MISA Self-assessment tool on priority endpoints for human health

Version 2018-07-16

Introduction: why this tool?

- This tool aims at helping you prepare the first thematic workshop of the MISA programme, which will **focus on information requirements for human health endpoints, possible adaptations, weight-of-evidence and read-across**. During the workshops, consortia (including their consultants) and ECHA will exchange on the interpretation/applicability of adaptation arguments, learn from comparing adaptation motivations and agree on the generic elements to include in the dossiers when using adaptations. This survey aims at facilitating the discussions. **Please note that the outcome of these surveys will NOT be communicated to ECHA, but Eurometaux will extract the questions posed (anonymised) and some key learning lessons to prepare the workshop with ECHA**.

- This survey focusses on 3 relevant groups of endpoints mainly relevant for substances >1000 t/y, identified as priority endpoints under the MISA programme:
  - **reproductive toxicity,**
  - **repeated dose toxicity and**
  - **mutagenicity.**

  However, this self-assessment tool can be completed for other tonnage bands. The assessor has the possibility to indicate when a requirement/request proves irrelevant for his/her lower tonnage band.

- For these endpoints, also data on lower tier testing approach (Annexes VII, VIII and IX) is requested to facilitate the comprehensive understanding of the basis for testing of adaptation/waiving of the higher tier endpoints (Annex X).

  For each of these priority endpoints, the following input from your registration file is needed to complete the self-assessment:
  - Summary of the test data (with emphasis on the key studies)
  - Information on the waivers
  - Information on the read-across approach followed (if relevant)

For the purpose of this self-assessment, waiver statements are compared to the standard waiving justification options listed for these endpoints in **IUCLID 6**, which are based on the provisions for data waiving in Annexes VII-X of REACH, and to the relevant provisions for data waiving from Annex XI.
The reason for doing so is to facilitate potential updates where/if relevant.

4. Some warning signs have been included and refer to endpoints/justifications that deserve specific attention (based e.g. on learning lessons from MSC discussions or compliance checks) 

Notes:

- For this self-assessment it is recommended to carefully consider the reliability/relevance of the existing data for any of the tests when/where relevant. In case any of those requirements have not been fulfilled for a key study it is recommended to consider evaluating/submitting an appropriate testing proposal.

- A key study to fill a data gap should comply with the required quality and relevance criteria of REACH. While a test can be conducted along the criteria, experience (e.g. compliance checks, MSC discussions) has demonstrated that some specific attention is required on the following points:
  - Is the highest testing dose high enough to prevent unbounded conclusions? Is it not below the derived DNEL/DMEL?
  - Whether the selected exposure pathway in case of repeated dose toxicity studies in particular is the most relevant to either demonstrate local or chronic effects?

  A failure in any of these aspects often leads to a testing decision by ECHA to repeat the specific test.

- Please do not hesitate to include all information you consider relevant in the template to ensure all important elements for discussion are identified ahead of the workshop!

- Your feedback on the template is of course utmost welcomed: waeterschoot@eurometaux.be, verougstraete@eurometaux.be

Let's start…

Substance(s) covered in this assessment

Please clarify if this self-assessment is run for a specific **substance** or a **group of related substances**?

☐ Specific substance name: …… and CAS number: ……

☐ Group of substances (please note that this is not necessarily grouping for read-across, this will be discussed for each endpoint separately):

- Group name: ……
- Group members name + CAS number:
  - ……..
  - ……..
  - ……..
  - ……..

Maximum tonnage band in case of a grouping: …….

Reproductive toxicity (IUCLID section 7.8; Annex VIII, 8.7.1; Annex IX&X, 8.7.2 & 8.7.3)

At Annex X level (registrations where at least one registrant has registered 1000 t/year or more) REACH requires four standard information requirements to be fulfilled for the reproductivity toxicity endpoint, either by test data, or by a justified adaptation or waiver:

- Screening for ***reproductive/developmental toxicity*** (e.g. OECD 421 or 422) (Annex VIII, 8.7.1
- ***Pre-natal Developmental Toxicity*** (PNDT, e.g. OECD 414) in a ***first species*** (Annex IX, 8.7.2)
- ***Pre-natal Developmental Toxicity*** (PNDT, e.g. ECD 414) in a ***second species*** (Annex X, 8.7.2)
- ***Extended One-Generation Reproductive Toxicity Study*** (EOGRTS, e.g. OECD 443) (Annexes IX &X, 8.7.3)

1. Test data

Please complete the following table for each type of test.

Have you submitted test data?

