Regulatory Toxicology and Pharmacology 140 (2023) 105385

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Making *in silico* predictive models for toxicology FAIR

Mark T.D. Cronin [a,*], Samuel J. Belfield [a], Katharine A. Briggs [b], Steven J. Enoch [a], James W. Firman [a], Markus Frericks [c], Clare Garrard [d], Peter H. Maccallum [d], Judith C. Madden [a], Manuel Pastor [e], Ferran Sanz [e], Inari Soininen [f], Despoina Sousoni [d]

[a] School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK
[b] Lhasa Limited, Granary Wharf House, 2 Canal Wharf, Holbeck, Leeds, LS11 5PS, UK
[c] BASF SE, APD/ET - Li 444, Speyerer St 2, 67117, Limburgerhof, Germany
[d] ELIXIR, Wellcome Genome Campus, Hinxton, Cambridgeshire, CB10 1SD, UK
[e] Research Programme on Biomedical Informatics (GRIB), Hospital del Mar Medical Research Institute (IMIM), Dept. of Medicine and Life Sciences (MELIS), Universitat Pompeu Fabra, Carrer Dr. Aiguader 88, 08003, Barcelona, Spain
[f] Synapse Research Management Partners SL, Calle Velazquez 94, planta 1, 28006, Madrid, Spain

ARTICLE INFO

Handling Editor: Dr. Lesa Aylward

Keywords:
In silico model
Toxicology
FAIR
QSAR
PBK
Next generation risk assessment
New approach methodologies

ABSTRACT

In silico predictive models for toxicology include quantitative structure-activity relationship (QSAR) and physiologically based kinetic (PBK) approaches to predict physico-chemical and ADME properties, toxicological effects and internal exposure. Such models are used to fill data gaps as part of chemical risk assessment. There is a growing need to ensure *in silico* predictive models for toxicology are available for use and that they are reproducible. This paper describes how the FAIR (Findable, Accessible, Interoperable, Reusable) principles, developed for data sharing, have been applied to *in silico* predictive models. In particular, this investigation has focussed on how the FAIR principles could be applied to improved regulatory acceptance of predictions from such models. Eighteen principles have been developed that cover all aspects of FAIR. It is intended that FAIRification of *in silico* predictive models for toxicology will increase their use and acceptance.

1. Introduction

The FAIR (Findable, Accessible, Interoperable, Reusable) principles have been universally accepted for sharing data and become fundamental to data storage since their publication in 2016 (Wilkinson et al., 2016). They are based around good practice for data management and stewardship relating to scientific data, such that data may be discovered and re-used for downstream investigations. The aim is to enshrine good practice of data capture, curation and storage such that they may be available for future researchers thus saving time and resources (Briggs et al., 2021). Regarding chemical safety assessment, access to data relating to the intrinsic hazards of a chemical, as well as its exposure, is highly desirable. As such, areas such as toxicology are increasingly investigating the FAIR principles to make historic and newly determined data available. There are numerous reasons to capture all these data, not only to avoid unnecessary repetition of animal tests and support the implementation of the 3Rs principles (Russell and Burch, 1959), but also due to the cost of testing and possible legal reasons for the avoidance of testing (e.g., including, but not limited to, EU Regulation, EC N°1223/2009 (European Commission, 2009)).

Chemical safety assessment also relies increasingly on computational modelling. Predictive models in computational toxicology are applied for a variety of purposes in approaches such as New Approach Methodologies (NAMs) in Next Generation Risk Assessment (NGRA) and Integrated Approaches to Testing and Assessment (IATA). The models are frequently used to meet information requirements, i.e., for compounds and endpoints where an experimental test has not been performed, as well as to provide lines of evidence to support an overall weight of evidence for a particular decision (Mahony et al., 2020). There are a great variety of endpoints and properties that may be predicted, ranging from physico-chemical properties to the prediction of toxicological effects themselves (e.g., regulatory endpoints) or mechanistic information (e.g., binding to a receptor) as well as properties relating to internal exposure such as Absorption, Distribution, Metabolism and Excretion (ADME).

There are a very broad range of predictive models that require consideration. These are often based around a form of quantitative structure-activity relationship (QSAR) models that may predict physico-

* Corresponding author. School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, United Kingdom.
E-mail address: m.t.cronin@ljmu.ac.uk (M.T.D. Cronin).

https://doi.org/10.1016/j.yrtph.2023.105385
Received 3 January 2023; Received in revised form 18 February 2023; Accepted 7 April 2023
Available online 8 April 2023

Abbreviations:

ADME	Absorption, Distribution, Metabolism and Excretion
API	Application Programming Interface
eTOX	Integrating bioinformatics and chemoinformatics approaches for the development of expert systems allowing the *in silico* prediction of toxicity
eTRANSAFE	Enhancing TRANslational SAFEty Assessment through Integrative Knowledge Management
EURL ECVAM	EU Reference Laboratory for Alternatives to Animal Testing
FAIR	Findable, Accessible, Interoperable, Reusable
IATA	Integrated Approaches to Testing and Assessment
log P	logarithm of the octanol-water partition coefficient
NAM	New Approach Methodology
NGRA	Next Generation Risk Assessment
PBK	physiologically-based kinetic
QMRF	QSAR Model Reporting Format
QSAR	quantitative structure-activity relationship
RDMkit	Research Data Management toolkit for Life Sciences

chemical and ADME properties or toxicological effects. More detailed physiologically based kinetic (PBK) and related models are available to describe internal exposure. Whilst QSAR was founded in transparent regression analysis models in the 1960s, there is now an enormous diversity to the modelling approaches applied (Madden et al., 2020). This position paper will focus on "knowledge-based" methods that may support chemical safety assessment. In this context, this implies that the methods are characterised by the fact that they start from a defined piece of knowledge (for example a series of chemicals of known biological properties) from which they derive an empirical model (a set of rules that describe a regularity between the properties of the objects). Such methods have common elements (e.g., a training set of chemicals, a computational algorithm, predictive quality parameters) and may be used in QSAR or PBK modelling. These may incorporate a variety of computational algorithms from regression analysis to machine learning approaches. Thus, for the purposes of this paper and defining the FAIR principles in the toxicological context, the term "*in silico* predictive model" used in this paper is assumed to be any knowledge-based computational algorithm that will assist with the prediction of properties relating to chemical safety assessment. Further detail on the components of predictive models for toxicology is given in Section 1.1.

