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t4 Report*

Glossary of Reference Terms for Alternative Test Methods and their Validation

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Summary

This glossary was developed to provide technical references to support work in the field of alternatives to animal testing. It was compiled from various existing reference documents coming from different sources and is meant to be a point of reference on alternatives to animal testing. Giving the ever-increasing number of alternative test methods and approaches being developed over the last decades, a combination, revision and harmonization of earlier published collections of terms used in the validation of such methods is required. The need to update previous glossary efforts came from the acknowledgement that new words have emerged with the development of new approaches, while others have become obsolete, and the meaning of some terms has partially changed over time. With this glossary we intend to provide guidance on issues related to the validation of new or updated testing methods consistent with current approaches. Moreover, because of new developments and technologies, a glossary needs to be a living, constantly updated document. An Internet-based version based on this compilation may be found at http://altweb.jhsph.edu/, allowing the addition of new material.

Keywords: 3Rs, alternatives, validation, glossary, ontology

1 Introduction

Predictive approaches in toxicology share the need for highly structured information as a starting point. In the last few years, an increasing number of publications about vocabulary and ontology played a key role in the standardization and organization of toxicological databases, improving the interoperability between toxicology resources by creating structures to support both R&D and risk assessment (Hardy et al., 2012 a,b). At present, a few diverse initiatives for developing vocabularies and ontologies exist, but they are insufficient for the creation of a common toxicology ontology/vocabulary supporting the increased needs of risk assessment.

Science has always developed a specific vocabulary and strict identification of terms, names, and concepts. Frequently, scientific terminology may be scattered between disciplines and too specific and difficult to define properly. For this reason, glossaries have been created in order to group definitions within a unique domain (or overlapping domains). Substantial ontology projects have also been adopted to unify existing information and give formal representation of a set of concepts within a singular domain and/or create a relationship between these concepts (Hardy et al., 2012b). However, science is always evolving and new terms and definitions are being created regularly. This is particularly true for rapidly evolving niches such as bioinformatics and computational or *in silico* predictive platforms and technolo-

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gies applied to life science. Therefore, an ontology framework also provides the basis for a shared vocabulary. In the specific field of validation of alternative methods, new testing approaches, standards and tools employed for data analysis are constantly replaced by newer technologies. For this reason, terminology applied to alternative testing approaches can be created *ad hoc* even within a single validation study, sometimes resulting in barriers to understanding or overly-technical language.

Though attempts to promote the use of unified scientific terminology and glossaries are common throughout disciplines, there is no specific scheduling of revisions and additions. There is a need not only to make the science of alternatives more understandable but to create a common, consolidated vocabulary to increase acceptance of new technologies. In the field of validation of alternative test methods, the most complete list of definitions and terms is still provided by the 2005 OECD Guidance Document No. 34 on "The Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment" (OECD 2005, ENV/JM/MONO(2005)14). In the last few years, alternative testing methods have been one of the most debated issues in toxicology and risk assessment, in large part due to the publication of *Toxicity Testing in the 21st Century: a Vision and a Strategy* (NRC, 2007b). Fresh thinking and emerging technologies have generated a variety of new approaches for generating more robust data for risk assessment by incorporating more mechanistic information into toxicity predictions. Moreover, since the publication of OECD No. 34 in 2005 several validations have been endorsed as scientifically sound, and some of these new testing strategies have been accepted as alternative testing approaches in regulatory risk assessment evaluation.[1] Other validations are ongoing, resulting in a significant number of new terms and concepts coming into common use. In 2007, our former colleagues of the European Centre for the Validation of Alternative Methods (ECVAM) created an extended glossary of terms used in the validation of alternative methods, expanding and implementing the internationally-agreed-upon (via OECD No. 34) definitions for terms used in the validation and acceptance of new testing methods, but it was never published. A few years later, an extended glossary is even more essential because of new terminologies and concepts, as well as terms that were overlooked in OECD Guidance Document No. 34 (e.g., those relating to toxicokinetics and pharmacokinetics). Moreover, as the possible mechanisms of toxicity of chemicals have been increasingly investigated and debated in the last few years, adding fresh mechanistic knowledge, we aimed to implement current approaches that include work toward pathways of toxicity in our glossary.

2 Objective

The field of predictive toxicology evaluates the potential adverse effects of chemicals and drugs by standard animal testing and, increasingly, through the development of *in vitro* and computational methods which can refine and reduce the need for animal testing. As extensively discussed by others (Hardy et al., 2012 a,b), to be more incisive and accessible, new technologies urgently need to develop open, public, and standardized vocabularies and ontologies. Such vocabulary development increases access to relevant information, clarifying terminologies across different sub-disciplines and leading to new scientific advances and acceptance of mechanism-based predictive toxicology. We hope this glossary will address these needs. By integrating and illustrating the increasing number and types of alternative approaches, as well as supporting new test system development and mechanistic research activities in risk assessment evaluation, we aim to provide increased scientific knowledge to professionals, governmental representatives, and consumers.

3 Context

Though the extended glossary seeks to provide strong technical references to support professionals working in the field, it is also intended to be used by others. For this reason, more general terms which are often mentioned or implied when dealing with alternatives to animal testing in other contexts are also added to the glossary. Specific terminologies or definitions related to different validated testing methodologies are beyond the scope of this glossary, but may be easily tracked down, for example, in the respective OECD testing guideline glossary.

4 Materials and methods

The glossary is largely drawn from previous terminology efforts. As discussed above, the major sources of terms include the OECD Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (OECD 2005, ENV/JM/MONO(2005)14), the 1997 report of the Interagency Coordinating Committee on the Validation of Alternative Methods (NIEHS, 1997), the IUPAC glossary of terms used in toxicology (Duffus et al., 2007), and the glossary of terms provided by the Agency for Toxic Substances and Disease Registry (ATSDR, 2009). All overlap substantially. Other documents are cited in the references section. To facilitate tracking, the most significant source used for the definition of each term has been indicated at the end of its definition. When the definition was identical to that taken from the source, this is indicated by "id" at the end of the definition. The definitions of the OECD Guidance Document were kept unchanged or minimally modified, as far as possible. Terms for which no primary source is given have been newly defined by the authors of this paper.

5 List of terms

3Rs (The principles of humane experimental technique): *Reduction* is any means of lowering the number of animals used

[1] http://www.alttox.org/ttrc/validation-ra/validated-ra-methods.html (last accessed 20.03.2014)

to obtain information of a given amount and precision. *Refinement* is any development that refines procedures to lessen or eliminate pain or distress to animals, or enhances animal well-being. *Replacement* is any scientific method employing non-sentient material, which may replace methods which use conscious living vertebrates.

3Rs alternative (Reliable, Robust and Relevant): When selecting the battery of *in vitro* and *in silico* methods addressing key steps in the relevant biological pathways (the building blocks of the Integrated Testing Strategies) it is important to employ standardized and internationally accepted tests. Each block should be producing data that are Reliable, Robust, and Relevant for assessing the specific aspect (e.g., biological pathway) it is supposed to address (Berg et al., 2011).

Absorbed dose: The amount of the environmental contaminant absorbed in body tissue or interacting with an organ's membrane surface (NRC, 1991; id).

Absorption: Penetration of a substance into an organism and its cells by various processes, some specialised, some involving expenditure of energy (active transport), some involving a carrier system, and others involving passive movement down an (electro-) chemical gradient (Nordberg et al., 2004).

Absorption barrier: Any of the exchange barriers of the body that allow differential diffusion of various substances across a boundary (e.g., skin, lung tissue, gastrointestinal tract wall) (US EPA, 1992; id).

Absorption factor: The fraction of an agent (e.g., a chemical) making contact with an organism that is systematically distributed in the organism (REAP, 1995; id).

Absorption fraction: The relative amount of a substance on the skin that penetrates through the epidermis into the body; reported as the unitless fraction of the applied dose or as the percent absorbed (US EPA, 1992; id).

Accumulation: See *bioaccumulation*.

Accuracy: The ability of a test system to provide a test result close to the accepted reference value for a defined property (Balls et al., 1995).

Acceptable Daily Intake (ADI): An estimate of the amount of a substance in food or drinking water, expressed on a bodyweight basis, that can be ingested daily over a lifetime without appreciable risk (standard human = 60 kg). The ADI is listed in units of mg per kg of body weight.[2]

Active ingredient: Component of a mixture responsible for the biological effects of the mixture (Duffus et al., 2007; id).