	Screening test	**PNDT (1st species)**	**PNDT (2nd species)**	**EOGRTS**	**RDT***
Yes • Substance tested (name + CAS number) • Guideline followed • GLP • Klimisch score of key study**	☐ _____ _____ _____ _____	☐ _____ _____ _____ _____	☐ _____ _____ _____ _____	☐ _____ _____ _____ _____	☐ _____ _____ _____ _____
Requested testing is suspended due to a **running appeal procedure**	☐	☐	☐	☐	N/A
No, but a **testing proposal** has been **submitted to ECHA and/or testing is ongoing** - Test substance (name-CAS) - OECD guideline number	N/A	☐ _____ _____ _____	☐ _____ _____ _____	☐ _____ _____ _____	N/A
No, and no testing is ongoing and no testing proposal has been submitted	☐	☐	☐	☐	N/A

*RDT ('Repeated Dose Toxicity'): please indicate when you have used repeated dose toxicity data for the assessment of the information requirements for reproductive toxicity.

**In case a Weight-of-Evidence approach is used, please indicate a summary of the different Klimisch scores (e.g. 3 x KL2, 2KL3, …)

If your answer was: '*No, and no testing is ongoing and no testing proposal has been submitted*' on any of the tests required, **please proceed with the following questions on waivers (section 2.):**

Did you receive and respond to an ECHA Compliance Check decision for this endpoint?

☐ Yes. Decision reference number: ……..
☐ No

2. Waivers and adaptations of data requirements

In your assessment, which of the following legal basis for adaptations/waivers did you use? Please double-check whether the conditions in the legal basis are fulfilled and explicitly justified and motivated (to the extent necessary with supporting data) in the dossier. Multiple boxes can be ticked.

The provisions below are the standard waiving justification options in IUCLID 6.2 for these endpoints, based on the provisions for data waiving in Annexes VII-X, and the relevant provisions for data waiving and adaptations from Annex XI.

WARNING: Options that are, based on previous experience, often not accepted by ECHA and hence require strong argumentation for acceptance, are marked with an exclamation mark. You may reconsider the endpoint and see whether you can use one of the other valid adaptation or waiving arguments (or a valid combination thereof). If not, testing may need to be considered.

	Screening test	PNDT (1st species)	PNDT (2nd species)	EOGRTS
Data are not required because of the (lower) **tonnage (band)** of the substance/group		☐	☐	☐
A screening study for reproductive/developmental toxicity does not need to be conducted because there is **evidence** from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods **that the substance may be a developmental toxicant** (study scientifically not necessary / other information available)	☐			
The study does not need to be conducted because **an extended one-generation reproductive toxicity study is available** (study scientifically not necessary / other information available)	☐			
The study does not need to be conducted because **a two-generation reproductive toxicity study is available** (study scientifically not necessary / other information available)	☐			☐
The study does not need to be conducted because **a pre-natal developmental toxicity study is available** (study scientifically not necessary / other information available)	☐			
The study does not need to be conducted because **the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented** (study scientifically not necessary / other information available)	☐	☐	☐	☐
The study does not need to be conducted because **the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented** (study scientifically not necessary / other information available)	☐	☐	☐	☐
The study does not need to be conducted because **relevant human exposure can be excluded** as demonstrated in the relevant exposure assessment (exposure considerations)	☐	☐	☐	☐

The study does not need to be conducted because (i) the substance is of **low toxicological activity** (no evidence of toxicity seen in any of the tests available), (ii) it can be proven from toxicokinetic data that **no systemic absorption** occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and (iii) **there is no or no significant human exposure** (exposure considerations; study scientifically not necessary / other information available)		☐	☐	☐
No further testing on fertility is necessary because the substance is **known to have an adverse effect on fertility**, meeting the criteria for classification as toxic for reproduction **category 1A or 1B**: may damage fertility (H360F), and the **available data are adequate to support a robust risk assessment** and classification and labelling (study scientifically not necessary / other information available)	☐			☐
No further testing for developmental toxicity is necessary because the substance is **known to cause developmental toxicity**, meeting the criteria for classification as toxic for reproduction **category 1A or 1B**: may damage the unborn child (H360D), and the **available data are adequate to support a robust risk assessment** and the classification and labelling of the substance (study scientifically not necessary / other information available)	☐	☐	☐	
The extended one-generation reproductive toxicity study does not need to be conducted for 100-1000 t tonnage band, if there are no results from available repeated dose toxicity studies that indicate adverse effects on reproductive organs or tissues, or reveal other concerns in relation with reproductive toxicity (study scientifically not necessary / other information available)				☐
Historical human data, such as epidemiological studies on exposed populations, accidental or occupational exposure data and clinical studies, was used to fulfil the endpoint and the conditions of Annex XI, 1.1.3 are fulfilled	☐	☐	☐	☐
Weight-of-evidence arguments were used to fulfil the endpoints (i.e. no key studies identified) and the conditions of Annex XI, 1.2 are fulfilled.	☐	☐	☐	☐

