Session II-4: Implementing the Three Rs – alternatives to legislation

Session II-4: Oral presentations

II-4-582

Information retrieval on alternative methods to animal experiments – one of the factors that affect implementation of the Three Rs in research and testing

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High-quality research and the protection of animals used for scientific purposes both demand the application of best tools to ensure that the 3Rs are appropriately considered and realized. It is essential that each animal experiment is carefully evaluated regarding its indispensability. The decision of whether or not an animal experiment is indispensable is to be based on the state of the scientific art and a scientific examination whether the pursued purpose cannot be achieved by alternative methods. In this context searching high-value information on alternatives to animal testing is discussed as one of the key elements to prove the indispensability of animal experiments. *Indispensability searches* are composed of several steps *which are based on each other*. They should start by defining the scientific objectives of research projects, followed by choosing appropriate information resources, compiling relevant search terms, creating search queries and documenting the search process.

To improve information dissemination on alternative methods at national level the National German Centre for the Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET) pursues a three-fold strategy. ZEBET's strategy consists of (1) capture of and supply of information – via AnimAlt-ZEBET database, (2) education in systematic search procedures as part of courses accredited by the Federation of Laboratory Animal Science Associations (FELASA), and (3) research in retrieval technology. ZEBET's strategy aims at supporting well-informed scientists and well-informed competent authorities responsible for proving the indispensability of animal experiments.

II-4-064

Shaping Three Rs behavior through an accreditation program

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For 45 years AAALAC International has reviewed and accredited institutional animal care and use programs. Today, AAALAC International accredits more than 830 programs in 34 countries around the world. AAALAC is uniquely positioned to assess animal care and use programs using internationally accepted standards and the peer-reviewed literature. To be accredited, institutions must comply with applicable regulations and policies regarding the use of animals in research, testing and teaching, but must also meet high-order principles embodied by AAALAC International such as implementing the Three Rs, ensuring the input of a qualified veterinarian to the program, ensuring review of the proposed animal work by an internal or external oversight body, and protecting personnel through a well-designed occupational health and safety program. The AAALAC process addresses those overarching areas as well as methods of housing, including enrichment; methods of ensuring competency of personnel; micro- and macro-environmental factors that may impact animal welfare; and methods of assessing and mitigating pain and/or distress, to name just a few. In this manner, AAALAC fosters a spirit of teamwork among the institution's professionals involved in the creative development, the critical review and the final implementation of research animal proposals. Over its long history, AAALAC has promoted the incorporation of the principles of replacement, refinement and reduction into accredited programs. Specific examples of program deficiencies identified by AAALAC and corrective measures taken by institutions will be described as examples of the way in which an international accreditation program can enhance animal welfare and the quality of science.

II-4-436

Scientist's views on Three Rs: Comparison of Canadian and UK scientists

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We surveyed Canadian animal-based scientists to benchmark their current understanding of the Three Rs and to identify where our organization's Three Rs resources should be focussed. A similar survey had previously been carried in the United Kingdom (UK). Both surveys found that refinement is the least understood "R" (just 49% [n=304] of Canadian participants included the concept of "minimizing pain and distress" in their definitions of refinement). Neither country's scientists view replacement as achievable. Half of Canadian participants said they could not replace because animals are the subject of the research (e.g. field research) or similar to their UK counterparts they "need to look at whole animal systems" (the reason given by 77% [n=1,343] of UK participants). Many Canadian scientists feel they already reduce as much as possible and further reduction may compromise individual experimental protocols. However, applying reduction strategies to research programs may have support from scientists: 77% of UK survey participants (n=1,529) identified data sharing or collaboration between research groups as possibilities for reduction. Both surveys found that Three Rs training delivered by national animal use regulators is appropriate. In Canada 65% (n=414) of participants learned about the Three Rs through CCAC training modules and other resources. Similarly, 57% (n=1,529) of UK participants learned about Three Rs from Home Office training courses. Although different methodologies were used for these surveys, comparing results further develops our understanding of scientists' views on Three Rs and the resources needed to support implementation

