ECHA Webinar: OECD QSAR Toolbox applications for REACH and beyond

QSAR Toolbox for the Evaluation of Small Production Volume New Chemical Substances under Chemical Substances Control Law in Japan

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Introduction

In 2020 an assessment flow chart for biodegradation and bioaccumulation has been introduced in the confirmation process of small volume new chemicals under CSCL (QSAR assessment flow chart)*.

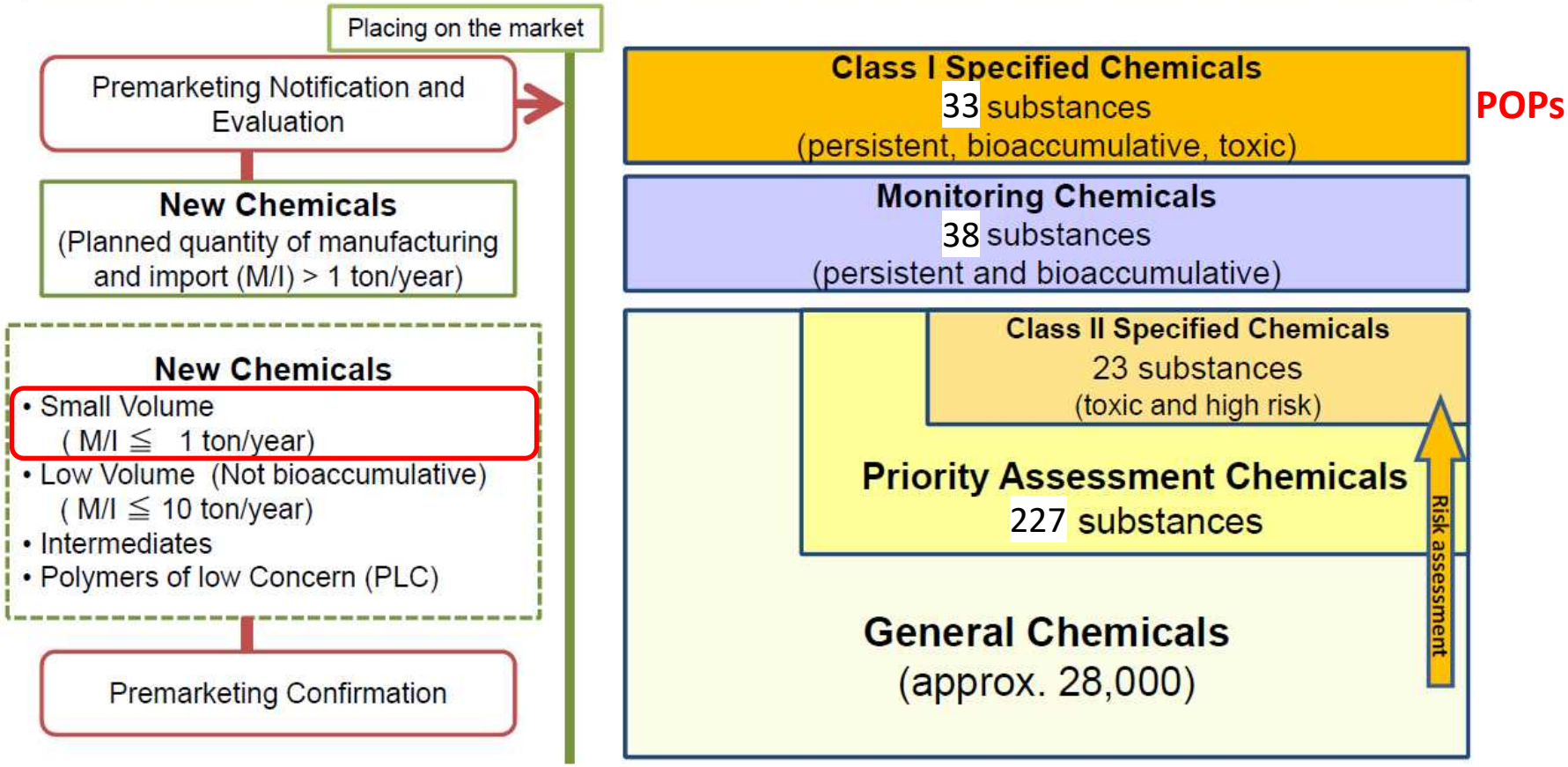
The QSAR assessment flow chart prioritizes chemicals based on the structural similarity to regulated chemicals and prediction results of biodegradation and bioaccumulation by QSAR and read-across.