Active metabolite: Metabolite causing biological and (or) toxicological effects (Duffus et al., 2007; id).

Acute reference dose: An estimate of a chemical substance, expressed on a bodyweight basis, to which a human population (including sensitive subgroups) can be exposed over a short period of time (24 h or less) without an appreciable risk of deleterious effects during a lifetime.[3]

Acute toxicity: 1) Adverse effects of finite duration occurring within a short time (up to 14 days) after administration of a single dose (or exposure to a given concentration) of a test substance or after multiple doses (exposures), usually within 24 h of a starting point (which may be exposure to the toxicant, or loss of reserve capacity, or developmental change, etc.). 2) Ability of a substance to cause adverse effects within a short time of dosing or exposure (Duffus et al., 2007; id).

Acute exposure: Contact with a substance that occurs once or for only a short time (up to 14 days) (ATSDR, 2009; id).

Adaptive response: In the context of toxicology, the process whereby a cell or organism responds to a xenobiotic so that the cell or organism will survive in the new environment that contains the xenobiotic without impairment of function (Keller et al., 2012; id).

Additive effect: A biologic response to exposure to multiple substances that equals the sum of responses of all the individual substances added together (ATSDR, 2009; id).

Additive effect: Consequence which follows exposure to two or more physico-chemical agents which act jointly but do not interact: the total effect is the simple sum of the effects of separate exposures to the agents under the same conditions (Duffus et al., 2007; id).

Adjunct test: A test that provides information that aids the interpretation of the results of other tests and/or provides information useful for the risk assessment process (NIEHS, 1997).

Adjuvant: A substance added to a drug to speed or increase the action of the main component (Duffus et al., 2007).

ADME: Generally used as the abbreviation for Absorption, Distribution, Metabolism, Elimination.

ADMET: Absorption, Distribution, Metabolism, Excretion, Toxicokinetics (Duffus et al., 2007; id).

Adsorption: Physical or chemical bonding of molecules of gas, liquid, or a dissolved substance to the external surface of a solid or the internal surface, if the material is porous, in a very thin layer (Allaby, 1990).

Adverse Effect: Change in morphology, physiology, growth, development, or lifespan of an organism which results in impairment of its functional capacity or impairment of its capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences.[3]

Adverse event: Occurrence that causes an adverse effect (Duffus et al., 2007; id).

Adverse Outcome Pathway (AOP): An AOP is a sequence of events from the exposure of an individual or population to a chemical substance through a final adverse (toxic) effect at the individual level (for human health) or population level (for ecotoxicological endpoints). The key events in an AOP should be definable and make sense from a physiological and biochemical perspective. AOPs incorporate the toxicity pathway and mode of action for an adverse effect. AOPs may be related to other mechanisms and pathways as well as to detoxification routes (OECD, 2013).

Adverse response: Changes that occur that result in impairment of functional capacity, often due to an insult that exceeds the

[2] http://www.who.int/foodsafety/chem/jecfa/glossary.pdf (last accessed 22.10.2013)

[3] http://www.reach-compliance.eu/english/REACH-ME/engine/sources/definitions.html (last accessed 20.03.2014)

capacity of the adaptive response to permit a return to the homeostatic state. Outcomes might include changes in morphology, development, lifespan, or growth of the organism. Although harder to define at the molecular level, potentially adverse responses might include alternations in gene expression, protein synthesis, or cell regulation.[4]

Agent: A chemical, physical, mineralogical, or biological entity that may cause deleterious effects in an organism after the organism is exposed to it (NRC, 1991; id).

Algorithm: A procedure for performing a complicated operation by carrying out a precisely determined sequence of simpler ones (Bullock and Stallybrass, 1977).

Alternative test: A test that reduces the numbers of animals required; refines procedures to lessen or eliminate pain or distress to animals or enhances animal well-being; or uses non-sentient material in place of conscious living vertebrates (OECD, 2005).

Animal testing: The use of non-human vertebrates in experiments (European Commission, 1986).

Animal welfare: The desire to prevent unnecessary animal suffering, ensuring a good quality of life and humane death. In particular, when they are under the care of humans: (a) Animals intended for use in research facilities or for exhibition purposes or for use as pets are provided humane care and treatment; (b) animals are given humane treatment during transportation in commerce.[5]

Antagonistic effect: A biologic response to exposure to multiple substances that is less than would be expected if the known effects of the individual substances were added together (ATSDR, 2009; id).

Apical (final) endpoint: An observable outcome in a whole organism, such as a clinical sign or pathologic state, that is indicative of a disease state that can result from exposure to a toxicant (Krewski et al., 2011; id).

Apoptosis: Active process of programmed cell death, requiring metabolic energy, often characterized by fragmentation of DNA, and cell deletion without associated inflammation (Duffus et al., 2007; id).

Applicability domain: The physicochemical, structural, or biological space and information that was used to develop a (Q)SAR model, and for which that model gives predictions with a given level of reliability (European Commission, 2002; id).

Assay: See *test method*.

Assessment factor (safety factor, uncertainty factor): Numerical adjustment used to extrapolate from experimentally determined (dose/concentration-response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur (OECD, 2004b).

Benchmark concentration (BMC): Statistically calculated lower 95% confidence limit on the concentration that produces a defined response (called the benchmark response or BMR, usually 5% or 10%) for an adverse effect compared to background, often defined as 0% or 5% (Duffus et al., 2007; id).

Benchmark dose (BMD): Statistically calculated lower 95% confidence limit on the dose that produces a defined response (called the benchmark response or BMR, usually 5% or 10%) of an adverse effect compared to background, often defined as 0% or 5% (Duffus et al., 2007; id).

Between-laboratory: A term sometimes used for inter-laboratory.

Between-laboratory reproducibility: See *inter-laboratory reproducibility*.

Bias: A systematic error or deviation in results or inferences from the truth.[6]

Bio-accumulation: Progressive increase in the amount of a substance in an organism or part of an organism or cells which occurs because the rate of intake exceeds the organism's ability to remove the substance from the body (Duffus et al., 2007; id).

Bio-activation: Metabolic conversion of a xenobiotic to a more toxic derivative or one which has more of an effect on living organisms (Duffus et al., 2007; id).

Bioavailability: Fraction of an administered dose that reaches the systemic circulation or is made available at the site of physiological activity. Usually, bioavailability of a substance refers to the parent compound, but it could refer to its metabolite. It considers only one chemical form. Please note: bioavailability and absorption are not the same. The difference between, e.g., oral absorption (i.e., presence in gut wall and portal circulation) and bioavailability (i.e., presence in systemic blood and in tissues) can arise from chemical degradation due to gut wall metabolism or efflux transport back to the intestinal lumen or presystemic metabolism in the liver, among other factors (Barton et al., 2006; id).

Bioconcentration: The accumulation of a chemical in tissues of an organism to levels greater than in the environment in which the organism lives.

Biodegradation: Breakdown of a substance catalysed by enzymes *in vitro* or *in vivo* (Duffus et al., 2007; id).

Bioinformatics: Discipline encompassing the development and utilization of computational facilities to store, analyse, and interpret biological data (Duffus et al., 2007; id).

Biokinetics (in toxicology): Science of the movements involved in the distribution of substances (Duffus et al., 2007; id).

Biologically significant effect: A response in an organism or other biological system that is considered to have a substantial or noteworthy effect (positive or negative) on the well-being of the biological system. Used to distinguish statistically significant effects or changes, which may or may not be meaningful to the general state of health of the system (US EPA, 2012; id).

Biomarker: Indicator signalling an event or condition in a biological system or sample and giving a measure of exposure, effect, or susceptibility (Duffus et al., 2007; id).

[4] http://www.scienceadvice.ca/en/assessments/completed/pesticides.aspx (last accessed 20.03.2014)

[5] http://history.nih.gov/research/downloads/AWA.pdf (last accessed 20.03.2014)

[6] http://www.cochrane.org/glossary (last accessed 20.03.2014)

Biotransformation: The transformation of a chemical compound within a living system (Jayjock et al., 2000).

Carcinogenicity: A substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumor formation is not relevant for humans.

Catch-up validation study: A validation study for a test method that is structurally and functionally similar to a previously validated and accepted reference test method. The candidate test method should incorporate the essential test method components included in performance standards developed for the reference test method, and should have comparable performance when evaluated using the reference chemicals provided in the performance standards (OECD, 2005; id).

