A Consistent Framework for Literature Reviews Improves Confidence in Environmental Risk Assessment of Pharmaceuticals

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Introduction

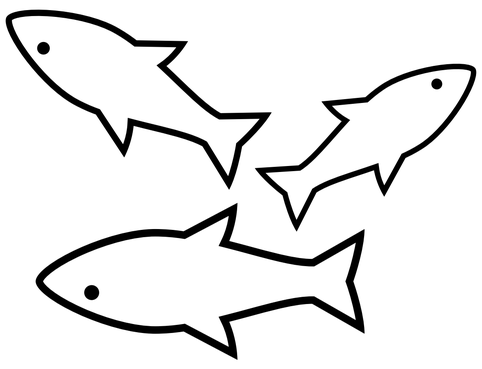
The 2024 European Medicines Agency (EMA) Guideline on Environmental Risk Assessment (ERA) of Human Medicinal Products encourages the use of literature studies as alternatives to requisite empirical studies and to minimize animal testing for active pharmaceutical ingredients (APIs). However, guidance on how to conduct such a literature search is lacking as is clarity on how to use the data resulting from the literature reviews, potentially leading to inconsistent use of the literature data. Hence, a framework has been proposed (see accompanying poster, **Tu384**) to screen for potentially relevant studies and to critically assess their relevance and reliability in a robust and consistent manner. Here, we provide a case study of how literature data on fish ecotoxicity studies can be used in the context of EMA-required ERA and the 3Rs principles to minimize animal use in research by finding alternatives to **R**eplace, **R**educing numbers, and **R**efining procedures, as intended in the Guideline. The focus on fish is to emphasize the need to minimize/avoid animal testing, but the challenges illustrated here apply to all applicable data under EMA-required ERA.

Literature data screening and use scenarios for fish ecotoxicity in EMA-required ERA

See accompanying poster (**Tu384**) for standard literature search criteria/ process for "Information Searching"

Initial literature screening

EMA ERA Guidance indicates to "use all relevant data available" (Section 3.1.4) which implies Approach 1 is preferred, but this is not clear.



Approach 1: All potentially relevant studies

Approach 2: Identify study with lowest endpoint value

Perform data assessment

See accompanying poster (**Tu384**) for the "Data Assessment" process

Perform data assessment

Repeat until most conservative reliable value is identified

Relevant and reliable

Limited relevance and/or reliability

Is data reliable?

NO

YES

Geometric mean or other values from relevant and reliable studies assigned as key value

Where possible use information in "weight of evidence (WoE)" evaluation

Most conservative reliable value assigned as key value

Case A: Robust approach to use all relevant and reliable data

Case B: Relevant studies have limitations for their use, but in a weight-of-evidence approach, can they reliably rule out a need for new fish tests or be used qualitatively to check consistency and plausibility of key studies' results?

Case C: More streamlined approach for data-rich APIs but likely to yield overly conservative toxicity value

Considerations for overall aquatic Predicted No Effects Concentration (PNEC) derivation:

- Does the available data indicate a critical data gap for a trophic level (algae, daphnia, fish)?
- If so, can the data gap be addressed using the WoE from existing literature (e.g., see **Case B** and **Scenario 6**)?

Scenario 1 (Case A)
Applicant 1 conducts a study under Good Laboratory Practices (**GLP** in Table 1) and also uses Approach A, but selects the NOEC from the GLP study
Key result for fish – 1000 µg/L

Scenario 2 (Cases C)
Applicant 2 does not conduct a GLP study but uses Approach 2 and finds the lowest NOEC that is "reliable" (**LIT_2** in Table 1)
Key result for fish – 10 µg/L
Achieves 3Rs objectives

Scenario 3 (Case A)
Applicant 3 does not conduct a GLP study and uses Approach 1 to find "reliable" data (**LIT_1** and **LIT_2** in Table 1)– uses geomean of NOECs
Key result for fish – 22.4 µg/L
Achieves 3Rs objectives

Scenario 4 (Case A)
Applicant 4 conducts a GLP study and applies Approach 1 to find "reliable" data – uses EC10 statistically derived from key literature dataset (**LIT_2** in Table 1)
Key result for fish – 54.6 µg/L

Scenario 5 (Case A)
Applicant 5 conducts a GLP study and used Approach 1 to find "reliable" data – uses geomean of acceptable NOEC data set (**GLP**, **LIT_1**, **LIT-2** in Table 1)
Key result for fish – 79.4 µg/L

Scenario 6 (Case B)
Applicant 6 uses Approach 1 and can only find data of "limited reliability" (**LIT_3** to **LIT_6**) – but avoids additional fish study because they find daphnia or algae are more sensitive
Key result for fish – Not required;
Achieves 3Rs objectives

Table 1. Hypothetical case inspired by fish toxicity dataset for a real API with known mode of action

Study	Study Description	Benchmark (Endpoint)[1]	Value (µg/L)[2]	Data Acceptability Assessment[3]
GLP	GLP OECD 210 Fish Early-Life Stage Toxicity with *Pimephales promelas*	32-d LOEC (hatch, survival, growth)	> 1000	**Relevant and Reliable without restriction**
		32-d NOEC (hatch, survival, growth)	1000	
LIT_1	Non-GLP OECD 210 Fish Early-Life Stage Toxicity with *Oryzias latipes*	30-d LOEC (hatch, survival, growth)	500	**Relevant and Reliable without restriction**
		30-d NOEC (hatch, survival, growth)	50	
LIT_2	60-d non-guideline study with *D. rerio*	60-d LOEC (survival, growth)	100	**Relevant and Reliable with restriction**
		60-d NOEC (survival, growth)	10	
		60-d EC10 (survival, growth)	54.6	
LIT_3	42-d study of mixture toxicity, including this API, with *P. promelas* at 3 exposure levels	42-d LOEC (survival, growth)	> 2.5	**Relevant but of Limited Reliability.** Usable in WoE Approach
LIT_4	21-d study with *Carassius auratus* at 2 exposure levels	21-d LOEC (survival)	> 1000	**Relevant but of Limited Reliability.** Usable in WoE Approach
LIT_5	4-month study with embryonic (and juvenile?) *Danio rerio* at 3 exposure levels	4-mo LOEC (survival, growth, reproduction)	> 5	**Relevant but of Limited Reliability.** Usable in WoE Approach
LIT_6	Full life cycle study of mixture toxicity, including this API with *P. promelas*	LOEC (hatch, development, growth)	> 0.79	**Limited Relevance and Limited Reliability.** Usable in WoE Approach
LIT_7	Non-GLP OECD 210 Fish Early-Life Stage Toxicity with *Cyprinus carpio* with this API and in mixture	32-d LOEC (hatch, survival)	< 10	**Limited Relevance and Not Reliable**

NOTES:
[1] Only ERA-relevant apical endpoints considered; d-days, mo-months, LOEC – the lowest tested concentration showing adverse effects, NOEC – the highest tested concentration showing no adverse effects.
[2] Values qualified with ">" indicates no effects at the maximum exposure tested and thus the LOECs are unbounded.
[3] Data acceptability assessments are preliminary and intended for illustrative purposes only.

Summary

- **This study illustrates multiple scientifically defensible scenarios and data integration approaches, that applicants could plausibly follow in using fish toxicity literature data to support EMA-ERAs.**
- **These various use cases/scenarios can potentially result in inconsistent or even incorrect use of the same literature data and thus result in unnecessary animal or other testing.**
- **To improve confidence in literature-dependent ERAs and testing decisions, a uniform and consistent framework for literature search and data assessments is required to promote appropriate data use and scientifically sound data integration.**

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