Session II-4: Poster presentations

II-4-103

An advisory center for the 3Rs

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The need for a qualified point of contact to provide advice on the 3Rs has been voiced in Switzerland for the past few decades by authorities, industry and researchers alike. Swiss legislation is currently one of the most advanced national animal welfare legislations in the world, and clearly demands the incorporation of the 3Rs into research projects. Nevertheless, all parties concerned stress that a noticeable lack of implementation of the 3Rs exists; this appears to be not so much due to missing goodwill, but to a considerable extent to deficits in knowledge about existing and feasible methods. Therefore, in order to overcome these difficulties and beginning June 2011, a 3R point of contact is planned as a joint venture between CAAT-Europe, the Doerenkamp Zbinden Foundation (DZF) and, if possible, other organizations specializing on alternative methods. The new point of contact provides practical advice for researchers, industry, and national authorities, helps with conceptualization of projects with regard to the 3Rs, and offers "tailor-made" presentations for specific working groups. In all cases, the advisory center is obliged to strict confidentiality. In light of the new EU Directive 2010/63, comparable points of contact will be required in Europe, if the aspired strengthening of the concept of 3Rs is not to remain a mere well-meant intention.

II-4-143

Benefits of post-approval monitoring

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Institutions where research teams use animals must apply best practices of animal use, and, more recently, establish a post approval monitoring (PAM). At the CRCHUM¸ PAM visits for protocols began in May 2008. The result of those visits is presented in visits reports that are sent to the institutional animal care committee as well as to the research teams. These reports, whether consistent or not, allow to identify the strengths and weaknesses in practices of the use of animals and better concentrate on the elements to improve. During the visits, the PAM helped identify refinement points that could be put into place.

Advice and refinement techniques mentioned in the visits reports are prepared in collaboration with the veterinarian and animal health technicians from the animal facility. The person responsible for the post approval monitoring meets the visited teams in order to communicate the report results. She discusses refinement points and the best way to implement them. For example, thanks to the combined efforts of everybody, we have succeeded in eliminating the use of barbiturates in survival surgeries, in favour of safer anaesthetics. In short, the visits are a pledge of quality and uniformity of care and gradually, are becoming a required element in the process of optimizing the care and in the creation of personalized training.

II-4-183

Nanoparticles in cosmetics: Does EU legislation allow animal testing – or not?

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In 2003, as a result of enduring public pressure, stepwise bans on animal testing for cosmetic ingredients and products and their marketing if tested on animals were implemented in the EU Cosmetics Directive. Concurrently, nanomaterials are increasingly being used in cosmetic products. Cosmetics range amongst the most important application areas for nanotechnological consumer products. Consequently, the 2009 European Cosmetics Products Regulation introduces specific provisions for nanomaterials, requesting a high level of human health protection.

In 2007, the European Commission's Scientific Committee on Consumer Products published an Opinion on the Safety of Nanomaterials in Cosmetic Products. The Committee expresses concerns about insufficient hazard information on nanomaterials, recognizes large data gaps in risk assessment methodologies and emphasizes that only *in vitro* methods specifically validated for nanomaterials are permissible for safety assessment. Until today, scientific problems, e.g. lack of relevant reference data, stand in the way of meeting this goal. Furthermore, cosmetic substances, such as nano-form titanium dioxide used in sunscreen products, are also produced for other purposes, and therefore might have been tested according to the REACH chemicals legislation, which includes animal testing.

The presentation discusses the animal testing implications of the diverging provisions. Also taking into account ongoing efforts to develop non-animal (nanomaterial) safety testing strategies, it proposes solutions on how to meet the citizens' expectation to purchase "cruelty-free" cosmetics. Notwithstanding all hurdles, the animal welfare provisions of the European cosmetics legislation have the potential for a success story, preventing animal testing without diminishing consumer safety – also for nanomaterials in cosmetics.

II-4-224

The industrial applicability of *in vitro* methods: the role of the In Vitro Testing Industrial Platform (IVTIP)

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IVTIP is an association of 45 companies with an active interest in (i) supporting and applying the principles of the 3Rs (Replacement, Reduction and Refinement of animal testing) for compound discovery, product development and assessment, and regulatory testing, and (ii) promoting the adoption of the fourth R (societal Responsibility). Member companies are represented globally from the following sectors: consumer products, pharmaceuticals, chemicals, cosmetics, and independent contract research organizations. IVTIP has established close contact with the European Commission in relevant Framework Programmes, ECVAM and EPAA. Recently, it has initiated a close collaboration with ESTIV and CAAT-Europe in order to improve the flow of relevant knowledge between academia, industry and regulatory authorities, to stimulate the application of *in vitro* tests by industry and to facilitate their acceptance by regulatory authorities. IVTIP endorses the US NRC's "Toxicity Testing in the 21st Century" strategy as the ultimate replacement of animal experimentation for regulatory/safety testing and focuses on the implementation of innovative strategies. IVTIP provides international discussion forums to address selected topics (e.g., "Toxicity Testing in the 21st Century" (Antwerp, Belgium, 2009), "Integrated Testing Strategies" (Geneva, Switzerland, 2010), and "Limitations of 3D Tissue Models" (Monaco, 2011)), and to identify and discuss novel tools, approaches and technologies in terms of relevance and applicability. The outcome of these discussion forums are published as peer reviewed papers in relevant journals. IVTIP has become an important stakeholder in the ongoing discussions on new regulations involving *in vitro* testing, thereby ensuring effective dissemination through transfer of both technology and knowledge.

