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Instructions for evaluating the reliability and relevance of ecotoxicity and nano-ecotoxicity studies using the CRED tool (Moermond et al. 2016) and the nanoCRED tool (Hartmann et al. 2017) available at scirap.org.

Introduction

Please use the Excel file available at www.scirap.org. Figure 1 presents the Excel sheet for assessing the reliability and relevance of (nano)ecotoxicity studies. This tool consists of 2 sections: reliability and relevance of the study. The reliability section is divided into specific categories: Test setup, Test compound, Exposure conditions, Statistical design and biological response. The relevance section contains criteria for both biological and exposure relevance.

No.	RELIABILITY	EVALUATION RESULT	COMMENT
	Test setup		
1	Is a guideline method (e.g., OECD/ISO) or modified guideline used? (of minor importance for study reliability)		
2	Is the test performed under GLP conditions? (of minor importance for study reliability)		
3	If applicable, are validity criteria fulfilled (e.g. control survival, growth)?		
4	Are appropriate controls performed (e.g. solvent control, negative and positive control)?		
	Test compound		
5	Is the test substance identified clearly with name or CAS-number? Are test results reported for the appropriate compound?		
6	Is the purity of the test substance reported? Or, is the source of the test substance trustworthy?		
7	If a formulation is used or if impurities are present: Do other ingredients in the formulation exert an effect? Is the amount of test substance in the formulation known?		
	Test organism		
8	Are the organisms well described (e.g. scientific name, weight, length, growth, age/life stage, strain/clone, sex, if appropriate)?		
9	Are the test organisms from a trustworthy source and acclimatized to test conditions? Have the organisms not been pre-exposed to test compound or other unintended stressors?		
	Exposure conditions		
10	Is the experimental system appropriate for the test substance, taking into account its physico-chemical characteristics?		
11	Is the experimental system appropriate for the test organism (e.g., choice of medium or test water, feeding, water characteristics, temperature, light/dark conditions, pH, oxygen content)? Have conditions been stable during the test?		
12	Were exposure concentrations below the limit of water solubility (taking the use of a solvent into account)? If a solvent is used, is the solvent within the appropriate range and is a solvent control included?		
13	Is a correct spacing between exposure concentrations applied?		
14	Is the exposure duration defined?		
15	Are chemical analyses adequate to verify concentrations of the test substance over the duration of the study?		
16	Is the biomass loading of the organisms in the test system within the appropriate range (e.g. < 1 g/L)?		
	Statistical design and biological response		
17	Is a sufficient number of replicates used? Is a sufficient number of organisms per replicate used for all controls and test concentrations?		
18	Are appropriate statistical methods used?		
19	Is a concentration-response curve observed? Is the response statistically significant?		
20	Are sufficient data available to check the calculation of endpoints and (if applicable) validity criteria (e.g., control data, concentration-response curves)?		

***Fig. 1** Categories of criteria in the reliability section of the CRED tool and the nanoCRED tool.*

Evaluating the study

When evaluating the study, indicate how well each criterion is met by selecting an alternative from the drop-down menu to the right of each criterion. In the EVALUATION RESULT column (Fig. 2), choose between “Fulfilled”, “Partially fulfilled”, “Not fulfilled”, “Not reported” and “Not determined”.

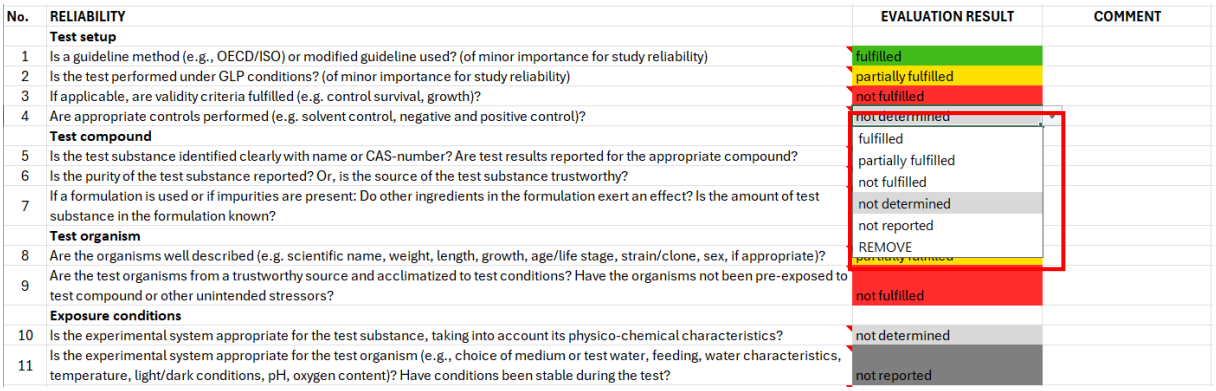

Fig. 2 *Drop-down menu for the criteria in reliability sections of the CRED tool and the nanoCRED tool.*

Guidance from Moermond et al. (2016) for the CRED tool and Hartmann et al. (2017) for the nanoCRED tool is provided by pointing to the criterion with the cursor (the criterion containing the guidance has a red right corner, Fig. 3).

