Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Toxicology

The virtual human in chemical safety assessment

Aldert H. Piersma, Jan van Benthem, Janine Ezendam, Yvonne CM. Staal and Anne S. Kienhuis

Abstract

This article reflects on possibilities for the application of emerging developments in artificial intelligence and machine learning in chemical safety assessment. A comparison is made between adverse outcome pathway networks and *in silico* neural networks. The issue of data sufficiency as to current knowledge of the toxicological mechanistic landscape as the basis for machine learning is discussed. Besides toxicology and chemistry, basic biology and physiology offer a wealth of information that can be used to develop the *in silico* virtual human. Several computational models for specific biological processes have been developed, providing proof of principle for *in silico* approaches for chemical safety assessment. In addition, *in silico* disease models are emerging that provide human-relevant approaches. Models need to be defined in a quantitative way and should also consider compound exposure and kinetics for determining which mechanisms in the body will be triggered. Ultimately, data from chemical information and dedicated *in vitro* assays, which inform about individual parameter effects, should be combined in the *in silico* model to predict safety at the level of the intact human. This is a significant challenge, and the stakes are high, but current rapid developments in complex computational modeling prompt investing in their application in chemical safety assessment.

Addresses

Centre for Health Protection, RIVM, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Corresponding author: Piersma, Aldert H (aldert.piersma@rivm.nl)

Current Opinion in Toxicology 2019, **15**:26–32

This review comes from a themed issue on **Risk assessment in toxicology**

Available online 3 April 2019

For a complete overview see the Issue and the Editorial

https://doi.org/10.1016/j.cotox.2019.03.009

Keywords

Virtual human, Chemical safety, Artificial intelligence, Adverse outcome pathway, *In silico*, *In vitro*, Computational modelling.

Neural networks and machine learning

Artificial intelligence is moving forward at accelerating speed, finding new applications in decision tools every day. A prequel hallmark of this development was the defeat in 1997 of the chess world champion Gari Kasparov by Deep Blue, a computer program based on brute calculating force [1]. It generated awareness that machines could do better than humans in mental performance. It took all the way to 2017 before in the Chinese game of Go the world champion Ke Jie was beaten by AlphaGo, a computer program relying on neural networks and machine learning [2]. Games have the characteristic that the rules are designed by humans and can be fully integrated in the computer model, providing all necessary background information, requiring brute calculating power to outperform humans. Software tools for facial recognition represent the next level of complexity, with biological information without preset rules as the input. It requires machine learning for which the success relies in part on the level of diversity of input faces rather than predefined rules as in games. Nevertheless, also on this subject, computers now equal or even outperform humans, opening many applications in a variety of sectors in society ranging from safety and security to medical diagnosis [3]. As an example, in the diagnosis of Turner syndrome by the analysis of facial features, a software tool did better than a group of human experts [4]. Similarly, in melanoma diagnosis, machine learning outperformed humans [5]. Remarkable applications have also been described in medical imaging for radiation therapy [6]. The question arises whether and to what extent chemical safety assessment can benefit from these innovative developments.

Neural networks and the toxicity pathway network

In the past half century, the toxicity assessment of chemicals in legal frameworks for chemical safety has largely relied on adverse health effect assessment in animal studies. More recently, the attention for the mechanisms involved in toxicity has been growing. Apart from ethical issues, this change was driven by increased awareness of species differences in mechanisms of action and kinetics, with the growing realization that adverse health effects in animals may not always correlate with those in humans be it in nature, sensitivity, or severity. The Toxicity Testing in the 21st Century report of the US National Academy of Sciences advocated the use of human data to predict human toxicity [7]. Similarly, it stated that animal-free assays for toxicity testing should preferably be based on the human biological system [8]. The combination of complementary assays

to predict all aspects of human toxicity requires their integration in a decision tool. Such a tool should be fed with data from a series of assays that represent rate-limiting steps in the system, leading to a toxicity prediction at the level of adverse health effects in the intact human. Mechanistic pathways combining key events that may be perturbed leading to an adverse health effect (adverse outcome pathways [AOPs]) are increasingly being described [9]. They can be integrated in a complex network that covers the selection of physiological pathways sufficient for integral toxicity assessment. Interestingly, AOP network graphics are highly reminiscent of schemes used to illustrate deep machine learning principles.

