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**Series on Testing and Assessment**

**No. 113**

# REPORT OF THE FOCUS SESSION ON CURRENT AND FORTHCOMING APPROACHES FOR CHEMICAL SAFETY AND ANIMAL WELFARE

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IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

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## ABOUT THE OECD

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**or contact:**

**OECD Environment Directorate, Environment, Health and Safety Division**

**2 rue André-Pascal**
**75775 Paris Cedex 16**
**France**

**Fax: (33-1) 44 30 61 80**

**E-mail: ehscont@oecd.org**

## FOREWORD

This document sets out the report of the Focus Session on Current and Forthcoming Approaches for Chemical Safety and Animal Welfare, which was held during the 45th Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology (9-11 February 2010). Information that was presented at the Focus Session is summarised in the Annex to this document.

The Joint Meeting agreed on conclusions of the Focus session and to declassification of this document during the meeting. It is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.

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## Introduction

1. The 3R-principles (Replacement, Reduction and Refinement[1]), were first laid down by Russell & Burch in 1959, in their publication "The Principles of Humane Experimental Technique". Over 25 years ago, the OECD recognised the need to protect animals in general and in particular those used in experimental work. The Second High Level Meeting of the Chemicals Group addressed this ethical issue and adopted the following statement:

*"The welfare of laboratory animals is important; it will continue to be an important factor influencing the work in the OECD Chemicals Programme. The progress in OECD on the harmonisation of chemicals control, in particular the agreement on Mutual Acceptance of Data (MAD), by reducing duplicative testing, will do much to reduce the number of animals used in testing. Such testing cannot be eliminated at present, but every effort should be made to discover, develop and validate alternative testing systems".*

## Focus Session Organisation

2. The Focus Session on current and forthcoming approaches for chemical safety and animal welfare had two main objectives:

- To take stock of OECD's progress regarding testing and assessment of chemicals and animal welfare.

- To exchange information on forthcoming new toxicological approaches that may have important consequences on animal welfare and chemical management in the future.

## Focus Session Progression

3. The Focus Session was held on 9 February 2010, as part of the 45th Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology. It was chaired by George Enei (Canada, Chair of the Joint Meeting). It was organised in two parts (see Table below). The first part was comprised of five presentations from the Secretariat, the United States, and WHO, followed by comments from the Joint Meeting. The second part was comprised of four presentations from the European Commission, the United States, the Business and Industry Advisory Committee (BIAC) and the International Council on Animal Protection in OECD Programmes (ICAPO), followed by a general discussion. The Annex to this document presents summaries of the presentations on progress achieved at OECD for the welfare of laboratory animals in the context of safety assessments, including work on Test Guidelines, molecular screening and toxicogenomics, (Q)SARs and Chemical Categories. It also presents summaries of the presentations on the US EPA ToxCast™ Program and Strategic Plan for evaluating the Toxicity of Chemicals, REACH and Animal Welfare, and views from BIAC and ICAPO on Chemical Safety and Animal Welfare.

[1] Replacement : The substitution for conscious lining higher animals of insentient material
Reduction: Reduction of the number of animals used to obtain information of given amount and precision
Refinement: Any decrease in the incidence or severity of inhumane procedure to those animals which still have to be used.

| Part 1 | |
|---|---|
| Introduction and presentation on *in vitro* test methods and methods using a reduced number of animals | Secretariat |
| Molecular Screenning and Toxicogenomics | Secretariat |
| ToxCast™ Program | United States |
| (Q)SAR and chemical categories | Secretariat |
| Considerations of the Modes of Action of Chemicals | WHO |
| Questions/Discussion | Joint Meeting |
| Part 2 | |
| Reach and Animal Testing | European Commission |
| Strategic Plan for Evaluating the Toxicity of Chemicals | United States |
| View on Chemical Safety and Animal Welfare | BIAC |
| View on Chemical Safety and Animal Welfare | ICAPO |
| Questions/Discussions/Conclusions | Joint Meeting |

**Joint Meeting Conclusions**

4. The Joint Meeting welcomed the presentations and noted that current and new scientific approaches for assessing effects of chemicals on human health and the environment may induce important changes in chemicals management and animal welfare. The Joint Meeting agreed on the following conclusions:

- The OECD plays a key and unique role in developing and promoting appropriate tools to evaluate chemical safety to protect human health and the environment. These tools are also important to address animal welfare concerns related to toxicity testing of chemicals at the international level.

- Considerable progress has been achieved in the development of screening and assessment tools for regulatory use by member countries and non members, such as Test Guidelines for *in vitro* test methods and the (Q)SAR Application Toolbox. They all contribute to Animal Welfare (3Rs) and already a number of animal tests have been replaced.

