



COSMETICS EUROPE:
REPORT ON THE 8TH WORLD CONGRESS ON
ALTERNATIVES & ANIMAL USE IN THE LIFE SCIENCES

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INTRODUCTION

The 8th World Congress on Alternatives and Animal Use in the Life Sciences (WC8) was held in Montreal in August 2011. Organised by the Canadian Council on Animal Care (CCAC), the event gathered together 850 participants from more than 50 countries to exchange ideas on alternative methods to animal testing.

The focus of the Congress was the '3Rs' – replacement, reduction and refinement. This is a principle to which the European cosmetics industry is strongly committed, not least through our work in groups such as the European Partnership for Alternative Approaches to Animal Testing (the EPAA is a voluntary collaboration between the European Commission, European trade associations, and companies from seven industry sectors, of which Colipa is a founding member).

This type of partnership also demonstrates Colipa's commitment to the overall theme of WC8 - 'Together It's Possible'. Collaborations between different groups are vital in order to make progress in the development of alternatives. However, it is also important to ensure that we work together not just in Europe, or in the United States, but in a transatlantic alliance.

WC8 provided an ideal opportunity to have discussions at a global level, in order to fit together several different parts of the alternatives puzzle. Several Colipa representatives participated actively in WC8 to share and exchange ideas. Such exchanges help bring us even closer to the replacement, reduction and refinement of animal testing, and constitute networks for valuable data-sharing.

International events like WC8 bring together the leading experts in alternatives to animal testing, and exhibits from a wide range of stakeholders. They help to facilitate stakeholder dialogue and create opportunities for further collaboration. They also play a key role in bringing science and policy together – something that helps to create better, evidence-based legislation and regulation.

There was much activity at WC8 - covering five themes, 55 sessions, 230 presentations and 400 posters. This report aims to bring to you a flavour of what was discussed on the issues that are most relevant for the cosmetics and personal care products sector. It provides an overview of the main outcomes and highlights the progress made to date on alternatives. It also outlines the main new scientific developments in the field and the remaining challenges as we strive for the replacement of animal testing.

At a time when the issue of animal testing – and in particular, animal testing of cosmetic ingredients – is entering the political spotlight, we hope that this report will be useful in providing some useful information on the current scientific state of play.



Bertil Heerink

Director-General, Colipa – The European Cosmetics Association

EXECUTIVE SUMMARY

WC8 – with its theme of ‘Together It’s Possible’ and its focus on the ‘3Rs’ of replacement, reduction and refinement – was an important platform for discussion, at a global level, of the challenges facing the use of animals in life sciences, including the development of alternative methods to animal testing.

Two of the biggest challenges facing the development of alternatives are the need for integrated testing methods and improved approaches to the validation of alternative methods. WC8 highlighted the need for integrated testing methods – a ‘toolbox’ approach that recognises the current scientific impossibility of ‘one-for-one’ replacement of animal tests, and the need for regulators to move with science in order to ensure acceptance of alternative approaches as quickly as possible. Allied to this, there is a need to accelerate validation processes – for example, by integrating regulators into the development process at an earlier stage to increase their understanding, and by ensuring full and open data-sharing.

WC8 also looked in-depth at recent developments in alternatives for particular health effects, or ‘endpoints’. Many of these endpoints remain complex, such as skin sensitisation. Five companies presented their approaches to developing non-animal testing strategies for skin sensitisation safety assessment at WC8, demonstrating the leading role being played by the European cosmetics and personal care products industry. However, while the new ‘toolbox’ of non-animal methods should soon be able to provide reliable *hazard* identification in this area in the coming years, *risk* assessment is some way off.

With regard to genotoxicity, ‘false positives’ remain a challenge. A Colipa ‘false positive’ programme was presented at WC8 and data suggests that it can help avoid nearly two-thirds of irrelevant results. There is also the possibility of new follow-up tests that replace animal tests with human skin equivalents and tests that replicate, *in vitro*, the critical stages in the development of cancer cells. Validation, however, is still some way off.

Discussions were also held on screening chemicals with endocrine activity. The ReProTect project already has seven extremely promising tests. However, the complexity of endocrine activity means more time is needed before a full *in vitro* approach will be available.

Alternative 3D models are showing promise for the evaluation of potential hazards from nanomaterials – but risk assessments are proving difficult to establish as there is a lack of knowledge about the way in which nanomaterials affect the body, and the quantities involved.

