PERSPEKTIVEN FÜR UMWELT & GESELLSCHAFT umweltbundesamt

First Austrian In Vitro In Silico Safety Science — Workshop

ENVIRONMENT AGENCY AUSTRIA umweltbundesamt

FIRST AUSTRIAN SCIENCE COORDINATION WORKSHOP FOR IN VITRO & IN SILICO APPROACHES TO SAFETY ASSESSMENT OF CHEMICALS AND ENVIRONMENTAL MEDIA

2017, February 16-17, Linz, Austria

Workshop Report

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CONTENT

ZUSAMMENFASSUNG

Die toxikologischen Wissenschaften umfassen zunehmend auch tierversuchsfreie Testmethoden. Diese Entwicklung in Richtung Realisierung einer tierversuchsfreien Sicherheitsbewertung im Rahmen der regulatorischen Toxikologie wird von der Gesellschaft und auch von der europäischen Gesetzgebung explizit gefordert und unterstützt. Im „*Ersten Österreichischen Wissenschafts-Koordinations-Workshop für In-vitro- und In-silico-Methoden zur Sicherheitsbewertung von Chemikalien und Umweltmedien*“ präsentierten und diskutierten 27 österreichische ExpertInnen aus Wissenschaft und Behörden individuelle wissenschaftliche Arbeitsschwerpunkte und entwickelten langfristige gemeinsame Ziele und notwendige praktische Herangehensweisen: Als erster Schritt wurde die “*Austrian Platform for in vitro & in silico safety science*” (AIVIS) gegründet. Sie soll wissenschaftliche Kooperationen und Arbeiten an der Schnittstelle zwischen Wissenschaft und Regulatorik fördern, Angebote zur spezifischen Fortbildung verbessern, die Wissenschaftskommunikation und Multi-Stakeholder-Kooperation stärken sowie eine intensivierte finanzielle Förderung und eine entsprechende Koordination für dieses Arbeitsgebiet aufbauen.

1 WORKSHOP OUTLINE & BACKGROUND

date: 2017, February 16 to 17, noon to noon

host: Institute of Bioinformatics, Johannes Kepler University, Linz, Austria

Background

The European Directive on the protection of animals used for scientific purposes (2010/63) requires the dedication of EU Member States to the development and validation of 3R[1] approaches and an improved communication between scientists and regulators in order to achieve suitable progress (Article 47). The European PARERE network[2] shall support this aim. Furthermore, on a policy level, the recent European Citizens Initiative "Stop Vivisection"[3] called for upgrading the field of research for 3R approaches, and a European scientific conference on non-animal methods and the way forward[4] was organized in December 2016. At a national level the United Kingdom, the Netherlands and Sweden have very recently developed roadmaps towards a broad regulatory use of non-animal technologies[5,6,7]. These initiatives are following the scientific advancements in the field - led for many years by large and growing international science communities, supported by many major international scientific conferences (e.g. the 9th World Congress on Alternatives and Animal Use in the Life Sciences[8]; ECHA 2016[9]; EUROTOX 2015[10]; ESTIV 2016[11]; EUSAAT 2016[12]) and recognized with OECD level work in many specific regulatory science expert groups. After the success achieved with the full replacement of animal methods with non-animal-methods in the field of dermal absorption, skin and eye irritation/corrosion and skin sensitization, more complex endpoints like non-genotoxic carcinogenicity, developmental neurotoxicity and organ toxicity

[1] **R**eplace, **R**educe, **R**efine animal testing conceptually developed by Russel und Burch 1958, The principles of Humane Experimental Technique, http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc

[2] https://eurl-ecvam.jrc.ec.europa.eu/about-ecvam/scientific-advice-stakeholders-networks/parere/parere-network

[3] http://stopvivisection.eu/en; supported by 1.17 million certified signatures

[4] http://ec.europa.eu/environment/chemicals/lab_animals/3r/scientific_conference_non_animal_approaches_en.htm

[5] http://nc3rs.org.uk/sites/default/files/documents/NonAnimalTechCO082_RYE_4_nrfinal2.pdf

[6] https://english.ncadierproevenbeleid.nl/latest/news/16/12/15/ncad-opinion-transition-to-non-animal-research

[7] http://www.kemi.se/global/rapporter/2017/rapport-1-17-kemikalieinspektionens-strategi-for-3r-fragor.pdf

[8] http://www.wc9prague.org/

[9] http://echa.europa.eu/news-and-events/events/event-details/-/journal_content/56_INSTANCE_DR2i/title/topical-scientific-workshop-new-approach-methodologies-in-regulatory-science

[10] http://eurotox2015.com/home/83/

[11] http://estiv.org

[12] http://eusaat-congress.eu

are the focus areas of regulatory science work at OECD level[13] and at European level[14] today. In line with these international activities and following the legal mandate under EU Directive 2010/63, a first Austrian science coordination workshop was conducted to collect, as a first step, current expertise and perspectives of scientists in Austria. A common agenda shall be developed to use and advance the science of *in vitro & in silico* approaches to safety assessment of chemicals and environmental media. This shall be followed up more broadly with future workshops with PARERE and other stakeholders at the science-policy interface.

Aims of the workshop

- collect the status quo and individual research perspectives in Austria to use and advance the science of novel in vitro & in silico approaches to safety assessment of chemicals and environmental media
- allow the development of synergies & collaboration between scientists in this field in Austria
- formulate common long term goals for science in this field
- collect ideas for practical steps towards these goals

Participants

invited experts: scientists contributing to the development of *in vitro & in silico* approaches to safety assessment in Austria and the Austrian PARERE Network, in total 27 people

Agenda

Feb 16, afternoon: presentations and round table discussion

- short presentation by each invited scientist on individual research interests and perspectives on cooperation
- round table discussion about potential synergies and collaboration

Feb 17, morning: discussion with pin-board to

- formulate common short to long term goals for scientific research on new *in vitro & in silico* approaches to safety assessment
- collect ideas for practical steps to reach these these goals

Output envisaged

- proposal for an Austrian short to long term science agenda
- publication of workshop report

[13] See OECD workplan: http://www.oecd.org/chemicalsafety/testing/oecd-guidelines-testing-chemicals-related-documents.htm; OECD EAGMST http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm

[14] http://www.eu-toxrisk.eu/

Working language

English (to support synergies in texting and presentation with other international work and to be open for collaboration with international scientists working in Austria)

Social dinner

Feb 16, evening

Steering group

Martin Paparella, Günter Klambauer, Maria Fürhacker, Paul Jennings

with the support of: Ministerium für ein Lebenswertes Österreich (BMLFUW), Abteilung V/5, Chemiepolitik und Biozide

2 INTRODUCTION

Article 47 of Directive 2010/63/EU on the protection of animals used for scientific purposes requires that Member States shall contribute to the development and validation of alternative approaches and take steps as they consider appropriate to encourage research in this field. Moreover, after consulting the Member States, the European Commission shall set the priorities for validation studies and Member States shall nominate a single point of contact to provide advice on the regulatory relevance and suitability of alternative approaches proposed for validation. This requirement was fulfilled with the European PARERE network consisting of one national contact point per Member State. Martin Paparella was nominated as the Austrian national contact point, and he consults with officially nominated colleagues from AGES about relevant inputs[15]. Furthermore, Member States shall, at national level, ensure the promotion of alternative approaches and the dissemination of information thereon. PARERE may also have a role in this context. In summary, there is a legal mandate to support research and communication in the field of *in vitro & in silico* science at national level and to consider the regulatory framework, and this workshop was aimed at serving the purpose of this mandate.

Furthermore, new approaches to testing and assessment are finally being harmonized at OECD level. As apparent from the OECD work programme, the focus has gradually shifted towards *in vitro & in silico* approaches in the last few years and the new OECD project submissions (SPSFs) for 2017 include only *in vitro* work[16]. Martin Paparella is the Austrian representative in the OECD Working Group of National Coordinators for the Test Guidelines Programme (OECD WNT) and currently vice-chair of this group. It is important to ensure good collaboration and communication between the Austrian *in vitro & in silico* science field and the regulatory OECD work. This will help to optimize potential output of Austrian research for regulatory purpose, bring relevant ongoing research work to OECD level in a timely manner and provide international scientific feedback in both directions.

Several scientific and regulatory drivers are supporting this increasing trend away from regulatory animal testing towards *in vitro & in silico* approaches. These drivers arise from the need

- to reduce the costs and time for regulatory toxicology
- to reduce animal suffering
- to turn regulatory toxicology into a socially fully appreciated working field that can be easily communicated to a broad general public
- to increase the availability of regulatory test data for many chemicals, including high to low volume production chemicals, environmental metabolites, impurities, reaction products and emerging environmental contaminants

[15] Günter Waxenecker, Barbara Zemann, Albert Bergmann, Britta Moebes-Hansen, Klemens Fuchs, Zeynep Erdem

[16] with the exception of one fish embryo project which is from a biological point of view a 3R method and from a legal (European) point of view not considered an animal test within the meaning of Directive 2010/63/EU

- to assess the multitude of nano-materials composition, forms and size distributions
- to increase possibilities for early screening and optimization of pharmaceuticals as well as green chemical engineering, i.e. testing of many chemical variants for (eco)toxicity in the phase of chemical design in order to reduce toxicity while optimizing chemical functionality (Maertens et al., 2014)[17]
- to assess mixture toxicity, which requires the testing of many mixture variants and/or a deeper understanding of the mode of action of individual components (EC 2014)[18]
- to assess environmental media including the use of bio-analytics to complement chemical analytics (Schroeder et al., 2016)[19]
- to increase the effectiveness of substituting the more hazardous chemicals by providing reliable data for an ample set of potential alternative chemicals (also in the low tonnage production range)
- to retest chemicals according to the level of progress achieved in the development of scientific and toxicological understanding as to be expected in many fields (including epigenetic mode of actions and endocrine disruption)
- to automate data integration and assessment procedures to improve (beyond the testing throughput) also the regulatory assessment throughput
- to mechanistically approach cross-species extrapolation for ample coverage of environmental toxicity; the multitude of potentially relevant species and environments makes standard animal testing impracticable for this purpose (Groh et al. 2015)[20]
- to improve the scientific basis for human health risk assessment by including human *in vitro & in silico* models
- to improve the reliability, relevance and accuracy of the current standard testing methods as well as predictive computational models
- for the European Commission: to develop, within the European 7th Environment Action Programme "Living well, within the limits of our planet"[21], a "Union strategy for a non-toxic environment" (which further stimulates the needs summarized above)

[17] Maertens, A., N. Anastas, P. J. Spencer, M. Stephens, A. Goldberg and T. Hartung (2014). "Green toxicology." ALTEX 31(3): 243-249.