II-4-228

Promoting the use and development of alternative methods for regulatory purposes and in research – ECVAM's DataBase service on ALternative Methods (DB-ALM)

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Since 2006 the DB-ALM (http://ecvam-dbalm.jrc.ec.europa.eu), ECVAM's DataBase service for ALternative Methods, is publicly available, providing ready-to-use information as peer-reviewed data sheets. The database includes alternative methods at all stages of development and validation. For the time being its focus is on toxicity assessment methods but not restricted to it and can be widened to mode of action and other experimental approaches. Today, 152 method-summary descriptions and 130 INVITTOX protocols are included providing all information needed to use the tests. In addition DB-ALM provides 82 evaluations and details on formal validation studies, 9163 test results, 5321 bibliographic references and contacts on over 200 persons/institutions active in the field of alternatives. Today, the service has over 2200 registered users from 75 countries coming from academia, industry and regulatory authorities.

Making information on alternatives easily accessible is key during authorisation processes for animal experiments. ECVAM will therefore continue to enhance its DB-ALM, both with regard to content and user interface. In addition, ECVAM's Search Guide project will provide search procedures and user guidance to facilitate the location of information on any 3Rs alternative together with an inventory of relevant resources. Its publication as a handbook and on the Internet is expected for this year. In future all ECVAM information resources will be accessible through a central access point nicknamed for the moment "CALISTO: ECVAM's Center of ALternatives Information SysTems & Orientation". This will include a tracking tool for ECVAM validations to allow stakeholders to follow the process from initial submission of a test to ECVAM until the validity is finally confirmed – or not.

II-4-282

Bridging the gap between validation and implementation: replacing animal use in vaccine batch potency testing

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As technologically advanced, high-throughput techniques are developed that can replace, reduce or refine animal use, harmonization of validated protocols between international regulatory authorities is necessary to foster wide-reaching implementation. Because regulatory acceptance does not guarantee that an approved non-animal method will be adopted for use by manufacturers and regulators, PETA's Regulatory Testing Division (RTD) has developed a multi-component process that (1) confirms the acceptability of data from novel methods by regulatory authorities, (2) distributes information on available and accepted non-animal approaches via stakeholder alerts, (3) publicizes accepted non-animal techniques, and (4) confirms manufacturer implementation of these methods.

By engaging with regulators and manufacturers, RTD employs this process to promote best practices while effectively reducing the reliance on older animal-use-intensive methods. This poster outlines the application of this paradigm to the use of non-animal vaccine batch potency tests, including detailed case studies of RTD's approach to fostering regulatory and industrial integration of *in vitro* erysipelas and leptospirosis vaccine batch potency tests. Successes include (1) verification of acceptance by regulatory authorities, (2) verification of use by vaccine manufacturers, (3) deletion of *in vivo* guidance documents, and (4) elimination of barriers to obtaining waivers for Target Animal Batch Safety Testing.

II-4-299

Animal protection through participation in the Organisation for Economic Co-operation and Development: The ICAPO model

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The International Council on Animal Protection in OECD Programmes (ICAPO), comprising eleven organisations representing more than 30 million members and supporters in Asia, Europe, North America, was granted invited expert status on the Test Guidelines Programme at the OECD in 2002. Since that time, ICAPO has sought to ensure the widest possible integration of non-animal testing methods in the OECD, an influential international organisation that develops harmonised guidelines and programmes for the assessment of chemicals. Through the use of internal and external scientific and policy experts, ICAPO advocates the replacement, reduction, and refinement of animal use within existing and new test guidelines. ICAPO participates in relevant OECD meetings and working groups, comments on OECD draft test guidelines and other documents, and nominates outside experts to take part in OECD activities on ICAPO's behalf. Activity topic areas include endocrine disruptors, (Q)SARs, nanomaterials, environmental and human health test guidelines, and existing chemical assessment approaches. This presentation will discuss ICAPO activities within the OECD and resulting outcomes, as well as opportunities and challenges inherent in working within the structure of the OECD. It will also discuss the International Council on Animal Protection in Pharmaceutical Programmes (ICAPPP), ICAPO's sister coalition formed to promote animal protection in pharmaceutical guidelines developed through tripartite agreement among Japan, Europe and the United States under the International Conference on Harmonisation (ICH). Unlike ICAPO, ICAPPP does not yet have official status but nevertheless has successfully implemented 3Rs initiatives within pharmaceutical guidelines.

