



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)*.

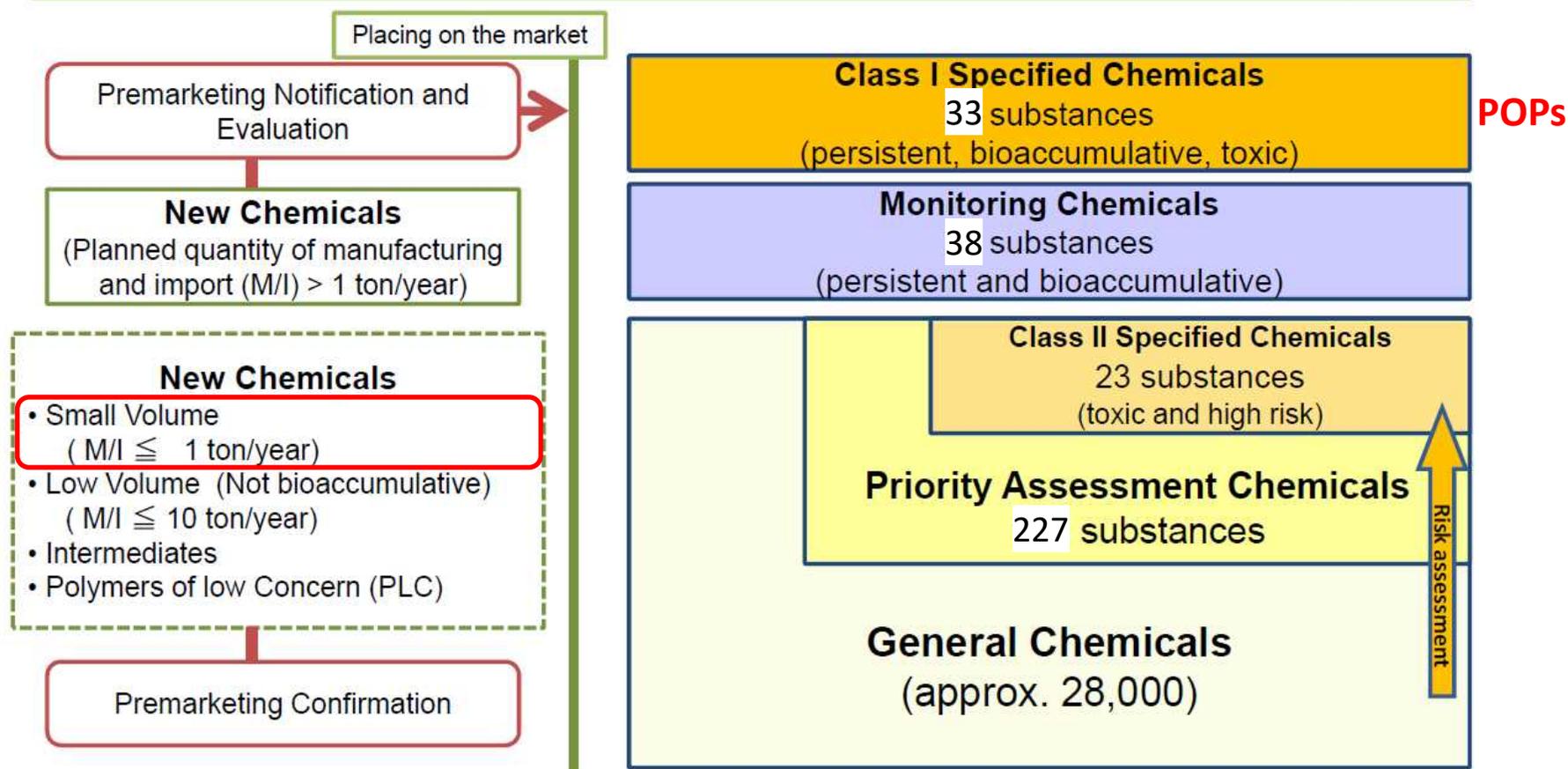
The QSAR assessment flow chart prioritizes chemicals based on the structural similarity to regulated chemicals and prediction results of biodegradation and bioaccumulation by QSAR and read-across.

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.



