ECHA
EUROPEAN CHEMICALS AGENCY

Topical Scientific Workshop on New Approach Methodologies in Regulatory Science

Helsinki, 19–20 April 2016

Background Document

Topical Scientific Workshop on New Approach Methodologies in Regulatory Science, 19–20 April 2016

The **primary objective of this workshop is to provide a forum to open a dialogue with stakeholders on how new approach methodologies (NAMs) can be used in a regulatory context in general and specifically how they can support read-across and prioritisation under legislative frameworks** such as REACH. The workshop draws inspiration from the EU research programme SEURAT-1 and the US Tox21 initiative, but also takes into account general progress from the scientific field. **NAMs include any *in silico*, *in chemico* or *in vitro* technique that may provide data or information that could support regulatory decision making.**

Disclaimer. This background document has been prepared by an external contractor to facilitate the discussion at the topical scientific workshop and does not necessarily represent ECHA's views or position.

1. Introduction

This document sets out the background, drivers and remit of ECHA's Topical Scientific Workshop on New Approach Methodologies in Regulatory Science, 19–20 April 2016. It is intended to provide a focused and directed summary of the area of science supporting legislation such as REACH, CLP and the Biocidal Products Regulation rather than a detailed and comprehensive review of the area. The document aims to inform, stimulate and support discussion and debate within the breakout sessions. The outcomes of the workshop should stimulate innovation and new thinking with regard to the use of NAMs in chemical hazard assessment.

It is recognised that the focus of this topical scientific workshop, especially Day 1, is on REACH and CLP. However, the principles of applying NAMs in a regulatory context apply to other schemes, e.g. in the EU for other products such as the Biocidal Products Regulation and are also valid for non-EU chemical legislations. With the other schemes, it should be remembered that the applicability of NAMs differs depending on the regulatory mandate i.e. some schemes do not empower the regulator to provide a standard data set.

1.1. Regulatory context

The **goal of this workshop is to gather information and answer questions as a support to implement current European legislation relevant to ECHA**, specifically relating to REACH, CLP and the Biocidal Products Regulation. REACH is a regulation of the European Union, adopted to improve the protection of human health and the environment from the risks that can be posed by chemicals, while enhancing the competitiveness of the EU chemicals industry. It also promotes alternative methods for the hazard assessment of substances to reduce the number of tests on animals (European Union, 2007). REACH allows for adaptations of the standard information requirements and the use of non-standard methods (ECHA 2011a), providing that the information is adequate for classification and risk assessment. Non-standard information can also be used to support other adaptations such as *in vitro* test results, read-across and in weight of evidence (WoE) approaches.

1.2. Current use of alternatives

ECHA supports reduction in animal testing to ascertain the hazardous properties of registered substances through data sharing and supporting the use of alternative methods and approaches. The use of alternatives includes *in silico* or

computational approaches, such as (quantitative) structure-activity relationships ((Q)SARs) and read-across, and the application of the broad context of *in vitro* methodologies such as specific validated methods through to high content mechanistically-based screening assays. ECHA supports the use of alternatives and consideration of non-standard data in a number of ways e.g. through extensive guidance; communication with registrants; funding activities such as the OECD QSAR Toolbox; input into case studies and opinion-forming research such as the EU SEURAT-1 Cluster and EU-ToxRisk Projects.

In addition to specific guidance from ECHA on the avoidance of unnecessary animal testing (ECHA, 2010), it is mandated to review and report every three years on the use of animal testing in submitted dossiers. So far, two significant reports have been produced (ECHA, 2011; 2014). One of the key, and initially surprising, findings of both reports was the high uptake and application of read-across in dossiers. Fewer dossiers contained (Q)SAR-based estimations than initially anticipated. There were, undoubtedly, many reasons for the uptake of read-across including its "apparent" simplicity; free availability of the OECD QSAR Toolbox; copious guidance etc. (Q)SAR-type approaches have, however, found more extensive application for the prediction of physicochemical and environmental fate parameters outside the official mandate analyses, and some short-term aquatic endpoints. Despite this, they were considered to be cumbersome and even unsuitable for regulatory purposes for the prediction of complex health-related and environmental endpoints.

To promote the use and uptake of read-across as a viable alternative to animal testing, and specifically to investigate the use of NAMs to support read-across or as part of broader strategies, ECHA has maintained strong collaborations and/or linkages with partners such as the European Commission's Joint Research Centre (EURL-ECVAM) and industry stakeholders. The recently completed SEURAT-1 Cluster of projects provided a platform to bring together researchers, industry and ECHA to investigate through case studies (some of which are brought to this workshop), the use of NAMs to support read-across and act as standalone predictors of toxicity with the ultimate aim of reducing reliance on animal testing.

1.3. Regulatory acceptance of read-across under REACH

The well-documented use of read-across in REACH dossiers does not imply regulatory acceptance in any process. To assist in achieving regulatory acceptance, ECHA has provided guidance on the reporting of read-across, stipulating the requirements e.g. for documentation, read-across hypothesis and argumentation (ECHA, 2012, 2013). Tools such as the OECD QSAR Toolbox can produce reports automatically to assist (although not wholly replace) the documentation process. However, **not all read-across assessments have been accepted by ECHA, leading to consideration of the reasons for non-acceptance**. This, in part, stimulated the development of the Read-Across Assessment Framework (RAAF) as a means of establishing a systematic approach to assessing read-across cases (ECHA, 2015).

Amongst others, some of the main reasons for read-across not being deemed acceptable under REACH included problems with substance identification, missing or inadequate evidence and the strength or relevance of the read-across argument (some of these issues are summarised by Ball et al. (2016)). Beyond (or even with) a trivial analogue approach, providing confirmatory evidence to justify read-across is complex and may also require significant expert judgement. For instance, structural similarity is a prerequisite for grouping in REACH; once a group has been formed, a prediction may be used to fill a data gap. This prediction needs to fulfil a number of crucial aspects as described by the RAAF to be scientifically convincing requiring evidence to support scientific explanations. Thus, there is interest in considering **evidence from NAMs to support predictions based on read-across**. In this manner, **data from NAMs may increase the confidence in a prediction**.

