The value of in silico chemistry in the safety assessment of chemicals in the consumer goods and pharmaceutical industries

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In silico toxicology prediction is an extremely challenging area because many toxicological effects are a result of changes in multiple physiological processes. In this article we discuss limitations and strengths of these in silico tools. Additionally, we look at different parameters that are necessary to make the best use of these tools, and also how to gain acceptance outside the modelling community and into the regulatory arena. As a solution, we propose an integrated workflow for combined use of data extraction, quantitative structure activity relationships and read-across methods. We also discuss how the recent advances in this field can enable transition to a new paradigm of the discovery process, as exemplified by the Toxicity Testing in the 21st Century initiative.

Introduction

Chemicals in drugs, food and consumer goods are an integral part of our everyday life whether they be ‘naturals’ or manmade. Although the regulatory needs and requirements for risk assessments differ between consumer goods and pharmaceutical industries, it is evident that the in silico approaches currently available can offer significant benefit to both of these sectors.

The well recognised definition of a good and successful drug is an appropriate balance of potency, efficacy, safety and favourable pharmacokinetics. For the drug industry, it is imperative that a chemical can reach its target with a concentration at the target site suitable for the desired efficacy and also below toxicity thresholds. To avoid late-stage failures in the discovery of new chemicals to be used as drugs, absorption, distribution, metabolism, elimination and toxicity (ADMET) studies are now mostly carried out at a much earlier stage of the discovery process [1–3]. However, owing to the use of combinatorial chemistry libraries and high-throughput screening (HTS), there has been a dramatic increase in the number of active chemicals. Consequently, the discovery process has struggled to keep up with this increase in influx of chemicals. Similarly within the consumer goods industry, late-stage failures are costly in terms of resource and time due to safety concerns and as such there is a strong rationale to bring safety assessments closer to the initial stages of the innovation pipeline where a larger pool of candidate compounds is available. Usually, the traditional safety methods centred around toxicological assessment and testing are unable to cope with the influx of new chemicals to be tested in a timely way. There is also growing interest in the development of alternative approaches to toxicity testing [4] that reduce, refine or replace the use of animals in safety assessment and also enable faster high throughput assessment of hazard and risk that is relevant to human safety assessment. To address this, there is a need for development of both in silico virtual models and also a better understanding of the effects of different chemicals on physiological processes. This could then be deployed for toxicological assessments at an earlier stage of the discovery process and for assessment of larger numbers of chemicals [5–9].

Why in silico?

In silico screening is typically a low cost high-throughput process, which can provide a fast indication of potential hazards for use in lead prioritisation [6–9]. As no physical compounds are required, these screens can be run on virtual compounds at early stages of discovery to prioritise chemicals for ADMET testing. Additionally, in silico tools can help provide a mechanistic understanding of these predictions, for example, to explain why a compound is predicted to be active or inactive. This information can then be used to re-engineer a chemical, alter its ADMET profile or design out the toxicity of new chemicals. These predictive models can be built either directly on data from in vitro assays (e.g. Ames bacterial
mutation assays) or directly on in vivo data (e.g. carcinogenicity, TD50s), and can also be used for understanding of in vitro to in vivo extrapolation. Following successful validation of a predictive model, it might be possible to have faster cycle times, lower costs, and early indication of drug failure, with a much reduced need for in vitro or animal testing. Depending upon the toxicology endpoint, some of these in silico tools and technologies are considered to be valid and are recognised by some regulatory agencies (e.g. for use in the European REACH initiative) [10]. A set of principles from the Organisation for Economic Co-operation and Development (OECD) must be followed to achieve regulatory acceptance of the predictive chemistry tools. These include questions around the defined endpoint (i.e. data used for modelling, applicability domain, methods, their mechanistic interpretation and appropriate measures of predictivity [11]). In the remainder of this article, we discuss the importance of these points, and why it is crucial to get them right to gain the full benefits of in silico chemistry.

