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THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

**GUIDANCE DOCUMENT ON THE REPORTING OF DEFINED APPROACHES TO BE USED
WITHIN INTEGRATED APPROACHES TO TESTING AND ASSESSMENT**

**Series on Testing & Assessment
No. 255**

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OECD Environment, Health and Safety Publications

Series on Testing & Assessment

No. 255

**GUIDANCE DOCUMENT ON THE REPORTING OF DEFINED APPROACHES TO BE USED
WITHIN INTEGRATED APPROACHES TO TESTING AND ASSESSMENT**

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among **FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD**

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris, 2016

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FOREWORD

With a view to assisting the evaluation of integrated approaches to testing and assessment (IATA) in regulatory decision-making within OECD Member Countries, this guidance document provides a set of principles for reporting defined approaches to testing and assessment that can be used as one of the components within IATA. Templates are also provided to enable a structured approach to their documentation in order to facilitate their evaluation.

A defined approach to testing and assessment consists of a fixed data interpretation procedure (DIP) applied to data generated with a defined set of information sources to derive a result that can either be used on its own, or together with other information sources within an IATA, to satisfy a specific regulatory need. Thus, a defined approach to testing and assessment can be used to support the hazard identification, hazard characterisation and/or safety assessment of chemicals.

This guidance is intended to be used alongside similar guidance aimed at harmonising the reporting of other IATA components such as QSARs, grouping and read-across strategies, and non-guideline in vitro methods.

The reporting templates provided in this document have been used to describe a number of defined approaches to testing and assessment for skin sensitisation hazard and potency predictions and the individual information sources used within these approaches. These approaches are presented in document ENV/JM/MONO(2016)29 and the associated Annexes. The reporting templates are conceived to be generally applicable although there is not yet experience with their use for reporting defined approaches developed for other toxicological endpoints. This document was endorsed by the Task Force on Hazard Assessment in June 2016.

This document is being published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, which has agreed that it be declassified and made available to the public.

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1. INTRODUCTION AND SCOPE

An Integrated Approach to Testing and Assessment (IATA) is an approach based on multiple information sources used for the hazard identification, hazard characterisation and/or safety assessment of chemicals. An IATA integrates and weights all relevant existing evidence and guides the targeted generation of new data, where required, to inform regulatory decision-making regarding potential hazard and/or risk. Within an IATA, data from various information sources (i.e. physicochemical properties, in silico models, grouping and read-across approaches, in vitro methods, in vivo tests and human data) are evaluated and integrated to draw conclusions on the hazard and/or risk of chemicals. Within this process, the incorporation of data generated with non-animal testing and non-testing methods is expected to contribute considerably to a reduction of testing in animals (OECD, 2013). The output of an IATA is a conclusion that, along with other considerations, informs regulatory decision making.

Ideally, an IATA should, wherever possible, be mechanistically informed (Tollefsen et al., 2014). In other words, it should be based on data that capture our knowledge of the mechanisms through which chemicals exert their toxicity. Understanding the likelihood of effects (e.g. initiation of a toxicity pathway) at lower levels of biological organisation (e.g. from structure-activity relationships and in vitro methods), can help inform whether testing at higher levels of biological organisation (i.e., in vivo) is warranted.

For some human endpoints, such as skin sensitisation, a mechanistically informed IATA can be based on an Adverse Outcome Pathway (AOP), which describes the linkages between the chemical interaction with a biological system at the molecular level and the subsequent biological effects at the subcellular, cellular, tissue, organ, and whole animal or population levels (OECD, 2012a; 2012b). An IATA can also be developed even if the current knowledge regarding the toxicological mechanism underlying the endpoint addressed has not been described in the form of an AOP. An example is the IATA for skin irritation and skin corrosion (OECD, 2014c). Although this IATA is not underpinned by an existing AOP, it nevertheless incorporates mechanistic information.