Cell viability: Parameter measuring total activity of a cell population, which, depending on the endpoint measured and the test design used, correlates with the total number and/or vitality of living cells.

Cellular response network: Interconnected pathways composed of the complex biochemical interactions of genes, proteins, and small molecules that maintain normal cellular function, control communication between cells, and allow cells to adapt to changes in their environment (NRC, 2007b; id).

Chemical category: A group of chemicals whose physico-chemical and human health and/or environmental toxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity (or other similarity characteristic) (OECD, 2007; id).

Chromosomal aberration: Abnormality of chromosome number or structure (Duffus et al., 2007; id).

Chronic: Long-term (in relation to exposure or effect). In experimental toxicology, chronic refers to mammalian studies lasting considerably more than 90 days or to studies occupying a large part of the lifetime of an organism (Duffus et al., 2007; id).

Chronic exposure: Long-term exposure, continued exposure or exposures occurring over an extended period of time, or a significant fraction of the test species' or of the group of individuals', or of the population's life-time (Duffus et al., 2007; id).

Coded chemicals: Chemicals that are labelled by code when delivered to the laboratory for testing, so that they can be tested without the laboratory personnel having knowledge of their identity or anticipation of the test results. Coded chemicals are used to avoid bias when performing laboratory tests or evaluating test results (OECD, 2005; id).

Computational approaches: See *in silico models*.

Concentration: Amount of a material or agent dissolved or contained in unit quantity in a given medium or system (OECD, 2004b; id).

Concentration-effect relationship: Relationship between the exposure, expressed in concentration, of a given organism, system, or (sub) population to an agent in a specific pattern during a given time and the magnitude of a continuously graded effect to that organism, system, or (sub) population (OECD, 2004b; id).

Concentration-effect curve: (exposure-effect curve) Graph of the relation between exposure concentration and the magnitude of the resultant biological change (Duffus et al., 2007; id).

Concentration-response curve: (exposure-response curve) Graph of the relation between exposure concentration and the proportion of individuals in a population responding with a defined effect (Duffus et al., 2007; id).

Concordance: The proportion of the outcomes of a test which are identical to an agreed upon reference. This term is often used interchangeably with accuracy (NIEHS, 1997).

Confidence interval: A range of values which bracket a point estimate; e.g., there is a 95% probability that the true value is contained in the 95% confidence interval (Jayjock et al., 2000; id).

Confidence limit: A confidence interval for a parameter is a range of values that has a specified probability (e.g., 95%) of containing the parameter. The confidence limit refers to the upper or lower value of the range (US EPA, 1995; id).

Confounding (in data analysis): Situation in which a measure of the effect of an exposure on risk is distorted because of the association of exposure with other factor(s), which influence the outcome under study (Duffus et al., 2007).

Control, negative: A separate part of a test system, treated with an item, to which it is known that the test system should not respond; the negative control provides evidence that the test system is not responsive under the actual conditions of the assay (OECD, 2004a; id).

Control, positive: A separate part of the test system, treated with an item to which it is known that the test system should respond; the positive control provides evidence that the test system is responsive under the actual conditions of the assay (OECD, 2004a; id).

Control, untreated: A separate untreated part of a test system that is kept under the original conditions; the untreated control provides baseline data of the test system under the conditions of the assay (OECD, 2004a).

Control, vehicle: A separate part of a test system, to which the vehicle for the test item is added; the vehicle control provides evidence for a lack of influence of the chosen vehicle on the test system under the actual conditions of the assay (OECD, 2004a; id).

Criterion: A standard by which something can be judged or decided.[7]

Cytotoxic: Causing damage to cell structure or function (Duffus et al., 2007; id).

Data analysis procedure (DAP): DAP refers to a procedure incorporating both a data interpretation procedure (DIP) and a prediction model (PM).

Data interpretation procedure (DIP): An interpretation procedure

[7] http://www.collinsdictionary.com/dictionary/english (last accessed 24.02.2014)

used to determine how well the results from the test predict or model the biological effect of interest (OECD, 2005; id).

Decision criteria: The criteria in a test method protocol that describe how the test method results are used for decisions on classification or other effects measured or predicted by the test method (OECD, 2005; id).

Degradation: Breaking down of complex substances to simpler ones as a result of, for example, chemical or biological processes.[3]

Derived Minimal Effect Level (DMEL): For non-threshold effects, the underlying assumption is that a no-effect-level cannot be established, so a DMEL therefore expresses an exposure level corresponding to a low, possibly theoretical risk, which should be seen as a tolerable risk.[3]

Derived No-Effect Level (DNEL): Level of exposure to the substance, below which no adverse effects are expected to occur. It is therefore the level of exposure to the substance above which humans should not be exposed. DNEL is a derived level of exposure because it is normally calculated on the basis of available dose descriptors from animal studies such as No Observed Adverse Effect Levels (NOAELs) or benchmark doses (BMDs).[3]

Dermal: Referring to the skin (ATSDR, 2009).

Dermal absorption: Absorption through the skin (ATSDR, 2009).

Dermal exposure: Contact with the skin by any medium containing chemicals, quantified as the amount on the skin and available for adsorption and possible absorption (US EPA, 1992).

Detection limit: The lowest concentration of a chemical that can reliably be distinguished from a zero concentration (ATSDR, 2009).

Developmental toxicity: Developmental effects refer to, e.g., growth and developmental retardation, malformations, and functional deficits in the offspring.[8]

Deviation (standard): Measure of dispersion of a frequency distribution equal to the positive square root of the variance.

Distribution: Dispersal of a substance and its derivatives throughout the natural environment or throughout an organism (Nordberg e al., 2004).

Dose: For chemicals, the dose is the amount of test substance administered, expressed as mass (e.g., grams or milligrams) or as mass of test substance per unit mass of test animal (e.g., milligrams per kilogram body mass), or as constant dietary concentrations (parts per million or milligrams per kilogram of food). For other potentially toxic agents, such as radiation, nanoparticles, or particulate matter, other units are used (European Commission, 2006a).

Dose rate: Dose per unit time, for example mg/day, or often expressed on a per-unit-body-weight basis (mg/kg-day) (US EPA, 1992).

Dose-response curve: A mathematical relationship between the dose administered or received and the incidence of adverse health effects in the exposed population; toxicity values are derived from this relationship (Jayjock et al., 2000).

Dose-effect relationship: Relationship between the total amount of an agent administered to, taken up, or absorbed by an organism, system, or (sub) population and the magnitude of a continuously-graded effect to that organism, system, or (sub) population (OECD, 2004b; id).

Dose-related effect: Any effect to an organism, system, or (sub) population as a result of the quantity of an agent administered to, taken up, or absorbed by that organism, system, or (sub) population (OECD, 2004b; id).

Dose response: Relationship between the amount of an agent administered to, taken up, or absorbed by an organism, system, or (sub) population and the change developed in that organism, system, or (sub) population in reaction to the agent (OECD, 2004b; id).

Dose-response assessment: The part of risk assessment which involves an analysis of the relationship between the total amount of an agent administered to, taken up, or absorbed by an organism, system, or (sub) population, and the changes developed in that organism, system, or (sub) population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population (OECD, 2005).

Dose response relationship: The quantitative relationship between the dose or level of exposure to a substance and the incidence or the extent of the adverse effect.[3]

EC_{50} (median effective concentration): Statistically derived median concentration of a substance in an environmental medium expected to produce a certain effect in 50% of test organisms in a given population under a defined set of conditions (Duffus et al., 2007).

ED_{50} (median effective dose): Statistically derived median dose of a chemical or physical agent (radiation) expected to produce a certain effect in 50% of test organisms in a given population or to produce a half-maximal effect in a biological system under a defined set of conditions (Duffus et al., 2007).

Effective concentration x%: Concentration of a tested substance causing x% changes in response (e.g., on growth) during a specified time interval.[3]

Effective dose x%: Dose of a tested substance causing an increased incidence of 10% during a specified time interval.3

Embryo: The early stages of growth and differentiation of an animal that in higher forms merge into fetal stages, but in lower forms terminate with the commencement of larval life.[9]

Empirical dose-response (EDR): Model describing the relationship between the concentration in the test medium and the degree of *in vitro* response; the EDR models would provide an estimate of some effective concentration at which a specified level of response occurs.

Empirical methods: Methods, the usefulness of which depends on a correlation or association between the endpoint measured and the biological effect of concern, rather than on known or demonstrated mechanistic relationships (NIEHS, 1997).

