ECHA
EUROPEAN CHEMICALS AGENCY

# How to prepare toxicological summaries in IUCLID and how to derive DNELs

## Practical Guide 14

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**Practical guide 14:**
**How to prepare toxicological summaries in IUCLID and how to derive DNELs**

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# 1. INTRODUCTION

In order to demonstrate the safe use of substances, registrants need to fulfil the information requirements as stipulated in Articles 10 and 12 of the REACH Regulation 1907/2006/EC in conjunction with Annexes I, VI, VII-X and XI to this regulation.

This document provides information on how to fill in the toxicological summaries in section 7 of IUCLID and on how to derive DNELs. The DNEL (Derived No Effects Level) is the level of exposure above which humans should not be exposed. There are two levels of toxicological summaries contained in IUCLID:

- Summaries of individual endpoints: A IUCLID endpoint summary (EPS) presents for one toxicological endpoint the information selected for being carried forward to the hazard assessment. It is based on the (robust) study summaries reported for that endpoint (see sections 7.1 to 7.12).
- Summary of toxicological information: The summary of toxicological information (IUCLID endpoint summary "Toxicological information") under section 7 integrates the endpoint specific summaries and presents the conclusion from the hazard assessment for each target group (worker, general population), route of exposure (oral, inhalation, dermal, eyes) and type of effect (long-term or short-term, local or systemic). The conclusion can be expressed as a quantitative threshold (e.g. DNEL or DMEL) or as a qualitative indicator of hazard.

Moreover, this document also explains how the conclusions from the hazard assessment impact the scope of the exposure assessment and type of risk characterisation.

It should be noted that this practical guide does not cover the preparation of robust study summaries and study summaries in IUCLID. For more information, see Practical Guide 3: How to report robust study summaries.

This practical guide does not cover the following assessments:

- Derivation of local dermal DNEL
- DMEL derivation
- Reporting of human data and use of human data for endpoint conclusions
- Endpoint summary for respiratory sensitisation
- Derivation of DNELs for acute systemic toxicity

For more comprehensive guidance on DNEL derivation, please see ***Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health***

# 2. SUMMARY OF REQUIREMENTS FROM REACH ANNEX 1

Annex I of the REACH Regulation defines how the human health hazard assessment should be done. It includes four steps: 1) Evaluation of non-human information 2) Evaluation of human information 3) Classification and labelling and 4) Derivation of DNEL(s).

The evaluation of non-human information comprises:

- The hazard identification for the effect based on all available non-human information.
- The establishment of the quantitative dose (concentration)-response (effect) relationship.

When it is not possible to establish the quantitative dose (concentration)-response (effect) relationship, then a qualitative assessment shall be included.

The choice of the study and dose descriptor to be carried forward in the hazard assessment should be based on the following rules:

- The study with the lowest dose descriptor should usually be chosen. However, several other factors should be taken into account, e.g. the conduct of the study, adequacy, relevance of test species, quality of results, validity of the test.
- If the study with the lowest dose descriptor is not chosen, this should be fully justified.

For identification of DNEL(s) the following should be taken into account:

- The DNEL shall reflect the likely route(s), duration and frequency of exposure.
- For some endpoints (e.g. mutagenicity), the available information may not enable a DNEL derivation.
- It may be necessary – depending on the identified uses (and the expected exposure) to identify different DNELs for each relevant human population.

In deriving DNELs, the following factors should be taken into account:

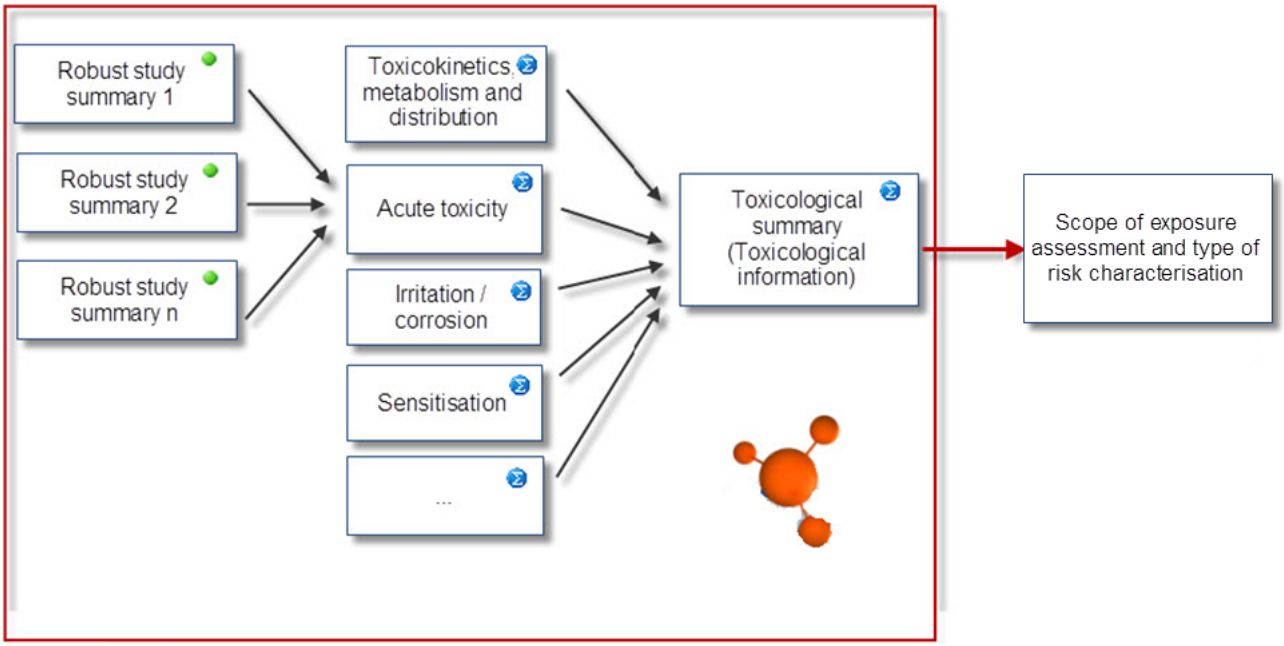
- The uncertainty caused by the experimental data and intra- and interspecies variation.
- The nature and severity of effects.
- The sensitivity of the human population to which the information on exposure applies.

If no DNEL can be derived, then this shall be clearly stated and fully justified.

# 3. WORKFLOW

Figure 1 presents the principal workflow from reporting the available studies endpoint by endpoint to the derivation of the Toxicological Summary in IUCLID for substances amounting to 10 tonnes or more per year, which is then carried forward to exposure assessment and risk characterisation.

**Figure 1: Workflow for the toxicological summaries**




1. The process starts with the reporting of the robust study summaries in the IUCLID endpoint study records. This step has been described in Practical Guide 3: How to report robust study summaries.

2. Then, if possible, one robust study summary (i.e. one IUCLID endpoint study record) is chosen to be used as a reference in the endpoint summary. However, if needed, all robust study summaries for a specific endpoint can be taken into account and referred to in the endpoint summary. The endpoint summary should also include an evaluation of the whole database, a discussion on findings and reasoning for the classification/non-classification.

3. Finally, information from all endpoint summaries is brought together in the (overall) toxicological summary. The hazard conclusions are made including either DNEL or DMEL derivations or qualitative hazard conclusions. Depending on the hazard conclusions, the scope of exposure assessment and the type of risk characterisations is determined.

# 4. FROM ROBUST STUDY SUMMARIES TO ENDPOINT SUMMARY

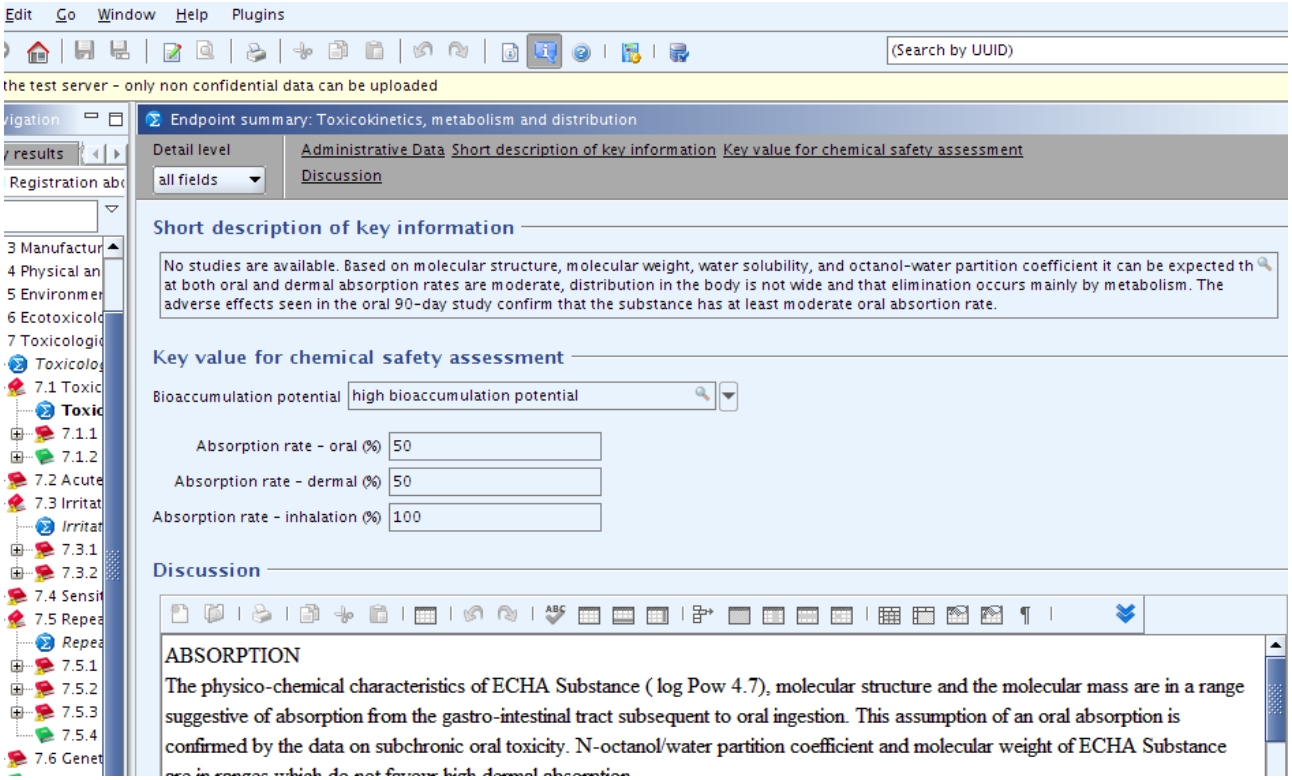
In the following sections, the registrant is guided on how to complete the fields related to each toxicological endpoint summary that may be used to derive hazard conclusions.

## 4.1 Toxicokinetics, metabolism and distribution (7.1)

This IUCLID endpoint summary includes:

- a free text field to provide a short description of the key information available;
- key values on the level of potential bioaccumulation and key values on absorption for the chemical safety assessment (CSA);
- a discussion field to provide further explanation and justifications on the choice of the key values.

**Figure 2: Example from IUCLID endpoint summary for toxicokinetics**




A description of the different fields available in the endpoint summary: Toxicokinetics, metabolism and distribution is given below:

### 4.1.1 Short description of key information

In this text field, the main study information for absorption, distribution, metabolism and excretion, or observations based on physicochemical properties should be described.

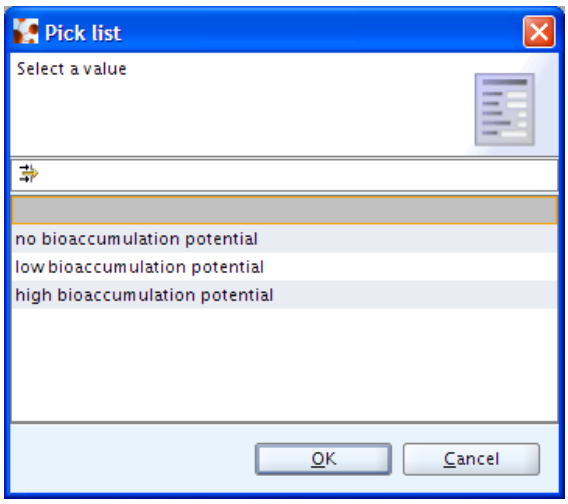
### 4.1.2 Key value for chemical safety assessment

Under this section, the key values on bioaccumulation and absorption rates should be given. This information is used for example in the context of route-to-route extrapolation or for discussing the potential internal dose in the CSA.

#### 4.1.2.1 Bioaccumulation potential

The concluding entry on bioaccumulation potential can be entered by selecting one of the available pick list entries (see figure below).

**Figure 3: IUCLID pick list for bioaccumulation**




The information is usually based on physicochemical properties (log Kow, molecular structure, and molecular weight) and on metabolism (if information is available).