- Development and use of new tools, for example the molecular screening relying on high throughput in *vitro* methods, will help to increase health protection through screening more chemicals for more endpoints (e.g. many new endocrine endpoints). These new tools, and their use in an integrated and weight of evidence approach aims to significantly reduce the number of animal tests.

## Annex: Summaries of Focus Session Presentations

### Test Guidelines and Animal Welfare

1. Since the adoption in 1981 of the first set of Test Guidelines, many of the short-, and long-term toxicity tests, as well as the genetic toxicity tests, have been developed or updated to introduce aspects of the 3R-principles[2]. Work on alternative test methods also recently started regarding Manufactured Nanomaterials.

2. A number of proposals for new or updated Test Guidelines for alternative test methods have been included in the work plan of the Test Guidelines Programme[3]; they are either under discussion or waiting for validation finalisation. Validating[4]/Peer reviewing alternative test methods being time and cost consuming, the OECD welcomes contributions from country agencies/institutes, from the European Centre for the Validation of Alternative Methods (ECVAM), the US Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the Japanese Centre for the Validation of Alternative Methods (JaCVAM), and expects future contributions from the International Cooperation on Alternative Test Methods (ICATM). Industry should also be recognised as a major player in the validation of alternative test methods.

3. Test Guidelines for *in vivo* test methods now request users to follow the provisions laid out in the OECD Guidance Document No.19 on "the Recognition, Assessment and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluations", published in 2000. This document gives practical guidance how to apply the 3R-principles, with an emphasis on Refinements, when performing tests using animals.

### In Vitro *Test Methods*

4. Test Guidelines for *in vitro* test methods have been validated and adopted for genotoxicity, skin corrosion, skin absorption, phototoxicity, ocular severe irritation and corrosion, as well as for screening potential endocrine disrupters. In addition to the 7 relatively old Test Guidelines for genotoxicity, there are 9 recent Test Guidelines for *in vitro* test methods (See Tables 1 and 2 of the section *Animal Welfare* available on the public website: www.oecd.org/env/testguidelines). It is important to stress that if proposals for fully validated test methods are submitted to the OECD, their adoption can be very fast. Thus, two Test Guidelines for *in vitro* test methods for identifying ocular corrosives and severe irritants (TG 437 and 438), proposed in 2008, have been adopted in 2009.

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[2] See Tables 1 and 2 in « Animal Welfare »
http://www.oecd.org/document/48/0,3343,en_2649_34377_40695856_1_1_1_1,00.html

[3] See Table 3 in « Animal Welfare »
http://www.oecd.org/document/48/0,3343,en_2649_34377_40695856_1_1_1_1,00.html

[4] The Guidance Document No. 34 on "the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment" was published in 2005. It provides the principles and criteria for how validation studies of new or updated, *in vitro* or *in vivo,* test methods should be performed. As a result of the adoption of Guidance Document 34, a considerably more harmonised validation and regulatory acceptance procedure has been achieved at the OECD and agreement by countries is greatly facilitated.

5. *In vitro* test methods often have limitations, but technical progress may allow an extension of their scope. The draft Test Guideline for an *in vitro* skin irritation assay, which should be adopted in 2010, is the first *in vitro* method to be used as a full replacement of an *in vivo* method. Other Test Guidelines for *in vitro* methods are expected to be used as part of a testing strategy.

6. An important issue, mostly related to *in vitro* test methods due to innovation in this field, is the proliferation of test method proposals for the same endpoints, and the inclusion of proprietary elements in test methods. To address this issue, performance standards are developed for many *in vitro* test methods for which Test Guidelines are developed. Performance standards, based on (a) validated test method(s), provide a basis for evaluating the comparability of another test method that is mechanistically and functionally similar.

7. Many new *in vitro* test methods, for which Test Guidelines are developed, use cell lines or other proprietary elements. In such cases, Material Transfer Agreements (MTAs) are required by the provider of the cell lines or other proprietary elements. These MTAs should not include conditions that would prevent or discourage the use of Test Guidelines. A recommended OECD MTA for the use of Test Guidelines, to be signed between the provider and the recipient, is under development. It should facilitate access to the proprietary elements of the test methods.