[8] http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment (last accessed 20.03.2014)

[9] http://www.thefreedictionary.com (last accessed 17.02.2014)

Endocrine disruptor: A substance, man-made or natural, which can interfere with the hormone systems of humans and wildlife, with potentially adverse effects, for example, on fertility and neural development (European Commission, 1999).

Endocrine modulator: An endocrine modulator is a compound or chemical that changes the function of the endocrine system, which makes and controls the hormones in the body.[10]

Endpoint: The biological or chemical process, response, or effect, assessed by a test (OECD, 2005; id).

ErC_{50}: EC_{50} in terms of reduction of growth rate.

Error: Any discrepancy between a computed, observed, or measured quantity and the true, specified, or theoretically correct value of that quantity. (a) *Random error:* in statistics, an error that can be predicted only on a statistical basis; (b) *systematic error* – in statistics, an error which results from some bias in the measurement process and is not due to chance, in contrast to random error (Jayjock et al., 2000).

ET_{50} (median lethal time): Statistically derived median time interval during which 50% of a given population may be expected to die following acute administration of a chemical or physical agent (radiation) at a given concentration under a defined set of conditions (Duffus et al., 2007).

Evidence-based toxicology (EBT): EBT is a process for transparently, consistently, and objectively assessing available scientific evidence in order to answer questions in toxicology. Particularly EBT: a) promotes the consistent use of transparent and systematic processes to reach robust conclusions and sound judgments; b) displays a willingness to check the assumptions upon which current toxicological practice is based to facilitate continuous improvement; c) recognizes the need to provide for the effective training and development of professional toxicologists; d) acknowledges a requirement for new and improved tools for critical evaluation and quantitative integration of scientific evidence; e) embraces all aspects of toxicological practice, and all types of evidence of which use is made in hazard identification, risk assessment, and retrospective analyses of causation; f) ensures the generation and use of best scientific evidence; g) includes all branches of toxicological science: human health assessment, environmental and ecotoxicology, and clinical toxicology; h) has the potential to address concerns in the toxicological community about the limitations of current approaches to assessing the state of the science; i) acknowledges and builds upon the achievements and contributions of Evidence Based Medicine/Evidence Based Health Care.[11]

Ex vivo: Literally, out of the living; refers to cells, tissues, or organs removed from the body of a living organism (Martin, 1985).

Expert involvement: See *peer involvement*.

Excretion: Process(es) by which an administered substance and/or its metabolites are removed from the body (known also as elimination).

Exposure: Contact of an organism with a chemical or physical agent, quantified as the amount of chemical available at the exchange boundaries of the organism and available for absorption; usually calculated as the mean exposure, and some measure of maximum exposure (Jayjock et al., 2000).

Exposure assessment: Evaluation of the exposure of an organism, system, or (sub) population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment (IPCS/OECD, 2004; id).

Exposure duration: In toxicology, usually three exposure durations are described: *(a) acute* (usually one time exposure); *(b) sub-chronic* (repeated for a fraction of a lifetime); and *(c) chronic* (repeated, for nearly or for an entire lifetime).

Exposure level: The amount (concentration) of a chemical at the absorptive surfaces of an organism.

Exposure scenario: A set of conditions or assumptions about sources, exposure pathways, amount or concentrations of agent(s) involved, and exposed organism, system, or (sub) population (i.e., numbers, characteristics, habits) used to aid in the evaluation and quantification of exposure(s) in a given situation (OECD, 2004b, id).

Extrapolation: Calculation, based on quantitative observations in exposed test species or *in vitro* test systems, of predicted dose-effect and dose-response relationships for a substance in humans and other biota including interspecies extrapolations and extrapolation to susceptible groups of individuals (Duffus et al., 2007; id).

False negative: A substance incorrectly identified by a test as negative (OECD, 2005).

False negative rate: The proportion of substances incorrectly identified by a test as negative (OECD, 2005).

False positive: A substance incorrectly identified by a test as positive (OECD, 2005).

False positive rate: The proportion of substances incorrectly identified by a test as positive (OECD, 2005).

Fate: Pattern of distribution of an agent, its derivatives, or metabolites in an organism, system, compartment or (sub) population of concern as a result of transport, partitioning, transformation, or degradation (OECD, 2004b; id).

Feasibility: Ability to be done or put into effect.[7]

Gaussian (normal) distribution: A unimodal symmetrical (bell-shaped) distribution where the most prevalent value is the mean (average) and the spread is measured by the standard deviation. Mathematically, the distribution varies from minus infinity with zero probability to plus infinity with zero probability (US EPA, 2012; id).

Genotoxicity: The capacity of a substance to alter the genetic material (DNA) of cells which may have adverse consequences for human health.

GLP: See *Good Laboratory Practice*.

Good Laboratory Practice (GLP): A set of principles that provide a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. GLP helps to assure regulatory authorities that the data submitted

[10] http://ihcp.jrc.ec.europa.eu/our_activities/food-consprod/endocrine_disrupters/intro/?searchterm=None (last accessed 20.03.2014)

[11] http://en.wikipedia.org/wiki/Evidence-based_toxicology (last accessed 20.03.2014)

are a true reflection of the results obtained during the study, and can therefore be relied upon when making risk/safety assessments.[12]

Hazard: 1) A biological, chemical, or physical agent with the potential to cause an adverse health effect (European Commission, 2002). 2) The inherent characteristic of a material, condition, or activity that has the potential to cause adverse effects to people, property, or the environment (Hodgson et al., 1998; id).

Hazard assessment: Consists in using the information about the intrinsic properties of the substance to make an assessment of hazard in the following areas: 1) Human health hazard assessment; 2) Human health hazard assessment of physicochemical properties; 3) Environmental hazard assessment; 4) PBT and vPvB assessment.[3]

Hazard characterization: The qualitative and, wherever possible, quantitative description of the inherent property of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose–response assessment and its attendant uncertainties. Hazard characterization is the second stage in the process of hazard assessment, and the second of four steps in risk assessment.

Hazard classification: Assignment of a chemical or product hazard into a category of severity based on the results of a standard test method for a specific toxic endpoint; most commonly used for labelling purposes (NIEHS, 1997; id).

Hazard identification: The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub) population. Hazard identification is the first stage in hazard assessment, and the first of four steps in risk assessment (OECD, 2005; id).

Hierarchical test approach: See *tiered testing approach*.

High-throughput screening (HTS): The use of robotics-based technology to screen large sets of substances for specific activities (OECD, 2004a).

IC_{50}: Can be estimated by determination of the concentration at which a marker chemical reduces the viability of the tissues by 50% after a fixed exposure time, see also ET_{50}.

Immunotoxicity: An immunotoxic compound can be defined as a compound that can alter one or more immune functions resulting in an adverse effect for the host.[13]

Incidence: Proportion or probability of individuals or animals exhibiting an effect that varies from zero to one, sometimes expressed as a percent from 0% to 100% (US EPA, 2012; id).

Ingestion: Oral intake of chemicals.

Inhalation: Intake of chemicals through the respiratory system.

In silico models: Computer-based estimations or simulations. Examples include structure–activity relationships (SAR), quantitative structure–activity relationships (QSARs), molecular modelling techniques, and expert systems (OECD, 2005).

Intake: Amount of a substance that is taken into the body, tissues, even cells regardless of whether or not it is absorbed: the total daily intake is the sum of the daily intake by an individual from food, drinking-water, and inhaled air (Duffus et al., 2007; id).

Intake rate: Rate of inhalation, ingestion, and dermal contact depending on routes of exposure.

Integrated testing strategy (ITS): In the context of safety assessment, an integrated testing strategy is a methodology which integrates information for toxicological evaluation from more than one source, thus facilitating decision-making. This should be achieved whilst taking into consideration the principles of the Three Rs (reduction, refinement, and replacement) (Kinsner-Ovaskainen et al., 2012; id).

Integrated testing strategy Type 1: Strategies to gather and analyze a broad range of data coming from different sources (epidemiological studies, animal data, *in vitro* data, read-across methodologies, etc.) and used to draw conclusions based on weight-of-evidence approaches (Kinsner-Ovaskainen et al., 2012; id).

Integrated testing strategy Type 2: Testing strategies composed of, e.g., a number of *in vitro* and *in silico* methods that, combined and weighted in a fixed way, would serve to replace some or all *in vivo* experimentation for a given toxicity endpoint (Kinsner-Ovaskainen et al., 2012; id).