Substantial progress is also being made on embryotoxicity, looking at individual factors. However, a full replacement of animal tests is still not foreseeable as developmental toxicity emerges from complex interactions that require computer modelling. Animal-free systemic toxicity testing faces similar issues, although technology is in development that can test reactions between organs, such as the liver, skin and hair. The ‘DETECTIVE’ FP7 project will perform for the first time an in-depth investigation of repeated-dose effects on reproductive and developmental toxicity.

There was also much discussion at WC8 about the need for improved partnerships in order to develop alternatives. Partnerships can help build a common understanding of the ‘3Rs’, and when they are visible and well-defined they can be very successful. A good example is the Toxicity Testing in the 21st Century (Tox 21) project in the United States, which is generating a wealth of data about the characterisation of toxic pathways. It is a project that shares many of the same values as the SEURAT-1 FP7 project that is co-funded by Colipa.

While Tox 21 is a public partnership, the European Partnership for Alternative Approaches to Animal Testing (EPAA) facilitates dialogue between industry, regulatory authorities and research institutions - different types of actors who do not usually speak to each other. PPPs (public-private partnerships) play a key role in maximising the impact of available resources, as well as helping the exchange of best practice and speeding up the acceptance of

alternatives. Colipa has been particularly active in the EPAA and many of the successful advances in alternatives have been developed by the cosmetics industry and are now used elsewhere. The EPAA stands out thanks in part to highly valuable political support and visibility.

International Cooperation on Alternative Test Methods (ICATM) promotes global coordination on the scientific validation and evaluation of alternatives. As the emphasis moves towards integrated testing, international talks on regulatory acceptance become ever more important.

Ethics is another global challenge, as standards are not uniform. Participants at the WC8 highlighted that any standardisation needs to be culturally sensitive. At present, ethical review is limited to the use of animals in experiments, with the '3Rs' concept not yet fully integrated. Where ethical review is used, it remains applicable only to refinement and reduction.

Indeed it was on these two 'Rs' – refinement and reduction – that the strongest focus of WC8 laid. The 'Montreal Declaration' that was adopted by the Congress concentrated on these areas, and less on replacement methods.

It was a strong recognition that much can be achieved in reduction – through data-sharing and better synthesis of evidence, for example – whereas there is less scope in the short term for replacement (a point also emphasised in the European Commission's recent report on Progress in the Development of Alternative Methods to Animal Testing for Cosmetics).

1. CHALLENGES AHEAD: INTEGRATION AND VALIDATION

1.1. THE NEED FOR INTEGRATED TESTING METHODS

WC8 highlighted the clear need for integrated testing methods: the development of a **combination** of alternative testing methods, with data-sharing, rather than a single method to replace a specific animal test. Despite the many developments demonstrated throughout the Congress, it remains scientifically impossible at present to have a 'one-for-one' replacement.

Given this impossibility, the **toolbox** approach is becoming progressively more important – a point recognised on numerous occasions at WC8.

The **'3Rs' concept** is also increasingly part of the thinking and work of scientists and researchers and being integrated into testing strategies.

However, **regulatory acceptance** is also important: the regulatory paradigm needs to shift with the science, towards integrated testing strategies. As integrated testing strategies grow in importance, they will be further developed and evaluated in order to ensure regulatory acceptance.

1.2. VALIDATION APPROACHES

Approaches to **validating** alternative testing methodologies were also discussed at WC8. It was widely recognised that validation processes should be accelerated, in order to speed up the move to full implementation of the '3Rs'.

For this acceleration to occur, it was felt that **regulators** should be integrated into the development process at an earlier stage. This would increase their understanding of the methodologies at hand, and so make it easier and quicker to support them at the validation stage.

It was also noted at WC8 that there is pressure on regulators to keep pace with scientific progress. For this, full and open **data-sharing** is required, as broader acceptance and use of alternative methods will require broader access to information, increased global communication between regulatory authorities, research institutions and manufacturers, and harmonisation of testing requirements and validation criteria.

ECVAM has recently proposed a new approach to **post-validation reviews**, in order to allow for further refinements of assays (an assay being an analysis to determine the presence, absence, or quantity of a particular substance or effect). A new data format will be developed to enhance knowledge about assays after their validation. Such post-validation reviews could open the door to new approaches to validation.