The overall assessment within an IATA is performed on the basis of a non-formalised Weight-of-Evidence (WoE) approach. A WoE determination means that expert judgement is applied on an *ad hoc* basis to the available and scientifically justified information bearing on the determination of hazard or risk. The overall assessment process within a WoE approach involves an assessment of the relative values/weights of different pieces of the available information (Hulzebos and Gerner, 2010). The WoE assessment needs to be transparently explained and documented to provide a credible rationale supporting the conclusion made. The information used within an IATA may include chemical structure, physicochemical properties (e.g. molecular weight, pKa, Log Kow), extrapolations from grouping approaches (e.g. formation of chemical categories and data gap filling by read-across), (Q)SAR predictions, results of in vitro tests, relevant animal and human data, and combinations thereof, e.g. results generated with defined approaches to testing and assessment.

A defined approach to testing and assessment consists of a fixed data interpretation procedure (DIP) used to interpret data generated with a defined set of information sources, that can either be used on its own, or together with other information sources within an IATA, to satisfy a specific regulatory need. The concept of DIP, taken from OECD guidance document 34 (OECD, 2005), is defined here as any algorithm for interpreting data from one or more information sources. The output of a DIP is typically a prediction (e.g. prediction of skin sensitisation potential from peptide binding data and/or chemical structure).

The aim of this guidance document is to provide a set of principles for reporting defined approaches to testing and assessment to facilitate their evaluation. Templates are also provided to enable a structured

and harmonised approach to their documentation. Consistent reporting will ultimately facilitate the evaluation of IATA in regulatory decision-making within OECD Member Countries. This guidance is intended to be used alongside similar guidance aimed at harmonising the reporting of other IATA components such as QSARs (OECD, 2007), grouping and read-across strategies (OECD, 2014a), and non-guideline in vitro methods (OECD, 2014b).

This document has been reviewed by the ad-hoc expert group who used this guidance document to describe a number of defined approaches to testing and assessment for skin sensitisation hazard and potency predictions and the individual information sources used within the approaches. These defined approaches to testing and assessment are presented in document ENV/JM/MONO(2016)29. The reporting templates provided in this guidance document are conceived to be generally applicable although there is not yet experience with their use for reporting defined approaches developed for other toxicological endpoints.

2. DEFINED APPROACHES TO TESTING AND ASSESSMENT AND THEIR ROLE WITHIN IATA

An IATA necessarily includes a degree of expert judgement (WoE), for example, in the choice of information sources and their weighting. An example of a simple approach to the documentation of WoE is presented in Annex II of the OECD guidance document on an IATA for skin corrosion and irritation (OECD, 2014c). The individual information sources that can be used within this IATA are grouped into "modules" according to the type of information provided (i.e. in vitro data, in vivo data, non-testing approaches, physicochemical properties etc.). Another example is presented in one of the case studies in guidance document ENV/JM/MONO(2016)29, in which a format for reporting the WoE assessment for skin sensitisation grouped into modules according to the "mechanistic level" of the information (i.e. toxicokinetic data, or toxicodynamic data related to Key Events within the AOP), is provided.

Some components of IATA, such as defined approaches to testing and assessment, can be standardised (i.e. rule-based). In a defined approach, (mechanistic) data generated by non-animal methods (i.e. in silico, in chemico, in vitro) and animal methods, deemed to be fit-for purpose, are evaluated by means of a fixed DIP. The result obtained can be used on its own to reach a conclusion, or together with other sources of information within an IATA.

A defined approach to testing and assessment can be designed in different ways, and may take for example the form of a Sequential Testing Strategy (STS) or an Integrated Testing Strategy (ITS).

A STS is a fixed stepwise approach for obtaining and assessing test data, involving interim decision steps, which, depending on the test results obtained, can be used on their own to make a prediction or to decide on the need to progress to subsequent steps. At each step, information from a single source/method is typically used by applying a prediction model associated with that source/method (Figure 1).

An ITS is an approach in which multiple sources of data or information are assessed at the same time by applying a variety of specific methodologies to convert inputs from the different information sources into a prediction (Figure 2). For this purpose, a variety of specific methodologies can be applied, such as statistical and mathematical models.