In this presentation, an overview of the QSAR assessment flow chart and the role of the QSAR Toolbox in the flow chart are introduced.

*https://www.meti.go.jp/policy/chemical_management/kasinhou/files/information/shinki/buntikukakuninflow_english.pdf

Overview of CSCL*

- The Japanese government conducts risk assessment in two phases, both before and after placing the substance on the market.
- Based on the result of risk assessment, the government may take measures to control risks associated with the chemical.



* https://www.meti.go.jp/policy/chemical_management/english/cscl/files/about/01CSCL.pdf

Pre-marketing Notification and Evaluation

Types of Procedure	Volume Limit	Required Test Data	# of Chemicals Notified in 2019
Normal	No limit	Biodegradation Bioaccumulation Human health toxicity Ecotoxicity	224
Low Volume	10 tons/year	Biodegradation Bioaccumulation	133
Small Volume	1 ton/year	Nothing (Confirmation by chemical structure)	25,801

Article 3, paragraph (1), item (v): **Confirmation** "*as determined by already available knowledge, etc., the relevant new chemical substance is not one that poses a risk to human health or cause damage to the inhabitation and/or growth of flora and fauna in the living environment by causing environmental pollution*"

Confirmed → Placing on the market

Not confirmed → Not placing on the market

New Confirmation Process

Previous

Picture of chemical structure

Submit

Visual confirmation

Evaluator

After 2020

mol file

Submit

QSAR Assessment Flow Chart

Prioritized chemicals

Support information

Evaluator

In new confirmation process, notifiers of small volume new chemicals have been required to submit electric data of chemical structure (mol file).

By using the submitted mol file, new confirmation process for small volume new chemicals with the QSAR assessment flow chart has started in 2020.

Approach to Confirmation of the Submitted Chemicals

1. Identify the analogues of the regulated chemicals:

- Class I Specified Chemicals (33 PBT chemicals)
- Monitoring Chemicals (38 PB chemicals)

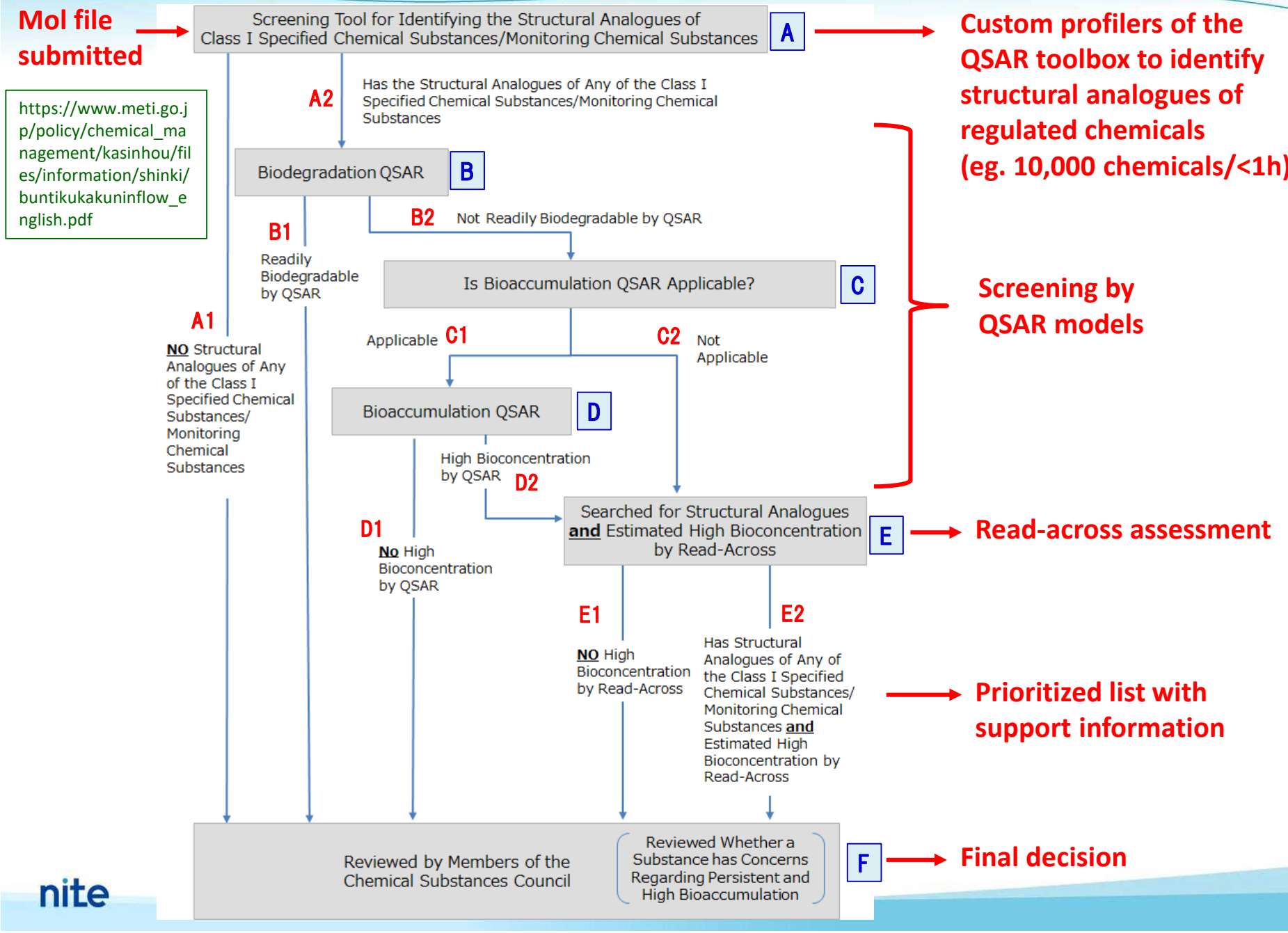
2. Application of QSAR and read-across to the analogues