Comparing the illustrations in Figure 1, it requires little imagination to observe that molecular initiating events in the AOP network find their parallel in the deep learning input layer, key events do parallel hidden layers, and adverse outcomes do parallel the output layer. Of course, there is a fundamental difference when comparing concrete key events in the AOP network with the virtual hidden layer components in the machine learning network. However, this difference might actually represent the added value of deep machine learning. Combining concrete toxicological input information, integrated at a higher virtual level of complexity, providing concrete output on chemical safety might improve chemical hazard and risk assessment.

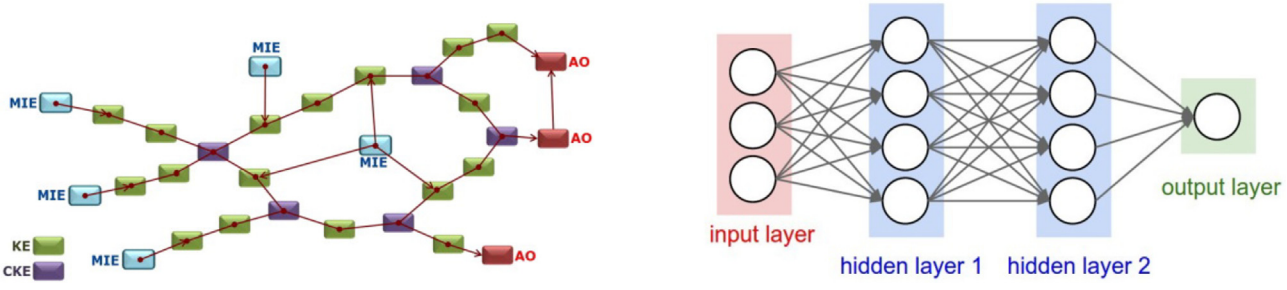
Data sufficiency for teaching the machine

For games such as chess and Go, the complete rules can be fed into the computer models, and their performance is merely dependent on brute calculating speed. Our knowledge of the underlying rules determining toxicity is limited, and this provides a challenge for *in silico* toxicity predictions. The performance of a computer model based on machine learning highly depends on the quality of its input. As an example, structure–activity modeling for predicting chemical toxicity has been shown to hit on this challenge [11]. Mechanistic knowledge on the perturbation of physiological pathways leading to adverse effects of chemicals is increasing rapidly. However, our current extent of mechanistic knowledge of toxicology may not suffice as yet for generating an integral model that sufficiently predicts all human toxicity quantitatively. Risk assessment decisions partly rely on expert judgment, for which the underlying reasoning is not always transparent and cannot easily be modeled. On the other hand, the number of toxic mechanisms is by definition finite [7], and some major mechanisms of toxicity can already be modeled *in silico*. The virtual embryo projects at the United States Environemntal Protection Agency (US EPA) provided initial proofs of principle that *in silico* models fed with molecular and cellular data from dedicated *in vitro* assays can mimic toxic mechanisms at the cellular level. Examples are palate fusion and blood vessel development [12–14]. For developing a reliable *in silico* toxicity prediction tool, the challenge is to combine all existing mechanistic knowledge in an inclusive quantitative network of interacting AOPs that covers physiological and toxicological knowledge to the extent necessary for reliable integrated toxicity prediction. Initiatives to describe such integrated mechanistic networks are underway [15–17]. Such activities are paramount for designing the *in silico* model and for the identification of data gaps in existing knowledge. It represents an iterative process of learning by doing.

Chemistry meets biology in toxicology

Chemistry and biology interact in a variety of ways with a variety of possible positive and negative consequences. Chemistry may enhance quality of life through consumer products, pharmaceuticals, and nutrition. Flame retardants enhance the safety of electric equipment, and preservatives enable the storage of food products for longer periods of time, protecting against decay. Chemistry has wide-ranging advantages in recovering health through pharmaceutical applications. Chemistry may also result in adverse health effects if potency, exposure levels, and timing combine to attain hazardous exposures. Given that toxicology is a meeting place between biology and chemistry, an *in silico* model for

