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Kidney-based in vitro models for toxicity testing

Jennings, P.

published in

Toxicology Letters
2018

DOI (link to publisher)

[10.1016/j.toxlet.2018.06.030](https://doi.org/10.1016/j.toxlet.2018.06.030)

document version

Publisher's PDF, also known as Version of record

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citation for published version (APA)

Jennings, P. (2018). Kidney-based in vitro models for toxicity testing. *Toxicology Letters*, 295(Supplement 1), S7-S8. [CEC4-02]. <https://doi.org/10.1016/j.toxlet.2018.06.030>

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CEC3-05**Predictive Tools and Databases for Toxicokinetics**

J.C. Madden

Liverpool John Moores University, School of Pharmacy and Biomolecular Sciences, Liverpool, UK

Physiologically-based kinetic (PBK) models are used to estimate internal exposure to chemicals and therefore contribute to a more realistic prediction of true potential to elicit a biological response. As such, PBK models are important for industry and regulators in the pharmaceutical, personal care product, food safety and other sectors. The models are predicated on the concentration-time curves of chemicals in blood and organs of interest. *In vivo* measurement is highly animal intensive therefore New Approach Methodologies, such as computational models that can leverage existing data, are more favourable. Predictive tools and data available to support the development of PBK models have expanded significantly in recent years, accompanied by a proliferation of measured data that can be used to validate models. Examples of resources include the KinPar database (<https://eurl-ecvam.jrc.ec.europa.eu/validation-regulatory-acceptance/toxicokinetics>), the online chemical database with modelling environment (oCHEM; <https://ochem.eu/home/show.do>) and the enzyme information system (www.brenda-enzymes.org/). The QSAR Toolbox (<https://www.qsartoolbox.org/>), developed to assist the risk assessment process, is particularly noteworthy. The Toolbox serves not only as a useful resource for the rational grouping of chemicals to enable read across predictions of activity/toxicity, but also as a significant repository of relevant databases. There is also a facility to import in-house databases into the Toolbox to assist analysis. An overview of data sources available to support the development and validation of PBK models, their usefulness and reliability will be presented.

<https://doi.org/10.1016/j.toxlet.2018.06.027>

CEC3-06**RVis: a freely available modelling platform**

G.D. Loizou

Health and Safety Laboratory, Health, Buxton, UK

The widespread adoption and application of physiologically based pharmacokinetic (PBPK) modelling in product development and safety assessment of chemicals has been hampered by criticism that these models are data hungry, resource intensive, complex and require high levels of mathematical expertise and programming skills. The use of PBPK models would be enhanced by the availability of a user-friendly, transparent and independently auditable, free-to-use platform for running models and analysing model structure and output. To address this need an application called RVis, is being developed using the open source syntax, R. The motivation for this tool is to provide an intuitive, user-friendly, freely available modelling platform for biologically based, quantitative safety and risk assessment of chemicals that ultimately would be useful for the full replacement of animal testing. The latter is an ambitious aim which requires the ability to predict equivalent human oral, dermal or inhalation target tissue concentrations consistent with concentration-response relationships of xenobiotics determined in alternative to animal systems. The prediction of human *in vivo* doses from *in vitro* human cell-line-based systems requires that the PBPK models are exercised in “reverse dosimetry” mode. RVis will include a module for this purpose which will deploy the most appropriate statistical techniques

for dose reconstruction. The general aim of RVis is to shift the emphasis away from the need for high levels of mathematical expertise and programming skills to the understanding of the biology of toxicity and disease underpinning chemical safety and risk assessment. Such a tool should make this powerful approach more readily accessible to safety toxicologists and risk assessors.

