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### Interview with Janez Potočnik, European Commissioner for Environment

A founding father in 2005 of the EPAA (together with former Vice President Verheugen) as the then Commissioner for Research, Janez Potočnik remains a patron of EPAA in his current capacity as Environment Commissioner. As part of his mandate, he now oversees dossiers on the protection of animals used for scientific purposes (the new Directive 2010/63/EU replacing Directive 86/609/EEC), the EU Test Method Regulation, as well as REACH and the Biocides Directive, both of which require the testing of chemical substances.

From 2002 to 2004 Mr Potočnik was Minister for European Affairs of the Republic of Slovenia, and was also Head of the Negotiating Team for the Accession of Slovenia to the EU.

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### Acute Toxicity Testing and Regulation

The EPAA Acute toxicity Task Force, together with representatives of the Humane Society International and the UK NC3Rs, reviewed the toxicity testing requirements in other industrial sectors, building on an initiative of the pharmaceutical sector. The results were published in 2010 in *Toxicological Sciences*<sup>1</sup>.

The conclusion was that there is scope for reviewing the regulatory requirements, thus contributing to better testing and better animal protection.

As a follow-up of this work, a workshop was organised in Brussels on 16 September 2010, involving regulators, academics, poison centre staff and industry representatives. The discussions focussed on two areas stemming from the review, i.e. assessing whether

- ❖ there are scientific drivers for acute toxicity testing and
- ❖ the available concordance of oral versus dermal acute toxicity testing data set is adequate to support the deletion of the requirement for dermal testing from relevant legislation.

Specific proposals were made for waivers that would deliver direct 3Rs benefits. The report and recommendations from the Workshop are available on the [EPAA website](#);

The EPAA will next discuss the key recommendations, which are applicable mainly to the chemical and agrochemical sectors, with the relevant stakeholders from industry and regulatory authorities, including relevant Commission working groups with national authorities.

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<sup>1</sup> ["Cross-Sector Review of Drivers and Available 3Rs Approaches for Acute Systemic Toxicity Testing"](#), T. Seidle et al, in *Toxicological Sciences*.



**J. Potočník, remains a patron of EPAA in his current capacity as Environment Commissioner.**

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## **Interview with Janez Potočník, European Commissioner for Environment**

Mr Potočník, the EPAA you launched in 2005 has completed its initial five years and partners have expressed their commitment to continue this unique partnership. In which direction could you see the EPAA moving during the next five years (2011-2015)?

**J. Potočník:** I very much welcome the new EPAA mandate, which maintains a commitment towards development, validation and acceptance of alternative approaches, and the push towards the replacement, reduction and refinement of animal testing.

This is particularly important in light of the recently adopted Directive 2010/63/EU on the protection of animals used for scientific purposes, which replaces and significantly improves the protection granted by Directive 86/609/EEC. The 3Rs principle is, for the first time, explicitly described and firmly established in EU legislation. Strict provisions will be brought in on how the 3Rs are to be implemented, and these will be applied to all sectors using animals under their own specific legislation, where it exists.

I hope and expect that we will see a lot of activity in the area of 3Rs development during the next five years. The promotion of alternatives is an ongoing task of the highest importance, and through the EPAA we have a unique opportunity to push forward innovative ways to replace, reduce and refine animal use, for the dual benefit of the animals and the consumer, who will profit from the better protection that modern toxicological testing methods promise.

**How will the new revised Directive influence safety testing across sectors?**

**J. Potočník:** Where safety testing is required by other legislation (be it for industrial chemicals, crop protection or cosmetics, to name just three examples) tests using animals must be carried out in compliance with the specific provisions of Directive 2010/63/EU. This means, for instance, that an ethical evaluation of the proposed tests using animals must be carried out, which fully takes into account the 3Rs, followed by a favourable decision made before authorisation for the project is given. In other words, the principle of the 3Rs is embedded in the new Directive and will have to be taken into account systematically each time animal use is considered – and whenever possible alternative methods must be used. In addition, when assessing the proposed animal experiment, non-confidential data derived from previous experiments must also be considered, as well as the statistical design of the proposed procedures, the re-use and avoidance of duplication of procedures, and the use of humane end-points.

Reducing the amount of animal testing is one of the objectives of the ongoing revision of the Biocides Directive. In light of this, the proposed Regulation to replace the Biocides Directive requires, as does REACH, that testing for regulatory purposes on vertebrate animals is undertaken only as a last resort, and that in the future it will not be possible to repeat animal testing for this purpose.

The simple fact that different products and sectors are subject to different rules, creates an opportunity for exchange of information between sectors, and this is precisely one of the core strengths of the EPAA. Similarly, the fact that more emphasis will be placed on alternative approaches, either through Directive 2010/63/EU or through sector specific legislation, implies that the efficient implementation of the 3Rs principles will remain a main priority in the years to come, and increases the potential for action by the EPAA.