Results obtained from the use of ***in vitro* methods were sufficient** and the conditions for waiving confirmation of the *in vitro* results as per Annex XI, 1.4 are fulfilled	☐	☐	☐	☐
Testing was waived as **technically not possible** (Annex XI, 2)	☐	☐	☐	☐
Other*	☐	☐	☐	☐

*If mentioned "other", please explain which kind of adaptation was used:

Please **insert** the **wording of the justification** for the adaptation/waiver that you used in your dossier, here below. Also assess whether the wording addresses each condition of the adaptation/waiver. Furthermore, the fulfilment of the conditions needs to be demonstrated, not just claimed.

WARNING!: Annex IX, Section 8.6.2, Column 2 states that 'The sub-chronic toxicity (90 days) does not need to be conducted if the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test', particularly if such a pattern is coupled with limited human exposure. MSC experience however shows that waiving a 90-day study on the basis of a 28-day is usually rejected if lacking extensive understanding of the Mechanism of Action (MoA) to appropriately justify the waiver request. A comparable reasoning applies to the waiving of the need for a chronic > 12 months study.

Therefore, check on whether data supporting your arguments -as to why the condition is fulfilled- are included:

3. Read-across

In your assessment, did you follow a read-across approach for the assessment of reproductive toxicity endpoints?

☐ Yes ☐ No

If yes, which read-across approach did you follow?

☐ Read-across based on grouping of substances (**category approach**)
- Category name: ……..
- Substances covered by the category:
  ……..
  ……..
  ……..
  ……..
- Source substance(s) for data on reproductive toxicity endpoints: ……..

☐ Read-across from supporting substance (**structural analogue or surrogate**)
- Source substance: ……..

How is the read-across approach **reported and justified/motivated**?

- Is the read-across approach reported according to the standards in IUCLID 6.2 (e.g. updated read-across selection under 'type of information', source and target study records for analogue approach, category entity for category approach)? ECHA guidance R.6.2 provides recommendations on how and what information to be reported in the category/read-across justification[1]
  ☐ Yes ☐ No ☐ Planned

- Do you use the assessment entity approach to report read-across?
  ☐ Yes ☐ No ☐ Planned

  If yes, which *assessment entity/entities* have been used?
  ☐ Registered substance as such, name(s): ……..
  ☐ Specific composition/form of the registered substance, name(s): ……..
  ☐ (Group of) constituent(s) in the registered substance, name(s): ……..
  ☐ Transformation of the registered substance, name(s): ……..

- Does your read-across justification follow the recommendations set by RAAF-HEALTH (Health Read-across assessment framework)[2]?
  ☐ Yes, ☐ No ☐ Planned

  If yes:
  - What is the selected scenario (1 to 6)? ……..

[1] https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf
[2] https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

- Are all assessment elements for the selected scenario properly addressed?
  ☐ Yes ☐ No
  If no, which were not and why? .....
  .....

- Is adequate and reliable supporting information provided to justify the score for each assessment element
  ☐ Yes ☐ No
  If no, which are the elements you faced some difficulties with to provide supporting information? .....
  .....

- Is the potential effect of the counter-ions investigated (in a quantitative or qualitative way)?
  ☐ Yes, ☐ No
  If no, why? .....
  .....

- Is the read-across hypothesis clearly formulated **AND** is the quality of the source data fulfilling the criteria on study quality and adequacy listed in Annex XI, section 1.5.
  ☐ Yes ☐ No

4. General

Most recent update of the dossier (year) for this endpoint: ……

Add any observations/learnings/questions on the Reproductive toxicity endpoint:

Repeated dose toxicity (IUCLID section 7.5; Annex VIII & IX, 8.6.1; Annex IX, 8.6.2; Annex X, 8.6.3)

At Annex X level (registrations where at least one registrant has registered 1000 t/y or more) REACH requires at least two standard information requirements to be fulfilled either by test data, or by a justified adaptation or waiver:

- ***Short-term repeated dose toxicity study*** (28-day, e.g. OECD 407) (Annex VIII / IX, 8.6.1)
- ***Sub-chronic toxicity study*** (90-day, e.g. OECD 408) (Annex IX, 8.6.2)

In addition, further testing may need to be considered:

- ***Long-term repeated toxicity study*** (≥ 12 months, e.g. OECD 452) (Annex X, 8.6.3)

1. Test data

Please complete the following table for each type of test.

