Chapter 1. Roles and responsibilities

Key message: *The in vitro method life cycle from development to their use for safety assessment purposes has a variety of key actors and the guidance identifies clearly their responsibilities, both individually and collectively.*

Key content: *Describes all target groups involved in the process e.g., in vitro method developers, test system (cells, tissues) providers, validation bodies, inter-governmental organisations for cooperation, suppliers of equipment, materials and reagents, in vitro method users (e.g., testing laboratories, large industries and small to medium enterprises), sponsors, receiving authorities and GLP monitoring authorities.*

Guidance for improved practice: *Besides the elements necessary for good scientific work in discovery, additional requirements, such as documentation, ownership, identity and genetic make-up, related to the in vitro method and the test system, are key for their in vitro method acceptance at regulatory level.*

Recommendations *are given for several of the target groups on how to put into practice their responsibilities for facilitating the development and implementation of in vitro methods for regulatory use.*

In vitro methods are often developed without the primary aim of being used for regulatory purposes, but are rather focused on the discovery of disease pathways or investigation of mechanisms of action induced by external factors causing cell disturbance. These methods however, can form the basis for future *in vitro* methods used either for safety assessment or for toxicity screening.

Many of the following organisations (e.g. validation bodies, receiving authorities) should not be considered as single entities but consist of a network of advisory (e.g. scientific, technical, ethical) bodies which feeds into the processes and roles detailed below.

1.1. *In vitro* method developers

In vitro method developer(s) refers to the person or entity who develops or has developed an *in vitro* method destined for regulatory use in human safety assessment.

Researchers aiming to develop *in vitro* methods suitable for regulatory testing purposes must be aware that beyond the definition, description and within-laboratory repeatability and reproducibility of the *in vitro* method, receiving authorities have additional quality requirements for test acceptance (OECD, 2005[1]). The *in vitro* method developer should keep in mind that the quality of historical data and documentation regarding the *in vitro* method will have a significant impact on the regulatory acceptance process.

Briefly, the *in vitro* method developer is responsible for providing a clearly written and well documented *in vitro* method description, and related Standard Operating Procedure(s) (SOP(s)), taking into consideration all aspects described in GIVIMP.

The developer's knowledge and understanding of the *in vitro* method is the basis for establishing an approach to control the *in vitro* method and to set for instance adequate acceptance criteria for the results obtained when running the *in vitro* method. Each developer should judge whether he or she has gained sufficient understanding of the *in vitro* method to provide a high degree of assurance to successfully propose the *in vitro* method for regulatory applications.

In vitro method developers should take into account the Intellectual Property (IP) guidelines and good licensing practices regarding test systems as set out on the OECD website[1] [2]. The Guidelines for the Licensing of Genetic Inventions[3] were adopted by OECD member countries in 2006. Although the Guidelines describe the principles and best practices for the licensing of genetic inventions used in human health care, the principles can generally be promoted in other areas in the field of regulatory testing of chemicals for the protection of human health and the environment. Currently an OECD guidance on best practices for licensing of protected elements in OECD test guidelines is in development.

New test guidelines proposals should provide information on Intellectual Property Rights (IPR) aspects, as transparently as possible. In particular, the following information is expected to be provided: "Describe if the *in vitro* method includes components, equipment or other scientific procedures that are covered (or pending) by IPR (e.g., patents, patent applications, industrial designs and trademarks) and/or intended to remain confidential. Information should be provided on the overall availability of the IPR-protected components including whether they are commercially available or require a Material Transfer Agreement or other licensing agreements. In addition, the possibility of providing a generic description of the IPR-covered component/test system as well as any

other element intended to remain confidential should be disclosed and whether Performance Standards have been developed for the *in vitro* method."[4]

The development of Performance Standards[5] was agreed as the solution to overcome concerns regarding market monopoly (e.g. where a commercial provider could take a disproportionate financial advantage due to the inclusion of proprietary elements in test guidelines). The development of Performance Standards will also enable the development of similar test methods and facilitate their validation.

As the use of mammalian, including human, cells and tissues is critical for the development and implementation of *in vitro* methods for regulatory use in human safety assessment, already in the early stages care has to be taken regarding their ownership, their identity and genetic make-up and who can control their fate. A number of treaties, laws, and regulations help to guide the ethical collection of human-derived specimens (Allen et al., 2010[2]).