With a view to facilitating the evaluation of IATA in regulatory decision-making, it is important that the various components and information sources used within the IATA are characterised and documented to the extent possible in terms of their applicability, limitations and performance. This includes the need to transparently describe any defined approaches to testing and assessment that are used within IATA, along with their information sources. A template for reporting defined approaches to testing and assessment is provided in Annex I, and a template for reporting individual information sources is provided in Annex II. These templates should be used alongside the reporting formats for other IATA components, such as QSARs (OECD, 2007), grouping and read-across strategies (OECD, 2014a) and non-guideline test methods (OECD, 2014b).

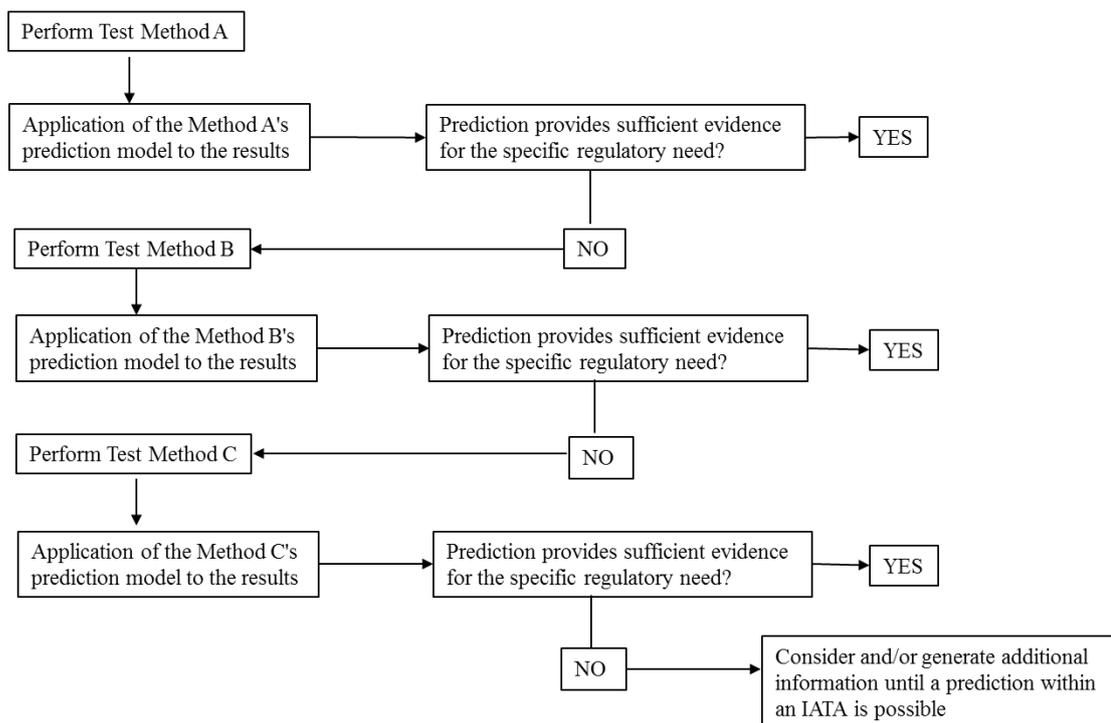


Figure 1: Generic example of a Sequential Testing Strategy (STS). The prediction obtained in each step can be used on its own if it is fit-for-purpose, or it can be used with other sources of information within an IATA.