***Methods using a reduced number of animals***

8. Reduction of the number of animals is often a solution for the assessment of hazards for which no *in vitro* test method has been proposed. The most noteworthy achievement is probably the deletion of the much criticised Test Guideline 401 on Acute Toxicity Testing, and its replacement with Test Guidelines 420, 423 and 425, introducing reduction and refinement. Other examples are the Local Lymph Node Assay (Test Guideline 429) introducing refinement and reduction compared to Test Guideline 406 (Skin Sensitisation) and the Test Guideline 428 on "Skin Absorption: In Vitro Method" offering an alternative method to Test Guideline 427, among others. A new Test Guideline with a reduced number of animals was adopted in 2009 as an alternative to TG 403 on acute Inhalation Toxicity. Reduction of animal use is also one of the main objectives of the draft Test Guideline for an Extended One Generation Reproductive Toxicity Study, which is close to adoption.

***Mutual Acceptance of Data (MAD)***

9. The MAD Council Decisions [C(81)30 and C(97)114] have a major impact on testing practices. MAD guarantees that data generated in the testing of chemicals in an OECD member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice (GLP), shall be accepted in other member and adhering non OECD economies for purposes of assessment and other uses relating to the protection of man and the environment. These proactive Council Decisions avoid test duplication and therefore save animals when animal tests are required. Thousands of animals are saved every year thanks to MAD. And animal saving will increase with the increasing number of non OECD economies adhering to MAD (South Africa, Slovenia, Israel, and Singapore are already full adherents; India,Brazil, Argentina and Malaysia initiated the process and are provisional adherents to MAD).

## Molecular Screening and Toxicogenomics

### *Molecular Screening and the US ToxCast™ Program*

10. The OECD work on Molecular Screening started in 2007. It is led by the United States and based on the US ToxCast™ Program (see Box 1). The objective of this work is to develop large batteries of high-throughput screening *in vitro* assays that can be applied rapidly to thousands of chemicals to identify those that need further evaluation, thereby limiting the number of chemicals subjected to animal testing. Member countries and Stakeholders have been invited to contribute to the ToxCast™ Program through the generation of additional assays and/or nomination of additional chemicals.

11. An OECD Extended Advisory Group met three times in the US, the Netherlands, and Paris [ENV/JM/RD(2009)2]. Several sub-groups are now working on elucidation of signalling pathways and modes of action (thyroid signalling, PPAR alpha associated pathways, cancer epigenetics, sensitization / immunotoxicity, Developmental / Reproductive effects, and Developmental neurotoxicity). Very recently, work started on the application of rapid screening and genomic technologies (see below) to ecotoxicology.

**Box 1: US ToxCast™ Program: Application of high throughput screening to identify profiles of biological activity** (Robert J Kavlock, NCCT/ORD/US Environmental Protection Agency)

ToxCast™, the United States Environmental Protection Agency's chemical prioritization research program, is developing methods for utilizing computational chemistry and bioactivity profiling to predict potential for toxicity and prioritize limited testing resources (www.epa.gov/tocast). In Phase I, the proof-of-concept component, the EPA has focused upon evaluating chemicals with an existing, rich toxicological database in order to provide an interpretive context for the high through put screening data. This set of 320 reference chemicals, largely food use pesticides, represents numerous structural classes and phenotypic outcomes. The *in vivo* datasets include standard chronic bioassays in the rat and the mouse as well as developmental toxicity and multigenerational studies. All the toxicity information is contained in a relationship database, ToxRefDB, facilitating comparison with the in vitro data. The bioactivity data is derived from a broad spectrum of more than 500 readouts from cell-free biochemical assays, cell-based phenotypic assays, and model organisms. Data analysis includes both supervised (selecting particular assays or pathways known to be associated with toxicities and testing for association with phenotypes) and unsupervised (univariate, multivariate and clustering) approaches. Phase II of the program, is scheduled to begin later this year. ToxCast is part of a larger government effort (Tox21) being conducted jointly by EPA, the National Toxicology Program of the National Institute of Environmental Health Sciences, and the National Institutes of Health Chemical Genomic Center that is obtaining high throughput screening data on more than 2000 chemicals, with plans to expand to nearly 10000 chemicals in 2009.

### *Toxicogenomics*

12. Toxicogenomics is defined as a study of the response of a genome to hazardous substances, using "omics" technologies such as genomic-scale mRNA expression (transcriptomics), cell and tissue-wide protein expression (proteomics), and metabolite profiling (metabolomics), in combination with bioinformatic methods and conventional toxicology. This emerging science could provide tools in various ways, such as for improving the understanding of mechanisms of toxicity, reducing uncertainty in grouping of chemicals for assessments, and providing alternative methods for chemical screening, hazard identification and characterisation.