The total number of published, or publicly available, QSARs, PBK and other computational models that could support chemical safety assessment is unknown; given the resources described in Table 1, e.g., C-QSAR, a conservative estimate would be 10,000+ models. Likewise, the vast majority of endpoints and chemistries for which QSARs have been developed are currently only sparsely and heterogeneously documented, and not easily searchable. This makes the task of finding a useable model for a particular purpose very difficult, in particular when searching for key required variables such as endpoint, chemistry, type of model etc. There has been a concomitant growth in the use of software programmes which are freely or commercially available. The reality is that we may be missing out on the opportunity to use potentially valid and useful models, simply due to their lack of accessibility and findability (Worth, 2020). In addition, there is often very poor documentation of existing models, and the existing documentation often contains errors, such that even when a QSAR may be found, it may not be possible to reproduce it (Patel et al., 2018; Piir et al., 2018), a problem being particularly noted in the artificial intelligence community (Knight, 2022).

This paper aims to set out a vision for the full diversity of *in silico* toxicology models that may be suitable for chemical risk assessment to be FAIR. It does this by assessing the requirements for making predictive

Table 1
A selection of resources available to assist in the sharing of *in silico* models for toxicology.

Resource	Description	Source	Reference(s) and/or URL
Databases and other compilations of models, with predictive capability			
C-QSAR	A licensable collection of over 18,000 regression-based QSARs for a large number of endpoints	BioByte Corp., Covina CA, USA	http://www.biobyte.com/bb/prod/cqsarad.html; Kurup (2003)
COSMOS NG	A freely available knowledge hub with predictive capability and links to *in silico* models and profilers	MN-AM, Nürnberg, Germany; Columbus OH, USA	https://www.ng.cosmosdb.eu/; Yang et al. (2021)
Danish QSAR Database	A freely available on-line repository of QSAR model estimates for more than 600,000 substances including physico-chemical properties, environmental fate, bioaccumulation, eco-toxicity, absorption, metabolism and toxicity	Danish Technical University, National Food Institute, Copenhagen, Denmark	https://qsar.food.dtu.dk/; Chinen et al. (2020)
eTRANSAFE	A collaborative project aiming at collecting and sharing drug safety related data and developing *in silico* predictive models based on them	The eTRANSAFE Consortium	https://etransafe.eu/; https://www.imi.europa.eu/projects-results/project-factsheets/etransafe
oCHEM	A freely available on-line resource that allows for the creation, storage, dissemination and use of QSARs	Helmholtz Zentrum München, Neuherberg, Germany	https://ochem.eu; Sushko *et al.* (2011)
QSAR DataBase (DB)	An open on-line platform for the organisation, storage and use of QSARs. Searchable by a number of criteria. Contains over 500 QSARs which each given a unique identifier (DOI).	Institute of Chemistry, University of Tartu, Estonia	https://qsardb.org/; Ruusmann et al. (2015)
Models reporting formats			
In silico protocols	Guidelines on performing expert review of *in silico* models for a variety of toxicological endpoints	Consortium led by Instem, Columbus OH, USA	A large number of articles including Myatt et al. (2018), Ruiz et al. (2018)
OECD Guidance Document on the characterisation, validation and reporting of PBK models for regulatory purposes	A harmonised template to record all relevant information regarding a PBK model	OECD	https://www.oecd.org/chemicalsafety/risk-assessment/guidance-document-on-the-characterisation-validation-and-reporting-of-physiologically-

(*continued on next page*)

Table 1 (*continued*)

Resource	Description	Source	Reference(s) and/or URL
			based-kinetic-models-for-regulatory-purposes.pdf
QSAR-ML	An open XML format for the exchange of QSAR datasets		Spjuth et al. (2010)
QSAR Model Reporting Format (QMRF)	A harmonised template to summarise and report the key information of QSAR models		https://www.oecd.org/chemicalsafety/risk-assessment/validationofqsarmodels.htm; Worth (2010)
Model repositories, without predictive capability			
GitHub	Free-to-use provision of repositories for the distribution of QSARs, documentation etc., as well as R code, KNIME Workflows and similar tools	GitHub Inc.	https://github.com/
JRC QSAR Model Database	An historical archive of some 150 QMRFs that had been submitted to EURL ECVAM. The archive is no longer updated but may be downloaded free-of-charge.	European Commission's Joint Research Centre, EU Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM), Ispra, Italy	http://data.europa.eu/89h/e4ef8d13-d743-4524-a6eb-80e18b58cba4; EC JRC (2020)
PBK database	A freely available collection of the details of over 7,500 PBK models for 1,150 chemicals with details of model, species, chemicals etc.	European Commission's Joint Research Centre, EU Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM), Ispra, Italy	Thompson et al. (2021)
Other initiatives relevant to the sharing of models for chemical safety assessment			
BioModels	A freely available repository of mathematical models representing biological systems. Whilst most models in BioModels are not relevant to *in silico* toxicology, there are some examples of PBK models. Models generally do not have predictive capability	European Bioinformatics Institute, European Molecular Biology Laboratory, UK	https://www.ebi.ac.uk/biomodels/; Glont et al. (2018); Malik-Sheriff et al. (2020); Tiwari et al. (2021)
FAIRsharing	A curated, informative and educational resource on data and metadata standards, inter-related to databases and data policies encompassing a collection of registries – including some that are applicable to toxicology. The ELIXIR Toxicology Community is making use of this service to collate toxicology standards.	FAIRsharing team	https://fairsharing.org/
Research Data Management toolkit for Life Sciences (RDMkit)	An online guide which contains guidance for data management with a specific page for toxicology data	ELIXIR	https://rdmkit.elixir-europe.org/toxicology_data
RO-crate	A freely available resource which allows packaging of research data with their metadata	The University of Manchester, UK	https://w3id.org/ro/crate
The FAIRcookbook	An online, open and live resource for the Life Sciences to make and keep data FAIR. It contains recipes for FAIRification – some of which are directly applicable to toxicology or model inputs.	ELIXIR	https://faircookbook.elixir-europe.org/content/home.html

models FAIR in *in silico* toxicology, current initiatives to share such models, and how the FAIR principles that are currently aligned for data sharing could be adapted for predictive models. It does not intend to provide an in-depth methodology of *how* FAIRification of models may be achieved, but to highlight the topic and make recommendations for the steps forward to be made to increase the availability and sharing of predictive models.