The rationale for the indicated value can be explained in the discussion field below.

#### 4.1.2.2 Absorption rates

The information is usually based on physicochemical properties (log Kow, molecular structure, and molecular weight).

### 4.1.3 Discussion

The interpretation of the results should be done in this section. This includes for example:

- a discussion on the potential data gaps;
- the relevance of the results for the risk assessment. For example, the extent to which the results from an animal study are relevant for human health.

## 4.2 Acute toxicity (7.2)

This IUCLID endpoint summary includes for each route of exposure the following elements:

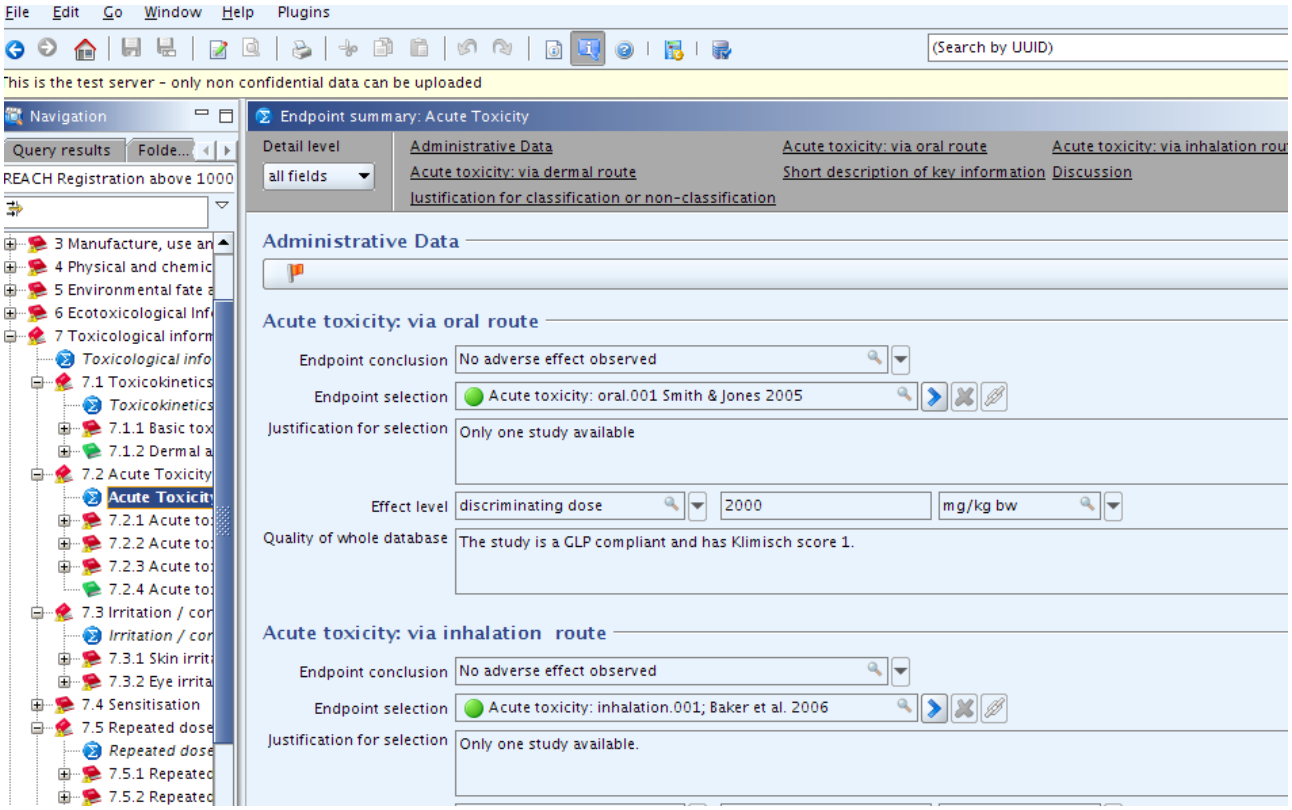
- a pick list to report the conclusion for this endpoint;
- a link to the selected study records (robust study summaries) supporting the conclusion;
- a free text field for the justification for the selection of this study;
- a type of dose descriptor (from pick list) and a value for the effect level identified in that study;
- a free text field to characterise the quality of the whole database for this endpoint.

The following text fields are available to provide consolidated information across the three

routes:

- a free text field to describe the key information extracted from the robust study summaries;
- a free text field to add further explanation and argumentation on the conclusions drawn for this endpoint (Discussion);
- a free text field to compare the endpoint summary with the classification and labelling criteria, in order to justify the classification or non-classification.

**Figure 4: Example from a IUCLID endpoint summary for acute toxicity**

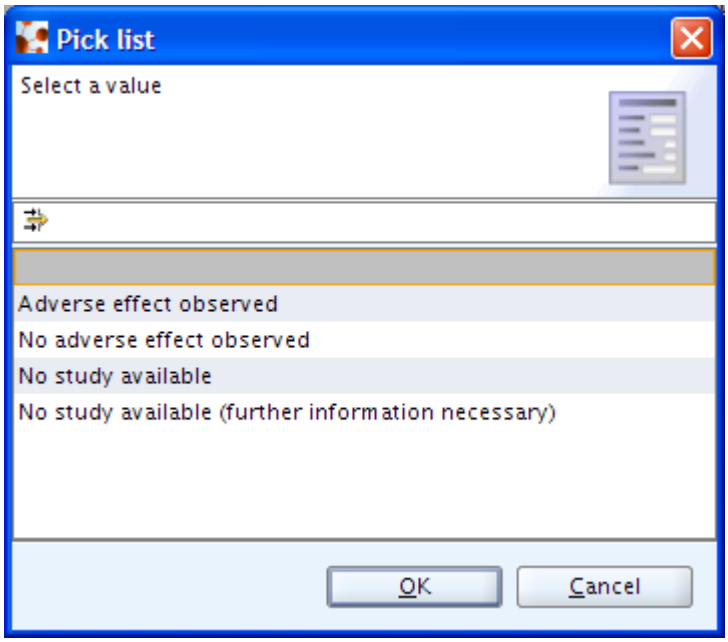



For all three endpoints (oral, inhalation and dermal acute toxicity), an "endpoint conclusion" should be selected. The endpoint conclusion should be based on the mortality of the animals. The nature and reversibility of severe effects other than mortality should be considered.

### 4.2.1 Endpoint conclusion

The pick list available for the endpoint conclusion is:

**Figure 5: IUCLID for endpoint conclusion for acute toxicity**




The following table gives an overview of the different options available in IUCLID.

| Endpoint Conclusion Options | When Option is Appropriate |
|---|---|
| Adverse effects observed | If mortality or severe effects were observed in any of the studies. (It should be noted that animals which are humanely killed due to compound-related distress and pain should be recorded as compound related deaths). |
| No adverse effects observed | If a study is available and if no animal(s) died or no severe effects were observed at limit dose level |
| No study available | Give justification |
| No study available (further information necessary) | Not relevant for acute toxicity since no testing proposal is needed to perform Annex VII or VIII studies |

### 4.2.2 Endpoint selection (robust study summary selection)

A link to the robust study summary on which the endpoint summary conclusion is based may be selected here. Through this link, the original source of information remains traceable for the subsequent assessment and reporting steps. The study that gives rise to the highest concern should be chosen. In principle, human data should be used when available. However, a reliable dose descriptor is rarely available based on human data.

The following factors, among others, must be taken into account when the robust study summary is selected: 1) quality of the study, e.g. Klimisch score, 2) duration of the study, 3) whether or not the study is GLP compliant. Available epidemiological data are preferred provided that they are reliable and relevant.

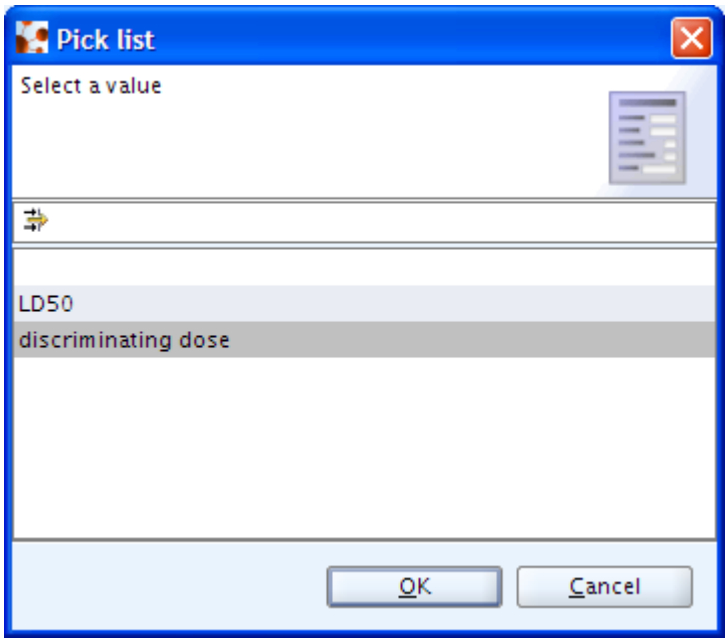
### 4.2.3 Justification for selection

The justification for selection is needed especially if the study (robust study summary) with the lowest dose descriptor is not selected. The justification could include for example that the study with the lowest dose descriptor is of low quality or that the effect observed is not relevant for humans. Justification should always be given if no robust study summary is

chosen for an endpoint summary.

### 4.2.4 Effect level

**Figure 6: IUCLID pick list for effect level of acute toxicity**




LD50 (LC50 for inhalation) should usually be chosen. If no adverse effects were observed, the effect level equals the limit dose.

### 4.2.5 Quality of whole database

The following factors should be considered as they may have an impact on the hazard assessment:

- To what extent does the available information as a whole meet the tonnage driven data requirement of REACH (the completeness of the database)?
- Reliability and consistency across different studies: the quality of the testing method should be taken into account, the size and statistical power of the study design, biological plausibility, dose-response relationships and statistical testing.

### 4.2.6 Short description of key information

The main findings should be presented here.

### 4.2.7 Discussion

The interpretation of the results should be given in this section. This includes for example:

- Discussion on the potential data gaps
- Relevance of the results for the risk assessment. For example, the extent to which the results from an animal study are relevant for human health.

### 4.2.8 Justification for classification or non-classification

The endpoint summary should be compared against the classification criteria. The reasons for fulfilling or not fulfilling the classification criteria should be presented.

Please note that the classification itself is reported in section 2 of IUCLID.

## 4.3 Irritation/corrosion (7.3)

This IUCLID endpoint summary includes for each route of exposure the following elements:

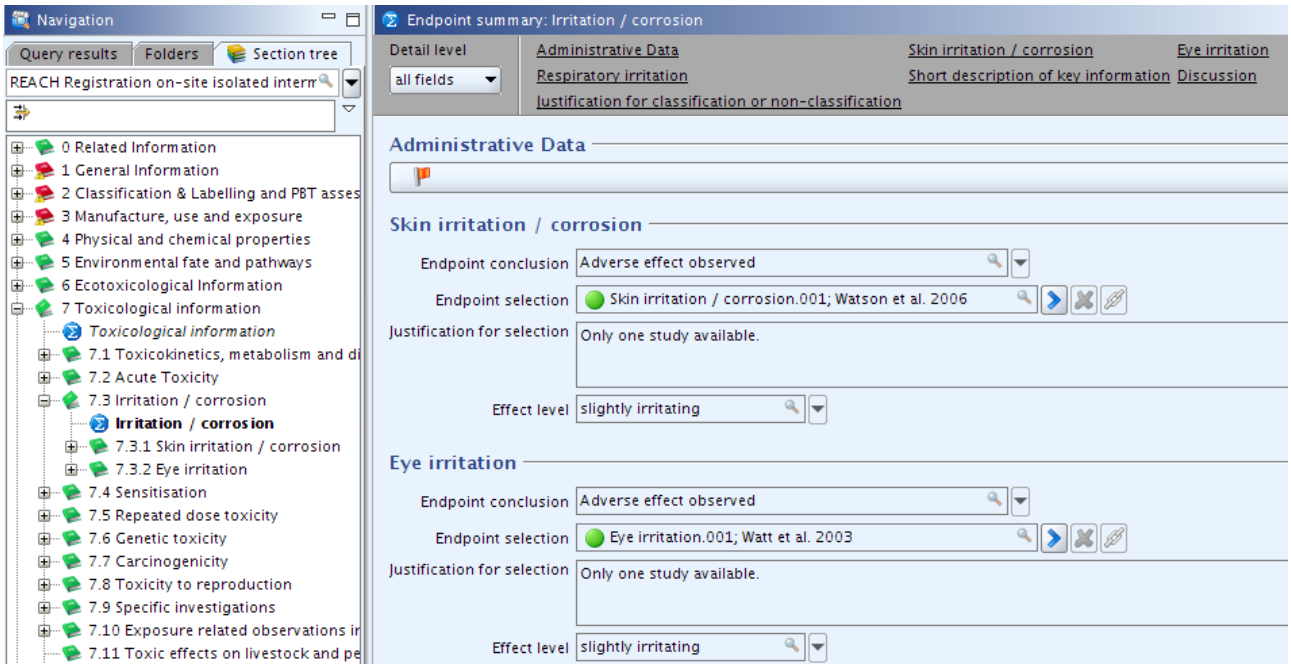
- a pick list to report the conclusion for this endpoint;
- a pick list to indicate the level of effect in a qualitative manner.
- For skin and eye irritation/corrosion the following elements are additionally available:
- a link to the selected study records (robust study summaries) supporting the conclusion;
- a free text field for the justification of the selection of the study.