[18] https://eurl-ecvam.jrc.ec.europa.eu/news/assessment-mixures-report **and** https://ec.europa.eu/jrc/en/science-update/current-and-future-approaches-assessment-combined-exposure-multiple-chemicals

[19] Schroeder, A. L., G. T. Ankley, K. A. Houck and D. L. Villeneuve (2016). "Environmental surveillance and monitoring-The next frontiers for high-throughput toxicology." Environ Toxicol Chem 35(3): 513-525.

[20] Groh, K. J., R. N. Carvalho, J. K. Chipman, N. D. Denslow, M. Halder, C. A. Murphy, D. Roelofs, A. Rolaki, K. Schirmer and K. H. Watanabe (2015). "Development and application of the adverse outcome pathway framework for understanding and predicting chronic toxicity: I. Challenges and research needs in ecotoxicology." Chemosphere 120: 764-777.

[21] http://ec.europa.eu/environment/action-programme/

The goal is to develop a win-win-win-win situation:

- WIN for science through increased funding and activities in the alternatives field in Austria, creating an internationally competitive track and increasing public awareness of such activities which aim to move safety science to emerging animal-free technologies and which are supported by a legal mandate.
- WIN for regulation through better tools for the improvement of human and environmental health safety, which can be communicated more easily to the broader general public
- WIN for the economy through new incentives for the development and marketing of new testing tools, new specialized testing services, and new green chemicals
- WIN for society and animals by improving the welfare of humans and animals

3 PRESENTATION OF SPECIFIC RESEARCH ACTIVITIES AND INTERESTS OF INDIVIDUAL PARTICIPANTS

See one-pagers from each participant in Annex 1.

4 RESULTS OF THE WORKSHOP

It was explained and discussed what the scientific development of *in vitro & in silico* approaches to safety assessment can offer in terms of potential long term achievements. Furthermore, the practical short and medium term steps that are needed in Austria to reach these envisaged goals were highlighted. The discussion started in small groups of participants and was followed by presentations via pin-board moderation cards and a plenary discussion.

In the following, a summary is given of the proposals made by the participants of the workshop: Long term achievements, medium term steps and short term steps (the latter appear in a green font colour on a light grey background).

Potential long term achievements

- The long term goals summarized in the introductory notes on the first half day were confirmed (see introduction)

Steps to establish a new platform for the scientific development of *in vitro & in silico* safety methods

- There was general agreement that a platform should be established which focuses on the development and communication of *in vitro & in silico* safety science (proposed name: AIVIS – **A**ustrian ***I**n **V**itro* and ***I**n **S**ilico* Safety Science Platform)
- In order to be workable, the platform (AIVIS) requires the support of a secretariat with adequate funding which needs to be made available as soon as possible and on a long term basis
- The representatives from the ministries who were present were asked to consider appropriate funding for such a secretariat
- The platform (AIVIS) will, on an annual basis, create and agree working programmes that build on the tasks and responsibilities developed and suggested during the workshop. These proposals are summarized in the following section.

Steps to improve education, training and support for various stakeholders in Austria

- Elect an AIVIS expert board that offers support for various institutions such as
  - FWF (Austrian Science Fund), e.g. for project reviews or suggestions for other international reviewers with specific *in vitro* or *in silico* expertise (*in vitro* / *in silico* project applications should not be reviewed by general scientists or toxicologists, but by specialists in this emerging field)
  - Ministries and agencies, e.g. for the discussion of data and method assessment and use
  - Universities and FHs (e.g. University of Applied Sciences Vienna), e.g. for mutual support of training

- Establish AIVIS – OECD – PARERE interface collaboration
  - to optimize potential output of Austrian research for regulatory purposes
  - to present relevant ongoing Austrian research work to PARERE or at OECD level in a timely manner in order to receive international feedback
  - to provide Austria-specific scientific feedback on other international OECD and PARERE work
  - to provide input to OECD work, e.g. Adverse Outcome Pathway (AOP) development and review

- Develop an Austria-wide doctoral excellence programme for *in vitro & in silico* safety science, including
  - a doctoral college (training at various universities and departments)
  - an Austrian research network
    - using a bottom-up strategy that builds on national research competence
    - which is open both to applied and basic research, the latter being important to ensure a deeper scientific understanding of appropriate mechanisms and methods and to build confidence within the growing scientific community
    - which supports projects that complement other international work but may also include some redundancies, in order to ensure reliability and resilience of international research
  - funding for the development of the programme, for the advisory board and regulatory input;
    - to be discussed with FWF
    - BB3R programme (Berlin-Brandenburg 3R)[22] provides an example of what could also be done in Austria; Austrian collaboration with BB3R could be envisaged, e.g. in terms of sharing project reviewers
- Develop an Austrian Summer School for *in vitro & in silico* approaches, including regulators as target audience; develop "regulator ambassadors" who transfer knowledge to their colleagues in the field
- Develop specialized practical hands-on training for researchers and regulators, collaboration with CAAT academy[21]
- Develop a programme to be offered at the secondary level of education (schools)

Steps towards improved science collaboration

- aim for at least one AIVIS meeting for coordination and communication per year
- organize workshops to understand and discuss
  - the development and regulatory use of the OECD's AOP concept and Effectopedia
  - how to validate new *in vitro & in silico* approaches that provide qualitative and quantitative information on specific modes of action rather than the regulatory standard endpoints that can be observed with animal tests

[22] http://www.bb3r.de/en/index.html

  - how to integrate complex omics data with other data for regulatory use
  - the uncertainties and complexities of current animal based assessment approaches, their relevance for the validation of *in vitro & in silico* approaches; how adversity may be defined on the basis of *in vitro & in silico* methods and the need to develop endpoints and classifications in addition to current regulatory endpoints (see e.g. Paparella et al. 2017[23])
  - whether the current regulatory endpoints are the most appropriate ones (considering *inter alia* epigenetics)?
- Provide an overview of available databases and relevant institutions at European level and improve, or if necessary establish, an entity for toxicological and computational data management (data curation, consolidation and structuring) as well as knowledge management (for guidance on the definition of data needs for regulatory applications)
- Establish specific AIVIS task forces and ensure overarching coordination
  - for e.g. *in silico* work, barrier work, environmental media work
  - to structure and align available scientific knowledge and regulatory needs
  - to define specific goals (within the individual task forces) and identify related gaps of knowledge and data
  - to support small inter-laboratory comparisons or feasibility studies, where needed

    This needs collaboration between scientists and regulators as well as funding, e.g. via COST[24] actions (although COST needs multiple European partners).
- Support the integration of European research activities, e.g. by considering ERIC (European Research Infrastructure Consortium) which is currently available for biobanking and clinical trials; develop proposals and discuss them with EURL ECVAM/PARERE
- Contribute to national 3R centre coordination meetings at EURL ECVAM
- Map the Austrian landscape of *in vitro & in silico* approaches; including actors, supportive interest groups, obstacles and risks, embedded in the international landscape[25]

Steps towards improved science communication

- Map *in vitro & in silico* science experience available in Austria and establish a database with Austrian *in vitro & in silico* science experts including their key expertise
- Link the database of AIVIS experts with international platforms (The ASTOX/EUROTOX expert list is not specifically designed for *in vitro & in silico* science experience.)
- Communicate quality criteria for *in vitro* method developers: OECD Good *In Vitro* Method Practices (GIVIMP)[26]

[23] Paparella, M., A. Colacci and M. N. Jacobs (2017). "Uncertainties of testing methods: What do we (want to) know about carcinogenicity?" ALTEX 34(2), 2017: 235-252; doi: 10.14573/altex.1608281

[24] European framework supporting cooperation among researchers across Europe

[25] important read: Marie-Jeanne Schiffelers, Animal testing, 3R models and regulatory acceptance, Technology Transition in a Risk-averse Context, ISBN 978-90-393-6567-0

- Identify relevant GLP laboratories in Austria
- Provide an overview of available *in vitro & in silico* methods[27], specifying those that are
  - internationally validated/agreed or
  - further up in the development to validation pipeline

  and summarize gaps and highest research/development needs
- Develop specific dossiers on new approaches and development, comparable with the Nanodossiers, in the form of easily understandable communication papers
- Create a low-maintenance website for the AIVIS platform to publicly share relevant information and provide information about current activities including a list of experts, publications, information on workshops, projects, funding, etc..
- Meet co-players in Austria such as
  - the Nanoinformations-Platform
  - RepRefRed-Austria (Graz, focus on refinement and reduction, recently established)[28]
  - Personalized Medicine
  - ASTOX[29]
  - BioNanomed
  - BioNanoNet[30]
  - ABC3Rs (Austrian Biomimetic Centre 3Rs)
  - C3RCI (Comprehensive 3Rs Centre Innsbruck)
  - … (list to be completed)

Steps towards improved funding

- Establish regular contact and discussion with funding bodies
- Develop improved funding perspectives, e.g.
  - a new funding body, set up specifically for *in vitro & in silico* approaches
  - private investors
  - the (local) pharmaceutical industry
  - found a foundation
  - crowd funding
  - … (to be amended)

[26] http://www.oecd.org/env/ehs/testing/OECD_Draft_GIVIMP_in_Human_Safety_Assessment.pdf

[27] See also EURL ECVAM status reports: https://eurl-ecvam.jrc.ec.europa.eu/eurl-ecvam-status-reports

[28] http://www.reprefred.eu/en/welcome.html

[29] http://www.astox.at/

[30] https://www.bionanonet.at/

- With a view to funding and to promote funding activities, support and explain the development of commercial perspectives in the *in vitro & in silico* science field through early communication with regulators and society on potential needs, e.g.
  - for the development, validation and marketing of new *in vitro & in silico* tools and methods
  - for offering specialized *in vitro & in silico* testing and assessment services to industry
  - for the development of new, greener chemicals, biocides, pharmaceuticals etc.
- Establish a working group for coordination and priority setting in the field of *in vitro & in silico* science
  - based on agreements with regulators, industry and NGOs
  - enhancing the visibility of the AIVIS field by jointly informing on scientific and regulatory achievements
  - developing a stakeholder landscape and culture which is supportive for the necessary change in science and regulation
  - which is supported by specific funding, including full-time employment
  - providing funding for focused research (in addition to other sources for funding)
  - considering the success of e.g. NC3Rs in the UK

5 CONCLUSIONS

There was general agreement that a platform should be established which focuses on the development and communication of *in vitro & in silico* safety science (proposed name: AIVIS – Austrian Platform on *In Vitro & In Silico* safety science). In order to be workable, the platform (AIVIS) requires the support of a secretariat with adequate funding which needs to be made available as soon as possible and on a long term basis. The representatives from the ministries who were present were asked to consider appropriate funding for such a secretariat. The suggestions for further progress will be elaborated via dedicated action lists and AIVIS sub-group work and in response to feedback from the ministries involved and potential funding bodies. At least one meeting a year is envisaged to support continuous AIVIS work throughout the year.