Table. Class I Specified Chemicals

(https://www.nite.go.jp/chem/jcheck/top.action?request_locale=en)

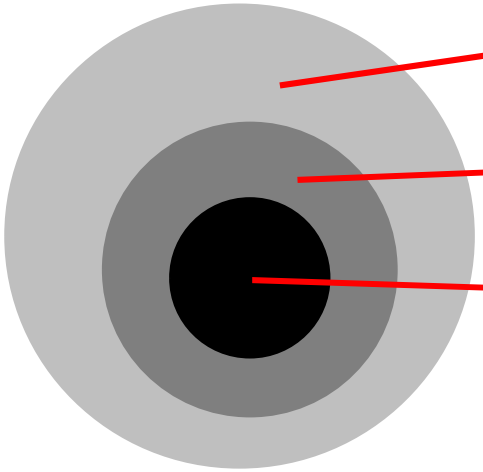
Cabinet Order No. *	Class I Specified Chemical Substance Name
1	Polychlorinated biphenyls
2	Polychlorinated naphthalenes (only those containing 2 or more chlorine atoms in the molecule)
3	Hexachlorobenzene
4	1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-exo-1,4-endo-5,8-dimethanonaphthalene (Synonym: Aldrin)
5	1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-exo-1,4-endo-5,8-dimethanonaphthalene (Synonym: Dieldrin)
6	1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-endo-5,8-dimethanonaphthalene (Synonym: Endrin)
7	1,1,1-Trichloro-2,2-bis(4-chlorophenyl)ethane (Synonym: DDT)
8	1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene, 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-m analogous compounds (Synonym: Chlordane or Heptachlor)
9	Bis(tributyltin) oxide
10	N,N'-Ditolyl-p-phenylenediamine, N-Tolyl-N'-xylyl-p-phenylenediamine, or N,N'-Dixylyl-p-phenylenediamine
11	2,4,6-tri-tert-butylphenol

QSAR Assessment Flow Chart for Small Volume New Chemicals under CSCL



A. Screening Tool for Identifying Analogues of Regulated Chemicals

Custom profiles for the QSAR Toolbox



Level1: Similar to CSCL regulated chemical*
(using substructure/conservative)

Level2: Very similar to CSCL regulated chemical*
(using similarity)

