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## Session II-3: Public law – the Three Rs in regulation addressing animal use

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### Session II-3: Oral presentations

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II-3-104

#### **Good regulatory practice: Directive 2010/63/EU, a missed opportunity?**

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Consideration at WC6 of whether regulation drove, managed or monitored change concluded that regulatory frameworks for the use of animals for experimental and other scientific purposes should adopt a flexible approach to anticipate, promote and make provision for technical progress in science and animal welfare; and reflect the evolution of informed societal and political thinking. It was argued that regulation should focus on what must be achieved and why, rather than how it is to be achieved.

Directive 2010/63/EU, concluded in September 2010 and taking effect in EU Member States in January 2013, will shape the regulation of animal use for experimental and other scientific purposes, and public policy in Europe with respect to the 3Rs, for the foreseeable future. A superficial analysis of the structure and contents of the new Directive indicates a desire to adopt a flexible approach, and confirms that in a number of areas where

it is foreseen there will be evidence to support improved science and animal welfare progress can be made by updating technical annexes. However, a more rigorous analysis identifies areas where the focus is on modest or ambiguous minimum provisions, frameworks and inputs rather than outputs and outcomes, and the need for a structured and well-resourced programme to properly maintain and update the technical annexes.

In the context of the 3Rs this presentation considers lessons learned from the interpretation and implementation of Directive 86/609/EEC; the drafting of Directive 2010/63/EU; its implementation by Member States; and the resources and systems required to ensure that the new EU regulatory system keeps abreast of technical progress, and informed societal and political thinking.

II-3-475

#### **The Animal Welfare Act: a regulatory roadblock**

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The Animal Welfare Act (AWA) became law after development of the 3Rs principles. However, these principles were not incorporated into the legislation. This is one of the fundamental reasons the AWA has become a barrier to the development and implementa-

tion of alternatives to animal testing in the United States. Though many people assume the AWA was adequately designed to protect animals used in testing, it has become abundantly clear that it was not. Attempts to amend and reform the AWA to require a more



serious and modern consideration of the welfare of animals have been unsuccessful, and worse, oftentimes counterproductive.

Further, the AWA does not incorporate a notion of ongoing scientific development in its regulatory regime. This is part of the reason legal analysis, regulatory science and risk management are mired in decades old notions. Concepts such as legal liability protection, intellectual property protection, private property and profit trump considerations such as animal welfare, shared scientific knowledge, scientific development and efficient and humane resource management.

This presentation will address some of the fundamental flaws in the AWA in order to learn from these mistakes as we look for regulatory changes that will incorporate the 3Rs principles and implement the National Research Council's vision and strategy for toxicity testing in the 21<sup>st</sup> Century. The future of chemical toxicity testing is being written now. Unless we change the dated legal and scientific formulas we have been using, the outcomes will not change.

II-3-522

## How different countries control animal experiments outside recognised establishments

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The laws of different countries show considerable variety in controls and monitoring and enforcement approaches, but adherence to the 3Rs is a common theme. Scientific whaling provides a good example of how robust different systems are for ensuring application of the 3Rs in a difficult research environment outside of the normal controls of a research establishment. The activities may be in international waters and outside the

scope of national legislation, inspection is difficult, and on site there is rarely staff with the animal's interest at heart. It shares features with research on wild animals and on farms. This paper will explore how different countries' laws on animal experimentation provide control on such work, and consider how good monitoring and effective enforcement could be obtained.

II-3-210

## From mouse to machine: how have attitudes and individuals affected the progress of the Three Rs in shellfish toxin testing?

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European safety monitoring programmes to detect marine biotoxins in shellfish harvested for human consumption have relied heavily on the use of Mouse Bioassays (MBAs) because, until recently, these have been the only method acceptable under food hygiene legislation. However, these bioassays cause significant suffering to the animals used and are considered to have some serious scientific drawbacks. This combination of factors has driven a need for change in how such testing is performed.

Attitudes of those involved at all levels have been critical to successfully minimising animal use. Much of the drive for change has come from highly motivated individuals. At a local level, co-operation has been needed among animal technicians, the veterinary staff caring for the animals, scientists involved in both the monitoring programme and in developing alternative technologies, and laboratory managers (due to the staff and financial resource costs created by moving away from the *status quo*).

