Regulatory Toxicology: Progress in Law

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Chapter 4

Regulatory Toxicology: Progress in Law

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The legislative contexts for product regulation and animal welfare legislation in the European Union and the United States of America are very different. They offer very disparate opportunities for accommodating novel and alternative methods for regulatory toxicology. In this chapter we present a summary of laws and political decision processes, which is complemented by a description of recent developments. The Center for Alternatives to Animal Testing (CAAT), in the United States at Johns Hopkins School of Public Health, and in Europe at the University of Konstanz, Germany, is among the few voices of science directly informing policy-makers through policy programs on scientific opportunities. These opportunities should be accommodated in legislation and the developments should be parallel on both sides of the Atlantic. The example of CAAT's policy activities is used to show how scientific advocacy can impact on policy making.

Introduction

To defend against contamination of the environment and protect public health, we need to deploy the best science in toxicology and biomedical research. This approach has so far required the use of millions of animals every year to assess the safety of substances and products. No reliable data are available for the United States, but recently extrapolated European data suggest that 5–10 million

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animals are used for this purpose worldwide every year. Programs, such as the Registration, Evaluation, Authorisation and Restriction of CHemicals (REACH), the European Chemical legislation from 2006, a possible reauthorization of the United States Toxic Substances Control Act (TSCA) from 1976, and new programs for nanoparticles, will increase this number. In contrast to basic research and drug discovery, which are very much driven by scientific and economic considerations, the regulatory use of animals is stipulated by policy and legislation. Such regulatory testing accounts for 25% of all animal use and has a lighthouse function for other areas because it is endorsed by validation and international harmonization. The toolbox of toxicology is remarkable in that, despite scientific progress, it represents a continuously growing number of primarily animal tests that have changed little since their introduction decades ago.

Laboratory animals are generally used to screen for health effects in humans and, at best, the relevance of any finding is afterwards assessed with modern mechanistic studies. Humans, however, are not 70 kg rats, and the need to revamp regulatory toxicology is increasingly being recognized. The major driving forces are the need for improved public health protection and animal welfare, as well as the steep costs in time and money associated with animal research. Further, animal models are limited in their ability to predict human health effects and inherently yield low throughput in the current system. Novel testing concepts must be based on the rapidly expanding understanding of how substances harm humans—that is, the pathways of toxicity. This concept was voiced prominently in the National Research Council's 2007 document *Toxicity Testing in the 21st Century – a Vision and a Strategy* (Tox 21) (*1*). This report has created an atmosphere of departure in toxicology; it has opened the door to revise current practices and reduce animal usage dramatically. The Johns Hopkins Center for Alternatives to Animal testing (CAAT US) is closely involved in setting this vision into action. CAAT US aims for paradigm and culture shifts to enable the use of modern, humane science for public health. Figure 1 illustrates the activities of CAAT US in the overall context.

CAAT US also steers a number of research activities, most prominently a National Institutes of Health transformative research grant project for mapping the entirety of pathways of toxicity (*2*, *3*), termed the human toxome. With a large consortium, CAAT US started mapping the human toxome for endocrine disruptors. Most importantly, this project will develop the pathways of toxicity concept further by defining how to identify, validate, annotate and share pathways of toxicity via a public database (*4*). CAAT US also works with the regulatory community on these efforts with the aim of bringing the findings to the policy maker community as well. The research on developmental neurotoxic effects forms proof-of-principle work for identifying pathways of toxicity.

The legislative contexts in the United States and the European Union (EU) are summarized below, along with CAAT's activities in both these regions to accelerate change with the goal of accommodating new and alternative approaches for the safety assessment of substances.