1.4. Summary

There is a regulatory, ethical, business and scientific rationale for developing NAMs for hazard and risk assessment that can be applied successfully in a regulatory setting. To improve acceptance of NAMs within REACH registration dossiers and other regulatory processes, a stakeholder dialogue is needed. This workshop, with its associated case studies and other presentations, provides an opportunity to develop a participant-based set of recommendations and conclusions that will provide ECHA with a direction for the use of NAMs in regulatory processes.

2. New approach methodology data to support regulatory decisions under REACH

2.1. Case studies and major outcomes for hazard assessment using read-across

This section provides some background to support Theme 1 and the breakout sessions of the topical scientific workshop. It focuses on the use of read-across to assist in regulatory decisions and how this may be supported by NAM data.

2.1.1. Current status of read-across to support regulatory decisions: guidance and other literature

An annual snapshot of the information submitted by companies to comply with the REACH legislation is provided by ECHA (2016a). This gives **a critical examination of the quality of the registration dossiers** and the testing proposals. The evaluation of the dossiers under REACH focuses on three different areas, namely:

- examination of testing proposals submitted by registrants;
- compliance check of the dossiers submitted by registrants; and
- substance evaluation.

The report contains comment and advice on how (Q)SARs and read-across have been performed in the dossiers, common errors and recommendations for registrants.

The official guidance supporting the use of grouping and read-across for REACH is provided by ECHA (2008). The **guidance provides the registrant with information on the concept of a category and practical information on methods to build a coherent category, perform read-across, report the prediction** and (computational) tools that may support this process.

The ECHA guidance is supported, but not replaced, by that from the OECD (2014a) which provides further illustration of the analogue and category approaches to supplement the earlier EHCA guidance. Further documents from industry as well as the peer-reviewed literature that provide comment and advice are listed below.

The **uptake of read-across into dossiers, and hence its regulatory application to fill data gaps, has been extensive for many endpoints** (cf. ECHA, 2011, 2014). To illustrate the uptake of read-across, Figure 1 summarises the information provided by ECHA (2014: Table 12.1), the data indicate that across all endpoints over one third of dossiers used read-across within key studies. This suggests a steady uptake of the read-across paradigm as compared to other alternative approaches.

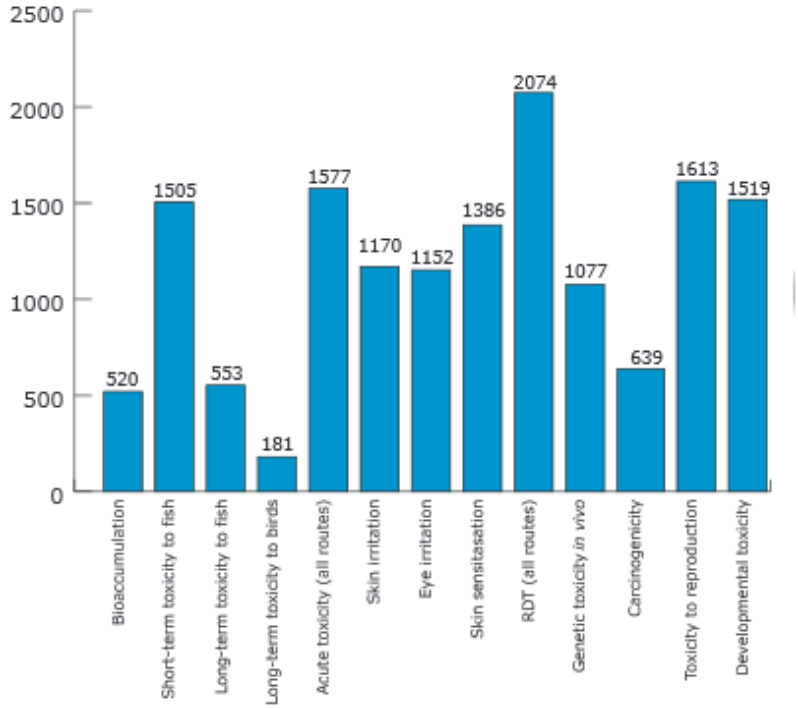

Figure 1. Number of substances with read-across identified by endpoint (taken from ECHA, 2014).

There is a growing literature to support the use of read-across, although to a much less extent the support of read-across by NAM data. The literature can be considered to be guidance (e.g. ECHA, 2008; OECD, 2014a as described above), further supporting information (e.g. ECETOC, 2012), and literature describing case studies and supplementary comments, some of which is summarised below.

The basis for much of the guidance and literature is gleaned from the categories developed for high production volume chemicals through the OECD and early read-across studies between the European Union and the USA. These activities date, in part, to the early 1990s and have been summarised by EC-JRC (2007).

Various publications supplement, but do not replace, the guidance offered by ECHA. Some relevant articles and the topics they relate to are:

- Illustration of case studies for read-across highlighting read-across (Berggren et al. (2015); Blackburn et al. (2011; 2014; 2015); Cronin et al. (2013); Patlewicz et al. (2013a, b; 2014a; 2015a); Wu et al. (2010, 2013)) – relevant case studies are described in more detail in the next section.
- An example of a strategy and template(s) for undertaking read-across (Schultz et al., 2015)
- Approaches to defined uncertainty associated with read-across and read-across arguments within comparative frameworks, allowing for the possible assignment of confidence to a prediction (Ball et al. 2014; Blackburn et al., 2014; Patlewicz et al., 2015a; Schultz et al., 2015).

A broad review of the literature reveals an increasing number of publications per year in this area. A number of case studies on "structure-based" read-across have been provided and interest is now moving to areas of practical aspects of acceptability through the definition of uncertainty and confidence. However, relatively little is provided in the current literature on grouping and read-across on how NAM data may be used – hence, the interest in feedback and comments to direct this area in ECHA's topical scientific workshop.

As a response to the growing feedback, and especially the issues identified by the ECHA evaluation progress reports, ECHA published the RAAF in 2015 (ECHA, 2015). The RAAF presents the methodology applied by ECHA to assess the use of read-across for

regulatory submissions. The aim of the RAAF is to provide a transparent and structured approach to the scientific evaluation of read-across justifications made by registrants in their dossiers. However, it is not intended to replace official guidance. At this time, little is known about how the RAAF may assist in the application of NAM data. This will, in part, be presented at the topical scientific workshop.

