

<u>HEALTH.2010.4.2.9-1:</u> <b>Optimisation of current methodologies and development of novel methods to achieve functional differentiation of human-based target cells <i>in vitro</i></b>	AcuteTox	ARTEMIS	carcinoGENOMICS	COMICS	ESNATS	EXERA	InVivo PharmaForInviT ■	InVivo PharmaForInviT ■	LIINTOP	MEMTRANS	NanoTEST	OpenTox	OSIRIS	PREDICT-IV	PREDICTOMICS	ReProTec	SCARLET	Sensitiv	TOXDROP	Start-Up/CONAM◆
<b><u>a) Optimize stem cell technology for human-based target cells for toxicology</u></b>																				
<i>In vitro</i> differentiation of stem cells into cells that are of toxicological relevance			•		•	•	•		•						•	•				
Reproducibly generating organ-specific cells			•		•	•	•								•			•		
Scale-up for producing the quantities for high-throughput analysis			•		•	•	•				•					•				
High yield of progenitor cell types expressing biomarkers <i>in vivo</i> .			•		•	•	•													
Handling that efficiency declines as these progenitor mature differentiated cells.			•		•	•	•				•							•		
Improving intermediate stages to increase yields of mature, organ-cells.			•		•															
Sequential exposure of growth factors for reflecting ( <i>in vivo</i> ) embryogenesis			•		•															
Intermediate cell types (transit-amplifying cells) obtaining sufficient cells for large-scale.			•				•													
<b><u>b) Refinement of cell culture systems for long-term toxicity testing</u></b>																				
The maintenance of the differentiated phenotype, functional level, for long-term toxicity.			•		•	•	•		•						•	•				
Counteract dedifferentiation <i>in vitro</i> based on mimicking physiological <i>in vivo</i> situation.			•			•									•					
Culturing on extracellular matrix, co-cultivation another cell type			•			•	•		•						•	•		•		
Culturing with physiologically relevant chemical compounds to the cell culture medium.			•			•	•								•	•		•		
<b><u>c) Exploitation mechanistically-driven methods to control cellular differentiation</u></b>																				
Interfering posttranslational modifications for functional differentiation long-term					•				•											
Genetic and epigenetics for differentiation process at the most upstream regulatory level					•				•		•									
Exploiting “-omics” technology					•		•		•					•	•	•		•		
Altering expression profile of microRNA species, determinants of differentiation.									•											
◆ Dissemination task of results – no research but service – applicable for all – also networks for partners ■ Instruments for communication with the stakeholders and to facilitate transfer of methods from inventions to commercially available methods. Dissemination																				



<p><b><u>HEALTH.2010.4.2.9-3:</u></b>  <b>Establishment of endpoints and intermediate markers in human-based target cells with relevance for repeated dose systemic toxicity testing.</b></p>	AcuteTox	ARTEMIS	carcinoGENOMICS	COMICS	ESNATS	EXERA	InVivoPharma/ForInVitox ■	LIINTOP	MEMTRANS	NanoTEST	OpenTox	OSIRIS	PREDICT-IV	PREDICTOMICS	ReProTec	SCARLETT	Sensitiv	TOXDROP	Start-Up/CONAM ◆
<p><b><i>a) Functional parameters as predictive signals of human long-term toxicity</i></b></p>																			
<p>Functional endpoints, the most relevant parameters of the physiological <i>in vivo</i> situation of the organism, highly relevant to assess the toxicological effects and a refinement of the “-omics”-based markers (see 3.b).</p>			•	•	•	•				•			•	•	•		•		
<p>Identify functional organotypic parameters of human long-term toxicity at the cellular level.</p>			•							•			•	•	•				
<p><b><i>b) “-omics”-based markers as predictive signals of human long-term toxicity</i></b></p>																			
<p>Determination and evaluation of genomic with strong relevance for human toxicity</p>	•		•	•	•	•	•	•					•	•	•		•		
<p>D:o proteomic</p>					•	•	•						•	•	•		•		
<p>D:o metabolomic</p>			•		•	•	•						•	•	•				
<p>D:o system biological markers</p>			•		•	•				•			•	•	•				
<p>Testing markers for their predictive capacity for systemic and long-term toxicity</p>	•		•		•	•							•	•					
<p></p>																			
<p><b><i>c) Integration of markers for enhancement of human long-term predictive capacity</i></b></p>																			
<p>Valid test battery with combinations of “-omics”-based and functional parameters to enhance predictive capacity of screening systems.</p>	•		•	•	•			•		•			•	•	•		•		
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<u>HEALTH.2010.4.2.9-4:</u> Computational modelling and estimation techniques	AcuteTox	ARTEMIS	carcinoGENOMICS	COMICS	ESNATS	EXERA	Invitroheart/Vitrocellomics	LIINTOP	MEMTRANS	NanoTEST	OpenTox	OSIRIS	PREDICT-IV	PREDICTOMICS	ReProTec	SCARLETT	Sensitiv	TOXDROP	Start-Up/CONAM◆
<b>a) Threshold of toxicological concern for the safety assessment of cosmetic ingredients</b>																			
Improvement /adaptation necessary before applied to cosmetic ingredients											•		•	•					
Development and validation of toxicological (e.g. carcinogenicity) databases			•	•				•		•	•	•							
New databases based on classified as human carcinogens, probably or likely human carcinogens, and for non-cancer toxicological endpoints			•	•							•	•							
<b>b) Computational chemistry in the safety assessment of cosmetic ingredients</b>																			
(Q)SAR and read-across methods incorporating kinetic and metabolic studies										•	•	•		•	•				
If <i>in silico</i> approaches identify packages that can be supported over the long-term.										•	•			•	•				
Grouping approaches, could be potentially considered for ingredients of cosmetics.										•	•	•							