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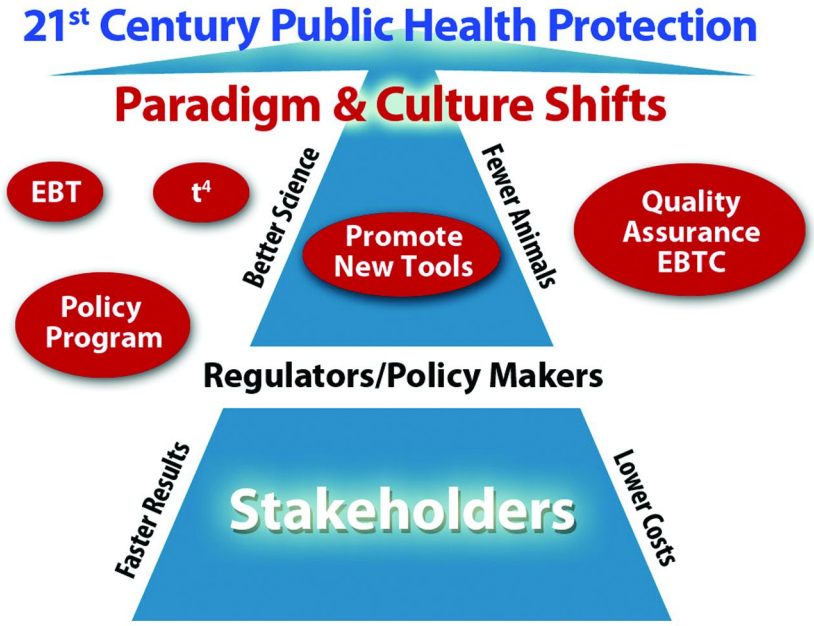

Figure 1. The vision and strategic work components of the Johns Hopkins Center for Alternatives to Animal Testing (CAAT). EBTC, Evidence-based Toxicology Collaboration; t[4], Transatlantic Think Tank for Toxicology.

United States Legislation and Policy

Food and Drug Law

In the United States, the Food and Drug Administration (FDA), which is part of the Department of Health and Human Services, is the primary federal agency that regulates food and drink (including components and additives) for human and animal consumption (*5*), drugs (including biologicals, such as vaccines and blood), medical devices, cosmetics, tobacco products and radiation-emitting products. The majority of the FDA's legal authority is found in the Federal Food, Drug, and Cosmetic Act (FFDCA), first enacted in 1938 and amended many times since. The United States Department of Agriculture (USDA) and the FDA concurrently regulate some foodstuffs, such as meat and poultry. The USDA has jurisdiction in processing plants and the FDA regulates meat and poultry after they leave the plants (*5*).

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Food additives are defined as any substances that are intended for use in or to affect characteristics of food, and will become part of such food (*6*). They must be shown to be safe under the intended conditions of use through testing by the procedures set out in the FDA Redbook (*7*) and according to the FDA's principles of toxicological testing for food (*8*). Some food additives are classified as "generally recognized as safe" (GRAS). The burden of showing that a substance should be classified as toxic in this way is on the registrant of the compound. Compounds added to the GRAS list after 1958 have needed scientific evidence of safety obtained from required tests (*5*, *7*).

The FFDCA does not require that cosmetic products and their ingredients be regulated by the FDA before they are placed on the market, with the exception of color additives. Nevertheless, cosmetics (and their ingredients) must be safe for consumers under labeled or customary conditions of use. Companies and individuals who market cosmetics have a legal responsibility for the safety of their products and ingredients (*9*).

Neither the FFDCA nor FDA's regulations require specific tests to demonstrate the safety of individual products or ingredients. Rather, the FDA has consistently advised manufacturers to use whatever testing is necessary to ensure the safety of their products and ingredients, but to ensure that it be substantiated in a number of ways: "*the safety of a product can be adequately substantiated through (a) reliance on already available toxicological test data on individual ingredients and on product formulations that are similar in composition to the particular cosmetic, and (b) performance of any additional toxicological and other tests that are appropriate in light of such existing data and information*" (*10*, *11*). The cosmetics companies have established a scientific review process, called the Cosmetics Industry Review (*12*), which conducts safety assessments of new cosmetics and ingredients. These assessments rely on published studies, but, if needed, new safety testing can be developed.

The FDA has authority to regulate the drug discovery process and approves all drugs before they can be sold and used in the United States. It has divided drug discovery into two phases: pre-approval, before introduction to the market, and post-approval after introduction to the market. Toxicity testing is carried out during the pre-approval period by the companies seeking approval of the drugs. The FDA reviews manufacturers' applications to market drugs in the United States and continues its oversight of drug safety and effectiveness as long as the drug is on the market (*13*).