2.1.2. Case studies considered at the topical scientific workshop

To stimulate scientific discussion, a number of **case studies for read-across will be highlighted at the topical scientific workshop**. These have, in part, been derived from the work in the SEURAT-1 Cluster of projects as well as other contributions from industry. The case studies were designed, to some extent at least, to address the issues of how and whether NAM data can support read-across and how the RAAF may assist in determining this.
The case studies considered are fully documented. Participants are requested to appraise themselves with this documentation before the workshop. Briefly, the case studies considered cover the following topics:

- **Read-across of repeated dose toxicity data for the perfluorinated alkyl acids**. This is an example of a category of direct acting toxicants, with the hypothesis that the mechanism of action is the same for all category members. The use of NAM data is illustrated with evidence from ToxCast.
- **Read-across of repeated dose data for unsaturated alcohols**. This category is considered to consist of compounds that require metabolic activation, termed indirectly acting toxicants. NAM data are provided by SEURAT-1.
- **Read-across of repeated dose data for phenoxy herbicides**. The consistency within this category has been addressed with NAM through the use of metabolomics data from BASF.

The analysis of these case studies through the RAAF will be presented.

2.1.3. The challenge to the participants

Participants at the topical scientific workshop should consider the case studies through the documentation provided and by the presentations. The aim is to allow participants to determine, through instruments such as the RAAF, how read-across arguments can be improved with the use of NAM data. Other issues that may be addressed include how the difference in structure within the category will impact on toxicodynamics (which may be addressed through the NAM data) and toxicokinetics (for which less evidence is available).
Amongst other topics, **participants are encouraged to make recommendations on the basis of the case studies and their prior knowledge on how NAM could be used and improved to support read-across (and other) approaches for regulatory decisions and the role of the RAAF in assisting the use of NAM data**.

2.1.4. Summary

Read-across has been used to support regulatory decision making globally for more than 30 years. It has received considerable attention in REACH and has been seen in approximately one third of registration dossiers. The RAAF has been developed to provide greater awareness and understanding of the issues to be addressed to account for the uncertainties relevant to a read-across assessment.
One method of decreasing uncertainty in read-across could be the application of NAM data with case studies being presented to illustrate various approaches. High-throughput screening (HTS) data (e.g. from ToxCast) provide confirmation of consistency of mechanism of action within a category; *in vitro* data may support mechanism and effects. These may be applied in a read-across scenario or as part of a larger strategy (see Section 2.4). **The role of the RAAF to assist in the understanding of the use of NAM data will be investigated.**
Thus, NAMs provide the possibility to support the implementation of the regulatory

framework. Given the information provided in this section, and the case studies presented in particular, participants are asked to comment on a series of questions that will be designed to provide ECHA input on:

- *How can NAMs and other non-animal evidence support reasoning for read-across and the formation of chemical categories?*
- *What are the barriers and limitations in use of NAM for data gap filling (read-across) in hazard assessment?*

These questions will be addressed by the breakout sessions and in the panel discussion.

2.2. Screening technologies – *in silico* and *in vitro*

It is a clear principle of REACH that, to obtain the information necessary to assess the hazards and risks of the registered substance, potential registrants are obliged to use available data, *in vitro* test methods and/or non-testing property estimation methods, as well as data sharing to the fullest extent to avoid unnecessary testing on animals. [Note, this does not include *in vitro* methods that were recently accepted and recognised for assessment of skin/eye irritation/corrosion (cf. ECHA 2016b)]. This section describes methods – termed screening and priority setting technologies – in the context of REACH, CLP and the Biocidal Products Regulation. It provides some background to support Theme 2 of the topical scientific workshop.

For the context of this workshop, screening technologies are considered broadly to include:

- *In silico* approaches – for instance, the current status of read-across is described in Section 2.1.
- *In vitro* approaches – Section 2.3 describes some of the uses of *in vitro* approaches to regulatory decision making.

2.2.1. *In silico* approaches

***In silico* approaches encompass any read-across, category or (quantitative) structure-activity relationship ((Q)SAR) approach to regulatory decision making**. Worth et al. (2014) have reviewed the state of the art of alternative methods, including *in silico* approaches to address regulatory submissions from REACH, CLP and the Biocidal Products Regulation. ECHA (2008) has provided guidance on the use of these approaches for regulatory decisions.

ECHA has made the following recommendations regarding the role of various *in silico* approaches within REACH, which are also applicable to other legislation:

- Results from a read-across approach should be adequate for the purposes of classification and labelling and/or risk assessment
- To use (Q)SAR predictions instead of testing, they must meet the conditions set out in REACH Regulation Annex XI, Section 1.3.
- Results from *in silico* and *in vitro* approaches can be used as part of a weight-of-evidence approach or as elements leading to a test strategy.

2.2.2. *In vitro* approaches

For the context of this document, ***in vitro* screening technologies encompass any non-standard test described**, at least partially, in Section 2.3.1. Thus, it is intended to include **information from -omics, HTS and some *in vitro* assays, which are not used directly for the prediction of hazard**. Worth et al. (2014) have also reviewed the state of the art of *in vitro* approaches to address regulatory submissions.

Other excellent sources of information on *in vitro* methods exist e.g. Bal-Price and Jennings (2014). Briefly, NAMs are likely to include HTS and high-content screening (HCS) technologies e.g. ToxCast, Tox21 and SEURAT-1. These allow for the simultaneous testing of a large number of chemicals and provide a comprehensive analysis of cellular changes at the levels of the transcriptome, proteome or metabolome.

In general, HTS assays run in multi-well plates, in concentration response format yielding a quantitative read-out at each concentration and (when run using cells) have simultaneous cytotoxicity measures. HTS assays can probe many specific key events (KEs), such as a molecular initiating event (MIE), or an intermediate step associated with an (adverse outcome) pathway that can potentially lead to adverse health outcomes.

ECHA (2010) state that **results obtained from suitable *in vitro* methods may indicate the presence of a certain dangerous property – this may be relevant for screening**. They may also be **important in relation to understanding the mode of action of the substance**, hence suggesting that NAM data may confirm the **mechanistic hypothesis of a read-across**.