At a national regulatory level there have been issues with the conflicting requirements of legislation protecting animals used in scientific procedures and over-specification of methods in the Food Hygiene Regulations. This has necessitated negotiations between Government Regulators at science and policy levels to resolve conflicts. Lack of clarity in the process for validation of alternative methods has proved a significant obstacle. Decisions made by regulators have had the potential to impact on the shellfish industry, necessitating their involvement in the process of change.

Cross-disciplinary discussion and good communication has been essential at all levels in order to implement change. Trust has had to be developed and maintained. Individual personalities have impacted significantly on the speed of progress. Compromise has been necessary by all parties.



## Session II-3: Poster presentations

II-3-188

### **New EU Directive 2010/63/EU on the protection of animals used for scientific purposes: Animal welfare aspects of the transposition into national law**

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In the European Union, the new EU Directive 2010/63/EU on the protection of animals used for scientific purposes has been adopted in 2010 to replace Directive 86/609/EEC. EU Member States (MS) must transpose the provisions of the Directive into national law by November 2012.

From the animal welfare perspective the new Directive is disappointing in several respects: For instance, there will be no rigorous restrictions on the use of non-human primates and even experiments on great apes remain possible. Researchers may still use animals even where scientifically approved 3Rs methods exist. The authorisation procedure is far from being stringent and transparent. Generally, MS may not adopt stricter national rules.

However, the Directive provides standards that will improve animal welfare at least in some MS. All MS now must establish an au-

thorisation system involving a cost/benefit analysis. Transparency and quality control will be improved by the requirement to publish non-technical project summaries and by retrospective assessment of selected projects. Some specific provisions of the Directive allow for stronger national rules, e.g. banning the use of great apes or long-lasting severe procedures. The Directive could also become a driving force for promoting the 3Rs as it demands specific respective activities on both the national and EU level.

European animal welfare organisations will continue to strive towards having the highest animal welfare standards taken up on national levels. We demand effective measures to implement and control a transparent, meaningful and accountable protection of laboratory animals.

II-3-191

### **Analysis of EU-legislation in terms of consistency and state-of-the-art regarding the implementation of the 3Rs in the data requirements to identify potential for further improvement**

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Present and future EU legislation on the protection of animals used for scientific purposes (Directives 86/609/EEC and 2010/63/EU) requires that, wherever alternative methods recognised by EU legislation are available, they have to be used instead of animal tests. Unfortunately, this principle is not implemented to its full extent when it comes to risk assessment that chemicals and new products have to undergo prior to their authorisation and placement on the market. In a recent study, the Animal Welfare Academy screened data requirements of relevant EU laws and provisions regarding chemicals (REACH), biocides, pesticides and food safety and found that test methods as part of the risk assessment do not reflect the state-of-the-art of science and technology. Most of the data requirements we investigated still require testing on animals

for many toxicological endpoints, even though 40 alternative testing methods accepted on EU or OECD level (ICCVAM, Mar 2011) are at hand. This unacceptable state of affairs is due to a multitude of reasons. These may range from shortage of manpower to implementing existing knowledge and expertise in the field of alternative methods to unclear and misleading statements on the applicability and state of validation of alternative methods. In conclusion, we strongly suggest a homogeneous EU-wide strategy for all areas involving risk assessment of substances with the aim to better implement the 3Rs and comply with the Directives 86/609/EEC and 2010/63/EU. As a positive side-effect, this would clearly simplify data requirements, save costs on various levels and improve product safety for consumers.



II-3-298

## Regulatory changes and the resultant effect on alternatives consideration in the United States

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Guidelines and regulations regarding animal use in research, teaching, and testing emanate from several government agencies and humane organizations, the most influential and wide reaching being the USDA (United States Department of Agriculture), NIH (National Institutes of Health), and AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care). All three have made recent changes in their requirements and expectations, affecting both scientist and institution. This poster

will outline the recent changes, and how these changes relate to animal care and the 3Rs.