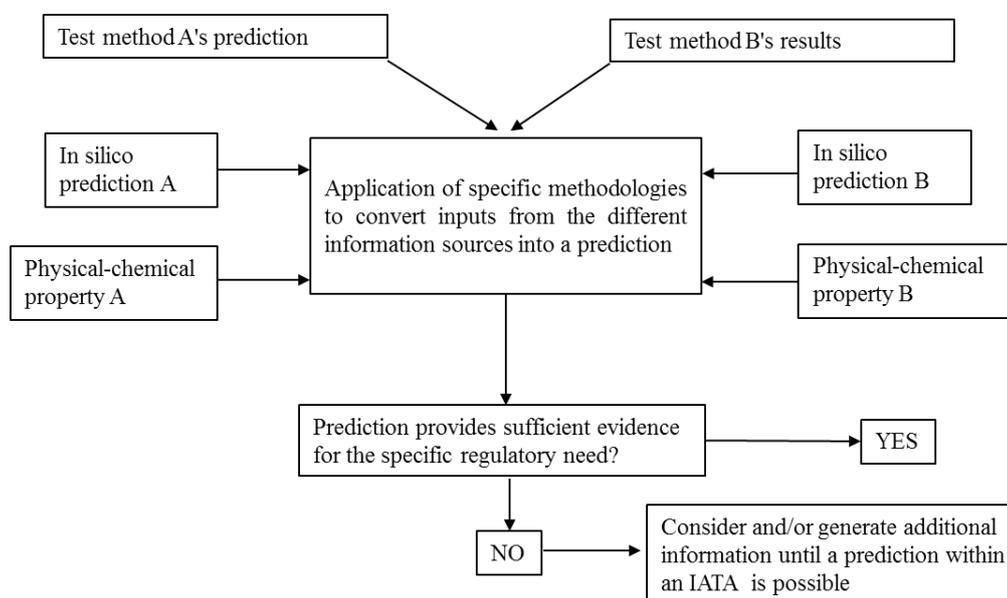


Figure 2: Generic example of an Integrated Testing Strategy (ITS). The prediction obtained can be used on its own if it is fit-for-purpose, it can be used with other sources of information within an IATA.

3. GENERAL PRINCIPLES FOR THE REPORTING OF DEFINED APPROACHES TO TESTING AND ASSESSMENT BASED ON MULTIPLE INFORMATION SOURCES

To facilitate the regulatory use of a defined approach to testing and assessment, which is based on a fixed DIP and a defined set of information sources, the defined approach should be associated with the following set of information:

1. A defined endpoint
2. A defined purpose
3. A description of the underlying rationale
4. A description of the individual information sources used
5. A description of how data from the individual information sources are processed
6. A consideration of the known uncertainties

Principle 1: *A defined endpoint*

Ensures clarity in the endpoint addressed, which could be related to human health (e.g. skin sensitisation), ecotoxicology (e.g. Daphnia reproduction), environmental fate (e.g. bioconcentration, bioaccumulation) or non-apical endpoints (mechanistic effects).

Principle 2: *A defined purpose*

Ensures clarity in the purpose for which the defined approach is proposed, which may include a specific regulatory application, e.g. contribution to the prediction of skin sensitisation hazard potential of chemicals and sub-categorisation according to the Globally Harmonised System (GHS) of classification and labelling (i.e. Sub-categories 1A and 1B).

Principle 3: *Underlying rationale*

Ensures transparency in the rationale used for constructing the defined approach. The rationale may be anchored to an existing AOP or to other mechanistic information on the endpoint being addressed. In the case of an AOP-informed defined approach, the extent to which the information sources cover key events in the AOP should be clearly described.

Principle 4: *Description of individual information sources used*

Ensures transparency in the methods and other information sources used. The description should include the known strengths and limitations of the source(s). Information sources include data generated with testing methods (in chemico, in vitro, in vivo), non-testing approaches (in silico models such as QSAR, grouping and read-across), physicochemical properties and exposure information if relevant.

Principle 5: *Description of how the data generated by the individual information sources are used*

Ensures transparency in how the data, generated by the different information sources used within the defined approach, are processed to derive a prediction/assessment (i.e. by the means of a fixed DIP). The description should ideally include a schematic representation (e.g. flowchart or decision tree) to illustrate the DIP. For example the data may be assessed in a step-wise manner as within STS or integrated by using specific methodologies (e.g. statistical, mathematical models) as within ITS.