The following participants offered to act as steering committee for the establishment of the platform (AIVIS): Martin Paparella, Günter Klambauer, Paul Jennings, Maria Fürhacker, Doris Marko, Winfried Neuhaus, André Gaszo

6 LIST OF PARTICIPANTS

Surname	First name	Scientific Institution
Achleitner	Bettina	BMWFW: Federal Ministry of Science, Research and Economy; Vienna
Ehrlich	Veronika	Shire Vienna
Erdem	Zeynep	Austrian Agency for Health and Food Safety Vienna
Falb-Naderer	Olivia	BMLFUW: Bundesministerium für Land- und Forstwirtschaft, Umwelt und Wasserwirtschaft; Vienna
Francic	Vito	Medical University of Graz
Fürhacker	Maria	University of Natural Resources and Life Sciences Vienna
Gostner	Johanna	Medical University of Innsbruck
Grillari	Johannes	Evercyte GmbH Vienna
Haslinger	Alois	BMWFW: Federal Ministry of Science, Research and Economy; Vienna
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Jennings	Paul	Medical University of Innsbruck
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Lukas	Arno	Emergentec Biodevelopment GmbH Vienna
Marko	Doris	University of Vienna
Mohr	Thomas	ScienceConsult – DI Thomas Mohr KG Guntramsdorf
Neuhaus	Winfried	Austrian Institute of Technology GmbH Vienna
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Pfaller	Walter	Medical University of Innsbruck
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Schröder	Klaus	NP Life Science Technologies Linz
Wetzer	Barbara	University of Applied Sciences Technikum Vienna
Wilflingseder	Doris	Medical University of Innsbruck
Wimmer	Martin	BMLFUW: Bundesministerium für Land- und Forstwirtschaft, Umwelt und Wasserwirtschaft; Vienna
Zdrazil	Barbara	University of Vienna, Department of Pharmaceutical Chemistry, Pharmacoinformatics Research Group

Participants

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Back: Bettina Achleitner, Arno Lukas, Klaus Schröder, Berthold Huppertz, Martin Wimmer, Barbara Wetzer, Johannes Grillari, Vito Francic, Gloria Rose, Barbara Zdrazil, Thomas Mohr, Dominik Rünzler, Martin Paparella
Front: Ingrid Hauzenberger, Paul Jennings, Alois Haslinger, Maria Fürhacker, Günter Klambauer, Olivia Falb-Naderer, Zeynep Erdem, Doris Wilflingseder, Brigitte Landesmann, Veronika Ehrlich, Doris Marko, Johanna Gostner, Walter Pfalle

ANNEX 1: ONE-PAGERS FOR SPECIFIC RESEARCH ACTIVITIES AND INTERESTS OF INDIVIDUAL PARTICIPANTS

Summary of current activities and research interests

Veronika Ehrlich, PhD, ERT (European Registered Toxicologist)
Sr. Scientist Toxicology
Regulatory Toxicology, Nonclinical Development
Baxalta Innovations GmbH, now part of Shire (Pharmaceutical Industry)
veronika.anna.ehrlich@shire.com; www.shire.com

Experience in the field of in vitro Science:
Development and application of an in vitro screening battery for different endpoints of general toxicity, genotoxicity and endocrine activity assays for non-intentionally added substances (NIAS) in packaging (Nestlé Research); integration of in vitro, in silico and exposure data for toxicological risk assessment

Current tasks comprise the coordination of an internal 3R Task Force with the aim to refine practices in animal research, to detect/foster opportunities for replacement methods and to reduce our animal numbers to the minimum required. Representing Shire in the EFPIA (European Federation of Pharmaceutical Industries and Associations) RAW Expert Group as well as the IQ 3R Leadership Group

Implemented methods @ Shire and research interests:

- In silico genotoxicity assessment; performed according to ICH M7 (SME *Bernhard Majer*)
- In silico metabolite prediction of API related impurities or by-products (SMEs Reinhard Stidl, *Bernhard Majer*)
- Efficacy in vitro in early development / proof of concept studies → case by case model development
- Immunogenicity assessment (SME *Mantas Malisauskas*) for lead identification and optimization for entry into preclinical development, in order to predict the immune response for a protein and to minimize animal usage and the risk of an immunogenic response in animals in general and NHPs.
  - in silico immunogenicity assessments (presence of MHC class I and II T-cell epitopes for biotherapeutics and ranking of compounds)
  - in vitro validation of in silico results – recombinant protein systems as well as human cellular assays
  - aggregation hot spot prediction (structure re-arrangements predicted in silico based on AS-sequence) - in order to exclude drug candidates from development or to reduce the number of animal tests needed
- Additional research interests to help foster the 3Rs in preclinical drug development
  - Risk and immunogenicity or protein aggregates (potentially tests in primary human cells? Currently there is no comprehensive approach available)
  - Species comparison in organ specific toxicity and metabolism in vitro

Replacements or mechanistic information studies for pharma relevant toxicity / target organ endpoints for product development (genotoxicity, carcinogenicity, reproductive toxicity, blood parameters, immune system and information on target organ specific toxicity)

Dr. Zeynep N. Erdem, MScTox

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Short overview (maximum one page) of your actual activities and research interests in the field of in Vitro & in Silico Approaches to Safety Assessment of Chemicals and Environmental Media

Actual activities:

- Risk assessment of PPP regarding health hazards
  - Evaluation of in vitro and QSAR results submitted by companies
- Application of QSAR tools for data gaps as a first-glance approach in case of data gaps
- Participation in workshops
  - Omics workshop
  - Austrian Science Coordination WS

Interests:

- Development of guideline documents for new methods, especially reg. in silico assessments
  - Clear definition of certain cut-off criteria (e.g. applicability domains, reliability indices)
  - Exact knowledge about when to use which statistical methods (e.g. Hierarchical, single model, group contribution, FDA etc..)
  - Standardized, scientifically accepted and valid tools that lead to reproducible results
- Staying informed and up to date with new technologies

Research Group Prof. Barbara Obermayer-Pietsch,

Medical University Graz

Barbara Obermayer-Pietsch is a professor of osteology and endocrinology at the Medical University of Graz. She is also head of the Endocrinology Lab Platform for routine and research hormonal and metabolic analyses at the University Clinic in Graz and head of the EndoGeneLab. In addition, she is deputy director of the FWF DK Molin for scientific activities and board member of the European Society of Endocrinology and the European Calcified Tissue Society.

Coming from a clinical and experimental background, her expertise covers a wide range of research topics from cell metabolism to clinical applications. Her teams' research work includes cell culture experiments ranging from isolation and cultivation of human primary cells, endocrine cell lines (e.g. NCI-H295R as a model for steroidogenic tissues), hormonal, metabolic and microbiome analyses, mouse studies and clinical studies. In addition, the Endocrinology Lab Platform, which is a fully equipped routine and research laboratory for endocrinology and metabolism at the Medical University Graz, offers the possibility to perform measurements of various clinical parameters and biomarkers by ELISAs, RIAs, mass spectrometry, gene expression techniques from tissue and blood as well as high throughput genotyping.

The groups' interests in the field of toxicology mainly concentrate on endocrine disrupting chemicals and phytoestrogens. Recent research activities include isolation and cultivation of primary testicular Leydig cells, in view of vitamin D stimulated androgen production [Hofer D et al., JCEM 2014], or assessing the impact of a microbiome produced phytoestrogen after soy product ingestion in women in view of hormonal and microbiome changes [Lindheim L et al., PLOS 2017].

Our present view is that many different cell lines are available to study aberrant effects of endocrine disrupting chemicals, but most of them are tumour derived and therefore do not reflect the physiological function of primary cells or organs, while the continuous isolation of primary cells from different human donors is expensive, time consuming and frequently impairs the reproducibility of results. Therefore, our vision for the future of research in this field involves the development of stable cell lines from normal endocrine human tissues, which would offer a highly needed option for standardization of testing, while reducing the need for laboratory animal use.

Universität für Bodenkultur Wien
University of Natural Resources and Life Sciences, Vienna

Department of Water, Atmosphere and Environment
Institute of Sanitary Engineering and Water Pollution Control

Leiter: Univ.Prof. DI Dr. Thomas Ertl

Vienna, Jannuary 23rd, 2017

Overview activities and research interests in the field of in-vitro & in-silico approaches to Safety Assessment of Chemicals and Environmental Media

Maria Fürhacker BOKU University Vienna

My personal interest in the field of *in-vitro & in-silico* methods is connected with a new paradigm for the assessment of water quality. There are weaknesses and knowledge gaps of the current testing and evaluation methods when it comes to real world exposures and its inter-chemical interactions as part of mixture exposures. There is strong evidence that chemicals with common specific modes of action can produce combination effects, the current approach of risk assessment seems to be too simple. In the water sector, whole effluent or whole sample evaluations would be required to improve hazard assessment of water and wastewater and to evaluate treatment options to avoid potentially harmful effects to humans and the environment.

My interest is to connect the research outcomes of the use of alternative *in-vitro & in-silico* methods that are intended for the hazard and safety assessment of chemicals with applications in the drinking water, wastewater and environmental sector to evaluate complex samples in the future.

In 2012/13 in search for new monitoring techniques based on *in-vitro* methods we did a joint project with Regina and Giovanni Grillari “New effect assessment tools for emerging contaminants – NEAT-EC” to find out, if and how *in-vitro* methods could be applied for the prediction of negative effects in waste water effluent, drinking water and the surface water assessment. for the decision on treatment requirements.

I contributed to the ARCEM project (Austrian research cooperation on endocrine modulators) and did some studies on hospital wastewaters and street runoff, including effect monitoring. Although my part was technical, I was very interested in effect-monitoring and therefore I cooperated with the cancer research institute and the German Umweltbundesamt.

I am currently the chair of the IWA (International Water Association) specialist group “Assessment and control of hazardous substances in water”, I am also the Vice-Chair of the Austrian ÖWAV group “Spurenstoffe” and I am representative of the Water Quality Group in ÖVGW the interest group of the water works. I am also involved in the SETAC “OMICS” group.