There are definitions of the term "suitable" which means sufficiently well-developed according to internationally-agreed test development criteria (e.g. the European Centre for the Validation of Alternative Methods (ECVAM) pre-validation criteria). The current validation criteria are designed for "classical" *in vitro* assays e.g. those developed as replacements for animal testing, rather than HTS or -omics type data.

A number of recommendations for using *in vitro* data have been made by ECHA, including:

- Data generated from (validated and pre-validated) *in vitro* test methods can be used under REACH as long as the information for the hazard endpoint is sufficient for the purpose of classification and labelling and/or risk assessment.
- Advanced *in vitro* technologies may provide valuable information on the mode of action of the substances and can be part of a read-across and category justification as described in Section 2.1.
- *In vitro* data produced using other methods (i.e. non-prevalidated methods) can be used only as supportive information (e.g. as part of a weight-of-evidence justification).
- Methods should be adequately documented and limitations described and, where possible, addressed.

2.2.3. Strengths and weaknesses of using non-standard data for regulatory decisions

One of the purposes of the topical scientific wWorkshop is to identify strengths and weaknesses of the use of *in silico* and *in vitro* data for screening and priority setting (with an emphasis on REACH). Various presentations will address this.

There are many obvious strengths and weaknesses of non-standard data for regulatory decisions:

- Strengths: (potential) low cost, compliance with the "spirit" of REACH i.e. avoidance of testing, mechanistic basis, amenable to supporting AOP development and implementation etc.
- Weaknesses: lack of toxicokinetic and/or exposure relevance, lack of direct understanding and relationship to apical endpoints, for non-validated assays uncertainty of their meaning and applicability etc.

Definition of the weaknesses, in particular, can be helpful in defining uncertainties in predictions, and in providing recommendations. This is also related to the problems of inadequate or false predictions. In particular, should *in silico* and *in vitro* assays be optimised to minimise false positives or false negatives, or for overall accuracy? The different optimisation of assays may affect its implementation of screening and prioritisation.

2.2.4. Summary

REACH requires, where possible, the avoidance of animal testing for regulatory decision making. ECHA does not prescribe the specific use of "validated" alternatives, but that the

use of non-standard data must be justified. Scenarios where different types of *in silico* and/or *in vitro* data may be used are defined. A number of presentations will be made at the topical scientific workshop to demonstrate the current use of non-standard data, and so-called screening technologies in particular, to assist in the regulatory decision-making process. The intention here is to **illustrate how NAM data can be applied, leading to a better understanding of the role of (big) data and strategies to implement them**.

Participants are requested to respond to these issues and provide input into how these technologies can be best applied for regulatory purposes, specifically:

- *How can NAMs and other non-animal evidence be used for screening and prioritisation?*
- *What is the acceptability and application of NAMs in different regulatory schemes?*
- *With regard to the establishment of relevance and reliability for the purpose of the screening and prioritisation, what type of quality assurance can/should be applied to data from NAMs?*

These questions will be addressed in the panel discussion and may be touched upon in the breakout sessions.

2.3. Applying big data

2.3.1. Context and examples of big data

We live in an era of "big data" referring to data compilations so large and complex that they go beyond the traditional capabilities of data analysis tools. The big data concept has spread throughout society and commerce and has spawned its own industry and research community, as well as new informatics approaches and tools. The use of the term "toxicological big data" is becoming more widespread as we gain access to some of the resources described in this section. Sections 2.3 and 2.4 of this document are intended to provide some background to support Theme 3 of the topical scientific workshop.

There are many potential advantages of analysing big data, albeit with the associated costs of their collection, storage and informatics requirements. Information can be derived from big data that would not be apparent from smaller data sets. In addition, information derived from larger data matrices is expected to be more significant, even if the data themselves may sometimes be of poor or variable quality. In the same way, the advantages of the use of big data for regulatory applications should outweigh the costs.

With regard to the support of read-across predictions, or indeed read-across predictions from biological similarity, it is preferable not to limit what may be considered "big data", and to include any usable data source. In this context, no quantification is implied about what is termed a "big data set", or what it may include. **The purpose within the workshop is to consider any usable biological or chemical compilations of "big data" that may not necessary have been considered previously, and provide an opinion on their utility**.

Being pragmatic, for the purposes of this workshop, big data may include (but are not limited to):

- Data derived from various molecular biology techniques, also known as "-omics" data
  - e.g. TGGates, DrugMatrix, van Ravenzwaay et al. (2012).
  - Available for relatively few compounds, but many data per compound, potentially high quality, possibly useful when a specific mechanism is triggered, require proof-of-concept.
- High-Throughput Screening of mechanistic relevance
  - e.g. Tox21, ToxCast etc.
  - More compounds, large numbers of assays, variable quality and care required in use.
- *In vitro* and *in chemico* data sources including cell based, receptor binding,

reactivity assays etc.
    - e.g. ChEMBL, PubChem etc.
    - Enormous data resources, highly variable (and unassessed) in terms of quality and relevance.
- *In vivo* data
    - e.g. eChemPortal, US EPA AcTOR, ECHA DB etc.
    - Relatively small, variable, but often high, quality assessed by e.g. Klimisch scores, details on effects as a function of dose and time.
- Lastly, whilst not necessarily biological in nature, the thousands of physicochemical properties and structural descriptors that may be measured or calculated can be considered as big data
    - e.g. CDK, Dragon, ToxPrint etc.
    - Relatively large data sets, consistent, provided based on definitive molecular structures, require some structure-activity relationship in order to be rationalised, descriptor selection is necessary.