The increasing recognition of the need for various non-animal test methods to be used in combination should be welcomed. It entails, however, more integrated testing, as well as improved and more flexible ways of validating assays. Post-validation reviews could provide a workable solution.

2. THE 3Rs : NEW ADVANCES IN SCIENCE

2.1. DEVELOPMENTS IN THE ASSESSMENT OF SKIN SENSITISATION

The area of **skin sensitisation** – an allergic reaction to a chemical, which worsens with subsequent exposure – remains complex. However, significant developments have been made, and were highlighted at WC8.

Colipa supported a session on skin sensitisation at WC8. At this session, five companies presented their approaches to developing non-animal testing strategies for skin sensitisation safety assessment.

The cosmetics and personal care products industry currently applies a **range of approaches** to reduce the need for animal test data to support skin sensitisation safety assessments.

RECOGNISING PROGRESS IN THE DEVELOPMENT OF ALTERNATIVES TO ANIMAL TESTING

JULIA FENTEM FROM UNILEVER WAS AWARDED THE **RUSSELL AND BURCH AWARD**

Julia Fentem, a Unilever scientist, received the prestigious Russell and Burch award for her overall work and crucial contribution to the enhancement of alternative methods to the use of animal testing. This year, the Humane Society of the United States (HSUS) awarded the chosen scientist with the US\$5,000 prize.

The award, established in 1991 in honour of William Russell and Rex Burch, creators of the '3Rs' approach, is offered to scientists with outstanding achievements in one of the 3Rs. The winners are chosen based on their scientific achievements and the importance of their contribution, as well as on their professional engagement in the field of research for alternatives to animal testing.

A '**non-animal toolbox**' is in development, with some non-animal test methods currently being evaluated. The majority of the toolbox methods have proven to be successful in predicting the potential for skin sensitisation (which means the identification of a *hazard*) and also help to define the potential for skin allergy without the need for new animal test data.

Speakers at WC8 highlighted the **leading role of industry** – and in particular the cosmetics and personal care products industry - in the development of the skin sensitisation toolbox. Colipa, representing the European industry, participates in various international research efforts to explore the processes of skin sensitisation and to develop new *in vitro* and *in silico* test methods.

However, gaps do remain. Various methods are available to assess the **hazard** of skin sensitisation; however, there is still limited ability to predict reliably the **risk** of skin sensitisation. Reliable *hazard* identification may be possible in the coming years, but it will take many more years until a *risk* assessment can be achieved comprehensively with the new toolbox.

2.2. ADVANCES IN THE AREA OF GENOTOXICITY TESTING

The issue of '**false positives**' – *in vitro* test findings that have no relevance for the actual human risk - remains a particularly significant challenge in the areas of genotoxicity and carcinogenicity testing. A first check of the toxicity of a substance is carried out in a 'Tier I assay' (to determine the presence, absence, or quantity of a particular genotoxic effect).

The results of the Colipa 'false positive' programme were presented at WC8. The data suggest that a selection of more relevant cells and toxicity measures can **avoid a large proportion (more than 60%) of irrelevant results** from Tier I testing. Scientists from Health Canada presented data generated with an '*in vitro* version' of the 'Muta™ Mouse Transgenic Rodent (TGR) Mutation Assay' which confirmed the trend observed in the Colipa project. The data generated had been presented to the OECD working group that is dealing with the revision of the OECD genotoxicity testing guidelines.

Where there is a 'positive' result in a Tier I assay that identifies a potential hazard, follow-up 'Tier II assays' are still required. These Tier II tests have traditionally used animals (*in vivo* testing). However, instead of moving to *in vivo* tests, Tier II assays are now increasingly being carried out using **human skin equivalents and the 'Cell Transformation Assay' (CTA)**, which measures the impact of a substance on individual cells, *in vitro*.

The status of pre-validation of these reconstructed skin genotox assays was presented at WC8. Speakers highlighted its **good reproducibility** and improved specificity (correct identification of negatives) compared to standard Tier I *in vitro* tests.

Another promising development is the pre-validation of the CTA, which was presented by ECVAM. The CTA has been proposed as a **valuable alternative** to the traditional rodent carcinogenicity test as it replicates the critical stages in the development of cancer cells, generates cells that can cause tumours, and can detect genotoxic and non-genotoxic carcinogens.