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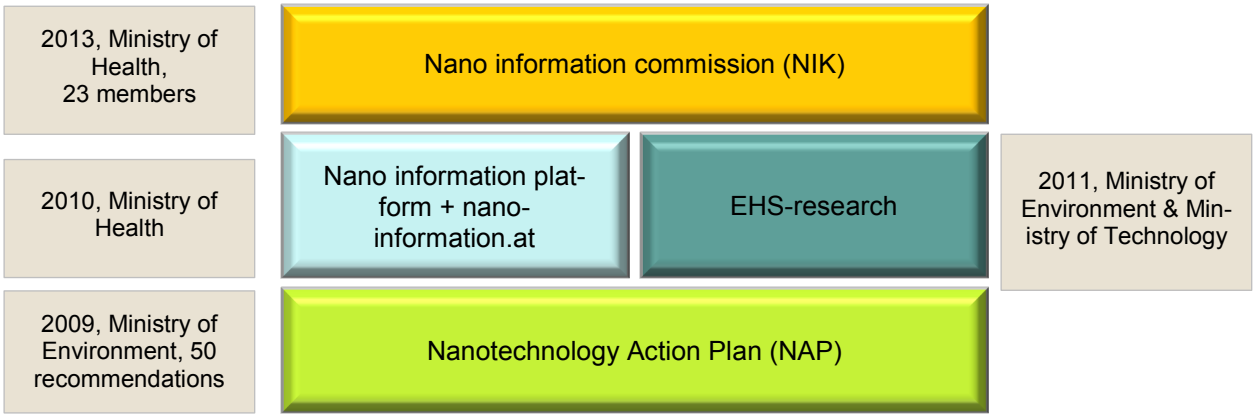
Vienna, February 22nd 2017

NanoTrust – Nano Uncertainty & Risk Governance

André Gazsó & Gloria Rose

NanoTrust is a key player in developing the Austrian nano risk governance landscape and plays an important role in maintaining the different instruments and networks developed to tackle safety and risk issues. Additionally, the NanoTrust project leader currently holds the chair of the Nano information commission (NIK), an advisory board of the Ministry of Health.

Austrian Nano Risk Governance Landscape:



Source: Gazsó, André (2015) NanoTrust – Nano Risk Governance: Extending the Limits of Regulatory Approaches through Expert Dialogues. 5th Molecular Materials Meeting, Singapore/SINGAPORE

NanoTrust initially started in 2007 with the aim of collecting knowledge available on safety and regulatory questions, and to organize and analyse this knowledge. These are tasks one is always confronted with when dealing with new technologies or new materials and products, as they always go hand-in-hand with the need for safety and governance issues to be object of systematic investigation. At an early stage of a new development one is often working with uncertainties rather than risks (risks have unknown outcomes with probabilities which can be measured, while uncertainties have unknown outcomes with unmeasurable probabilities). It is vital to create robust and regulatory relevant knowledge at stages with high uncertainty. In the case of NanoTrust this process of knowledge creation was primarily organized in the form of transdisciplinary expert dialogues.

Within NanoTrust we dealt with the identification of potential dangers for health and environment at a stage in development where not much could yet be determined, due to lacking experience in the field. We now wish to make use of the experiences in early-phase risk evaluation gained through NanoTrust in the past ten years in other related areas. Of particular interest to us are areas in which the precautionary principle applies, namely areas with a justified benefit and reasons to assume there are potential risks, as well as an expected need for regulation to arise in the next few years.

In our experience effective measures can be taken to handle situations of high uncertainty. For example, the nano information commission, nano information platform and Nanotechnology Action Plan are all elements of implementing the precautionary principle and are attempts to get a handle on uncertain situations. Key in the case of nanotechnology was an independent committee or organization with the capacity to handle knowledge acquisition and an interdisciplinary evaluation process. Efforts have been strongly inter- and even transdisciplinary, with networks being strongly trust-based and dependent on communication efforts. Functional trust-based networks can be long-lasting and evolve into more formalized types of cooperation (i.e. NIK). The preparatory phase (including network-building) is very time-consuming and efforts to include regulatory authorities and stakeholders should be made as early as possible and run in parallel with the development of technologies.

Innovation can be promoted by efficient uncertainty/early stage risk management.

Overview of actual activities and research interests in the field of in Vitro & in Silico Approaches to Safety Assessment of Chemicals and Environmental Media

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Research interests include the toxicology, bioactivity and analytics of volatile compounds, natural products and synthetic chemicals. Central aspects are investigations into ***volatile organic compounds (VOC)***, e.g. by focusing on effects of low-dose and long-term exposures of indoor air pollutants on an air-liquid interface (ALI) lung cell model [1]. For this purpose, a novel ***exposure platform for airborne treatments*** has been developed by an interdisciplinary team of engineers, biologists and biotechnologists at the Medical University of Innsbruck in cooperation with the Bioenergy2020+ in Graz. A major goal of the primary studies was to develop and evaluate an exposure strategy with all necessary analytical methods including online measurements in the atmosphere above target cells, as working with volatile compounds requires thorough monitoring of real assay concentrations. In a follow up study funded by the FWF (T703), more detailed investigations are currently underway, comparing the effects of airborne and topical application of ***essential oil*** constituents on ALI models of lung and skin. Building on the knowledge gained so far, we are co-operating with researchers from the Imperial College London in order to analyse ***skin and lung sensitizers*** in epithelial-immune cell co-culture systems.

Immunotoxicology is a key interest of previous and ongoing research, with a particular focus on ***pteridine and tryptophan metabolism*** [2]. The latter is a metabolic checkpoint pathway for immune system activation and is linked to toxicology due to the activation of the arylhydrocarbon receptor by the downstream metabolite kynurenine. The underlying immunobiochemistry of both pathways and the application of these biomarkers in healthy, diseased and chemically exposed individuals have been a topic of interest for my collaboration partner Prof. Dietmar Fuchs over the past 25 years. The *in vitro* model of mitogen-stimulated human peripheral mononuclear cells has been recognized as reliable tool for investigating both immunosuppressive and activating effects of diverse chemicals [3], drugs [4] and also of nanoparticles [5], by using tryptophan breakdown and neopterin formation as readouts. Since the colon is considered to be the largest lymphoid organ, studies on the tryptophan pathway have been of major interest in projects dealing with food components [6], for some of which consumption studies were also performed [7, 8].

In addition to the aforementioned pathway focused readouts, unbiased data acquisition strategies such as gene expression analysis have been applied in some previous studies. These have been shown to be advantageous to depict the signalling changes in situations where prior knowledge of key processes was insufficient such as in the case of ***low VOC doses*** [1] or in ***complex mixtures*** [9]. In this context the ***integration of unbiased methods with selected pathway-focused bioassays*** has been considered to be helpful in assessing relevant activities in a dose-depended manner [10].

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Research and Training activities (related to 3R field)

Johannes Grillari, Department of Biotechnology, BOKU and Evercyte GmbH

Research activities

Johannes Grillari's research focus is on the molecular and physiological changes that occur during cellular aging, their impact on organismal aging, and the role of stress on health and aging. As several stressors that are related to aging are toxicants, he is also interested in basic mechanisms of toxicology. In addition, he is interested in engineering of mammalian cells to establish relevant and standardizable cell model systems and cell factories. Therefore, he has contributed specifically to following topics:

- Cellular senescence: from molecular mechanisms in vitro to effects of senescent cells in vivo on various organs including skin
- Functional role of microRNAs in cellular senescence
- Functional role of RNA modifying proteins in cellular senescence
- miRNAs as biomarkers for age-associated diseases including osteoporosis
- Establishing human cell models including mesenchymal stem cells, iPS, kidney cells, endothelial cells, keratinocytes
- Non-coding RNAs as tools for cell engineering of Chinese hamster ovary cells

Running projects:

- In3# (ITN H2020) – An integrated interdisciplinary approach to animal-free nanomaterial and chemical safety assessment
- Christian Doppler Laboratory on Biotechnology of Skin Aging
- RiboDACH (D-A-CH; FWF I2514): The role of specialized ribosomes in stress resistance and healthy aging
- BioTOP (Doctoral College; FWF): Biomolecular Technology of proteins
- SYBIL (EU FP7): Systems biology for the functional validation of genetic determinants of skeletal diseases
- FRAILOMIC (EU FP7): Validation of -omics-based biomarkers for diseases affecting the elderly
- EVtrust (EuroTransBio): The development of an extracellular vesicle therapy for brain damage repair after stroke

Training activities (3R related)

Masters/PhD Training program

- 791.118 Regulation of cellular metabolism (Boku, Vienna), 2h VO
- 791.322 Regulation of cellular metabolism (Boku, Vienna), 3h PR
- 791.416 Instructional course IVb – Transcriptomics (biotop)
- 791.333 Biology of Aging (Boku, Vienna), 2h VS
- 772.308 Genetic Model Organisms in Biotechnology (Boku, Vienna), 1h, VU

Overview on publications

- ORCID: 0000-0001-5474-6332
- 105 SCI publications; *h*-factor 26 (Scopus); 31 (google Scholar), total IF ~500; total citations ~2500; 4,8 IF/publication, 15 average citations per publication
- Guest editor of 3 special issues of SCI Journals
- 5 book chapters
- 6 contributions to conference proceedings
- 10 patents filed, 3 issued
- Around 400 conference contributions (posters and oral presentations)

Short overview of my actual activities and research interests in the field of in Vitro & in Silico Approaches to Safety Assessment of Chemicals and Environmental Media

Prof. Berthold Huppertz, PhD
Professor of Cell Biology
Director and CEO, Biobank Graz
Chair, Organizational Unit of Research Infrastructure (OFIS), including

- Biobank Graz,
- Center for Medical Research, and
- Biomedical Research (central animal facility at Medical University of Graz)
  Medical University of Graz, Austria
- Director and CEO of Biobank Graz, one of the largest clinical biobanks in Europe:
  - Focus on specialized scientific services, infrastructure and technologies to foster personalized medicine and therapies;
  - Enabling use of human samples for basic research and clinical studies;
  - Distribution of 20,000 to 30,000 samples/year for biomedical research projects;
- Chair of OFIS:
  - Planning of setting up an animal-based biobank (mouse) to reduce use of animals;
    - Establishment of a joint IT platform
      Data on mouse strains
      Data on mouse experiments
      Data on mouse tissues
    - Establishment of a mouse biobank
      Tissues of control animals
      Tissues of animals from long term experiments
  - Close cooperation with the CellBank at Medical University of Graz
    - Access to common cell lines
    - Development of new cell lines
    - Isolation and culture of primary cells
- Professor of Cell Biology:
  - Developing organ-on-a-chip systems in cooperation with the Technical University of Vienna (placenta) to be used as test systems for transfer of molecules (e.g. medications) across the placental barrier;
  - Testing and further developing predictive biomarkers for pregnancy pathologies;

Research and Training activities (related to 3R field)

Paul Jennings

Research activities

My main research focus is to understand the molecular processes involved in chemical induced perturbations, adaptation to- and recovery from these perturbations. To this end, I have been focusing on the following topics:

- Improved human renal *in vitro* models (eg. Renal – RPTEC/TERT1 and human induced pluripotent stem cell derived podocytes and proximal tubule cells)
- Mechanistic understanding using integrated omic approaches in carefully designed exposure scenarios (transcriptomics, proteomics, metabolomics and epigenetics)
- The understanding of how cells deal with stress and the delineation of stress response pathways, including oxidative stress (Nrf2), DNA damage (p53), hypoxia (HIF-1alpha) and the unfolded protein response.
- Chemical induced dedifferentiation and recovery after exposure
- *In vitro* biokinetic studies
- Integrating cheminformatics, kinetics and dynamics into computational systems toxicological models
- Collaboration with specialists to build tiered integrated approaches for testing and assessment (IATA) / integrated testing systems (ITS) – (eg. BBB, liver, lung, brain, heart, skin) which are regulatory relevant (i.e. built with application to Adverse Outcome Pathways)
- Understanding genetic diversity of dynamics and kinetics using iPSC.
- Development of clinically-translational mechanistic biomarkers (e.g. IL-19, HO-1 and LCN2)

Running projects:

- OpenRisk (RIA H2020) – Open e-Infrastructure to Support Data Sharing, Knowledge Integration and in silico Analysis and Modelling in Safety Assessment
- In3# (ITN H2020) – An integrated interdisciplinary approach to animal-free nanomaterial and chemical safety assessment.
- EUToxRisk (RIA H2020) – An Integrated European 'Flagship' Programme Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st century
- StemBANCC (IMI-1 – EFPIA / EU) – Stem cells for drug discovery
- PhytoTEAM (industry funded) – Toxicology Efficacy Absorption Metabolism Screening of plant extracts.