1.1. Anatomy of an in silico predictive model for toxicology

For the purposes of this paper, a more detailed description of what we understand by a "model" is provided in this sub-section. In particular, it is important to identify the model components, analyse how they are generated, and who may own their intellectual property. Once this is established, it becomes easier to determine which components of a model can be shared and how this may be achieved.

Knowledge-based, predictive models result from training a certain "modelling engine" with a collection of objects, often called "training series" in the QSAR field. The training results in the identification of regularities between properties and annotations of the training series, which are captured in a collection of rules, mathematical functions, or a mixture of both. The outputs are analysed to interpret and understand the relationships between the object properties and the annotations. A characteristic of the models is the expectation of their ability to be applied to new objects so that they can predict annotations from the object properties.

In this generic description of models, the modelling engine describes a component of a predictive workflow, including all the algorithms required to reduce the object properties and annotations to a collection of mathematical variables (descriptors), normalise and scale them appropriately and apply machine learning algorithms. This workflow should have a software implementation to be functional and thus be able to build a model from a training series and predict object annotations for new objects, starting from a previously built model. In this description, we therefore identify the constitutive elements of the models which

must be considered in this article.

- The training series
- The modelling engine
- The model

This general description is shown schematically in Fig. 1 using a simple illustration. In Fig. 1 a toxicity value is related by regression analysis to a single molecular property, namely the logarithm of the octanol-water partition coefficient (log P), a property that is strongly related to toxicity (Cronin, 2006). In reality, the types of models that may be created could comprise one of many different "modelling engines" with potentially very high dimensionality in property space. The derived model can be used to predict an unknown toxicity for a new chemical providing the property value(s) are available. The latter function, i.e., use of the model, is utilised by the end-user and, as noted below, this is now often wrapped in a workflow for ease of application. Fig. 1 also confirms that the modelling engine cannot produce predictions on its own before it is applied to a training series to produce a model. Moreover, the same modelling engine can be used to train an unlimited number of models.

As a consequence of the complexity of what comprises a model, the model can be shared in different ways. For example, a modelling engine connected to a collection of models can be made available online, thus allowing users to predict the annotations of new chemicals. This shared model does not require any access to be given to the model itself, which is only visible via the modelling engine. Moreover, access to the modelling engine can be limited to using pre-built models for prediction or allowing other functionalities, such as retraining existing models or developing new ones. Examples of this method are online modelling servers including oCHEM (Sushko et al., 2011) or the QSAR DB (Ruusmann et al., 2015). It should be noted, however, that the use of models as "black boxes", i.e., without transparent description, may limit use for certain applications, for instance in the waiving of a requirement for a test to support regulatory decisions.

Other means of model sharing include the distribution of the pre-built models in computational formats that locally installed instances of modelling engines can use (the so-called workflow in Fig. 1). This method requires access to the modelling engines, ideally as open source. Examples of this method are models distributed as KNIME workflows (Steinmetz et al., 2015) or models developed using Flame (Pastor et al., 2021).

Regarding ownership of the model and intellectual property rights, it is also essential to consider the model components. Model developers own the resultant model, however that may be defined. When sharing models using an online server, the model owner can limit access to the prediction functionality on a per-model basis. In addition, it should be remembered that if a model is built with a proprietary modelling engine, whilst the model developer owns the model, the use of the model, for instance to make a prediction on a new chemical, could require access to the modelling engine.

2. Need for FAIR *in silico* predictive models for toxicology

In silico predictive models in toxicology are typically built on data for chemicals (with defined structure) adding value by creation of predictive capability. The models are based on the properties, or calculated structural descriptors, of molecules that should, in theory at least, be responsible for the biological effect and, where assessed, potency (Madden et al., 2020; Cronin et al., 2022b). The intimate relationship between the effect data and descriptors allows for mechanistic clarity and is crucial to give evidence for causality. The relationship between descriptors and effects may be based on knowledge of a mechanism of action, or possibly derived from molecular initiating, or key, events in a relevant adverse outcome pathway (Cronin and Richarz, 2017). The effect data modelled may represent any aspect of chemical safety assessment, but mainly are based on the endpoints needed to make a safety assessment decision, e.g., the endpoint required for a regulatory submission. The numbers of chemicals used to train the model may vary from as few as 5–10, up to the 1000s or even more. As such, different types of modelling algorithms have been applied, with machine learning approaches being seen as the solution to the largest data matrices. As noted above, this position paper will concentrate on knowledge-based models.

There are many uses for *in silico* models in chemical safety assessment, ranging from the rapid screening of toxicity in chemical libraries through to acting as surrogates for tests in regulatory submissions. For the latter, protocols have been established to provide means to evaluate a model with a view to making predictions from them acceptable for a particular purpose, e.g., the OECD Principles for the Validation of (Q)

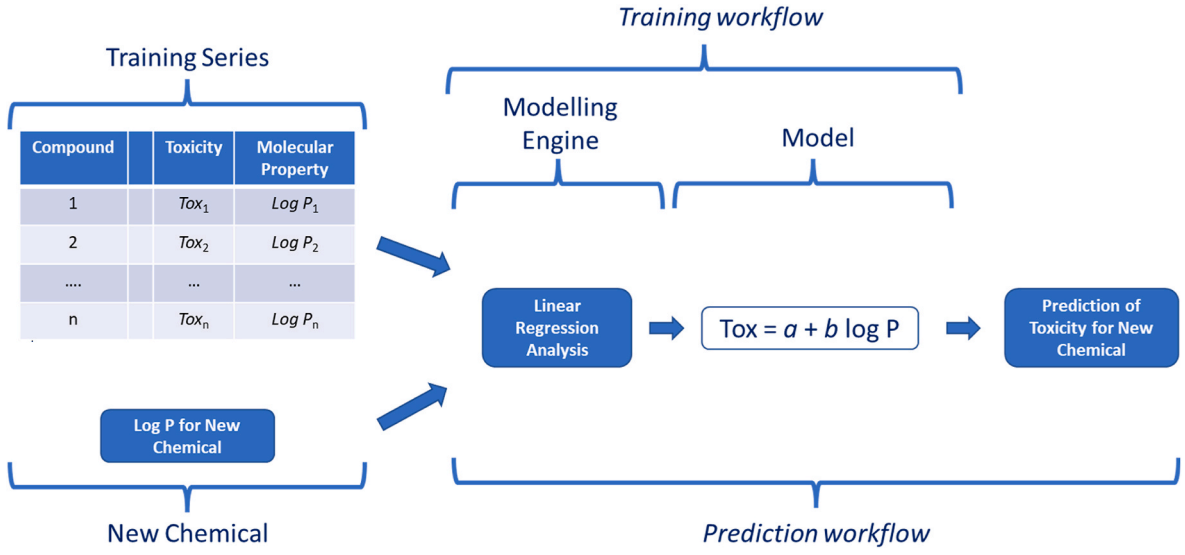

Fig. 1. A schematic representation of a simple *in silico* predictive model for toxicity, namely a regression analysis on one descriptor (logarithm of the octanol-water partition coefficient (log P)), showing the interrelationship between the components of the model and the workflows for training the model and making predictions (the data for the new chemical may flow either into the analysis, e.g., for normalisation, or the model itself). Meta data may be associated with multiple aspects of the model, from all data in the training series, to the model itself.