13. In 2003 and 2004, OECD and IPCS organized twin workshops in order to develop a strategy concerning the future application of toxicogenomics in regulatory assessment of chemical safety. The first workshop on human health aspects was held in Berlin[5], led by the IPCS. The OECD took the lead of the second workshop held in Kyoto (Japan), which focused on eco-toxicological aspects. A report of the Kyoto workshop was published in 2005 (Series of Testing and Assessment No.50, ENV/JM/MONO(2005)10). In the preparation for the Kyoto workshop, the OECD Secretariat conducted a survey on existing toxicogenomic tools in OECD member countries. The Advisory Group on Toxicogenomics agreed on performing a follow-up survey on available "omics" tools. The result of the follow-up survey, led by Japan, was published in January 2009 (Series of Testing and Assessment No.100, ENV/JM/MONO(2008)35).

**(Q)SARs and Chemical Categories**

14. (Quantitative) Structure-Activity Relationships [(Q)SARs] are used to estimate properties of a chemical based on its molecular structure and can thus provide information on hazards of chemicals without animal testing. To facilitate practical application of (Q)SAR approaches in regulatory contexts by governments and industry and to improve their regulatory acceptance, the OECD has developed various outcomes such as the **principles for the validation of (Q)SAR models**, **guidance documents** as well as the **(Q)SAR Application Toolbox**, as outlined below.

***Validation of (Q)SAR models***

15. Although a variety of (Q)SAR models have been developed, and some models have been used in assessment of chemicals in some countries for many years, transparent validation process and objective determination of the reliability of (Q)SAR models are crucial in order to further enhance the regulatory acceptance of (Q)SAR models.

16. In November 2004, the OECD member countries agreed on the principles for validating (Q)SAR models for their use in regulatory assessment of chemical safety [see http://www.oecd.org/dataoecd/33/37/37849783.pdf]. These agreed principles provide member countries with a basis for evaluating regulatory applicability of (Q)SAR models and will contribute to their enhanced use for more efficient assessment of chemical safety.

17. In February 2007, the OECD published a Guidance Document on the Validation of (Q)SAR Models [see http://appli1.oecd.org/olis/2007doc.nsf/linkto/env-jm-mono(2007)2] with the aim of providing guidance on how specific (Q)SAR models can be evaluated with respect to the OECD principles. This guidance document also contains a check list for the validation, a reporting format for the validation and validation case studies. It is specifically aimed at model developers who are encouraged to show how their models comply with the validation principles, so that regulators can decide whether a model can be used for the intended regulatory purpose.

***Grouping chemicals into categories***

18. Grouping of chemicals into (eco)toxicologically meaningful categories is an alternative *ad hoc* way to apply (Q)SAR methodology to fill data gaps. A chemical category is a group of chemicals whose physico-chemical and human health and/or environmental toxicological properties and/or environmental

[5] The summary report of the workshop is available at the IPCS website:

http://www.who.int/ipcs/methods/toxicogenomics/en/

fate properties are likely to be similar or follow a regular pattern as a result of structural similarity or a common underlying mechanism of action. As a result, it is possible to extend the use of measured data to similar untested chemicals by read-across or trend analysis, and reliable estimates that are adequate for classification and labelling and/or risk assessment can be made without further testing.

19. This methodology has been used in the OECD HPV Chemicals Programme as well as in numerous national/regional assessment schemes since 1998 and has contributed significantly to the reduction of the use of test animals.

20. The latest version of the OECD Guidance on Grouping of Chemicals was published in 2007 [see http://appli1.oecd.org/olis/2007doc.nsf/linkto/env-jm-mono(2007)28]. Work is underway to refine the guidance to expand the number of chemicals that can be assessed with this approach.

***OECD (Q)SAR Application Toolbox***

21. The (Q)SAR Application Toolbox is a software application intended to be used by governments, chemical industry and other stakeholders in filling gaps in (eco)toxicity by using the chemical category concept. The Toolbox incorporates information and tools from various sources into a logical workflow and allows users to systematically group chemicals into categories and fill data gaps without animal testing.

22. The main steps of the workflow of the Toolbox are:

1. Identification of relevant structural characteristics and potential mechanism or mode of action of an untested target chemical.

2. Identification of other chemicals that have the same structural characteristics and/or mechanism or mode of action and for which experimental results are available.