2.3.2. How big data can, and have been, used for regulatory applications

The possibilities for using big data for regulatory decision making, with regard to omics (ECETOC, 2008; 2010; 2013) and HTS data (Judson et al., 2008, 2010, 2012) have been considered for some time. Only more recently have specific case studies and illustrations been identified. **The roles of big data to support regulatory decision include**:

- Being the **argument for read-across** i.e. a form of biological similarity or profiling.
    - e.g. Kleinstreuer et al. (2011; 2014) utilised Tox21 and ToxCast data to perform what was termed bioactivity-based read-across (BaBRA) to allow for similarity to be assessed;
    - Van Ravenzwaay et al. (2012) illustrated the concept using metabolomics data.
    - Grafström et al. (2015) developed the concept of the predictive toxicogenomics score (PTGS).
- Providing **supporting evidence** to reduce the uncertainty associated with a read-across argument by providing confirmatory evidence to a mechanistic hypothesis
    - e.g. the SEURAT-1 case study on unsaturated alcohols demonstrated reduction of uncertainty through application of ToxCast data.
- **Defining categories** in a multivariate biological and chemical space.
    - e.g. Zhu et al. (2014) and Kim et al. (2016) demonstrated that including both ToxCast and structural information can enrich the read-across and similarity assessment.
- Create the **basis of strategy** for e.g. an ITS.
    - e.g. Kleinstreuer et al. (2011) and Kroese et al. (2015) demonstrated that information from multiple assays can be used as a surrogate for complex whole animal tests.
    - e.g. Urbisch et al. (2015) conceptualised a strategy for prediction of skin sensitisation potential
- **Linkage from the AOP** to predictive model
    - e.g. Edwards et al. (2016) demonstrated the support that can be provided to AOPs in terms of identifying pathways and providing experimental evidence.

Most current applications of big data have focused on screening and prioritisation, but there is growing evidence of their use for further regulatory applications.

2.3.3. Challenges for using big data for regulatory applications

The use of big data for regulatory applications is in its infancy, there remain a number of challenges, such as:

- The **scoping of the role of big data** for regulatory applications – what, when and

how will they be used.

- Understanding, assessing and assigning **data quality metrics** – which types of data are usable in what context.
- Usable and meaningful **data mining** and **statistical approaches** that provide value to the transparent use of alternatives.
- The inherently **inter-correlated nature** of biological and physicochemical property descriptor data and the redundancy that may be present in such data.
- **Organising and visualising** data practically e.g. informatics approaches that make the data amenable and attractive to toxicologists and risk assessors.
- **Education** – for toxicologists and risk assessors of their meaning; for the creators of big data sets of the problem to be addressed; and for informaticians to create practical and usable tools to apply.
- **Practical illustrations** and **case studies** to support and demonstrate the use of big data for regulatory applications.

2.3.4. Summary

The concept of big data in toxicology is becoming a reality providing mechanistic, response and chemical information and knowledge; such data have a huge potential to redefine the toxicological landscape.

Participants are requested to consider the applications and priorities for development in this area, to address the challenges defined, specifically addressing the question:

- *How can NAM, non-animal evidence and standard in vivo data be combined with sufficient robustness to provide practical solutions to regulatory problems?*

This question will be addressed in the panel discussion.

2.4. Challenges to incorporate new approach methodologies to support regulatory decisions

There is a clear motivation for using data and information from NAMs to support regulatory decisions. The implementation of this concept requires consideration of current and aspirational strategies to integrate the outputs into a framework for regulatory decision making as well as identification of the key areas that could and should be addressed. This section outlines these issues.

2.4.1. Existing strategies for using "non-standard" data in regulatory decisions

The concept of using information other than standard toxicological tests to support regulatory decisions is not new, and indeed is a cornerstone of the REACH Regulation. The types of non-standard data that may be applied are described in Sections 2.2 and 2.3. **To utilise these data to enable regulatory decisions, there has been much interest and research, leading to the concepts of the integrated testing strategy (ITS) and integrated approach(es) to testing and assessment (IATA),** amongst others, to allow consideration of non-test and other data. The intention of such approaches is to combine "evidence" that individually may not be sufficient for to make a regulatory decision but combined may form a "weight-of-evidence".

A full and critical analysis of the strategies for combining evidence to make a regulatory decision is beyond the scope of this document; however, some of the key advances are summarised in Table 1.

Table 1. A selection of strategies and techniques to combine toxicological evidence to make and/or support regulatory decisions

Strategy / Technology	**Description / Status / Comment**	**Indicative Reference(s)**
ORISIS EU Project ITS	ITS presented for series of REACH-related endpoints. Demonstrated that a sequential consideration of information is possible. Supported by a software tool.	Vermeire et al. (2013)
ECHA guidance on collecting, organising and using non-animal test data	Provides background and framework, regulatory context and guidance on using alternatives, sources of information and creating a weight of evidence.	ECHA (2010, 2016b)
Mode of Action (MoA) Framework	Provides a framework, roadmap and case examples explicitly addressing weight of evidence considerations in mode of action/species using conventional data sources and new approaches.	Meek et al. (2014); SCENHIR (2012)
Application of Adverse Outcome Pathways (AOPs)	Studies have developed IATA and strategies to use (and identify gaps) in non-standard data for regulatory decisions based around the knowledge from AOPs.	Burden et al. (2015); Edwards et al. (2016); OECD (2014c); Patlewicz et al. (2014b, 2015b)
Integrated Approaches to Testing and Assessment (IATA)	OECD has supported the developed of IATA, or formalised approaches to utilise the information contained within AOPs/MoA to inform develop of strategies to alternative testing. Case studies for IATA are being considered by the OECD. The OECD (2014c) has also provided guidance on how to utilise information from non-standard (*in vitro*) assays.	OECD (2014b; 2014c)
SEURAT-1 Conceptual Framework and *ab initio* case study	The SEURAT-1 conceptual framework provides a rational integrated assessment and is being informed by and illustrated with reference to the so-called SEURAT-1 *ab initio* case study.	Berggren (2015); Gocht et al. (2014)
Weight of evidence (WoE) considerations	EFSA's PROMETHEUS project (Promoting methods for evidence use in scientific assessments) (2014–2016) aims to improve means of dealing with data and evidence (i.e. for collecting/extracting, validating/appraising, analysing and integrating data and evidence) and increasing their consistency.	ECHA (2010a); EFSA (2015)

2.4.2. Data sharing: practicalities and platforms

Data sharing and providing adequate informatics support to retrieve and utilise available data, including those from NAMs, is a key challenge to supporting their use for regulatory purposes. ECHA supports the legal sharing of their data when possible, whilst protecting the rights of industry. Specifically, ECHA is committed to expanding the capabilities of computational tools through access to carefully-selected parts of the non-confidential registration data, with full protection of the rights of the data owners. ECHA is currently analysing how to make the data more readily available to a wider audience (e.g. academia, companies, researchers, regulators) in a way that respects the ownership of companies (ECHA, 2016). This could support the implementation of NAM data for grouping and potentially for data gap filling.