II-4-344

The use of nonhuman primates in research: The Association of Primate Veterinarians as an educational resource for enhancing primate welfare

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The Association of Primate Veterinarians (APV) was founded in 1973 and consists of over 400 veterinarians around the world engaged in nonhuman primate breeding, care and oversight in research, zoo, and sanctuary settings. The organization recognizes the continuing need for judicious use of nonhuman primate models in scientific research for the foreseeable future. Because of their advanced cognitive capacity, APV accepts that nonhuman primates are difficult to manage well in captivity, that research use should be highly scrutinized and limited to the most essential studies, and that accepted standards and conditions for management of these species in captivity must be constantly scrutinized and refined to enhance animal welfare. Unfortunately, significant differences exist internationally in acceptable standards for nonhuman primate care and use, which may result in deficiencies in animal well-being. To achieve international harmonization of high standards of care, APV has as its vision to promote excellence in nonhuman primate knowledge, care, and compassion for better health and science. A key role of the organization is to develop, educate, and disseminate best practices for refinements in nonhuman primate care and management. APV has developed and published a number of guidelines documents to assist veterinarians, researchers, and animal care committees to enhance animal well-being. The organization also promotes a number of other educational tools, symposia, fellowships, and international veterinary exchanges to further the knowledge of those working with these species. This poster will describe APV's role in educating veterinarians and the research community in refinement of nonhuman primate care and use.

II-4-373

Application of alternative toxicological methods in safety testing of perfumery and cosmetic products in Russia

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In 2010, the Single Customs Union between Russia, Belarus and Kazakhstan was set up. The countries' participants of the Customs Union accepted the basic document "Uniform sanitary-epidemiologic and hygienic requirements to goods subject to sanitary and epidemiological supervision (control)". This document confirms the use of alternative *in vitro* methods for testing medical articles and equipment, personal care products, baby goods, household chemicals, and perfumery and cosmetic products (PCP).

In the practice of PCP control in Russia alternative methods began to be applied widely under the active participation and collaboration of research centers of The Russian Academy of Medical Sciences, Preventive Toxicology Division from the Centre of Hygiene and Epidemiology in Moscow of Rospotrebnadzor, RNIITO Rosmedtekhnologij. The Russian association of manufacturers of PCP, COLIPA, and leading manufacturers of PCP, in particular Unilever & SEAC, supported Russian toxicologists in this direction.

The development of alternative methods for safety testing of PCP in Russia is conducted in a number of directions:

– Revealing correlation between *in vitro* toxicity indicators and different selective effects on the laboratory animals;
– The research of schemes for alternative testing;
– Research of toxicity of different kinds of products on several *in vitro* test objects simultaneously for revealing the most adequate models.

Human skin fibroblasts, cattle sperm cells, luminescent bacteria and the HET-CAM test are used as test models. Three alternative *in vitro* methods have been confirmed for safety testing of PCP in Russia. The method of ultrasound dopplerography on the HET-CAM vessels for irritation testing of PCP is currently at the "statement stage".

II-4-387

Implementation of *in vitro* replacement technologies in regulatory drug testing – an innovation systems perspective

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The replacement of *in vivo* methods by *in vitro* methods in regulatory drug testing is rare. The aim of this research is to identify barriers and drivers of the replacement of *in vivo* methods by *in vitro* methods in Europe.

We studied two cases. The first case is the Draize eye test. Since 2009, the *in vivo* test is partly replaced by *in vitro* methods. The second case concerns EPO potency testing. Since the eighties, financial and scientific efforts have been made to replace the *in vivo* EPO potency test with *in vitro* methods; however the efforts failed to deliver expected outcomes. The innovation systems approach is used to identify the drivers and barriers regarding replacement of *in vivo* methods by *in vitro* methods in regulatory drug testing in Europe, such as the presence or absence of legislative pressure, legitimacy, and funding. Combining and comparing the outcomes resulted in an overview of potential barriers and drivers, and an indication of which of these factors are critical for replacement of *in vivo* methods by *in vitro* methods in regulatory drug testing. Policy makers could use these results to formulate policies that enable the replacement of *in vivo* methods by *in vitro* methods in regulatory drug testing.