Recently completed (still working on):

- DETECTIVE (Seurat) – Cosmetics Europe / EU - identify, develop and evaluate relevant biomarkers and surrogate endpoints in vitro that can be used for safety assessments and repeated dose toxicity testing relevant for humans.
- Predict-IV – 7th Framework – Profiling the toxicity of new drugs: a non animal-based approach integrating toxicodynamics and biokinetics
- CarcinoGENOMICS – 6th Framework – Novel alternative method approaches in carcinogenicity and mutagenicity.

Training activities (3R related)

Masters/PhD Training program

- Alternatives to animal experimentation (3Rs replacement refinement and reduction) Innsbruck and Vienna – 15 to 30 h course
- Marie Curie In3 coordinator – extensive PhD training program developed to train 15 PhD students in a wide variety of aspects for animal free safety assessment (starts next year)

Safety Science Training – European Society of Toxicology

- Omic base technologies in in vitro toxicology – 1h lecture
- In vitro methods for testing genetic toxicity and carcinogenicity 1h lecture

CAAT Europe Training Academy – Two day work shop with frontal and hands on training

- "Kidney toxicity testing & best practices"
- Integrated and omics and biokinetics for understanding mechanisms of chemical induced nephrotoxicity
- Cell culture and *in vitro* toxicity training

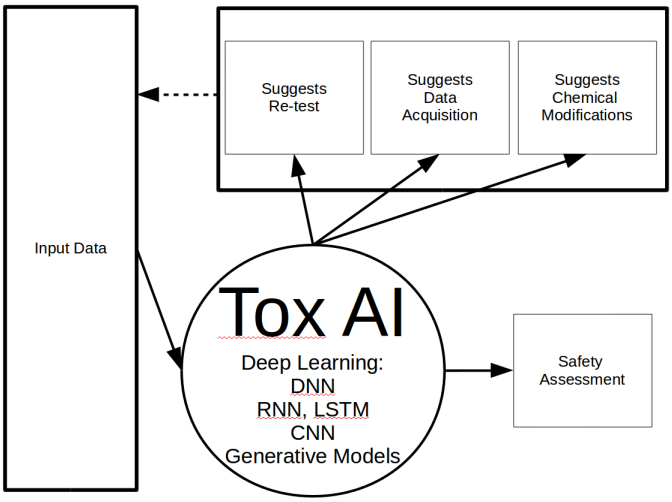
Günter Klambauer
Institute of Bioinformatics, Johannes Kepler University Linz
klambauer@bioinf.jku.at

Research activities

I develop computational models for prediction of biological effects of chemical compounds. These in-silico models are based on machine learning methods, such as Deep Learning. I have shown that Deep Learning is currently the machine learning method with the highest performance at modeling toxicity assays because it can naturally the multi-task setting [1]. Concretely, my research activities involve the following

- Algorithmic improvements of Deep Learning methods, novel machine learning methods
  - Deep neural networks [3]
  - Convolutional neural networks
  - Self-normalizing networks [5]
- Toxicity prediction based on
  - chemical descriptors (in-silico)
  - biological descriptors, e.g. imaging data
- Toxicogenetics modeling [2]
  - Include an individual's genetic features, e.g. CNVs [4], into the models

Research goals in toxicology: Development of an artificial intelligence for decision making in toxicology.



Source: G. Klambauer

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Actual reserach activities and interests- Environmental Toxicology Group

Head Siegfried Knasmüller
Inst. of Cancer Resrach, Inner Medicine I,MUW,
Vienna

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Our interest concerns the development of new in improved vitro assays for routine testing of genotoxins and also for acute toxicity assessment of chemicals. It is known that the currently used „classical" cell lines do not reflect the metabolism of chemicals due to lack of xenobiotic drug metabolizing enzymes; therefore exogenous activation mixtures are added to „mimic" the biotransformation of toxins. At present the in vitro assays lead to many „false positive" therefore animal experiments are conducted which could be avoided by better(i.e. more reliable) cells. It is known that certain human derived liver cells line retained to a certain extent the activities of phase I and phase II enzymes which activate/detoxify genotoxic carcinogens but no targeted evaluation has been conducted. Therefore we tested a large number of such lines in experiments with repre-sentatives of different classes of DNA reactive carcinogens in genotoxicity experiments. Most cell types were found to be non responsive, but promising results were obtained with some of them .The latter lines were further characterized in regard to their karyotype,p53 status, growth kinetics and enzymatic characteristics which are relevant for their use in routine tests . One highly promising line is currently further evaluated in regard to its suitability for gentoxicity texting with a panel of model compounds (ECVAM list) . Furthermore attempts are be made in collaboration with a Slovenian partner to insert transcription factors which may lead to a further improvement of their usefulness for the detection of mutagenic carcinogens.

EUROPEAN COMMISSION
DIRECTORATE-GENERAL JOINT RESEARCH CENTRE
Directorate F - Health, Consumers and Reference Materials
Unit F.3 - Chemical Safety and Alternative Methods, incorporating the European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM)

A short overview of activities and research interests in the field of in Vitro & in Silico Approaches to Safety Assessment of Chemicals and Environmental Media

Brigitte Landesmann

I work for the European Commission's Joint Research Centre (JRC) in Ispra, Italy.

The Chemical Safety and Alternative Methods Unit incorporates the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM), which is legally anchored in Directive 2010/63/EU on the protection of animals used for scientific purposes. Our unit promotes the scientific and regulatory acceptance of non-animal tests which are of importance to biomedical sciences, through research, test development and validation, and the establishment of a specialised database service. Our main activities relate to the PREDICTION of adverse outcomes or disease, the VALIDATION of new *in vitro* methods and the DISSEMINATION of knowledge of alternative approaches

The current research and development activities in the field of alternatives predominantly focus on the integration of a variety of testing and non-testing methods such as in vitro technologies, bioinformatics and computational toxicology into Integrated Approaches to Testing and Assessment (IATA). IATA are based on Adverse Outcome Pathways (AOP), a mechanistic knowledge framework that describes a logical sequence of causally linked events at different levels of biological organisation, which follows exposure to a chemical and leads to an adverse effect in humans or the environment.

I am mainly involved in the generation, dissemination and application of AOP knowledge. In the context of the FP7 SEURAT-1 research initiative I developed an AOP to liver fibrosis which is among the first AOPs that were endorsed by the OECD and published on their website. I collaborate with the OECD AOP KB (AOP knowledge base) development team, as a member of the OECD AOP training group I organised and presented several AOP training courses (for EFSA, Eu-ToxRisk collaborators) and currently I am organising an international JRC summer school on alternative approaches for chemical risk assessment.

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Participant profile overview

Arno Lukas
emergentec biodevelopment GmbH

Arno Lukas is co-founder and managing partner of emergentec biodevelopment GmbH and has a track record of more than 15 years in successful realization and exploitation of life science IT solutions, with translational research expertise spanning from discovery to pre-clinical drug and biomarker development.

He accomplished his PhD degree as Biochemist at the department of Theoretical Chemistry and Structural Biology of the University of Vienna, Austria and worked as visiting scientist at the F.R.A.E.-C.N.R. Institute, Bologna, Italy, the Humboldt University of Berlin, Germany and the Los Alamos National Laboratory, New Mexico, USA.

Arno Lukas is member of the management team of national and large scale European Union R&D projects and has authored and co-authored more than 40 publications and book contributions in the area of computational & systems biology, toxicology and Life Sciences IT.

Area of activity

At emergentec we focus on an integrative, big data concept: molecular annotation and models serving as composite of the molecular process landscape characterizing the pathophysiology of clinical phenotypes. We on this basis evaluate biomarkers (as proxies for the molecular process landscape), drug targets (for addressing relevant aspects of the molecular pathophysiology), and drug Mechanism of Action (for matching disease pathophysiology and a drug's molecular effect). Our lead platform e.valuation embeds fit-for-purpose analysis workflows for biomarker, target and drug assets - adding precision from translational research to clinical development.

Our technology allows the comparison and analysis of molecular models of physiological states or drug mechanisms of action, which may include states leading to or representing toxicity. Therefore we are driving the development and evaluation of general, theoretical concepts to characterize physiological states of in vitro and in vivo models and concepts to improve toxicity/efficacy extrapolation and respective biomarker use from in vitro / in vivo results to human.

Keywords: Decision support and scoring technology; marker, target and drug evaluation; hypothesis generation; molecular network models of diseases and drug mechanism of action

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Research activities

Main research interests focus on molecular mechanisms of food constituents including natural constituents as well as potential contaminants. Mechanistic studies address issues on application-limiting toxicity of bioactive food constituents with special emphasis on cellular responses to modulators of redox-sensitive pathways (Nrf2/ARE) and potential interference with topoisomerases, DNA repair and potential mutagenicity. Current studies aim to unravel combinatory effects of naturally occurring mycotoxin mixtures and the possible protective role of polyphenols.

In silico approaches are applied for prediction of structure-activity relationships e.g. for identification of hormonally active contaminants.

Available test systems to assess:

- In vitro test battery for bioactivity and toxicity profiling in mammalian cells (tumorigenic versus non-transformed cells)
- Metabolic profiling
- Estrogenicity testing in vitro
- Topoisomerase interference, impact on DNA integrity and repair
- Impact on redox-sensitive pathways
- Toxicological profiling of emerging mycotoxins
- Test strategies for chemical mixtures
- Impact of biomechanical stimulation of cells on toxicity
- Immunomodulatory properties of test compounds in vitro

Qualification and Teaching Activities:

Prof. in Food Chemistry at the University of Vienna; European Registered Toxicologist; Current chair of the Austrian Society of Toxicology; Member of the BfR (Federal Institute for Risk Assessment, Berlin, Germany) committee for contaminants and other undesirable substances in the food chain; Member of the Senate Commission of the German Research Foundation (DFG) for Food Safety (SKLM).