The following text fields are available to provide consolidated information across the three routes:

- a free text field for a short description of the key information extracted from the robust study summaries
- a free text field to add further explanation and argumentation on the conclusions drawn for this endpoint (Discussion)
- a free text field to compare the endpoint summary with the classification and labelling criteria, in order to justify the classification or non-classification.

**Please note: respiratory irritation is not covered in this section.**

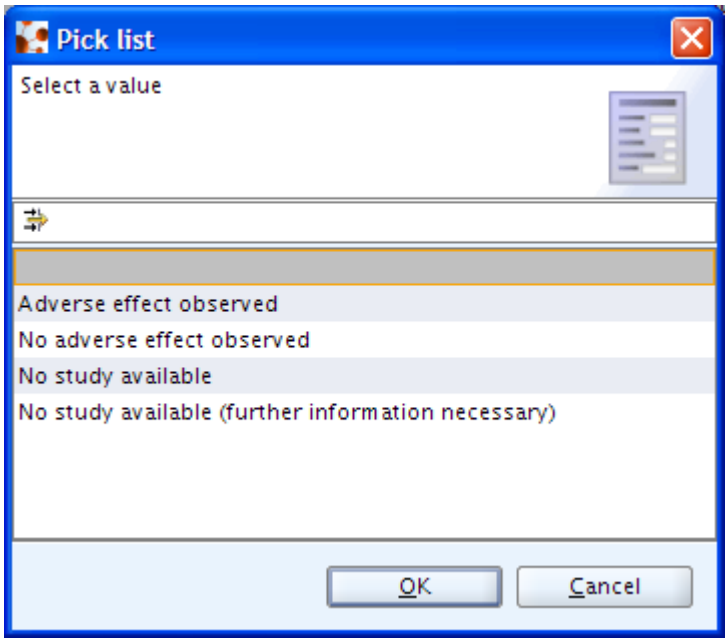
**Figure 7: Example from a IUCLID endpoint summary for irritation**



### 4.3.1 Endpoint conclusion

The pick list available for the endpoint conclusion is:

**Figure 8: IUCLID pick list for endpoint conclusion**




The following table gives an overview of the different options available.

| Endpoint Conclusion Options | When Option is Appropriate |
|---|---|
| Adverse effects observed | The substance meets the classification criteria for irritation/corrosion/serious eye damage |
| No adverse effects observed | The substance does not meet the classification criteria for the respective endpoint |
| No study available | Give justification |
| No study available (further information necessary) | Not relevant for skin/eye irritation/corrosion since no testing proposal is needed to perform Annex VII or VIII studies |

### 4.3.2 Endpoint selection (robust study summary selection)

A link to the robust study summary on which the endpoint summary conclusion is based may be selected here. Through this link, the original source of information remains traceable for the subsequent assessment and reporting steps. The study that gives rise to the highest concern should be chosen. In principle, human data should be used when available. However, a reliable dose descriptor is rarely available based on human data.

The following factors, among other things, must be taken into account when the robust study summary is selected: 1) quality of the study e.g. Klimisch score, 2) duration of the study, 3) whether or not the study is GLP compliant. Available epidemiological data is preferred provided that they are reliable and relevant.

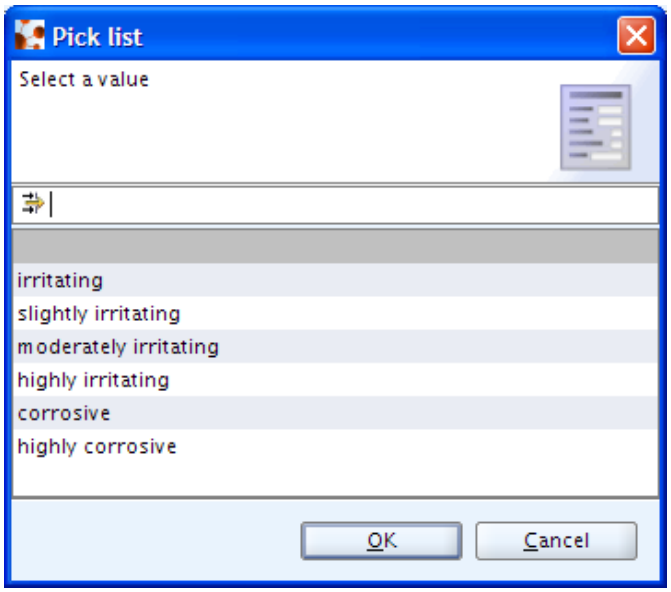
### 4.3.3 Justification for selection

The justification for selection is needed especially if the study (robust study summary) with the lowest dose descriptor is not selected. Justification could include, for example, that the study with the lowest dose descriptor is of low quality or that the effect observed is not relevant for humans. Justification should always be given if no robust study summary is chosen for an

endpoint summary.

### 4.3.4 Effect level

**Figure 9: IUCLID pick list for effect level of skin / eye irritation / corrosion**




The effect level should only be selected if the substance meets the classification criteria for corrosion/irritation. If the substance is to be classified in Category 1A, 1B, or 1C for skin and Category 1 for eyes, the effect level "corrosive" should be chosen. If the substance is classified in Category 2 (both skin and eyes), the effect level "irritating" should be chosen.

### 4.3.5 Short description of key information

The main findings from the selected studies should be presented here.

### 4.3.6 Discussion

The interpretation of results should be given in this section. This includes for example:

- Discussion on the potential data gaps.
- Relevance of the results for the risk assessment. For example, the extent to which the results from an animal study are relevant for human health.

### 4.3.7 Justification for classification or non-classification

Here the endpoint conclusions should be compared against the classification criteria. The reasons for fulfilling or not fulfilling the criteria should be given. Please note that the classification itself is reported in section 2 of IUCLID. Please also note that for the irritation/corrosion endpoint, the conclusions are driven by classification. If applicable, the reasons why adverse effects reported in robust study summaries do not lead to the classification of the substance (and thus "no hazard identified") should be explained.

## 4.4 Sensitisation (7.4)

This IUCLID endpoint summary includes for each route of exposure the following elements:

- a pick list to report the conclusion for this endpoint;

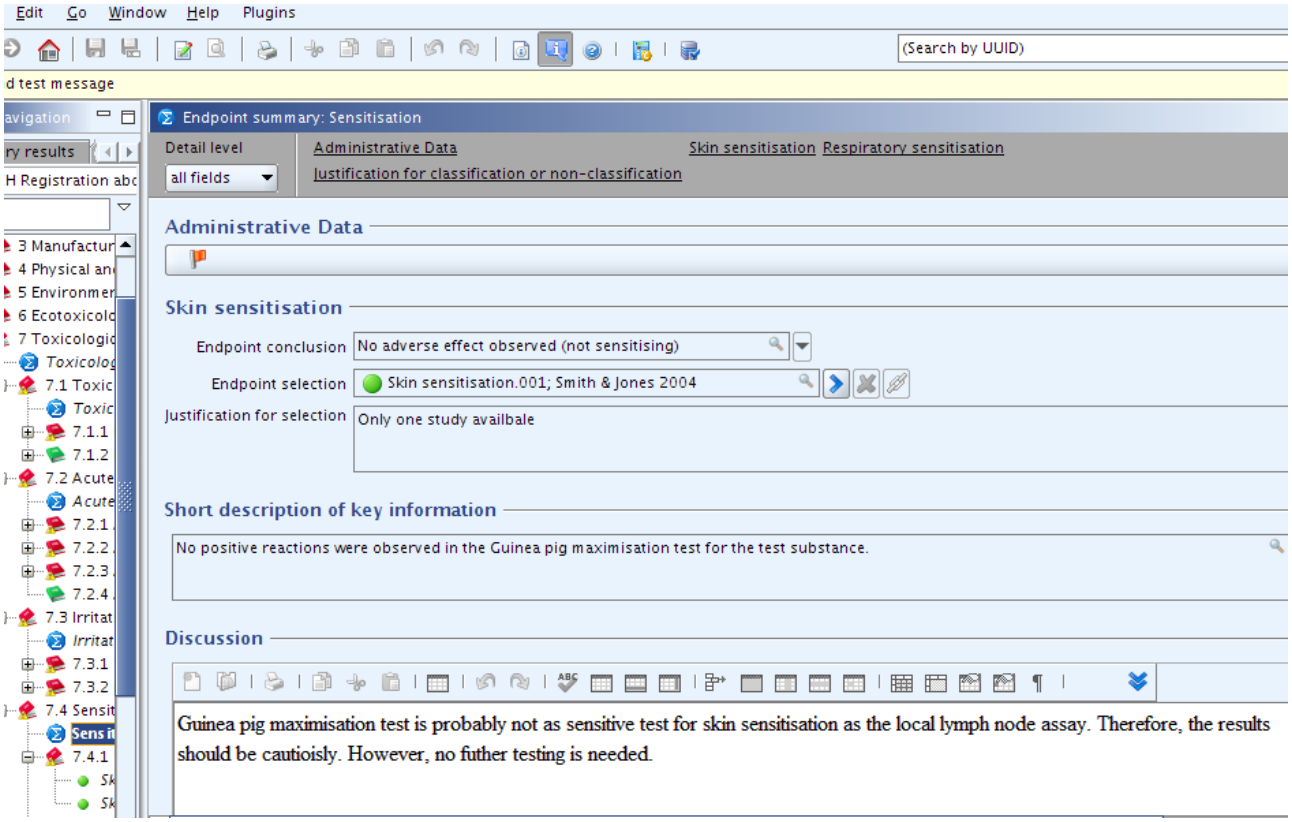
- a link to the selected study record (robust study summary) supporting the conclusion;
- a free text field for the justification of the selection of the study;
- a free text field for a short description of the key information extracted from the robust study summaries;
- a free text field to add further explanation and argumentation on the conclusions drawn for this endpoint (Discussion).

The following text field is available to provide consolidated information across the two routes:

- a free text field to compare the endpoint summary with the classification and labelling criteria, in order to justify the classification or non-classification.

**Please note: this section does not cover respiratory sensitisation**

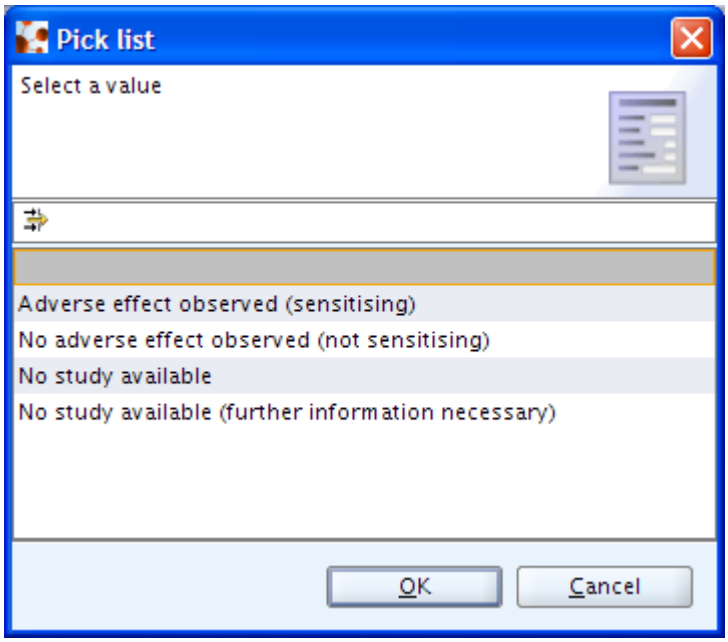
**Figure 10: Example of the IUCLID endpoint summary for skin sensitisation**




### 4.4.1 Endpoint conclusion

The pick list available for the endpoint conclusion is:

**Figure 11: IUCLID pick list for endpoint conclusion for sensitisation**




The following table gives an overview of the different options available.

| Endpoint Conclusion Options | When Option is Appropriate |
|---|---|
| Adverse effects observed | The substance is classified for sensitisation |
| No adverse effects observed | The substance is not classified for sensitisation |
| No study available | Give justification |
| No study available (further information necessary) | Not relevant for the sensitisation since no testing proposal is needed to perform Annex VII or VIII studies |

### 4.4.2 Endpoint selection (robust study summary selection)

A link to the robust study summary on which the endpoint summary conclusion is based may be selected here. Through this link, the original source of information remains traceable for the subsequent assessment and reporting steps. The study giving rise to highest concern should be chosen. In principle, human data should be used when available. However, a reliable dose descriptor is rarely available based on human data.