Have you submitted test data?

	Short-term	Sub-chronic	Chronic/other
Yes • Substance tested (name + CAS nr) • Exposure route* • Guideline followed • GLP • Klimisch score of key study**	☐ _____ _____ _____ _____ _____	☐ _____ _____ _____ _____ _____	☐ _____ _____ _____ _____ _____
Requested testing is suspended due to a **running appeal procedure**	☐	☐	☐
No, but a **testing proposal** has been submitted to ECHA **and/or testing is ongoing**		☐	☐
• Test substance ID (name and CAS)		_____	_____
		_____	_____
• OECD Guideline number		_____	_____
No, and no testing is ongoing and/or no testing proposal has been submitted	☐	☐	☐

*Exposure route: see question below

**In case a Weight-of-Evidence approach is used, please indicate a summary of the different Klimisch scores (e.g. 3 x KL2, 2KL3, …)

With regard to the exposure route:

- Oral route: was the relevance of the specific method of administration considered (e.g. by gavage, via diet, …?
  ☐ Yes ☐ No
- Inhalation route: did the study include relevant information on the particle size used/needed?
  ☐ Yes ☐ No

If your answer was: *'No, and no testing is ongoing and no testing proposal has been submitted'* on any of the tests required, please proceed with the following questions on waivers (section 2.)

Did you receive and respond to an ECHA Compliance Check decision for this endpoint?

☐ Yes. Decision reference number: ……..

☐ No

2. Waivers and adaptations of data requirements

In your assessment, which of the following legal basis for adaptations/waivers did you use? Please double-check that the conditions in the legal basis are fulfilled and explicitly justified and motivated (to the extent necessary with supporting data) in the dossier. Multiple boxes can be ticked.
The provisions below are the standard waiving justification options in IUCLID 6.2 for these endpoints, based on the provisions for data waiving in Annexes VII-X, and the relevant provisions for data waiving and adaptations from Annex XI.

WARNING: Options that are, based on previous experience, often not accepted by ECHA and hence require strong argumentation for acceptance, are marked with an exclamation mark. You may reconsider the endpoint and see whether you can use one of the other adaptation or waiving arguments (or a valid combination thereof). If not, testing may need to be considered.

	Short-term	**Sub-chronic**
Data are not required because of the (lower) **tonnage (band)** of the substance/group	☐	☐
A **short-term toxicity study does not need to be conducted because a reliable sub-chronic (90 days) or chronic toxicity study is available**, conducted with an appropriate species, dosage, solvent and route of administration study scientifically not necessary/other information available)	☐	
A **short-term toxicity study does not need to be conducted because a sub-chronic (90 days) or chronic toxicity study is proposed**. The criteria of column 2 are fulfilled, which suggest that a longer-term study is appropriate rather than the short-term study, and a testing proposal has been accordingly submitted	☐	

	Short-term	Sub-chronic
A short-term toxicity study does not need to be conducted because **relevant human exposure can be excluded** as based on the provided thorough and rigorous exposure assessment (exposure conditions)	☐	
A **short-term toxicity study by the oral route does not need to be conducted because an appropriate inhalation study is available** and **inhalation is the most appropriate route** of administration as based on the provided thorough and rigorous exposure assessment **and** other evidence as requested by A.VIII, 8.6.1 column 2 has been fulfilled (exposure considerations; study scientifically not necessary / other information available)	☐	
A **short-term toxicity study by the oral route does not need to be conducted because an appropriate dermal study is available** and **dermal is the most appropriate route** of administration as based on the provided thorough and rigorous exposure assessment (exposure considerations; study scientifically not necessary / other information available)	☐	
A **sub-chronic toxicity study (90 days) does not need to be conducted because a reliable short-term toxicity study (28 days) is available showing severe toxicity effects** according to the relevant criteria for classifying the substance, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure (study scientifically not necessary / other information available)		☐
A **sub-chronic toxicity study (90 days) does not need to be conducted because a reliable chronic toxicity study is available**, conducted with an appropriate species and route of administration (study scientifically not necessary / other information available)		☐
A **sub-chronic toxicity study (90 days) by the oral route does not need to be conducted because an appropriate inhalation study is available** and **inhalation is the most appropriate route** of administration as based on the provided thorough and rigorous exposure assessment and other evidence as requested by A.VIII,8.6.2 column 2 (exposure considerations; study scientifically not necessary / other information available)		☐
A **sub-chronic toxicity study (90 days) by the oral route does not need to be conducted because an appropriate dermal study is available** and **dermal is the most appropriate route** of administration as based on the provided thorough and rigorous exposure assessment and other evidence as requested by A.VIII,8.6.2 column 2 (exposure considerations; study scientifically not necessary / other information available)		☐
A sub-chronic toxicity study (90 days) does not need to be conducted because the **substance is unreactive, insoluble and not inhalable** and there is **no evidence of absorption** and **no evidence of toxicity in a 28-day 'limit test'** and **human exposure is limited**		☐