Principle 6: *Consideration of known uncertainties*

Facilitates consistency in the interpretation of the DIP result, which is typically a prediction. Where feasible and relevant, uncertainty in predictions should be evaluated in the light of the following considerations:

- a) the relevance of the “model structure” of the DIP, e.g. the extent of coverage and weighting of AOP key events and other mechanistic considerations;
- b) the level of confidence (reliability of prediction) associated with the application of the DIP to different chemicals;
- c) the variability of the input data used (generated by the information sources);
- d) the variability of the output data associated with the gold standard (e.g. animal or human) data used as benchmark data, especially when these are used as the basis for regulatory decision making (Worth and Cronin, 2001; Hoffmann et al., 2005; Hoffmann 2015; Adriaens et al., 2014) and;
- e) any other known source of uncertainty (e.g. uncertainty in estimated exposure levels that are used in a safety assessment).

In each case, the magnitude and impact of the sources of uncertainty should be considered.

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DEFINITIONS

The definitions presented here have been agreed by the group of experts charged with the drafting of this guidance and are to be considered working definitions for the purpose of this document.

Data Interpretation Procedure (DIP): is defined here as any fixed algorithm for interpreting data from one or typically several information sources. The output of a DIP is typically a prediction of a biological effect of interest. A DIP is rule-based in the sense that is based for example on a formula or an algorithm (e.g. decision criteria, rule or set of rules) that do not involve expert judgment. This definition has been taken and adapted from OECD guidance document 34.

Defined Approach to Testing and Assessment: A defined approach consists of a fixed data interpretation procedure (DIP) (e.g. statistical, mathematical models) applied to data (e.g. *in silico* predictions, *in chemico*, *in vitro* data) generated with a defined set of information sources to derive a prediction. In contrast to the assessment process within Integrated Approaches to Testing and Assessment (IATA), that necessarily involves some degree of expert judgment, predictions generated with defined approaches are rule-based and can either be used on their own if they are deemed to fit-for-purpose or considered together with other sources of information in the context of IATA.

Information source: Physicochemical properties (e.g. molecular weight, pKa, Log Kow etc.), testing methods (i.e. *in chemico*, *in vitro*, *in vivo* methods), non-testing methods (e.g. QSARs predictions, extrapolation from chemical grouping approaches), and any other source that can generate relevant information for the purpose of the assessment within a defined approach or IATA.

Integrated Approach to Testing and Assessment (IATA): Approach based on multiple information sources that integrates and weights all relevant existing evidence and guides the targeted generation of new data, where required, to inform regulatory decision-making regarding potential hazard and/or risk. An IATA necessarily includes a degree of expert judgement, for example, in the choice of information sources and their weighting. Nevertheless, some of the IATA components, such as defined approaches to testing and assessment, can be standardised (i.e. rule-based).

ANNEX I: TEMPLATE FOR REPORTING DEFINED APPROACHES TO TESTING AND ASSESSMENT BASED ON MULTIPLE INFORMATION SOURCES

This template is designed to report defined approaches to testing and assessment that can be used within Integrated Approaches to Testing and Assessment (IATA). A defined approach to testing and assessment (hereafter a "defined approach") consists of a defined set of information sources and a fixed Data Interpretation Procedure (DIP). If a given section of the template is not pertinent to the defined approach, this should be clearly stated ("not applicable") and explained as far as possible. In cases where information for a specific section of the template is not available this should be reported ("not available"). When compiling the template please remove all explanatory text in italic.

1. Summary

Summarise the information in the template in order to provide a concise overview of the proposed defined approach.