The following factors, among others, must be taken into account when the robust study summary is selected: 1) quality of the study e.g. Klimisch score, 2) duration of the study, 3) whether or not the study is GLP compliant. Available epidemiological data or other human data are preferred, provided that they are reliable and relevant.

### 4.4.3 Justification of selection

The justification for selection is needed especially if the study (robust study summary) with the lowest dose descriptor is not selected. Justification could include, for example, that the study with the lowest dose descriptor is of low quality or that the effect observed is not relevant for humans. Justification should always be given if no robust study summary is chosen for an endpoint summary.

### 4.4.4 Short description of key information

The main findings should be presented here.

### 4.4.5 Discussion

The interpretation of results should be given in this section. This includes for example:

- Discussion on the potential data gaps.
- Relevance of the results for the risk assessment. For example, the extent to which the results from an animal study are relevant for human health.

### 4.4.6 Justification for classification or non-classification

In this section, the endpoint conclusions should be compared against the classification criteria. The reasons for fulfilling or not fulfilling the criteria should be given. Please note that the classification itself is reported in section 2 of IUCLID.

## 4.5 Repeated dose toxicity (7.5)

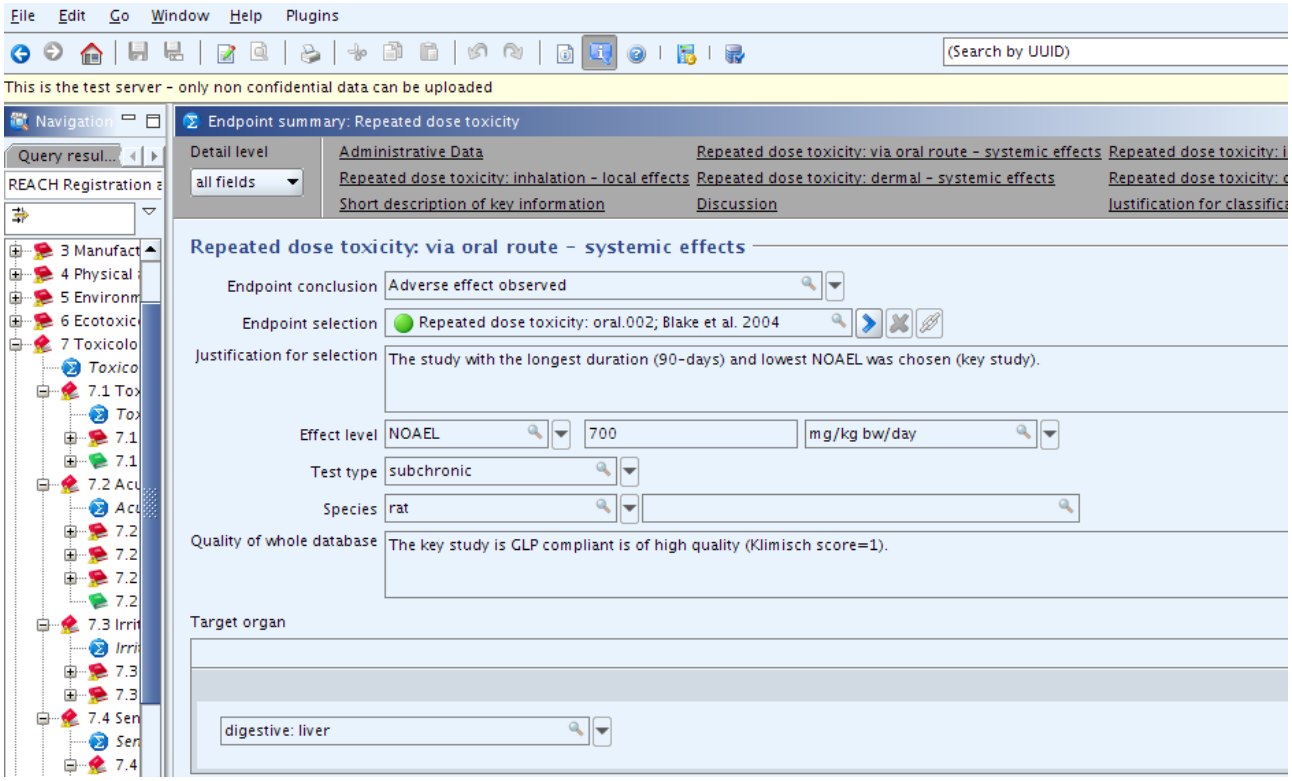
This section also applies to endpoints 7.9.1 Neurotoxicity and 7.9.2 Immunotoxicity. This IUCLID endpoint summary includes the following elements for each route of exposure:

- a pick list to report the conclusion for this endpoint;
- a link to the selected study records (robust study summaries) supporting the conclusion;
- a free text field for the justification of the selection of the study;
- the type of dose descriptor (from pick list) and a value for the effect level identified in that study;
- a pick list for the test type and a pick list for the species in that study;
- a free text field to characterise the quality of the whole database for this endpoint;
- a pick list to flag the target organ of highest concern.

The following text fields are available for providing consolidated information across the three routes (oral, dermal and inhalation):

- a free text field for a short description of the key information extracted from the robust study summaries
- a free text field to add further explanation and argumentation on the conclusions drawn for this endpoint (Discussion)
- a free text field to compare the endpoint summary with the classification and labelling criteria, in order to justify the classification or non-classification.

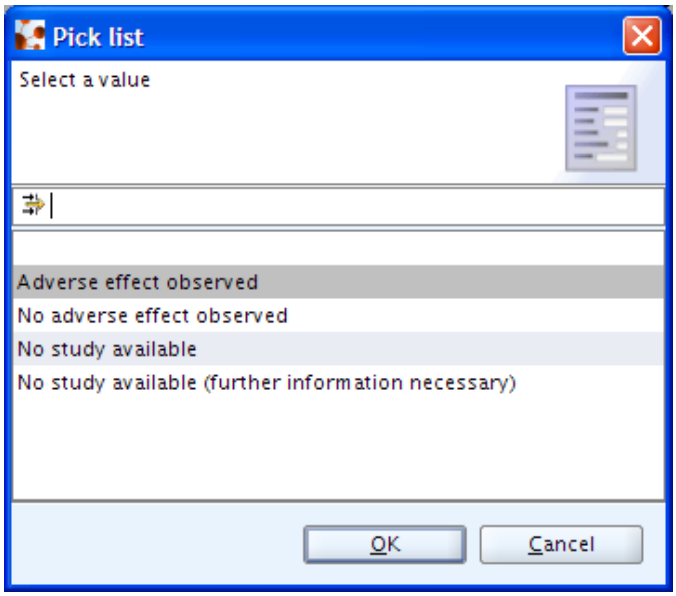
**Figure 12: Example from a IUCLID endpoint summary for repeated dose toxicity**




### 4.5.1 Endpoint conclusion

The pick list available for the endpoint conclusion is:

**Figure 13: IUCLID pick list for endpoint conclusion for repeated dose toxicity**



The following table gives an overview of the different options available.

| Endpoint Conclusion Options | When Option is Appropriate |
|---|---|
| Adverse effects observed | Adverse effects observed at or below limit dose level |
| No adverse effects observed | No adverse effects observed at or below limit dose level |
| No study available | Provide justification |
| No study available (further information necessary) | The dossier contains a testing proposal for repeated dose toxicity (90-day study) |

### 4.5.2 Endpoint selection (robust study summary selection)

A link to the robust study summary on which the endpoint summary conclusion is based may be selected here. Through this link, the original source of information remains traceable for the subsequent assessment and reporting steps. The study giving rise to the highest concern should be chosen. In principle, human data should be used when available. However, a reliable dose descriptor is rarely available based on human data.

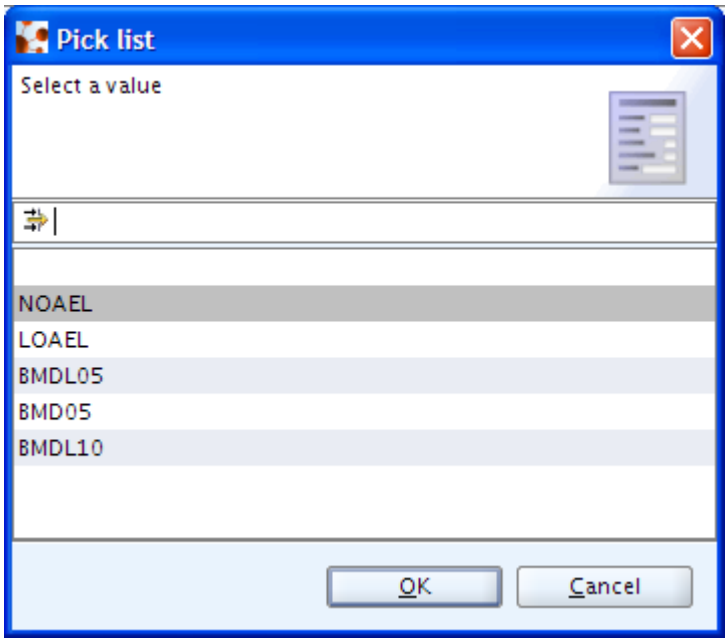
The following factors, among other things, must be taken into account when the robust study summary is selected: 1) quality of the study e.g. Klimisch score, 2) duration of the study, 3) whether or not the study is GLP compliant. Available epidemiological data are preferred provided that they are reliable and relevant.

### 4.5.3 Justification for selection

A particular justification for the selection is needed if a short-term study (e.g. 28-day study) is selected instead of a long-term study (e.g. 90-day study), a low quality study instead of a high quality study or a non-GLP study instead of a GLP compliant study.

### 4.5.4 Effect level

**Figure 14: IUCLID pick list for effect level for repeated dose toxicity**

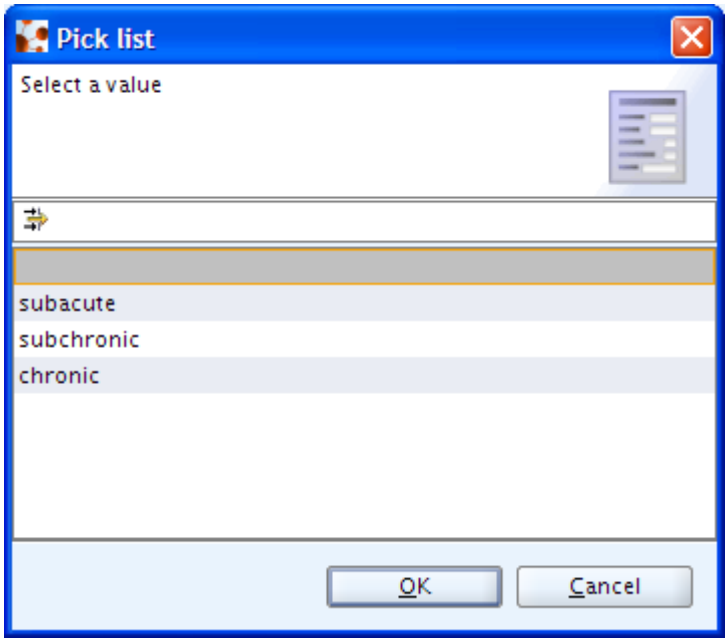



The primary dose descriptor in this endpoint summary is the NOAEL or NOAEC – in some studies also the BMDL (benchmark dose level). The LOAEL or LOAEC should be used only if an NOAEL/NOAEC is not available. If the dose descriptor in the robust study summary is

expressed in ppm/ppb, it should first be converted to ng/m3 or µg/m3 or mg/m3. For inhalation and dermal routes, there is also the possibility to report results on local effects.

### 4.5.5 Test type

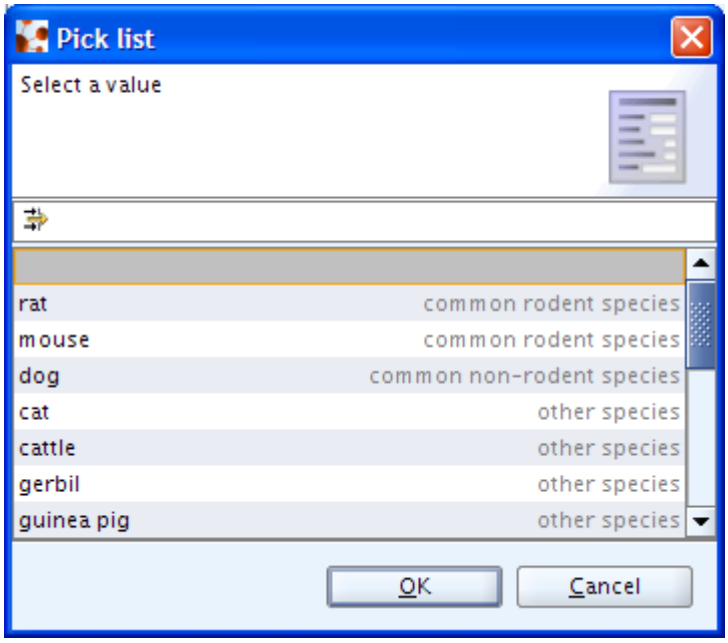
**Figure 15: IUCLID pick list for test type for repeated dose toxicity**




The test type should be the same as in the selected robust study summary. This information is used in DNEL derivation.