Figure 1



Schematic AOP (left) and machine learning (right) networks. AOP scheme from Ref. [10]. AOP, adverse outcome pathway; MIE, molecular initiating event; KE, key event; CKE, critical key event; AO, adverse outcome.

toxicology should learn from chemistry knowledge as much as from the biology of the system. In the pharmaceutical industry, the connections between small molecules, disease states, and genes are integrated by the so-called connectivity mapping [18]. Expert systems for structure–activity relationships of chemicals have been developed for decades, and some have achieved high predictive values in specific chemical and toxicological niches [19–22]. In a recent publication, we described the development of quantitative ontology for toxicological risk assessment [23,24]. Ontology was defined herein as the quantitative network of AOPs that allows *in silico* modeling as a predictive tool for chemical toxicity. Three main areas of information feed ontology: human biology, chemistry, and toxicology. In toxicology, there is a wealth of existing knowledge, in humans, from animal studies, and increasingly from *in vitro* molecular, cellular, and organoid assays that can feed into the ontology. The integration of knowledge from these areas is the challenge for building an ontology of sufficient detail to feed the *in silico* model for reliable toxicity predictions.

The need for *in silico* toxicity modeling to be quantitative

As increasingly mechanistic pathways are being described and integrated, it is essential that the interactions among all steps in these pathways are well understood quantitatively and incorporated in the *in silico* model to underpin predictions of toxicity. The physiology of the intact individual continuously adapts to its ever-changing environment through a wealth of homeostatic processes, precluding that changes in, for example, temperature, humidity, and nutrition and also in xenobiotic exposures, resulting in adverse health effects. Integrated *in silico* models for toxicity prediction should encapsulate these homeostatic control mechanisms to provide reliable predictions of toxicity. This is a particular challenge if these models are to be fed with results from *in vitro* assays only. *In vitro* models by necessity represent limited biological domains, usually lacking the integral homeostatic control mechanisms that are crucial for discriminating adaptive from adverse changes. Therefore, an array of complementary *in vitro* assays should be available to provide comprehensive information on all rate-limiting key events on the road toward adverse health effects. The integration at the homeostatic control level is a challenge to be addressed in the *in silico* modeling.

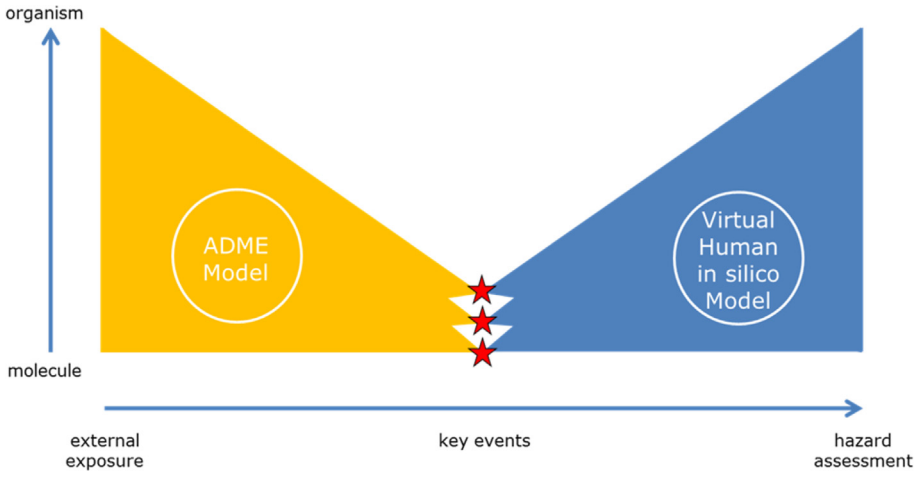
As an example, thyroid homeostasis is highly controlled in physiology. Its disruption can lead to serious adverse health effects, including metabolic disorders and disturbed prenatal brain development [25,26]. Effects on thyroid hormone production can be assessed in *in vitro* assays, but the interpretation of adversity thereof is not straightforward based on these tests only [27–29]. Moreover, the recent inclusion of thyroid hormone assessments in *in vivo* animal studies for regulatory safety assessment has again prompted the discussion on how to interpret statistically significant changes in one hormone in the absence of other changes in thyroid homeostasis and without observed adverse health effects [30,31]. Quantitative *in silico* models for thyroid homeostasis are increasingly being described [25,32]. They both illustrate the extent of the challenges we face in building the virtual physiological human and provide proofs of principle that such *in silico* approaches for studying perturbations are feasible.