Level3: Match to CSCL regulated chemical*

POPs: Match to POPs chemical other than CSCL regulated chemical*

Chemical structure → **QSAR Toolbox Profilers**

Not categorized
→A1 : No structural analogues of any of the CSCL regulated chemicals

Level 1 or Level 2
→A2 : Has the structural analogues of any of the CSCL regulated chemicals

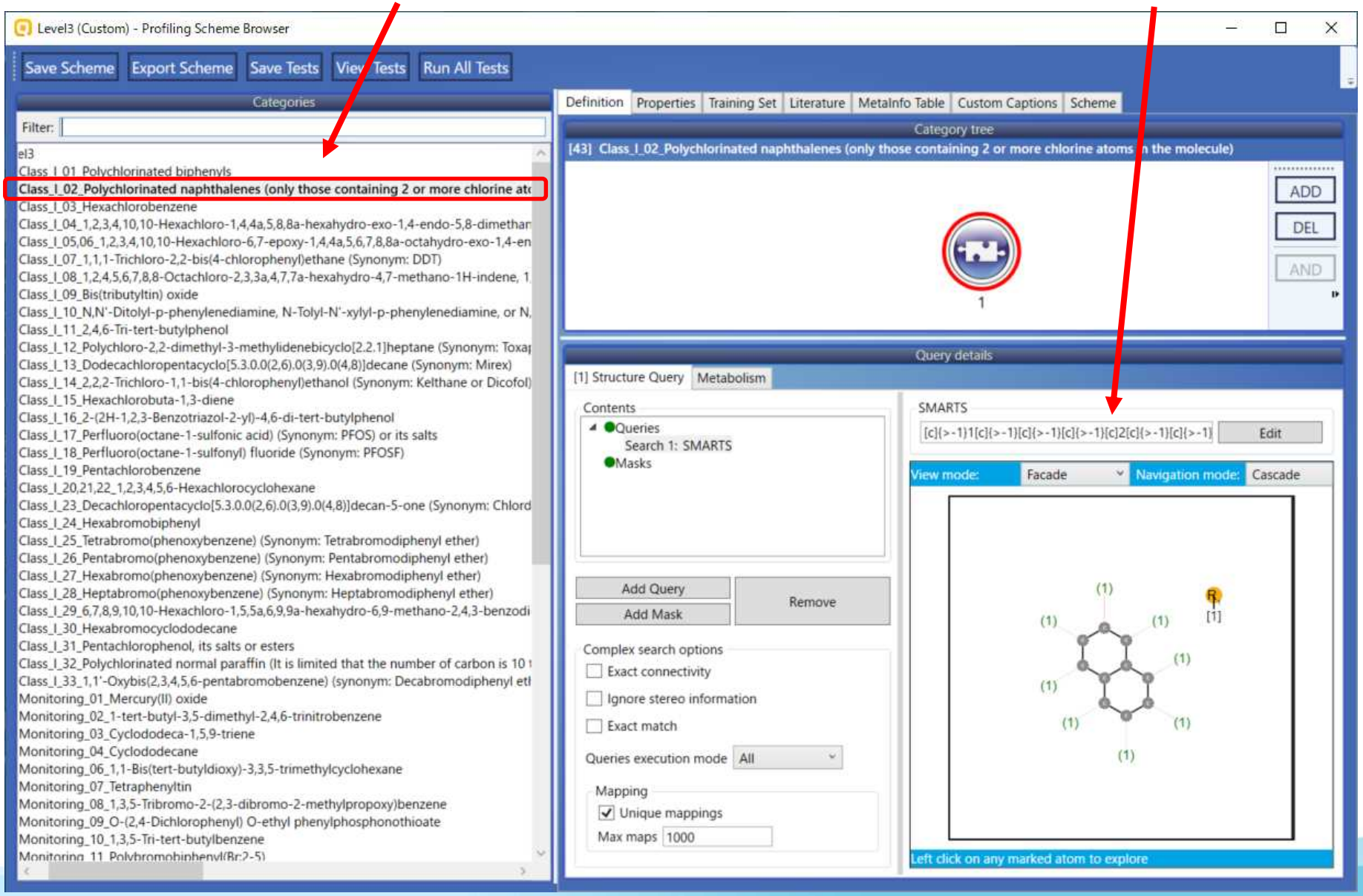
Level 3 or POPs
→ Match to a regulated chemical (will be not confirmed)

