How to bring your registration dossier in compliance with REACH

Tips and Hints - Part 5

Dissociation constant

Reko Lehtilä

12 February 2014

REACH Annex IX information requirement

COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
7.16 Dissociation constant	7.16 The study need not be conducted if: • the substance is hydrolytically unstable (half-life less than 12 hours) or is readily oxidisable in water, or • it is scientifically not possible to perform the test for instance if the analytical method is not sensitive enough.

Dissociation constant 1(2)

- Important for the understanding of the environmental partitioning behaviour of a substance.

- It may affect the adsorption of the substance on soils and sediments and absorption into biological cells.

Dissociation constant 2(2)

- May influence the ADME properties of a substance and consequently its effects on human health

  - Absorption, Distribution, Metabolism, and Excretion

Dissociation constant property 1(2)

- Dissociation is the reversible splitting of a substance into two or more chemical species, which may be ionic.

$$RX \leftrightarrow R^{+} + X^{-}$$

- There can be several dissociative groups in a molecule.
  - Examples carboxylic acids RCOOH and amines RNH_2

Dissociation constant property 2(2)

- In the IUCLID technical dossier, the acidic dissociation constant pK_a is reported.

$$pK_a = pH - \log_{10}\left(\frac{[X^-]}{[HX]}\right)$$

Integrated testing strategy (ITS) for dissociation constant

- Dissociation constant properties of the substance should be analysed according to the ITS presented in ECHA Guidance

  - Chapter R.7a: Endpoint specific guidance, Version 2.4 – February 2014, p. 149
  - http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf

ITS starting point; ionisable functional groups present? 1(4)

- If the substance cannot dissociate due to a lack of relevant functional groups, dissociation constant is irrelevant and testing information does not need to be provided.

Tip: You may select the adaptation “study scientifically unjustified” and provide a justification; e.g. “Adaptation is based on Annex IX 7.16 column 2; There are no dissociative groups present in the substance.”

ITS starting point; ionisable functional groups present? 2(4)

- Dissolution of salts from their crystal lattice into individual ions is not intended to be covered by the endpoint dissociation constant.
- Example NaCl

Tip: You may select the adaptation “study scientifically unjustified” and provide a justification; e.g. “Adaptation is based on Annex IX 7.16 column 2; the substance is a salt without any dissociative groups present.”

ITS starting point; ionisable functional groups present? 3(4)

- Salts may be constructed with moieties that have dissociative properties
  - Examples: $BaCO_3$ is predicted to have pKa values 6.05, and 10.64 and ammonium sulphate is predicted to have a pKa value of 8.86 for the ammonium ion

- Therefore, it is not sufficient to have a salt to use column 2 adaptation possibilities for the endpoint. The anion and cation moieties of the salt may still contain dissociative groups.

ITS starting point; ionisable functional groups present? 4(4)

- Examples of ionisable functional groups
  - Carbonates and sulphates are ionisable functional groups
  - Overall molecular properties affect the ionisation potential of a functionality e.g. hydroxyl group in phenol has pK_a 9.95 but in ethanol pK_a 15.9.

Tip: Use QSAR methods to verify possible dissociative properties of the substance.

How to address complex mixtures

- For complex mixtures (e.g. UVCBs*) estimation of the representative constituent's pKa values, if appropriate, should be considered.

- For multi-constituent substances, pK_a values can be reported separately for different constituents.

* UVCB, Unknown, of Variable Composition, or of Biological Origin

Annex IX, section 7.16 Column II adaptation possibilities 1(5)

COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
7.16 Dissociation constant	7.16 The study need not be conducted if: • the substance is hydrolytically unstable (half-life less than 12 hours) or is readily oxidisable in water, or • it is scientifically not possible to perform the test for instance if the analytical method is not sensitive enough.

Annex IX, section 7.16 Column II adaptation possibilities 2(5)

- Column 2 adaptations can be used in IUCLID 5 by following this generic example:

Select the adaptation "*study scientifically unjustified*" and provide a justification; e.g. "*Adaptation is based on Annex IX 7.16 column 2; Substance is hydrolytically unstable*.", further details can be added.

Annex IX, section 7.16 Column II adaptation possibilities 3(5)

- Dissociation constant endpoint property is not required if the substance is hydrolytically unstable (half-life less than 12 hours)

Tip: To use adaptation you should have a hydrolysis study available in the dossier.