2. General information

2.1 Identifier: *Provide a short and informative title for the defined approach and an acronym (if applicable).*

2.2 Date: *Report the date (day/month/year) of this document version.*

2.3 Author(s) and contact details: *Indicate the name and the contact details of the author(s) of the template.*

2.4 Template update(s): *Indicate the date (day/month/year) of any update of the template, the name and contact details of the author(s) of the updates and list which sections and fields have been modified. The template can be updated for a number of reasons such as additions of new information and corrections in accordance.*

2.5 Reference to main scientific papers: *List the main bibliographic references (if any) to original papers describing the defined approach.*

2.6 Proprietary aspects: *Indicate whether any component of the defined approach is proprietary (individual information sources, or the DIP) and specify the type of information that cannot be disclosed or is not publicly available. If the defined approach contains proprietary elements indicate whether it can still be widely implemented and used and provide an explanation.*

3. Endpoint addressed

3.1 Endpoint: *Specify the endpoint, such as any human health related (e.g. skin sensitisation) or environmental adverse effect (e.g. short-term toxicity to fish), environmental fate (e.g. bioaccumulation, biodegradation), biokinetic (ADME/TK) properties or others that can be measured and therefore predicted by the proposed defined approach and indicate whether it addresses (or partially addresses) an endpoint being predicted by an existing test guideline.*

3.2 Species: *Indicate the species for the endpoint being modelled (if appropriate).*

3.3 Additional information about the endpoint: *Summarise the existing knowledge of the main chemical/biological mechanisms underlying the endpoint or property addressed by the proposed defined*

approach. If such knowledge is available in the form of an AOP (e.g. as in the case of skin sensitisation) a reference should be made to the relevant document (and the AOP wiki entry if available).

4. Definition of the purpose and regulatory relevance

Describe the purpose for which the defined approach has been developed. This may be to detect chemicals with a specific toxicological potential, to assess the potency of a chemical in inducing a toxic effect, to classify chemicals on the basis of their mode of action (e.g. capacity to bind to specific receptors) etc.

Indicate the regulatory relevance (i.e. intended application) of the defined approach. This may be: a) screening for priority setting in view of further evaluation; b) hazard identification/characterisation; c) risk assessment; d) other (please specify). If more than one purpose is possible, please state this under d).

5. Rationale underlying the construction of the defined approach

Describe the rationale used to construct the defined approach. This should include an assessment of the linkage of the individual information sources used to the known chemical and biological mechanisms underlying the endpoint being addressed. In case the defined approach is informed by existing AOP(s), the extent of coverage of the AOP key events (including MIE) should be described and the reason for the choice of a specific information source addressing a specific key event, possibly in the light of other existing similar existing information sources, should be provided. In addition in case of use of a non-guideline information source addressing the same key event of a method described in existing guidelines (e.g. OECD TGs), this should be justified. The rationale should also make reference to exposure/toxicokinetic considerations, where relevant.

6. Description of the individual information sources used (see Annex II)

List the information sources employed within the proposed defined approach (e.g. physico-chemical properties, non-testing (in silico) methods and testing (in chemico, in vitro, in vivo) methods, including the response(s) measured and the respective measure(s) (e.g. in chemico binding to synthetic peptides, expressed as % peptide depletion). Detailed descriptions of in chemico, in vitro, and in vivo methods should be provided using the template for reporting individual information sources (see Annex II). QSAR models if not already described elsewhere should be reported using the QSAR Model Reporting Format (QMRF), and individual predictions, if applicable, should be reported using the QSAR Prediction Reporting Format (QPRF). Both reporting formats are accessible at: https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/qsar_tools/QRF.

7. Data interpretation procedure applied

Describe the DIP used. Indicate whether the output of the DIP is qualitative or quantitative. If possible, provide a workflow to illustrate the manner in which the DIP should be applied.

8. Chemicals used to develop and test the DIP

8.1 Availability of training and test sets:

Indicate whether a training set (i.e. chemical data used in the development of the DIP) and test set (i.e. chemical data used to evaluate the DIP) are available (e.g. published in a paper, stored in a database etc.) or appended to this template. If it is not available, explain why. Example: “It is available and attached”; “It is available and referenced”; “It is not available because the data set is proprietary”; “The data set could not be retrieved”.

8.2 Selection of the training set and test set used to assess the DIP:

If the training set and test set are available please describe the rationale for their selection (i.e. availability of high quality in vivo data for the endpoint being predicted, coverage of the range of effects observed in vivo, coverage of diverse physicochemical properties, coverage of structural diversity, others).