SARs (OECD, 2007) and criteria for the characterisation of uncertainties (Belfield *et* al., 2021; Cronin et al., 2019, 2022a). These principles have enabled frameworks to capture QSAR models – notable being the QSAR Model Reporting Format (QMRF) (Worth, 2010). However, there are no standardised means or requirement to share the models. The current lack of model sharing policies constitutes a clear argument for advancing towards the definition of a FAIR models' policy.

It is clear that making models FAIR will assist in the capture, discovery and sharing of QSAR and PBK models and numerous other approaches. It also provides an opportunity to develop and standardise the documentation of models. In addition, making models FAIR will support the independent verification of models which will, in turn, improve trust in models. This will allow for greater use of models to make predictions and encourage global harmonisation of models and modelling approaches. Harmonisation of the terminology used to describe and record models will be a key factor in their standardisation and sharing, since not harmonising the description of models will decrease the possibilities of easy searching and retrieval of models from repositories. FAIR will also ensure greater reproducibility of models, the lack of which has been highlighted as a fundamental issue (Patel et al., 2018; Piir et al., 2018), enabling the replication or re-use of models. Progress in toxicology is already underway with efforts to standardise approaches and improve collaboration (Martens et al., 2021). Likewise, there has been recent progress in the FAIR Principles for Research Software, the so-called FAIR4RS principles (Chue Hong et al., 2022). There will be several mutual benefits in aligning the FAIR principles for *in silico* models for toxicology with the FAIR4RS principles. Specifically, these mutual benefits will be the possibility of international agreement and harmonisation on this topic (where currently none exists), identification of needs and priorities of the FAIR approach for such models, and the establishment of a set of practical, bespoke, principles to enable model sharing, amongst other benefits.

It is not only essential that researchers can find models easily and efficiently, but also to support regulatory submissions from modellers. With regard to regulatory submission, the IMI2 eTRANSAFE (Enhancing TRANslational SAFEty Assessment through Integrative Knowledge Management) project, building on the foundations of the IMI1 eTOX (Integrating bioinformatics and chemoinformatics approaches for the development of expert systems allowing the *in silico* prediction of toxicity) project, is developing a variety of *in silico* models to support the safety assessment of pharmaceuticals (Pognan et al., 2021), including a framework for a cooperative development of predictive models and their usage (Pastor et al., 2021). Previous work in these projects has developed a scheme to demonstrate verification of models and reproducibility of predictions (Hewitt et al., 2015). Such a scheme provides evidence that a model is FAIR, subsequently increasing confidence in the models and their predictions, in particular regarding the use of predictions in regulatory submissions.

3. Current initiatives to share *in silico* toxicology models

There continues to be attempts to support the sharing of *in silico* models for toxicology. A non-exhaustive selection of these resources is summarised in Table 1. It is noted that not all the resources listed in Table 1 are for sharing models directly – it also includes protocols and general information resources. The resources offered in Table 1 represent a wide variety of approaches ranging from commercial to publicly available, those offering a predictive capability (i.e., a chemical structure can be entered to obtain a prediction) and those without this capability, as well as formats and approaches to capture models and other resources. Of the resources identified in Table 1, it is arguable that the QSAR DB goes the furthest to achieving FAIR principles for the sharing of models, with reference to making QSAR FAIR made on their website. There also exists a huge number of databases containing information that may support the generation of *in silico* models (Pawar et al., 2019), with these acknowledged but not summarised in this section.

4. Development of FAIR principles for *in silico* models

The FAIR principles, originally devised for data sharing, are herein adapted to the needs of *in silico* modelling. It is important to understand the context of the FAIR principles related to data sharing, which aimed to "*define characteristics that contemporary data resources, tools, vocabularies and infrastructures should exhibit to assist discovery and reuse by third-parties*" (Wilkinson et al., 2016). With regards to sharing *in silico* models, all of these concepts are valid, especially with the overall concept of facilitating "*discovery and reuse"* in addition to the other benefits, such as verification and trust, noted above, which will improve the utility and acceptance of models. Whilst the FAIR principles for data sharing do not specifically include verification and trust, they do indeed go further in other areas, emphasising the requirement "*to improve knowledge discovery through assisting both humans, and their computational agents, in the discovery of, access to, and integration and analysis of, task-appropriate scientific data and other scholarly digital objects*" (Wilkinson et al., 2016). Within the context of *in silico* predictive models, we take this to mean that the model itself should be shared, in a useable form, either directly (by sharing an accessible prediction service) or indirectly (by sharing the components and precise instructions to reproduce the model).

Following the spirit of the FAIR principles for data sharing, we have adapted the FAIR requirements to the context of the *in silico* predictive models. Specifically, these requirements intend to ensure that a model can be located, i.e., it is *Findable*; that once located, the model and appropriate meta-data are retrievable, i.e., it is *Accessible*; the model is defined in a manner that it can be integrated with other software, i.e., it is *Interoperable*; and that predictions can be made by a robust, well-annotated version of the model, that will make the same predictions regardless of the platform and software used, i.e., it is *Reusable*.

The FAIR principles for the sharing of *in silico* predictive models are summarised below (principles marked with an asterisk are the same, or adapted from, those for data sharing). At this time, these principles apply to the sharing of models rather than quality of the underlying data or the validity of predictions from the models. They extend and clarify the original FAIR principles for data sharing to specifically allow for and promote the sharing of *in silico* models for toxicology. The principles for the FAIR sharing of *in silico* models for toxicology are:

To be *Findable*.