The results of the ECVAM pre-validation show potential, and the CTA assay was praised by participants at WC8 as a valuable addition to the genotoxicity testing toolbox.

2.3. OTHER KEY DEVELOPMENTS IN ALTERNATIVE METHODS

ENDOCRINE-ACTIVE SUBSTANCES

WC8 highlighted the need for new approaches to address the complex task of screening chemicals with **endocrine activity** (those that can have an impact on hormones). Many new *in vitro* models for modulating endocrine activity are currently under evaluation, and in the EU in particular much research is being conducted to evaluate chemicals with endocrine-disrupting potential using *in vitro* tests.

One example is the development of the **ReProTect** project, for which 25 different assays were developed to identify adverse effects. Seven extremely promising tests have emerged, covering different stages and mechanisms.

However, despite promising approaches currently undergoing evaluation, the area of endocrine activity is extremely complex and **more time is needed** before a full *in vitro* approach will be available.

NANOTOXICOLOGY

Delegates at WC8 heard that alternative methods will be essential for evaluation of the increasing number of nanomaterials currently under development. **Alternative 3D models** appear especially well-suited for evaluating potential *hazards* from nanomaterials.

Nonetheless, the challenge remains in characterising the way in which nanomaterials affect the body, and the quantities involved. As such, it is currently difficult to establish appropriate extrapolations of **exposure** in order for *risk* assessments to be carried out.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data acquisition strategies and methods are evolving. However, embryotoxicity is a **highly complex, multi-factorial process**. The individual factors involved are under research, and novel tailored assays are under development. While substantial progress is being made, a full replacement is not immediately foreseeable.

'High-throughput screening' (HTS) studies are providing a rich source of data that can be applied to chemical profiling to address the sensitivity and specificity of molecular targets, biological pathways, and cellular and developmental processes. The US Environmental Protection Agency's **ToxCast** project is testing 960 unique chemicals (for drugs, pesticides, and other uses) in over 500 distinct assays in order to check for developmental toxicity.

Early findings suggest that developmental toxicity does not emerge from a simple molecular stream but from a **complex interaction**, which requires computer modelling using a predictive 'Virtual Embryo' framework. Potential regulatory applications including predicting developmental effects and prioritising environmental chemicals for targeted testing.

SYSTEMIC TOXICITY

Animal-free systemic toxicity and ADME (absorption, distribution, metabolism and excretion) testing that can accurately predict human exposure represent one of the major challenges for science, regulatory bodies and industry. This is principally due to the fact that **modern test system engineering focuses mainly on single organs**, rather than systemic combinations of organs.

However, a 'multi-organ-chip' (MOC) platform technology is in development. This is a self-contained microtissue bioreactor, the shape of a standard microscope slide, which can test **reactions between organs**. The current MOC supports human micro-scale liver tissue and skin organoids, as well as micro hair follicles. The next generation of MOC prototypes - combining human liver and skin organoids within a common circulatory system - is under discussion.

The **'DETECTIVE' project** (part of an integrated research strategy towards the replacement of animal testing set up as a €50m FP7 project funded by Colipa and the European Commission) has 15 partners addressing the development of biomarkers of long-term toxicity in human target cells. DETECTIVE will perform for the first time an in-depth investigation of repeated-dose effects on epigenetics - how environmental factors affect our genes and how this may be passed on to our offspring.

3. THE ROLE OF PARTNERSHIPS IN ADVANCING THE '3Rs'

3.1. THE ROLE OF PARTNERSHIPS

The successful development of alternatives can be achieved only through **forward-thinking collective action** at a global level between partners who are willing to share information. Successful partnerships have generated science-based breakthroughs in the '3Rs', gaining credibility in the research community and creating trust in the use and acceptance of alternatives.

In addition, partnerships can help develop a common understanding of the '3Rs', and assist in the alignment of positions. The potential for partnerships to be successful increases when they are highly visible and have a defined role. The **Toxicity Testing in the 21st Century (Tox 21) project**, for instance, was presented at WC8 for its successful collaboration between the US Environment Protection Agency, the National Institutes of Environmental Health Sciences, the National Institutes of Health, and the Food and Drug Administration.

Tox 21 has made **significant progress** in generating a wealth of data about the characterisation of toxic pathways.

To date, it has produced data on 1408 substances of the 11,000 it aims to assess. However, this data remains somewhat difficult to interpret: not all substances can be linked to toxic pathways. As a result, a knowledge gap still exists, despite the best efforts of researchers to close them.