The need for quantitative *in silico* modeling not only pertains to toxicodynamics, leading from initiating event at the molecular level to the adverse outcome in the individual but also similarly relates to the preceding toxicokinetics, leading from external exposure of the individual to the arrival (as to timing and dosing) of the compound at the target tissue site(s), where toxicity can be initiated at the molecular level [24,33]. Kinetics and dynamics are equally important aspects of toxicity and should both be modeled quantitatively for integral toxicological safety assessment (Figure 2).

Toward the virtual human in toxicological safety assessment

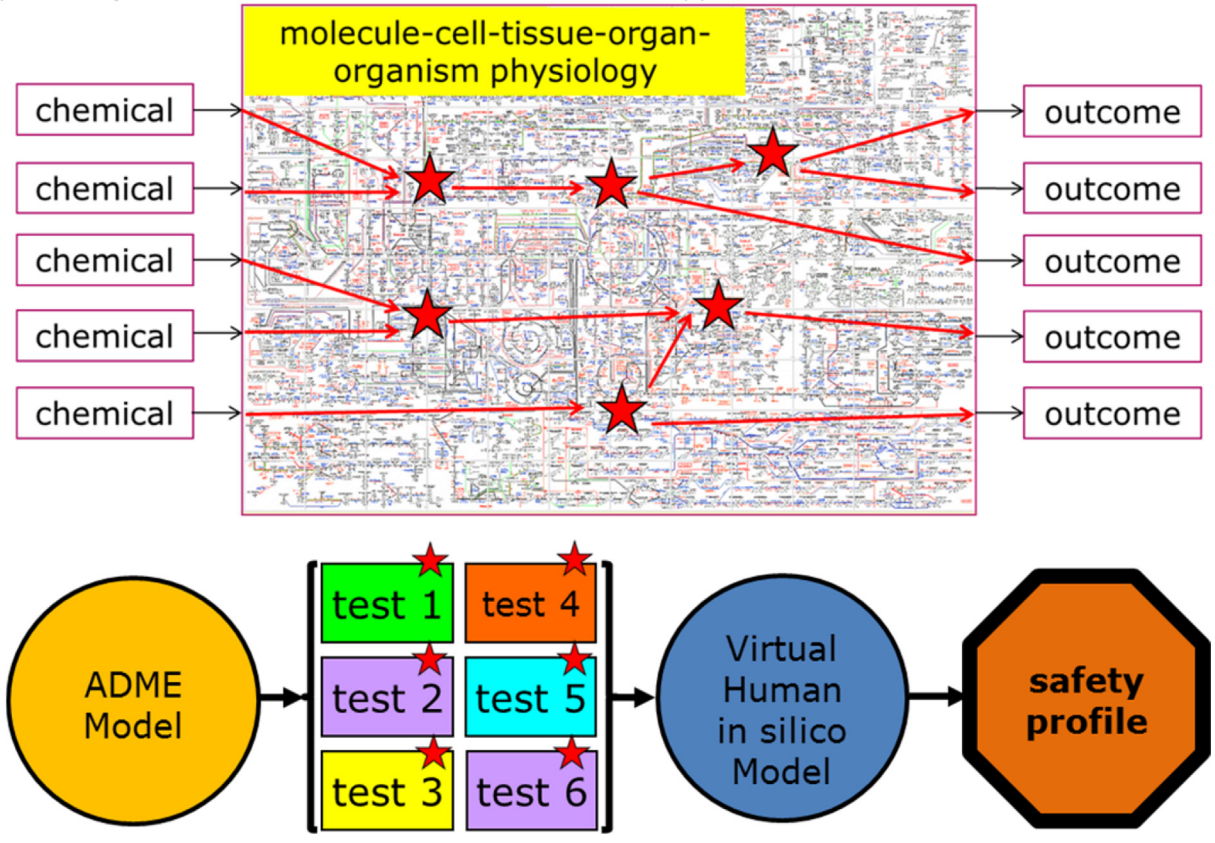
The digital information era is resulting in vast and growing databases on the physiology of health and disease that revolutionizes clinical practice [34,35]. The integration of that knowledge is ongoing in digital tools from which, for example, optimal treatments can be deduced. The current major European project aimed at mapping the virtual physiological human and the digital patient (http://www.vph-institute.org/video/the-digital-patient.html) has taken on this challenge, addressing a host of human organ systems. Therapeutic applications are increasing, for example, for cardiac disease, diabetes, thyroid disease, and depression [36–39]. In addition, these approaches allow for personalized medicine by fine-tuning models based on individual parameter settings [35]. Similar paths can of course be envisaged in human toxicology. Based on the *in silico* modeling of human physiology, toxicity can be modeled. Quantitative concentration-dependent parameter changes after chemical exposure measured *in vitro* can be fed into the *in silico* physiological model developed to provide the quantitative integration of toxicity at the whole-body level (Figure 3). Recent developments in this area are promising, but the integration of different organ functions into one model is still a significant challenge. The validity of this approach depends on the quality of the *in silico* model. Validation of this approach will be principally different from classical validation of alternative methods for animal testing [40]. Although existing animal data have been instrumental in revealing toxicity mechanisms, they do represent a detour on the road from human