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

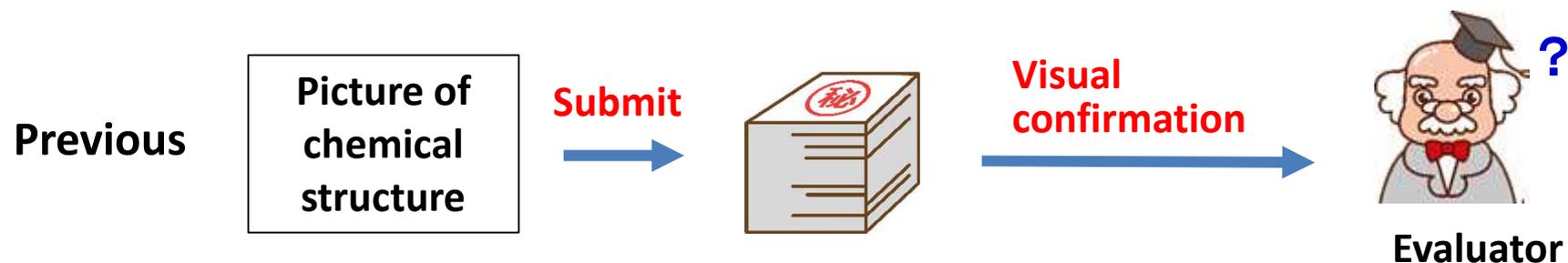


Article 3, paragraph (1), item (v): **Confirmation** *“as determined by already available knowledge, etc., the relevant new chemical substance is not one that poses a risk to human health or cause damage to the inhabitation and/or growth of flora and fauna in the living environment by causing environmental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

Confirmed → Placing on the market

Not confirmed → Not placing on the market

New Confirmation Process



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

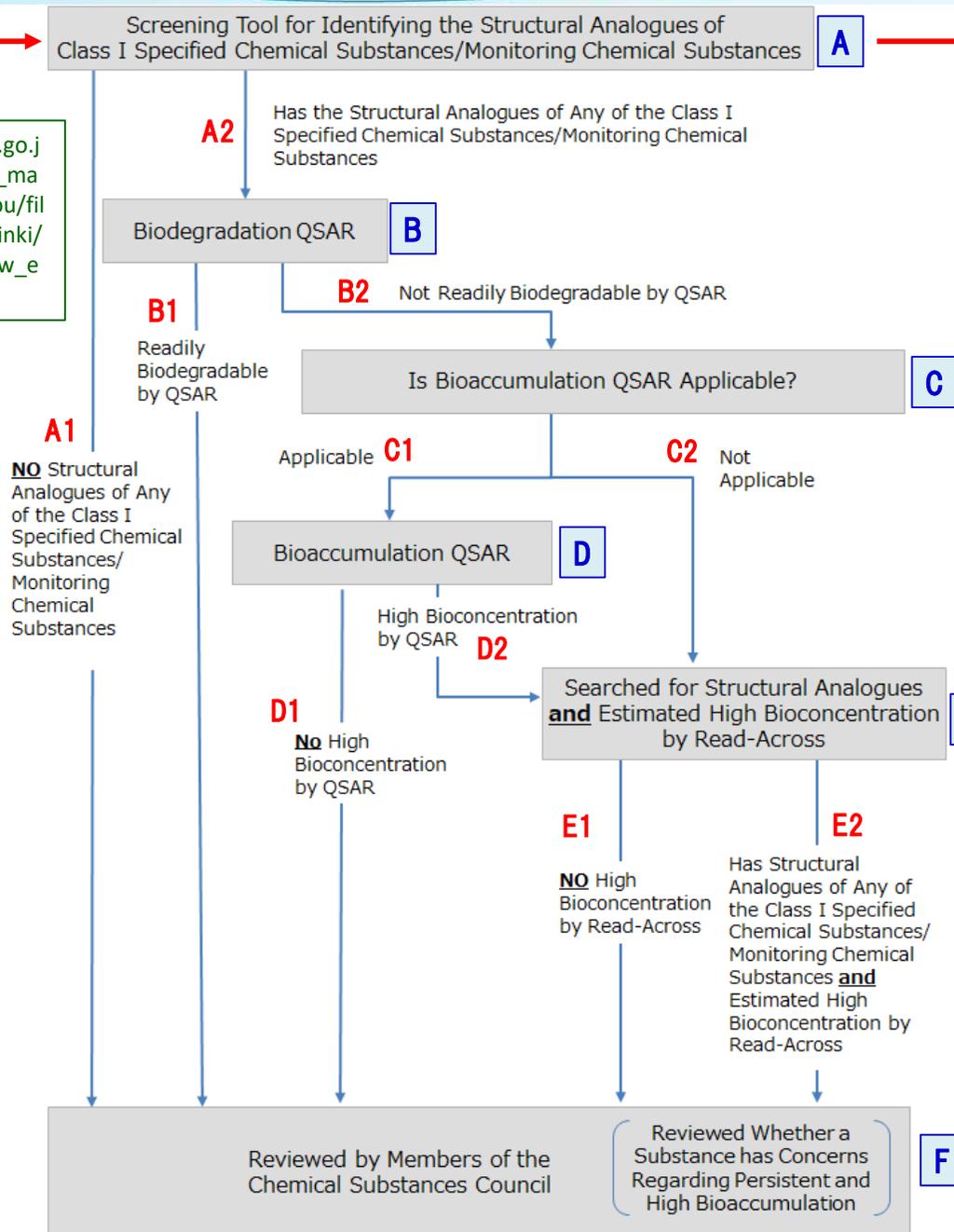
(https://www.nite.go.jp/chem/jcheck/top.action?request_locale=en)