II-4-416

Animal protection laws and regulations in India

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India has one of the most comprehensive animal protection laws. India's Constitution, in Section 51A (g), prescribes that it is the fundamental duty of every Indian citizen to have compassion for all living creatures. The Prevention of Cruelty to Animals Act 1960, and the Breeding of and Experiments on Animal (Control and Supervision) Rules 1998, provide for avoidance of experiments on animals wherever possible, and where animal are used they shall not be subjected to any cruelty. These provisions are enforced by an independent Committee for the Purpose of Control and Supervision of Experimentation on Animals (CPCSEA), under the Ministry of Environment and Forests. The use of animals must be first reviewed and approved by the Institutional Animal Ethics Committee (IAEC).

The other most significant legal provision to animals is embodied in the Indian Wildlife (Protection) Act, 1972. Bonnet monkeys, rhesus monkeys, sharks, freshwater frogs, etc., are given legal protection. In compliance with the directions of the Hon'ble High Court of Delhi dated 19 May 1997, the Central Board of Secondary Education has decided to make dissection of animals optional to the students of Senior Secondary Classes. The University Grants Commission (UGC) has set up an Expert Committee to look into the possibility of banning dissection of animals for studies in zoology in colleges and universities. But the problem lies in the practice and enforcement. If only the laws are properly implemented and practiced, the animals in India will be the happiest lot.

II-4-451

Enhancing implementation of the 3Rs in daily practice – which way to go?

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In the Netherlands, like in many other countries, researchers are obliged by law to apply 3R methods in research using animals. Finding and implementing the 3Rs, however, remains a difficult task according to the results of our local and national survey among researchers. In the national survey questionnaires were also sent to Animal Welfare Officers (AWO) and members of Animal Ethic Committees (AEC). These groups also indicated that they experience practical difficulties in their legal obligations to apply the 3Rs. Implementation of 3R methods seems mainly to depend on a positive 3R-attitude of the researcher, a motivating and cooperative working environment, and an efficient professional network.

During an intensive workshop, researchers, AWOs and AEC members elaborated on how 3R implementation in practice can be enhanced. It was the first time in the Netherlands that these different professions, affiliated with different organizations (including academia, industry and contract research organizations), came together to discuss this topic in depth. The workshop resulted in 6 consensus statements covering policy, education and daily practice.

During the 8th World Congress of Alternatives the recommendations, based on the consensus statements, will be presented including the state of affairs concerning the first spin-off activities. In part, these survey results led to a focus shift of our research group towards implementation of systematic reviews of animal studies, a transparent and thorough method for accumulating and analyzing all relevant animal studies. Other suggestions for improvement will be made throughout the whole research chain, from public to researcher, from editor to legislator.

II-4-469

Prioritising promising 3R research, a helpful classification scheme

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The Netherlands have known a strong research tradition in the development of 3R methods, with the ultimate objective to decrease animal use and animal suffering as effectively and efficiently as possible. Unfortunately, the (inter)national acceptance and implementation of many of these methods tend to lag behind and thus, 3R expectations may not be fully realized.

Improvement of the exchange of knowledge between fundamental and applied research would help promising, innovative 3R methods on their way from development to implementation and use. To improve knowledge exchange within such specific promising research areas demands an interactive, tailor-made and chain-based approach, including activities ranging from raising awareness among a new generation of researchers, to the implementation of 3R methods into (inter)national law and legislation. But how do we define the most promising research areas and developments for the 3Rs?

A classification scheme was drawn up by the NKCA to help governmental authorities, researchers, companies and NGOs to prioritise their ongoing and new research activities. The scheme includes a set of criteria to classify research areas/projects as promising or less relevant for the ultimate application of 3R-alternatives. The classification criteria were divided in three categories; the scale of the problem, chance of success, and impact on animal use. Based on ethical, scientific, political or practical factors, increased value can be assigned to some specific criteria within these categories.

The classification scheme will be presented in the poster. It will also be available on request, by contacting the authors.