ECHA also supports the OECD QSAR Toolbox (OECD, 2016). It provides a means of searching databases – including non-standard data, profiling target molecules according to mechanistic and structural approaches, grouping and ultimately read-across. ECHA has provided similar sets of data to those provided to AMBIT to the OECD QSAR Toolbox (ECHA, 2016). In addition ECHA has provided an introduction to the use of the OECD QSAR Toolbox as well as case studies demonstrating its use for read-across and data gap filling (ECHA, 2014a, b, 2015a). Other information, guidance and case studies are freely available from OECD (2016).

Numerous other tools and platforms are available to support grouping and read-across, as well as other predictive methodologies, further information is available from ECETOC (2012) and ECHA (2012, 2016c). For example, the AMBIT platform can be searched in a variety of means, facilitating grouping and similarity searches. The overall aim is that AMBIT should improve the availability and usability of data to industry users (CEFIC, 2016).

2.4.3. Other identified challenges to the incorporation of new approach methodologies to support regulatory decisions

In addition to data sharing and the provision of informatics, there are a number of other challenges to the incorporation of NAMs to support regulatory decisions. These are summarised below:

- The **role of new approach data** to support regulatory decisions requires further consideration e.g. within IATA or ITS.
- **Gaining acceptance for regulatory purposes of NAM**. This is encouraged by ECHA and the OECD, and provisions for the recording of such data are provided e.g. OECD (2014c). The advantages can be described in the context of the RAAF, which has the possibility to rationalise the increase in understanding and support of a read-across hypothesis and argument.
- Acceptance relies, in part in an appreciation of **when the WoE is sufficient to make a particular regulatory decision** e.g. a different WoE may be acceptable for prioritisation as opposed to hazard assessment and/or classification and labelling.
- Gaining acceptance also relies in part in the identification, **characterisation of uncertainty, and hence confidence that may be associated with the read-across prediction**. At the heart of this issue is the consideration of when molecules can be considered to be similar, and whether NAM data can support this.
- The **quality, acceptability and relevance of NAM data** are currently little understood with regard to their use for regulatory decision making. This has been addressed to a limited amount with regard to some of the IATA case studies presented e.g. OECD (2014b) but further work is required in this area. For instance, are data from omics studies of higher quality and impact than those for screening technologies and when and how can they be used respectively?
- The **better implementation of toxicokinetics is required for the use of NAM**

data. Currently, NAMs may be considered to support hazard assessment but better illustration and assessment of bioavailability may be required to support particular exposure scenarios and an understanding of when the point-of-departure has been exceeded, and for which endpoint. Voluntary programmes could help to realise this information, or it could be generated from new tests that will be performed in any event.

- "***Bang for the buck***" – the added value of data from NAM is not currently appraised and hence cost-effectiveness is not known. In other words, when does the financial reason for utilising NAM become compelling as compared to *in vivo* testing and what other (non-financial) information should be considered e.g. animal welfare, relevance to human risk assessment?

Given the information provided and challenges outlined in this section, participants are asked to provide ECHA input on:

- *How can NAMs data be used to address interspecies extrapolation and human relevance?*

This question will be addressed in the panel discussion.

2.5. Expectations from the ECHA Topical Scientific Workshop on New Approach Methodologies in Regulatory Science

The ECHA Topical Scientific Workshop on New Approach Methodologies in Regulatory Science brings together an influential group of stakeholders to help direct activities at a crucial period of time when new technologies can truly have an impact on the regulatory framework. In particular, ECHA would like attendees to help form recommendations and increase our understanding in the following key areas:

Present day

- A **critical appraisal of the current state of the art** of read-across and how read-across arguments could be improved using NAMs focusing on these advantages and limitations.

Short-term

- **Recommendations for required areas of guidance, specifically for NAM**s, that could be used to address or support read-across, for a particular regulatory need.
- **Proposals for NAMs to be prioritised**, ideally methods that could be used immediately or with little further development to support regulatory approaches.
- **Recommendations for NAMs that show potential**, but may require (rapid) development in terms of their scientific applicability or relevance to a regulatory issue.

Medium- to long-term

- **Recommendations for the longer-term placement of NAMs to solve regulatory issues**. These should be visionary and aspirational to establish new paradigms and information sources, directing the research and development communities to solve the current problems with current testing and alternative approaches to support risk assessment. This can include an appreciation of, but is not limited to e.g. combining toxicokinetics and -omics studies with classical *in vivo* tests, constructing alternative test batteries for increased coverage and relevance of alternative data to apical endpoints, 3D tissue modelling and used for screening tests, optimised *in silico* approaches etc.

3. References

Ball N, Bartels M, Budinsky R et al. 2014. The challenge of using read-across within the EU REACH regulatory framework; how much uncertainty is too much? Dipropylene glycol methyl ether acetate, an exemplary case study. *Regul Toxicol Pharmacol* 68: 212-221.

Ball N, Cronin MTD, Shen J et al. 2016. Toward Good Read-Across Practice (GRAP) guidance. *ALTEX* doi: 10.14573/altex.1601251.

Bal-Price A, Jennings P. 2014. In Vitro Toxicology Systems, 583pp. Humana Press, New York, US.

Berggren E. 2015. Ab initio Case Study. In: Gocht T, Schwarz M (Eds) Towards the replacement of in vivo repeated dose systemic toxicity testing. Volume 5, pp. 89-90.

Berggren E, Amcoff P, Benigni R et al. 2015. Chemical safety assessment using read across: How can novel testing methods strengthen evidence base for decision making? *Environ Health Perspect* 123: 1232-1240.

Blackburn K, Bjerke D, Daston G et al. 2011. Case studies to test: A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments. *Regul Toxicol Pharmacol* 60: 120-135.

Blackburn K, Stuard SB. 2014. A framework to facilitate consistent characterization of read across uncertainty. *Regul Toxicol Pharmacol* 68: 353-362.

