#H584

Experiences with a Desk-Based Programme to Determine Endocrine Disruption Potential According to the CLP Regulation

Authors: B.L. Ross[1], M. Matzke[1], P. Remuzat[2], K.B. Paul[1], J. Miller[1], J. Marshall[1], S. Watters[1] and D.S. Carson[1]

Affiliation: [1]Blue Frog Scientific Limited, Edinburgh, United Kingdom; [2]Blue Frog Scientific SAS, Lyon, France

*Corresponding author: bryony.ross@bluefrogscientific.com

WHO/IPCS (2002): "An endocrine disruptor is an exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."

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Introduction

Implementation of new endocrine disruption (ED) hazard classes in the CLP regulation (Regulation (EC) No 1272/2008) and increasing regulatory scrutiny under REACH (EU & UK), the Biocidal Products Regulation (BPR) and the Plant Protection Products Regulation (PPPR) means ED assessment of substances/actives must be proactively addressed to ensure compliance and market access.

Endocrine Disruption (ED), is defined as a substance which meets all of the following criteria:

a. it shows an adverse effect in [an intact organism or its progeny]/[non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;

b. it shows endocrine activity, i.e. it has the potential to alter the function(s) of the endocrine system

c. the substance has an endocrine disrupting mode of action, i.e. there is a biologically plausible link between the adverse effect and the endocrine activity.

Combining expert judgement and key regulatory guidance documents, we developed a pragmatic, stepwise approach to assessment of ED properties based on available or alternative information (Fig. 1).

Data are gathered according to OECD Conceptual Framework level (Fig. 2) & applied to a tiered approach to evaluation.

This approach allows rapid screening, aids in the fulfilment of the requirements under the new CLP hazard classes, avoids additional animal testing, and aligns with state of the art of scientific regulatory science.

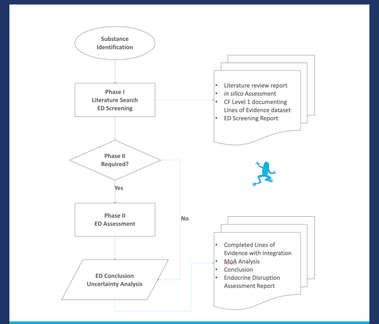

Figure 1: Overview ED assessment Blue Frog Scientific (BFS) approach – based on ECHA/EFSA, 2018 & OECD GD 150a

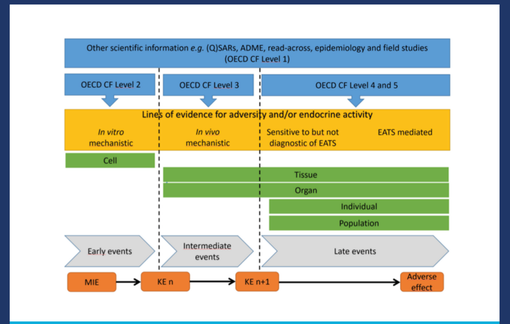

Figure 2: Conceptual Framework Level according to OECD GD 150 (OECD GD150, 2018; DOI:10.1787/9789264304741-en). KE: Key Event; MIE: Molecular Initiating Event. The arrows linking KEs represent KE relationships. It should be noted that borders between CF levels are not absolute in terms of parameters measured or their contribution to the weight of evidence.

Phase I ED Screening

Literature Search
- Literature Search & Sift.
- Literature Evaluation.

DB Searches & In Silico Profiling
- Generate CF Level 1 data & in silico profile.
- Establish initial evidence base for subsequent stages of the ED assessment and ensure consistency with the regulatory conceptual framework.

Screening for Endocrine Relevant Effects
- Existing data subject to targeted review by CF level, with the aim of screening for adverse effects which may be plausibly linked with any EATS or non-EATS endocrine modes of action.
- Screening should consider any relevant impurities or transformation products in line with the cut-off values used for PBT/SVHC assessments.

ED Screening Report
- Summarises available data, interpretation & any conclusions that can be drawn at screening level
- Existing data will be organised into relevant CF levels in the report to assist.

Phase II ED Screening

Study Monitoring
- Provide scientific and organisational support for studies to be conducted at external contract laboratories, should any new testing activities be planned as part of the project strategy.

ED Assessment
- Conduct a full Endocrine Disruption Assessment in accordance with relevant regulatory requirements and specific guidance (e.g. OECD GD 150, ECHA/EFSA 2018 and CLP guidance v5.0 2024).