Pre-approval drug development is a tightly guarded process at pharmaceutical companies, and, while some information is available publicly about how corporate testing strategies are developed and what tests are used, broader information is generally not widely shared. DeGeorge and colleagues (*14*) provided a detailed discussion about how toxicology testing is used in the development of anti-cancer drugs. Another example of how the pre-approval process works is set out on the website of the United States National Cancer Institute's Developmental Therapeutics Program (*15*). First, cell lines are employed to explore the basic toxicological properties of a compound. Next, animal tests are used to learn about metabolism and basic pharmacology (*16*), as animal data are required for an investigational new drug (IND) application. According to FDA, the IND

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application must contain pre-clinical data in three broad areas of study—animal, pharmacology and toxicology—to permit an assessment of reasonable safety for initial testing in humans. The FDA almost always requires data from formally designed, conducted, and analyzed clinical (human) trials to make a decision on a drug's safety and effectiveness. The IND application must be filed by the drug's sponsor (usually its manufacturer) before clinical testing can start, and must include the proposed clinical study design and the principal investigator's qualifications (*13*).

Environmental Law

Environmental law regulates human activity in order to limit ecological impacts that that threaten public health and diversity (*17*). More than 100 laws make up the body of environmental law and are largely organized by category (e.g. endangered species) and/or media (e.g. clean air). The United States Environmental Protection Agency (EPA) is the primary regulatory agency in charge of environmental regulation (*18*). The EPA is organized along media lines (air, water, waste, toxics, etc.).

Two major environmental laws are closely associated with toxicity testing – the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). TSCA governs chemicals in commerce, giving the EPA the authority to call for testing in certain limited circumstances. Under TSCA, chemicals in commerce are divided into two groups: existing and new. Existing chemicals (those in commerce at the time that TSCA's regulations came into effect) do not require testing to remain on the market unless the EPA determines that they are creating a risk of harm. Under section 4 of TSCA, the EPA must, by rule, require the chemical industry to test a chemical for its environmental or health effects if it makes either what is known as a hazard finding or an exposure finding (*19*). EPA must make a hazard finding if

- the chemical poses an unreasonable risk of injury to health or the environment
- there are insufficient data about the chemical to predict its health or environmental effects
- testing is necessary to develop data on these effects.

EPA must make an exposure finding if

- the chemical will be produced in substantial quantities and
    - it may enter the environment in substantial quantities
    - there may be substantial human exposure to the chemical
- there are insufficient data about the chemical to predict its health or environmental effects
- testing is necessary to develop data on these effects (*19*).

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When EPA makes either of these findings for a chemical, the agency must write regulations, for which testing is required. The test rule will develop health and environmental data if there are gaps. In totality, data presented to the EPA must convince the agency that the chemical does not present an unreasonable risk of injury to health or the environment.

New chemicals and new uses of old chemicals cannot be marketed until EPA approves a pre-manufacture notice or a significant new use regulation (*20*). No new testing need be done; available information, which might include animal toxicity testing, can be submitted. The EPA can, however, ask for additional information to confirm whether the chemical is safe.

Under the FIFRA all pesticides, fungicides, herbicides and rodenticides require testing before being allowed on the market. This testing involves a series of toxicity tests that are outlined in the regulations and guidance developed to ensure data and information requirements of TSCA and FIFRA were satisfied (*19*). A key indicator of EPA policy on toxicity testing is the Series 870 Health Effects Test Guidelines, issued by EPA's Office of Chemical Safety and Pollution Prevention (*21*). The EPA guidelines are harmonized with those published by the Organization for Economic Cooperation and Development (OECD). The testing methodologies set forth in the Series 870 Guidelines primarily reflect traditional mammalian approaches to toxicity testing. Although some of the guidelines do contain *in vitro* methodologies, these appear to be exceptions to the general rule.

In 2008, the EPA Office of Research and Development entered into a Memorandum of Understanding with the National Institute of Environmental Health Sciences/National Toxicology Program and the National Human Genome Research Institute/National Institutes of Health Chemical Genomics Center to launch Tox 21. In 2010, the FDA formally joined this collaboration. Starting from the premise that "[t]he convergence of science, technology, regulatory need, and public opinion has produced an historic opportunity to transform toxicology and risk assessment into more accurate, rapid, and cost-effective sciences," the parties to Tox 21 explain that its purpose is to guide the construction and governance of a detailed research strategy to make the National Research Council Committee's vision a reality (*19*, *22*).