Choosing the right data
Because toxic effects are still responsible for some 20% of the late-stage failures in drug development, there is an urgent need for in silico tools that can be used to estimate the toxicology profile of a chemical [6]. Typically, adverse reactions are not discovered until after market release. This is an expensive scenario that is all too common in the discovery of new drugs and chemicals. The most relevant data usually comes from human clinical trials, which can be very expensive to generate and also limited in number of data points. The data chosen for modelling toxicity has to be chosen wisely for any given toxicity endpoint. For example, in the case of genetic toxicity, there is a large body of in vitro data available from Ames testing compared with limited in vivo data (e.g. carcinogenicity in different species). While the in vitro data provides a comprehensive model training set, it must be noted that the final goal of in silico models is to predict the in vivo effects in humans for a given chemical. One must therefore choose in vitro toxicity endpoints carefully keeping its relationship and relevance to the in vivo data in mind. It is clear that the use of animals has limitations, for example, humans are not 70 kg rats, we absorb/metabolise chemicals differently; we live longer (enabling certain diseases to develop, prompting evolutionary adaptations to protect against them); and we are exposed to a multitude of environmental factors [12,13]. The models are clearly only as good as the data they are based on, there is still no replacement for the expression ‘garbage in, garbage out’ [14]. Before modelling any data, the modeller needs to ensure the quality of the datasets from different sources and standardisation procedures must be in place to cope with data in different formats. With the recent advances in HTS, chemical synthesis and biological screening, there is no shortage of publicly or commercially available databases that can be used as data sources for these models [15]. A recent article discusses some of these issues and has also evaluated the consequences of both random and systematic errors with chemical structure curations in well-known datasets [16]. Some useful electronic resources that contain data suitable for toxicity model building are listed in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Database</th>
<th>Brief description</th>
<th>Refs</th>
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<tbody>
<tr>
<td>ACToR – Aggregated Computational Toxicology Resource</td>
<td>ACToR (Aggregated Computational Toxicology Resource) is a collection of databases collated or developed by the US EPA National Center for Computational Toxicology (NCCT). Data includes chemical structure, physico-chemical values, in vitro assay data, expo</td>
<td>ACToR: <a href="http://actor.epa.gov/actor/actor_help_20080903.htm">http://actor.epa.gov/actor/actor_help_20080903.htm</a></td>
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<tr>
<td>ChEMBL</td>
<td>Contains calculated properties (e.g. log P molecular weight, Lipinski parameters, among others) and abstracted bioactivities (e.g. binding constants, pharmacology and ADMET data)</td>
<td>ChEMBL: <a href="https://www.ebi.ac.uk/chembl/">https://www.ebi.ac.uk/chembl/</a></td>
</tr>
<tr>
<td>Comparative Toxicogenomics Database (CTD)</td>
<td>Find associations between gene/proteins, environmental chemicals and toxicology</td>
<td>Comparative Toxicogenomics Database: <a href="http://ctd.medlib.org/">http://ctd.medlib.org/</a></td>
</tr>
<tr>
<td>CPDB (The Carcinogenic Potency Database)</td>
<td>Provides a broad perspective on possible cancer hazards from human exposures to chemicals that cause cancer in high dose rodent cancer tests</td>
<td>The Carcinogenic Potency Project: <a href="http://potency.berkeley.edu/">http://potency.berkeley.edu/</a></td>
</tr>
<tr>
<td>NTP (National Toxicology Program)</td>
<td>It contains toxicity studies from shorter duration tests and from genetic toxicity studies, which includes both in vitro and in vivo tests. It also contains the immunotoxicity, developmental toxicity and reproductive toxicity studies</td>
<td>National Toxicology Program: <a href="http://ntp-apps.niehs.nih.gov/ntp_tox/">http://ntp-apps.niehs.nih.gov/ntp_tox/</a></td>
</tr>
<tr>
<td>RepDOSE</td>
<td>Repeat dose study data for dog, mouse and rat. Shows effects of chemicals on target organs. Studies are rated by reliability</td>
<td>RepDOSE: <a href="http://www.fraunhofer-repdose.de/">http://www.fraunhofer-repdose.de/</a></td>
</tr>
<tr>
<td>ToxRefDB</td>
<td>ToxRefDB (Toxicity Reference Database) captures thousands of in vivo animal toxicity studies on hundreds of chemicals</td>
<td>EPA: <a href="http://www.epa.gov/nctt/toxrefdb/">http://www.epa.gov/nctt/toxrefdb/</a></td>
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Choice of methods
The three main predictive chemistry approaches, such as structure activity relationships (SAR), quantitative structure activity relationships (QSAR) and read-across, have been used in the past for the prediction of several toxicology endpoints.