	Short-term	Sub-chronic
Historical human data, such as epidemiological studies on exposed populations, accidental or occupational exposure data and clinical studies, was used to fulfil the endpoint and the conditions of Annex XI, 1.1.3 are fulfilled	☐	☐
Weight-of-evidence arguments were used to fulfil the endpoints (i.e. no key studies identified) and the conditions of Annex XI, 1.2 are fulfilled.	☐	☐
Results obtained from the use of ***in vitro* methods were sufficient** and the conditions for waiving confirmation of the *in vitro* results as per Annex XI, 1.4 are fulfilled	☐	☐
Testing was waived as **technically not possible** (Annex XI, 2)	☐	☐
Other*	☐	☐

*If mentioned "other", please explain which kind of adaptation was used:

Please **insert** the **wording of the justification** for the adaptation/waiver that you used in your dossier. Also assess whether the wording addresses each condition of the adaptation/waiver. Furthermore, the fulfilment of the conditions needs to be demonstrated, not just claimed. Therefore, check on whether data supporting your arguments as to why the condition is fulfilled are included:

3. Further testing

Criteria that may indicate the need for long-term repeated dose toxicity testing (Annex X, Col. 2, 8.6.**3):**

Should you tick any of the following boxes, the need for proposing a long-term repeated dose toxicity study had to be assessed. Should you tick a box but have decided not to submit a testing proposal, it may be advisable to include the reasoning for not proposing testing in the registration dossier:

☐ The **frequency and duration of human exposure** indicates that a longer-term study is appropriate and **serious or severe toxicity effects of particular concern** were observed in the 28-

day or 90-day study for which the **available evidence** is **inadequate for toxicological evaluation or risk characterisation** (Annex X, Col. 2, 8.6.3, 1st indent)

☐ The **frequency and duration of human exposure** indicates that a longer term study is appropriate and **effects shown in substances with** a **clear relationship in molecular structure** with the substance being studied **were not detected in the 28-day or 90-day study** (Annex X, Col. 2, 8.6.3, 2nd indent)

☐ The **frequency and duration of human exposure** indicates that a longer term study is appropriate and the substance **may have** a **dangerous property that cannot be detected in** a **90-day study** (Annex X, Col. 2, 8.6.3, 3rd indent)

Criteria that indicate the need for further testing (studies (Annex IX, 8.6.2, Column 2, Annex X, Col. 2, 8.6.**4**):

Should you check any of the following boxes, the need for proposing further studies has to be assessed.

☐ The 90-day study **did or could not identify a NOAEL** unless the reason for this is the absence of adverse toxic effects (Annex IX, 8.6.2, Col. 2, para. 5, 1st indent)

☐ **Toxicity of particular concern** (e.g. serious/severe effects) (Annex X, Col. 2, 8.6.4, 1st indent)

☐ There are **indications of an effect** for which the **available evidence is inadequate for toxicological evaluation and/or risk characterisation**. In such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects (e.g. immunotoxicity, neurotoxicity) (Annex X, Col. 2, 8.6.4, 2nd indent)

☐ There is a **particular concern regarding exposure** (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity is observed) (Annex X, Col. 2, 8.6.4, 3rd indent) read-across

4. Read-across

In your assessment, did you follow a read-across approach for the assessment of repeated dose toxicity endpoints?

☐ Yes ☐ No

If **yes**, which read-across approach did you follow?

☐ Read-across based on grouping of substances (**category approach**)

- Category name: ……..
- Substances covered by the category:
  ……..
  ……..
  ……..
  ……..

- Source substance(s) for data on reproductive toxicity endpoints: ……..

☐ Read-across from supporting substance (**structural analogue or surrogate**)

- Source substance: ……..

How is the read-across approach **reported and justified/motivated**?