Inter-laboratory reproducibility: A measure of the extent to which different qualified laboratories, using the same protocol and testing the same substances, can produce qualitatively and quantitatively similar results. Inter-laboratory reproducibility is also referred to as between laboratory reproducibility (OECD, 2005).

Intra-laboratory repeatability: A determination of the closeness of agreement between test results obtained within a single laboratory, when the procedure is performed independently under repeatability conditions, i.e., in a set of conditions including the same measurement procedure, same operator, same measuring system, same operating conditions, and same location, and replicated measurements over a short period of time.[14]

Intra-laboratory reproducibility: A determination of the extent to which qualified people within the same laboratory can independently and successfully replicate results using a specific protocol at different times (OECD, 2005; id).

In vitro: Literally, in glass; refers to maintenance outside the body of a living organism in an artificial environment (Martin, 1985).

In vivo: Literally, in the living; refers to within the body of a living organism (Martin, 1985).

Irritation: Local effects on the skin, in the eyes, or in the respiratory system, which are considered to be reversible.

Key events: Steps along the pathway that represent intermediate events, typically at the different levels of biological organization which are experimentally or toxicologically associated

[12] http://acts.oecd.org/Instruments/ShowInstrumentView.aspx?InstrumentID=263&InstrumentPID=263&Lang=en&Book=False (last accessed 20.03.2014)

[13] http://alttox.org/ttrc/toxicity-tests/immunotoxicity/way-forward/corsini/ (last accessed 20.03.2014)

[14] http://www.westgard.com/glossary-of-iso-terms.htm (last accessed 10.10.2013)

with an adverse outcome pathway (OECD, 2012).

LC_{50}: The LC_{50} (median lethal concentration) is a statistically-derived concentration of a substance that can be expected to cause death during exposure or within a fixed time after exposure in 50% of the animals exposed for a specified time. The LC_{50} value is expressed as mass of test substance per standard volume of air (milligrams per liter). LC_{50} also applies to 50% cell death in *in vitro* tests, where it is expressed as mass of substance per standard volume of liquid (European Commission, 2006a).

LD_{50}: The LD_{50} (median lethal dose) is a statistically derived single dose of a substance that can be expected to cause death in 50% of dosed animals. The LD_{50} value is expressed in terms of mass of test substance per unit mass of test animal (milligrams per kilogram) (European Commission, 2006a; id).

Lethal dose (LDx): Corresponds to the dose of a tested substance causing x% lethality during a specified time interval.[3]

Lead laboratory: The laboratory selected to perform the initial development of a standardized and optimized test method protocol, and to train the other laboratory personnel in the protocol procedures for the performance of an inter-laboratory validation study (OECD, 2005).

Lethal concentration (LC): Concentration of a substance in an environmental medium that causes death following a certain period of exposure (Duffus et al., 2007; id).

Lethal concentration x%: Corresponds to the concentration of a tested substance causing x% lethality during a specified time interval.[3]

Lifetime exposure: Total amount of exposure to a substance in a lifetime (for humans usually assumed to be 70 years).

Limit dose: refers to a dose/concentration at an upper limitation on testing (e.g., 2,000 or 5,000 mg/kg) (OECD, 2008a).

Linear dose-response: A pattern of frequency or severity of biological response that varies proportionately with the amount of dose or concentration of an agent.

Lowest observed effect concentration (LOEC): Lowest tested concentration at which, in a study, a statistically significant effect is observed in the exposed population compared with an appropriate control group.[3]

Lowest observed effect level (LOEL): Lowest concentration or amount of a substance (dose), found by experiment or observation, that causes any alteration in morphology, functional capacity, growth, development, or lifespan of target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure (Duffus et al., 2007; id).

Lowest observed adverse effect level (LOAEL): Lowest concentration or amount of a substance (dose), found by experiment or observation, which causes an adverse effect on morphology, functional capacity, growth, development, or lifespan of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure (Duffus et al., 2007; id).

Margin of exposure (MOE): The ratio of the no observed adverse effect level (NOAEL) to the estimated exposure dose (US EPA, 1997).

Maximum tolerable concentration (MTC): Highest concentration of a substance in an environmental medium that does not cause death of test organisms or species (denoted by LC_0) (Duffus et al., 2007; id).

Maximum tolerable dose (MTD): Highest amount of a substance that, when introduced into the body, does not kill test animals (denoted by LD_0) (Duffus et al., 2007; id).

Maximum tolerable exposure level (MTEL): Maximum amount (dose) or concentration of a substance to which an organism can be exposed without leading to an adverse effect after prolonged exposure time (Duffus et al., 2007; id).

Mechanism (mode) of toxicity/mechanism (mode) of action: Specific biochemical interactions through which a substance produces its effect. Mechanism (mode) of action refers to a detailed description, often at molecular level, of the means by which an agent causes a disease state or other adverse effect (NRC, 2007b; id).

Mechanistically based test methods: Test methods based on an understanding of the biological mechanisms underlying the effect of interest.

Meta-analysis: The use of statistical methods to summarize the results of independent studies (Glass, 1976; id).

Me-too test: A colloquial expression for a test method that is structurally and functionally similar to a validated and accepted reference test method. Such a test method would be a candidate for catch-up validation (OECD, 2005; id).

Metabolic transformation: Biotransformation of a substance that takes place within a living organism (Duffus et al., 2007; id).

Metabolic activation (bio-activation): Biotransformation of a substance to a more biologically active derivative (Duffus et al., 2007; id).

Metabonomics: Evaluation of cells, tissues, or biological fluids for changes in metabolite levels that follow exposure to a given substance in order to determine the metabolic processes involved, to evaluate the disruption in intermediary metabolic processes that results from exposure to that substance, or to determine the part of the genome that is responsible for the changes. Note: Although "metabolomics" and "metabonomics" are frequently used as synonyms, there is a growing consensus that there is a difference in that "metabolomics" places a greater emphasis on comprehensive metabolic profiling, while "metabonomics" is used to describe multiple (but not necessarily comprehensive) metabolic changes caused by a biological perturbation (Duffus et al., 2007; id).

Minimum performance standards: See performance standards.

Mixture: Used in the context of the UN GHS (1) as a mixture or solution composed of two or more substances in which they do not react (Duffus et al., 2007).

Model: A schematic description of a system, theory, or phenomenon that accounts for its known or inferred properties and may be used for further study of its characteristics.

Modeling: Use of mathematical and statistical equations and software to simulate and predict process of exposure.

Modular approach: A general conceptual framework that combines the use of retrospective and prospective approaches to validation. Modules address the assessment of both reliability and relevance in a combined approach (OECD, 2005).

Molecular initiating event: The initial point of chemical-biological interaction within the organism that starts the pathway (OECD, 2011).

Molecular screening: Molecular screening combines rapid screening methods with toxicogenomics with the objective of applying biochemical and cellular genomic methods to category analysis. The premise of molecular screening of toxicity is driven by interactions with cellular targets of one form or another so to initially assess toxicity, one must identify the proper target of concern and an appropriate assay is needed to assess the likelihood of interaction with the chemical(s) of concern (OECD, 2008b; id).

Mutagen: Agent that can induce heritable changes (mutations) of the genotype in a cell as a consequence of alterations in or loss of genetic material (Duffus et al., 2007; id).

Mutagenicity: Ability of a chemical to cause changes in the genetic material.[15]

Mutation: Any relatively stable heritable change in genetic material that may be a chemical transformation of an individual gene (gene or point mutation), altering its function, or a rearrangement, gain, or loss of part of a chromosome that may be microscopically visible (chromosomal mutation) (Duffus et al., 2007; id).

Nanomaterial: A manufactured (or engineered) nano-sized and nanostructured material (European Commission, 2012).

Nanoparticle: Microscopic particle whose size is measured in nanometers, often restricted to so-called nanosized particles (NSPs; <100 nm in aerodynamic diameter), also called ultrafine particles (Duffus et al., 2007; id).

Nanotoxicology: Scientific discipline involving the study of the actual or potential danger presented by the harmful effects of nanoparticles on living organisms and ecosystems, of the relationship of such harmful effects to exposure, and of the mechanisms of action, diagnosis, prevention and treatment of intoxications (Duffus et al., 2007; id).

Negative predictive value: See predictive value (negative).

Neurotoxicity: The study of the adverse effects of chemical, biological, and certain physical agents on the nervous system and/or behavior during development and in maturity (Harry et al., 1998).