Reference data to assess the relevance of *in vitro* methods are typically from surrogate animal studies ("*in vivo* animal data"), but can also be derived from other sources. This is especially important for areas where the mechanism of action is not preserved across species, e.g. metabolism, CYP induction (Sinz, Wallace and Sahi, 2008[3]), and where the availability of human reference data for the mechanism studied is essential. Human data can be obtained from epidemiological, clinical or other resources. In the case of prospective generation of human reference data, approval will need to be sought from an independent committee subject to national laws[6].

When *in vitro* method developers conclude their *in vitro* method is sufficiently developed, they can then proceed to an in-house performance assessment (see Section 8.3). When such internal assessment is successful, they can submit the *in vitro* method to a validation body for the formal validation of the method, or, can organise the validation by themselves. The *in vitro* method developers should be able to prove that the *in vitro* method they offer to the validation body is robust, reliable, relevant, and supported by high quality data as described in the present guidance.

In order to have the *in vitro* method considered for regulatory acceptance, the *in vitro* method developer needs to contact the appropriate national coordinator[7] to prepare a Standard Project Submission Form (SPSF) for a new Test Guideline, or in the case of 'me-too' *in vitro* methods for addition to the relevant Performance Based Test Guideline (PBTG) (OECD, 2016[4]). Project proposals for new Test Guidelines need the active support of receiving authorities in at least one member country, and have to meet a regulatory need in member countries.

1.2. Test system providers

In vitro test systems are mainly biological systems, quite often consisting of tissues or cell lines. Test systems can be developed in-house (i.e. by the *in vitro* method developer), acquired from other laboratories or purchased from a cell culture bank, either academic or commercial. The OECD consensus document, Compliance of Laboratory Suppliers with GLP Principles, recommends that test system providers should adhere to a formal quality system, such as International Standard ISO 9001 (OECD, 2000[5]).

The responsibility for the quality and documentation of the test system rests entirely with the test facility (Section 5.2), however, the role of the supplier is crucial in aiding the facility meet these quality requirements, e.g. test systems characterisation requirements

can often be directly fulfilled by information from the supplier (OECD, 2000[5]). Accredited/certified providers generally provide extensive documentation on the origins and characterisation of the test system and may also offer advice/services, such as quality assurance guidance, cell culture maintenance, and safety practices for use and disposal of the test system, including transport and containment[8] (OECD, 2004[6]) (Coecke et al., 2005[7]).

It is difficult, if not impossible, to identify cell lines from different origins and ensure that they are not cross-contaminated, misidentified or mixed-up (The European Collection of Authenticated Cell Cultures ECACC Handbook – Fundamental Techniques for ECACC Cell Lines[8]), based solely on morphology and/or culture characteristics (Section 5.6). Infection or contamination of a cell line with an adventitious virus or mycoplasma may significantly change the characteristics of the cells but again such contamination may not be visibly evident. The test system provider should therefore provide documentation the cell line's authenticity including verification of its identity and proof to be free of cross-contamination by other cell lines (Section 5.6) and/or contamination caused by bacteria, yeast or fungi, mycoplasma (Section 5.7). Additional information on the origin and culture history of the cell line, ideally including its transfer among laboratories and repositories, its manipulation (physicochemical or genetic), and details on the types of tests carried out for the detection and (if applicable) elimination of contamination should be made available, so as to provide complete tracking of the cell line provenance. In some cases, e.g., cell lines established many years ago may lack some aspects of their provenance and their origin may be unknown. It is therefore recommended to confirm that the cells in current use are assessed against a previously authenticated stock (where available), either in a cell bank or in the laboratory of the originator.

Test systems sourced from recognised cell culture banks (Table 1.1) are unlikely to be contaminated with microorganisms, unless stated otherwise, and generally provide adequate documentation, usually in the form of a Certificate of Analysis, including a Short Tandem Repeat (STR) profile.