ED Assessment Report
- Prepare report, documenting available data in detail, interpretation & conclusions on classification.
- Describes data sources & quality; assesses endocrine activity & adversity; integrates lines of evidence & evaluates biological plausibility, clearly distinguishing between empirical findings, mechanistic interpretation, and weight-of-evidence reasoning.

Case Study 01

Screening of Data poor UVCB (REACH)

Dataset: 1 chronic/carcinogenicity study, 2 developmental toxicity studies and 3 historical repeated dose studies.

Limitations: Lack of modern data on the substance → Data gaps identified: testing proposals for studies required to meet REACH registration at Annex X submitted.

Screening outcome:

- EAS modality: no evidence from current dataset. To be re-reviewed on generation of CF level 5 data.
- T modality: Some indication of potential activity, but insufficient evidence to fulfil ED criteria. To be re-reviewed on generation of CF level 5 data.
- Current ED Conclusion: Data lacking.

CF Level 1/2	profiling identified alerts relevant to T modality
CF Level 3	no data
CF Level 4	2-year feeding study (1990s, K2): follicular adenoma, hyperplasia | liver weight increase + hepatocellular hypertrophy Non-guideline gavage teratology study via gavage (1990s, K2): increased post-implantation loss Non-guideline gavage developmental toxicity study (1990s, K4):
CF Level 5	no data

Case Study 02

Data-rich organic chemical with multiple legacy studies (REACH)

Dataset: 5 mechanistic studies (in vitro/in vivo), 4 repeated dose, 1 mutagenicity & 6 reproductive toxicity studies with relevant data.

Limitations: age of studies, lack of parameters considered key for establishing endocrine activity/adversity (e.g. clinical chemistry, hormone measurements),

Screening outcome:

- EAS modality: weight of evidence does not support assignment of ED classification
- T modality, dataset includes i) evidence of endocrine activity, ii) some evidence of adversity in an intact organism or its offspring or future generations, and evidence to support iii) a biologically plausible link between the activity and adverse effect.
- Current ED Conclusion: ED Category 2, with recommendation on potential follow up studies (CF level 3) should registrant wish to pursue a strategy to remove self-classification.

CF Level 1/2	*In silico profiling* - Moderate probability of activity: E,T,S | Low probability: A *In vitro assays* - +ve outcomes for all T assays, indicative of activity Toxcast – strong indication of nuclear receptor interaction
CF Level 3	+ activity (Ix in vivo study)
CF Level 4	Evidence of adversity: Embryo mortality and fertility impacts (adversity) | multiple lines of evidence reporting liver weight increase and microscopic level damage | Some effects reported which could be disregarded upon further review of data (viability of offspring, resorptions, implantations, pregnancy rates, pituitary adenoma/carcinoma) | Indication of pituitary adversity, but without clear dose response Other: Findings relating to pancreas, pituitary and adrenal glands which contributed to wider weight of evidence (1960s, K4): increased liver weight
CF Level 5	Evidence of adversity: Increased testes weight, disregarded due to lack of dose dependency and evidence from HCD | consistent increase in liver weight and associated microscopic changes.

Case Study 03

New chemical registration identifying endocrine relevant effects in OECD 422 Reproductive/Developmental and Repeated Dose toxicity screening study

Dataset: OECD 422 combined repeated dose/ reproductive toxicity screening study.

Limitations: Given the complex, nuanced results produced within this dataset, the power of the group size is a limiting factor (n=10/sex/group). Dose setting requirements for studies to support EU REACH often lead to such pronounced systemic effects it is difficult to discern primary and secondary impacts on reproductive, developmental or ED relevant parameters. This was the case in this study.

Screening outcome:

- EAS modality: no evidence to support assignment of ED classification.
- T modality: complex dataset with some T modality relevant evidence but insufficient to meet criteria for ED classification.
- Current ED Conclusion: Data lacking. A further assessment will follow generation of new CF Level 5 data (testing proposal submitted to support to tonnage update).

CF Level 1/2	*In silico profiling* – Moderate probability T activity | Low probability: EAS
CF Level 3	No data
CF Level 4	Clear evidence of systemic toxicity, severity increasing with dose, driven by dose setting requirements under ECHA Systemic Liver organ weight and cholesterol (but not LDL/HDL) increase, hypertrophy of periportal hepatocytes, and thyroid follicular
CF Level 5	No data

Conclusions

Here, we demonstrate how this structured flow of activities allows us to support pragmatic assessment of complex datasets.

Using this approach, we are able to generate robust, coherent strategy to support conclusions on ED which are in compliance with the new CLP requirements for hazard communication on endocrine disruption, and support longevity of registration for applicants.