Blackburn K, Daston G, Fisher J et al. 2015. A strategy for safety assessment of chemicals with data gaps for developmental and/or reproductive toxicity. *Regul Toxicol Pharmacol* 72: 202-215.

Burden N, Sewell F, Andersen ME et al. 2015. Adverse Outcome Pathways can drive non-animal approaches for safety assessment. *J Appl Toxicol* 35:971-975.

CEFIC (European Chemical Industry Council). 2016. LRI Workshop on AMBIT and Read-across.CEFIC-LRI (Long-range Research Initiative) Workshop, brussels. Avaiable from: http://cefic-lri.org/events/lri-workshop-on-ambit-aead-across/

Cronin MTD, Madden JC, Enoch SJ et al. 2013. Chemical Toxicity Prediction: Category Formation and Read-Across, 191pp. Royal Society of Chemistry, Cambridge, England.

EC-JRC (European Commission - Joint Research Centre) 2007. A Compendium of Case Studies that helped to shape the REACH Guidance on Chemical Categories and Read Across [EUR 22481 EN]. (Eds): Worth A, Patlewicz G. Institute for Health and Consumer Protection (IHCP), Luxembourg. Available from: http://www.ecy.wa.gov/beyondwaste/pdf/EUR_22481_EN.pdf

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 2008. Workshop on the application of 'omics technologies in toxicology and ecotoxicology: case studies and risk assessment. Workshop Report No. 11. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels. Available from: http://www.ecetoc.org/publications

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 2010. 'Omics in (eco)toxicology: case studies and risk assessment. Workshop Report No.19. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels. Available from: http://www.ecetoc.org/publications

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 2012. Category approaches, read-across, (Q)SAR. Technical Report No 116. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels. Available from: http://www.ecetoc.org/publications

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 2013. 'Omics and risk assessment science. Workshop Report No. 25. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels. Available from: http://www.ecetoc.org/publications

ECHA (European Chemicals Agency). 2008. Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.6: QSARs and Grouping of Chemicals. 134pp. European Chemicals Agency, Helsinki, Finland. Available from: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

ECHA (European Chemicals Agency). 2010. Practical Guide 10 - How to avoid unnecessary testing on animals [ECHA-10-B-17-EN]. 19pp. European Chemicals Agency, Helsinki, Finland. Available from:

http://echa.europa.eu/documents/10162/13655/pg_avoid_animal_testing_en.pdf

ECHA (European Chemicals Agency). 2010a.Practical guide 2: How to report weight of evidence [ECHA-10-B-05-EN]. 26pp. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/13655/pg_report_weight_of_evidence_en.pdf

ECHA (European Chemicals Agency). 2011. The Use of Alternatives to Testing on Animals for the REACH Regulation 2011 [ECHA-11-R-004.2-EN]. 69pp. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2011_en.pdf

ECHA (European Chemicals Agency). 2011a. Guidance on information requirements and chemical safety assessment, Chapter R.5: Adaptation of information requirements [ECHA-2011-G-15-EN]. 28pp. European Chemicals Agency, Helsinki, Finland. Available from: https://echa.europa.eu/documents/10162/13643/information_requirements_r5_en.pdf

ECHA (European Chemicals Agency). 2012. Practical Guide 6 — How to report read across and categories [ECHA-10-B-11.1-EN]. 32pp. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/13655/pg_report_readacross_en.pdf

ECHA (European Chemicals Agency). 2013. Grouping of Substances and Read-across Approach — An illustrative example [ECHA-13-R-02-EN]. 11pp. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/13628/read_across_introductory_note_en.pdf

ECHA (European Chemicals Agency). 2014. The Use of Alternatives to Testing on Animals for the REACH Regulation: Second Report under Article 117(3) of the REACH Regulation [ECHA-14-A-07-EN]. 131pp. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2014_en.pdf

ECHA (European Chemicals Agency). 2014a. Illustrative examples with the OECD QSAR Toolbox workflow. Part 1: Introductory note [ECHA-14-R-06-EN]. 12pp. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/21655633/illustrative_example_qsar_part1_en.pdf

ECHA (European Chemicals Agency). 2014b. Illustrative examples with the OECD QSAR Toolbox workflow.Part 2: Case studies [ECHA-14-R-07-EN]. 46pp. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/21655633/illustrative_example_qsar_part2_en.pdf

ECHA (European Chemicals Agency). 2015. Read-Across Assessment Framework (RAAF) [ECHA-15-R-07-EN]. 38pp. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/13628/raaf_en.pdf

ECHA (European Chemicals Agency). 2015a. Illustrative examples with the OECD QSAR Toolbox workflow. Part 2b [ECHA-15-R-23-EN]. 23pp. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/21655633/illustrative_example_qsar_part2b_en.pdf

ECHA (European Chemicals Agency). 2016. ECHA gives out registration data to support development of non-test methods. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/view-article/-/journal_content/title/echa-gives-out-registration-data-to-support-development-of-non-test-methods

ECHA (European Chemicals Agency). 2016a. ECHA Evaluation Documents available from: http://echa.europa.eu/eu/regulations/reach/evaluation

ECHA (European Chemicals Agency). 2016b Information toolkit. Avaiable from: http://echa.europa.eu/en/support/information-toolkit

ECHA (European Chemicals Agency). 2016c. Practical Guide 5 — How to use and report (Q)SARs [ECHA-16-B-09-EN]. 28-32 p. European Chemicals Agency, Helsinki, Finland. Available from: http://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf

Edwards SW, Tan YM, Villeneuve DL et al. 2016. Adverse Outcome Pathways—Organizing toxicological information to improve decision making. *J Pharmacol Exper Therapeut* 356:170-181.

EFSA (European Food Safety Authority). 2015. Principles and process for dealing with data and evidence in scientific assessments. *EFSA J* 13: 4121-4157. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/4121

European Union. 2007. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. *Off J Eur Union* L136, 29.05.2007, 3–280.

EU-ToxRisk Project. More information available from: http://www.eu-toxrisk.eu/

Gocht T, Berggren E, Ahr HJ et al. 2014. The SEURAT-1 Approach towards Animal Free Human Safety Assessment. *ALTEX* 32:9-24.

