 in http://bit.ly/2iPogDO

– Sharing best practices from member states
– Visiting and training of member state regulatory agencies to disseminate emerging regulatory practices as well as newly validated tests

Enforcement of implementation of new approaches

– Strategies for actually transitioning to new methods are needed, which exist only for alternatives to animal testing, but even here often fail to bring methods to use. We earlier coined the term "post-validation" for this (Bottini et al., 2008).

The European Commission, as defined by the Treaty on the Functioning of the European Union[68] in Article 4, shares competences among others on environment, consumer protection, and safety concerns in public health. This can unavoidably lead to conflicts and differences in risk management. As seen lately with the discussions on endocrine disrupting chemicals (EDC), DGs had taken parallel actions at the beginning and succeeded only at the very end to wrap-up everything under one umbrella. The file can be moved from one DG to another but the staff rarely follows along with it. This automatically creates a loss of knowledge and expertise, meaning that the new DG has to take a fresh look at it. The consequences are quite severe at the end of the day. The EDC criteria were implemented about four years after the original deadline. Would this have been avoided if an ESSI had been in place? This is hard to say. An externalized body that focuses all the issues might help to concentrate the decision-making process. A permanent body with scientific expertise in these complex issues that engages with the whole chain of actors may speed-up actions and therefore save costs and manpower. On one hand, lobbying entry points seem more probable when multiple DGs are involved than with a decentralized and remote agency, as apparently intended when scientific committees where moved to Luxemburg. On the other hand, a decentralized agency can facilitate the dialogue since it is the unique entry point for discussion.

It appears that the portfolio of activities envisaged for ESSI has societal value meriting a major investment, such as the creation of an agency. The topic is timely in the context of TTIP (Transatlantic Trade International Partnership). ESSI represents a tremendous opportunity for transatlantic harmonization by facilitating, e.g., recognition of the Tox-21c toolbox on the European side and of recent EU regulations on the US side. This would in the end speed up the access to and exchange of regulated products between the EU and US market. Nevertheless, it is being said that the creation of new EU agencies is over. For the time being, a smaller solution, as already envisaged as a virtual network by the European Commission in their 2013 answer to the European Parliament (Box 1) might help explore and shape such structures. However, we know how long-lived compromises are. A number of questions will in any case have to be answered: Would such a structure be redundant to existing ones? How can it be empowered? Should this structure have a concrete basis or would a formal network with regular meetings be sufficient? We strongly believe that such discussion and any step toward implementation would serve the safety of consumers and patients.

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[68] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12012E/TXT&from=EN

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Conflict of interest

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