



Highlight report: Launch of a large integrated European in vitro toxicology project: EU-ToxRisk

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Abstract The integrated European project, EU-ToxRisk, proudly sees itself as “flagship” exploring new alternative-to-animal approaches to chemical safety evaluation. It promotes mechanism-based toxicity testing and risk assessment according to the principles laid down for toxicology for the twenty-first century. The project was officially launched in January 2016 with a kickoff meeting in Egmond aan Zee, the Netherlands. Over 100 scientists representing academia and industry as well as regulatory authorities attended the inaugural meeting. The project will integrate advances in in vitro and in silico toxicology, read-across methods, and adverse outcome pathways. EU-ToxRisk will continue to make use of the case study strategy deployed in SEURAT-1, a FP7 initiative ended in December 2015. Even though the development of new non-animal methods is one target of EU-ToxRisk, the project puts special emphasis on their acceptance and implementation in regulatory contexts. This €30 million Horizon 2020 project involves 38 European partners and one from the USA. EU-ToxRisk aims at the “development of a new way of risk assessment.”

The program intends to drive the required paradigm shift in toxicology toward animal-free, mechanism-based integrated approaches for chemical safety assessment (Leist et al. 2008; NRC 2007; Rovida et al. 2015a, b; Sauer et al. 2015; Scholz et al. 2013). Bennard van Ravenzwaay coordinating the contribution of BASF as a consortium partner pointed out during his inaugural lecture that “this project is rather about regulatory risk assessment than about methods.”

The focus of this 6-year project lies on repeated dose systemic toxicity involving liver, kidney, lung, and the nervous system, as well as on developmental/reproductive toxicity (Hengstler et al. 2012). Particular attention will be paid to the establishment of pragmatic read-across procedures incorporating mechanistic and toxicokinetic knowledge as well as hazard and risk assessment strategies for chemicals with minimal background information (Basketter et al. 2012; Carrio et al. 2015; Patlewicz et al. 2014; van der Burg et al. 2015). EU-ToxRisk will use its resources in order to establish in 3 years’ time a novel read-across approach in Europe, especially fit for evaluating REACH compounds. A quantitatively structured read-across system will use existing data as well as providing new information, including data from high-throughput transcriptomics (Pallocca et al. 2016; Rempel et al. 2015; Grinberg et al. 2014; Jennings et al. 2013; Schaap et al. 2015), high-content imaging of cell stress pathways (Wink et al. 2014; van Vliet et al. 2014; Jennings 2013) in vitro systems (Godoy et al. 2013; Krug et al. 2013), and mathematical modeling to extrapolate to the in vivo situation (Ghallab et al. 2016; Schliess et al. 2014). Moreover, EU-ToxRisk intends to establish a biological read-across approach, adding biological descriptors to toxicological and chemical descriptors (EU-ToxRisk 2015; Zhu et al. 2016). Due to the potential of chemical and biological read-across approaches and

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the importance of good practice guidelines to this field, EU-ToxRisk's first workshop on February 26 in Brussels presented the new "Good Read-Across Practice guidance" (Ball et al. 2016) and other relevant initiatives among stakeholders.

EU-ToxRisk coordinator Bob van de Water from the University of Leiden introduced the mission. The overall EU-ToxRisk mission is to develop a quantitative adverse outcome pathway (qAOP) concept for regulatory purposes integrating relevant *in vitro* and *in silico* technologies required for the assessment of chemical safety in humans (Leist et al. 2014; Luechtefeld et al. 2015; Muller et al. 2015; Jennings 2013). The concept of EU-ToxRisk was commented by Magdalini Sachana (OECD), an external advisor of the project with the words: "I was delighted to see that adverse outcome pathways (AOPs) and integrated approaches to testing and assessment (IATA) play a central role in almost all the work packages of the project (Tollefsen et al. 2014; Bal-Price et al. 2015; Gocht et al. 2015). I look forward receiving more information and outputs from the project."

EU-ToxRisk already works on more than ten case studies, and the consortium partners will begin evaluating the predictivity of a battery of assays soon, using data-rich chemicals. Later, case studies will be established for less characterized new classes of compounds. The consortium has already established a task force, which will critically assess the robustness and applicability of the proposed human cell model systems for these case studies. "The case studies with selected compounds will remain focused on adverse human consequences, i.e., provide relevant concentration–response models, and tipping points of homeostasis in order to predict safe exposure levels" as to Carl Westmoreland (Unilever—EU-ToxRisk partner) (Shah et al. 2015). "The importance of building toxicokinetics and toxicodynamics within EU-ToxRisk for weight of evidence approaches in risk assessment" was emphasized by Derek Knight representing ECHA (Berggren et al. 2015; Daston et al. 2015; Gocht et al. 2015). Regarding the case studies, Thomas Steger-Hartmann from Bayer HealthCare commented as an external advisor of the project: "The well-organized and conducted kickoff meeting prepared the stage for an ambitious project that has the potential to change existing safety assessment paradigms. The backbone of the project plan are the case studies. A big part of the success of the project will depend on the thoughtful selection of test compounds, assay systems, and benchmark data for evaluation" (Jennings et al. 2014).

Russell Thomas from the US EPA stated that "I was impressed with the enthusiasm of the scientists involved in the project and the willingness to move beyond basic research and to apply their science to practical, but

important questions facing society in testing chemicals for human safety. There appears to be multiple points of intersection between the EU-ToxRisk project and the research being undertaken by the U.S. EPA (Shah et al. 2015; Bouhifd et al. 2015; Kleinstreuer et al. 2014) in the National Center for Computational Toxicology (Liu et al. 2015; Huang et al. 2014). Collaboration at these points of intersection would benefit both organizations and allow us to achieve much more together than in isolation. I look forward to working with and advising the EU-ToxRisk project. It is poised to have a significant impact on the way we evaluate chemicals for human safety."

The excellent start of the project was helped by extensive preparations by the scientific steering team and the coordinator of the project already in 2015, in order to optimize and refine information flow and work flow of the project. Due to the latter, a remarkable positive and enthusiastic atmosphere during the meeting was notable which is rather exceptional for a kickoff meeting of such a large-scale project. The spirit of all participants of all fourteen work packages was remarkably optimistic and stimulating. If the project keeps up this level of dynamics and thrives, a lot is to be expected for the near future and the coming 6 years.

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