SAR
This approach is associated with the local reactivity of chemicals and includes reactivity of functional groups also called structural alerts, pharmacophores or toxicophores [17–20]. This technique can be an invaluable tool in the in silico prediction of toxicity because it is simple and easy to understand, and highlights the presence of certain substructures within the molecule that can be related to an adverse reaction. Also, this alert approach can help provide mechanistic understanding of an observed adverse outcome. SAR usually works well with binary classifications and has been used for highlighting fragments of several toxicology endpoints, including Ames, carcinogenicity, hepatotoxicity and skin sensitisation [20].

QSAR
This approach provides the statistical relationship between the toxicity of a chemical and its physicochemical properties and structural characteristics. Different QSAR and machine learning methods have different ways of deriving these approximations to provide information about the toxic effect of chemicals [21]. Like SAR, this approach can work with binary classification [22–24] but also works with continuous data, such as rodent carcinogenicity and chronic toxicity data [25,26].

Read-across
Read-across of hazard data is a well recognised method for predicting the hazard profile of a substance where endpoint data are lacking by linking it to structurally similar compounds for which experimental data are available for a given endpoint [27,28]. This enables for a read-across approach to be used to predict the toxicity of those members of a chemical family for which no direct toxicology data are available.

To fully capitalise on the opportunities presented by these in silico tools, they need to be transparent and provide as much support and confidence behind each prediction as possible. As all biological endpoints (especially toxicity) are often the combination of multiple phenomena, most in silico models end up being complex [21,25,26]. There has to be balance between model interpretation, complexity and its predictive power. Depending on the endpoint, probabilistic and statistical QSAR methods (involving complex algorithms) might provide superior results as compared with simple SAR methods as it has been shown in the case of genotoxicity modelling [22–24]. The modelling algorithm linking molecular descriptors to the output variable needs to be chosen so that it takes the complexity of the particular relationship into account, otherwise overfitting (in case a complex modelling procedure is used) or insufficient predictivity of a model (in case a simple modelling procedure is used) might result. In case a complex algorithm is used in building the models, users might think that the models are an ‘algorithmic jungle’ and consequently, the benefits of the models could be easily misunderstood [29]. The precise choice of descriptors and modelling methods for a given model is generally dictated by the complexity of the process that underlies the given toxicity event, regulatory considerations, such as the OECD QSAR guidelines and the personal preference of the model developer. For example, for the drug-induced phospholipidosis, the potentially toxic excessive accumulation of phospholipids in cells/tissues might be described with simple descriptors, such as the presence of a positive charge/basic substituent and high lipophilicity [30]. By contrast, for example P450 inhibition or hERG binding are complex receptor-mediated processes, which arguably require complex non-linear modelling methods [31–33]. However, like with any complex problem, the task of building an understanding is much easier if this can be broken into different simple processes. A study [34] shows and suggests how in silico models for hERG inhibition can be used as early screening tools for eliminating potent hERG inhibitors from chemical libraries in early drug discovery. This could serve as an alternative to the more expensive and time consuming experimental assessments, or the model could be used to prioritise sending predicted inhibitors for experimental assay [34,35]. The choice of method, its transparency and its mechanistic interpretation might have an important role in getting the full benefits of these approaches, and also the acceptance of these tools outside the modelling community and into the regulatory arena. Table 2 lists some of the popular free open source software for prediction of various toxicity endpoints. The methods used in this table varies from simple SAR methods to complex QSAR methods.

Importance of applicability domain
In silico models might not perform well if a predicted chemical is beyond the chemical space where the models were developed [36–38]. Therefore, applicability domain is one of the main reasons for the QSAR/SAR model failure owing to the difference in chemical space of compounds that were used to develop and apply the models. This leads to the issue of whether global or local models should be used. Global models usually contain a large and diverse set of chemicals. These are generally suited to dealing with non-congeneric structural data and also when semi-quantitative predictions are needed. An example is discussed in a recent study for Ames test predictions [24]. By contrast, local models are built on a particular chemical series containing a small set of closely related chemicals and hence these local models might have a small applicability domain. An example of this has been shown for the Ames predictions for the aromatic amines [39]. In silico modellers should therefore highlight the validity of these in silico models by selecting and obtaining experimental data from new compound sets with structures different from those in the original model training sets [40]. For a bad model, accuracy measures tend to be biased towards the training set, but its performance then decreases when tested with a new set of chemicals [19].