II-4-476

Animal welfare and Three Rs education: Filling the gap in interdisciplinary studies

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Scientific developments and evolving humane standards are pointing more than ever in the direction of finding alternatives to using animals as test models. However, the educational systems responsible for introducing attorneys, veterinarians, life scientists, social scientists and others to the 3Rs concept and also to animal welfare laws and regulations is woefully inadequate. With limited exceptions, law schools offer minimal instruction in animal law, regulatory decision making or risk management. Veterinary schools fail to provide their students with sufficient training in recognizing and reducing laboratory animal pain, or with the scientific theoretical framework for doing so. Many other graduate science programs minimize the importance of understanding and embracing the 3Rs and other animal welfare principles, and very few address the legal and social implications of decisions related to animal welfare.

These educational failures are structural; they are not dependent upon a particular school or discipline. Therefore the changes which must be made are also structural. If changes do not occur within the educational training of the professional schools, their graduates will not be well prepared to address the legal, social, scientific, economic and international issues related to animal testing today.

This presentation explores some of the history of animal welfare education in law schools, veterinary schools and other graduate science programs; explains why the 3Rs have not become an essential part of American education; and provides suggestions for change.

II-4-482

Improving 3Rs information in research publications

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This presentation will argue the case for making researchers more 3R-aware by expecting clear objectives and information on experimental design, refinements and husbandry practices in research papers. Currently some papers even fail to describe adequately the purpose of the study (5% of the 271 papers scrutinised by Kilkenny et al., 2009) so neither referees nor readers can judge whether replacement alternatives could have been considered, or alternative, more efficient designs or refinements used. There is typically no discussion of why the particular animal, model, design or group size was chosen, nor of what was done to minimise severity. It is usually not clear how the animals were selected for the experimental manipulations, how they were caged, or what if any environmental enrichment there was. Additional information available online could easily indicate why an option was chosen as well as giving details of what was done, and some of this might be expressed succinctly enough to be in the main text. Provision of such information would stimulate researchers to think of alternatives, and disseminate ideas for improved design and refinements applicable to a particular area of study more widely than local ethical review or networking.

Reference

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II-4-519

The American Veterinary Medical Association's Animal Welfare Committee: Educating veterinarians and the public regarding best practices for animal welfare

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The American Veterinary Medical Association (AVMA) represents a diverse group of over 81,500 veterinarians. A strategic priority for the AVMA is to be a leading advocate and authoritative resource for animal welfare, both for the veterinary community and the public at large. Veterinarians should be willing and capable to speak authoritatively on animal welfare and the principles of the 3Rs in all environs where animals are used. The AVMA's strategically diverse Animal Welfare Committee (AWC) and Animal Welfare Division (AWD) are charged with proactively identifying animal welfare concerns and opportunities, critically evaluating information including stakeholder concerns, and determining what actions might be most appropriate and effective to address concerns. In cases where no or insufficient information exists, the AWC recommends plans to address the knowledge gap in animal welfare. To educate veterinarians about refinements in veterinary medical care, the AWC has developed a set of policies that addresses many aspects of animal use, as sporting animals, food sources, research subjects, and companion animals. These policies are regularly reviewed and updated by the AWC to incorporate up-to-date evidence for enhancing animal welfare. The AVMA also sponsors national and international educational sessions and symposia related to animal welfare, as well as publications and projects that significantly impact animal care and use globally, including the AVMA's Guidelines on Euthanasia, Model Dog Care Act, and a planned Model Animal Welfare Veterinary Curriculum. This poster will address the role of the AVMA AWC and AWD in educating veterinarians and the public about animal welfare refinements.

II-4-524

AltTox.org: Communication platform for 21st Century Toxicology

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"21st Century Toxicology" deserves 21st century communication tools. AltTox.org is an interactive, online resource for professionals interested in advancing toxicology to better protecting human health or to reduce reliance on animal use. AltTox is intended to supplement more conventional means of sharing information, such as books, journals, and static websites. Its scope goes beyond that of websites that cover the activities of individual institutions or organizations. At the same time, it maintains a sharp focus on *in vitro* and *in silico* methods and relevant integrated testing strategies, and does not dilute its coverage by addressing other toxicological methods, fields of biomedical science, or areas of alternative methods. AltTox users include scientists, regulators, advocates, politicians, and others in industry, government, academia, and non-governmental organizations worldwide. The site provides relevant, concise, and up-to-date content, written in accessible language, as well as an interactive community platform (AltTox Forum), an extensive set of essays on "The Way Forward," a calendar of upcoming meetings, and listings of a variety of helpful resources. The website averaged over 8,000 visitors per month over the past year (an increase of 25% from the previous year) and nearly 17,000 page views per month. The website has a global reach, with 40% of visits from North America, 32% from Europe, and 22% from Asia. AltTox currently has approximately 60 "Way Forward" essays, over 1,200 subscribers to our monthly newsletter (AltTox Digest), and over 300 registered members of the AltTox Forum. Interested parties are encouraged to visit and contribute to AltTox regularly.