Table 1.1. Cell culture collections (banks)

Cell culture collections	Country	Web site
American Type Culture Collection (ATCC)	USA	http://www.atcc.org
CellBank Australia	Australia	www.cellbankaustralia.com
Coriell Cell Repository	USA	http://locus.umdnj.edu/ccr
Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ)	Germany	http://www.dsmz.de
European Collection of Animal Cell Cultures (ECACC)	UK	http://www.camr.org.uk
Japanese Collection of Research Bioresources (JCRB)	Japan	http://cellbank.nihs.go.jp
RIKEN Gene Bank	Japan	http://www.rtc.riken.go.jp
UK Stem Cell Bank (UKSCB)	UK	http://www.nibsc.org/ukstemcellbank

The test system provider must provide all relevant safety information, in compliance with national and international regulations, for the transport, use and disposal, including containment in the case of an accident. Where the *in vitro* method developer is also the test system provider or where the test system has been acquired from other laboratories, the *in vitro* method developer must ensure the availability of the test system both in the short and long term and as such take on all responsibilities associated with a test system provider regarding documentation and quality control.

The Guidance on Good Cell Culture Practice: A Report of the Second ECVAM Task Force on Good Cell Culture Practice (GCCP) (Coecke et al., 2005[7])provides a minimal set of requirements for documentation. However the documentation requirements listed in Table 1.2 may not be feasible in all cases when working with cells or tissues of animal or human origin, and in particular when animal-derived tissues are obtained from abattoir operations[9]. The OECD GLP document No 14 (The Application of the Principles of GLP to *in vitro* Studies) states that some characteristics of the test systems can be fulfilled with assistance from the supplier, however the performance when evaluated with appropriate reference items, including positive, negative, and untreated and/or vehicle controls, where necessary, is the responsibility of the relevant study director (OECD, 2004[6]).

Table 1.2. Examples of data requirements to be documented concerning the origins of cells and tissues

	Isolated organs and tissues of animal origin	Primary cultures of animal origin	All materials of human origin	Cell lines
Ethical and safety issues	+	+	+	Applicable, if human or involving recombinant DNA or pathogens
Species/strain	+	+	+	+
Source	+	+	+	+
Sex	+	+	+	+
Age	+	+	+	+
Number of donors	+	+	If applicable	na
Health status	+	+	+	+
Any special pre-treatment	+	+	+	+
Organ/tissue of origin	+	+	+	+
Cell type(s) isolated	+	+	+	+
Isolation technique	+	+	+	+
Date of isolation	+	+	+	+
Operator	+	+	+	+
Supplier	+	+	+	+
Informed consent	na	na	+	If human, may be applicable
Material transfer agreement	na	na	+	+
Medical history of donor	na	na	+ (if available)	If human, may be applicable (if available)
Pathogen testing	If applicable [a]	If applicable [a]	+[a]	+[a]
Shipping conditions	+	+	+	+
State of material on arrival	+	+	+	+
Biosafety classification	+	+	+	+
Cell line identification and authentication	na	na	na	+
Mycoplasma testing	na	na [b]	na [b]	+

Notes:
1. Screening tests for animal colonies or donors of cells and tissue may be appropriate.
2. May be important if material is preserved for longer term use (e.g. as feeder layers for other cultures).

na = not applicable
Source: (Coecke et al., 2005[7])

1.3. Validation bodies

The role of national and international organisations, such as OECD related working groups, EURL ECVAM, ICCVAM, JaCVAM, Health Canada, KoCVAM, etc., is to promote and facilitate *in vitro* method validation for regulatory acceptance to replace, reduce or refine (3Rs) *in vivo* testing. The validation body's responsibility is to contribute to both an effective validation process and to ensure the quality of the validated *in vitro* method.

The basic principle of validation is to assess that an *in vitro* method is fit for its intended use. To this end, the validation process generally consists of the generation, collection and evaluation of data to establish scientific evidence that the *in vitro* method is capable of consistently producing data that is reliable (reproducible) and relevant for the intended purpose. For further information regarding validation concepts, challenges, processes and useful tools see Chapter 04 in Validation of Alternative Methods for Toxicity Testing (Griesinger et al., 2016[8]).

While details can differ between validation bodies, the overall goal of the process of validation is to improve the international acceptance of test methods. To this end, the OECD has drafted a guidance document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment No. 34 (OECD, 2005[1]). The document promotes a "modular approach to validation", where the information needed to support the validity of a test method is organised into modules (Hartung, 2004[9]). Several practical aspects need to be considered in the design and validation of *in vitro* methods (Coecke et al., 2016[10]), if the ultimate aim is to generate a dataset that can support the development of an international test guideline. OECD GD 34 provides information on the following aspects:

- test definition (including purpose, need and scientific basis);
- within-laboratory repeatability and reproducibility;
- between-laboratory transferability;
- between-laboratory reproducibility;
- predictive capacity (accuracy);
- applicability domain; and,
- performance standards.