Grafström RC, Nymark P, Hongisto V et al. 2015. Toward the replacement of animal experiments through the bioinformatics-driven analysis of 'omics' data from human cell cultures. *ATLA* 43:325-332.

Judson RS, Richard A, Dix D et al. 2008. Actor--Aggregated Computational Toxicology Resource. *Toxicol Appl Pharmacol* 233: 7-13.

Judson RS, Houck KA, Kavlock RJ et al. 2010. In vitro screening of environmental chemicals for targeted testing prioritization: the ToxCast project. *Environ Health Perspect* 118: 485-492.

Judson RS, Martin MT, Egeghy P et al. 2012. Aggregating data for computational toxicology applications: the U.S. Environmental Protection Agency (EPA) aggregated computational toxicology resource (ACToR) system. *Int J Mol Sci* 13: 1805-1831.

Kim MT, Huang R, Sedykh A et al. 2016. Mechanism profiling of hepatotoxicity caused by oxidative stress using the antioxidant response element reporter gene assay models and big data. *Environ Health Perspect*, DOI: 10.1289/ehp.1509763.

Kleinstreuer N, Judson R, Reif D et al. 2011. Environmental impact on vascular development predicted by high throughput screening (HTS). *Environ Health Perspect* 119: 1596-1603.

Kleinstreuer N, Houck K, Yang J et al. 2014. Bioactivity profiling of a diverse 800 chemical library in human primary cell systems. *Nature Biotechnol* 32: 583-591.

Kroese ED, Bosgra S, Buist HE et al. 2015. Evaluation of an alternative in vitro test battery for detecting reproductive toxicants in a grouping context. *Reprod Toxicol* 55: 11-19.

Meek ME, Boobis A, Cote I et al. 2014. New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. *J Appl Toxicol* 34: 1–18.

OECD (Organisation for Economic Co-operation and Development). 2014a. Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Guidance on Grouping of Chemicals, Second Edition. Series on Testing & Assessment No. 194.[ENV/JM/MONO(2014)4]. OECD Publishing, Paris, France. Available from: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono%282014%294&doclanguage=en

OECD (Organisation for Economic Co-operation and Development). 2014b. New Guidance Document on an Integrated Approach on Testing and Assessment (IATA) for Skin Corrosion and Irritation. Series on Testing & Assessment No. 203. [ENV/JM/MONO(2014)19]. OECD Publishing, Paris, France. Available from: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)19&doclanguage=en

OECD (Organisation for Economic Co-operation and Development) 2014c. Guidance Document for Describing Non-Guideline In Vitro Test Methods. Series on Testing & Assessment No. 211. [ENV/JM/MONO(2014)35]. OECD Publishing, Paris, France. Available from: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO%282014%2935&doclanguage=en

OECD (Organisation for Economic Co-operation and Development) 2016. The OECD QSAR Toolbox for Grouping Chemicals into categories. Available from: http://www.qsartoolbox.org/

Patlewicz G, Ball N, Booth ED et al. 2013a. Use of category approaches, read-across and (Q)SAR: general considerations. *Regul Toxicol Pharmacol* 67: 1-12.

Patlewicz G, Roberts DW, Aptula A et al. 2013b. Workshop: use of "read-across" for chemical safety assessment under REACH. *Regul Toxicol Pharmacol* 65: 226-228.

Patlewicz G, Ball N, Becker RA et al. 2014a. Read-across approaches – misconceptions, promises and challenges ahead. *ALTEX* 31: 387-396.

Patlewicz G, Kuseva C, Kesova A et al. 2014b. Towards AOP application – implementation of an integrated approach to testing and assessment (IATA) into a pipeline tool for skin sensitization. *Regul Toxicol Pharmacol* 69:529-545.

Patlewicz G, Ball N, Boogaard PJ et al. 2015a. Building scientific confidence in the development and evaluation of read-across. *Regul Toxicol Pharmacol* 72: 117-133.

Patlewicz G, Simon TW, Rowlands JC et al. 2015b. Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes. *Regul Toxicol Pharmacol* 71:463-477.

SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks). 2012. Memorandum on the use of the scientific literature for human health risk assessment purposes – weighing of evidence and expression of uncertainty, [doi:10.2772/86755]. 46pp. Available from: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_s_001.pdf

Schultz TW, Amcoff P, Berggren E, et al. 2015. A strategy for structuring and reporting a read-across prediction of toxicity. *Regul Toxicol Pharmacol* 72: 586-601.

SEURAT-1 Cluster. More information available from: http://www.seurat-1.eu/

Urbisch D, Mehling A, Guth K et al. 2015. Assessing skin sensitization hazard in mice and men using non-animal test methods. *Regul Toxicol Pharmacol* 71: 337-351.

Van Ravenzwaay B, Herold M, Kamp H et al. 2012. Metabolomics: a tool for early detection of toxicological effects and an opportunity for biology based grouping of chemicals-from QSAR to QBAR. *Mutat Res* 746: 144-150.

Vermeire T, Aldenberg T, Buist H et al. 2013. OSIRIS, a quest for proof of principle for integrated testing strategies of chemicals for four human health endpoints. *Regul Toxicol Pharm*acol 67: 136–145.

Worth A, Barroso J, Bremer S et al. 2014. Alternative Methods for Regulatory Toxicology — A State-of-the-art review.Report EUR 26797 EN, 461pp. Ispra, Italy: European Commission, Joint Research Centre, Institute for Health and Consumer Protection. Available from: http://echa.europa.eu/documents/10162/13634/echa_jrc_sla_report_en.pdf

Wu S, Fisher J, Naciff J et al. 2013. Framework for identifying chemicals with structural

features associated with the potential to act as developmental or reproductive toxicants. *Chem Res Toxicol* 26: 1840-1861.

Wu SD, Blackburn K, Amburgey J et al. 2010. A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments. *Regul Toxicol Pharmacol* 56: 67-81.

Zhu H, Zhang J, Kim MT et al. 2014. Big data in chemical toxicity research: the use of high-throughput screening assays to identify potential toxicants. *Chem Res Toxicol* 27: 1643-1651.