No observed adverse effect level (NOAEL): Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or lifespan of the target organism under defined conditions of exposure (Duffus et al., 2007; id).

No observed effect concentration (NOEC): Highest tested concentration at which, in a study, no statistically significant effect is observed in the exposed population compared with an appropriate control group.[3]

No observed effect level (NOEL): Greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or lifespan of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure (Duffus et al., 2007; id).

Non-animal testing: Alternative methods to animal testing such as chemical and biological read-across, *in vitro* results, *in vivo* information on analogues, quantitative structure-activity relationships (QSARs), and exposure-based waiving.[3]

Non-apical endpoint: Intermediate or sub-organism level event below that of the apical endpoint.

Nonlinear dose-response model: Mathematical relationship that cannot be expressed simply as the change in response being proportional to the amount of change of some function of dose (US EPA, 2012).

Omics technologies: Emerging technologies such as genomic-scale mRNA expression, transcriptomics, metabolomics and proteomics providing tools (in combination with bioinformatics methods and conventional toxicology) for improving the understanding of mechanisms of toxicity, reducing uncertainty in grouping of chemicals, and providing alternative methods for screening of chemicals.

Operational characteristics: Operational characteristics of a test refers to its performance under typical conditions, as measured by its reproducibility, its sensitivity, specificity, positive and negative predictivity, and concordance (where appropriate), and the types of substances that the test is effective or ineffective at identifying.

Optimized test protocol: A test protocol that has been revised and improved based on the results obtained in prevalidation studies (OECD, 2005).

Organ: A part of the body composed of more than one tissue that forms a structural unit responsible for a particular function or functions (Martin, 1985; id).

Organ toxicity: Any detrimental change in organ physiology, biochemistry, or morphology (Hodgson et al., 1998; id).

Organism: Any living thing which may consist of a single cell or a group of differentiated but interdependent cells (Martin, 1985; id).

P-value: In testing a hypothesis, the probability of a type I error (false positive); the probability that the sample (experimental) results are compatible with a specific hypothesis (US EPA, 2012; id).

Pathway of Toxicity (PoT): Changes in normal biological processes, e.g., cell function, communication, and adaptation to environmental changes which, when sufficiently perturbed, are expected to result in adverse health effects (NRC, 2007b).

Pathway perturbation: Critical alteration of a toxicity pathway by an environmental agent or its metabolites that can impair normal biological function to such an extent that an adverse health effect may occur (Krewski et al., 2011).

Partial replacement test: A test method that enables animal reduction by replacing an animal test for one or more of its endpoints (but not all of them), a limited range of substances (but

[15] http://altweb.jhsph.edu/resources/glossary.html (last accessed 20.03.2014)

not all substances), or a limited range of the response values. A partial replacement test can contribute to the complete replacement of an animal test when used in a complementary fashion in a tiered testing strategy (OECD, 2005; id).

Peer involvement: The interaction of outside experts of comparable expertise and experience with those performing the work during the development of a scientific product. Such interaction adds to the scientific credibility of the product; also *expert involvement* (OECD, 2005).

Peer review: A documented critical review of a specific scientific work or product, conducted by experts independent of those who performed the original work, but who are collectively comparable in technical expertise (OECD, 2005).

Performance: Manner or quality of functioning.[7]

Performance standards: Standards based on a validated test method, used for evaluating the comparability of a proposed test method that is mechanistically and functionally similar to the validated one. Included are: 1) essential test method components; 2) a minimum list of reference substances selected from among the substances used to demonstrate the acceptable performance of the validated test method; and 3) the levels of accuracy and reliability which the proposed test method should demonstrate when evaluated by using the minimum list of reference substances (OECD, 2005).

Persistence (bio-persistence): Long-term presence of a substance (in a biological system) due to resistance to degradation and/or elimination.

Pharmacodynamics: Process of interaction of pharmacologically active substances with target sites in living systems, and the biochemical and physiological consequences leading to therapeutic or adverse effects (Duffus et al., 2007; id).

Pharmacokinetics: Process of the uptake of drugs by the body, the biotransformation they undergo, the distribution of the drugs and their metabolites in the tissues, and the elimination of the drugs and their metabolites from the body (Duffus et al., 2007; id).

Pharmacological or toxicological screening: Pharmacological or toxicological screening consists of a specified set of procedures to which a series of compounds is subjected to characterize pharmacological and toxicological properties and to establish dose-effect and dose-response relationships (Duffus et al., 2007; id).

Physiologically based pharmacokinetic model (PBPK model): A computer model that describes what happens to a chemical in the body. This model describes how the chemical gets into the body, where it goes in the body, how it is changed by the body, and how it leaves the body (ATSDR, 2009; id).

Positive predictive value: See Predictive value (positive).

Potency: The potency of a substance is a measure of its ability to produce a given effect, relative to that of other substances producing the same effect. It is derived from the relationship between the incidence or intensity of the effect and the dose or concentration required to elicit this effect (NIEHS, 1997).

ppb: Parts per billion (ATSDR, 2009; id).

ppm: Parts per million (ATSDR, 2009; id). (One ppm is equivalent to 1 milligram of something per liter of water (mg/l) or 1 milligram of something per kilogram of soil (mg/kg). It is a way of expressing very dilute concentrations of substances).

Prediction model: A procedure used to convert the results from a test method into a prediction of the toxic effect of interest. A prediction model contains four elements: a definition of the specific purpose(s) for which the test is to be used, a definition of all possible results that may be obtained, an algorithm that converts each test result into a prediction of the toxic effect of interest, and an indication of the accuracy of the prediction (NIEHS, 1997; id).

Predicted no effect concentration (PNEC): Concentration that is expected to cause no adverse effect to any naturally occurring population in an environment at risk from exposure to a given substance.

Predictive toxicology: The use of -omics technologies information from a known toxicant to predict the toxicological class of an unknown compound (Wilhelm, 2008; id).

Predictive model: In general terms predictive models are mathematical algorithms or equations used to derive predictions. In the field of validation predictive models make use of structure activity relationships (SAR) or quantitative structure activity relationships (QSAR) to predict the activity of a chemical lacking data by comparing its structure to a chemical with experimental data that is associated with specific activity.

Predictive value: See *predictive value (positive)* and *predictive value (negative)*.

Predictive value (negative): The proportion of correct negative responses among substances indicated as negative by a test method. Negative predictive value is a function of the sensitivity and specificity of the test method and of the prevalence of negatives among the substances tested (OECD, 2005).

Predictive value (positive): The proportion of correct positive responses among materials indicated as positive by a test method. It is one indicator of test method accuracy. Positive predictive value is a function of the sensitivity and specificity of the test method and of the prevalence of positives among the substances tested (OECD, 2005).

Prevalence: The proportion of substances producing the effect of interest in the population of substances considered (OECD, 2005).

Prevalidation: The initial phase(s) of a validation study. A small-scale study intended to obtain preliminary information on the relevance and reliability of a test method. Based on the outcome of those studies, the test method protocol may be modified or optimized to increase intra-laboratory and/or inter-laboratory reproducibility and accuracy in subsequent validation studies (OECD, 2005; id).

Primary cells: Cells freshly isolated from human, animal, or plant sources. Freshly isolated primary cells may rapidly dedifferentiate in culture, and they have a limited lifespan. Primary cell cultures commonly require complex nutrient media, supplemented with serum and other components. Consequently, primary cell culture systems are extremely difficult to standardize (OECD, 2004a).

Proficiency: The demonstrated ability to properly conduct a test method prior to testing unknown substances.

Proficiency chemicals (substances): Reference chemicals included in the performance standards that can be used by laboratories to demonstrate technical competence with a standardized test method.

Proficiency testing: Comparative testing involving several groups of laboratories or analysts performing the same analyses on the same samples and comparing results.

Proprietary material: A material over which a party exercises private ownership, control, or use, usually to the exclusion of other parties, and which may be the subject of intellectual property law.

Proprietary test method: A test method over which a party exercises private ownership, control, or use, usually to the exclusion of other parties, and which may be the subject of intellectual property law.

Prospective validation: An approach to validation when some or all information necessary to assess the validity of a test are not available, so new experimental work is required (OECD, 2005; id).

Proteomics: The study of proteomes, which are collections of proteins. Proteins carry out the functions encoded by genes (NRC, 2007a).