Although TSCA establishes the principal legal framework under which industrial chemicals are regulated (and toxicity testing for those chemicals occurs), pesticides are treated separately and come within the purview of FIFRA. Enacted in its modern form in 1972, FIFRA establishes the framework for pesticide regulation in the United States. The EPA's authority under FIFRA is a balancing standard: the EPA must balance congressional mandate to prevent unreasonable adverse effects on the environment while taking into account the economic, social, and environmental costs and benefits of the use of any pesticide. (Pesticides tolerances are further regulated under the FFDCA, as discussed above.)

Unlike TSCA, FIFRA places the burden to demonstrate a chemical's safety on the manufacturer, not on the EPA. Testing is required but FIFRA does not have provisions on chemical data and testing that approach the level of detail seen in TSCA. The statute places the details of this process almost entirely within the discretion of the EPA Administrator, who must publish and revise guidelines

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specifying the kinds of information that will be required to support the registration of a pesticide (*19*).

The EPA also regulates pesticide tolerances on food. It can establish or leave in effect a tolerance for a pesticide residue in or on a food only if it determines that the level is safe. The term safe means that there is a reasonable certainty that no harm will result from aggregate exposure to the chemical residue through dietary and all other exposures. The EPA is required to pay particular attention to information concerning the effects of exposure on infants and children. In setting a tolerance, the EPA is allowed to take into account available data and information on both anticipated and actual (measured) residue levels of a pesticide in or on food. Under certain circumstances, in assessing chronic dietary risk, the EPA can also consider available data and information on the percentage of food actually treated with the pesticide (*23*).

EU Legislation and Policy

From the EU perspective, there are a number of actors to be identified that interact closely with policy makers in order to support and/or shape law based on science and vice versa. These individuals and entities are:

- The European Commission (EC)
- The European Parliament (EP)
- The Council of the EU

The EC

The EC is the only EU institution that has the initiative to propose and draft laws at the EU level. Beginning in 1967, the Parliament-elected Commissioner, supported by a Directorate General (DG), was assigned to the area of Research, Innovation and Science. Other current DGs involved in research include the following: Agriculture and Rural Development, Climate Action, Communications Networks, Content and Technology (Connect), Education and Culture, Energy, Enterprise and Industry, Environment, the Joint Research Centre (JRC), Mobility and Transport, and Regional Policy. Notably, the EU bodies that drive science programs and funding are the European Research Executive Agency and the European Research Council.

The JRC

The JRC has been the DG in charge of science for EU policy support since 1959, although it was originally created to fulfill requirements under the European Atomic Energy Community (Euratom) treaty in Rome in 1957. Since its inception the JRC has extended its expertise to other fields important to policy making, such as life sciences, energy, security and consumer protection. It now comprises seven scientific institutes, each with its own specialty, located in five different

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countries across Europe: Ispra (Italy), Geel (Belgium), Petten (Netherlands), Karlsruhe (Germany) and Seville (Spain).

Scientific Committees

When preparing its policy and proposals relating to consumer safety, public health and the environment, the EC relies on independent scientific committees to provide it with sound scientific advice and draw its attention to new and emerging problems.

Since March, 2009, three scientific committees represented by a panel of experts have met regularly in Luxembourg and consulted with the EC on (a) consumer safety, (b) health and environmental risks and (c) emerging and newly identified health risks.

The committee is renewed every 5 years. Whenever it is felt necessary, the scientific committees can call on additional expertise from a pool of scientific advisors and a database of experts.

Chief Scientific Adviser for the EU and President's Science & Technology Advisory Council

In 2012, Anne Glover was appointed the first Chief Scientific Adviser for the EU. The Chief Scientific Adviser may be consulted on any topic linked to science, such as science communication and promotion advising the President of the Commission on specific topics, commenting on topics such as the safety and risk assessment of genetically modified organisms and overseeing debate (e.g. whether to take a threshold or non-threshold approach for testing endocrine disrupting chemicals (*24*)).

The President's Science & Technology Advisory Council was established in January 2013, and is chaired by the Chief Scientific Adviser. It is meant to be an independent and informal group of science and technology experts from academia, business, and civil society. The Council covers a broad range of disciplines and unites expertise from the European Research Area.

