**TEMPLATE FOR WEIGHT OF EVIDENCE / UNCERTAINTY**

**IN HAZARD ASSESSSMENT**

**Note to the reader:**

In order to improve the application of WoE approach within REACH/CLP/BPR processes and increase transparency in regulatory decision making this document provides a structured template for presenting the WoE approach/ uncertainty.

The use of the template across processes in addition to contributing to transparency it guides on what needs to be considered in a WoE approach; however, as such it does not provide guidance on how to perform the assessment as this will be case by case based and dependent on problem formulation.

The template takes into account the existing tables provided in ECHA Guidance documents (where relevant), the templates from WHO/IPCS MoA framework, the templates from OECD AOP and IATA guidance documents.

The template contains some instructions on what is expected under each section. In addition it provides links to the Background Document and to other Guidance documents relevant to the section. For each section of the template it is recommended to look at the corresponding sections of the Background document and examples.

The proposed tables for presenting the information can be modified as needed on a case by case basis. Examples using the template are available in the Background Document for WoE approach/Uncertainty.

In the case of Mode of action analysis / Human relevance the available templates (**WHO/IPCS Mode of Action Analysis Framework Templates**) at <https://echa.europa.eu/support/guidance-on-reach-and-clp-implementation/formats> should be used instead of the template for Weight of Evidence / Uncertainty.

# **Section 1**

## **Problem Formulation**

Problem formulation can be phrased either as general text in relation to a specific process or can have additional sub-questions that would assist the assessor to perform WoE / uncertainty analysis.

The level of uncertainty / confidence that will be acceptable depends on the goals set within the problem formulation.

For examples of problem formulation further information is available at the background document.

# **SECTION 2**

## **Collection and documentation of all information**

## **Documentation of search strategy & documentation/reporting of evidence**

ECHA Guidance (IR/CSA R2-R6) provides a list of sources to be used for the collection of relevant evidence in regulatory hazard assessment. Examples include eChemPortal, QSAR Toolbox for search of similar substances, web search engine machines (Science Direct, PubMed etc.).

It is recommended to include the key words searched for in the case of collection of evidence from web search engines.

IUCLID or the Evaluation report/assessment should be used for the documentation of the search strategy by registrants and dossier submitters.

A reference to an Annex or the IUCLID dossier (where relevant) is preferred for large data sets; the tabular format below can include a summary list of the evidence to be used in the WoE approach.

It might be relevant to indicate the reason for inclusion or exclusion of the information/evidence in the WoE approach. This can be done once the assessment under Sections 2 and 3 are performed and can be recorded in this section for clarity.

When search engines have been used it is beneficial to record and present the keywords searched.

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| **Source Name** | **Date of search** | **Type of information/evidence** | **Link/Reference** | **Keywords Searched** | **Reason for inclusion / exclusion from WoE approach** |
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# **SECTION 3**

## **Assessment of quality of individual evidence**

For each line of evidence assessment the elements on relevance, adequacy and reliability need also to be reported separately to address the assessment of the Quality of Data (further information within the Background Document and the ECHA Guidance IR/CSA R.4).

Depending on the application and the type and amount of evidence available it might be relevant in some cases to have more than one table for different type of evidence assessment (e.g. one for QSAR related evidence, one for in vitro etc.).

Low quality data should also be recorded with justification on their usefulness and depending on how they fit within the integration of evidence step a decision can be made on whether they should give less weight. Information may be dismissed only if it is not relevant for the endpoint in question.

For regulatory processes (REACH, BPR) the ECHA Guidance IR/CSA R.4 provides the elements for the assessment of the quality of data (on the basis of reliability, relevance and adequacy) and completeness.

The Klimisch criteria are proposed for the assessment of reliability of experimental data. Other criteria might be considered similar to the Klimisch scoring and can be used as well. For evidence/studies that cannot be rated with the use of Klimisch criteria, the assessment of reliability is considered within the frame of the integration of evidence regarding consistency/specificity (see Section 4) and other quality indicators (adequacy, relevance), rather than dismissing the evidence beforehand.

For other type of evidence (e.g. QSAR, use of read-across, non-standard in vitro assays) ECHA Guidance provides criteria for their assessment (ECHA Guidance IR/CSA R.4 & R.6).

For the assessment of relevance according to ECHA Guidance IR/CSA R.4:

* Was the substance tested representative for the substance as being registered?
* Has the appropriate species been studied?
* Is the route of exposure relevant for the population?
* Were appropriate doses/concentrations tested?
* Were the critical parameters influencing the endpoint considered adequately?

These questions might not be suitable for all type of evidence, and the relevance of the information can be considered in the integration step.

For the assessment of adequacy according to ECHA Guidance IR/CSA R.4: Define the usefulness of data for hazard/risk assessment purposes. Where there is more than one study for each endpoint, the greatest weight is attached to the studies that are the most relevant and reliable.

The adequacy would also need to be seen in an iterative mode with the elements addressed under the step of Integration and Weighing of Evidence taking into account the question(s) of the problem formulation.