3. Use of the existing experimental data to fill the data gap(s) by read-across or trend analysis.

23. A first version of the Toolbox was released in 2008 [see http://www.oecd.org/env/existingchemicals/qsar]. Further development is ongoing and the releases of versions 2.0 and 3.0 are scheduled for October 2010 and October 2012. The objective of the further development of the software is to expand and to refine the practical application of the chemical category concept and ultimately to ensure that the approach works uniformly for all discrete organic chemicals and for all regulatory endpoints

**REACH and Animal Testing**

***Introduction***

24. European Union (EU) legislation addresses animal welfare concerns in the development and the implementation of chemicals legislation, exemplified through the EUs legislation on cosmetics, biocides, pesticides and industrial chemicals. This section illustrates how this is done by considers in the specific case of Regulation (EC) 1907/2006 on Registration, Evaluation, and Authorisation of Chemicals (the so-called REACH Regulation), however parallels are also drawn to these pieces of legislation in some cases.

25. Regulation (EC) 1907/2006 on Registration, Evaluation, and Authorisation of Chemicals (the so-called REACH Regulation) is concerned principally with the need to ensure that chemical substances are marketed and used in such a way that they do not adversely affect human health or the environment. However, REACH also sets the objective of promoting the development of alternative methods. This is captured in Article 1(1) of REACH states that REACH aims "*to ensure a high level of protection for*

*humans and the environment, including the promotion of alternative methods for assessment of hazards of substances*".

26. Under REACH, manufacturers or importers of chemical substances are required to submit registration dossiers containing information on the properties of the substance ( e.g. physico-chemical properties, toxicity, ecotoxicity), what it is used for and how the risks associated with its use and manufacture can be controlled. A lot of the information needed for registration, requires tests to be carried out on the substance. In order to protect workers, consumers and the environment, some of these tests involve the use of vertebrate animals such as mice, rats and fish. However, the REACH registration and evaluation process is designed to try and minimize such testing.

***Alternatives to Animal Testing***

27. REACH gives precise indications of what information should be included in a registration dossier and how that information should be generated. However, information on the intrinsic properties of substances may be generated by means other than tests and the Regulation and its Annexes give clear indications of how and when this can be done.

28. Article 13.1 of the Regulation reads as follows:

*Information on intrinsic properties of substances may be generated by means other than tests provided that the conditions set out in Annex XI are met. In particular, for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across).*

29. Article 13.1 also recognizes that some tests on vertebrate animals may be omitted if this can be justified on the basis of information relating to exposure or risk reduction measures.

30. Article 13 of REACH also requires that the related legislation containing the approved and standardized methodologies for testing chemical substances (the so-call Test Method Regulation) should be regularly reviewed with a view to introducing validated, alternative methods or to refining existing procedures in order to reduce both the number of animals used and the level of suffering[6]. REACH also gives ECHA the possibility to directly recognize internationally agreed test methods.

***Data Sharing and Avoidance of Unnecessary Testing under REACH***

31. Testing on vertebrate animals for the purposes of REACH shall be undertaken only as a last resort and the Regulation includes detailed provisions to avoid the duplication of testing. Companies wishing to submit a registration dossier for the same substance are required to share data generated through testing on vertebrate animals and there are also provisions for arbitration procedures should registrants fail to come to an amicable agreement. Data sharing provisions designed to avoid duplicate testing are also include the Unions legislation on biocides and plant protection products.

32. For higher tonnage chemicals the information requirements set down in REACH include data generated by second/third tier toxicity tests carried out on vertebrate animals (e.g. multiple generation toxicity studies, developmental toxicity studies),. However, REACH recognizes that many potential registrants may not have access to such test data and therefore allows for the possibility to include test

[6] The OECD Test Guideline Programme is one of the main sources of new or revised test methods implementing the 3Rs

proposals as part of the registration dossier. These test proposals are assessed by the Chemicals' Agency and also submitted to a public consultation inviting third parties to submit scientifically valid studies that may obviate the need for the toxicity test to be carried out by the registrant.

***Directive 86/609/EEC on the protection of animals used for experimental purposes***

33. In addition to the specific requirements of REACH as described above, all animal testing carried out in order to fulfill the requirements of this Regulation must also comply with Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes. This Directive establishes a common-legal framework for the sourcing, housing and treatment of animals used for experimental purposes in the EU.

34. On 5 November 2008 the Commission presented a proposal to the Council and the European Parliament to update this Directive and the negotiations on this proposal are still ongoing. It's aim is to strengthen the current legislation inter alia through a compulsory authorisation of projects using animals including a systematic ethical review to explicitly assess the application of the concept of the 3Rs (Replacement, Reduction and Refinement), to improve the rules regarding the welfare of experimental animals and to further foster the development of alternative methods.

35. Central for the implementation of the chemicals regulation in both the current directive and the Commission's proposal for a revision are:

- The requirement that if another method is reasonably and practically available which suits the purpose but uses less or no animals, or is likely to cause less pain, suffering, distress or lasting harm, then this other method must be used.