The EP

The EP, as stated in the Treaty of Lisbon (*25*), deals with research framework, among other topics. In a nutshell, the Treaty of Lisbon makes the EP a stronger lawmaker by bringing over 40 new fields within the co-decision procedure, under which the EP has equal rights with the EC. (Co-decision is in contrast to the consultation procedure, where the EP only provides an opinion.) The areas covered by co-decision include agriculture, energy security, immigration, justice and home affairs, health, and structural funds.

Science and Technology Option Assessment

Political issues increasingly require expert consultation about scientific progress in order for the Members of the EP to decide legislation (e.g. new

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regulations on *in vitro* medical devices, clinical trials, Horizon2020, etc.). The role of the Science and Technology Option Assessment (STOA) is to coordinate requests from the EP Members and, more generally, from the EP committees (e.g. Committee on Industry, Research and Energy or Committee on the Environment, Public Health and Food Safety) for overview and accurate information on ongoing legislative processes. Furthermore, it is the function of STOA to bring experts together on an ad hoc basis, as well as for scientific panels, to reply to the EP needs.

Raising awareness on new trends and/or disrupting technologies is also part of STOA. For example, in 2013, over 17 workshops were held at the EP to discuss issues such as risk and innovation to balance benefits and hazards or how to feed the world in 2050.

Intergroups

Intergroups can be formed by Members of the EP from any political group and any committee. Their aim is to enable informal exchanges of views on particular subjects and promote contact between EP Members and civil society. These groups are not EP bodies and, therefore, might not express the opinion of the EP. During the last parliamentary term (2009–2014) more than 25 intergroups were established.

In this context, the intergroup Welfare and Conservation of Animals works on different aspects of animal welfare and conservation and animal experimentation, including alternatives to animal testing. An intergroup on risk assessment is in the process of getting established for the next parliamentary term.

Council of the EU

The Council of the EU provides and defines the general political directions and priorities for the EC. It does not exercise legislative functions per se, although it sits with the EC and EP to discuss the files. These meetings are known as trilogue. The council consists of the heads of state or government leaders of the EU Member States, together with the Council President and the EC President. Each Member State has a permanent representation in Brussels that always includes a counselor for research and innovation.

EU Legislative Framework and Tools To Promote Alternatives to Animal Testing

In contrast to the United States, the EU has a number of legal mechanisms in place to promote alternatives to animal testing.

Treaty of the Functioning of the EU

Animal welfare is incorporated as a European value in Article 13 of the Treaty of the Functioning of the EU:

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> "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 an EU policy area. Nevertheless, promotion and use of alternative test methods and the principle of replacement, reduction and refinement (3Rs) are anchored elsewhere within the EU legislation (see later 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.

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. If a member state fails to pass the required national legislation, or if the national legislation does not adequately comply with the requirements of the directive, the European Commission may initiate legal action against the member state in the European Court of Justice. 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.

Directive 2010/63/EU

On January 1, 2013, EU Directive 2010/63/EU on the protection of animals used for scientific purposes (*26*) entered into force for the 28 EU Member States. It repealed the previous Directive 86/609/EEC. Since it is a directive, it allows Member States certain flexibility in the transposition of the Directive into national laws. Among the purposes of this Directive are to give scope; harmonize the current EU understanding of what defines an animal; map the resources, including identifying competent people and authorities; establish a common framework; and promote collaboration of the Member States with the EC to disseminate animal welfare in the EU.

The new Directive applies to live non-human vertebrate animals, including independently feeding larval forms and fetal forms of mammals from the last third of their normal development, and live cephalopods. The directive refers directly to the 3Rs.

Member States must assist the EC in identifying and nominating suitable specialized and qualified laboratories to carry out validation studies of alternative methods.

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Cosmetics

The Cosmetics Directive provided the regulatory framework for phasing out animal testing for cosmetics purposes (*27*). It establishes a testing ban on finished cosmetic products and cosmetic ingredients on animals and 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 (EU 1223/2009), which replaced the Cosmetics Directive from July 11, 2013.