- Is the read-across approach reported according to the standards in IUCLID 6.2 (e.g. updated read-across selection under 'type of information', source and target study records for analogue approach, category entity for category approach)? ECHA guidance R.6.2 provides recommendations on how and what information to be reported in the category/read-across justification[3]
  ☐ Yes ☐ No ☐ Planned

- Do you use the assessment entity approach to report read-across?
  ☐ Yes ☐ No ☐ Planned

  If yes, which *assessment entity/entities* have been used?
  - ☐ Registered substance as such, name(s): ……..
  - ☐ Specific composition/form of the registered substance, name(s): ……..
  - ☐ (Group of) constituent(s) in the registered substance, name(s): ……..
  - ☐ Transformation of the registered substance, name(s): ……..

- Does your read-across justification follow the recommendations set by RAAF-HEALTH (Health Read-across assessment framework)[4]?
  ☐ Yes ☐ No ☐ Planned

  If yes:
  - What is the selected scenario (1 to 6)? ……..
  - Are all assessment elements for the selected scenario properly addressed?
    ☐ Yes ☐ No
    If no, which one not and why?.....
  - Is adequate and reliable supporting information provided to justify the score for each assessment element
    ☐ Yes ☐ No
    If no, which are the elements you faced some difficulties with, to provide supporting information? .....
    .....
  - Is the potential effect of the counter-ions investigated (in a quantitative or qualitative way)?
    ☐ Yes, ☐ No
    If no, why? .....
    .....

[3] https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf
[4] https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

- Is the read-across hypothesis clearly formulated **AND** is the quality of the source data fulfilling the criteria on study quality and adequacy listed in Annex XI, section 1.5.
  ☐ Yes ☐ No

……..

5. General

Most recent update of the dossier (year) for this endpoint: ……

Add any observations/learnings/questions

Mutagenicity (IUCLID section 7.6; Annex VII, 8.4.1; Annex VII, 8.4.2&8.4.3; Annex IX&X, 8.4)

At Annexes IX and X levels, REACH has three standard information requirements to be fulfilled either by test data, or by a justified adaptation or waiver:

- ***In vitro* gene mutation study in bacteria** (ivtGMB, e.g. OECD 471 & 472) (Annex VII, 8.4.1)
- ***In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study** (ivtCM/ivtMS, e.g. OECD 473) (Annex VIII, 8.4.2)
- ***In vitro* gene mutation study in mammalian cells** (ivtGMM, e.g. OECD 476) (Annex VIII, 8.4.3)

In addition, further testing may need to be considered:

- **A 1st *in vivo* somatic cell genotoxicity study** (Annex IX, Col. 2, 8.4, para. 1)
- **A 2nd *in vivo* somatic cell genotoxicity study** (Annex X, Col. 2, 8.4, para. 1)
- **Investigations for germ cell mutagenicity** (Annexes IX and X, Col. 2, 8.4, para. 2)

Somewhat different than for the other endpoints, REACH requires further testing depending on the outcome of the initial tests listed above. This follow-up needs to be used within a testing strategy (see further under 3).

1. Test data

Please complete the following table for each type of test.

Have you submitted test data?

IN VITRO STUDIES	**ivtGMB**	**ivtCM/ivMS**	**ivtGMM**	**Other**
Yes	☐	☐	☐	☐
• Substance tested (name + CAS nr)	_____	_____	_____	_____
	_____	_____	_____	_____
• Guideline followed	_____	_____	_____	_____
• GLP	_____	_____	_____	_____
• Klimisch score of key study**	_____	_____	_____	_____
Requested testing is suspended due to a **running appeal procedure**	☐	☐	☐	☐

**In case a Weight-of-Evidence approach is used, please indicate a summary of the different Klimisch scores (e.g. 3 x KL2, 2KL3, …)

IN VIVO STUDIES	**in vivo gene mutation**	**in vivo clastogenicity/ aneugenicity**	**unspecific DNA damage in vivo (i.e. Comet assay)**
Yes • Substance tested (name + CAS nr) • Guideline followed • GLP • Klimisch score of key study **	☐ _____ _____ _____ _____ _____	☐ _____ _____ _____ _____ _____	☐ _____ _____ _____ _____ _____
Requested testing is suspended due to a **running appeal procedure**	☐	☐	☐
No, but a **testing proposal** has been submitted to ECHA **and/or testing is ongoing** • Test substance ID (name + CAS) • Guideline	☐ _____ _____ _____	☐ _____ _____ _____	☐ _____ _____ _____
No, and no testing is ongoing and no testing proposal has been submitted	☐	☐	☐

**In case a Weight-of-Evidence approach is used, please indicate a summary of the different Klimisch scores (e.g. 3 x KL2, 2KL3, …)

If your answer was: *'No, and no testing is ongoing and no testing proposal has been submitted'* on any of the tests required, please proceed with the following questions on waivers (section 2.)