**The EPAA theme for 2010 was Reduction and Refinement (2R) and we have recently tried to highlight the importance, in the short and medium term, of reduction and refinement strategies. What are your thoughts on this?**

**J. Potočník:** Although replacement of animal use has always been and remains the ultimate goal of the European Commission, I see reduction and refinement, the 2Rs-approach, of animal use as very important parts of our strategy of promoting alternative methods for ultimately replacing animal experiments. In fact, it is often the case that significant animal welfare benefits can be realised much faster through this type of approach.

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### Interview with Janez Potočnik, European Commissioner for Environment

I believe there are many and varied 2Rs-focused projects ongoing in companies and research establishments but also much scope for improvement. The challenge is to share discoveries and best practices between scientists and animal care takers, implement them, bring coherence of 2R approaches within research; use the expertise of industry and promote best practice within companies but also in universities and other research establishments. In addition, there is a need to convince regulators that 2Rs approaches are valid, and should not be ignored. I welcome and encourage any work the EPAA carries out in this area with these aims in mind, and consider that the October Workshop on 2Rs produced interesting and challenging recommendations. The Workshop proved again that the EPAA is an excellent platform where significant expertise can be brought together, exchanged and disseminated. I particularly support the efforts being made to involve regulators and regulatory experts as much as possible in the ongoing discussions.

In the meantime will the Commission be doing more to increase the number of alternative methods?

**J. Potočnik:** For the first time the EU will have a reference laboratory for alternative methods, as ECVAM (European Centre for the Validation of Alternative Methods) will be afforded this status and a stronger role through Directive 2010/63/EU. It will continue to co-ordinate scientific validation of alternative methods and their application in a regulatory context, but we have now added to its tasks to also promote the development and use of alternative methods in the areas of basic and applied research. ECVAM shall act as a focal point for the exchange of information on alternative methods and promote dialogue between legislators, regulators, and all relevant stakeholders, in particular industry, biomedical scientists, consumer organisations and animal welfare groups. I know that EPAA has this dialog also high on its agenda and it is therefore only logic that ECVAM plays and will continue to play an active role in the EPAA. I think that this will be a win-win cooperation with clear benefits for both parties.

Over the last 20 years, the EU contribution to 3Rs research amounts to some €200 million. Under the 7<sup>th</sup> Framework Programme (FP7), approximately €65 million has been committed so far for the funding related to alternative method development. The recent joint initiative of the Commission and the cosmetics industry added another 50 million which are earmarked to address the big challenge posed by repeated dose toxicity, a field that could consume huge numbers of animals if no alternatives can be found.

Finally, considerable effort is being made to speed up the introduction of new alternative test methods to the Test Method Regulation as they become available. Under the revised Directive alternative methods in the area of regulatory testing that are officially recognised by EU legislation, must be used.

One of the lessons of the initial five-year period is the need to involve regulators at a very early stage. How is the Commission involving regulators and legal risk assessors during the development of new alternative methods, to make them more relevant in a regulatory context?

**J. Potočnik:** Overall, communication is extremely important. I therefore want Commission services to liaise with the various Commission working parties that they chair, in which authorities and stakeholders participate. I would also argue for an increase in dialogue with the legal risk assessors working in the scientific committees of the Commission and of the various agencies. We are also keen to bring early regulatory relevance assessment into the priority setting for the validation of alternative approaches. ECVAM will also work on streamlining the procedure and ensuring that as validation progresses all stakeholders are kept informed and have the possibility to comment and contribute. To this end the single points of contact for assessing the regulatory relevance of alternative methods have been identified by the Member States. This network will be managed by ECVAM and will be asked to provide a preliminary assessment of regulatory relevance (PARERE) for all sufficiently developed procedures that are submitted to ECVAM for validation. The idea is that the scientific validation which follows will focus on test methods that have the best potential to be considered suitable for clearly identified regulatory purposes – and that therefore will be used.

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### Interview with Janez Potočnik, European Commissioner for Environment

As part of this strategy, Directive 2010/63/EU requires Member States to nominate single points of contact to provide advice on the regulatory relevance and suitability of alternative approaches proposed for validation, and I have been informed that most Member States have already identified or are in the process of identifying their contact points. These contact points will form an essential link between the European and national regulatory bodies.

How important is the role of public/private collaboration such as the EPAA?

**J. Potočnik:** What is striking about the EPAA is that this partnership is voluntary and covers a wide range of sectors, which altogether form a very significant part of the European fabric. Participation by industry, in other words trade federations and individual companies, and Commission services, demonstrates a true commitment to finding approaches which can replace, reduce and refine animal use. The EPAA creates opportunities for cross-sector exchange of best practices, experience and know how and it demonstrates how the pooling of resources, knowledge, and creative thinking can lead to the development of innovative and viable approaches, and lead to real benefits for animal welfare, the European consumer and environment, and industry.