This *public* partnership has gone a long way in advancing research into alternative methods as well as gaining visibility and recognition for alternative testing methods. However, **partnerships come in various shapes and sizes**, and no one model can claim to be most effective. Indeed, the Tox21 partnership has demonstrated the advances that can be achieved by *public* institutes, while at the same time the EPAA showcases collaboration between *public* and *private* partners.

3.2. THE EPAA, A MODEL FOR PPPs SUPPORTING THE ADVANCEMENT OF THE '3Rs'

Partnerships between industry, regulatory authorities and research institutions provide a forum for enhanced interdisciplinary communication and coordination in advancing the '3Rs' approach. They **facilitate dialogue between different types of actors** who do not usually

RECOGNISING PROGRESS IN THE DEVELOPMENT OF ALTERNATIVES TO ANIMAL TESTING

R. NOTE, H. NOCAIRI, M. THOMAS, L. BOUROUF, G. OUÉDRAOGO, J.-R. MEUNIER FROM L'ORÉAL RESEARCH UNIT IN AULNAY-SOUS-BOIS AND J. MCKIM JR FROM CEETOX, INC. WERE AWARDED

THE WC8 POSTER AWARD



The award goes to the authors of the best posters, chosen by Alternatives Congress Trust members during WC8 itself. The selection criteria include the level and the quality of the presentation, the scientific merit of the work on which the poster is based and the input in the further application of the '3Rs' approach.

The authors were honoured for their work entitled: 'Development of an integrative approach for the prediction of systemic toxicity: Combination of cell toxicity, pharmacological and physical chemical properties'.

speak to each other, and play an essential role in maximising the impact of available resources, help the exchange of best practice, and speed up the acceptance of alternatives.

The European Partnership for Alternative Approaches to Animal Testing (**EPAA**) is a voluntary public-private partnership between the European Commission, European trade associations and companies from seven industry sectors – including Colipa. Partners are committed to identifying research needs, developing novel approaches and sharing knowledge to promote the development, acceptance and validation of alternatives approaches to further the ‘3Rs’ in to the use of animals for regulatory purposes.

The cosmetics and personal care products industry has been particularly active in the EPAA; indeed, **many of the successful advances in alternatives have been developed by the cosmetics industry**, and are now also used in the pharmaceutical and chemical industries.

Due to its focus on regulatory compliance and work across multiple sectors, the EPAA stands out among other partnerships that are being set up to coordinate research projects. In addition to this, strong support from the European Commission, including from Commissioners, has given the EPAA **highly valuable political support and visibility**.

EPAA held its own session at the WC8 as well as presenting in a separate session on public-private partnerships (PPPs). The latter session discussed the value of PPPs, which allow for the exchange of new ideas, meeting new people, sharing of concepts and the enablement of common understanding, as well as the creation of the possibility of dialogue between those who normally do not interact. The session also highlighted that **PPPs** flourish where legislation is open and flexible, and where they can have a definite role in searching for the best method of implementation.

Another session at WC8 highlighted some of the imperatives for **successful partnerships** – notably that partners are forward-looking, and that they are willing to share data (often requiring an ‘honest broker’ and partners who understand that a failure to share data will mean that they are left behind).

3.3. INTERNATIONAL COOPERATION ON ALTERNATIVE TEST METHODS (ICATM)

ICATM is a voluntary international initiative comprising national validation organisations in Europe, the USA, Canada, South Korea and Japan to **promote coordination** on the scientific validation and evaluation of alternative *in vitro* toxicity testing methods.

Collectively, ICATM has **several aims**: develop validation studies; increase independent scientific peer reviews; enhance harmonised recommendations on the usefulness and limitations of alternative methods; avoid duplication of effort and maximise limited resources; and support the timely international adoption of alternative methods.

Since joining in March this year, Korea has made significant progress and both **Korea and Japan** are conducting substantial research into method development projects.

The successful collaboration of organisations working together to validate alternatives to animal testing in their jurisdictions can bring about change. It is hoped that single assay projects, which encounter delays due to the lack of international coordination between validation bodies, will be compensated by **increased international acceptance**. As the emphasis moves towards integrated testing, international discussions on the regulatory acceptance of these testing strategies will need to take place.