- A strengthening of the work of the European Centre for Validation of Alternative Methods (ECVAM) as well as calling for an increased participation of the Member States in the validation process.

***Conclusions***

36. REACH aims at a high level of protection for humans and the environment. To achieve this aim, REACH sets up a number of mechanisms designed to minimize animal testing. These mechanisms include requirements for registrants to collect available information, to share available data with other registrants and only perform testing on vertebrate animals if the available data is insufficient for protecting humans and the environment. Furthermore, in most cases a proposal to conduct animal testing is subject to verification by the European Chemicals Agency before the actual testing can be conducted. Other Union legislation, such as that governing biocides, pesticides and cosmetics, also have mechanisms which assure a minimum of animal testing or the avoidance of such testing altogether.

37. The Laboratory Animals Directive provides a legal basis to ensure that testing can only be done if it observes the 3Rs principle and for the EU to work collaboratively in the development of alternative methods, an obligation which equally applies to REACH.

**USEPA Strategic Plan for Evaluating the Toxicity of Chemicals**[7]

38. Toxicity Testing sits on the cusp of a transformational change, a change that will require the overhaul of regulatory toxicity testing programs, the confidence of stakeholders, harmonization among governments, and the talents of countless scientists the world over. The current approaches present challenges in accommodating increasingly complex and evolving regulatory needs such as evaluating the sensitivity of different life-stages, considering the risks of chemical mixtures, and understanding the cumulative risk of multiple and diverse chemical exposures. While these challenges are great, advances in computational, informational, and molecular sciences promise a wealth of new scientific tools to meet such needs.

39. The EPA has long recognized the potential application of emerging science to toxicity testing and risk assessment (U.S. EPA 2002, 2004, 2007), notably by commissioning the National Research Council (NRC) in 2004 to review existing strategies (NRC 2006) and develop a long-range vision for toxicity testing and risk assessment (NRC 2007). Their 2007 report, *Toxicity Testing in the 21st Century: a Vision and a Strategy*, envisions a landmark transformation that focuses on identifying and evaluating "toxicity pathways," cellular response pathways responsible for adverse health effects when sufficiently perturbed by exposure to environmental agents. In vitro bioassays based on such toxicity pathways have the potential to enable rapid and cost-effective evaluation of chemicals while significantly reducing animal testing.

40. To position itself to make most effective use of such collaborations and to ensure an internally coordinated and integrated approach, EPA established a cross-Agency workgroup under the auspices of EPA's Science Policy Council. This workgroup produced a *Strategic Plan for the Future of Toxicity Testing at EPA* (U.S. EPA 2008) that provides a blueprint for ensuring the ability of EPA to incorporate this new science paradigm into toxicity testing and risk assessment practices.

41. The Strategic Plan recognizes that the challenges EPA faces in implementing such a transformation are significant, as the new toxicity testing paradigm will change the nature of the methods, models, and data that inform hazard identification, dose response, exposure assessment, and risk characterization. However, the plan also recognizes that regulatory activities across the Agency stand to undergo significant improvements. For example, several offices have an ongoing need for tools to screen and prioritize chemicals for evaluation in longer-term, whole-animal studies. Research towards this end focuses on identifying toxicity pathways, using in vitro assays to characterize the ability of chemicals to perturb those pathways (through ToxCast™), and developing simple, reliable screening models to predict chemical exposure. Ultimately predicting *in vivo* effects in humans will be aided by creating physiological

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tissue models that integrate (1) the dynamics and characteristics of exposure and dose, (2) the dynamics of perturbed molecular pathways, and (3) processes leading to alterations of cell state.

42. The Strategic Plan also recognizes that integrating such tools into toxicity testing and risk assessment at regulatory agencies like EPA will require an iterative and long-term process of institutional change achieved through a step-wise implementation. Regulators, stakeholders, and the public must be confident that the new types of data can be used to effectively protect public health, so education and transparent communication with stakeholders on the strengths, limitations, and uncertainties of the new paradigm will be critical. Ultimately the testing paradigm must be evaluated via a comprehensive development and review process, involving public comment, expert peer review, and harmonization with other agencies and international organizations.

**BIAC's View on Chemical Safety and Animal Welfare**

43. Currently new and emerging chemical legislations at the national and regional levels can create a patchwork of sometimes conflicting rules and procedures. Differences in national regulatory requirements may increase the costs and time needed for the launch of new and innovative substances and lead to trade restrictions and distortions in international competition.