II-4-549

Programming study on 3R alternatives; how to focus 3R efforts in the Netherlands

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In 2010-2011, the Netherlands Knowledge Centre on Alternatives to animal use (NKCA) published the Programming Study on 3R alternatives, which was aimed at finding out how and in which research fields in The Netherlands, the knowledge exchange between fundamental and applied research needs improvement in order to get promising, innovative 3R-alternatives from development to implementation and application. The following aspects of stimulating 3R-alternatives are included: 1) priorities in ongoing and future activities (research, development and implementation); 2) recommendations for a more integrated approach of 3R-alternatives development; 3) the international context; 4) creating a favorable 3R research climate. Also included are the chains and legal frameworks of different application domains, to identify areas where (inter)national harmonization is desirable/essential for the implementation of 3R methods. A classification scheme (presented in a different poster) was drawn up to classify research areas/projects as promising or less relevant for the ultimate application of 3R-alternatives. Within fundamental research, the most promising research fields are: 1) development of human medicines; and 2) research towards cancer and other human diseases; and in applied research: 1) quality control of human medicine and biologicals (including sera and vaccines); and 2) toxicological risk assessment. Improved knowledge exchange within these areas demands an interactive, chain-based approach, including activities ranging from raising awareness among researchers to the implementation of 3R methods into (inter)national law and legislation. A strong dialogue on this subject between policymakers, research, corporate businesses and society will be needed. Our report is available on request by contacting the authors.

II-4-593

A new class of biomimetic, *in silico* models designed for increasing research efficiency while reducing animal use

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The new class of biomimetic, *in silico* models is fundamentally different from models used by the European Commission's BioSim Network (http://biosim-network.eu/). BioSim's plan, using established methods (simulation models of cellular and pharmacological processes constructed using continuous mathematics), was to obtain a deeper understanding of pathological and pharmacological processes, with the ultimate goal of achieving more rational drug development coupled with reductions in the need for animal experiments. We explain why the approach was stymied. Our objective has been the same, but our approach and methods have been designed specifically for achieving a reduction in the need for animal experiments. We build analogues of biological wet-lab counterparts: concretized, explanatory hypotheses about the mechanistic consequences of xenobiotic interventions built using object and agent oriented software components (Hunt et al., 2008, 2009; Hunt and Ropella, 2011). Interchangeable components link coarse-grained systemic phenomena to fine-grained molecular details. We draw on two examples (*in silico* livers and epithelial cells) to explain how the biological wet-lab side of the R&D process might function when these models and methods are fully implemented. Accumulated mechanistic knowledge is easily measured and visualized in action. Components within analogues validated for many compounds can use programmed "intelligence" to automatically parameterize for, and respond to, a new, not previously seen compound based on its physicochemical properties. Encouraging exploration of this new model class (by the R&D community) will help make clear how its scientific use will lower costs and expedite achieving R&D objectives. Animal use will be reduced because *in silico* experimentation will focus the scientific question being asked, and that will incrementally reduce the need for exploratory animal experiments.

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II-4-596

Effecting change in animal welfare at a national level – The role of the Canadian Veterinary Medical Association

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Refining animal welfare practices is a key priority for the Canadian Veterinary Medical Association. The organization is a national science and ethics based resource for veterinarians, veterinary students, provincial and federal governments, and the public regarding animal welfare standards for all species. Through the actions of its Animal Welfare Committee (AWC), the CVMA seeks to educate members and others regarding acceptable practices for animal care and use, leading to enhancement of animal well-being. The CVMA's AWC achieves their goals in a number of ways. Leadership and active advocacy for enhancing animal welfare is demonstrated through development of position statements that consider current knowledge and scientific evidence to refine treatment and care of animals. These position statements are developed with member consultation and advice from pertinent stakeholder groups. In addition, the CVMA's AWC develops and disseminates educational tools, such as posters on various topics, for veterinarians, students, and the public, which are strategically geared to create shifts in thinking about currently accepted practices; maintains a roster of spokespersons to address national animal welfare issues, publishes peer-reviewed papers on current animal welfare topics; and develops codes of management and husbandry practice for species not covered by national producer organizations. The CVMA takes an active advocacy and lobbying role at a national level with a number of nongovernmental and governmental organizations and committees to effect policy changes in accepted best practices for animal welfare. This poster will explore the CVMA's role in effecting enhancements for animal welfare in Canada.