Forefront among the changes are the updated USDA Animal Care Resource Guide, the proposed adoption and implementation by NIH of the Guide for the Care and Use of Laboratory Animals, 8<sup>th</sup> edition, and AAALAC's recent adoption of three resources to be used as standards for animal care program evaluation.

II-3-359

## The Brazilian law that regulates animal use does not improve the reduction concept of 3Rs

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The Brazilian law number 11,794 that regulates animal use in scientific research and education states that reuse of the same animal is not allowed after reaching the main aim of the research project. Our group works with pyrogen, skin and eye irritation tests for the routine quality control of biologicals, medical devices, large volume parenterals, cosmetics, topical medicines and cleaning products, as well as for comparing *in vitro* and *in vivo* assays. Rabbits that did not receive a pyrogenic sample used to be reused in one of the irritation tests. Usually we use 1,200 rabbits per year for all of those activities. If the reuse of animals is banned, almost half of this number will be needed to perform irritation tests. It is understood that the rabbit pyrogen

test is not a severe one, and can be classified as a mild assay, so it does not offer a high level of suffering to animals that prevents them from participating in another assay. Recently, the European Union reviewed the animal Directive and it is stated that "reuse should be balanced against any adverse effects on their welfare" and that "it should be considered on a case-by-case basis". This Directive also allows the reuse of animals if the previous procedure was "mild" or "moderate". So, it is strongly recommended that Brazilian animal law must be reviewed, in order to allow the reuse of animals in some circumstances where the good sense contributes to animal reduction.

II-3-362

## Comparison of the pyrogen *in vivo* methods described in Brazilian and European pharmacopoeias: which one contributes to animal reduction?

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The Brazilian Pharmacopoeia follows the American methodology and differs from the European in the experimental design. This study compared how both methods can affect the final result and which one has the more stringent criteria. The agreement and/or disagreement between the results of pharmacopoeias were analyzed by: a) 44 samples of the sector with the result of repetition; b) hypothetical data using the threshold value of fever of 0.5°C; and c) 451 number combinations in a computer program simulating the first test (3 animals). If all animals presented temperature rise equal to 0.5°C, the Brazilian Pharmacopoeia would present result “pyrogen” after an 8 animals test, whereas the European Pharmacopoeia would present “non-pyrogen” after a 12 animals test. It demonstrates that European Pharmacopoeia does not consider the elevation

of 0.5°C as an indicator of fever and may use more animals, besides being less stringent. Both the routine and the computer data showed that the Brazilian Pharmacopoeia was more rigid at low temperature rise (up to 1.15°C). Between 1.2°C and 2.6°C the pharmacopoeias had the same result forwarding the product to “go to next stage”. The European Pharmacopoeia was stricter in high temperature rise (above 2.7°C). The results indicate that the methodological differences may generate uncertainty in the evaluations of the protocols according to the country where the product was manufactured and the interference in the interpretation of results may lead to a different conclusion about pyrogenicity of a sample. Besides, European Pharmacopoeia uses more animals, not contributing to Reduction.

II-3-369

## The need for establishing a training and educational system for animal use and care personnel in Brazil

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In 2008, Brazil published Law 11,794 aiming to regulate the scientific use of animals. In Brazil, a significant number of the laboratory animal care personnel is autodidact, what many times may lead to biased procedures. The number of opportunities to study laboratory animal science have grown in the last decade nevertheless, the need for formal training and for continuing education systems are still a must. The Ethics Committee on Animal Use of the Oswaldo Cruz Foundation (CEUA/FIOCRUZ) imposes that all proposals describe how the personnel involved in activities were trained, justifying the individual ability to perform the procedures described. When a proposal is approved by CEUA/FIOCRUZ, the involved personnel could be considered indirectly licensed to perform those activities. Taking FELASA procedures as an example, it is evident that people involved in

working with animal breeding or experimentation should be trained and categorized. Effective ways of moving forward to implement this concept in Brazil are: i) harmonization of procedures related to animal science activities by ABNT, a Brazilian institution that publishes technical procedures; ii) inclusion of the training framework in the INMETRO (Brazilian accreditation institution) system; and iii) definition of the training program to be offered by accredited institutions throughout the Country. CEUA/FIOCRUZ members are convinced that once those actions are implemented the quality of animals used in science will be improved, issues of animal welfare will be taken care of and the approval process by the Brazilian CEUAs and its control by society and government will be improved.