F1 *Each model is assigned a globally unique and persistent identifier and different versions are assigned distinct identifiers

F2 Models are described with rich meta data covering all aspects of the model, for example:

- F2.1 Models are associated with searchable meta data for the property or endpoint to be predicted
- F2.2 Models are associated with searchable meta data or descriptions of the chemicals (e.g. InCHI or SMILES), or chemical class(es), within the model, or a description of its applicability domain

F3 *Models' (meta)data clearly and explicitly include the identifier of the model they describe and are registered or indexed in a searchable resource

F4 Models are registered or indexed in a searchable resource

- F4.1 Models' identifiers should be optimised to allow for use in multiple search engines

To be *Accessible*.

A1 *Models are retrievable by their identifier using a standardised communications protocol

- A1.1 The model (and any associated protocol represented by the model meta data) is openly accessible or reimplementable

A1.2 The model (and any associated protocol) allows for an authentication and authorisation procedure, where necessary

A2 Model (meta)data are accessible even when the model is no longer available, unless restricted for commercial, ethical or data protection reasons (e.g., blinding of confidential chemical structures)

To be *Interoperable*.

I1 The models and their (meta)data are described in a standardised manner, i.e., standards to define chemical structures, endpoints, molecular descriptors and modelling algorithms

I2 The model reads, writes and exchanges data in a way that meets domain-relevant community standards

I3 The model must be interoperable with other software, e.g., with a clearly defined input/output i.e., with an appropriate Application Programming Interface (API) for shared web services

I4 *(Meta)data use a formal, accessible, shared, and broadly applicable language for knowledge representation

I5 *(Meta)data use vocabularies that follow FAIR principles

I6 The model includes qualified references to other objects, such as molecular descriptors

To be *Reusable*.

R1 The model is available for its use in some format (e.g., source code, executable, library or service)

R2 The usage license of the model should be clearly defined and appropriate to encourage its use

R3 The storage of the model and (meta)data should be done on a sustainable and future-proofed platform, anticipating the impact on the availability of software changes over time

R4 Software includes qualified references to other software, e.g., so that the correct molecular descriptors can be obtained, either as part of the model or storage of the molecular descriptors software or experimental protocol

R5 *(Meta)data are richly described with a plurality of accurate and relevant attributes

R5.1 * The model and its (meta)data are associated with detailed provenance

R6 *The model and its (meta)data meet domain-relevant community standards for documentation

5. Priorities to make models FAIR

To make models for toxicology FAIR, there is an urgent need for an internationally agreed vision and an associated roadmap to achieve this goal. Only when stakeholders, including potential funders, agree will progress be achieved.

In order to stimulate progress, it must be recognised that the benefits to the FAIRification of *in silico* predictive models go beyond the simple advantages of being able to share models successfully. The benefits include making a useable resource that can assist chemical safety assessment, as well as being interrogated to understand the applicability domain of models, and where data gaps exist in the domain. There is also a societal responsibility to enable access to models created and to record the outputs of research efforts. The modelling community must be challenged to make harmonised and useable models. This will reinforce the credibility of models and demonstrate responsible, ethical, transparent and efficient science. We therefore start with the premise of the acceptance, understanding and promotion of the FAIR principles for modelling globally, even if fine details need to be resolved.

There will inevitably be a number of issues that require further development and acceptance, beyond the current state of the art, to achieve the goal of FAIR *in silico* models. From the outset it must be appreciated that key to the development of any data resource to be used in predictive modelling is the harmonisation of the terminology for reporting models. This could start with harmonised ontologies for endpoints, for which much work has already been undertaken, for instance Boyles et al. (2019) and Ravagli et al. (2017), but for which a single authoritative standard is still lacking. It will also require harmonised ontologies to describe the models e.g., for statistical and machine learning methods, definitions of molecular descriptors and chemical identifiers. In addition, harmonisation will be required in the definition of the methods for analysis of model performance, such as provided by Walsh et al. (2021). Much of this could be adapted from that already used for QMRF and elsewhere for ontologies for statistics (Zheng et al., 2016). Whilst progress has been made, it is clear that harmonisation of terminology for endpoints and models is still one of the greatest challenges to be undertaken.

It is also clear that the widescale sharing of models will need appropriate investment in the repository(ies) and resources to maintain the platform on which any repository is based. Whilst some progress has been made, there is still a need for a sustainable means to share models. Comparable efforts to store models do exist e.g., BioModels, and remain active and on-line due to the creation of an appropriate business model. Relying on free storage resources is one way forward, but will be extremely limited in terms of the search capabilities and practical use.

The FAIR principles on accessibility do not preclude restrictions on access but they do require metadata longevity and for the access protocols and access authorisation used to adhere to open standards and be clearly defined (Wise et al., 2019). However, in the case of training and test datasets used to build and validate the model there may be legal (e.g., IPR protection) and ethical (e.g., patient confidentiality) reasons, as well as commercial ones, that would preclude open access. The consequence of restricting access to data must be appreciated and a means to provide adequate access to the data is required. In addition to restrictions on data, there needs to be provision for understanding and sharing of models either created in proprietary software, or where the models themselves are restricted (for instance for commercial reasons). A means to respect the intellectual property of models needs to be created such that these models remain FAIR, thus increasing the possibilities for their use and acceptance.

6. Conclusions

There is an undoubted, and urgent, need to make *in silico* predictive models for toxicology FAIR. We believe this is an achievable goal and, given appropriate resources, much progress could be made in the short to medium term. There are numerous reasons and benefits to the FAIRification of *in silico* models, the most fundamental is to make models available and accessible to all enabling and supporting the 3Rs. It is highly probable that chemical risk assessors are missing out on opportunities to use *in silico* models simply as they may not know of their existence. Similarly, due to poor documentation, *in silico* models may be used inappropriately, e.g., out of applicability domain or for the incorrect endpoint. The ultimate sustainability of *in silico* models is also a key advantage. It is unacceptable that research efforts should be placed into modelling, often from public funding, that are unfindable or unusable. Finally, having open and transparent models, easily accessible, will increase trust for all users. This will be especially important for regulatory submissions where governmental agencies can re-run models to check predictions for the target and similar chemicals.

In order to achieve the goal of making *in silico* models in toxicology FAIR, the priorities and an overall strategy should be devised. This will need agreement at multiple levels, across industrial sectors, stakeholders and geographical regions. The intention is that the FAIR principles described in this paper will act as a template for FAIR principles to be applied to all models of biology.