Although validation is an important step, not all modules/aspects of validation are indispensable for regulatory acceptance. It is important to emphasise that only robust methods can be accepted, i.e. reproducibility and transferability have to be demonstrated, thus validation is not entirely indispensable. After successfully demonstrating the validity of an *in vitro* method to a validation body, the method can be presented to the OECD for regulatory acceptance, depending on the Member State, e.g. in the US, it must be posted in the Federal Register for comment and then FDA and EPA need to separately evaluate comments and follow up by posting final guidance in the federal register. Once *in vitro* methods are consolidated within an OECD test guideline (TG), data produced by using those methods are mutually accepted by all OECD Members and MAD-adhering Country Authorities, unless specific national regulatory requirements are not met.

1.4. Inter-governmental organisation for cooperation

A framework for cooperation between inter-governmental organisation was established in the critical areas of validation studies, independent peer review, and development of harmonised recommendations to ensure that alternative methods/strategies are more readily accepted worldwide.

The International Cooperation on Alternative Test Methods (ICATM)[10,11,12] was formally established in 2009 through a collaboration involving EU, US, ,Japan and Canada. Representatives now include, EU (EURL ECVAM), the US (NICEATM/ICCVAM), Japan (JaCVAM), Canada (Health Canada), and Korea (KoCVAM). Although not yet formally partners, the Brazilian Center for the Validation of Alternative Methods (BraCVAM) and China also actively participate.

ICATM partners are working together to promote enhanced international cooperation and coordination on the scientific development, validation and regulatory use of alternative approaches.

1.5. Suppliers of equipment, materials and reagents

While the responsibility for the quality and fitness for use of equipment and materials rests entirely with the management of the test facility, it is in the suppliers' interests to meet these requirements where possible. Suppliers are recommended to comply with formal national or international standards or to be accredited within various national schemes, where appropriate (OECD, 2000[5]). Selection of suppliers should follow a formal documented process and should be reviewed regularly to ensure that equipment, materials and reagents meet the facility's requirements.

When performing established *in vitro* testing methods, the test results can only be accepted if the equipment, materials and reagents used are of proven quality as established by formal testing or evaluation procedures.

Equipment suppliers should provide all information necessary to operate and maintain the equipment, including equipment and software manuals and quality and safety conformation certificates and warranties. For complex equipment it is recommended that the manufacturer install the equipment and provide the necessary documentation to confirm the correct functioning of the equipment according to the manufacturer's specifications (Section 4.1).

Characteristics of the supplied materials and reagents should be appropriately documented in adequate quality documents such as a certificate of analysis, batch release certificate or similar.

1.6. *In vitro* method users

In vitro method user(s) herein refers to the person(s) or entity that uses the finalised *in vitro* method. As the final goal of these *in vitro* methods is to be included in a regulatory framework, the majority of these users will be GLP compliant test facilities. GLP test facilities' responsibilities are described in the OECD Principles of GLP[13] or equivalent GLP principles as defined in national legislation.

In vitro method users should document their competency to perform a test in compliance with a specific OECD TG, e.g., by running the proficiency chemicals (Section 8.4.) or checking the performance of the method (Chapter 8).

Non-GLP *in vitro* method users can also profit from the use of the GIVIMP guidance. In these cases no regulations exist and no responsibilities are defined, however it is highly recommended to apply all necessary good scientific, technical and quality practices that this guidance describes so as to reduce the uncertainties in the results produced by the *in vitro* method. Appropriate accreditation, e.g., ISO/IEC 17025[14], may be requested or recommended in some cases.

The responsibility for the quality, integrity and compliance (where applicable) of all data generated and reported rests entirely with the *in vitro* method user(s), who must also verify and assure that the quality of all products and materials used in the generation of said data meets the required specifications as described in the *in vitro* method and/or other regulatory guidelines. To be able to prove this, *in vitro* method users will need to work with preferred or approved suppliers who are selected on predefined criteria (e.g., ISO certification, controlled transport, technical support, assured delivery, batch selection, etc.).

1.7. Sponsor

Studies are often initiated by a sponsor who is responsible for ensuring that a study is conducted according to certain requirements e.g., GLP (OECD, 1998[11]).