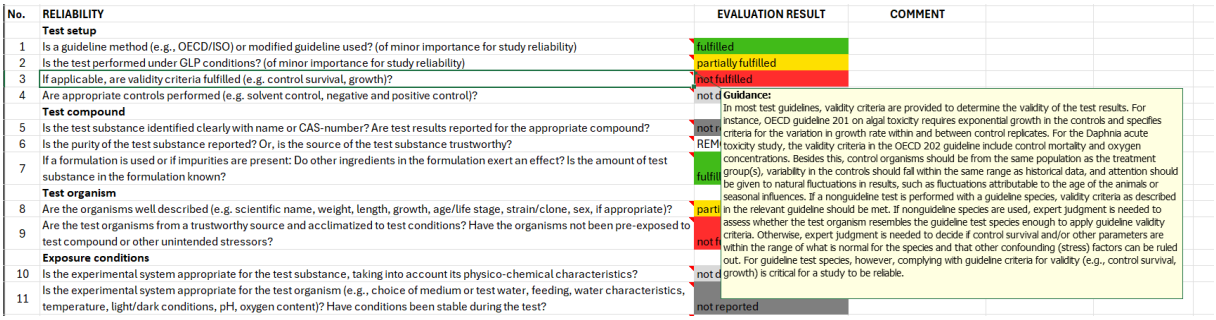

Fig. 3 *Guidance for evaluating each criterion in the CRED tool and the nanoCRED tool.*

Motivations and notes can be added in the "COMMENT" column (Fig. 4).

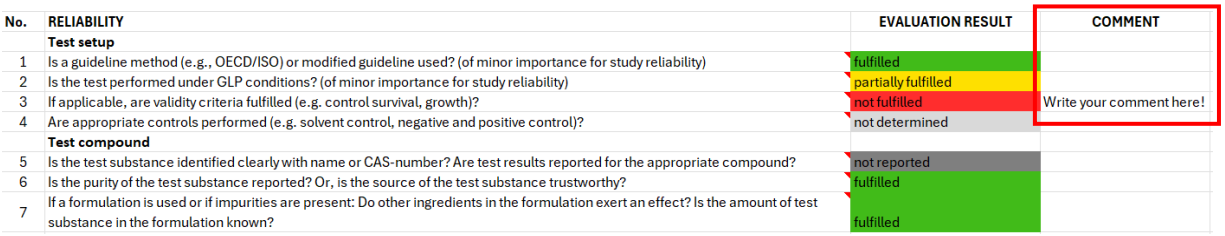

Fig. 4 *Writing a note in the "COMMENT" column.*

Removing criteria

Criteria that are not applicable to the specific study or question being assessed may be removed from the evaluation by clicking “REMOVE”. Motivations for removing criteria can be given in the comment fields. Please note that removing criteria will affect the colour profile and score, and this may be important to consider when comparing studies within the same study design. Criteria from the relevance section cannot be removed.

Interpreting the results

The results of the study assessment are shown below the relevance section of the CRED tool and the nanoCRED tool. In the colour profile (Fig. 5), the evaluations of reliability and relevance are illustrated in bar charts, showing green for fulfilled criteria, yellow for partially fulfilled and red for criteria that were not fulfilled. Criteria that were "not determined" and “not reported” are shown as grey and dark grey, respectively. The bar charts do not include criteria that have been removed.