Did you receive and respond to an ECHA Compliance Check decision for this endpoint?

☐ Yes. Decision reference number: ……..

☐ No

2. Waivers and adaptations of data requirements

In your assessment, which of the following legal basis for adaptations/waivers did you use? Please double-check that the conditions in the legal basis are fulfilled and explicitly justified and motivated (to the extent necessary with supporting data) in the dossier. Multiple boxes can be ticked.
The provisions below are the standard waiving justification options in IUCLID 6.2 for these endpoints, which are based on the provisions for data waiving in Annexes VII-X, and the relevant provisions for data waiving and adaptations from Annex XI.

WARNING: Options that are, based on previous experience, often not accepted by ECHA and hence require strong argumentation for acceptation, are marked with an exclamation mark. You may reconsider the endpoint and see whether you can use one of the other adaptation or waiving arguments (or a valid combination thereof). If not, testing may need to be considered.

	ivtGMB	ivtCM/ivMS	ivtGMM
An *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study does not need to be conducted because adequate data from an *in vivo* cytogenicity test are available (study scientifically not necessary / other information available)		☐	
An *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study does not need to be conducted because the **substance is known to be carcinogenic category 1A or 1B or germ cell mutagenic category 1A, 1B or 2** (study scientifically not necessary / other information available)		☐	
An *in vitro* gene mutation study in mammalian cells does not need to be conducted because adequate data from a reliable *in vivo* mammalian gene mutation test are available (study scientifically not necessary / other information available)			☐
An *in vitro* gene mutation study in mammalian cells does not need to be conducted because a positive result was found in *in vitro* gene mutation study in bacteria (study scientifically not necessary / other information available)			☐
An *in vitro* gene mutation study in mammalian cells does not need to be conducted because a positive result was found in *in vitro* cytogenicity study in mammalian cells (study scientifically not necessary / other information available)			☐
An *in vitro* gene mutation study in mammalian cells does not need to be conducted because a positive result was found in *in vitro* micronucleus study (study scientifically not necessary / other information available)			☐
Historical human data, such as epidemiological studies on exposed populations, accidental or occupational exposure data and clinical studies, was used to fulfil the endpoint and the conditions of Annex XI, 1.1.3 are fulfilled	☐	☐	☐
Weight-of-evidence arguments were used to fulfil the endpoints (i.e. no key studies identified) and the conditions of Annex XI, 1.2 are fulfilled.	☐	☐	☐
Testing was waived as **technically not possible** (Annex XI, 2)	☐	☐	☐
Other*	☐	☐	☐

*If mentioned “other”, please explain which kind of adaptation was used:

Please **insert** the **wording of the justification** for the adaptation waiver that you used in your dossier. Also assess whether the wording addresses each condition of the adaptation/waiver. Furthermore, the fulfilment of the conditions needs to be demonstrated, not just claimed. Therefore, check on whether data supporting your arguments as to why the condition is fulfilled are included:

3. Further testing

Further *in vivo* mutagenicity **testing is not** a **standard** information requirement at Annexes VIII, IX or X level. It **has however to be considered whether** further testing is **required.** As these tests are not standard information requirements it is not required to provide waivers or adaptations to justify the absence of the tests in the dossier **provided that no positive results were obtained in any of the *in vitro* tests.**
The further follow-up requirements and testing strategy are well described in a recent ECHA document[5]

The In *Vivo Mammalian Alkaline Comet Assay* (TG489), the *in vivo* chromosome aberration Assay (TG 475), the Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays ('TGR') -OECD 488 and the *In Vivo Micronucleus test* (TG 474) are often considered in this respect with the two latter tests being the most appropriate to follow-up on concerns of chromosomal aberrations.

1. A 1st *in vivo* somatic cell genotoxicity study (Annex IX, Col. 2, 8.4, para. 1)

An *in vivo* somatic cell genotoxicity study shall be proposed, if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no reliable results available from an *in vivo* study.

☐ **None of the *in vitro*** genotoxicity **studies** in Annex VII or VIII **was positive**. Therefore, no *in vivo* somatic cell genotoxicity study is indicated. In this case, neither Section III.D.2. or III.D.3 apply and the **self-assessment can be concluded here**.

☐ At least **one** of the ***in vitro*** genotoxicity studies in Annex VII or VIII **was positive**. Proceed to the next questions.