CrediT author statement

Mark T.D. Cronin: Conceptualization; Writing - Original Draft; **Samuel J. Belfield**: Conceptualization; Writing - Review & Editing; **Katharine A. Briggs:** Writing - Review & Editing; **Steven J. Enoch:** Writing - Review & Editing; **James W. Firman:** Writing - Review & Editing; **Markus Frericks:** Writing - Review & Editing; **Clare Garrard:** Conceptualization; Writing - Review & Editing; **Peter H. Maccallum:** Conceptualization; Writing - Review & Editing; **Judith C. Madden:** Writing - Review & Editing; **Manuel Pastor:** Conceptualization; Writing - Review & Editing; **Ferran Sanz:** Conceptualization; Writing - Review & Editing; **Inari Soininen:** Writing - Review & Editing; **Despoina Sousoni:** Conceptualization; Writing - Review & Editing.

Funding

This research received funding from the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) under grant agreement eTRANSAFE (777365), the European Union's Horizon 2020 ELIXIR-CONVERGE Project (871075) and research and innovation programme under grant agreement No 964537 (RISK-HUNT3R).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

This research received funding from the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) under grant agreement eTRANSAFE (777365). The intellectual contribution of partners in the IMI2 JU FAIRplus project (802750) is also gratefully acknowledged. These Joint Undertakings receive support from the European Union's Horizon 2020 research and innovation programme and EFPIA companies in kind contribution. This research also received funding from the European Union's Horizon 2020 ELIXIR-CONVERGE Project (871075) and research and innovation programme under grant agreement No 964537 (RISK-HUNT3R).

References

Belfield, S.J., Enoch, S.J., Firman, J.W., Madden, J.C., Schultz, T.W., Cronin, M.T.D., 2021. Determination of "fitness-for-purpose" of quantitative structure-activity relationship (QSAR) models to predict (eco-)toxicological endpoints for regulatory use. Regul. Toxicol. Pharmacol. 123, 104956.

Boyles, R.R., Thessen, A.E., Waldrop, A., Haendel, M.A., 2019. Ontology-based data integration for advancing toxicological knowledge. Curr. Opin. Toxicol. 16, 67–74.

Briggs, K., Bosc, N., Camara, T., Diaz, C., Drew, P., Drewe, W., Kors, J., van Mulligen, E., Pastor, M., Pognan, F., Ramon Quintana, J., Sarntivijai, S., Steger-Hartmann, T., 2021. Guidelines for FAIR sharing of preclinical safety and off-target pharmacology data. ALTEX 38, 187–197.

Chinen, K.K., Klimenko, K., Taxvig, C., Nikolov, N.G., Wedebye, E.B., 2020. QSAR modeling of different minimum potency levels for *in vitro* human CAR activation and inhibition and screening of 80,086 REACH and 54,971 U.S. substances. *Comput. Toxicol.* 14, 100121.

Chue Hong, N.P., Katz, D.S., Barker, M., Lamprecht, A.-L., Martinez, C., Psomopoulos, F. E., Harrow, J., Castro, L.J., Gruenpeter, M., Martinez, P.A., Honeyman, T., Struck, A., Lee, A., Loewe, A., van Werkhoven, B., Jones, C., Garijo, D., Plomp, E., Genova, F., , et al.RDA FAIR4R, W.G., 2022. FAIR principles for research software (FAIR4RS principles), 1.0. https://doi.org/10.15497/RDA00068.

Cronin, M.T.D., 2006. The role of hydrophobicity in toxicity prediction. Curr. Comput. Aided Drug Des. 2, 405–413.

Cronin, M.T.D., Bauer, F.J., Bonnell, M., Campos, B., Ebbrell, D.J., Firman, J.W., Gutsell, S., Hodges, G., Patlewicz, G., Sapounidou, M., Spînu, N., Thomas, P.C., Worth, A.P., 2022a. A scheme to evaluate structural alerts to predict toxicity – assessing confidence by characterising uncertainties. Regul. Toxicol. Pharmacol. 135, 105249.

Cronin, M.T.D., Enoch, S.J., Madden, J.C., Rathman, J.F., Richarz, A.-N., Yang, C., 2022b. A review of *in silico* toxicology approaches to support the safety assessment of cosmetics-related materials. Comput. Toxicol. 21, 100213.

Cronin, M.T.D., Richarz, A.-N., 2017. Relationship between adverse outcome pathways and chemistry-based *in silico* models to predict toxicity. Appl. in Vitro Toxicol. 3, 286–297.

Cronin, M.T.D., Richarz, A.-N., Schultz, T.W., 2019. Identification and description of the uncertainty, variability, bias and influence in quantitative structure-activity relationships (QSARs) for toxicity prediction. Regul. Toxicol. Pharmacol. 106, 90–104.

EC JRC (European Commission, Joint Research Centre), 2020. JRC QSAR model database. European Commission, Joint Research Centre (JRC). PID. http://data.europa.eu/89h/e4ef8d13-d743-4524-a6eb-80e18b58cba4.

European Commission, 2009. Regulation (EC) No 1223/2009 of the European parliament and of the council of 30 november 2009 on cosmetic products. Off. J. Eur. Union L342, 59–209.

Glont, M., Nguyen, T.V.N., Graesslin, M., Hälke, R., Ali, R., Schramm, J., Wimalaratne, S. M., Kothamachu, V.B., Rodriguez, N., Swat, M.J., Eils, J., Eils, R., Laibe, C., Malik-Sheriff, R.S., Chelliah, V., Le Novère, N., Hermjakob, H., 2018. BioModels: expanding horizons to include more modelling approaches and formats. Nucleic Acids Res. 46, D1248–D1253.

Hewitt, M., Ellison, C.M., Cronin, M.T.D., Pastor, M., Steger-Hartmann, T., Munoz-Muriendas, J., Pognan, F., Madden, J.C., 2015. Ensuring confidence in predictions: a scheme to assess the scientific validity of *in silico* models. Adv. Drug Deliv. Rev. 86, 101–111.

Knight, W., 2022. Sloppy use of machine learning is causing a 'Reproducibility Crisis' in science. Wired 10 August 2022, available at: https://www.wired.com/story/machine-learning-reproducibility-crisis/. Wired 10 August 2022, available at:

Kurup, A., 2003. C-QSAR: a database of 18,000 QSARs and associated biological and physical data. J. Comput. Aided Mol. Des. 17, 187–196.

Madden, J.C., Enoch, S.J., Paini, A., Cronin, M.T.D., 2020. A review of *in silico* tools as alternatives to animal testing: principles, resources and applications. ATLA 48, 146–172.