Annex IX, section 7.16 Column II adaptations possibilities 4(5)

- Endpoint property is not required if it is scientifically not possible to perform the test for instance if the analytical method is not sensitive enough.
- This adaptation requires a detailed justification on which analytical methods would be required and why these methods are not sensitive enough for the substance.

Tip: Consider QSAR predictions

Annex IX, section 7.16 Column II adaptations possibilities 5(5)

- Low solubility will only prevent performance of the test for substances which remain highly insoluble and undetectable by analytical techniques in the presence of water miscible solvents.

Tip: OECD TG 112 "Dissociation Constants in Water" allows the use of a small amount of a water-miscible solvent to aid dissolution of sparingly soluble substances.

Annex XI adaptations possible?

- Including
  - Weight of evidence WoE (Section 1.2)
  - QSAR (Section 1.3)
  - Read across (Section 1.5)
  - Testing is technically not possible (Section 2)

- Read the criteria carefully, and justify adequately according to these.

- Indicate the precise reference of the legal background for adaptations

Weight of Evidence adaptation, (Annex XI, 1.2)

- At least 2 independent pieces of evidence
- One study record for each piece of evidence
- Endpoint summary: your own conclusion
- ECHA Practical guide 2: How to report weight of evidence: http://echa.europa.eu/documents/10162/13655/pg_report_weight_of_evidence_en.pdf

“Testing is technically not possible” adaptation (Annex XI, section 2)

- Expected to be limited to
  - Highly reactive or unstable substances
  - Substances which in contact with water emit flammable gases

QSAR predictions (Annex XI, 1.3) 1(3)

- If an estimated pKa value suggests that the substance will dissociate significantly at environmentally relevant pH, a test may be required to confirm the result.
  - i.e. if the predicted pK_a is in the range of 2-10, then dissociation occurs in environmentally relevant pH 4-9

QSAR predictions (Annex XI, 1.3) 2(3)

- If the predicted dissociation constant values are <2 or >10, QSAR estimations are sufficient.
  - However the generic QSAR requirements should be fulfilled, e.g. target molecule should be within the applicability domain of the prediction.*

*For calculated values use QMRF (Q)SAR Model Reporting Format, QPRF (Q)SAR Prediction Reporting Format

More info:
http://ihcp.jrc.ec.europa.eu/our_labs/predictive_toxicology/qsar_tools/QRF

QSAR predictions (Annex XI, 1.3) 3(3)

- Reporting should follow the requirements of Annex XI 1.3.
  - ECHA Practical guide 5: How to report (Q)SARs
  - http://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf
- However, in general, pKa values that are measured with a suitable method are preferred to QSAR predictions.

Grouping of substances and read-across approach (Annex XI, 1.5)

- Adequate and reliable documentation
- Scientifically sound arguments
- Assumptions supported with (experimental) data
- ECHA Practical guide 6: How to report read-across and categories: http://echa.europa.eu/documents/10162/13655/pg_report_readacross_en.pdf

Standard guideline

- OECD test guideline 112 (Dissociation constants in water, adopted May 1981)

- Describes three laboratory methods to determine the pKa of a substance.
  - Titration method, spectrophotometric methods and conductometric method

- The three methods are appropriate for particular types of substances as described in the test guideline.

Reporting of the experimental study 1(7)

- All dissociation events should be covered
  - All components and their different dissociation events should be taken into account.
  - QSPR predictions may be used to plan the study.

Reporting of the experimental study 2(7)

- Fill in quantitative fields
  - This helps in ECHA's evaluation and when ECHA disseminates data for the public
- Materials and methods
  - type of method;
  - test guideline followed.
- Test material
  - test material identity.

Reporting of the experimental study 3(7)

- Results and discussion
  - concentration of the substance;
  - test results as pKa-value(s);
  - temperature of the test medium (ºC).

Reporting of the experimental study 4(7)

- Any deviation from the guideline method used (and reasons for it) or any other special consideration should be reported.

- In cases where there is more than one source of data, the endpoint summary under results and discussion should provide a justification for the selection of the key study.

Reporting of the experimental study 5(7)

- Report the constituents of the test material used to demonstrate the relevance of the study for your substance

- Document the validity of the study (i.e. that the validity criteria of the test method are met)

Reporting of the experimental study 6(7)

- Report quantitative results as numeric values
- Document the method used (test conditions, validity etc.)

Reporting of the experimental study 7(7)

- How to report robust study summaries, Practical Guide 3
  - http://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf

Questions?

To the Q&A panel (between 11:00 and 13:30, Helsinki time), or

To the ECHA helpdesk (any time): http://echa.europa.eu/contact/helpdesk-contact-form