II-4-605

Canadian Association for Laboratory Animal Medicine: Promoting research animal welfare coast-to-coast

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The Canadian Association for Laboratory Animal Medicine/ L'Association Canadienne de la Médicine des animaux de laboratoire (CALAM/ACMAL) was founded in 1982 and is the national organization that represents the interests of Canadian laboratory animal veterinarians working to support the humane care and use of animals used in research, teaching, and testing. The vision of the organization is to be recognized and respected as leaders in laboratory animal welfare. The central document to the CALAM/ACMAL vision is the Standards of Veterinary Care, which was last updated in 2007. The document emphasizes that CALAM/ACMAL and its individual members have a responsibility to provide leadership in developing best practices for the humane care and use of animals in research, teaching, testing and production, with due consideration of the 3Rs: replacement of animals used, when possible; reduction of numbers of animals used; and refinement of techniques and procedures employed. CALAM/ACMAL recognizes that the well-being and welfare of animals used in research, teaching, and testing are the main focus for all laboratory animal veterinary roles and responsibilities. For laboratory animal veterinarians, animal welfare includes physical and behavioral aspects of an animal's condition, evaluated in terms of environmental comfort, freedom from pain and distress, and provision of appropriate social interactions. The organization promotes a number of educational tools, symposia, and fellowships to veterinary students and veterinarians to facilitate the exchange of knowledge and harmonization of standards of veterinary care for Canadian laboratory animal veterinarians. This poster will describe CALAM/ACMAL's role in promoting research animal welfare.

II-4-713

REACH regulation: Ensuring safety of industrial enzymes – is animal testing necessary?

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Enzymes for technical applications have to be registered under the EU chemicals regulation, REACH. The enzyme industry has to ensure that production, handling and use of the enzymes is safe throughout the supply chain for consumers, workers and the environment. Enzymes are produced by fermentation and categorized as UVCB's (Unknown/Variable composition, Complex reaction products or Biological materials). Identity and sameness is based on enzyme identification according to the specific catalytic activity of the enzyme.

The safety documentation of an enzyme product consists of two elements, safety of the enzyme protein and safety of the non-enzymatic constituents derived from the fermentation process. Apart from being potential respiratory sensitizers and the minor risk of skin/eye irritation for some proteases, enzymes in general have a low risk profile. Safety of the "other constituents" is therefore in focus and is closely linked to the safety of the production strain used for the fermentation. However, when an enzyme of known catalytic identity has been produced by a well-characterized, non-pathogenic production strain following good manufacturing practices then this enzyme should be regarded as safe for use. According to our experience, future toxicological testing of enzymes can be avoided by applying read-across and data waiving without extensive *in vivo* toxicology programs. Risk assessment includes exposure assessment related to the few possible hazards mentioned above. If required, relevant *in vitro* alternatives will be applied for specific issues.

In conclusion, hazard characterization of biological substances like enzymes requires an alternative approach compared to the hazard characterization of "classical" chemicals.

II-4-715

A partnership between the Australian National University and the MAWA Trust leads to the establishment of the Australian Centre for Alternatives to Animal Research

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As a result of the implementation of successive editions of the *Australian Code of Practice for Care and Use of Animals for Scientific Purposes*, and representative participation in the *World Congresses on Alternatives and Animal Use in the Life Sciences*, the Australian National University (ANU) has made significant progress with implementation of the 3Rs. This is true of refinement methodologies, the replacement of animals in teaching, and research animal reduction through the Ethics Committees' recognition of statistical validity requirements for experimental animal numbers. Progress, however, towards the aim of animal replacement in fundamental biomedical research, which is widespread at the ANU, is slow.

The Medical Advances Without Animals Trust (MAWA) operates an independent medical research trust fund and is committed to advancing methodologies that replace the use of animals and animal products in biomedical research. To stimulate greater interest and activity in this regard, MAWA awarded funds to the ANU for a Fellowship and the appointment of an Associate Professor in Alternatives to provide scientific leadership in replacement research. A key objective of the ANU and MAWA partnership is to establish *The Australian Centre for Alternatives to Animal Research* (ACAAR) to support the development of non-animal research alternatives across Australia. The ongoing research focus associated with the Centre will be directly on human biology and thus has the additional advantage of encouraging the translation of fundamental medical advances to the clinic. The ANU based research programme will begin by developing alternative methodologies using international expertise in computational biology and bioinformatics.