If other tools/ methodologies are used for the assessment of quality of individual lines of evidence they should be mentioned explicitly with a link to the methodology and justification for their applicability in the WoE analysis.

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| **Type of Evidence / Source Name - Reference** | **Relevance** | **Reliability** | **Adequacy** |
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# **SECTION 4**

## **Integration & Weighing of evidence (WoE analysis)**

## **Application of Levels of Confidence**

The elements of consistency/specificity and likelihood are usually considered necessary for any WoE integration step although the degree of elaboration might differ depending on the problem formulation. They are based on the Bradford Hill considerations as used within the WHO/IPCS MoA framework but can be generalised to fit any hazard assessment. Elements such as temporality (see further below) are often more relevant for complex toxicological endpoints.

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| --- | --- | --- | --- | --- | --- |
| **Type of Evidence** | **Consistency & Specificity** | **Likelihood/**  **Biological Plausibility** | **Temporality** | **Confidence / Strength of Evidence** | **Remaining Uncertainty** |
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| **Conclusion from overall confidence** |  | | | | |

**Consistency & Specificity**

Refers only to the evidence available. For different types of evidence consistency and specificity can be addressed to document:

* if the evidence available for the specific case (e.g. chemical assessment) is consistent with the remaining evidence (e.g. information from a structurally similar chemical substance indicated fertility effects and is consistent with the substance experimental data on fertility parameters and an alert from a QSAR profiler),
* or for example if all the evidence points to the same direction (positive effects only or negative effects only).

Other examples of defining consistency and specificity from the WHO/IPCS MoA framework are available at WHO/IPCS Mode of Action Analysis Framework Templates<https://echa.europa.eu/support/guidance-on-reach-and-clp-implementation/formats>

**Likelihood / Biological Plausibility**

Refers only to other broader knowledge: Does the hypothesis make sense based on broader knowledge (e.g. biology, established mode of action)?

**Temporality**:

Needed on a case by case basis (mostly relevant in Mode of action analysis when data allows such analysis). Is there a logical order in the occurrence of an effect on the basis of the evidence available?

**Levels of Confidence /Strength of Evidence:** Confidence levels/strength of evidence can be assigned to individual evidence and to the overall evidence assessment. Confidence levels are derived taking into account the outcome of the weighing of the evidence (both individually and collectively) using the metrics/criteria specified in the corresponding steps of the WoE approach (such as adequacy, relevance, reliability for individual evidence assessment, and consistency/specificity, plausibility/likelihood, temporality for WoE analysis). Confidence levels can be usually expressed as high, medium or low. The confidence levels for each line of evidence should feed to the judgement of the overall confidence level that take into account all the evidence in an integrated and weighed mode. For each line of evidence confidence levels can have as underlying documentation:

1. Qualitative elements (e.g. Likelihood/ Biological plausibility)
2. Semi (quantitative) elements (e.g. temporality)

Level of confidence of each line of evidence is derived by combining the quality assessment elements of each line of evidence (relevance, adequacy, reliability) with the consistency and plausibility elements.

**Conclusion from Overall confidence:** The elements of completeness and adequacy for purpose (as described in ECHA Guidance IR/CSA R.4) could be reflected e.g. in the conclusion from the overall confidence part.

Further information on tools/methodologies for derivation of confidence levels are available in the background document.

**Remaining Uncertainty:** Depending on the case, the remaining uncertainty can be recorded in this section as a result of the levels of confidence for each line of evidence (e.g. high confidence would mean low uncertainty). However the uncertainty components can be further elaboration in Section 5 below if considered necessary, or as part of the conclusions and further needs.

# **SECTION 5**

## **Uncertainty Analysis**

Depending on the case, it might be appropriate to record uncertainties in a separate table to address the source of the uncertainty and the impact to the assessment.

The elaboration of confidence levels, and their underlying documentation, would in general depend on the needs defined by each process and problem formulation.

Uncertainty analysis can be qualitative (similar to the derivation of confidence levels in Section 4 of this template) or (semi-)quantitative.

For the latter, further Guidance on analysing and recoding in more detail uncertainty is available within ECHA Guidance IR/CSA R.19

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| --- | --- | --- | --- |
| **Source of Uncertainty** | **Nature of Uncertainty** | **Magnitude of uncertainty** | **Impact to the assessment** |
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# **SECTION 6**

## **Conclusions**

In this section the conclusions in relation to the questions/issues formulated in Section 1 of the template should be clearly recorded with the reference to the overall confidence levels / remaining uncertainty (as derived in Sections 4 and 5).

Recommendations in case additional work is foreseen as outcome of the WoE approach should be clearly stated.

Examples can be:

* Additional information/evidence to increase confidence for a particular part of the WoE approach
* Additional analysis by use of higher tier methodologies (e.g. PBPK modelling, statistical approaches to define remaining uncertainty in quantifiable manner – probabilistic approaches).