### 4.5.6 Species

**Figure 16: IUCLID pick list for species for repeated dose toxicity**




The species selected should be the same as in the selected robust study summary.

### 4.5.7 Quality of the whole database

The following factors should be considered as they may have an impact on the hazard assessment:

- The extent to which the available information as a whole meets the tonnage driven data requirement of REACH (the completeness of the database).
- Reliability and consistency across different studies. Here, the quality of the testing method should be taken into account, the size and statistical power of the study design, biological plausibility, dose-response relationships and statistical testing.

### 4.5.8 Target organ

If there are several target organs, the target organ in which the adverse effects gives rise to highest concern should be selected i.e. the organ that is associated with the dose descriptor.

### 4.5.9 Short description of key information

The main findings should be presented here.

### 4.5.10 Discussion

The interpretation of results should be given in this section. This includes for example:

- A discussion on the potential data gaps.
- The relevance of the results for the risk assessment. For example, the extent to which the results from an animal study are relevant for human health.

### 4.5.11 Justification for classification or non-classification

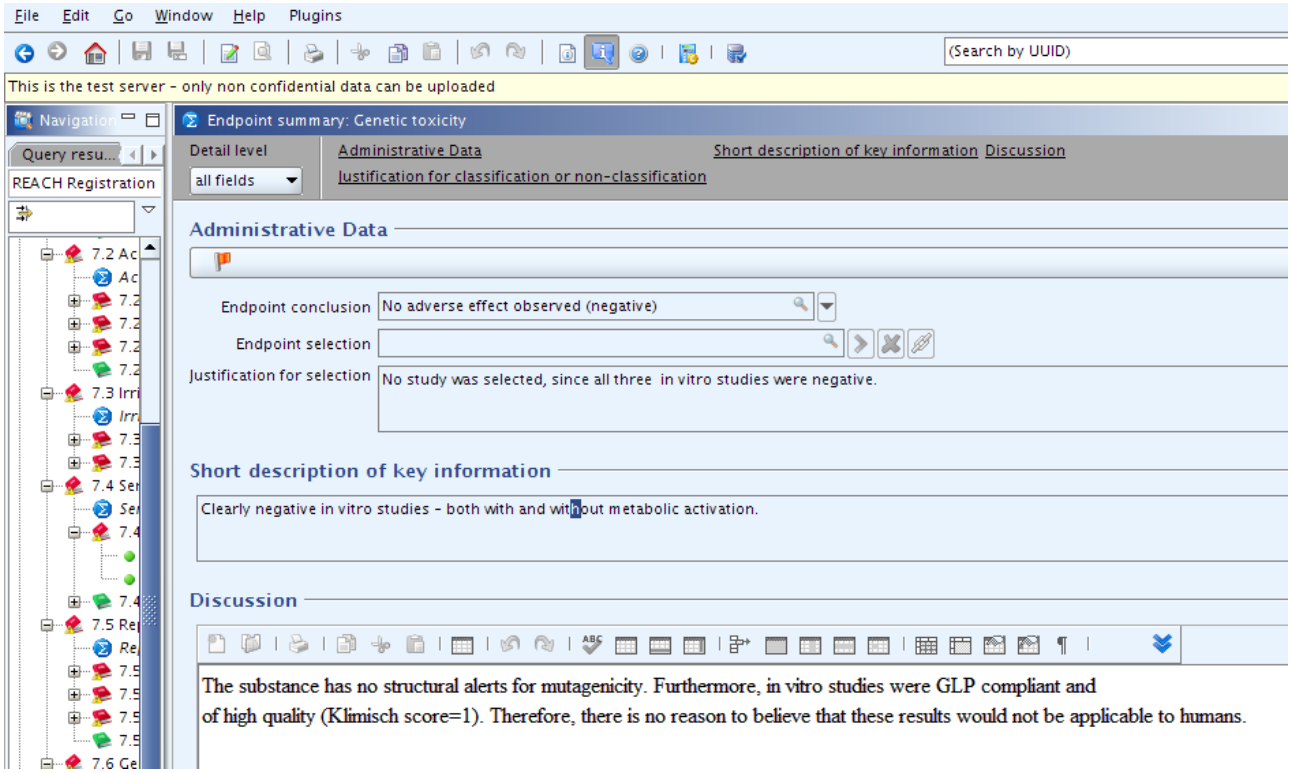
In this section, the endpoint conclusions should be compared against the classification criteria. The reasons for fulfilling or not fulfilling the criteria should be presented. Please note that the classification itself is reported in section 2 of IUCLID.

## 4.6 Genetic toxicity (7.6)

This IUCLID endpoint summary includes the following elements:

- a pick list to report the conclusion for this endpoint;
- a link to the selected study records (robust study summaries) supporting the conclusion;
- a free text field for the justification of the selection of the study;
- a free text field for a short description of the key information extracted from the robust study summaries;
- a free text field to add further explanation and argumentation on the conclusions drawn for this endpoint (Discussion);
- a free text field to compare the endpoint summary with the classification and labelling criteria, in order to justify the classification or non-classification.

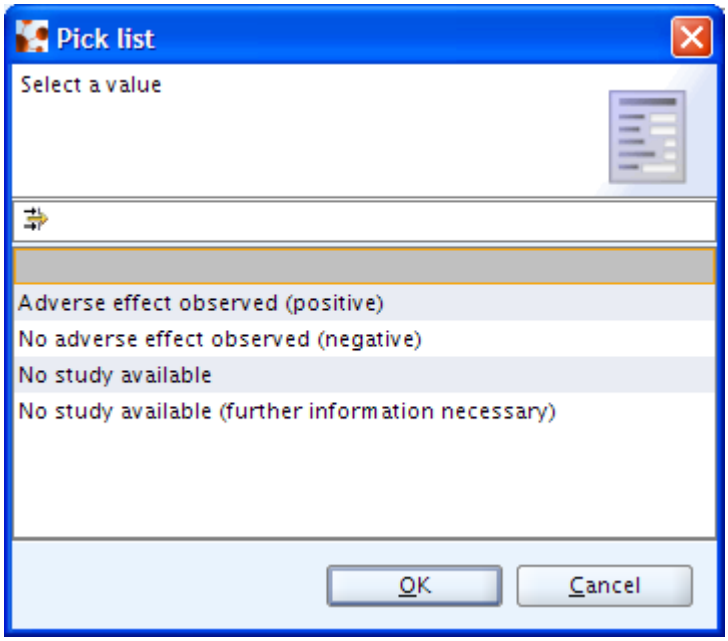
**Figure 17: Example from a IUCLID endpoint summary for genetic toxicity**




### 4.6.1 Endpoint conclusion

The pick list available for the endpoint conclusion is:

**Figure 18: IUCLID pick list for endpoint conclusion for genetic toxicity**



The following table gives an overview of the different options available:

| Endpoint Conclusion Options | When Option is Appropriate |
|---|---|
| Adverse effects observed | The substance is mutagenic, e.g. positive *in vivo* study for any of the endpoints (gene mutation/chromosome aberration). |
| No adverse effects observed | The substance is not mutagenic. Overall conclusion: the substance is not mutagenic |
| No study availabe | Give justification |
| No study available (further information necessary) | The dossier contains a testing proposal for *in vivo* genotoxicity |

### 4.6.2 Endpoint selection (robust study summary selection)

A robust study summary should be selected in situations where there is only one *in vitro* study available (Annex VII substances), or if there is only one positive study (*in vitro* or *in vivo*) in the dossier. In all other cases, there is no need to select robust study summary.

### 4.6.3 Justification for selection

A justification for the selection is needed if the short-term study is selected instead of the long-term study, a low quality study instead of a high quality study or a non-GLP study instead of a GLP compliant study.

### 4.6.4 Short description of key infomation

The main findings should be presented here.

### 4.6.5 Discussion

The interpretation of results should be given in this section. This includes for example:

- A discussion on the potential data gaps.
- The relevance of the results for the risk assessment. For example, the extent to which the results from an animal study are relevant for human health.

### 4.6.6 Justification for classification or non-classification

In this section, the endpoint conclusions should be compared against the classification criteria. The reasons for fulfilling or not fulfilling the criteria should be presented. Please note that the classification as such should be presented in section 2 of IUCLID.

## 4.7 Carcinogenicity (7.7)

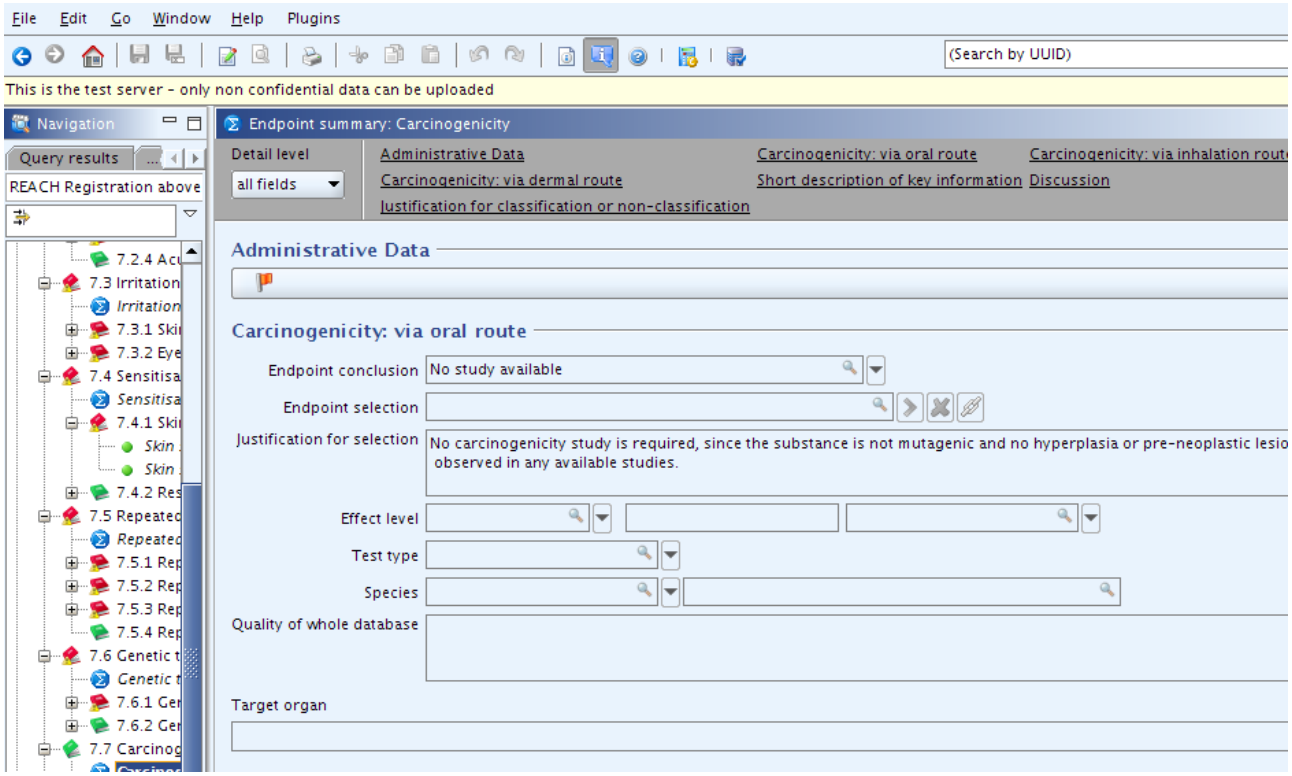
This IUCLID endpoint summary includes the following elements for each route of exposure:

- a pick list to report the conclusion for this endpoint;
- a link to the selected study records (robust study summaries) supporting the conclusion;
- a free text field for the justification of the selection of the study;
- a type of dose descriptor (from pick list) and a value for the effect level identified in that study;
- a pick list for the test type and a pick list for the species in that study;
- a free text field to characterise the quality of the whole database for this endpoint;
- a pick list to flag the target organ of highest concern.