REACH

In 2007, REACH legislation (EC 1907/2006) came into force. This Regulation relates to chemicals and their safe use (*28*). 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 animal testing but does not oblige 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."*

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 (EC 440/2008), 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.*"

Regulation for Food Additives, Enzymes and Flavorings

The Regulation on food additives, food enzymes and food flavorings (EC 1331/2008) states that "*It is envisaged, in particular, that food additives, food enzymes and food flavorings, to the extent that the safety of food flavorings must be assessed ... must not be placed on the market or used in foodstuffs for human consumption, in accordance with the conditions laid down in each sectoral food law, unless they are included on a Community list of authorised substances*". The

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guidance for submission for food additive evaluations refers to Directive 2010/63/EU and the 3Rs. These two elements must be considered whenever toxicological test methods are necessary. Moreover, the use of a tiered testing approach is developed to encourage the test performers to use *in silico* or *in vitro* tests, as well as validated test methods, under OECD standards, in use for REACH or listed under EC 440/2008.

CAAT Science Strategy and Policy Program

CAAT US is committed to support the paradigm change in regulatory safety assessments enshrined in Tox 21. Lessons can be learned from more than two decades of development and validation of alternative methods (*29–31*). Increasingly, the limitations of animal-based approaches, which we developed over almost a century, have revealed themselves (*32*). We have argued elsewhere that a revolutionary rather than an evolutionary change is required (*33*). Of note, however, is that the new methods also come with many limitations (*34–36*).

Development of Concepts To Enable Implementation of Tox 21

Beside the technological developments, conceptual steering is necessary to enable transition to new approaches and bring together different elements for a new regulatory approach (*37*). With the Transatlantic Think Tank for Toxicology, CAAT has launched a series of workshops and concept papers to promote discussion on this subject. With the creation of CAAT in Europe (CAAT Europe) in March, 2010, this program has a strong and unique transatlantic component (*38*). CAAT Europe complements the strategic initiative as a member of the American Consortium on EU Studies (ACES), an official EU Center of Excellence, and strengthens the two-way communication across the Atlantic. We believe that no approach accepted only on one side of the Atlantic will advance humane science as well as a meeting of minds leading to international harmonization. The costs per year for two workshops are borne by the Doerenkamp-Zbinden Foundation, Switzerland, and additional partners enable further projects on a case-by-case basis. In almost 5 years the program has resulted in more than 25 published workshop reports and commissioned whitepapers.

Assessment of the State of the Art in Toxicology

The doors for a novel approach to safety assessments must be opened by a fair and objective evaluation of current practices. A role model for effecting these changes is evidence-based medicine (EBM), which has been suggested as a template for addressing validation (*29*, *39*, *40*). The Cochrane Collaboration has engaged 27,000 physicians, scientists and health care providers to produce more than 5,000 guidance documents evaluating clinical practices. Because of the transparency and objectivity of the process, as well as its scientific rigor, when EBM guidance is available, it is considered the best available for a given

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clinical question. A similar process, evidence-based toxicology (EBT) (*41*), can and should be developed to guide the evaluation of drugs, chemicals and other entities. It is noteworthy that one of the authors (T. H.) holds the first chair for EBT worldwide. The first conference was held in 2012, hosted by the EPA (*42*). In this context, a consensus paper on the validation of high-throughput assays was prepared (*43*).

Quality Assurance of New Approaches

Emerging technologies and numerous initiatives to promote their use to assess toxicity are being seen worldwide. To assist in the culture change and paradigm shift that we advocate, it is important to establish a mutually beneficial dialog between stakeholders. This dialogue will focus on quality assurance of the novel tools. Traditionally, this was attempted by formal validation; this approach has two principal problems:

- It is costly, takes a long time and is not amenable to change on the basis of new developments in technology, as any change invalidates the validation
- Validation is done using current, imperfect, traditional animal-based methods as the point of reference and thus cannot lead to a paradigm shift

Therefore, a mechanism that assures quality without these limitations is necessary. CAAT's toxicity testing symposia touched on this issue, which was taken up in detail at a CAAT organized conference, *21st Century Validation for 21st Century Tools*, in July, 2010. From that conference, a steering group was formed that includes representatives from CAAT, the EPA, the FDA, the National Institute of Environmental Health Sciences/National Toxicology Program, the American Chemistry Council, CropLife America, the pharmaceutical industry, the Humane Society of the US, the Institute for In-Vitro Sciences, and the International Life Sciences Institute / Health and Environmental Sciences Institute. The group has embraced the concept of EBT as a substitute for traditional validation (*44*) and views the development of this concept as a prime opportunity to collaborate toward change in regulatory toxicology. This group promotes a private–public partnership called the Evidence-based Toxicology Collaboration (EBTC) (*45*) between agencies and industry to promote quality assurance and implementation of new approaches. The EBTC was inaugurated on March 10, 2011, as a satellite activity to the 50th Society of Toxicology conference in Washington, DC, (*46*). A European branch was launched one year later, as a satellite activity to EuroTox in Stockholm, Sweden, 2012. CAAT provides the secretariat for EBTC. While the costs for individual evaluations of new methods must be borne by their developers and promoters, a central steering and publically available repository for guidance and reference documents is necessary (similar to the Cochrane library for EBM).