Mahony, C., Ashton, R.S., Birk, B., Boobis, A.R., Cull, T., Daston, G.P., Ewart, L., Knudsen, T.B., Manou, I., Maurer-Stroh, S., Margiotta-Casaluci, L., Muller, B.P., Nordlund, P., Roberts, R.A., Steger-Hartmann, T., Vandenbossche, E., Viant, M.R., Vinken, M., Whelan, M., Zvonimir, Z., Cronin, M.T.D., 2020. New ideas for non-animal approaches to predict repeated-dose systemic toxicity: report from an EPAA Blue Sky Workshop. Regul. Toxicol. Pharmacol. 114, 104668.

Malik-Sheriff, R.S., Glont, M., Nguyen, T.V.N., Tiwari, K., Roberts, M.G., Xavier, A., Vu, M.T., Men, J., Maire, M., Kananathan, S., Fairbanks, E.L., Meyer, J.P., Arankalle, C., Varusai, T.M., Knight-Schrijver, V., Li, L., Dueñas-Roca, C., Dass, G., Keating, S.M., Park, Y.M., Buso, N., Rodriguez, N., Hucka, M., Hermjakob, H., 2020. BioModels — 15 years of sharing computational models in life science. Nucleic Acids Res. 48, D407–D415.

Martens, M., Stierum, R., Schymanski, E.L., Evelo, C.T., Aalizadeh, R., Aladjov, H., Arturi, K., Audouze, K., Babica, P., Berka, K., Bessems, J., Blaha, L., Bolton, E.E., Cases, M., Damalas, D.E., Dave, K., Dilger, M., Exner, T., Geerke, D.P., Grafström, R., Gray, A., Hancock, J.M., Hollert, H., Jeliazkova, N., Jennen, D., Jourdan, F., Kahlem, P., Klanova, J., Kleinjans, J., Kondic, T., Kone, B., Lynch, I., Maran, U., Martinez Cuesta, S., Ménager, H., Neumann, S., Nymark, P., Oberacher, H., Ramirez, N., Remy, S., Rocca-Serra, P., Salek, R.M., Sallach, B., Sansone, S.-A., Sanz, F., Sarimveis, H., Sarntivijai, S., Schulze, T., Slobodnik, J., Spjuth, O., Tedds, J., Thomaidis, N., Weber, R.J.M., van Westen, G.J.P., Wheelock, C.E., Williams, A.J., Witters, H., Zdrazil, B., Županič, A., Willighagen, E.L., 2021. ELIXIR and Toxicology: a community in development. F1000Research 2021 10 (ELIXIR), 1129. https://doi.org/10.12688/f1000research.74502.1.

Myatt, G.J., Ahlberg, E., Akahori, Y., Allen, D., Amberg, A., Anger, L.T., Aptula, A., Auerbach, S., Beilke, L., Bellion, P., Benigni, R., Bercu, J., Booth, E.D., Bower, D., Brigo, A., Burden, N., Cammerer, Z., Cronin, M.T.D., Cross, K.P., Custer, L., Dettwiler, M., Dobo, K., Ford, K.A., Fortin, M.C., Gad-McDonald, S.E., Gellatly, N., Gervais, V., Glover, K.P., Glowienke, S., Van Gompel, J., Gutsell, S., Hardy, B., Harvey, J.S., Hillegass, J., Honma, M., Hsieh, J.-H., Hsu, C.-W., Hughes, K., Johnson, C., Jolly, R., Jones, D., Kemper, R., Kenyon, M.O., Kim, M.T., Kruhlak, N.L., Kulkarni, S.A., Kümmerer, K., Leavitt, P., Majer, B., Masten, S., Miller, S., Moser, J., Mumtaz, M., Muster, W., Neilson, L., Oprea, T.I., Patlewicz, G., Paulino, A., Lo Piparo, E., Powley, M., Quigley, D.P., Reddy, M.V., Richarz, A.-N., Ruiz, P., Schilter, B., Serafimova, R., Simpson, W., Stavitskaya, L., Stidl, R., Suarez-Rodriguez, D., Szabo, D.T., Teasdale, A., Trejo-Martin, A., Valentin, J.-P., Vuorinen, A., Wall, B.A., Watts, P., White, A.T., Wichard, J., Witt, K.L., Woolley, A., Woolley, D., Zwickl, C., Hasselgren, C., 2018. *In silico* toxicology protocols. Regul. Toxicol. Pharmacol. 96, 1–17.

OECD (Organisation for Economic Cooperation and Development), 2007. Guidance Document on the Validation of (Quantitative) Structure-Activity Relationships. ENV/JM/MONO. OECD, Paris, p. 154, 2.

Pastor, M., Gómez-Tamayo, J.C., Sanz, F., 2021. Flame: an open source framework for model development, hosting, and usage in production environments. J. Cheminf. 13, 31.

Patel, M., Chilton, M.L., Sartini, A., Gibson, L., Barber, C., Covey-Crump, L., Przybylak, K. R., Cronin, M.T.D., Madden, J.C., 2018. Assessment and reproducibility of quantitative structure–activity relationship models by the nonexpert. J. Chem. Inf. Model. 58, 673–682.

Pawar, G., Madden, J.C., Ebbrell, D., Firman, J.W., Cronin, M.T.D., 2019. *In silico* toxicology data resources to support read-across and (Q)SAR. Front. Pharmacol. 10, 561.

Piir, G., Kahn, I., García-Sosa, A.T., Sild, S., Ahte, P., Maran, U., 2018. Best practices for QSAR model reporting: physical and chemical properties, ecotoxicity, environmental fate, human health, and toxicokinetics endpoints. Environ. Health Perspect. 126, 126001.

Pognan, F., Steger-Hartmann, T., Díaz, C., Blomberg, N., Bringezu, F., Briggs, K., Callegaro, G., Capella-Gutierrez, S., Centeno, E., Corvi, J., Drew, P., Drewe, W.C., Fernández, J.M., Furlong, L.I., Guney, E., Kors, J.A., Mayer, M.A., Pastor, M., Piñero, J., Ramírez-Anguita, J.M., Ronzano, F., Rowell, P., Saüch-Pitarch, J., Valencia, A., van de Water, B., van der Lei, J., van Mulligen, E., Sanz, F., 2021. The eTRANSAFE project on translational safety assessment through integrative knowledge management: achievements and perspectives. Pharmaceuticals 14, 237.