The sponsor should actively verify that the study is conducted in accordance with all Principles of GLP. The sponsor should verify that the involved test facility including, if applicable, any test sites are able to conduct the study in accordance with the GLP Principles. For example, the sponsor could monitor the involved test facility and, if applicable, any other test site also involved in the study, prior to and during the conduct of the study. In addition, the sponsor might also check the compliance status of a test facility as determined by the national GLP compliance monitoring authority.

The sponsor should be aware, however, that only the study director remains ultimately responsible for the scientific validity and the GLP compliance of the study.

The sponsor should also ensure the integrity of each unaltered study report submitted to receiving authorities.

- The sponsor may be responsible for providing the test item. To ensure that there is no mix-up of test items the sponsor should, in cooperation with the test facility, define a mechanism to allow verification of the identity of the test item for each study.
- Often the sponsor is responsible for characterisation of the test item. In that case, the study director should ensure that this is explicitly mentioned in the study report.
- Where the sponsor is responsible for the characterisation of the test item, the sponsor is expected to disclose all information regarding the characterisation of the test item to the study director, and should be explicitly stated in both the study plan and the final report.

- The sponsor should inform the test facility about any potential risks of the test item to human health and environment as well as any necessary protective measures and disposal procedures.
- In some countries the sponsor should formally approve the study plan by dated signature.
- The name and full address of the sponsor should be mentioned in the study plan and study report.
- Where the study materials including study plan, raw data, specimens and samples of test and reference items and final reports are transferred to the sponsor, the sponsor assumes the responsible for ensuring that all materials are archived in accordance with the GLP Principles.

On the basis of the outcome of the studies the sponsor may decide to submit a test item for registration to the receiving authorities.

1.8. GLP monitoring authorities

GLP Monitoring Authorities (MAs) are established by the governments of OECD Member States and MAD-adherent countries. Some countries have only one MA, while others have more than one e.g., in Japan there are eight MAs while in the US there are two MAs, the US Environmental Protection Agency (EPA) and the US Food and Drug Administration (FDA). The OECD maintains a list of links to national web sites on GLP, including information on MAs[15].

For studies conducted for regulatory purposes, the responsibility for evaluating the results of the study lies with the regulatory reviewer at the receiving authority. However, this evaluation can only be effective if the study data can be relied upon. GLP ensures that the quality and integrity of the data can be demonstrated and the conduct of the study reconstructed.

The OECD expects member countries to establish national MAs, a body or bodies responsible for monitoring the GLP compliance of test facilities within their territories and according to national legal and administrative policies. In the European Union (EU), facilities included in the GLP monitoring programme of the GLP Monitoring Authority are inspected on a regular basis, approximately every two to three years. Routine monitoring inspections also include study audits. In addition, MAs can be requested by a receiving authority to conduct specific study audits as a result of concerns raised following the review of a regulatory submission. The MA has ultimate responsibility for determining the GLP compliance status of test facilities and/or GLP studies. The MA also has responsibility for taking any action based on the results of test facility inspections or study audits which are deemed necessary.

The respective national compliance MAs are also responsible for the exchange of information on the compliance of test facilities inspected, and should provide relevant information concerning their procedures for monitoring compliance. They have the responsibility to facilitate the MAD (Section 9.2) multilateral agreement, which states that test data generated in OECD countries and full adherent countries – (Argentina[16], Brazil, India, Malaysia, South Africa and Singapore)[17] in accordance with OECD Test Guidelines and the OECD Principles of GLP shall be accepted in other member countries

by regulatory bodies for assessment purposes and other uses relating to the protection of human health and the environment[18].

1.9. Receiving authorities

Receiving authorities receive non-clinical safety data as part of regulatory submissions and they must ensure that the legal requirements are met. Receiving authorities include the European Chemicals Agency (ECHA), European Medicines Agency (EMA), European Food Safety Authority (EFSA), as well as various national agencies that are responsible for assessing safety data such as, for example, the US EPA, FDA and Department of Agriculture (USDA) and in Japan the Ministry of Health, Labour and Welfare (MHLW) and the Ministry of Agriculture, Forestry and Fisheries (MAFF).