The secretariat assumes the following responsibilities:

- Central coordination of the steering group, organization of EBTC and the appointment of evaluation committees

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- A standing committee for horizontal EBT method development (meta-analysis, quality scoring tools, probabilistic risk assessment etc.)
- An Internet portal for guidance and reference materials.
- Public relations

CAAT US Policy Program

CAAT launched its education, advocacy and outreach program in February 2007. This US policy program is aimed at educating policy makers and legislators about the need for alternatives to the use of animals in toxicity and safety testing and in biomedical research. It advocates for humane sciences in government research and regulations. In the longer term, the CAAT program strives to create a legislative and policy culture that values the lives of animals and promotes the use of alternatives and humane sciences.

Policy makers and regulators represent the best opportunity for a cultural shift and change in regulatory toxicology. CAAT's policy program is recognized as a point of reference and expertise among the policy and decision-making community, especially in the US. During the past 4 years, CAAT has successfully positioned itself as the go-to organization for information on Tox 21 and implementation of the National Academy of Sciences' vision and strategy for toxicity testing. Through its education on Capitol Hill, consensus and constituency building and written materials and presentations, the policy program has been instrumental in advocating the relationship between humane sciences and environmental health protection.

CAAT has developed an effective set of messages regarding humane science and public health protection, which it will continue to bring to policy makers, both at federal agencies and on Capitol Hill (*47*). Our fundamental approach is to find champions for alternatives in toxicity testing and biomedical research. In addition, we reach out to policy makers at US federal agencies that are important to the culture change and paradigm shift we seek.

A key element of CAAT's policy program has been creating and strengthening the relationships with important constituencies, such as the environmental law and policy and animal law communities. One particularly effective tool in constituency building has been the joint implementation of four symposia devoted to new methods in toxicity testing and implementation of the National Academy of Sciences' report. In addition to the benefit of producing intellectual capital, which can be effectively used in education and advocacy, these symposia have helped unite a diverse group of stakeholders to further cement this coalition.

Another goal is strengthening institutional care and use committees (IACUCs) by educating lawyers and religious leaders to serve as public members. These committees are required under US federal laws to oversee animal research and every IACUC is required to have a non-scientist member of the community. Many non-scientist members are ill equipped to understand and meaningfully contribute to the discussions about animal protocols that IACUCs review. CAAT seeks to create a group of appropriately trained and educated non-scientists who, if appointed to IACUCs, can make a difference in these critically important

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committees. This will be achieved through research, and (if feasible) a pilot program. CAAT has established a certified program in humane sciences and toxicology policy in Johns Hopkins School of Public Health, and any individual who completes the curriculum can be awarded this certificate. In the past 3 years CAAT has brought 90% of the certificated curriculum online, and the full program will shortly be available worldwide.

CAAT US has established a strategic partnership with the EU delegation in the United States through its selection as part of ACES. This effort is complemented by CAAT EU. For example, ACES funded a symposium held by CAAT on toxicity testing entitled *Implementing the US NAS Toxicity Testing Report: An EU Perspective on the Way Forward*. This symposium allowed CAAT to leverage its policy efforts. To take advantage of the momentum gained from this symposium and of policy developments in Europe (e.g. REACH, the seventh amendment of the Cosmetics Directive and the novel Laboratory Animal Welfare Directive), CAAT will continue to expand its activities through ACES and continue with joint briefings for congressional staff and information days.

CAAT Europe Policy Program

CAAT Europe was established in February 2012, and cemented CAAT's role as a transatlantic bridge for the 3Rs and as a global scientific voice for bringing the 3Rs, humane science, and novel technologies into law, regulations, and guidance.