Ravagli, C., Pognan, F., Marc, P., 2017. OntoBrowser: a collaborative tool for curation of ontologies by subject matter experts. Bioinformatics 33, 148–149.

Ruiz, P., Schilter, B., Serafimova, R., Simpson, W., Stavitskaya, L., Stidl, R., Suarez-Rodriguez, D., Szabo, D.T., Teasdale, A., Trejo-Martin, A., Valentin, J.-P., Vuorinen, A., Wall, B.A., Watts, P., White, A.T., Wichard, J., Witt, K.L., Woolley, A., Woolley, D., Zwickl, C., Hasselgren, C., 2018. *In silico* toxicology protocols. Regul. Toxicol. Pharmacol. 96, 1–17.

Russell, W.M.S., Burch, R.L., 1959. The Principles of Humane Experimental Technique. Methuen.

Ruusmann, V., Sild, S., Maran, U., 2015. QSAR DataBank repository: open and linked qualitative and quantitative structure–activity relationship models. J. Cheminf. 7, 32.

Spjuth, O., Willighagen, E.L., Guha, R., Eklund, M., Wikberg, J.E.S., 2010. Towards interoperable and reproducible QSAR analyses: exchange of datasets. J. Cheminf. 2, 5.

Steinmetz, F.P., Mellor, C.L., Meinl, T., Cronin, M.T.D., 2015. Screening chemicals for receptor-mediated toxicological and pharmacological endpoints: using public data to build screening tools within a KNIME workflow. Mol. Inform. 34, 1710–178.

Sushko, I., Novotarskyi, S., Körner, R., Pandey, A.K., Rupp, M., Teetz, W., Brandmaier, S., Abdelaziz, A., Prokopenko, V.V., Tanchuk, V.Y., Todeschini, R., Varnek, A., Marcou, G., Ertl, P., Potemkin, V., Grishina, M., Gasteiger, J., Schwab, C., Baskin II, Palyulin, V.A., Radchenko, E.V., Welsh, W.J., Kholodovych, V., Chekmarev, D., Cherkasov, A., Aires-de-Sousa, J., Zhang, Q.Y., Bender, A., Nigsch, F., Patiny, L., Williams, A., Tkachenko, V., Tetko, I.V., 2011. Online chemical modeling environment (OCHEM): web platform for data storage, model development and publishing of chemical information. J. Comput. Aided Mol. Des. 25, 533–554.

Thompson, C.V., Firman, J.W., Goldsmith, M.R., Grulke, C.M., Tan, Y.-M., Paini, A., Penson, P.E., Sayre, R.R., Webb, S., Madden, J.C., 2021. A systematic review of published physiologically-based kinetic models and an assessment of their chemical space coverage. ATLA 49, 197–208.

Tiwari, K., Kananathan, S., Roberts, M.G., Meyer, J.P., Shohan, M.U.S., Xavier, A., Maire, M., Zyoud, A., Men, J., Ng, S., Nguyen, T.V.N., Glont, M., Hermjakob, H., Malik-Sheriff, R.S., 2021. Reproducibility in systems biology modelling. Mol. Syst. Biol. 17, e9982.

Walsh I, Fishman D, Garcia-Gasulla D, Titma T, Pollastri G, ELIXIR machine learning focus group, harrow J, psomopoulos FE, tosatto SCE (2021) DOME: recommendations for supervised machine learning validation in biology. Nat. Methods 18: 1122–1127..

Wilkinson, M.D., Dumontier, M., Aalbersberg, I., Appleton, G., Axton, M., Baak, A., Blomberg, N., Boiten, J.-W., da Silva Santos, L.B., Bourne, P.E., Bouwman, J., Brookes, A.J., Clark, T., Crosas, M., Dillo, I., Dumon, O., Edmunds, S., Evelo, C.T., Finkers, R., Gonzalez-Beltran, A., Gray, A.J.G., Groth, P., Goble, C., Grethe, J.S., Heringa, J., t Hoen, P.A.C., Hooft, R., Kuhn, T., Kok, R., Kok, J., Lusher, S.J., Martone, M.E., Mons, A., Packer, A.L., Persson, B., Rocca-Serra, P., Roos, M., van Schaik, R., Sansone, S.-A., Schultes, E., Sengstag, T., Slater, T., Strawn, G., Swertz, M. A., Thompson, M., van der Lei, J., van Mulligen, E., Velterop, J., Waagmeester, A., Wittenburg, P., Wolstencroft, K., Zhao, J., Mons, B., 2016. The FAIR Guiding Principles for scientific data management and stewardship. Sci. Data 3, 160018.

Wise, J., de Barron, A.G., Splendiani, A., Balali-Mood, B., Vasant, D., Little, E., Mellino, G., Harrow, I., Smith, I., Taubert, J., van Bochove, K., Romacker, M., Walgemoed, P., Jimenez, R.C., Winnenburg, R., Plasterer, T., Gupta, V., Hedley, V., 2019. Implementation and relevance of FAIR data principles in biopharmaceutical R&D. Drug Discov. Today 24, 933–938.

Worth, A.P., 2020. Computational modelling for the sustainable management of chemicals. Comput. Toxicol. 14, 100122.

Worth, A.P., 2010. The role of QSAR methodology in the regulatory assessment of chemicals. In: Puzyn, T., Lesczynski, J., Cronin, M.T.D. (Eds.), Recent Advances in QSAR Studies: Methods and Applications. Springer, Dordrecht, The Netherlands, pp. 367–382.

Yang, C., Cronin, M.T.D., Arvidson, K.B., Bienfait, B., Enoch, S.J., Heldreth, B., Hobocienski, B., Muldoon-Jacobs, K., Lan, Y., Madden, J.C., Magdziarz, T., Marusczyk, J., Mostrag, A., Nelms, M., Neagu, D., Przybylak, K., Rathman, J.F., Park, J., Richarz, A.-N., Richard, A.M., Ribeiro, J.V., Sacher, O., Schwab, C., Vitcheva, V., Volarath, P., Worth, A.P., 2021. COSMOS Database and Next Generation: a database and knowledge hub to leverage biological data from public resources in collaboration with regulatory offices for cosmetics and food ingredients. Comput. Toxicol. 19, e100175.

Zheng, J., Harris, M.R., Masci, A.M., Lin, Y., Hero, A., Smith, B., He, Y., 2016. The Ontology of Biological and Clinical Statistics (OBCS) for standardized and reproducible statistical analysis. J. Biomed. Semant. 14, 53.