Figure 2



From external exposure to hazard assessment at the organism level, via key events triggered at the molecular level. ADME (absorption, distribution, metabolism, excretion) represents compound kinetics; the Virtual Human *in silico* Model represents the adverse outcome pathway network.

Figure 3



Schematic representation of the application of the virtual human in toxicological safety assessment. The virtual human (the physiological map box) challenged by chemicals will lead to adverse outcomes through a limited number of pathways, in which critical rate-limiting steps occur, indicated here graphically by red stars. Testing these aspects in quantitative *in vitro* tests combined with kinetic information provides the basis for feeding the integrated *in silico* model for predicting the resulting safety profile in humans. ADME, absorption, distribution, metabolism, excretion.

exposure to human risk. In principle, the description of human physiology *in silico* will provide a more direct representation of human hazard and risk than the non-human animal model. It will have to prove itself in actual practice as comparisons with existing (largely animal-based) systems are limited based on the principal limitations of the latter. Although much work needs to be done in designing a reliable virtual human toxicology model, the growing applications of virtual models in medicine mentioned previously provide promising landmarks toward the success of such an approach.

Will machine learning revolutionize regulatory chemical safety assessment?

Recently, several workshops have addressed the question of how innovative approaches in chemical safety assessment, focusing on the human and avoiding animal testing, will change the regulatory landscape [41–45]. First, an evolutionary scenario can be described, in which changes would occur one by one within the current regulatory frameworks. This could ultimately result in stepwise replacement of animal studies. Alternatively, as an underlying concept, a revolutionary approach would start from building the human physiological model for chemical safety assessment, incorporating all existing knowledge in an integrated *in silico* model. The model would be fed by data from testing a chemical in dedicated *in vitro* assays for critical rate-limiting steps in the physiological regulatory network. Thus, the *in silico* model would provide the integrated safety assessment for the tested chemical [24,43,44]. The latter system would develop by combining biological, chemical, and toxicological knowledge irrespective of current regulatory frameworks and would most probably require reformulation of practical requirements for regulatory chemical safety assessment. The bottom line is that safety assessment through the virtual human has to prove itself in actual practice, based on experience in the human. It can partly be built on classical comparison with animal studies, carefully considering qualitative and quantitative species differences in mechanistic pathways, but for validation purposes, it should ideally rely on integral modeling of human physiology. In addition, the credibility and acceptability of a computer model has a psychological aspect and partly depends on the extent to which the model is understood. As scientific reliability of such a system is growing, it is important to simultaneously raise confidence of all stakeholders, including the general public. This is not playing games such as chess or Go, both in terms of the nature of the underlying rules as to the importance of the subject for society. Of course, the stakes are incomparably high when it comes to the protection of human health. Although major hurdles still need to be overcome, accelerating advances in machine learning and *in silico* modeling of human development, physiology, and disease suggest that the virtual human and its application in chemical safety assessment may be closer at hand than anticipated heretofore.