The program operates along three axes. First, CAAT Europe facilitates cross-sector networking and promotes dialogue. More than 100 face-to-face meetings have been held with EP officials (e.g. Members of the EP, Members' assistants, and policy advisers) since the setup of the EU policy program. All the relevant stakeholders—industry (e.g. cosmetics, chemicals, plant protection, and consumer products), non-governmental organizations, the EC, and ministries or regulatory agencies in Member States—have been contacted. Additionally, cooperation with academia representatives' offices in Brussels facilitates contact between EP Members and the corresponding national 3Rs scientists or regulators.

The second axis is regulatory monitoring, lobbying and/or advocacy for alternatives to animal testing on EU legislative files.2012 and 2013 were busy years for science owing to the preparatory work to launch the next European research-funding scheme, named Horizon 2020, on January 1, 2014. This scheme is aligned with the multiannual financial framework, which also starts in 2014 and ends in 2020. The total worth of the framework €80 billion and was launched with €15 billion assigned to the first 2 years. Although, at first glance, the spending seem impressive, the total corresponds to less than 1% of the total assigned to the multiannual financial framework, where more than 40% goes to the Common Agriculture Policy.

Among other topics, regulations on clinical trials, medical devices and *in vitro* diagnostic devices have been debated in the past 2 years by the EU institutions. Some of these files are still not closed.

Following strong public opinion concerns, the EP has also tackled endocrine disrupters by writing the "own initiative report" *Protection of Public Health on*

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Endocrine Disrupters. As mentioned before, the EP has no power to propose new laws. Nevertheless, in order to respond to public pressure, the EP decided to take the lead even if the final report had no more value than a consultation.

The third axis is dissemination and communication. In the past 2 years, to inform EP Members and stakeholders about ongoing legislative works, CAAT Europe suggested and/or participated in workshops held at the European Parliament on multiple topics, such as the following:

- *The Human Toxome*, May, 2012
- *Advancing safety science and health research under Horizon 2020 with innovative non animal tools*, October, 2012
- *The Human Toxome project and endocrine disruption testing*, December, 2012, at the Intergroup on the Welfare and Conservation of Animals.
- *Worldwide Implementation of the 3Rs in Regulatory Toxicology: What are the Leadership Challenges and Opportunities?*, March, 2013
- *New Regulatory Science in Systems Toxicology*, March, 2013
- *Understanding Endocrine Disruptors available methodologies; what can we learn from experience to date?*, United States Mission to the EU, November, 2013
- *Hazard/Risk Assessment from the EU and the US perspectives*, November, 2013

Output and Outreach

Members of the EP or policy advisers may ask CAAT Europe for advice and briefing on topics linked with alternatives to animal testing on an ad hoc basis. Members of the EP have invited representatives of CAAT Europe to participate to Parliamentary events, such as *Risk in innovation: balancing benefits and hazards*, held in January, 2013, and organized by STOA. Likewise, stakeholders have invited CAAT Europe to participate in workshops and explain views on alternatives to animal testing.

In March 2013, CAAT Europe applied for two specific lots out of nine after a call for tenders organized by STOA on behalf of the EP. These were Life Sciences for Human Well-Being and Safety and Security Technologies. In early 2014, CAAT Europe was listed as an official expert contact point for the EP for a period of 4 years.

Conclusions

The state and the dynamics of the political landscape for regulating products in the US and Europe are very different: Europe has taken over from the US as a pacemaker of novel legislation. The accelerating unification process now including 28 member states with 530 million citizens led to enormous efforts in harmonizing and creating legislation, with more than 70% of the national legislations now originating on the EU level. Therefore this chapter included also a description of players on the European side involved in this process. In

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contrast, the US has not seen major new legislations for product safety in decades; however, a number of well-established agencies exist, which fill the existing framework with innovative approaches. Notably, the European counterparts are usually more administrative executers of the legislation. The situation varies also for the different industrial sectors with large grade of harmonization for drugs, similar requirements for pesticides and tremendous differences for cosmetics' ingredients and environmental chemicals.

The need to embrace new approaches to product safety is increasingly perceived on both sides of the Atlantic. This requires information for policy-makers and agencies on technical opportunities and in a globalized economy also about the developments in other major economic regions. The example of the policy programs of the Centers for Alternatives to Animal Testing in the US and Europe were given to demonstrate how academia can help shape and accelerate this process. This is in the best interest not only of the animals to be spared, but also of consumers and patients world-wide to benefit from modern safety sciences.

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