The responsibility of the receiving authorities is to check that test data are obtained according to available OECD TGs (where applicable) and guidance documents and that they use the data accordingly in their evaluations and according to the regulatory framework. With regard to GLP studies, the receiving authorities verify whether the reported study was conducted in compliance with GLP (Section 1.8). The level of GLP compliance verification depends on the particular receiving authority and the specific legal framework. Receiving authorities may request a study audit if a concern about the GLP compliance status of the study is identified or in case the responsible test facility has not been inspected by the responsible national GLP monitoring authority. Receiving authorities may additionally indicate to *in vitro* method developers where they see a need for new or better methods, and to validation bodies which methods deserve priority in the validation.

In vitro methods are becoming more and more accepted for regulatory use and some regulation requiring toxicological data, allow or even encourage the use of alternative methods. Multiple legislational frameworks, e.g., US Federal agencies (Schechtman, 2002[12]) and EU Directive 2010/63/EU[19], in various regions of the world have statements that include reference to the "3Rs" or that express support for the replacement, reduction, and refinements of animals use where feasible.

The U.S. EPA's Office of Pesticide Programs (OPP) is developing and evaluating alternative approaches to replace or amend more traditional methods of toxicity testing and uses so-called Integrated Approaches to Testing and Assessment (IATA) (see Strategic Vision for Adopting 21st Century Science Methodologies[20]), with the immediate goal to significantly reduce the use of animals in acute effects testing.

As a result of these developments European and national regulatory bodies tend to increasingly accept data generated by alternative methods, especially from validated *in vitro* methods. Data generated using non-validated *in vitro* methods may be accepted as supportive information or when mechanistic data are required. Although the applicability of *in vitro* methods to meet regulatory needs may be different in individual OECD member countries, many countries have adopted the principles of Replace, Reduce and Refine (3Rs) and are proactively supporting the use and implementation of alternative methods[21].

EMA expresses in a number of documents their vision and action plans towards the implementation of the 3Rs principles (EMA, 2014[13]). Besides established formal validation processes by recognised institutions such as the Centres for the Validation of Alternative Methods (CVAMs) and The European Directorate for the Quality of

Medicines & HealthCare (EDQM), multiple and flexible approaches are considered acceptable to demonstrate scientific validity of new testing approaches and their fitness for regulatory use, either as pivotal, supportive or as exploratory mechanistic studies (EMA, 2016[14])

Notes

1. See: http://www.oecd.org/chemicalsafety/testing/intellectual-property-in-oecd-test-guidelines.htm
2. See: http://www.oecd.org/sti/sci-tech/intellectualpropertyinbiotechnologyandthelifesciences.htm
3. See: http://www.oecd.org/science/biotech/36198812.pdf
4. See: http://www.oecd.org/chemicalsafety/testing/intellectual-property-in-oecd-test-guidelines.htm
5. See: http://www.oecd.org/chemicalsafety/testing/performance-standards.htm
6. See: https://www.moh.gov.sg/content/dam/moh_web/Publications/Guidelines/Human%20Biomedical%20Research/2007/IRB%20Operational%20Guidelines_14-12-07_formatted.pdf
7. See: https://www.oecd.org/chemicalsafety/testing/national-coordinators-test-guidelines-programme.htm
8. See: http://www.sigmaaldrich.com/life-science/cell-culture/learning-center/ecacc-handbook.html
9. Justification should be provided when documentation requirements listed in Table 2 are not followed.
10. See: https://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/international-partnerships/index.html
11. See: https://ec.europa.eu/jrc/en/eurl/ecvam/alternative-methods-toxicity-testing/advisory-bodies/icatm
12. See: http://www.jacvam.jp/en_effort/icatm.html
13. See: http://www.oecd.org/chemicalsafety/testing/oecdseriesonprinciplesofgoodlaboratorypracticeglpandcompliancemonitoring.htm
14. See: https://www.iso.org/standard/66912.html
15. See: http://www.oecd.org/chemicalsafety/testing/linkstonationalwebsitesongoodlaboratorypractice.htm
16. See: Full adherence for Argentina only applies to industrial chemicals, pesticides and biocides
17. See: http://www.oecd.org/env/ehs/non-memberadherentstotheoecdsystemformutualacceptanceofchemicalsafetydata.htm
18. See: http://www.oecd.org/env/ehs/mutualacceptanceofdatamad.htm
19. See: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:EN:PDF

20. See: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-21st-century-science

21. See: https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/in-vitro-methods

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