Conflict of interest

Nothing declared.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Harding LB: *L Deep Blue win a giant step for computerkind*. The Guardian; 1997 (12 May).

2. Russell J: *Google's AlphaGo AI wins three-match series against the world's best Go player*. techcrunch.com; 2017 (May 25).

3. Phillips PJ, *et al.*: **Face recognition accuracy of forensic examiners, superrecognizers, and face recognition algorithms**. *Proc Natl Acad Sci USA* 2018, **115**:6171–6176.

4. ** Chen S, *et al.*: **Development of a computer-aided tool for the pattern recognition of facial features in diagnosing Turner syndrome: comparison of diagnostic accuracy with clinical workers**. *Sci Rep* 2018, **8**:9317.
This study aimed to develop a computer-assisted tool for the pattern recognition of facial features for diagnosing Turner syndrome (TS). The accuracy of this system was satisfactory and better than the diagnosis by clinicians. However, the system necessitates further improvement for achieving a high diagnostic accuracy in clinical practice. This study stipulates a well-performing application of artificial intelligence in clinical practice, showing the added value of deep learning approaches.

5. ** Haenssle HA, *et al.*: **Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists**. *Ann Oncol* 2018, **29**:1836–1842.
Deep learning convolutional neural networks (CNN) may facilitate melanoma detection. A CNN's diagnostic performance was compared with a large international group of 58 dermatologists, including 30 experts. Most dermatologists were outperformed by the CNN. Irrespective of any physicians' experience, they may benefit from assistance by a CNN's image classification. This study stipulates a well-performing application of artificial intelligence in clinical practice, showing the added value of deep learning approaches.

6. Sahiner B, *et al.*: **Deep learning in medical imaging and radiation therapy**. *Med Phys* 2018, **46**:e1–e36.

7. Krewski D, *et al.*: **Toxicity testing in the 21st century: a vision and a strategy**. *J Toxicol Environ Health B Crit Rev* 2010, **130**:51–138.

8. Bouhifd M, *et al.*: **The human toxome project**. *ALTEX* 2015, **32**:112–124.

9. OECD: **Guidance document for the use of adverse outcome pathways**. In *Developing integrated approaches to testing and assessment (IATA) series on testing & assessment*; 2016. No. 260.

10. Bal-Price A, Meek MEB: **Adverse outcome pathways: application to enhance mechanistic understanding of neurotoxicity**. *Pharmacol Therapeut* 2017, **179**:84–95.

11. Combes RD: **Challenges for computational structure–activity modelling for predicting chemical toxicity: future improvements?** *Expert Opin Drug Metabol Toxicol* 2011, **7**:1129–1140.

12. ** Hutson MS, *et al.*: **Computational model of secondary palate fusion and disruption**. *Chem Res Toxicol* 2017, **30**:965–979.
To improve the capacity to predict developmental effects from chemical-induced cellular alterations, a multicellular agent-based model was built in CompuCell3D that recapitulates the cellular networks and collective cell behavior underlying growth and fusion of the mammalian secondary palate. The virtual palate model was executed with theoretical chemical perturbation scenarios to simulate switch behavior leading to a disruption of fusion following chronic and acute chemical exposures. This computer model adds to similar systems models toward an integrative "virtual embryo" for simulation and

quantitative prediction of adverse developmental outcomes following genetic perturbation and/or environmental disruption. This study provides proof of principle that mechanism-based *in silico* models for processes in embryogenesis can be used to predict effects of chemical exposures.

13. Kleinstreuer N, *et al.*: **A computational model predicting disruption of blood vessel development**. *PLoS Comput Biol* 2013, **9**, e1002996.

14. Knudsen T, *et al.*: **Predictive models and computational toxicology**. In *Teratogenicity testing: methods and protocols*. Edited by Barrow PC, Totowa, NJ: Humana Press; 2013:343–374.