A. Screening Tool for Identifying Analogues of Regulated Chemicals

Level3 profiler

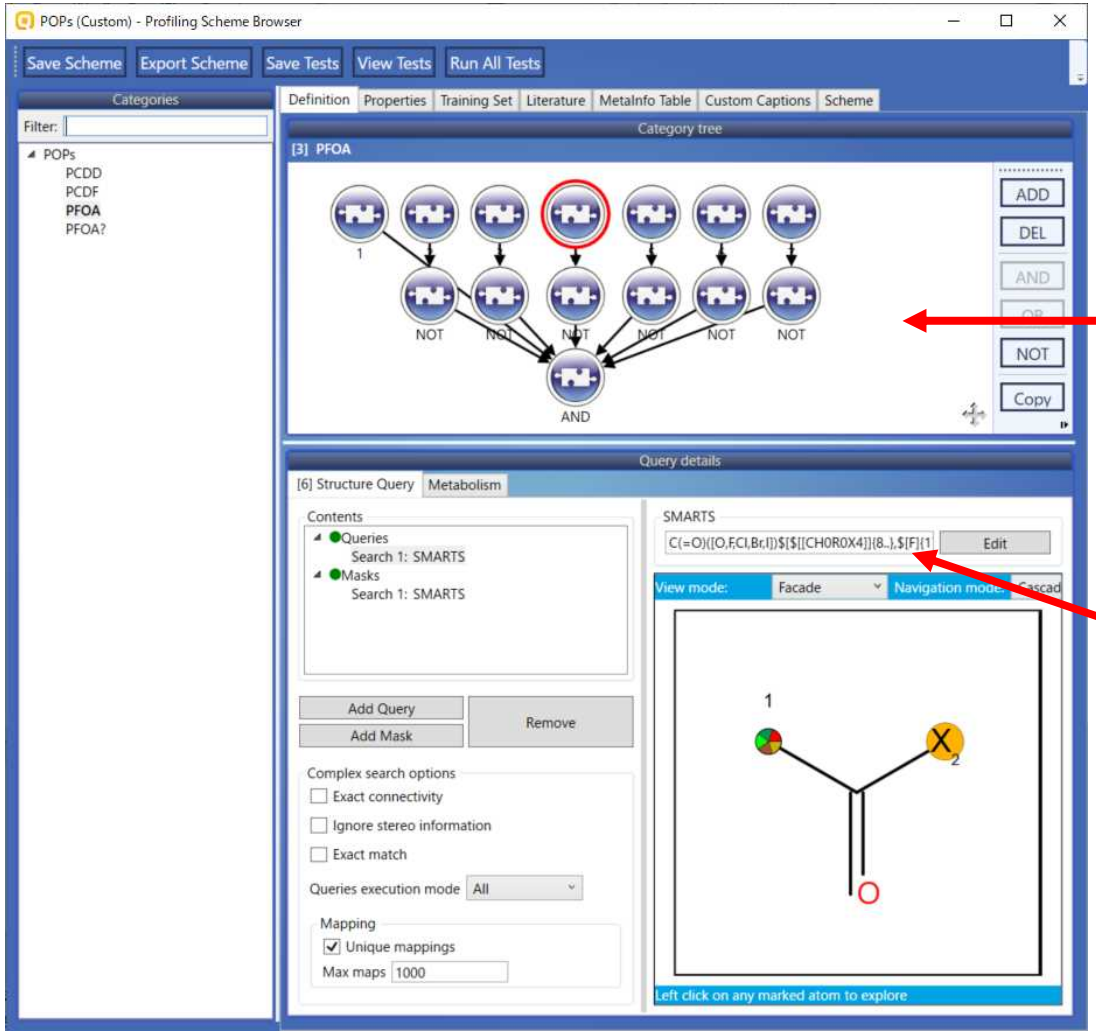
List of regulated chemicals under CSCL

Structural definition by CSCL



A. Screening Tool for Identifying Analogues of Regulated Chemicals

POPs profiler



Structural definition by Stockholm Convention on Persistent Organic Pollutants

"Perfluorooctanoic acid (PFOA), its salts and PFOA-related compounds" means the following:

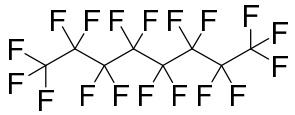
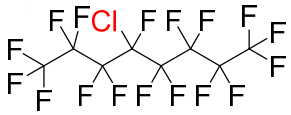
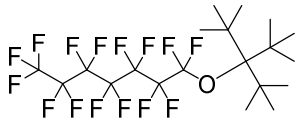
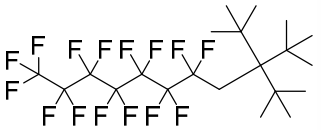
(i) Perfluorooctanoic acid (PFOA; CAS No: 335-67-1), including any of its branched isomers;

……

SMARTS

C(=O)([O,F,Cl,Br,I])$[$[[CH0R0X4]]{8..},$[F]{17..}]{..;x}

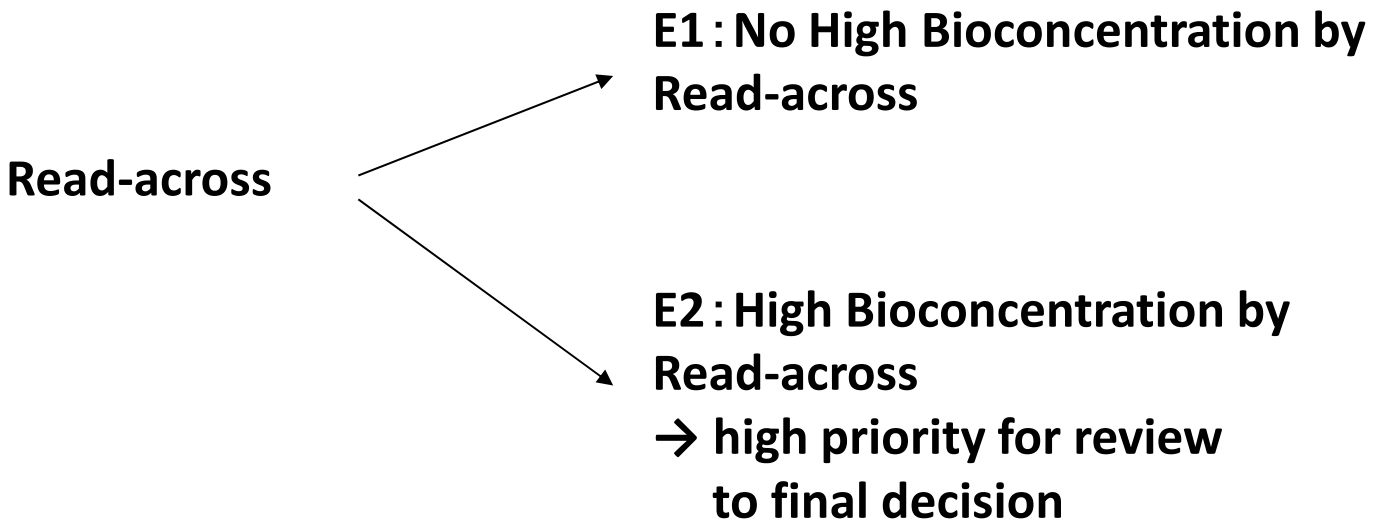
A. Screening Tool for Identifying Analogues of Regulated Chemicals

Profiling	1 [target]	2	3	4
Structure				
Structure info				
Profiling				
Custom				
Level1	14A	14A	14A	14A
Level2	Class_I_17_Perfluoro(octane-1-sulf... Class_I_18_Perfluoro(octane-1-sulf... Monitoring_27_Perfluoro(1,2-dime... Monitoring_35_Perfluorooctane Monitoring_36_2,2,3,3,4,4,5-Heptaf...	Class_I_17_Perfluoro(octane-1-sulfo... Class_I_18_Perfluoro(octane-1-sulfo... Monitoring_27_Perfluoro(1,2-dimeth... Monitoring_35_Perfluorooctane Monitoring_36_2,2,3,3,4,4,5-Heptafl...	(N/A)	(N/A)
Level3	Monitoring_35_Perfluorooctane	(N/A)	(N/A)	(N/A)
POPs	(N/A)	(N/A)	(N/A)	PFOA

E. Read-across

Available knowledge related to the bioaccumulation of the target chemical such as analogue chemicals with experimental test data are gathered for read-across.