4. ETHICAL VALUES

At WC8 there was also a session on ethics and ethical review in animal testing. It was generally acknowledged that the criteria used for ethical reviews of animal experiments are **not uniform across the globe**. This is due to a range of factors, including different levels of scientific knowledge, diverging animal welfare criteria, social and cultural contexts, and professional judgment. Although a degree of standardisation in this respect is desirable, participants at the WC8 maintained that cultural differences do need to be taken into account.

Ethical review remains limited to the use of animals in experiments, and the '3Rs' concept is not yet fully integrated. Where ethical review is applied, it remains applicable only to refinement and reduction. However, **ethical considerations could gain in importance** by their extension to other aspects of animal testing (for instance, publications in scientific journals or acceptance at conferences), helping to raise awareness of and promote the '3Rs'.

GLOSSARY OF TERMS

Assay: An analysis to determine the presence, absence, or quantity of a particular substance or effect

Carcinogen: Any substance that is directly involved in causing cancer

Carcinogenicity: The ability or tendency of a substance to produce cancer

Developmental toxicity: The adverse effects on a child's development that may result from exposure to substances during pregnancy

Embryotoxicity: The adverse effects on an embryo of a substance that crosses the placental membrane.

Endocrine activity: Structural and/or functional changes to the endocrine system that may result from exposure to chemicals and which can harm the hormone system

Endpoint: How exposure to a particular hazard affects human health

Epigenetics: How environmental factors affect our genes and how this may be passed on to our offspring

False positive: A test result that is positive when in fact there is no hazard

Genotoxicity: Toxic effect of chemical or physical agents on the hereditary material (DNA) and on the genetic processes of living cells

In vitro test: A test performed in an artificial environment outside any living organism (such as in a test tube, for example). Latin translation means literally 'in glass'

In vivo test: A test performed in (or on) a living organism. Latin translation means literally 'in life'

In silico tools: Computer-based applications that can compliment *in vitro* and *in vivo* procedures. Latin translation means literally 'in silicon'

Nanotoxicity: The adverse effects of interactions of nanoparticles with biological systems

Organoids: A structure that resembles an organ

Reproductive toxicity: The adverse effects on a reproductive system that may result from exposure to substances outside the body

Skin sensitisation: An allergic reaction to an irritant that results in the development of skin inflammation and itchiness. Unlike **skin irritation**, the skin reacts more to the substance with every subsequent exposure

Systemic toxicity: The potential adverse effects of medical devices on the body's organs and tissues which are away from the site of contact. For a substance to have systemic toxic effects, it must be absorbed by the body and distributed by the circulation to places in the body where it then exerts toxic effects

Toolbox: A series of different non-animal tests that can be used in conjunction to form a viable alternative to an animal test

Toxicology: The study of the symptoms, mechanisms, treatments and detection of poisoning – either chemical, physical or biological – especially the poisoning of people, or the ecosystem

HAZARD AND RISK

Hazard is the intrinsic way in which a substance, object or situation may cause harm, whereas **risk** is the chance that harm will actually occur, and is based on *exposure* to the hazard.

LIST OF ABBREVIATIONS

'3Rs': The reduction, refinement and replacement of the use of animals in life sciences

CCAC: Canadian Council on Animal Care

CTA: Cell Transformation Assay

DETECTIVE: Detection of endpoints and biomarkers of repeated dose toxicity using *in vitro* systems (FP7 project)

ECVAM: European Centre for the Validation of Alternative Methods

EPAA: European Partnership for Alternative Approaches to Animal Testing

FP7: Seventh Framework Programme for research and development (European Union)

HSUS: Humane Society of the United States

HTS: High throughput screening

ICATM: International Co-operation on Alternative Test Methods

MOC: Multi-organ chip

OECD: Organisation for the Economic Co-operation and Development

PPPs: Public-private partnerships

SEURAT: Safety Evaluation Ultimately Replacing Animal Testing (FP7 project)

TGR: Transgenic Rodent

Tox 21: Toxicity Testing in the 21st Century

WC8: 8th World Congress on Alternatives and Animal Use in the Life Sciences

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COSMETICS EUROPE – THE PERSONAL CARE ASSOCIATION
AVENUE HERRMANN-DEBROUX 40, 1160 BRUSSELS
T. +32 2 227 66 10, F. +32 2 227 66 27
WWW.COSMETICSEUROPE.EU