How to make best use of (Q)SAR methods
It is important that the models built are continuously validated and refined based on new data and understanding the cause of the apparent ‘failure’ cases. It is well known that each individual model has its own problems and pitfalls [41–43]. For example, in the case of the expert derived structural alert approach [17–20], where the presence of a small fragment can be correlated with a
particular toxicity endpoint. In this approach, the steric and electronic environment surrounding a given structural alert fragment are easily ignored but these factors can either diminish or enhance its toxicity. Moreover, this method is only designed for highlighting positives (i.e. if no alerts are present, it does not mean the chemical will not have any toxic effects), and also the role of these small fragments towards many tox endpoints is not well understood [44]. Where possible, modellers should employ several predictive models for a single endpoint to produce better consensus predictions [43]. For example in the case of predicting an Ames test outcome, integration of human derived structural alerts with artificial intelligence systems for Ames in a consensus modelling manner has been shown to provide advantages over that of a single model (User’s Guide for T.E.S.T: http://www.epa.gov/nrmrl/std/cppb/qsar/testuserguide.pdf).

It is also possible that some models might be better at predicting some subclasses of chemicals; it is therefore also possible to create substructure-localised consensus models by taking into account the strengths of each model for a particular substructural class (User’s Guide for T.E.S.T: http://www.epa.gov/nrmrl/std/cppb/qsar/testuserguide.pdf) [45,46]. It should be noted that consensus modelling might not offer any advantages in cases where a strong model is integrated with many weaker models, in cases like these consensus prediction might even offer low predictivity over single model due to noise addition from the weaker models.

Before model building, modellers need to have a clear picture about where and how models will be used. It is important to highlight the benefits and limitations of each model so that users are able to understand when and why models might fail. Users of the models also need to be aware of each step in the model building workflow, including which data was used in the model building exercise, which descriptors were used and what is the role of each descriptor. For example, if a model is built on simple 2D descriptors or fragments then it might not be able to highlight differences in toxicity of stereo-isomers or even similar chemicals in 2D representations. It is often seen that the interpretation of the success of models depends on their use and the expectations of the user [47]. Therefore it is not surprising that for the same data and same model, one user might find value in the model, whereas for another user the same model might be of little value. For users it is therefore important to know the building process of models and expectations from it especially when these might be promoted for use in a regulatory setting.

SAR, QSAR and read-across are data mining approaches, which involve analysis of the structural features of sets of chemicals to generate rules that enable users to predict outcomes for new chemicals. The use of these approaches in a more systematic and integrated workflow is suggested in Fig. 1. For any given target chemical, one of the first steps should be to look for what is known already for that chemical by use of text and data extraction techniques. If there are gaps in the data, the next step should be to fill these gaps using close analogues. Here, the strength of available evidence should be judged on a case-by-case basis. For example, in a case where there are many close analogues with similar toxicology profiles, confidence will be much higher as compared with a case where there are few close analogues with a mixed toxicology profile. QSAR might be used as the final step if there is no toxicology data available either on exact or close analogues, but all the points about applicability domain and confidence in predictions discussed above should be taken into account.

**Limitations of (Q)SAR approaches**

Overall it also needs to be noted that these individual (Q)SAR in silico toxicological methods are hazard identification methods and in most of cases they do not take dose and exposure into account unless a exposure–response relationship has been studied. Therefore, in general, these will not predict toxicity in isolation, but provide useful supplementary information for the overall risk assessment process. For example, the aromatic nitro group is a
A well known fragment that triggers a structural alert for carcinogenicity, but if a chemical containing this fragment has very low exposure or bioavailability, it is questionable whether this prediction will be realised. Therefore, whenever possible, internal exposure (i.e. the amount taken up and distributed as free plasma concentration within an organism) should be taken into account by using either in silico or in vitro ADME data. Ideally, results of predictions should be combined with other evidence and data for consideration for the risk assessments.