44. In BIAC's view, the OECD Environment, Health and Safety program plays a major role by helping to reduce barriers to trade, optimize the use of resources, and save time and money of both governments and for industry through co-operative work on the testing of chemicals, pesticides, biotechnology products, and manufactured nanomaterials. This is particularly the case for the OECD role in promoting appropriate measures to address animal welfare concerns related to chemical testing.

45. The leadership of OECD in assuring scientifically sound test guidelines is the foundation of Mutual Acceptance of Data (MAD). MAD is one of the most important elements of global cooperation to assure that chemicals and their products can be assessed accurately and used safely and effectively around the world without unnecessary duplication of animal studies. Recognizing the interdependencies of a global economy, the United Nations Environmental Program (UNEP) initiated a Strategic Approach to International Chemical Management (SAICM) in 2006. SAICM's core policy objectives (risk reduction, knowledge and information, governance, capacity building, and illegal traffic) include numerous areas of activity in which OECD and BIAC both have a long-standing, and substantial, record of impactful work.

46. In line with the SAICM objectives, BIAC strongly advocates for the development of national chemicals management capacities that adhere to risk-based principles in order to foster greater consistency and transparency in regulatory systems. Rather than taking positions on specific country or regional approaches to chemical policy BIAC strongly supports the incorporation of a set of "Principles for Chemical Management Systems" into existing and forthcoming policies. These principles promote:

- science and risk-based decision making
- tiered, targeted and risk-based approach to chemical evaluations
- leveraging existing information to reduce redundant testing and use of animals
- transparency and shared responsibility along the chain of commerce
- improved public confidence in chemical policies

47. BIAC firmly believes that a balanced combination of regulations and voluntary industry programs is the best way to achieve safe management of chemicals. Therefore, in addition to meeting global regulatory requirements, the international chemical industry, through the International Council of

Chemical Associations (ICCA), has intensified its voluntary programs to complement existing laws by providing a high level of both technical guidance and economic expertise.

48. ICCA launched two voluntary initiatives as its contribution to the UN SAICM process at the first International Conference on Chemicals Management (ICCM-1) in February of 2006: The Responsible Care® Global Charter, a renewed commitment to expand the implementation of Responsible Care globally, and the Global Product Strategy (GPS). GPS highlights the chemical industry's commitment to chemical safety, applying safe and environmentally sound management practices, and sharing and making relevant information publicly available. Both initiatives aim to reduce existing differences in the safe handling of chemical substances among developing, emerging and industrialized countries and to support national, regional, and international chemicals policies.

49. The importance of science to decision-making on the safety of chemicals is more evident today than ever before. Implementation of REACH in the EU, initiatives to modernize the Toxic Substances Control Act (TSCA) in the US, the Japanese Revision of Chemical Substances Control Law (CSCL) and industry's obligations under SAICM are drivers for seeking information about chemical exposures and hazards. Acquiring pertinent information is crucial to risk assessment, risk management, and risk mitigation. However, improving the knowledge base on chemicals is often linked to an increase in the number of animals used for toxicity testing. There is a growing interest in moving away from extensive in vivo testing to intelligent testing strategies or tiered approaches where existing knowledge from alternative approaches (e.g., structure activity relationships, in vitro data, relevant in vivo data from existing studies of related substances) are combined with estimates of exposure to determine what specific additional testing, if any, is appropriate to characterize potential risks with an adequate degree of scientific certainty. The OECD program provides an excellent forum for member countries and industry to join forces, share the work of chemicals evaluation, harmonize national regulatory requirements including test guidelines and thus eliminate unnecessary or duplicative testing and assessment, thereby reducing the use of animals. This leads to improved efficiencies in animal welfare, testing, and chemical assessment, as well as cost savings for both governments and industry.

50. BIAC fully appreciates and shares public concern for animal welfare in research and in the safety assessment of chemicals. However, BIAC also recognizes that some aspects of safety assessment still require data derived from animal studies. Nonetheless, BIAC – in partnership with major stakeholders such as OECD – is exploring realistic opportunities to Reduce, Refine and Replace (the 3Rs) the use of animals in safety assessment. BIAC's commitment is to promote and support where feasible the development and use of scientifically robust and reliable alternative approaches to safety assessment that embrace the 3Rs, while maintaining the ability to ensure human and environmental safety.

51. Since 1999, the chemical industry's Long-Range Research Initiative (LRI) has addressed the science needed to reduce and refine animal testing. LRI's mission is to identify and fill gaps in our understanding about the hazards posed by chemicals and to improve the methods available for assessing the associated risks, thereby enabling industry and regulators to make informed decisions based on high quality information. Launched in 1999 and implemented under the responsibility of three regional centers (US, Japan, and Europe) more than US$200 million have been invested in the LRI so far. The high scientific quality of the LRI results supports the mutual international acceptance of tests as established by OECD, which has been a major breakthrough in minimizing animal testing.