The following text fields are available to provide consolidated information across the three routes (oral, dermal and inhalation):

- a free text field for a description of the key information extracted from the robust study summaries;
- a free text field to add further explanation and argumentation on the conclusions drawn for this endpoint (Discussion);
- a free text field to compare the endpoint summary with the classification and labelling criteria, in order to justify the classification or non classification.

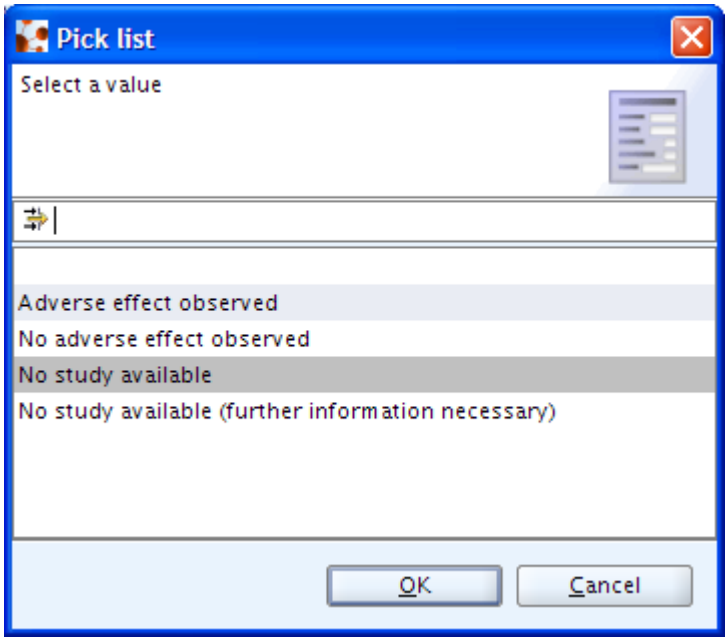
**Figure 19: Example from a IUCLID endpoint summary for carcinogenicity when no study is available**




## 4.7.1 Endpoint conclusion

The pick list available for the endpoint conclusion is:

**Figure 20: IUCLID pick list for endpoint conclusion for carcinogenicity**



The following table explains the different options available.

| Endpoint Conclusion Options | When Option is Appropriate |
|---|---|
| Adverse effects observed | The substance is carcinogenic |
| No adverse effects observed | The substance was not found to be carcinogenic in the available study(ies) |
| No study available | Give justification |
| No study available (further information necessary) | The dossier contains a testing proposal for carcinogenicity |

### 4.7.2 Endpoint selection (robust study summary selection)

A link to the robust study summary on which the endpoint summary conclusion is based may be selected here. Through this link, the original source of information remains traceable for the subsequent assessment and reporting steps. The study giving rise to the highest concern should be chosen. In principle, human data should be used when available. However, a reliable dose descriptor is rarely available based on human data.

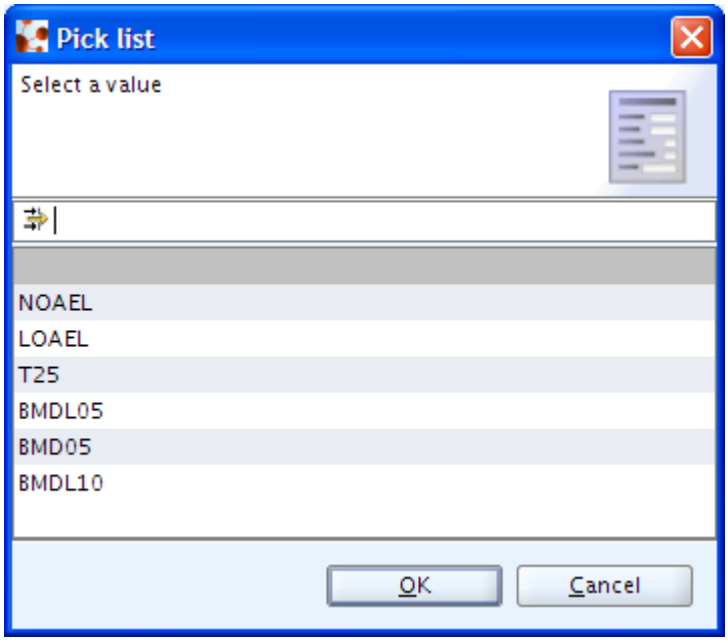
The following factors, among other things, must be taken into account when the robust study summary is selected: 1) quality of the study e.g. Klimisch score, 2) duration of the study, 3) whether or not the study is GLP compliant. Available epidemiological data are preferred, provided that they are reliable and relevant.

### 4.7.3 Justification for selection

A justification for the selection is needed if a short-term study is selected instead of a long-term study, a low quality study instead of a high quality study or a non-GLP study instead of a GLP compliant study.

### 4.7.4 Effect level

**Figure 21: IUCLID pick list for effect level for carcinogenicity**




The selection of the dose descriptor should only refer to carcinogenic effects. Other effects and dose descriptors should be reported in the section “Short description of key information”.

T25 should be selected if it is assumed that there is no threshold for the carcinogenicity. Other dose descriptors are to be selected if a threshold for carcinogenicity has been identified.

### 4.7.5 Test type

Most of the *in vivo* carcinogenicity studies are chronic studies.

### 4.7.6 Species

The species should be the same as that which was reported in the selected robust study summary.

### 4.7.7 Quality of the whole database

The following factors should be considered as they may have an impact on the hazard assessment:

- The extent to which the available information as a whole meets the tonnage driven data requirement of REACH (completeness of the database).
- Reliability and consistency across different studies. Here, the quality of the testing method should be taken into account, the size and statistical power of the study design, biological plausibility, dose-response relationships and statistical testing.

### 4.7.8 Target organ

The organ in which cancer was observed should be specified. If cancer was observed in several organs, the target organ in which the adverse effects gives rise to highest concern should be selected, i.e. the organ that is associated with the dose descriptor.

### 4.7.9 Short description of key information

The main findings should be presented here.

### 4.7.10 Discussion

The interpretation of results should be given in this section. This includes for example:

- a discussion on the potential data gaps;
- the relevance of the results for the risk assessment. For example, the extent to which the results from an animal study are relevant for human health.

### 4.7.11 Justification for classification or non-classification

In this section, the endpoint conclusions should be compared against the classification criteria. The reasons for fulfilling or not fulfilling the classification criteria should be presented. Please note that the classification itself is reported in section 2 of IUCLID.

## 4.8 Toxicity to reproduction (7.8)

This IUCLID endpoint summary includes the following elements for each route of exposure and separately for fertility and for developmental toxicity:

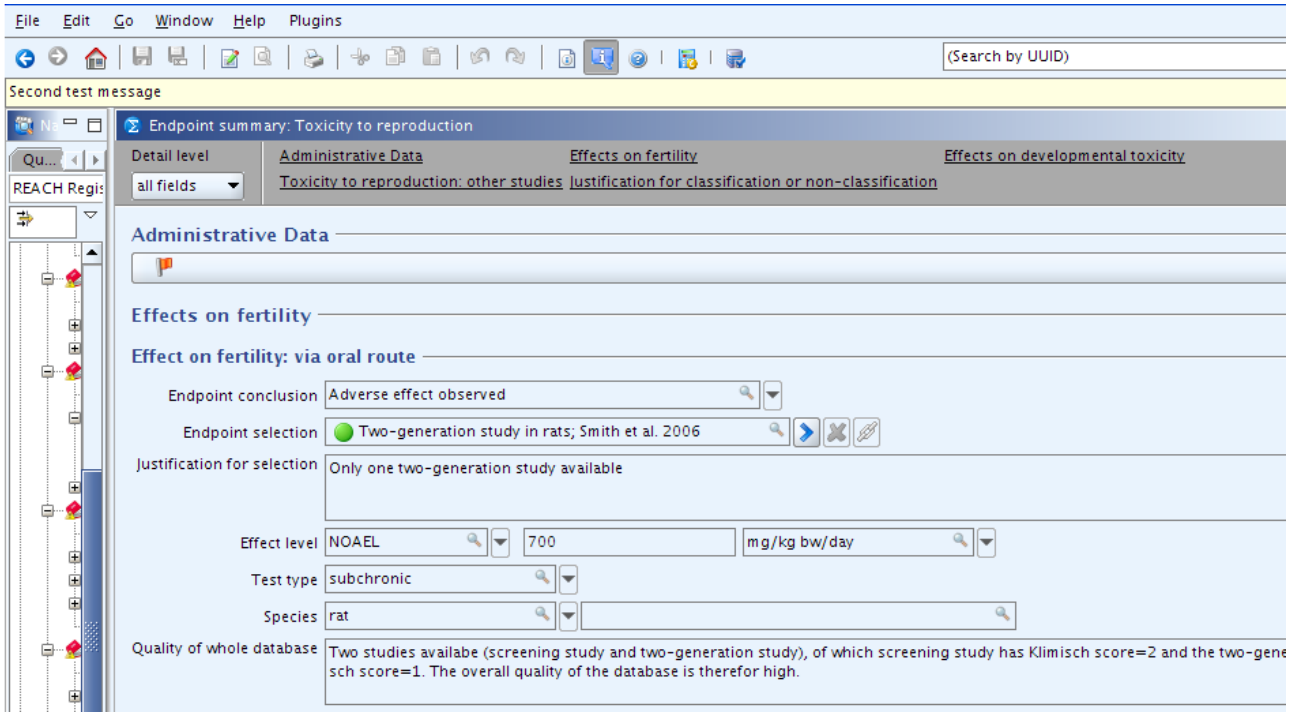
- a pick list to report the conclusion for this endpoint;
- a link to the selected study records (robust study summaries) supporting the conclusion;
- a free text field for the justification of the selection of the study;

- a type of dose descriptor (from pick list) and a value for the effect level identified in that study;
- a pick list for the test type and a picklist for the species in that study;
- a free text field to characterise the quality of the whole database for this endpoint.

The following text fields are available separately for fertility and for developmental toxicity to provide consolidated information across the three routes:

- a free text field for a description of the key information extracted from the robust study summaries;
- a free text field to add further explanation and argumentation on the conclusions drawn for this endpoint (Discussion);
- a free text field to compare the endpoint summary with the classification and labelling criteria, in order to justify the classification or non-classification.

**Figure 22: Example from a IUCLID endpoint summary for toxicity reproductive**




### 4.8.1 Endpoint conclusion

The pick list available for the endpoint conclusion is:

The following table explains the different options available.

| Endpoint Conclusion Options | When Option is Appropriate |
|---|---|
| Adverse effects observed | Adverse reproductive effects observed at or below the limit dose level |
| No adverse effects observed | No adverse reproductive effects observed at or below the limit dose level |
| No study available | Give justification |
| No study available (further information necessary) | The dossier contains a testing proposal for reproductive toxicity (only for Annex IX and X studies) |

### 4.8.2 Endpoint selection

A link to the robust study summary on which the endpoint summary conclusion is based may be selected here. Through this link, the original source of information remains traceable for the subsequent assessment and reporting steps. The study that gives rise to the highest concern should be chosen. In principle, human data should be used when available. However, a reliable dose descriptor is rarely available based on human data.

The following factors, among others, must be taken into account when a robust study summary is selected: 1) quality of the study e.g. Klimisch score, 2) duration of the study, 3) whether or not the study is GLP compliant. Available epidemiological data are preferred, provided that they are reliable and relevant.

### 4.8.3 Justification of selection

A justification for the selection is needed if a short-term study is selected instead of a long-term study, a low quality study instead of a high quality study or a non-GLP study instead of a GLP-compliant study.

### 4.8.4 Effect level

The dose descriptor for the specific effect of reproduction should be reported here. The dose descriptor for other effects (e.g. maternal toxicity) should be reported in the section: Short description of key information.

### 4.8.5 Test type

The two-generation study (OECD 416) and the extended one-generation study (OECD 443) are to be reported as "subchronic" studies. The pre-natal developmental toxicity study and the screening study for reproductive toxicity (OECD 421/422) are to be reported as subacute studies.

### 4.8.6 Species

The species should be the same as that which was reported in the selected robust study summary.

### 4.8.7 Quality of the whole database

Here the following factors should be considered as they may have an impact on the hazard assessment:

- The extent to which the available information as a whole meets the tonnage driven data requirement of REACH (the completeness of the database).
- Reliability and consistency across different studies. Here, the quality of the testing method should be taken into account, the size and statistical power of the study design, biological plausibility, dose-response relationships and statistical testing.

### 4.8.8 Short description of key information

Since there are no separate fields for parental and offspring dose descriptors available for the effect level, both dose descriptors should be reported in this section. This applies both to fertility and developmental endpoints.

### 4.8.9 Discussion

The interpretation of results should be given in this section. This includes for example:

- a discussion on the potential data gaps;
- relevance of the results for the risk assessment. For example, the extent to which the results from an animal study are relevant for human health.