Another limitation for most of the current (Q)SAR approaches is that they mostly do not consider metabolites of the parent chemicals, this is usually true for endpoints like hERG, skin sensitisation, among others [34,35]. When properties are calculated for prediction of a toxicology endpoint, it is usually conducted on a parent chemical structure, whereas it could be a metabolite which is responsible for the toxicity. However, clearance by metabolism can also have an important role in the actual exposure to a given chemical. Safety guidance has been produced, with triggers for concern based on the abundance of metabolites relative to total material or relative to parent material levels [48,49]. Others have proposed a strategy in which absolute exposure to metabolites (rather than a relative comparison with parent or total drug-related material) in humans triggers further consideration of metabolite safety [50]. It is possible to predict metabolites using several computational approaches (METASITE [51], METEOR [52], MetaPrint2D [53], among others). However, it should be noted that the majority of these methods simply predict qualitatively the metabolites that could be formed and do not estimate the probability or amount of each metabolite being formed.

By definition, all of these in silico models for toxicity are simulations of reality; the interplay of complex physiological processes that lead to toxicity presents a real challenge for creating reliable predictive models [5]. But greater confidence can be obtained if all other possible information, including limitations of models, applicability domain, metabolites and exposure are combined together for the risk assessments [42,47].

Concluding remarks
Experimentalists generally prefer to generate ‘wet’ data on all the chemicals, irrespective of what the odds of success might be in terms of late-stage failures. With a lack of confidence in the accuracy of a predictive model, in silico tools tend to carry little weight in a risk assessment. As a result, the level of acceptance of predictions by users outside the computational chemistry and modelling groups tends to be low. There is need to be transparent wherever possible and modelling methods need to be chosen carefully, including confidence factors and reasoning behind each of the predictions. Every modeller must be encouraged to promote their use in the context of realistic expectations of these tools. Modellers need to do more than just generate large numbers of data points, they need to work within multi-disciplined program teams to provide the support needed for the decision-making process in a project. As more and more validated case examples are passed through these different in silico approaches it might help in gaining confidence and understanding of these tools [19,54,55].

Keeping all the above in mind, it is not surprising that the acceptance of these predictive tools continues to be difficult, but if the existing issues can be appropriately addressed, it might eventually be well worth the effort. In addition there are commercial and consumer pressure to find and use alternatives for less environmental impact and also less animal testing. Therefore an
opportunity exists for these in silico methods to demonstrate real value as part of a suite of alternative technologies and gain public support of this area of science.

There is also need for computational chemistry tools to align with other information sources (e.g. from systems biology, hazard, metabolites and exposure) to develop real or virtual models of tissues, organs and physiological processes that could be used for the toxicological assessments. For toxicity assessments, information from other sources could be applied as part of a tiered system along with predictions from computational tools. As suggested in Fig. 2, the first tier could be used for alerts, (Q)SAR and read-across methods could be used for hazard identification. These tools might represent a fast method and filter to enrich a biological screen with desired ADMET profiles. Indeed, many major pharmaceutical companies have already adopted virtual screening methodologies to complement in vitro HTS methods [56,57].

It is also important for these tools to move beyond hazard rankings and possibly move towards estimation of in vivo responses based on in vitro or in silico data. As discussed above predictions based just on in silico for prioritising chemicals might over- or under-estimate the potential risk of these chemicals owing to differences in bioavailability, clearance and exposure. Physiologically based pharmacokinetic (PBPK) models can take in vitro and in silico data inputs and can predict concentration versus time profiles. It has been shown in the past that PBPK models are superior to other more empirical methods for interspecies scaling and prediction of human pharmacokinetics [58]. This approach could be the second tier described in Fig. 2 integrating both dosimetry and human exposure information with the in silico, high-throughput, toxicity screening data to provide a better safety risk assessment. A recent article [59] has shown the combined use of experimental assays, computational tools, and exposure assessment by performing analysis on a subset of 35 ToxCast chemicals.