Teaching in food chemistry and toxicology in different curricula (chemistry, nutritional sciences etc) at the University of Vienna. In addition, courses are given in the postgraduate Toxicology Course at the Medical University Vienna as well as the Food Toxicology Course of the German Society of Toxicology at the University of Kaiserslautern. Starting in autumn 2017, I will teach Food Toxicology as a Visiting Professor at the University of Parma.

Dr. Thomas Mohr
CEO of ScienceConsult – DI Thomas Mohr KG

staff scientist/scientific coworker at the Medical University of Vienna – Institute of Cancer Research.

The research focus/focus of activity of ScienceConsult is

- computational biology with a focus on network analyses of -omics data. However, our expertise encompasses analysis of -omics data from generating and/or acquiring raw data, preprocessing and QC, up to generation 4 and 5 methods such as Signaling Pathway Impact Analysis and Weighted Gene Coexpression Analysis. We also try to connect genomic traits with transcriptomics, proteomics data and clinical traits. The strength of ScienceConsult is bridging biology and bioinfromatics which is greatly facilitated by our experience in both the wet as well as the dry-lab.
- Development of in vitro test systems to replace in vivo tests resp. de novo development of in vitro tests. In this field we are involved in the project „Biorelation“ chaired by the ofi Technologie & Innovations GmbH and the EUREKA Project „Airclean“ chaired by ScienceConsult.
  - Biorelation aimes at replacing in vivo sensitation tests with in vitro tests employing a battery consisting of HPLC, dendritic cell activation and stress response activation. ScienceConsult provided as third party expertise in establishing cell systems, FACS analysis and ELISA techniques.
  - AirClean aims at testing filter systems for their biological effectiveness by investigation of the effect of particles which have passed the filter on the gene expression of bronchial epithelial cells. This project combines in silico database analysis to uncover potential biomarkers with cell culture to validate them.
- My tasks with the university encompass providing computational biology support for the Institute of Cancer Research. My research, however, focuses on the application of network based methods (e.g. WGCNA) to investigate differences between tissue and tumour types (e.g. normal and tumour associated endothelial cells in hepatocellular carcinoma) and to determine key driver genes and regulatory networks for pathophysiological processes (e.g. inflammation and angiogenesis). Within this task we utilize publicly available databases such as ArrayExpress, Gene Expression Omnibus and The Cancer Genome Atlas as well as self generated data.

BIOLOGICAL BARRIER GROUP

Biological barriers in health and disease

Biological barriers are responsible for the maintenance of the homeostasis of the surrounded tissue. They represent interfaces between body fluids and tissues and are responsible for a proper communication between organs. The functionality of biological barriers is very often altered during diseases. For example, in the case of the blood-brain barrier (BBB) – protecting the central nervous system (CNS) – changes were found for a plethora of CNS-related diseases (Alzheimer's disease, stroke, traumatic brain injury, multiple sclerosis, epilepsy, pain, brain tumour, Parkinson disease, bacterial and viral infections, ALS, hypertension, lysosomal storage diseases, …). Currently, it is discussed that these functional alterations are causally linked to disease progressions, and therefore several therapeutic strategies targeting biological barriers are under development. These changes can also modulate the pharmacokinetics and pharmacodynamics of active compounds (chemicals, environmental toxins, drugs). Therefore, it is essential to work with validated physiological as well as validated disease models already in early safety and preclinical studies (the ill, not the healthy patient will be treated). We can provide access to e.g. human BBB models with *in vivo* like phenotype and compare results obtained with models of other species (e.g. murine) in order to account for species differences.

COMPETENCIES: We offer over 14 years experience with models of biological barriers (e.g. lung, kidney, oral mucosa, blood-brain barrier), in detail:

- Models based on mouse, porcine or human cells (primary, immortalized, hiPS-based)
- drug transport studies
- nanoparticle, liposomal or protein transport studies
- effects of compounds on functional barrier properties (paracellular, transport, metabolic barrier) and toxicity studies
- corresponding molecular analysis (mRNA, protein level) and screening technologies (epigenetics, NGS,..)
- static Transwell models for short-term studies
- dynamic hollow-fiber models for long-term, chronic studies
- disease models for e.g. inflammation, cerebral ischemia
- development of novel disease models, crossvalidation with *in vivo* models

If you are interested, we would like to invite you to contact us to speak about further details and possibilities.

Best regards,

WINFRIED NEUHAUS, Priv.-Doz. DI Dr.
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Molecular Diagnostics
AIT Austrian Institute of Technology GmbH
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Environment Agency Austria / Martin Paparella

The Environment Agency Austria (EAAu) is the expert authority of the federal government in Austria for environmental protection and environmental control. It provides i.a. the **PARERE and OECD/EU Testing methods Coordinator** on behalf of the Austrian ministry: The Directive on the protection of animals used for scientific purposes (2010/63) requires the dedication of Member States to the development and validatation of in vitro & in silico approaches and an improved communication between scientists and regulators in order to achieve suitable progress (Article 47). The European network for "preliminary analysis of regulatory relevance of new alternative methods (PARERE)" shall support this aim and, more specifically, the communication between Austrian regulators and the European Reference Laboratory, the European Centre of the Validation of Alternative Methods (EURL ECVAM). Martin Paparella develops and coordinates, upon receipt of EURL ECVAM requests, the Austrian regulatory PARERE opinions on European validation needs and priorities. Furthermore, Martin Paparella also develops and coordinates Austrian national opinions on the standardization of eco- and human toxicological test guidelines for the OECD Test Guidelines Programme and the European Testing Methods Regulation. He also is the current Vice Chair (2015-2018) of the OECD Working Group of National Coordinators for the Test Guidelines Programme (WNT), which is the group responsible for final decisions on a scientific level. Martin Paparella also teaches aspects of in vitro toxicology within the postgraduate university course for toxicology at the Medical University of Vienna and within a course on environmental management at the FH Technikum Wien. EAAu is also responsible for regulatory (animal and in vitro) data requirements in the context of the European Registration, Evaluation and Authorisation of Chemicals (REACH Regulation) and the European Regulation of Biocidal products.

Martin Paparella makes contributions to the science of in vitro method development and validation within international expert working groups, at the moment with a focus on carcinogenicity. He has special interest in uncertainty analysis and is a leading expert in international scientific work on the uncertainties and complexities of regulatory standard animal testing and assessment approaches, aiming inter alia to understand and agree on the limitations of their use as reference data for new approaches. Furthermore, this work aims at recognizing how adversity may be defined within the in vitro tissue, cellular and sub-cellular context, such that it increases the probability of an adverse outcome at individual or population level. Considering all uncertainties and complexities, also standard animal tests cannot provide more than this. Taking a long term view, this work shall ultimately support the evolution of concepts of regulation, e.g. by creating a new in vitro mode of action GHS toxicity class and potency subcategories, covering critical exposure levels for an increasing list of toxicity pathways, rather than the actual GHS toxicity classes per se and e.g. by testing a large number of chemicals for a limited number of relevant and well characterized toxicity pathways rather than testing a few chemicals within black box animal tests.

Apart from conducting in-depth scientific research in the field of carcinogenicity, Martin Paparella aims at expanding his work into other fields including ecotoxicity. Furthermore, he aims at better supporting work on in vitro and in silico science at the science regulatory interface as well as at the educational improvement of skills and knowledge in the regulatory arena. This workshop serves to identify the interests and the possibilities in this area for reaching these goals in Austria and beyond.

Paparella M., Colacci A., Jacobs M.N. 2017. Uncertainties of testing methods: What do we (want to) know about carcinogenicity? ALTEX https://doi.org/10.14573/altex.1608281

Jacobs, M. N., Colacci, A., Louekari, K., Luijten, M., Hakkert, B. C., **Paparella, M**., Vasseur, P. 2016. International regulatory needs for development of an IATA for non-genotoxic carcinogenic chemical substances. http://www.altex.ch/resources/altex_2016_4_359_392_Jacobs11.pdf

Paparella M., Daneshian M., Hornek-Gausterer R., Kinzl M., Mauritz I., Mühlegger S. Uncertainty of Testing Methods – What Do We (Want to) Know? Food for Thought. 2013. Alternatives to Animal experimentation 30, 111-124. http://www.altex.ch/resources/raltex_2013_2_131_144_Paparella1.pdf

Bal- Price A., Crofton K.M., Leist M., Allen S., Arand M., Buetler T., Delrue N., FitzGerald R.E., Hartung T., Heinonen T., Hogberg H., Hougaard-Bennekou S., Lichtensteiger W., Oggier D., **Paparella M.**, Axelstad M., Piersma A., Rached E., Schilter B., Schmuck G., Stoppini L., Tongiorgi E., Tiramani M., Monnet-Tschudi F., Wilks M.F., Ylikomi T., Fritsche E. 2014. Creating a Developmental Neurotoxicity Testing (DNT) Roadmap for Regulatory Purposes. Archives of Toxicology 2015 89(2):269-87.

Research activities and interests at the Department of Biochemical Engineering

Dominik Rünzler
Head of Department Biochemical Engineering

The Department is responsible for the research focus *Tissue Engineering and Molecular Life Science Technologies* at the University of Applied Sciences Technikum Wien.

Research Projects based on *in vitro* methods

- City of Vienna Project "Endocrine Disruptors in Water": establishment of research methods for detecting estrogenic effects in e.g. waste water samples
- FFG COIN *New*Tissue: New concepts for 3D cell culture using biomaterials as scaffolds
- City of Vienna Competence Team *reac*Tissue: mechanical stimulation of 3D cell-constructs in bioreactors for muscle, cartilage and tendon tissue
- FFG COIN *Disease*Tissue: development of disease models for e.g. osteoarthritis using bioreactor for mechanical stimulation
- City of Vienna Competence Team *signal*Tissue: signal transduction/mechanotransduction in 3D cell culture for optimized control of functional tissue regrowth

Research Infrastructure and Established *in vitro* Assays

- *Danio rerio* wild-type AB in zebrafish culture system Bench-top ZebTec: Fish Embryo Acute Toxicity (FET) Test OECD 236
- DanioVision System for tracking of zebra fish larvae and data evaluation using EthoVision: Zebrafish larvae mobility assay
- *Daphnia magna* mobility assay (OECD 202) using DanioVision/EthoVision System for tracking
- *RT-gillW1* cell culture: 2D & 3D cytotoxicity assays (Alamar Blue, Cell Cycle Analysis, Calcein AM)
- *Biomphalaria glabrata* freshwater gastropod as bioindicator for endocrine disruptors assessed by qPCR of ovipostatin and yolk ferritin as possible biomarkers
- *Freshwater Alga, Growth Inhibition Test (OECD 201)*

Dr. Klaus R. Schröder
Dipl.-Biol.

Method Development:

During my employment at Henkel KGaA & Co.KG and Phenion GmbH & Co.KG, Düsseldorf, I was engaged in the development of acute toxicity assays. These dealt with the establishment of tissue equivalents for eye and skin irritation as well as skin sensitisation. In the field of genotoxicity testing my group developed a COMET and micronucleus assay with epidermal and full thickness skin equivalents, as well as a micronucleus assay using the Hen's Egg Test (HET) system.