Can you describe the links between the area of regulatory testing i.e. the scope of the EPAA, and the wider area of testing, which includes research?

**J. Potočnik:** The term 'regulatory testing' describes an area where testing is required by law, be it national or EU legislation, for example for industrial chemicals, pesticides, or food safety. Regulatory testing is carried out to ensure that a substance is safe before placing it on the market. More testing than for pure regulatory purposes takes place during the development phase of a new drug or other substance to ensure its efficacy and usefulness, e.g. when investigating treatment for illness, and for ensuring safety of the ultimate product before it is exposed to regulatory testing. However, the vast majority of animal experiments happen for basic research purposes, mostly with transgenic animals, where we see even an increase of animal numbers in the recent past. It is against that background that asking ECVAM to promote the use of alternatives in basic research was important and where the request to get all animal experiments approved and assessed in advance could have the biggest impact on overall testing numbers.

Finally, what message would you like to give to the EPAA members?

**J. Potočnik:** The new Directive 2010/63/EU will significantly improve animal welfare in the European Union. To harvest its full potential, I am looking forward to an intelligent transposition by the Member States; a transposition which optimises the use the available resources, streamlines the processes and facilitates bringing alive the Three Rs at every level, and in a manner that makes our research and industry more competitive. Once it is implemented, we will be able to lay claim to having the highest standards of experimental animal welfare in the world.

The EPAA is a unique private-public partnership that can be seen as a model for other parts of the world. The Commission appreciates the commitment of industry to link forces with the Commission and the progress made over the last 5 years. The EPAA has demonstrated in its first five-year mandate that together we can trigger progress in achieving a balance of the many interests of the key players in the field and advancing more precise and humane science.

For the future, my suggestion would be to try to improve the outreach of EPAA to the regulatory risk assessors and risk managers. If they embrace better the opportunities that alternative procedures offer, a huge incentive will be created to put more resources into developing such methods. This, on the other hand will require that science is better informed about the need of risk assessors and risk managers – and EPAA is perfectly placed to bridge also this gap. Therefore I can only invite EPAA to continue its good work of promoting the development and use of alternative approaches for regulatory purposes.

The topic of reproductive toxicity was selected to be conducted first, as a pilot project

To provide an up-to-date picture of the state-of-the-art alternative methods at all stages of development, validation and/or regulatory acceptance

### Thematic reviews

Following the Dissemination Workshop, in November 2009, the EPAA Dissemination & Communication Platform decided to promote, under the "market place" concept, a mechanism by which regulators, industry and other parties are provided with concise, comprehensive and peer-reviewed information in the form of Thematic Reviews regarding existing Replacement, Reduction or Refinement methods (3Rs) for regulatory safety testing, their potential and limitations.

Following a survey launched early 2010 with the EPAA partners, the topic of reproductive toxicity was selected to be conducted first, as a pilot project, under the coordination of ECVAM. The aim of the project is to provide an up-to-date picture of the state-of-the-art alternative methods at all stages of development, validation and/or regulatory acceptance for the area of reproductive toxicity testing of chemicals and/or formulations.

The review does not cover methods to detect developmental neurotoxicity and methods to identify endocrine disruptors – this might be subject to a separate review. The review, focusing mainly on in vitro methods, was conducted from June to December 2010 by a scientific consultant under the overall coordination of ECVAM and with financial support by the industry members of EPAA.

In addition to the literature expert searches and the information made available by ECVAM's database service, a questionnaire was developed and used to collect input of EPAA companies (and industry in general) on the use of in vitro methods. No general conclusions about the use of the available in vitro methods in industry can be drawn from the responses to the survey. However, some interesting observations were noted, namely that the post implantation Whole Embryo Cultures (WEC), the Embryonic Stem Cells (EST; mouse and human) and the Zebrafish Embryo Assay are used more frequently at the respondent companies from the chemical and pharmaceutical industry. The other in vitro tests seem to be used in more particular cases.

The results of the review were used for revising and updating the sector Reproductive Toxicity testing of the publicly available "DataBase service on ALternative Methods to animal experimentation" (DB-ALM) at <http://ecvam-dbalm.jrc.ec.europa.eu>. This allows benefiting from the data retrieval facilities and the large scientific and regulatory community that is subscribed to this service ensuring a wide and targeted distribution of the project outcome.

The outcome will be published via periodical releases during the first semester 2011 and be announced via the DB-ALM newsletters and the EPAA website.

To complete the review addressing in more depth the actual use of all 3Rs methods, a second industry survey on the use of in vivo Reduction and Refinement methods and approaches for reproductive toxicity will follow in 2011.