[5] https://echa.europa.eu/documents/10162/21650280/oecd_test_guidelines_genotoxicity_en.pdf

2. A 2nd *in vivo* somatic cell genotoxicity study (Annex X, Col. 2, 8.4, para. 1)

A second *in vivo* somatic cell genotoxicity study may be necessary, if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and the quality and relevance of all the available data – including the first somatic cell study – are insufficient.

☐ **Yes, a testing proposal** according to the testing strategy is submitted

☐ **No, no testing proposal** was submitted and no data on a second genotoxicity study are available

In the case you did not report test data or a testing proposal and testing is not ongoing, please explain why:

☐ The **quality and relevance of all available data** was considered. It was found to be **sufficient**. No second *in vivo* somatic cell genotoxicity study is needed.

☐ The need for a second somatic cell genotoxicity study was **not yet considered**. (It should be considered at this stage)

3. Investigations for germ cell mutagenicity (Annex IX and X, Col. 2, 8.4, para. 2)

If there is a positive result from an *in vivo* somatic cell study and if on the basis of all available data, including toxicokinetic evidence, no clear conclusions about germ cell mutagenicity can be made, it shall be considered whether to investigate germ cell mutagenicity.

☐ **Yes, a testing proposal** according to the testing strategy is submitted

☐ **No, no testing proposal** was submitted and no data on a second genotoxicity study are available

In the case you did not report test data or a testing proposal and testing is not ongoing, please explain why:

☐ The quality and relevance of all available data was considered. It was found to be sufficient. No germ cell mutagenicity study is needed

☐ There was a **positive result from** an ***in vivo* somatic cell study**. However, available **data allowed** to reach a **clear conclusion about germ cell mutagenicity**

☐ **Germ cell mutagenicity was further investigated**

☐ There was a **positive result from** an ***in vivo* somatic cell study**. **No clear conclusion about germ cell mutagenicity** could be drawn. However, germ cell mutagenicity has **not yet been further investigated / considered** (In that case this endpoint should be reconsidered)

WARNING: a non-appropriate selection of the tissues of impact for the Muta *in vivo* tests, COMET (TG 489) and TGR (TG 488) may make the result incomplete or inappropriate for use under the REACH requirements.

4. Read-across

In your assessment, did you follow a read-across approach for the assessment of mutagenicity endpoints?

☐ Yes ☐ No

If yes, which read-across approach did you follow:

☐ Read-across based on grouping of substances (**category approach**)

- Category name: ……..
- Substances covered:

  ……..
  ……..
  ……..
  ……..

- Source substance(s) for data on mutagenicity endpoints: ……..

☐ Read-across from supporting substance (**structural analogue or surrogate**)

- Source substance: ……..

How is the read-across approach **reported and justified**? :

- Is the read-across approach reported according to the standards in IUCLID 6.2 (e.g. updated read-across selection under 'type of information', source and target study records for analogue approach, category entity for category approach)? ECHA guidance R.6.2 provides recommendations on how and what information to be reported in the category / read across justification[6]

  ☐ Yes ☐ No ☐ Planned

- Do you use the assessment entity approach to report read-across?

  ☐ Yes ☐ No ☐ Planned

  If yes, which *assessment entity/entities* have been used?

  ☐ Registered substance as such, name(s): ……..
  ☐ Specific composition/form of the registered substance, name(s): ……..
  ☐ (Group of) constituent(s) in the registered substance, name(s): ……..
  ☐ Transformation of the registered substance, name(s): ……..

- Does your read-across justification follow the recommendations set by RAAF-HEALTH (Health Read-across assessment framework)[7]?

  ☐ Yes ☐ No ☐ Planned

  If yes:

  - What is the selected scenario (1 to 6)? ……..

[6] https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf
[7] https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

- Are all assessment elements for the selected scenario properly addressed?
  ☐ Yes ☐ No
  If no, which one not and why?.....

- Is adequate and reliable supporting information provided to justify the score for each assessment element
  ☐ Yes ☐ No
  If no, which are the elements you faced some difficulties with to provide supporting information? .....
  .....

- Is the potential effect of the counter-ions investigated (in a quantitative or qualitative way)?
  ☐ Yes ☐ No
  If no, why? .....
  .....

- Is the read-across hypothesis clearly formulated **AND** is the quality of the source data fulfilling the criteria on study quality and adequacy listed in Annex XI, section 1.5.
  ☐ Yes ☐ No

  .....

5. General

Most recent update of the dossier (year) for this endpoint: .....

Add any observations/learnings/questions

THANK YOU!!!