Several test systems were validated within the industry research network of the cosmetic body "Cosmetics Europe".

At BioMed-zet Life Science GmbH, Linz, I was engaged in the development of in vitro assays for R&D purposes of different industrial sectors. My group combined different alternative assays of different complexity, from cell culture to 3D tissue culture to HET.

Body activities:

At Cosmetics Europe I was member the expert groups skin irritation and sensitisation, eye and systemic toxicity, setting up research programmes, that cover interests of the cosmetics industry. This work was combined with similar activities at the EPAA.

In my position as member of the expert group "Alternativmethoden zum Tierversuch" of the German Ministry of Education and Research (BMBF) I was reviewing applications dealing with all aspects of 3Rs.

I consulted the ethics commission of the Austria Wirtschaftsservice, aws, concerning appropriate combination of cell based assays and animals studies in "preseed" and "seed financing" applications.

I am member of the scientific advisory board of the Berlin-Brandenburg research platform BB3R.

Recent interest:

Recently I founded the start-up company "NP Life Science Technologies KG". Our interest is the development and production of 3D scaffolds for applications in tissue engineering and regenerative medicine. We are focussing on the anorganic polymer polyphosphazene.

NP Life Science Technologies KG
Hafenstrasse 47-51
4020 Linz
Klaus.schroeder@nplifescience.com

In vitro and *in silico* approaches within the curriculum of the master´s program – actual activities and interests

Barbara Wetzer, Deputy Program Director
Technisches Umweltmanagement und Ökotoxikologie
University of Applied Sciences Technikum Wien

The Master program covers two different topics: Ecotoxicology and Environmental Management.

Actual Activities:

Several Courses with *in vitro* approaches, a.o.:

- Environmental Chemistry: overview and introduction
- Aquatic Ecotoxicology (incl. Lab Course): standard mammalian cell culture techniques and epithelial RTgill W1 cell line from rainbow trout
- Terrestric Ecotoxicology (incl. Lab Course)
- Epigenetics in Ecotoxicology
- Endocrine Disruptors (incl. Lab Course): T47D-KBluc luciferase reporter assays for estrogens

Courses with *in silico* approaches, (no details):

- Current topics in Ecotoxicology: QSAR
- Specific Environmental Chemistry: QSAR

Interests:

- implement new approaches, technologies, methods,
- dissemination of current research
- train students according to actual demands in research, regulatory and policy
- give master students the possibility to do their master theses in collaboration with different institutions

Research and Training activities (related to 3R field)

Doris Wilflingseder
Division of Hygiene and Medical Microbiology, Medical University of Innsbruck

Research activities

Doris Wilflingseder's research focus is on studying host/pathogen (HIV-1, fungi, bacteria) interactions including various aspects of opsonization, which is found in the body during acute and chronic phase of infection. We are interested in infectious synapse formation and signalling events after binding of differentially opsonized pathogens to dendritic cells (DC), macrophages, epithelial cells and the impact of the opsonization pattern on induction of a proper immune response during infection. To study these interactions in a more ´*in vivo*´-like situation, we are interested in setting up relevant and standardisable 3D models, i.e. lymph node or respiratory models. Thus, Doris Wilflingseder has contributed to following topics:

- Role of the opsonization pattern on DC modulation
- Role of T cell polarization after exposure to differentially opsonized HIV-1
- Molecular characterization of dendritic cell function following exposure to differentially opsonized HIV-1 or fungi
- Impact of co-infections (HIV-1, chlamydia) on antigen-presenting capacity of DCs
- Establishment of a perfused 3D respiratory system comprised of NHBE/SAE cells, dendritic cells and macrophages
- Establishment of various DC subsets from $CD34^+$ umbilical cord blood cells

Running projects

- Stand-alone FWF project (P24598)
- PhD Program in Molecular Cell Biology and Oncology (MCBO) at the Medical University of Innsbruck
- CD Laboratory of Invasive Fungal Infections (Cornelia Lass-Flörl)

Training activities
Masters/PhD Training program

- 021201Modul 2.12: Infektion, Immunologie und Allergologie
- 030801Klinische Mikrobiologie
- 041025Immunological Methods – Innate Immunity
- 041501Molecular Cell Biology and Oncology

Overview on publications

- orcid.org/0000-0002-5888-5118
- 40 SCI publications, h-index=18, https://scholar.google.at/citations?hl=de&user=c6_ibSoAAAAJ&view_op=list_works&sortby=pubdate
- 2 book chapters

Other activities

- Deputy head of the Austrian Society for Alternative Biomodels (RepRefRed Society, T3Rs, http://www.reprefred.eu/en/welcome.html)
- Reviewer for MRC UK, ARS Journal, Journal of Immunology, ALTEX, Intervirology
- Board member of the Austrian Society of Allergology and Immunology (ÖGAI)
- Member of the habilitation committee (Medical University Innsbruck)

Pharmacoinformatics Research Group, Department of Pharmaceutical Chemistry, University of Vienna

Barbara Zdrazil, Gerhard F. Ecker

Following a **holistic pharmacoinformatic approach** we combine multi-dimensional annotation, structural modelling of proteins, structure-based drug design, chemometric and in silico chemogenomic methods, statistical modelling and machine learning approaches to **develop predictive computational systems** for **transporters and ion channels**. The validation and optimisation of the obtained *in silico* models by **strong links to experimental groups** is an integral part of these activities. Furthermore, we aim at developing **tools for *in vitro* to *in vivo* translation** and for **toxicity prediction**.

Current toxicity-related projects that we are involved in include:

The eTOX project aimed to develop **a drug safety database from the pharmaceutical industry legacy toxicology reports and public toxicology data;** innovative in silico strategies and novel software tools to better predict the toxicological profiles of small molecules in early stages of the drug development pipeline; **IMI project**; duration: **Jan 2010 – Dec 2016**

"**An Integrated European 'Flagship' Programme Driving Mechanism-based Toxicity Testing and Risk Assessment** for the 21st century" – is a European collaborative project funded by the EU Framework Programme for Research and Innovation, **Horizon 2020**; **Jan 2016 – Dec 2021**

"Translational quantitative systems toxicology to improve the understanding of the safety of medicines". The philosophy underlying this proposal is to build on existing PK-PD models that have a physiological basis and define systemic as well as specific organ/cell exposure to drug and metabolites in a holistic fashion, and to develop translational quantitative systems-based toxicological models for each of the four organs that are the focus of this call; IMI2 project; duration: Jan 2017 – Dec 2021

ANNEX 2: AIMS FOR IMPROVING THE APPLICABILITY OF IN VITRO AND IN SILICO APPROACHES AS DISCUSSED IN PREVIOUS INTERNATIONAL WORKSHOPS

The aims for an improved applicability of *in vitro & in silico* approaches were recently discussed at other international workshops as well – such as the ICATM[31] Workshop on October 4-5 2016 in Ispra/Italy and the PARERE/ESTAF and EUToxRisk collaboration Workshop on November 8-11 2016 in Ispra/Italy, and the European Commission Scientific Conference on non-animal approaches - the way forward on December 6-7, 2016 in Brussels.

In the following a summary is given by Martin Paparella, who attended these workshops in his role as Austrian PARERE and OECD WNT representative and who presented these results at the workshop in Linz by way of introduction to the discussion of common AIVIS aims and potential steps forward on the second half day.

specific aims for *in vitro*/*in silico* science:

- improve QIVIVE (quantitative *in vitro* to *in vivo* extrapolation modelling to translate *in vitro* concentrations to corresponding *in vivo* exposure doses)
- characterize and improve *in vitro* metabolism
- scientifically review uncertainties and complexities of regulatory standards for *in vivo* approaches, *inter alia* with the aim to understand and agree on limitations of their use as reference data for new approaches
- study and discuss how adversity may be defined conceptually in the cellular and sub-cellular context (in such a way that it increases the probability of an adverse outcome at individual or population level)
- review and assemble available knowledge on mechanisms of action and systems biology (such as – but not exclusively – AOPs) to provide scientific understanding and explanations of why and how we are using non-animal methods
- develop a new baseline, i.e. a new definition of reference data, against which new methodologies can be validated
- pursue – as long term goals – (multi-)organ-on-a-chip technology and other biotechnologies, e.g. high-throughput gene expression microarrays, as potential complementary approaches

specific aims for *in vitro*/*in silico* approach based regulation:

- evolve the way we regulate:
  - e.g. create a new *in vitro* mode of action GHS toxicity class and potency subcategories, covering critical exposure levels for an increasing list of toxicity pathways, rather than the actual GHS toxicity classes *per se* and
  - e.g. test a large number of chemicals for a limited number of pathways versus the current approach of testing a few chemicals in black box animal tests (for a high number of unknown pathways, including irrelevant ones and missing relevant ones)
- standardize and internationally harmonize *in vitro*/*in silico* approaches by integrating several *in vitro*/*in silico* methods (in contrast to just standardizing/harmonizing individual methods)

[31] International Cooperation on Alternative Test Methods; https://eurl-ecvam.jrc.ec.europa.eu/glossary/glossary?search_text=ICATM

- develop a new agreement between regulators and industry on acceptable risk based on new *in vitro*/*in silico* approaches
- support collaboration between regulators and scientists
- harmonize data requirements internationally, also between different regulatory fields (especially important for the uptake of new approaches by industry)
- ensure that new approaches are not more expensive than standard animal testing
- ensure that the methods are available for use in several regions of the world
- improve risk communication: zero risk is impossible – whatever type of method is used
- improve communication with the public (seems to be sceptical or not informed about new scientific possibilities)
- stimulate cultural change and political will
- adapt technical guidance and legal requirements to new approaches
- provide the resources necessary for all these developments
- consider when we will be ready to define ‘sunset dates’ for the phasing out of animal testing with respect to the specific regulatory needs (e.g. classification or limit value derivation for the various regulatory fields)