The QSAR Toolbox is used for searching the analogue chemicals.



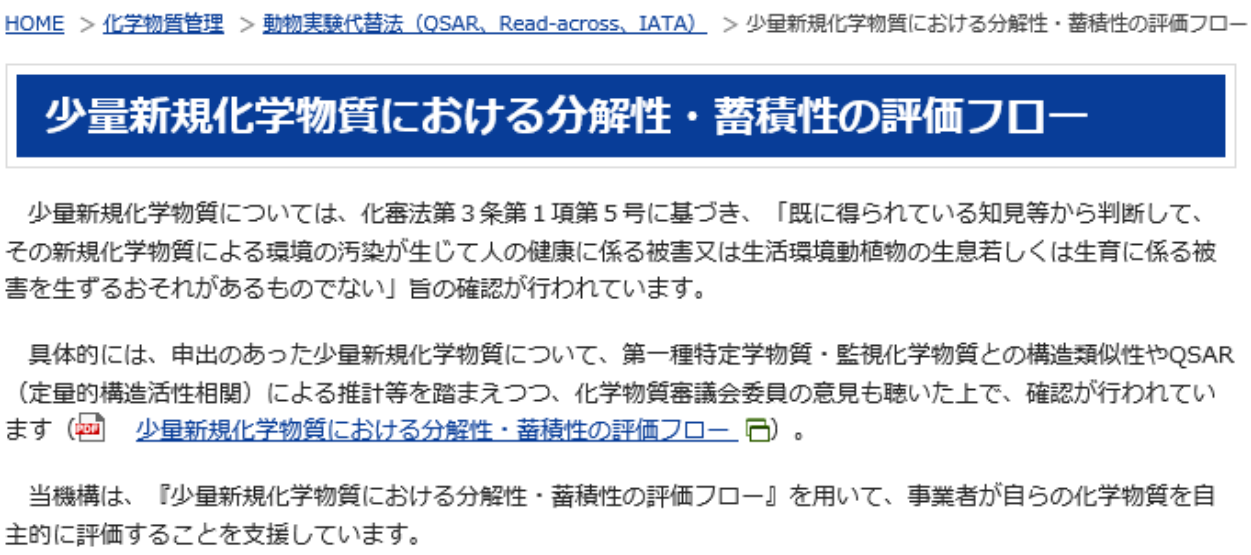
Support

The QSAR assessment flow chart is published, and the profilers used in the flow chart can be downloaded from NITE's web site.

By using them, companies can foresee the possibility of the confirmation of their chemicals in advance of notification.

NITE supports companies to utilize QSAR assessment flow chart (Tutorials, Seminar, Helpdesk *etc.*)

https://www.nite.go.jp/chem/qsar/syouryou_QSAR.html



HOME ＞ 化学物質管理 ＞ 動物実験代替法（QSAR、Read-across、IATA） ＞ 少量新規化学物質における分解性・蓄積性の評価フロー

少量新規化学物質における分解性・蓄積性の評価フロー

少量新規化学物質については、化審法第３条第１項第５号に基づき、「既に得られている知見等から判断して、その新規化学物質による環境の汚染が生じて人の健康に係る被害又は生活環境動植物の生息若しくは生育に係る被害を生ずるおそれがあるものでない」旨の確認が行われています。

具体的には、申出のあった少量新規化学物質について、第一種特定学物質・監視化学物質との構造類似性やQSAR（定量的構造活性相関）による推計等を踏まえつつ、化学物質審議会委員の意見も聴いた上で、確認が行われています（ 少量新規化学物質における分解性・蓄積性の評価フロー ）。

当機構は、『少量新規化学物質における分解性・蓄積性の評価フロー』を用いて、事業者が自らの化学物質を自主的に評価することを支援しています。

Summary

In 2020 an assessment flow chart for biodegradation and bioaccumulation has been introduced in the confirmation process of small volume new chemicals under CSCL (QSAR assessment flow).

By introducing the QSAR assessment flow chart the efficiency of the confirmation process of small volume new chemicals is remarkably improved and scientific evidence used for confirmation is clarified.

The QSAR Toolbox plays an important role to improve the efficiency in categorizing chemicals for the QSAR assessment flow chart.

NITE supports companies to utilize the QSAR assessment flow chart.