15. * Pittman ME, *et al.*: **AOP-DB: a database resource for the exploration of Adverse Outcome Pathways through integrated association networks**. *Toxicol Appl Pharmacol* 2018, **343**:71–83.
To support the discovery and development of adverse outcome pathways (AOPs), the AOP-DB is introduced, an exploratory database resource that aggregates association relationships between genes and their related chemicals, diseases, pathways, species orthology information, ontologies, and gene interactions. The AOP-DB acts as a hypothesis-generation tool for the expansion of putative AOPs, as well as the characterization of potential AOPs, through the creation of association networks across these biological entities. Finally, the AOP-DB provides a useful interface between the AOP framework and existing chemical screening and prioritization efforts. This study stresses the need for structured big data information sources at the basis of developing integrated mechanistic models of adverse outcome pathways in toxicology.

16. Knapen D, *et al.*. *Adverse outcome pathway networks I: development and applications*, vol. 37(6); 2018:1723–1733.

17. Villeneuve DL, *et al.*. *Adverse outcome pathway networks II: network analytics*, vol. 37(6); 2018:1734–1748.

18. De Abrew KN, *et al.*: **Grouping 34 chemicals based on mode of action using connectivity mapping**. *Toxicol Sci* 2016, **151**: 447–461.

19. Ford KA, *et al.*: **Comparative evaluation of 11 in silico models for the prediction of small molecule mutagenicity: role of steric hindrance and electron-withdrawing groups**. *Toxicol Mech Methods* 2017, **27**:24–35.

20. Bhhatarai B, *et al.*: **Evaluation of TOPKAT, toxtree, and derek nexus in silico models for ocular irritation and development of a knowledge-based framework to improve the prediction of severe irritation**. *Chem Res Toxicol* 2016, **29**:810–822.

21. * Cronin MTD, *et al.*: ***In* silico prediction of organ level toxicity: linking chemistry to adverse effects**. *Toxicol res* 2017, **33**: 173–182.
The prediction of chronic toxicity may be improved by considering organ level effects, as opposed to modelling the no-observed-adverse-effect level itself. This review focusses on the use of structural alerts to identify potential liver toxicants. In silico profilers, or groups of structural alerts, have been developed based on mechanisms of action and informed by current knowledge of Adverse Outcome Pathways. These profilers are robust and can be coded computationally to allow for prediction. However, they do not cover all mechanisms or modes of liver toxicity and recommendations for the improvement of these approaches are given. This study shows the case of *in silico* structure–activity modelling in chemical safety.

22. Wu S, *et al.*: **Framework for identifying chemicals with structural features associated with the potential to act as developmental or reproductive toxicants**. *Chem Res Toxicol* 2013, **26**:1840–1861.

23. Hessel EVS, Staal YCM, Piersma AH: **Design and validation of an ontology-driven animal-free testing strategy for developmental neurotoxicity testing**. *Toxicol Appl Pharmacol* 2018, **354**:136–152.

24. Staal YCM, *et al.*: **Advanced toxicological risk assessment by implementation of ontologies operationalized in computational models**. *Appl in vitro toxicol* 2017, **3**:325–332.

25. ** Hassan I, *et al.*: **Neurodevelopment and thyroid hormone synthesis inhibition in the rat: quantitative understanding within the adverse outcome pathway framework**. *Toxicol Sci* 2017, **160**:57–73.
A quantitative adverse outcome pathway was developed where serum thyroxin (T4) reduction following inhibition of thyroperoxidase in the thyroid gland are related to deficits in fetal brain TH and the development of a brain malformation, cortical heterotopia. These data show the potential of in vivo assessments and computational descriptions of biologic responses to predict the development of this structural brain malformation and use of quantitative adverse outcome pathway approach to evaluate brain deficits that may result from exposure to other TH disruptors. This study shows that quantitative adverse outcome pathways can be applied to toxicity prediction, in this case of thyroid modulation and brain maldevelopment.

26. Sinha RA, Singh BK, Yen PM: **Direct effects of thyroid hormones on hepatic lipid metabolism**. *Nat Rev Endocrinol* 2018, **14**:259–269.

27. Leusch FDL, *et al.*: **Comparison of in vitro and in vivo bioassays to measure thyroid hormone disrupting activity in water extracts**. *Chemosphere* 2018, **191**:868–875.

28. Murk AJ, *et al.*: **Mechanism-based testing strategy using in vitro approaches for identification of thyroid hormone disrupting chemicals**. *Toxicol Vitro* 2013, **27**:1320–1346.