<https://doi.org/10.1016/j.toxlet.2018.06.028>

CEC 4 – Organ-specific *in vitro* modelling: state-of-the-art**CEC4-01****Liver-based *in vitro* models for toxicity testing**

M. Vinken

Vrije Universiteit Brussel, In vitro Toxicology, Brussels, Belgium

Because of its unique location and function in the organism, the liver is a frequent target for systemic toxicity. Therefore, a lot of attention has been paid and is still being paid to the establishment and further optimization of liver-based *in vitro* models that can assist in predicting hepatotoxic potential of chemicals. As such, they can be divided in 2 main classes, namely liver-derived *in vitro* models and stem cell-derived *in vitro* models. The former include whole isolated perfused livers, liver slices, isolated hepatocytes, liver cell lines and subcellular liver fractions. These liver-derived *in vitro* models will be discussed in the first part of this presentation, including an overview of their advantages, disadvantages and applications. Focus will be put on primary hepatocytes and their cultures, which are considered as the gold standard in the field of liver-based *in vitro* modelling. In particular, strategies to increase their longevity and hence to maintain their functional differentiated phenotype in culture will be presented. In the second part of the presentation, a brief overview of stem cell-derived *in vitro* models will be provided, namely hepatocyte-like cells differentiated from human adult stem cells or human embryonic stem cells by exposure to specific cytokines and growth factors as well as human induced pluripotent stem cells.

<https://doi.org/10.1016/j.toxlet.2018.06.029>

CEC4-02**Kidney-based *in vitro* models for toxicity testing**

P. Jennings

Vrije Universiteit Amsterdam, Division of Molecular and Computational Toxicology, Amsterdam Institute for Molecules, Medicines and Systems, Amsterdam, Netherlands

Each kidney consists of approximately 1 million nephrons at birth. De novo nephrogenesis does not occur after birth and there is no strong evidence suggesting that the adult kidney harbours resident stem cells. Thus, the kidney unlike the liver is not a highly rejuvenative organ, which is most likely an evolutionary compromise allowing the anatomical complexity required for high function and the maintenance of the very narrow margins required for whole body homeostasis. Indeed, the kidney is an extremely accomplished organ and can carry out 100% of its duties with only a fraction of the nephrons we are born with. However, we continually lose nephrons through-out life and will, all things being equal, eventually breach the renal functional reserve and enter end-stage-renal disease. Thus, anything that contributes to chronic renal failure has the potential to seriously curtail life quality and life-span. Aging populations and associated risk factors such as diabetes and heart disease, have pushed chronic kidney disease (CKD) incidence to

unprecedented levels (currently at 10% of the European population). Due to the role of the kidney in elimination of waste products, renal cells, particularly the proximal tubule, will internally process the majority of drugs and chemicals, and thus often have higher concentrations of these compounds than any other cell in the body. Compounds that injure renal epithelial cells can initiate and/or accelerate CKD. In this lecture, I will discuss the various human *in vitro* models employed in *in vitro* nephrotoxicity testing, including primary cells, cell lines and induced pluripotent stem cell models.

<https://doi.org/10.1016/j.toxlet.2018.06.030>

CEC4-03

Lung-based *in vitro* models for toxicity testing

S. Constant

Epithelix, Plan-les-Ouates, Switzerland

The main function of the human airway epithelium is to generate sterile atmosphere in the alveolar region where the gas exchange occurs. As the first line of defence against airborne pathogens, the airway epithelium acts as key barrier through mucociliary clearance and innate immune defence mechanisms. Airway epithelium is also an important immuno-regulator through production of key messengers and physical interactions with immune cells. Upon activation, respiratory epithelial cells react by producing pro-inflammatory cytokines, chemokines and metalloproteinases to recruit and activate immune cells such as neutrophils, basophils, or to initiate the adaptive immunity via dendritic cells. Interest in the use of 3D reconstituted human *in vitro* tissues (ALI cultures) is increasing in recent years for the study of respiratory diseases such as Asthma, Chronic Obstructive Pulmonary Disease (COPD), Bacterial and viral infections, etc.

Genetic and epigenetic diversity in ALIs with single donors allow stratification and patient specific profiling in toxicology and drug testing. On the other hand, ALIs generated with a mixture of cells from several individuals give a snapshot of global reaction of a small population when exposed to a chemical compound.