52. Recognizing the importance of animal welfare, BIAC:

- Encourages the use of alternatives approaches to animal testing when the scientific data generated by these alternatives are useful for risk assessment and acceptable to regulatory bodies.

- Links the validation and implementation of alternative methods to existing regulations, in order to agree on a common interpretation of results achieved with alternative methods.

- Encourages further research to develop new testing paradigms (e.g. such as the 2007 NAS Report on toxicity testing in the 21st century, which focuses on mammalian toxicity), with a systematic transition to these new approaches once they are sufficiently validated.

- Works to implement integrated (tiered) testing approaches that use results-based prioritization to focus testing on chemicals of greatest concern to public health, thus reducing the total amount of testing and animal research necessary to protect public health and the environment.

- Supports using available hazard *and* exposure data to prioritize substances for further evaluation, to efficiently use resources and reduce the use of lab animals.

- Supports integrating various government and industry chemical evaluation initiatives, grouping chemicals with similar characteristics, reducing duplication of testing and, therefore, the total number of laboratory animals tested.

- Supports coordinated testing programs and mutual acceptance of data that minimizes requirements for individual countries or industries to duplicate testing.

- Encourages agencies to work within the framework of the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM), the European Center for Validation of Alternative Methods (ECVAM) and the Japanese Center for Validation of Alternative Methods (JaCVM), and internationally within OECD, to ensure the acceptability of data from alternative approaches in the context of science- and risk-based decision-making on chemical safety.

- Suggests that the removal of local test protocols which require repetition of tests on vertebrate animals already conducted as a condition for product approval is an integral part of the OECD outreach process. The MAD principle remains essential to prevent unnecessary use of laboratory animals.

**ICAPO's View on Chemical Safety and Animal Welfare**

53. OECD has made positive progress toward the refinement, reduction and replacement of animals in chemical testing subsequent to the involvement of ICAPO in 2002. Recent accomplishments in the 3Rs by the Secretariat and member countries are praiseworthy and appreciated by the ICAPO Secretariat and its members. We are also pleased to serve as invited experts to a number of Environment Directorate efforts, and look forward to continuing to participate in these and hopefully other activities in the future.

54. There is still much work to be done: in the coming years an unprecedented worldwide increase in the use of animals in chemical testing is expected. ICAPO believes that the OECD is uniquely positioned facilitate advances in technology and policy that will reduce and replace animals in chemical testing on a global scale. In turn, the increasing availability of new non-animal methods and approaches to testing will allow improvements in chemical assessment, including the assessment of more chemicals, doses, formulations, and exposure scenarios than currently possible.

55. Ongoing projects in the Environment Directorate show great promise, including the OECD Advisory Group on Molecular Screening and Toxicogenomics and the (Q)SAR Application Toolbox

Management Group. The recent refocusing of the Task Force on Hazard Assessment and its interest in exploring ways to promote the use of "weight of evidence," integrated assessment and similar concepts also showcases member countries' recognition that more can be done with available data, and that data gap "wish lists" are best avoided.

56. The Secretariat's efforts to increase the efficiency of the WNT's work have clearly resulted in quicker implementation of some alternative methods. The work of the WNT and VMG-Non Animal with performance-based TGs and other novel solutions to *in vitro* regulatory policy questions are to be commended, and ICAPO is eager to continue to assist with these efforts. We support projects that bring parity to the OECD portfolio, such as the review of fish test guidelines currently underway. ICAPO urges member countries to bring such parity to the WNT Work Plan, and to avoid creating new test guidelines of dubious multinational and/or multi-sectoral regulatory value, particularly where these involve animals.

57. ICAPO has recently been invited to participate in WPMN SG7 (Alternative Methods), and urges member countries to increase their efforts within this essential activity. The safety testing of nanomaterials presents an enormous challenge to current toxicological approaches, and therefore an important opportunity to create more appropriate, human-relevant screening and testing methods from the outset.

58. ICAPO believes that the OECD has an integral role to play as the science of toxicology and the policies that apply this science evolve. Workshops such as IATA and MOA are good examples. Through these and similar initiatives, the OECD can act as a global forum to link ongoing efforts in different regions and countries as "21$^{st}$ century toxicology" is developed, assessed, and implemented. ICAPO looks forward to active participation in this process in the near and distant future, for the benefit of animals in laboratories and better human health and environmental protection.