### 4.8.10 Justification for classification or non-classification

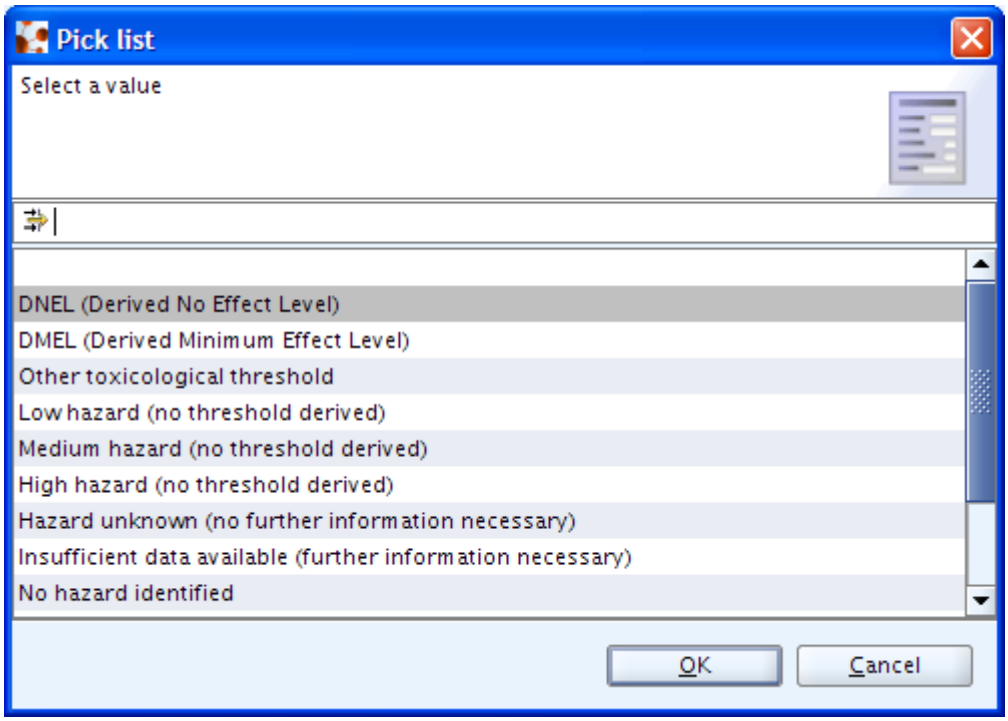
Here endpoint conclusions should be compared against the classification criteria. The reasons for fulfilling or not fulfilling the criteria should be presented. Please note that the classification itself is reported in section 2.

# 5. FROM ENDPOINT SUMMARIES TO SUMMARY OF TOXICOLOGICAL INFORMATION

In the summary of "Toxicological information" under section 7 of IUCLID, all the information from the endpoint summaries are drawn together in order to derive conclusions across all the endpoints. These conclusions refer to the hazards for the particular target groups (worker and general population), to the routes of exposure (oral, inhalation, dermal, eyes) and to the type of effects (acute, chronic, local, systemic). The conclusions include:

- Derivation of **DNELs or DMELs** from the dose descriptors giving rise to the highest concern (usually the lowest NOAEL/LOAEL) per route of exposure and type of effect.
- Derivation of a qualitative description of the level and type of hazard (**low, medium or high hazard**) for threshold effects like irritation or sensitisation if no dose descriptor is available. This also applies for non-threshold effects for which no DMEL can be derived (e.g. mutagenicity).
- The statement "**no hazard identified**" for a route of exposure and type of effect, if no adverse effects have been observed at the limit dose in the reported studies.
- Statements related to the conclusion that the available information does not support a conclusion on the hazards of the substance for a certain route of exposure or type of effect. This may include two assessment cases:
    - **hazard unknown (no further information necessary)**: to be justified, e.g. testing technically not possible and exposure assessment describes the use conditions under which exposure is prevented
    - **insufficient data available (further information necessary)**: e.g. testing proposed.

**Figure 23: IUCLID pick list for hazard assessment conclusion**



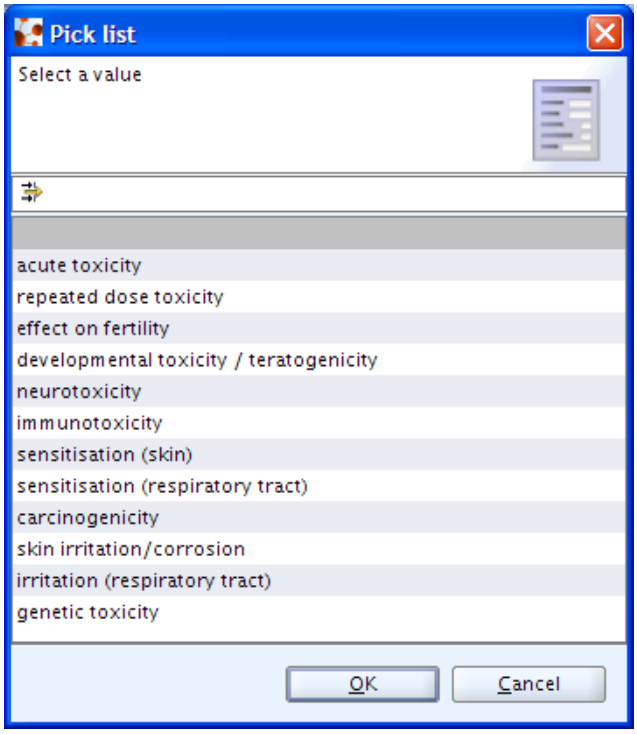

## 5.1 Most sensitive endpoint

There may be cases where both a quantitative and qualitative endpoint hazard conclusions are

available for the same route (and type of effect). The selection of the most sensitive endpoint may not be obvious. In order to ensure consistency between the hazard assessment and the exposure assessment (including risk management measures), the assessor should provide a transparent argumentation on whether the qualitative hazard conclusion or the quantitative hazard conclusion should drive the risk management.

Below is an example of the pick list available in IUCLID:

**Figure 24: IUCLID pick list for most sensitive endpoint**




## 5.2 DNEL derivation

DNEL (Derived No Effects Level) is the level of exposure above which humans should not be exposed. The risk to humans can be considered to be adequately controlled if the estimated levels of exposure do not exceed the appropriate DNEL. Guidance on DNEL derivation is available in ***Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health***

This section gives advice and exemplifies how to report DNELs in most common cases (dose descriptor identified in repeated dose toxicity or reproductive toxicity studies). It does not specifically address the following cases:

- Reporting of DNELs based on human data
- Derivation of DNELs for acute systemic toxicity
- Derivation of local dermal DNELs

### 5.2.1 Endpoints contributing to the derivation of DNELs

According to Guidance R.8, the following DNELs are expected to be derived in a hazard assessment (by default), unless the non-availability of a DNEL is justified. The table below provides an overview of the potential DNELs to be determined:

**Table 1: DNELs that may need to be derived**

| Exposure pattern | Worker | General population |
|---|---|---|
| Acute - inhalation, systemic effects | X | X |
| Acute – dermal, local effects | X | X |
| Acute – inhalation, local effects | X | X |
| Long-term – dermal, systemic effects | X | X |
| Long-term – inhalation, systemic effects | X | X |
| Long-term – oral, systemic effects | Not relevant | X |
| Long-term – dermal, local effects | X | X |
| Long-term – inhalation, local effects | X | X |

DNELs for systemic effects are expressed as mg/kg bw for both dermal and oral routes. For the inhalation routes (both systemic and local) the effects are expressed as mg/m3.

For repeated dose toxicity and for reproductive toxicity it is expected that a DNEL can be derived if the information requirements in Annex VIII to XI are fulfilled. If no adverse effects were observed for any of these endpoints at limit dose level, the "No hazard identified" could be chosen.

If local respiratory effects are observed in the repeated dose toxicity study by the inhalation route, a local DNEL should be derived.

For carcinogenicity, the determination of a DMEL is expected if the adverse effects have no threshold (genotoxic carcinogens). For threshold effects (non-genotoxic carcinogens) DNELs should be derived.

For genetic toxicity, it is usually not possible to derive a DNEL.

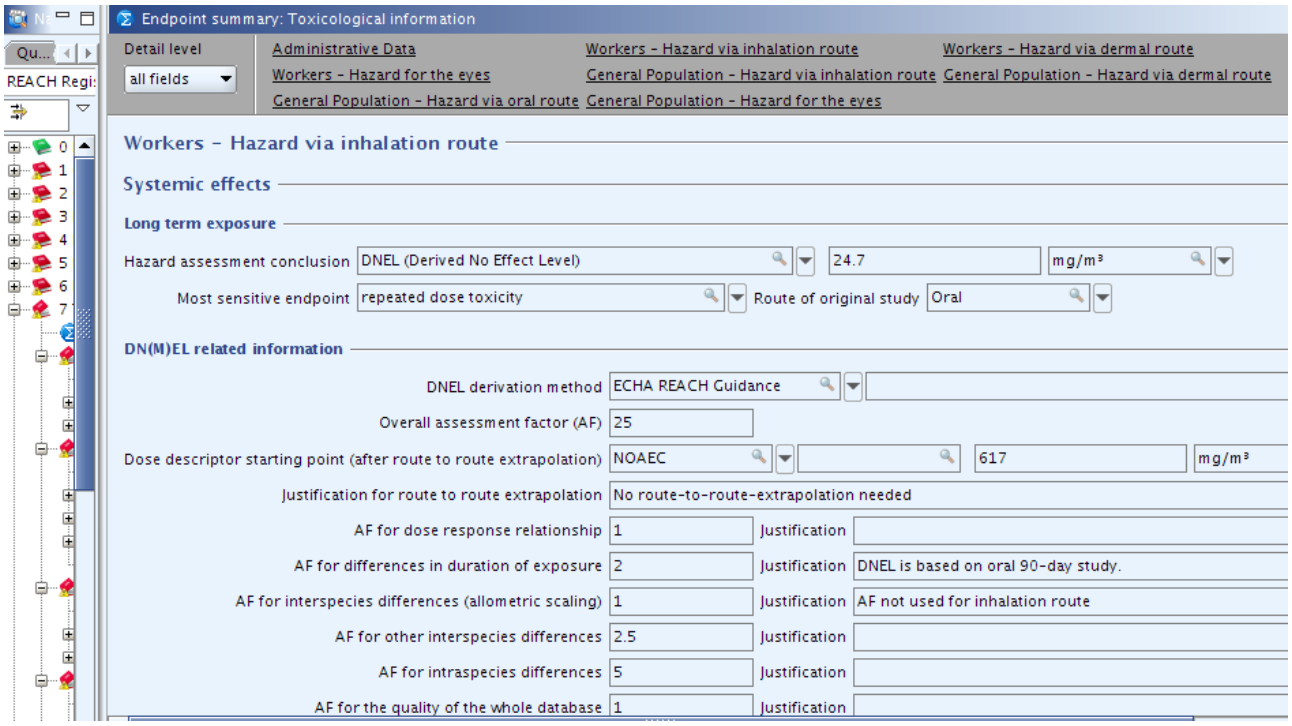
For acute toxicity (systemic), only in some cases may it be possible to derive a DNEL from acute studies.

### 5.2.2 Overview on DNEL Information to reported in IUCLID

In order to ensure transparency in the DNEL derivation, IUCLID enables the reporting of a set of information together with the DNELs for each route of exposure and type of effect. This includes:

- a pick list for the DNEL derivation method and a free text field for the justification if it deviates from the method laid down in ECHA Guidance;
- a value for the overall assessment factor, values for the specific assessment factors and free text fields for the justification of the applied assessment factors;
- values for the dose descriptor starting point (after route-to-route extrapolation where applicable, see 5.2.3.1) and a free text field for explanations on the route-to-route extrapolation;
- a free text field for any further justification and comment.

**Figure 25: Example from a IUCLID toxicological summary ("Toxicological information") for DNEL derivation**




### 5.2.3 DNEL Derivation Method

If an approach is taken other than the method used in ECHA's REACH Guidance, then this should be justified in the section: Justification and comments.

#### 5.2.3.1 Dose descriptor starting point

The DNEL derivation for an endpoint starts from the dose descriptor giving rise to the highest concern. Modification of the original dose descriptor may be necessary to derive the correct starting point for a route for which no study was carried out (route-to-route extrapolation). This approach may be used to derive long-term systemic inhalation/dermal DNELs from the NOAEL of an oral study. Route-to-route extrapolation is not applied for local effects.

Route-to-route extrapolation is normally based on the equations presented in Table 2.