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### Extended one-generation

In November 2010, the OECD Joint Meeting endorsed for final approval by the OECD Council in 2011 the draft guideline for the Extended One-Generation Reproductive Toxicity Study (EOGRS).

This is considered as a major success, to which EPAA has largely contributed. Back in 2006, [EPAA and ECVAM workshops](#) undertook to adapt the ILSI Health and Environmental Sciences Institute published strategy for agricultural chemical safety assessment (ACSA) for a wider use, in particular on testing chemicals under REACH. EPAA industry partners (BASF, Bayer Crop Science, Dow, Syngenta) initiated feasibility studies on the extended one-generation study protocol.

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An EPAA project team established to further progress the application of the 3Rs and the consistency approach for improved vaccines quality control

### Extended one-generation

At the same time, an OECD expert group was set up at the end of 2007 to develop a draft guideline and evaluate the validity of the endpoints used. A draft test guideline (TG), proposed and promoted by Germany, the Netherlands and the U.S, was eventually agreed by the OECD Joint Meeting in November 2010. The adoption by the OECD Council is expected to follow.

Other steps need to be taken before the EOGRTS will generate its full potential. With its current status as a "stand alone" Test Guideline (TG), regional and national authorities have room for manoeuvre as far as testing requirements are concerned (with as a result variations in numbers of animals to be used). Therefore the different regulatory authorities, including those of the EU, must still decide on the use and conditions of use of the guideline.

In February 2011, the Commission and national authorities in charge of REACH, took the commitment to adopt by June 2011 a Roadmap on regulatory acceptance of the OECD guideline in the EU REACH legal framework. This implies to assess the legal possibilities in the current legislation to consider other approaches where the 2<sup>nd</sup> generation, DNT and DIT cohorts are or are not included in the EOGRTS test protocol systematically. This would include identifying how the EOGRTS TG fits into the overall testing strategies for:

- Assessing reproductive toxicity in REACH and CLP
- Analysing the compatibility of the EOGRTS TG with the information annexes in REACH
- Evaluating how the OECD guideline should be incorporated into the EU Test Method Regulation
- Obtaining a reliable estimate of the costs to industry associated with the various EOGRTS options

In parallel, European Commission services will examine how to introduce the EOGRTS under Regulation 1107/2009 concerning the placing of plant protection products on the market.

In the meantime, companies have started to introduce on a case-by-case basis testing proposals referring to the EOGRTS and ECHA is investigating the scientific and legal possibilities to deal with these testing proposals.

The EPAA partners will continue efforts to facilitate the optimal application and regulatory acceptance of this approach.

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### Vaccines Kick-off meeting - 7 April

Following the successful workshop organised in January 2010 (report published in [Biologicals](#)), the EPAA established a project team to further progress the application of the 3Rs and the consistency approach for improved vaccine quality control.

The team, which is led by Dr Ian Ragan, plans a kick-off meeting on 7 April 2011 to engage the relevant stakeholders and set up a permanent scientific platform of interested parties, with experts from Academia, EDQM, OMCLs, ECVAM, EVM and IFAH-Europe, FDA, WHO and regulatory authorities.

On the basis of response at the kick-off meeting, a Technical Committee (with sections for human and veterinary vaccines) will be established. A further workshop will be organised in autumn 2011 to discuss with all relevant stakeholders on the pursuit of the consistency approach; it will aim at identifying current alternative initiatives amongst stakeholders, prioritising the tests to be replaced according to specific criteria, and recommending minimum validity criteria for acceptance of alternatives to *in vivo* testing methods.

## EPAA 2010 Conference

The Report of the [EPAA 2010 Conference](#), focusing on the Reduction and Refinement Strategies, is available on the EPAA website. It highlights the strong political support to the EPAA from various European Commissioners and representatives from industry, summarizes the main conclusions on Reduction and Refinement strategies.

It also announces the winners of the various EPAA awards, including the EPAA Science award, granted to Dr Felix Spöler of the Institute of Semiconductor Electronics of the Rheinisch-Westfaelische Technische Hochschule for his project, "Proving the relevance of the Ex Vivo Eye Irritation Test (EVEIT) as a self-contained in vitro substitute for the Draize Eye Irritation Test".

## EPAA 2011 Lead Theme and 2011 Annual Conference

The 2011 EPAA lead theme is "Integrated Testing Strategies (ITS) and their impact on Replacement, Reduction and Refinement Strategies".  
The 2011 Conference will take place on November 9, in Brussels.

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### ●●● UPCOMING EVENTS ●●●

**26 – 28 April 2011**

[IVTIP Spring 2011 Meeting](#) – In vitro reconstructed human tissue models as alternatives to animal testing: applicability and limitations  
Novotel, Monte Carlo, Monaco

**10 -13 May 2011**

[Third International Conference on Alternatives for Developmental Neurotoxicity Testing \(DNT3\)](#)

Varese, Italy