ANNEX 3: WORKSHOP AGENDA

Feb 16, afternoon: presentations and round table discussion

12:30h – 13:00h	**registration**	
13:00h – 13:30h	**welcome and introductory notes:**	
	13:00 – 13:05 – Sepp Hochreiter: Host, Head of institute	
	13:05 – 13:10 – Martin Wimmer: BMLFUW	
	13:10 – 13:15 – Steering Committee: Günter Klambauer, Paul Jennings, Maria Fürhacker, Martin Paparella	
	13:15 – 13:30 – Introduction to the Workshop: Martin Paparella	
13:30h – 15:30h	**short presentations on activities and research interests** (5 min talk, 5 min Q&A)	
	chairs: Paul Jennings, Günter Klambauer	
	13:30 – 13:40	Brigitte Landesmann
	13:40 – 13:50	Martin Paparella
	13:50 – 14:00	Paul Jennings
	14:00 – 14:10	Barbara Zdrazil
	14:10 – 14:20	Günter Klambauer
	14:20 – 14:30	Thomas Mohr
	14:30 – 14:40	Arno Lucas
	14:40 – 13:50	Doris Marko
	14:50 – 15:00	Vito Francic
	15:00 – 15:10	Johanna Gostner
	15:10 – 15:20	Doris Wilflingseder
	15:20 – 15:30	Johannes Grillari
15:30 – 16:00h	**coffee break**	
16:10 – 17:30h	**short presentations continued**	
	chairs: Maria Fürhacker, Martin Paparella	
	16:10 – 16:20	Berthold Huppertz
	16:20 – 16:30	Veronika Ehrlich
	16:30 – 16:40	Maria Fürhacker
	16:40 – 16:50	Dominik Rünzler
	16:50 – 17:00	Klaus Schröder
	17:00 – 17:10	Barbara Wetzer
	17:10 – 17:20	Gloria Rose
17:20 – 18:00h	**round table discussion on perspectives for synergies and collaboration**	
	chairs: Paul Jennings, Maria Fürhacker, Günter Klambauer, Martin Paparella	

19:00	social dinner in the city: Klosterhof

Feb 17, morning, discussion with pin-board

09:00h – 9:10h	Winfried Neuhaus (since not present on Feb 16: short presentation on activities and research interests (5 min talk, 5 min Q&A)
09:10h – 09:40h	wrap up from yesterday: Martin Paparella, Paul Jennings, Maria Fürhacker, Günter Klambauer
09:40h – 10:15h	small discussion groups to collect • common long to short term goals for scientific work on *in vitro & in silico* approaches to safety assessment • ideas for practical steps towards these goals
10:15h – 10:45h	coffee break
10:45h – 12:45h	presentation of results from small groups on pin-board, integration of results and discussion *chairs: Martin Paparella, Paul Jennings, Maria Fürhacker, Günter Klambauer*
12:45h – 13:00h	next steps, closing remarks Martin Paparella, Paul Jennings, Maria Fürhacker, Günter Klambauer

ANNEX 4: LIST OF AIVIS PLATFORM PARTNERS AND THEIR COMPETENCES

Surname	First name	Scientific Institution	mail	full contact as provided by e-mail	Key words for competence, link to individual homepage, if available
Achleitner	Bettina	BMWFW Federal Ministry of Science, Research and Economy	bettina.achleitner@bmwfw.gv.at	**Bettina Achleitner, MSc.** Federal Ministry of Science, Research and Economy Referat WF/V/3b (Gentechnik und Tierversuchswesen) Phone: +43 (1) 531 20-7115 (Durchwahl) bettina.achleitner@bmwfw.gv.at Rosengasse 2-6 1010 Wien, Austria	• www.bmwfw.gv.at/tierversuche • www.bmwfw.gv.at/gentechnik
Ecker	Gerhard	University of Vienna	gerhard.f.ecker@univie.ac.at	**Univ-Prof. Dr. Gerhard F. Ecker** University of Vienna Pharmacoinformatics Research Group Department of Pharmaceutical Chemistry Phone: +43-1-4277 55110 gerhard.f.ecker@univie.ac.at pharminfo.univie.ac.at Althanstraße 14 1090 Vienna, Austria	• in silico transporter profiling • data mining, data integration • machine learning for toxicity prediction • toxicological read across • http://livertox.univie.ac.at www.toxphacts.com http://pharminfo.univie.ac.at/people/gerhard-ecker/
Ehrlich	Veronika	Shire	veronika.anna.ehrlich@shire.com	**Veronika Ehrlich, PhD, ERT** Shire Regulatory Toxicology Non-clinical Development Phone: +43-1-20100-2471700 Mobile: +43-664-8120320 veronika.anna.ehrlich@shire.com DC-Tiwer, Donau-City-Str.7 1220 Vienna, Austria www.shire.com	• Regulatory Toxicology • In vitro Toxicology • 3Rs • Nonclinical Development • Toxicological Risk Assessment • Teaching (Postgraduate Toxicology Course Vienna)
Erdem	Zeynep	Austrian Agency for Health and Food Safety	zeynep.erdem@ages.at	**Dr. Zeynep N. Erdem, MscTox** Inst. for Plant Protection Products Division of Toxicology Phone: +43 50555 33469 Fax: +43 50 555 33404 zeynep.erdem@ages.at Austrian Agency for Health and Food Safety Spargelfeldstrasse 191, A-1220 Wien, Austria	• Regulatory toxicology, Risk assessment of plant protection products • Computational toxicology • Cancer research

Surname	First name	Scientific Institution	mail	full contact as provided by e-mail	Key words for competence, link to individual homepage, if available
Falb-Naderer	Olivia	BMLFUW Bundesministerium für Land- und Forstwirtschaft, Umwelt und Wasserwirtschaft	Olivia.falb-naderer@bmlfuw.gv.at	**Mag. Olivia Falb-Naderer** Federal Ministry of Agriculture, Forestry, Environment and Water Management Division V/5, Chemicals Policy and Biocides Stubenbastei 5, 1010 Vienna T +43 1 71100 612339 olivia.falb-naderer@bmlfuw.gv.at bmlfuw.gv.at	
Francic	Vito	Medical University of Graz	vito.francic@medunigraz.at	**Vito Francic, MSc** Medizinische Universität Graz Universitätsklinik für Innere Medizin Endokrinologie-Laborplattform Klin. Abt. für Endokrinologie und Diabetologie Auenbruggerplatz 15 A-8036 Graz tel. +43-316-385-12383 fax. +43-316-385-13428	
Fürhacker	Maria	University of Natural Resources and Life Sciences, Vienna	maria.fuerhacker@boku.ac.at	**Maria Fürhacker**, **Ao.Univ.Prof. Dipl.-Ing. Dr.nat.techn.** Universitätsdozent/in Institut für Siedlungswasserbau, University of Natural Resources and Life Sciences, Industriewasserwirtschaft und Gewässerschutz (SIG) Phone: +43 1 47654-81112 Mobile: +43 699 19221487 maria.fuerhacker@boku.ac.at Muthgasse 18 1190 Wien, Austria	• Micropollutants and EDS - effect based tools, standard setting, risk assessment, implementation of standards into wastewater and drinking water management • https://forschung.boku.ac.at/fis/suchen.person_uebersicht?id_in=67&menue_id_in=101&sprache_in=de
Gazsó	André	Austrian Academy of Sciences	agazso@oeaw.ac.at	**Dr. André Gazsó** Austrian Academy of Sciences (ÖAW) Institute of Technology Assessment (ITA) Phone: +431 51581-6578 agazso@oeaw.ac.at Strohgasse 45/5 1030 Vienna, Austria	• Projekt NanoTrust: http://www.oeaw.ac.at/ita/projekte/nanotrust/ueberblick
Gostner	Johanna	Medical University of Innsbruck	johanna.gostner@i-med.ac.at	**Dr.rer.nat. Johanna Gostner** Medical University of Innsbruck Medical Biochemistry Center for Chemistry and Biomedicine +43-(0)512-9003-70122 johanna.gostner@i-med.ac.at Innrain 80 6020 Innsbruck, Austria	• bioactivity and analytics of volatile organic compounds (VOC), natural products and synthethic chemicals; • immunometabolism with focus on aromatic amino acids and neopterin • https://www.i-med.ac.at/imcbc/staff_doc/johanna_gostner.html

Surname	First name	Scientific Institution	mail	full contact as provided by e-mail	Key words for competence, link to individual homepage, if available
Grillari	Johannes	Evercyte GmbH	Johannes.Grillari@evercyte.com	**Assoc. Prof. DI Dr. Johannes Grillari** University of Natural Resources and Life Sciences Department of Biotechnology, Phone: +43 1 47654 6231 johannes.grillari@boku.ac.at www.grillarilabs.at Muthgasse 18 1190 Vienna, Austria	• http://www.evercyte.com/ • ABC3Rs (Austrian Biomimetic Centre 3Rs) Lead – a newly BMWFW-funded infrastructure platform consisting of Medical University Innsbruck (MUI, Doris Wilflingseder), Medical University Graz (MUG, Rinner Beate) and BOKU, Vienna (Grillari Johannes), which aims at establishing innovative animal-free research approaches (infection and tumor models, iPSCs) based on novel technologies and teaching young scientists about 3Rs, homepage under construction
Haslinger	Alois	BMWFW Federal Ministry of Science, Research and Economy	alois.haslinger@bmwfw.gv.at	**MR Dr. Alois Haslinger** Federal Ministry of Science, Research and Economy Referat WF/V/3b (Gentechnik und Tierversuchswesen) alois.haslinger@bmwfw.gv.at Rosengasse 2-6 1010 Wien, Austria	• www.bmwfw.gv.at/tierversuche • www.bmwfw.gv.at/gentechnik
Hauzenberger	Ingrid	Environment Agency Austria	ingrid.hauzenberger@umweltbundesamt.at	**Mag. Ingrid Hauzenberger, MSc (Tox)** Umweltbundesamt GmbH Chemicals and Biocides Phone: +43-(0)1-313 04/3405 Fax: +43-(0)1-313 04/3211 Spittelauer Lände 5 1090 Wien, Austria http://www.umweltbundesamt.at	• POP Risk assessment committee (POPRC) Member (Stockholm Convention); • Flexible Member in European Biocidal Products Committee – Working Group (BPC-WG) • Regulatory Toxicology for Chemicals & Biocides
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Klambauer	Günter	Johannes Kepler University Linz	klambauer@bioinf.jku.at	**Dr. Mag. Günter Klambauer** Johannes Kepler University Linz Institute of Bioinformatics Computer Science Building (Science Park 3) Altenberger Str. 69, A-4040 Linz, Austria klambauer@bioinf.jku.at	• Algorithmic improvements of Deep Learning methods, novel machine learning methods: deep neural networks, convolutional neural networks, self-normalizing networks • Toxicity prediction based on: chemical descriptors (in-silico), biological descriptors, e.g. imaging data • Toxicogenetics modeling: include an individual's genetic features, e.g. CNVs, into the models • Development of an artificial intelligence for decision making in toxicology • http://www.bioinf.jku.at/people/klambauer/

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Toxicological science has been increasingly focused on animal-free and mechanism-based test methods. Society and European legislation explicitly demand support for this evolution towards the realization of animal-free safety assessment. During the *"First Austrian Science Coordination Workshop for In Vitro & In Silico Approaches to Safety Assessment of Chemicals and Environmental Media"* 27 Austrian experts from science and public authorities presented and discussed individual research interests and developed common long term goals and practical approaches: *The "Austrian Platform for In Vitro & In Silico safety science"* (AIVIS) was founded to foster science collaboration and work at the science-regulatory interface, improve offerings of education, strengthen science communication and to intensify and coordinate funding in Austria.

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