8.3 Supporting information on the training and test sets:

If the training and the test sets are available append them as supporting information preferably in the form of an Excel table. The following information on both sets should be reported where available and to the extent possible: a) chemical names (common names and/or IUPAC names); b) CAS registry numbers or other identification numbers; c) in case of multi constituent-substances, UVCB or mixtures, report the composition to the extent possible; d) reference data or classification(s) for each chemical (e.g. in vivo data); e) data from the individual information sources used in the defined approach; f) final result/prediction for each chemical.

8.4 Other information on the training and test sets:

If the training and/or the test sets are not available for inclusion as supporting information, indicate any other relevant information about the training and/or test sets (e.g. number and type of compounds). This will be useful to gain an appreciation of the chemical coverage etc.

9. Limitations in the application of the defined approach

Indicate the types of chemicals, in terms of their physicochemical and biological properties, structures and functional groups for which the defined approach is considered not to be applicable because of technical constraints in the testing of those chemicals (e.g. because of poor solubility, interference with the detection system, etc.).

Indicate the types of chemicals, in terms of their physicochemical and biological properties, structures and functional groups for which the defined approach is considered not to be applicable because such chemicals have been found to give unreliable results (e.g. non-reproducible results when the defined approach is applied multiple times or because of wrong predictions with respect to the reference classification).

10. Predictive capacity of the defined approach

Provide an indication of the extent to which the defined approach predicts the endpoint of interest by considering the associated information sources and by excluding chemical types identified in the

limitations above. Express the predictive capacity in terms of sensitivity, specificity and concordance, if applicable, or by other goodness-of-fit statistics (e.g. linear correlation analysis). Rationalise to the extent possible potential misclassifications (i.e. chemicals under-predicted or over-predicted with respect to the reference classification) or unreliable predictions for chemicals not identified in the limitations above.

11. Consideration of uncertainties associated with the application of the defined approach

11.1 Sources of uncertainty

Describe the uncertainties which are considered to be associated with the application of the defined approach by capturing the sources of uncertainty that for example may result from:

1. *The DIP's structure,*
 - *What are the uncertainties related to chosen DIP's structure?*
 - *How does the DIP's coverage or weighting of exposure/toxicokinetic information and/or AOP key events affect your confidence in the overall prediction?*
 - *How does one's confidence in the DIP's prediction vary between different chemicals?*
2. *The information sources used within the defined approach,*
 - *How does variability of the information source's data for a given chemical (i.e. reproducibility) affect one's confidence in the DIP's prediction?*
2. *Benchmark data used,*
 - *How does the reliability and relevance of the reference data for the target of the evaluation (e.g. human, environment) affect confidence in the DIP's prediction?*
3. *Others sources*

11.2 Impact of uncertainty on the DIP's prediction

Consider, to the extent possible, how the individual sources of uncertainty affect the overall uncertainty in the final prediction in the context of the defined approach's application.

12. References

If available, list other relevant references, weblinks etc., describing the defined approach in addition to the main bibliographic references reported under General Information (section 2.5).

13. Supporting information

Indicate whether supporting information is attached (e.g. external documents) to this template and specify its content and possibly its utility unless previously annotated in preceding sections.

14. Abbreviations and definitions

If any terms were abbreviated or need specific definitions, they could be provided in this section.