**Table 2: The most usual equations for route-to-route extrapolation**

| | | |
|---|---|---|
| **General population** | Oral to inhalation | Inhalation N(L)OAEC= oral N(L)OAEL*(1/1.15 $m^{3/}$kg/d)*($ABS_{oral}/ABS_{inh.}$) |
| | Oral to dermal | Dermal N(L)OAEC=oral (N(L)OAEL*( $ABS_{oral}/ABS_{dermal}$) |
| | Inhalation to oral | Oral NOAEL=Inhalatory N(L)OAEC/((1/1.15 $m^3$/kg/d)*( $ABS_{oral}/ABS_{inh.}$)) |
| | Inhalation to dermal | Oral NOAEL=Inhalatory N(L)OAEC/((1/1.15 $m^3$/kg/d)*( $ABS_{dermal}/ABS_{inh.}$)) |
| **Workers** | Oral to inhalation | Inhalatory N(L)OAEC= oral N(L)OAEL*(1/0.38 $m^3$/kg/d)*0.67*($ABS_{oral}/ABS_{inh.}$) |
| | Oral to dermal | Dermal N(L)OAEC=oral (N(L)OAEL*( $ABS_{oral}/ABS_{dermal}$) |
| | Inhalation to dermal | Dermal N(L)OAEL= Inhalatory N(L)OAEC/((1/0.38 $m^3$/kg/d)*0.67*($ABS_{dermal}/ABS_{inh.}$)) |

ABS=absorption rate

**Worked Example: The NOAEL from an oral 90-day study is 700 mg/kg bw/day →**

**For workers inhalation NOAEC:** $NOAEC_{corr}=NOAEL_{oral}$*(1/0.38 $m^3$/kg/d)*($ABS_{oral\text{-}rat}/ABS_{inh\text{-}human}$)*(6.7 $m^3$ (8h)/10 $m^3$ (8h)) = 700 mg/kg/d*(1/0.38 $m^3$/kg/d)*(0.5*1)*0.67=**617 mg/$m^3$**

It is assumed that the oral absorption rate is 50% of that of the inhalation absorption. $ABS_{oral/rat}$=oral absorption rate in rats, $ABS_{inh./human}$=inhalation absorption rate in humans.

**For the general population inhalation NOAEC:** $NOAEC_{corr}=NOAEL_{oral}$*(1/1.15 $m^3$/kg/d)*($ABS_{oral\text{-}rat}/ABS_{inh\text{-}human}$) = 700 mg/kg/d*(1/1.15 $m^3$/kg/d)*(0.5*1)=**304 mg/$m^3$**

It is assumed that the oral absorption rate is 50% of that of the inhalation absorption. AB $ABS_{oral/rat}$=oral absorption rate in rats, $ABS_{inh./human}$=inhalation absorption rate in humans.

**Justification for route-to-route extrapolation**

Justification is needed in exceptional cases, e.g. a route specific dose descriptor is available (e.g. NOAEC from 90-day study by inhalation route is available for the inhalation DNEL) but the registrant chooses to use route-to-route extrapolation, or where the dose descriptor giving the lowest DNEL is not chosen.

### 5.2.4 Reporting of assessment factors

A set of assessment factors should be applied to convert the dose descriptor into a DNEL. For an explanation on the background to these assessment factors, please consult ECHA Guidance R.8. Table 3 below provides a summary of the default assessment factors based on ECHA's methodology.

**Table 3: Default assessment factors for DNEL derivation**

| Type of assessment factor | | Default value Systemic effects | Default value Local effects |
|---|---|---|---|
| Interspecies | Differences in metabolic rate/body weight | Allometric scaling[1] | - |
| | Remaining differences | 2.5 | 2.5 |
| Intraspecies | Worker | 5 | 5 |
| | General population | 10 | 10 |
| Exposure duration | Subacute to chronic | 6 | 6 |
| | Subchronic to chronic | 2 | 2 |
| Dose-response | Starting point LOAEL/LOAEC | ≥3 | ≥3 |
| | Starting point NOAEL/NOAEC | ≥1 | ≥1 |

**Please NOTE**: Allometric scaling is usually not applied in the derivation of the inhalation DNEL. In that case, differences in the allometry are assumed to be compensated by differences in the respiration rate.

The explanation that follows gives advice on the different types of assessment factors:

- To take into account the interspecies differences, in most cases (exceptions: DNELs for inhalation and for local inhalation effects) assessment factors for both, allometric scaling and remaining difference, should be used. The assessment factor related to allometric scaling is dependent on the species used in testing. For inhalation, DNELs allometric scaling is usually not applied.
- To take into account intraspecies variations (between humans) for DNELs for workers, the assessment factor is 5 and for the general population it is 10.
- The exposure duration of the test from which the dose descriptor is taken, results in assessment factor of 2 or 6.
- If a LOAEL/LOAEC is used as a starting point for the DNEL derivation, an assessment factor of at least 3 should be used. However, if the adverse effects seen at this dose level were serious, a higher assessment factor should be used.
- If a NOAEL/NOAEC is used as a starting point for the DNEL derivation, the default assessment factor for this parameter is 1. However, if the effect seen at a higher dose level (LOAEL/LOAEC) is serious, then a higher assessment factor should be used. In addition, additional assessment factors can be used, e.g. for read-across.
- The overall assessment factor is the product of all the assessment factors (see example below).

**Worked Example**: The basis for the DNEL is an oral NOAEL (700 mg/kg bw/day) from an oral 90-day study (subchronic) in rat. $NOAEC_{corr}$ for the inhalation route for workers is 617 mg/m3 and for the general population 304 mg/m3 (see above for route-to-route extrapolation).

Tables 4a and 4b exemplify the assessment factors to be applied following the ECHA methodology:

[1] Rat:4, mouse:7, hamster:5, guinea pig:3, rabbit: 2.4, monkey:2, dog: 1.4

**Table 4a: Examples of the use of assessment factors in DNEL derivation (worker)**

| Route and type of effect | Workers |
|---|---|
| Inhalation<br>Long-term<br>systemic | AF for difference in duration of exposure: 2 (*DNEL is based on a 90 day study*)<br>AF for other interspecies differences (allometric scaling not used for inhalation): 2.5<br>AF for intra species differences:5 (for workers)<br><br>Overall Assessment Factor:2*2.5*5=25<br>**DNEL is**: 616 mg/$m^3$ /25=24.6 mg/$m^3$ |
| Dermal<br>Long-term<br>systemic | AF for difference in duration of exposure: 2 (*based on a 90 day study*)<br>AF for interspecies differences: 4 (*rat*)<br>AF for other interspecies differences: 2.5<br>AF for intra species differences:5 (*for workers*)<br><br>Overall Assessment Factor: 2*4*2.5*5=100<br>**DNEL is**: 700 mg/kg bw/day/100=7 mg/kg bw/day |
| Oral<br>Long-term<br>systemic | **Not relevant** |

**Table 4b: Examples of the use of assessment factors in DNEL derivation (consumer)**

| Route and type of effect | General population |
|---|---|
| Inhalation<br>Long-term<br>systemic | AF for difference in duration of exposure: 2 (*DNEL is based on a 90 day study*)<br>AF for other interspecies differences (allometric scaling not used for inhalation): 2.5<br>AF for intra species differences:10 (for general population)<br><br>Overall Assessment Factor:2*2.5*10=50<br>**DNEL is**: 304 mg/m$^3$ /50=6.08 mg/m$^3$ |
| Dermal<br>Long-term<br>systemic | AF for difference in duration of exposure: 2 (*based on a 90 day study*)<br>AF for interspecies differences: 4 ( *rat*)<br>AF for other interspecies differences: 2.5<br>AF for intra species differences:10 (*for gen. pop.*)<br><br>Overall Assessment Factor: 2*4*2.5*10=200<br>**DNEL is**: 700 mg/kg bw/day/200=3.5 mg/kg bw/day |
| Oral<br>Long-term<br>systemic | AF for difference in duration of exposure: 2 (*based on an oral 90 day study*)<br>AF for interspecies differences: 4 (*rat*)<br>AF for other interspecies differences: 2.5<br>AF for intra species differences:10 (*gen. pop.*)<br>AF for remaining uncertainties:<br><br>Overall Assessment Factor: 2*4*2.5*10=200<br>**DNEL is**: 700 mg/kg bw/day/200=3.5 mg/kg bw/day |

# 6. FROM TOXICOLOGICAL SUMMARY TO EXPOSURE AND RISK ASSESSMENT

The following section briefly explains how the conclusions of the hazard assessment, which is reported in section 7 of IUCLID impact on the scope of the exposure assessment and the type of risk characterisation.

## 6.1 Overview on chemical safety assessment types

The building of an exposure scenario is required where hazards have been identified for any of the toxicological endpoints. Depending on the conclusions of the hazard assessment, three types of risk characterisation and corresponding exposure estimation can be distinguished.

Table 5 summarises the elements of the three safety assessment types. The corresponding information on exposure and risk should be reported in Chapter 9 and 10 of the chemical safety report (CSR).

**Table 5: Safety assessment types**

| Risk Characterisation Type | Exposure Scenario (conditions of use) | Exposure estimation | Risk characterisation |
|---|---|---|---|
| Quantitative | Yes | Yes | RCR < 1 |
| Semi-quantitative | Yes | Yes | exposure < threshold + additional arguments to justify that exposure is low enough |
| Qualitative | Yes | may be required to demonstrate minimisation | control strategy corresponds to hazard |

Table 6 further differentiates a number of principal assessment cases for the three types of assessment.

**Table 6: Type of hazard assessment conclusion and the corresponding type of risk characterisation**

| Type of hazard conclusion reported in IUCLID | Related risk characterisation type |
|---|---|
| DNEL (Derived No Effect Level) | Quantitative |
| DMEL (Derived Minimum Effect Level) | Semi-quantitative |
| Other toxicological threshold | Semi-quantitative |
| Low hazard (no threshold derived) | Qualitative |
| Medium hazard (no threshold derived) | Qualitative |
| High hazard (no threshold derived) | Qualitative |
| Hazard unknown (no further information necessary) | Qualitative |
| Insufficient data available: further information necessary | Qualitative - testing proposal |
| No hazard identified | Not required |
| No DNEL required; short term exposure controlled by conditions for long-term | Not required |

## 6.2 No risk characterisation required

Based on the relevant endpoint summaries, it may be concluded that no hazards have been identified for a particular route of exposure and type of effect, and thus no exposure assessment is needed. For example, for acute systemic toxicity all the available information suggests that no adverse effects are observed in the relevant tests. Consequently, no particular assessment of peak exposure is required.

The same outcome may apply for cases where local effects after short-term exposure are observed, and the DNELs for local effects after long term (or repeated) exposure are available as well. In such a case, it is assumed that acute effects are prevented if the exposure remains below the long term DNELs. Hence, no risk characterisation is required for local short-term effects.

## 6.3 Quantitative risk characterisation

Where a DNEL can be derived, a quantitative risk characterisation is required in the chemical safety assessment (CSA). Based on the conditions described in the exposure scenarios, the corresponding exposure estimates are to be derived for the relevant exposure routes. These estimates are then to be compared with the DNELs. Exposure values may need to be derived for i) single event exposure or peak exposure (if relevant) or ii) for long-term exposure (e.g. daily average exposure). Control of risk is demonstrated if the risk characterisation ratio is below 1.

## 6.4 Semi-quantitative risk characterisation

Where a DMEL has been derived instead of a DNEL, a semi-quantitative risk characterisation is required in the CSA. Based on the conditions described in the exposure scenarios, the corresponding exposure estimates should be derived and compared with the DMEL. Demonstrating control of risk includes two elements: (i) the predicted exposure is below the DMEL, and (ii) additional arguments are provided that the control measures described in the exposure scenarios are suitable to minimise exposure.

The same risk characterisation type applies if other toxicological thresholds have been derived, for example DNELs under route a) of Annex XI.3 (exposure-based adaptation). In these cases, a comparison with the estimated exposure is also required together with a case-by-case argumentation on why the exposure is low enough to demonstrate control of risk.

## 6.5 Qualitative risk characterisation

Where no quantitative threshold is available, a qualitative risk characterisation is required in the CSA. This consists of an argumentation why the operational conditions and the risk management measures described in the exposure scenarios are sufficient to avoid the likelihood of the effects. Exposure estimates may be needed to show the level of exposure which is expected under the conditions described in the exposure scenario.

Three principal assessment situations can be distinguished:

- The substance meets the criteria to be classified for local effects and, based on the classification, the level of hazard and the corresponding exposure control strategy can be derived based on ECHA's Guidance on Information Requirements and Chemical Safety Assessment, Part E, Table E-3.1
- The available information is insufficient to make a conclusion on hazards. However, no further information on substance properties is necessary since exposure is unlikely to occur if the conditions reported in the exposure scenarios are implemented. This assessment type is applied for example:

  - if the information requirements are adapted according to Annex XI.3 (route b and c), or
  - if exposure via the inhalation route is assumed to be absent due to the low vapour pressure of the substance or the absence of dust under the conditions of use.

- Further information for the hazard assessment is needed and testing is proposed. The preliminary measures described in the exposure scenarios are expected to sufficiently control the exposure in the absence of results from the tests proposed. This should be justified in the risk characterisation.

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