Proposal for Utilizing QSARs for the Evaluation of New Chemicals under CSCL

7 November 2019

National Institute of Technology and Evaluation

Evaluation of Biodegradation and Bioaccumulation under CSCL

This is the initially implemented step in the evaluation scheme since the law was enacted (1973).

Since then experimental data for several thousands chemicals has accumulated.

This data has been used for developing a lot of QSAR models around the world.

QSAR prediction data are currently used as reference information in the evaluation under CSCL.

Acceptable Alternative Methods in the Evaluation of New Chemicals under CSCL

Endpoint	Standard Test Criteria	Alternative Methods	
		Criteria	Expert Judgement
Biodegradation	・BOD ≧60 %		・Read-across ・Structural Boundaries
Bioaccumulation	・BCF＜5000 L/kg (BCF＜1000 L/kg)	・logPow＜3.5 ・MW＞800	・Read-across

QSAR?

QSARs Used for Reference Information

Endpoint	Model (Developer)	Prediction Method (Descriptor)	Training Set	Accuracy
Biodegradation	BIOWIN5 (US EPA)	Liner regression (Substructure)	960 Chemicals (CSCL data)	80% (769/960)
	BIOWIN6 (US EPA)	Non-liner regression (Substructure)	960 Chemicals (CSCL data)	82% (790/960)
	CATALOGIC (Bourgas Univ.)	Metabolic simulator (Substructure)	2630 Chemicals (CSCL data)	94% (2466/2630)
Bioaccumulation	BCFWIN (US EPA)	Biliner regression (logP)	527 Chemicals (CSCL data etc.)	r^2 = 0.83 sd = 0.50
	Arnot-Gobas (Simon Fraser Univ.)	Mass balance model (logP, metabolism etc.)	482 Chemicals (CSCL data etc.)	No report
	Baseline model (Bourgas Univ.)	Parabolic regression (logP, metabolism etc.)	826 Chemicals (CSCL data etc.)	r^2 = 0.85

Discussion at the Committee Meeting Organized by METI (2018)

How to evaluate the reliability of a QSAR prediction result?

Evaluators (CSCL Council)

- Not only a QSAR prediction result but also the support evidence showing the reliability of the prediction are required for the evaluation.

Industry

- The type of support evidence to be provided should not be specified by the regulator. Any ideas from the applicant are to be considered in the evaluation.

- We suggest that for the time being the evaluations are conducted by comparing accumulated knowledge with proposals from applicants. The criteria for the acceptance of QSAR prediction results can be defind later.

- We agree to the suggestion as we need to gain the experience for the evaluation of QSAR prediction. However, it is necessary to limit the type of chemicals due to limited evaluation resources for the the time being.

Summary of the Proposal

Endpoint		Biodegradation		Bioaccumulation
CSCL Judgment		Readily biodegradable	Not readily biodegradable	Not highly bioaccumulative
Criteria	Structure	Aliphatic chain compounds (limited functional group)	Polycyclic hydrocarbons	Hydrocarbons Halogenated hydrocarbons
	QSAR prediction	All three QSARs predictions are readily biodegradable.	One of the three QSAR predictions is not readily biodegradable.	All three QSAR BCF predictions are less than each criterion.
	Other	Reliability of the QSAR predictions for the analogue chemicals are provided.		
		Evidence for readily biodegradable (e.g. based on metabolism) is provided.	Evidence for not producing stable metabolites is provided.	logPow (exp.)＜6
Rule		The new chemicals satisfying above criteria and approved by the council can be judged without experimental data.		

https://www.meti.go.jp/meti_lib/report/H30FY/000252.pdf