This talk will describe the *in vitro* upper and lower respiratory tract models currently available to simulate the human lung epithelial tissue barrier. Several applications of *in vitro* reconstituted ALI models in inhalation toxicity assessment will be discussed: (i) acute, long-term and chronic testing strategies including static or dynamic exposures; (ii) mucosal inflammation assessment; (iii) trans-epithelial permeability of xenobiotics; (iv) impact on mucociliary clearance and (v) goblet cell hyperplasia monitoring.

<https://doi.org/10.1016/j.toxlet.2018.06.031>

CEC4-04

Stem cell-based *in vitro* models: state-of-the-art tools to predict drug-induced tissue injury in humans

J. De Kock

Vrije Universiteit Brussel, In Vitro Toxicology, Jette, Belgium

The fact that the detection of drug toxicity is often not accurate and frequently occurs only late during the drug development process is of major concern for the pharmaceutical industry and jeopardizes the potential marketing of new chemical entities. Besides affecting human health, this also leads to a significant loss of resources and time for the pharmaceutical industry. One of the major reasons for this failure is that the safety of new potential drugs is still evaluated in animals or animal-based cell lines. However, efforts

at improving the predictability of drug-induced tissue injury in humans are rising due to the rapidly advancing field of human stem cell research. Human target cells for screening and assessment of adverse drug effects in humans can now be generated using pluripotent and multipotent stem cells as detailed *in vitro* differentiation protocols are established for almost all cell (sub) types. The introduction of state-of-the-art gene editing tools such as CRISPR/Cas9 in stem cell research provides a technology platform to mimic specific genetic polymorphisms or diseases in a dish. In addition, stem cell-based *in vitro* models can be used to evaluate adverse drug effects during the differentiation process thereby mimicking human developmental toxicity. The latter provides a major advantage over any other non-stem cell-based model. Ultimately, it will be possible to develop personalized toxicology to determine inter-individual susceptibility to adverse drug reactions at any stage of development and in health and disease.

<https://doi.org/10.1016/j.toxlet.2018.06.032>

CEC4-05

Three-dimensional models for *in vitro* toxicity testing

A.C. Gutleb

LIST, ERIN, Belvaux, Luxembourg

Complex 3D *in vitro* coculture systems are valuable tools to study biological processes at biological barriers or in a tissue in 3D orientation in a more realistic way than in the classic mono-cell type and mono-layer systems. Such 3D systems allow for example direct cell-cell interaction, may allow for cell migration, etc. that all may affect cellular responses. Existing 3D *in vitro* coculture models have been established based on stemcells, primary cells and cell lines using transwell inserts or 2D and 3D scaffolds that again influence the biological responses. Overall such models are expected to provide responses more closely resembling effects observable *in vivo*. In combination with modern systems biology approaches 3D *in vitro* co-culture systems are the next step to further replace *in vivo* experiments for example in drug development, hazard assessment and mechanistical toxicity studies as these models allow to follow transport across barriers, cell-cell communication but also to study indirect exposure effects.

<https://doi.org/10.1016/j.toxlet.2018.06.033>

CEC4-06

Beyond the Chip: Development and application of a micro-physiological flux analyzer

Y. Nahmias^{2,1}

¹ *Tissue Dynamics, Jerusalem, Israel*

² *The Hebrew University of Jerusalem, Bioengineering, Jerusalem, Israel*

Organ-on-chip technology aims to replace animal toxicity testing, but thus far demonstrated few advantages over traditional methods. Current methods to evaluate toxicity rely on end-point assays measuring tissue damage and cell death, resulting in limited kinetic and mechanistic information. We present the Tissue Dynamics platform capable of maintaining vascularized 3D liver, cardiac, and neural tissues for over a month *in vitro*. Tissues acquire physiological structure, physiological activity and show complex metabolic zonation. Tissue-embedded metabolic sensors for oxygen, glucose, lactate and glutamine permit the real-time quantification of intracellular fluxes and tissue level function. Change in metabolic function is the first indication of physiological stress, preceding any