Understanding the different mechanisms of how chemicals can affect biological structures, processes and pathways and thus can impact on physiological response is an important aspect of toxicology. This knowledge can help to predict the toxicity of chemicals, and it is also possible to plan ways to prevent exposure to toxic compounds and develop ways to antagonise the effects of the toxins. Both the complexity in the biological response and the lack of public availability for mechanistic data that can be modelled to relevant structural information are reasons that in silico approaches to date have had limited success in delivering in vivo relevant predictions. In view of this, the European commission Seventh Framework Programme (FP7) research joint technology programmes, the Innovative Medicines Initiative (IMI: http://www.imi.europa.eu/) funded with the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Safety Evaluation Ultimately Replacing Animal Testing (SEURAT1) project (Colipa: http://www.colipa.eu/news-a-events.html) funded.
with European Cosmetic, Toilery and Perfumery Association (Colipa), have undertaken several projects, such as eTox, Expert Systems for in silico Toxicity, and COSMOS. These programmes although focussed on different end goals of improving the efficiency of drug development (IMI) and non-animal alternatives to repeat dose toxicity respectively (SEURAT-1) they both aim to deliver improvements in the modelling of early prediction of in vivo human toxicity based on information and data available during early stages of the innovation pipeline. Furthermore mechanistic understanding of human toxicity forms [60] a central component of the National Research Council of the National Academies (NRC) vision and roadmap as described in ‘Toxicity Testing in 21st Century (TT21C): A Vision and a Strategy’ [61]. This vision is summarised as follows: ‘Advances in toxicogenomics, bioinformatics, systems biology, epigenetics and computational toxicology could transform toxicity testing from a system based on whole-animal testing to one founded primarily on in vitro methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin.’ The national toxicology programme (NTP) HTS initiative and the U.S. Environmental Protection Agency (EPA) Toxcast program [59,62] are two efforts that aim to utilise the technological advances in molecular biology and computational science. These aim to identify toxicological testing screens for mechanistic targets active within cellular pathways considered crucial to adverse health effects, such as carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity in humans. However, one of the main outstanding issues remains that knowing that changes in biological processes and perturbation in pathways occur might not be good enough: we need to define how much change is really required for a chemical to cause an adverse effect. These in silico techniques and preclinical testing (in vitro) serve a fundamental role in characterising the potential risks associated with chemicals. However, serious and sometimes rare and unexpected adverse events might be observed in clinical trials or post-approval, suggesting that crucial gaps exist in our understanding of the relationship between patient response and preclinical toxicology findings [12,13]. For example, non-clinical safety assessment are often conducted in normal healthy test systems and tends to be exposure-based; it does not attempt to evaluate the possible risk of rare or idiosyncratic responses that might arise from potential interactions with the presence or progression of disease or the genetic background or other exposures of patients and consumers. Therefore to improve the predictions of chemical safety several programmes mentioned above (e.g. TT21C, COSMOS, ToxCast, among others) have started to gain a better understanding of toxicity mechanisms by evaluating safety assessment data at multiple levels of biological organisation, including genes, proteins, pathways and cell/organ function. There is also need to develop computer models of cells, organs and system and develop clinical trial simulation models that can reveal interactions between drug or device effects, patient characteristics, and disease variables influencing outcomes [63]. As more and more case examples are passed through these different in silico approaches it might help to gain more understanding on how these should be linked together.

There is still a need for new methods to rapidly and accurately determine the toxic potential of both drug molecules and molecules contained in consumer product goods. In silico toxicology models, such as those discussed in this article, fit many of these criteria, and have seen widespread use in drug discovery applications. It should also be acknowledged that in silico tools have been in existence for a relatively short time compared with in vitro or in vivo methods, and have only taken up a pace in past 10 years. As these tools become increasingly user-friendly and transparent, and as more examples of successful applications are shown, it seems highly probable that in silico approaches might evolve rapidly. Meanwhile, modellers need to ensure that these tools are used appropriately and expectations of users are not raised above what a model can deliver. Rather than just a static tool sitting on its own in one corner it needs to be integrated with safety assessments and discovery programmes. By working alongside drug discovery programmes and with constant validation of these in silico methods against in vitro and in vivo data, predictive chemistry can become an increasingly important part of the decision-making process. Where possible as much information as possible needs to be integrated as required for individual toxicity assessments and used as part of a weight of evidence approach to calculate risk to the consumer. At present we have most of the individual components for building a platform for virtual models of tissues, organs and physiological processes that could be used for the toxicological assessments, but one of the main challenges will not be to see how these different components from different disciplines fit together. As discussed above, as more and more examples and case studies are pushed through we might become better and better in gaining knowledge and learn from these information rich technologies.

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