29. Zoeller RT, Tan SW: **Implications of research on assays to characterize thyroid toxicants**. *Crit Rev Toxicol* 2007, **37**: 195–210.

30. Beekhuijzen M, *et al.*: **The urgency for optimization and harmonization of thyroid hormone analyses and their interpretation in developmental and reproductive toxicology studies**. *Reprod Toxicol* 2018, **80**:126–130.

31. OECD: **New scoping document on in vitro and ex vivo assays for the identification of modulators of thyroid hormone signalling**. *OECD Series on Testing & Assessment* 2017, **207**.

32. Degon M, *et al.*: **A computational model of the human thyroid**. *Math Biosci* 2008, **212**:22–53.

33. Blaauboer BJ: **The integration of data on physico-chemical properties, in vitro-derived toxicity data and physiologically based kinetic and dynamic as modelling a tool in hazard and risk assessment. A commentary**. *Toxicol Lett* 2003, **138**:161–171.

34. Viceconti M, Hunter P: **The virtual physiological human: ten years after**. In *Annual review of biomedical engineering*; 2016: 103–113.

35. ** Chase JG, *et al.*: **Next-generation, personalised, model-based critical care medicine: a state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them**. *Biomed Eng Online* 2018, **17**.
This review examines the models and methods used to create virtual patients. Specifically, it presents the models types and structures used and the data required. It then covers how to validate the resulting virtual patients and trials, and how these virtual trials can help design and optimise clinical trial. Links between these models and higher order, more complex physiome models are also discussed. In each section, it explores the progress reported up to date, especially on core ICU therapies in glycemic, circulatory and mechanical ventilation management, where high cost and frequency of occurrence provide a significant opportunity for model-based methods to have measurable clinical and economic impact. The outcomes are readily generalised to other areas of medical care. This overview shows the current and growing breadth of applications of machine learning in clinical practice.

36. Stecka AM, *et al.*: **The use of a virtual patient to follow changes in arterial blood gases associated with therapeutic thoracentesis**. *Int J Artif Organs* 2018, **41**:690–697.

37. Larkin A, *et al.*: **Virtual simulation improves clinical decision-making in managing type 2 diabetes**. *Diabetes* 2018, **67**:A181.

38. Lubarda J, Braun R, Thase ME: **Improving management of major depressive disorder through virtual patient simulation**. *CNS Spectr* 2017, **22**:77.

39. Eisenberg M, Samuels M, DiStefano 3rd JJ: **Extensions, validation, and clinical applications of a feedback control system simulator of the hypothalamo-pituitary-thyroid axis**. *Thyroid : official journal of the American Thyroid Association* 2008, **18**: 1071–1085.

40. Piersma AH, *et al.*: **Validation redefined**. *Toxicol Vitro* 2018, **46**: 163–165.

41. Scialli AR, *et al.*. *Rethinking developmental toxicity testing: evolution or revolution?*, vol. 110(10); 2018:840–850.

42. Piersma AH, *et al.*: **Workshop on acceleration of the validation and regulatory acceptance of alternative methods and implementation of testing strategies**. *Toxicol Vitro* 2018, **50**:62–74.

43. Cote I, *et al.*: **The next generation of risk assessment multiyear study-highlights of findings, applications to risk assessment, and future directions**. *Environ Health Perspect* 2016, **124**:1671–1682.

44. * Wittwehr C, *et al.*: **How adverse outcome pathways can aid the development and use of computational prediction models for regulatory toxicology**. *Toxicol Sci : an official journal of the Society of Toxicology* 2017, **155**:326–336.

The systematic organization of knowledge into AOP frameworks can inform and help direct the design and development of computational prediction models that can further enhance the utility of mechanistic and *in silico* data for chemical safety assessment. A proposal for actively engaging the modeling community in AOP-informed computational model development is made. A vision is presented for how AOPs can be leveraged to facilitate development of computational prediction models needed to support the next generation of chemical safety assessment. This study shows the importance of and a practical approach of how adverse outcome pathways can be integrated into *in silico* systems for prediction of toxicity.

45. LaLone CA, *et al.*: **Advancing the adverse outcome pathway framework-An international horizon scanning approach**. *Environ Toxicol Chem* 2017, **36**:1411–1421.