<b>c) Predicting the dose at the target level upon long-term exposure</b>																			
Tools for kinetic modelling to predict target organ concentrations and the accumulation of chemicals and their metabolites in the context of exposure.				•				•	•	•			•		•				
Develop kinetic modelling that allows the effective <i>in vitro</i> concentration to the target organ level <i>in vivo</i> to be extrapolated.				•				•	•				•		•				
<b>d) PBPK modelling in the safety assessment of cosmetic ingredients</b>																			
PBPK modelling to integrate <i>in vitro</i> and <i>in silico</i> data to (ADME) models for decision making and risk assessment.										•	•	•	•	•					
Integrating physicochemical, <i>in vitro</i> , human and animal data and computational methods to develop a complete model of ADME for a particular compound										•	•	•	•	•		•			
No observable (adverse) effect concentration (NO(A)EC) as a measure of toxicity derived from <i>in vitro</i> repeated dose systems and PBPK predict a corresponding <i>in vivo</i> concentration-dose.										•	•			•					
Markers to support the application of the TTC														•		•			
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<b>HEALTH.2010.4.2.9-5: Systems biology for the development of predictive causal computer models</b>	AcuteTox	ARTEMIS	carcinoGENOMICS	COMICS	ESNATS	EXERA	In VitroPharma/ForinviT ■	In VitroPharma/ForinviT ■	LIINTOP	MEMTRANS	NanoTEST	OpenTox	OSIRIS	PREDICT-IV	PREDICTOMICS	ReProTec	SCARLET	Sensitiv	TOXDROP	Start-Up/CONAM ◆
<b>a) Identification and analysis of pathways for long-term toxicity by genetic tools</b>																				
Genetic tools “across species” for target and response pathways of the molecules			•				•					•								
Accessible for the “-omics”-based technologies			•				•									•				
Genetic tools for simple (yeast) closer to human pharmacokinetics, and human cell lines.			•				•					•								
D:o for complex ( <i>C. elegans</i> , <i>D. melanogaster</i> and zebrafish, modified mice.																				
Panel of selective compounds and the challenge of the different systems and dosages			•									•					•			
Identification target pathways with the long-term toxicity endpoints			•				•					•			•	•				
<b>b) Use of “-omics”- based techniques to identify mechanistic pathways involved in longterm toxicity effects</b>																				
“-Omics”- for sequencing, quantitative proteomics and NMR/MS.			•				•		•											
Validation technologies and protein over- and under-expression of selected compound																•				
Development /application of data integration tools			•									•								
Computational analysis for the different technologies.			•				•					•								
Identification of response pathways for the long-term toxicity effects			•													•				
<b>c) Development of causal predictive computer models for long-term toxicity effects</b>																				
Specific tissues, specific developmental stages or, ultimately, the entire organism												•								
Model systems integrate experimental data on different levels of cellular information from sub-topic 5.b and the selective information in sub-topic 5.a			•				•					•								
Modelling methodology can include quantitative and qualitative methods			•									•	•							
Approaches highly automated and able to access large network information			•									•	•							
Models large-scale, so strategy computing intensive simulations, e.g. grid computing.																				
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<b>HEALTH.2010.4.2.9-6: Integrated data analysis and servicing</b>	Start-Up/CONAM◆	TOXDROP	Sensitiv	SCARLETT	ReProTec	PREDICTOMICS	PREDICT-IV	OSIRIS	OpenTox	NanoTEST	MEMTRANS	LIINTOP	In Vivo Pharma/ForinviT■	In vitro heart/ Vitrocellomics	EXERA	ESNATS	COMICS	carcinoGENOMICS	ARTEMIS	AcuteTox
<b>a) Establishment of a dedicated web-based 'data warehouse'</b>																				
Centralised compilation of information and data of JRI	•		•						•	•										
Links with relevant public databases			•						•	•										
Projects of JRI - raw and processed data into this data warehouse			•						•	•										
Data analysed and outcome integrated into models for predicting repeated dose toxicity			•						•	•										
Feedback to projects to steer experiments allowing improvement iteratively			•						•	•										
Organised a sustainable source for toxicological research beyond JRI			•						•	•										
<b>b) Establishment of a database of selected model compounds</b>																				
High-quality repeated-dose toxicity <i>in vivo</i> data from animal studies and humans.			•						•	•										
cosmetic ingredients, industrial chemicals, pharmaceuticals, plant protection, biocides			•						•	•										
Selected model compounds, SOPs for data quality control, processing and analyses	•		•						•	•										
Compounds for training or validation, in collaboration with the cosmetic industry			•						•	•										
<b>c) Establishment of a repository for the selected model compounds</b>																				
Chemicals repository established and maintained beyond JRI									•											
<b>d) Setting up a cell and tissue bank for in vitro toxicity testing</b>																				
Establishment of a bank of cells, cell lines									•											
stem cells and stem cell lines																				
tissues																				
◆ Dissemination task of results – no research but service – applicable for all – also networks for partners ■ Instruments for communication with the stakeholders and to facilitate transfer of methods from inventions to commercially available methods. Dissemination																				