ANNEX II: TEMPLATE FOR REPORTING INDIVIDUAL INFORMATION SOURCES

Name of the information source	<i>Provide the name of the information source and the acronym (if applicable).</i>
Mechanistic basis including AOP coverage	<i>Describe the chemical and/or biological mechanism addressed by the information source and provide an indication of the plausible linkage of the modelled mechanism to the endpoint being predicted (i.e. mechanistic relevance). In case the information source is addressing a specific (key) event within an existing AOP, describe the extent to which the mechanistic basis of the information source relates to the chemical/biological mechanism covered by the (key) event. In case of cell-based or tissue-based test methods, describe how the experimental system (i.e. the cells or tissues) models the target tissue/organ. Biokinetic (ADME/TK) considerations should be described if appropriate.</i>
Description	<i>Provide a short description of the information source including the experimental system used and any relevant aspect of the procedure (e.g. time of exposure of the experimental system with the test chemical, number of doses/concentrations tested, number of replicates, concurrent testing of control(s) and vehicle(s), laboratory instruments/techniques used to quantify the response, etc.).</i>
Response(s) measured	<i>Specify the response(s) measured by the information source and its measure (e.g. in chemico binding to synthetic peptides, expressed as % peptide depletion).</i>
Prediction model	<i>Indicate whether there is a prediction model associated to the information source and its purpose. Briefly describe the prediction model and provide a reference to a paper or document where the prediction model is described (if available).</i>
Metabolic competence (if applicable)	<i>Specify whether the information source encompasses any metabolically competent system/step and, to the extent possible, how this relates to the situation in vivo.</i>
Status of development, standardisation, validation	<i>Indicate whether the information source is a) an officially adopted (standard) test method (e.g. a test method covered by an OECD Test Guideline); b) a validated but non-standard test method; c) a test method undergoing formal evaluation (e.g. prevalidation, validation, others); d) a non-validated test method widely in use; e) a non-validated test method implemented by a small number of users.</i>
Technical limitations and limitations with regard to applicability	<i>Indicate the chemicals and/or chemical categories (e.g. based on physicochemical properties or functional groups) for which the information source is not applicable because of technical limitations (e.g. highly volatile chemicals, poorly water soluble chemicals, solid materials, interference of the chemical with the detection system (e.g. coloured or autofluorescent chemicals interfering with spectrophotometric analysis). Indicate whether the information source is technically applicable to the</i>

	<i>testing of multi constituent-substances, UVCBs (substances of unknown or variable composition, complex reaction products or biological material) and mixtures. In addition indicate the chemicals and/or chemical categories for which the information source is technically applicable but has been experimentally shown to yield incorrect and/or unreliable predictions with respect to the reference classifications (e.g. false negative predictions with chemicals requiring enzymatic activation, high false positive rate for alcohols etc.).</i>
Weaknesses and Strengths	<i>Provide an indication of the strengths and weaknesses of the information source, compared to existing similar non-testing or testing methods, considering among others the following aspects: a) extent of mechanistic information provided and relevance (i.e. measurement of various responses in the same experimental model, limited or good coverage of the mechanisms at the basis of the target endpoint, predictive of responses in humans), b) level of information provided (single point estimate or dose-response information), c) level of performance (e.g. higher or lower reproducibility, predictive capacity etc.) d) extent of domain of applicability, e) number of chemicals with published information, f) costs involved in implementing the procedure g) others.</i>
Reliability (within and between laboratories) (if applicable)	<i>Describe the level of reliability of the information source (i.e. the agreement among results obtained from testing the same chemicals over time using the same protocol in one or multiple laboratories) and to what extent this has been characterised including the number of chemicals used for the assessment.</i>
Predictive capacity (if applicable)	<i>Describe the extent to which the information source predicts the effect of interest (this could either be a specific chemical/biological mechanism or an apical endpoint) by considering all existing evidence (as reported in scientific publications and as determined in validation studies). Express the predictive capacity in terms of sensitivity, specificity and accuracy if applicable or by other goodness-of-fit statistics (e.g. linear correlation analysis). Include the number of chemicals used in this assessment. Consider the reliability and relevance of the reference data for the target of the evaluation if possible.</i>
Proprietary aspects	<i>Indicate whether the information source is fully disclosed or contains proprietary elements. For proprietary elements, describe the information that cannot be disclosed or is not publicly available. If the information source contains proprietary elements indicate whether it can still be widely implemented and used and provide a justification.</i>
Proposed regulatory use	<i>Indicate the proposed regulatory use of the information source (e.g. stand-alone full replacement method, partial replacement method, screening method, others).</i>
Potential role within the Defined Approach	<i>Indicate the potential role of the information source within the Defined Approach.</i>