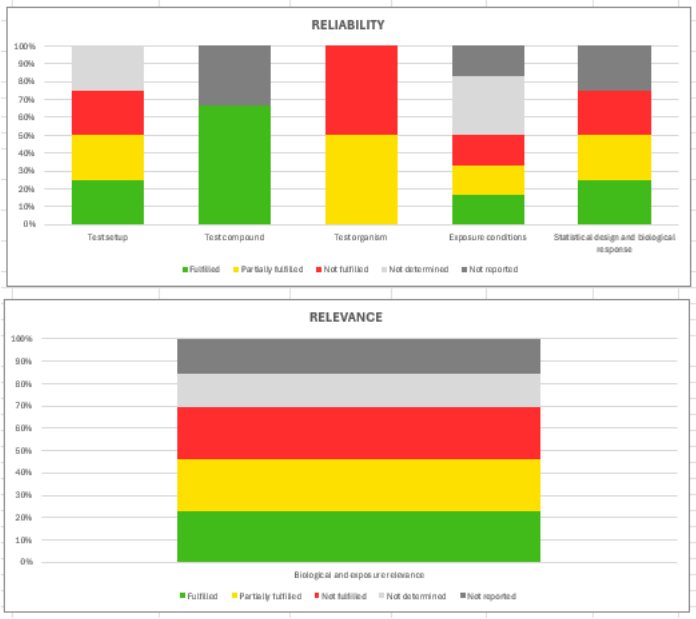

Fig. 5 *The evaluations of reliability and relevance are illustrated in bar charts.*

Assigning the study to reliability and relevance categories

The result of the SciRAP evaluation can be used, in combination with expert judgment, as basis for assigning studies into different reliability and relevance categories. This step is optional. The following categories are suggested:

a. Reliability categories

- *Reliable without restrictions:* All critical reliability criteria for this study are fulfilled. The study is well designed and performed, and it does not contain flaws that affect the reliability of the study.
- *Reliable with restrictions:* The study is generally well designed and performed, but some minor flaws in the documentation or setup may be present. Not reliable: Not all critical reliability criteria for this study are fulfilled. The study has clear flaws in study design and/or how it was performed.
- *Not assignable:* Information needed to make an assessment of the study is missing. This concerns studies that do not give sufficient experimental details and that are only listed in abstracts or secondary literature (books, reviews, etc.) or studies of which the documentation is not sufficient for assessment of reliability for one or more vital parameters.

b. Reliability categories - nanomaterials

- *Reliable without restrictions:* All critical and important reliability criteria are fulfilled or partially fulfilled. The study is well designed, performed and documented. Nanomaterial properties and behaviour in the test system is extensively documented. The experiment has been carried out according to methods that are considered scientifically appropriate for ecotoxicity testing of nanomaterials and where the physicochemical properties of the nanomaterial are considered in the test design. If (when) specific nanomaterial guidance or guidelines exist, the use of these may be considered favourable.
- *Reliable with restrictions:* Most critical and important criteria are fulfilled or partially fulfilled. The study is generally well designed, performed and documented, but some minor flaws in the documentation or setup may be present. Nanomaterial properties and behaviour in the test system is well documented. The experimental design and test method are considered scientifically appropriate for ecotoxicity testing of nanomaterials but may contain some minor flaws in documentation or setup.
- *Not reliable:* Not all critical reliability criteria are fulfilled or partially fulfilled. This mainly concerns studies which have clear flaws in study design and study conduction, and/or where the experimental design and test method are considered not to be scientifically appropriate for ecotoxicity testing of nanomaterials.
- *Not assignable:* Information needed to make an assessment of one or more critical and important criteria is missing. This concerns studies or data from the literature which do not give sufficient experimental details, or reports where the documentation is not sufficient for assessment of reliability for one or more critical parameters.

c. Relevance categories – all substances

- *Relevant without restrictions:* The study is relevant for the purpose for which it is evaluated.
- *Relevant with restrictions:* The study has limited relevance for the purpose for which it is evaluated.
- *Not relevant:* The study is not relevant for the purpose for which it is evaluated.
- *Not assignable:* Studies that do not give sufficient details since the result is presented in abstracts or secondary literature (books, reviews, etc.) or studies of which the documentation is not sufficient for assessment of relevance for one or more vital parameters.

Contact

For questions or comments, please contact Marlene Ågerstrand, Department of Environmental Science, Stockholm University, marlene.agerstrand@aces.su.se.

References

Hartmann NB, Ågerstrand M, Holten Lûtzhoft H-C, Baun A. 2017. "NanoCRED: A transparent framework to access the regulatory adequacy of ecotoxicity data for nanomaterial - Relevance and reliability revisited". NanoImpact, In press.

Kase R, Korkaric M, Werner I, Ågerstrand M. 2016. Criteria for Reporting and Evaluating ecotoxicity Data (CRED): comparison and perception of the Klimisch and CRED methods for evaluating reliability and relevance of ecotoxicity studies. Environmental Sciences Europe 28:7.

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