Protocol: The precise, step-by-step description of a test method that directs the laboratory as to how to perform the test method. The test method protocol includes the listing and description of all preparations, reagents, supplies, and equipment needed, and all criteria and procedures for generating and evaluating test data (OECD, 2005; id).

(Q)SAR [(Quantitative) Structure-Activity Relationship]: An expression used to consider, simultaneously, SARs and QSARs.

QSAR (Quantitative Structure-Activity Relationship): A QSAR is a theoretical model for making predictions of physicochemical properties, environmental fate parameters, or biological effects (including toxic effects in environmental and mammalian species). QSARs relate quantitative measures of chemical structure to continuous or categorical variables describing the property to be predicted (OECD, 2005).

Quality assurance: All the planned and systematic actions by which adherence to laboratory testing standards, requirements, and record keeping procedures, and the accuracy of data transfer, are assessed by individuals independent of those performing the testing (OECD, 2005).

Quality control: Operational techniques and activities that are used to fulfil given requirements for quality.[14]

Quantitative dose (concentration) – response (effect) relationship: Relationship between the total amount of an agent administered to, taken up, or absorbed by an organism, system or (sub) population and the changes developed in that organism, system, or (sub) population in reaction to the agent (Van Leeuwen and Vermiere, 2007).

Rapid screening methods: Techniques which assess molecular properties or *in vitro* responses. They range from simple structure-activity analyses to high-throughput, *in chemico* and cellular assays to mid-level throughput *in vitro* and *ex vivo* assays (OECD, 2008b).

REACH: European Community Regulation on chemicals and their safe use (EC 1907/2006). It deals with the Registration, Evaluation, Authorisation and Restriction of Chemical substances. The new law entered into force on June 1, 2007. The aim of REACH is to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. At the same time, innovative capability and competitiveness of the EU chemicals industry should be enhanced. (European Commission, 2013).

Read-across approach: Prediction from data for reference substance(s) within the group or "category" of substances by interpolation to other substances in the group (European Commission, 2006b).

Recovery: Process leading to partial or complete restoration of a cell, tissue, organ, or organism, following its damage from exposure to a harmful substance or agent (Duffus et al., 2007; id).

Reduction: A means of lowering the number of animals used to obtain information of a given amount and precision (Balls et al., 1995; id).

Reduction alternative: A new or revised test method that reduces the number of animals required (NIEHS, 1997; id).

Reference chemicals: Chemicals selected for use as a reference standard in the validation process, for which responses in the *in vitro* or *in vivo* reference test system or species of interest are considered to be known (OECD, 2005).

Reference dose (RfD): An estimate of a daily exposure to the human population (including sensitive groups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. This dose is usually derived by applying uncertainty factors to NOAEL.

Reference test method (gold standard): A test method against which the results from the new test method are being compared (OECD, 2005).

Reference species: The species used in the reference or traditional test with which a new or revised test is being compared. This may be the species of interest, or it may be a surrogate species when it is not possible to perform testing on the species of interest (OECD, 2005).

Refinement: Any development that refines procedures to lessen or eliminate pain or distress to animals, or enhances animal well-being.

Refinement alternative: A new or revised test method that refines procedures to lessen or eliminate pain or distress to animals, or enhances animal well-being (NIEHS, 1997; id).

Regulatory acceptance: The formal acceptance of a test method by regulatory authorities, indicating that the test method may be used to provide information to meet a specific regulatory requirement (OECD, 2005; id).

Relevance: Describes whether a test method is meaningful and useful for a particular purpose. It is the extent to which the measurement result and uncertainty can accurately be interpreted as reflecting or predicting the biological effect of interest (NIEHS, 1997).

Reliability: Reliability measures of the extent to which a test

method can be performed reproducibly within and between laboratories and over time, when performed by using the same protocol. It is assessed by calculating intra-laboratory and inter-laboratory reproducibility and intra-laboratory repeatability (OECD, 2005; id).

Repeatability: The closeness of agreement between test results obtained within a single laboratory, when the procedure is performed independently under repeatability conditions, i.e., under a set of conditions including the same measurement procedure, same operator, same measuring system, same operating conditions and same location, and replicated measurements over a short period of time.[14]

Replacement test method: A test which is designed to substitute for a test that is in routine use and accepted for hazard identification and/or risk assessment, and which has been determined to provide equivalent or improved protection of human or animal health or the environment, as applicable, compared to the accepted test, for all possible testing situations and substances (OECD, 2005; id).

Reproducibility: The agreement among results obtained from testing the same substance by using the same test protocol under repeatable conditions. The set of repeatable conditions must be defined and usually includes different operators, locations and time.[14]

Reproductive toxicity: Effects such as reduced fertility, effects on gonads and disturbance of spermatogenesis; this also covers developmental toxicity.[8]

Retrospective (validation): An assessment of the validation status of a test method carried out by considering all available information.

Ring testing: A multi-laboratory validation study, in which all laboratories test the same substances by using identical test protocols, sometimes referred to as round-robin testing. The purpose of the study is to determine the inter-laboratory and intra-laboratory reproducibility of a test method (OECD, 2005).

Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard (European Commission, 2002; id).

Risk assessment: A scientifically based process consisting of four steps: hazard identification, hazard characterization, exposure assessment, and risk characterization (European Commission, 2002; id).

Risk characterization: The qualitative and, wherever possible, quantitative determination, including a consideration of attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub) population, under defined exposure conditions. Risk characterization is the fourth step in the risk assessment process (IPCS/OECD, 2004; id).

Risk estimation: Quantification of the probability, including attendant uncertainties, that specific adverse effects will occur in an organism, system, or (sub) population due to actual or predicted exposure (OECD, 2004b; id).

Risk evaluation: Establishment of a qualitative or quantitative relationship between risks and benefits of exposure to an agent, involving the complex process of determining the significance of the identified hazards and estimated risks to the system concerned or affected by the exposure, as well as the significance of the benefits brought about by the agent (OECD, 2004b; id).

Robustness: The degree of sensitivity of test results to departures from the specified test conditions (OECD, 2005).

Round-robin testing: See *ring testing*.

Route of exposure: The way in which an organism may contact a chemical substance.[3]

Route of administration: Path by which a substance is taken into the body.[3]

Run: A run consists of one or more test substances tested concurrently with a negative and positive control.

S9 fraction: Supernatant fraction obtained from an organ (usually liver) homogenate by centrifuging at 9000g for 20 minutes in a suitable medium; this fraction contains cytosol and microsomes (Duffus et al., 2007; id).

Safety: Practical certainty that adverse effects will not result from exposure to an agent under defined circumstances. It is the reciprocal of risk (OECD, 2004b; id).

Safety Factor (or uncertainty factor): Composite (reductive) factor by which an observed or estimated no-observed-adverse effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk (OECD, 2004b; id).

SAR (Structure-Activity Relationship): A theoretical model for making predictions of physicochemical properties, environmental fate parameters, or biological effects (including toxic effects in environmental and mammalian species). SARs are qualitative relationships in the form of structural alerts that incorporate molecular substructures or fragments related to the presence or absence of activity (OECD, 2005).

Screen: See *screening test*.

Screening test: A screening test is a rapid, simple test method conducted for the purpose of classifying substances into a general category of hazard. The results of a screening test are generally used for preliminary decision-making in the context of a testing strategy (i.e., to assess the need for additional and more definitive tests). Screening tests often have a truncated response range, in that positive results may be considered adequate to determine if a substance is in the highest category of a hazard classification system without the need for further testing, but are not usually adequate without additional information/tests to make decisions pertaining to lower levels of hazard or the safety of the substance (OECD, 2005; id).

Sensitivity: The proportion of all positive/active substances that are correctly classified by a test method (OECD, 2005).

Sensitization: Allergic response or other adverse health effects caused by agents that can activate the immune system (US EPA, 2005).

Site of action: The particular cell or tissue type in which the molecular initiating event takes place.

Solvent/vehicle control: An untreated sample containing all components of a test system, including the solvent or vehicle that is processed with the test substance-treated and other con-

trol samples to establish the baseline response for the samples treated with the test substance dissolved in the same solvent or vehicle. When tested with a concurrent negative control, this sample also demonstrates whether the solvent or vehicle interacts with the test system.

SOP: See *Standard Operating Procedure*.

Source to Outcome Pathway: The complete understanding of the effects of a chemical substance from environmental contamination through to effects at the community level. It incorporates the AOP concept and hence toxicity pathways and MoA. The continuum or cascade of measurable events starting from release into the environment and ending at an adverse outcome (US EPA, 2005).