II-3-374

## Does Brazilian animal law really regulate animal use and improve the development of alternative methods?

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Brazil has recently published a new regulation (Law 11,794/08) that has thrown light on animal use in the country and opened the possibility for standardizing procedures and personnel training which, in turn, would improve the quality of animals used in science. If nothing else, this consequence of the law would widely justify the efforts to implement the new concepts and arrangements needed. Considering AAALAC International and other accreditation associations' quality standards, the Brazilian will develop partnerships with international corporations to develop and produce health products. The recent decision of the Brazilian Council for the Control of Animal Experimentation (CONCEA) to create an exception that favors industry autonomy concerning animal use, by excluding animals used in the production of bio-

logical products of the aim of the Law upsets the way forward to a controlled and good animal practice. This decision goes against the aim of the Law which is to regulate activities in teaching and scientific research, as stated, since the Law includes the production and quality control of biologicals as part of scientific research. Brazil, just 2.5 years after publishing the Law loses the opportunity to improve good animal use procedures and to raise the Brazilian animal user industry rating to internationally accredited and shows to the society that ends justify animal suffering and neglect. This exception will negatively impact on future and current international partnerships. If nothing changes there will be no need for the generation of alternative methods in the country since the industry won't need them.

II-3-441

## Animal suffering in US laboratories: efforts to tackle this critical issue

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Animal pain and distress not only impact animal welfare, but can also confound experimental variables and lead to poor scientific results. Inadequate attention to and relief of distress and pain remain widespread in the U.S. The Humane Society of the United States (HSUS) analyzed violations of the Animal Welfare Act by animal research institutions in 2009 and found that the most common violations were related to the Institutional Animal Care and Use Committee, including requirements for justifying experiments involving pain and distress. The HSUS also published an analysis of noncompliance with federal regulations at federally funded research institutions over a three month period and found that the majority of the reported incidents resulted in animal pain and distress, and 75% in animal

death. In order to increase attention to pain and distress overall, the HSUS is urging more than 500 U.S. colleges and universities to adopt internal policies to prevent animals in their laboratories from enduring severe pain and distress; more than 60 schools to date have done so. Current U.S. laws do not specifically prohibit procedures or conditions that cause severe distress and pain; however, the first-of-its kind legislation that would do so was introduced in the state of Maine in 2011. This presentation will describe the analyses of federal animal welfare violations to highlight the need to mitigate pain and distress, and will further describe HSUS's efforts to bring attention to the issues of pain and distress.



II-3-493

## Exclusion of birds, rats, and mice from legal protection in the U.S.: a science policy case study

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The Animal Welfare Act (AWA) is the only U.S.-wide law that governs use of animals in research. With the 1970 amendments, coverage under the Act was extended to any “warm-blooded animal that the Secretary [of Agriculture] may determine is being used”. However, in the process of writing the regulations to implement the law, the U.S. Department of Agriculture (USDA) chose to interpret that clause as having discretion to exclude the vast majority of warm-blooded animals used in research: mice and rats.

Animal protection groups objected and a federal judge called the exclusion “arbitrary and capricious”. However, the USDA’s determination remained in effect until a second judge’s critical assessment prompted a lawsuit settlement in 2000 and USDA agreed to proceed with timely regulatory process.

The legislative and regulatory history of the AWA is generally one of expanding protections, but in 2002, leadership in the U.S. Senate allowed an amendment to the Act that explicitly and decisively reversed the USDA’s agreement.

The case study provides a qualitative analysis of relevant policy considerations, drawing on court documents, legal articles and papers of the Alternatives Research & Development Foundation, which initiated the lawsuit against USDA. While Animal Law classes in the U.S. study this protracted debate and its legal outcome, key details, such as the effect on adoption of alternative methods, and opinion polls showing scientist support of regulation of these species, are often overlooked. The case study also makes recommendations for continued advancement of the AWA, including protection for birds, rats and mice not specifically excluded in the Act.