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Computational modelling of neural tube closure defects
ABSTRACT #458

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Closure of the caudal neural tube is a critical event that occurs early in development, around day 27 of human gestation. Failure of neural tube closure results in severe birth defects, such as spina bifida. These neural tube defects (NTD) are among the most prevalent human congenital malformations, which warrants specific attention in chemical safety assessment. Computational models of biological processes are likely to revolutionize chemical safety assessment in the near future. Such models can be used to predict the effect of chemical-induced gene expression changes and provide a template for establishing quantitative adverse outcome pathway networks. This study aims to develop an in silico model of the human neural tube closure, which will be applied to predict chemical-induced NTDs. By extensively mining the developmental biology and toxicology literature, we first created a physiological map of human neural tube closure. Based on the physiological map, we built a multicellular agent-based model using CompuCell3D. The constructed physiological map depicts the all-trans-retinoic acid (ATRA) related molecular pathways linked to the various cell types in which they occur, and their morphogenetic consequences, that lead to closure of the neural tube. The morphogenetic events driven by gene expression changes are visualized by the computational model. We simulated in silico the complex biological process of neural tube closure, in order to demonstrate the feasibility of this approach. At a later stage in the project, the computational model will be applied to predict chemical-induced changes in gene expression and cell characteristics. The predictions of the model will be validated using a set of dedicated in vitro assays in conjunction with existing knowledge on in vivo developmental neurotoxicity. Such computational models may ultimately provide an alternative in silico approach for chemical safety assessment without the use of animals.

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ASSESSING A BATTERY OF IN SILICO MODELS AS PREDICTION TOOL FOR COMPOUNDS EXERTING REPRODUCTIVE HEALTH EFFECTS
ABSTRACT #485

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Given the high attention to endocrine disrupting chemicals, there is an urgent need for the development of rapid and reliable approaches for the screening of large numbers of chemicals with respect to their endocrine disruption potential [1]. This study aimed at the assessment of the correlations between the prediction results of a battery of in silico tools and the reported observed adverse effects from in vivo reproductive toxicity studies. We used OpenVirtualToxLab (OVTL) software and the EndocrineDisruptome online tool [2,3] to model the binding affinities to nuclear receptors of 17 pesticides, 7 of which classified as reprotoxic substances under CLP. Then, we aligned the results of the in silico modelling with data from ToxCast assays and in vivo reproductive toxicity studies. Results from in vivo studies conducted according to OECD 415 and/or 443 modified with the aim of refinement and reduction of use of animals were retrieved from the archive of our GLP laboratory. Reproductive toxicity can be caused by various mechanisms; however, in this study, we demonstrated that the use of a battery of in silico tools for molecular modelling of binding to nuclear receptors can be useful for the prediction of potentially reprotoxic compounds. Detailed results will be provided in the poster.