Specificity: The proportion of all negative/inactive substances that are correctly classified by a test method (OECD, 2005).

Standard: 1) A widely adopted written specification, technical recommendation, or similar document; 2) a measurement standard, i.e., an accepted or approved example of something against which others are judged or measured (ISO/IEC, 2004).

Standard error: The standard deviation of an estimate.

Standard Operating Procedure (SOP): A formal, written procedure that describes in detail how specific routine and test-specific laboratory operations should be performed. SOPs are required by Good Laboratory Practice (OECD, 2005; id).

Statistical significance: The probability of obtaining a result that is not likely to occur randomly, but rather is likely to be attributable to a specific cause.

Statistically significant effect: In statistical analysis of data, a health effect that exhibits differences between a study population and a control group that are unlikely to have arisen by chance alone (US EPA, 1995).

Stochastic: Any phenomenon obeying the laws of probability.

Structural alerts: Atom-based fragments which, when present in a molecule, are an indication that a compound can be placed into a particular category (Schultz, 2010).

Subchronic effect: Biological change resulting from an environmental alteration lasting about 10% of the lifetime of the test organism (Duffus et al., 2007; id).

Substitute test method: A new or revised test method proposed for use in lieu of a currently used method, regardless of whether that method is for a definitive, screening, or adjunct test (NIEHS, 1997; id).

Surrogate: A test or species used in the place of another test or target species (NIEHS, 1997; id).

Synergistic effect: When applied to the area of hazardous materials a biologic response to multiple substances where one substance worsens the effect of another substance. The combined effect of the substances acting together is greater than the sum of the effects of the substances acting by themselves (ATSDR, 2009; id).

Systems biology: Study of the mechanisms underlying complex biological processes as integrated systems of many diverse, interacting components. It involves (1) collection of large sets of experimental data (by high-throughput technologies and/or by mining the literature of reductionist molecular biology and biochemistry); (2) proposal of mathematical models that might account for at least some significant aspects of this data set; (3) accurate computer solution of the mathematical equations to obtain numerical predictions; and (4) assessment of the quality of the model by comparing numerical simulations with the experimental data (Duffus et al., 2007; id).

Systems modelling: Abstract model that uses mathematical language to describe the behavior of a system (e.g., pharmacokinetic-based, physiologically-based pharmacokinetic, biologically-based, etc.) (OECD, 2008a).

Target organ: The organ in which the principal adverse effect of a toxicant is manifested (Hodgson et al, 1998; id).

Target species: The species for which information on the potential toxicity or effects of a substance is sought (OECD, 2005; id).

Teratogen: A substance that causes defects in development between conception and birth. A teratogen is a substance that causes a structural or functional birth defect (ATSDR, 2009; id).

Test: See *test method*.

Test battery: A series of tests, independent of each other, generally designed to complement each other and/or to measure a different component of a multi-factorial toxic effect, and which are usually performed at the same time or in close sequence. Test batteries typically tend to complement each other but are not integrated into a strategy.

Test kit: A ready-to-use compilation of all components necessary for the performance of an assay, test, or study (OECD, 2004a; id).

Test method development: The research process before pre-validation, in which a test protocol is developed and standardized. The purpose of test method development is to lead to a protocol, which is sufficiently detailed and comprehensive to enable the test method to undergo pre-validation (OECD, 2005).

Test method: A process or procedure used to obtain information on whether a substance or agent can produce a specified biological effect under specified conditions (OECD, 2005).

Testing strategy: The application of hazard assessment in an integrated and intelligent manner.

Threshold: Dose or exposure concentration of an agent below that a stated effect is not observed or expected to occur (OECD, 2004b; id).

Threshold of toxicological concern (TTC): Human exposure threshold value for a group of chemicals below which there should be no appreciable risk to human health (Duffus et al., 2007; id).

Tiered test scheme: Testing approaches based on sequential assessments, where a result at one tier is used to determine the next step, if any. It is usually a decision-tree type of testing; after each step, the information is assessed to determine whether a prediction for the toxicity endpoint can be made or whether further testing/analysis needs to be done. A tiered approach usually progresses from a review of existing literature and data to a review of data for related chemicals or formulations, to perhaps a SAR/(Q)SAR analysis, to simple *in vitro* screening assays, to the use of more complex *in vitro*

three-dimensional models, to testing in lower species, to the traditional animal test.[1]

Tissue: A multicellular aggregate of differentiated cells with specific functions as constituents of organisms (OECD, 2004a).

Tissue distribution: Reversible movement of a substance from one location in the body to another.

Tolerable Daily Intake (TDI): Estimate of the amount of a substance or contaminant in food or drinking water that can be ingested daily over a lifetime without appreciable health risk.

Toxicity pathways: Cellular response pathways that, when sufficiently perturbed, are expected to result in adverse health effects (NRC, 2007b; id).

Toxicodynamics: Process of interaction of potentially toxic substances with target sites, and the biochemical and physiological consequences leading to adverse effects (Duffus et al., 2007; id).

Toxicogenetics: Study of the influence of hereditary factors on the effects of potentially toxic substances on individual organisms (Duffus et al., 2007; id).

Toxicokinetics: Generally, the overall process of the absorption (uptake) of potentially toxic substances by the body, the distribution of the substances and their metabolites in tissues and organs, their metabolism (biotransformation), and the elimination of the substances and their metabolites from the body. In validating a toxicological study, the collection of toxicokinetic data, either as an integral component in the conduct of non-clinical toxicity studies or in specially designed supportive studies, in order to assess systemic exposure (Duffus et al., 2007; id).

Toxicogenomics: Scientific sub-discipline that combines toxicology with genomics to determine how an organism's genetic make-up influences its response to a toxic substance (Duffus et al., 2007; id).

Transcriptomics (or gene expression profiling): The study of mRNA – the intermediary step between genes and proteins that indicates genes that are active (as opposed to dormant or silent) (NRC, 2007a).

Transferability: The ability of a test method or of a procedure to be accurately and reliably performed in different, competent laboratories (NIEHS, 2003).

True negative: A substance correctly identified by a test as negative (OECD, 2005).

True negative rate: The proportion of substances correctly identified by a test as negative (OECD, 2005).

True positive: A substance correctly identified by a test as positive (OECD, 2005).

True positive rate: The proportion of substances correctly identified by a test as positive (OECD, 2005).

Uncertainty: 1) *In metrology:* Parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used. In assay methodology, confidence interval or fiducial limit used to assess the probable precision of an estimate. 2) *In toxicology:* Value used in extrapolation from experimental animals to man (assuming that man may be more sensitive) or from selected individuals to the general population. For example, a value applied to the no-observed-effect-level (NOEL) or no-observed-adverse-effect-level (NOAEL) to derive an acceptable daily intake (ADI) or tolerable daily intake (TDI). Note: The NOEL or NOAEL is divided by the value to calculate the ADI or TDI (Duffus et al., 2007; id).

Uptake: Entry of a substance into the body, into an organ, into a tissue, into a cell, or into the body fluids by passage through a membrane or by other means (Duffus et al., 2007; id).

Valid method: A method determined to be acceptable for a specific use and application (NIEHS, 1997; id).

Validated method: A test method for which the reliability and relevance for a specific purpose have been established in one or more validation studies (NIEHS, 1997; id).

Validation: The process by which the reliability and relevance of a particular approach, method, process, or assessment is established for a defined purpose (OECD, 2005; id).

Validation management group (VMG): An independent oversight group responsible for approving the design and implementation of a study, for selecting the participating laboratories, and for coordinating the evaluations of the study results. A VMG can also be called management committee or management team (OECD, 2005).

Variability: A source of uncertainty in biology and risk assessment, due to the fact that many parameters are best described not as point values but as probability distributions.

Variance: The mean square deviation of the variable around the average value. It reflects the dispersion of the empirical values around its mean (Eurostat, 2003).

Weight-of-evidence: The process of considering the strengths and weaknesses of various pieces of information in reaching and supporting a conclusion concerning the hazard potential of a substance.

Within-laboratory: also used for *intra-laboratory*.

Xenobiotic: A general term used to describe any chemical interacting with an organism that does not occur in the normal metabolic pathways of that organism. The use of this term in lieu of foreign compounds, etc., is gaining wide acceptance.[7]

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Conflict of interest

The authors declare no conflict of interest.

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