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

QSAR Assessment Flow Chart for Small Volume New Chemicals under CSCL

Mol file submitted

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



Custom profilers of the QSAR toolbox to identify structural analogues of regulated chemicals (eg. 10,000 chemicals/<1h)

Screening by QSAR models

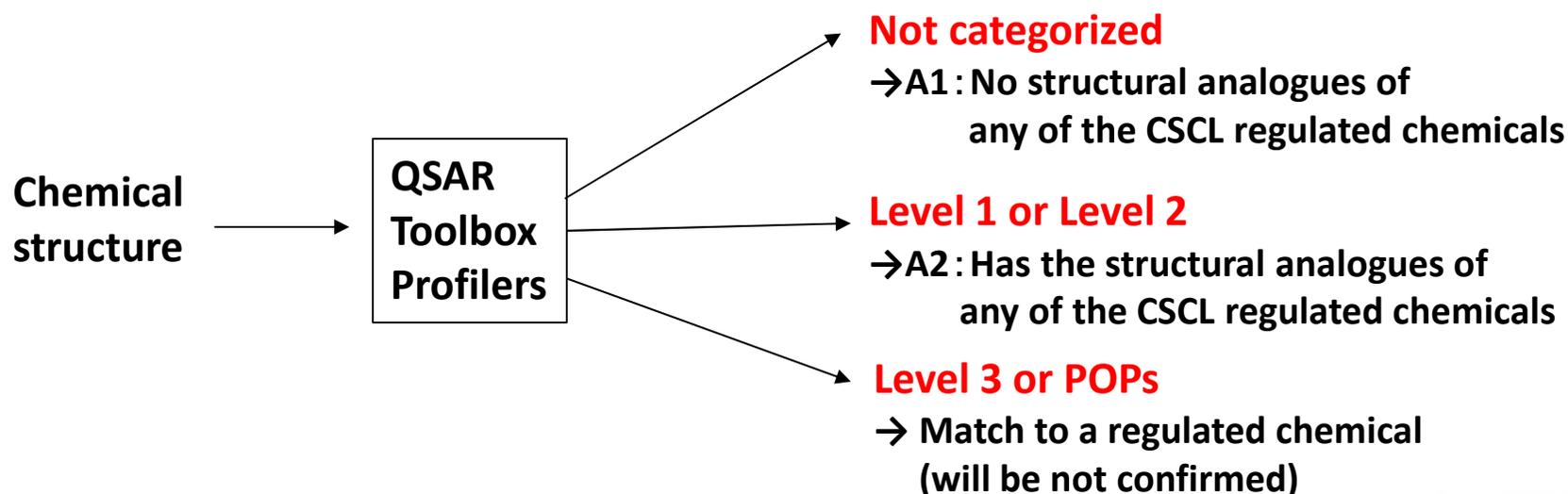
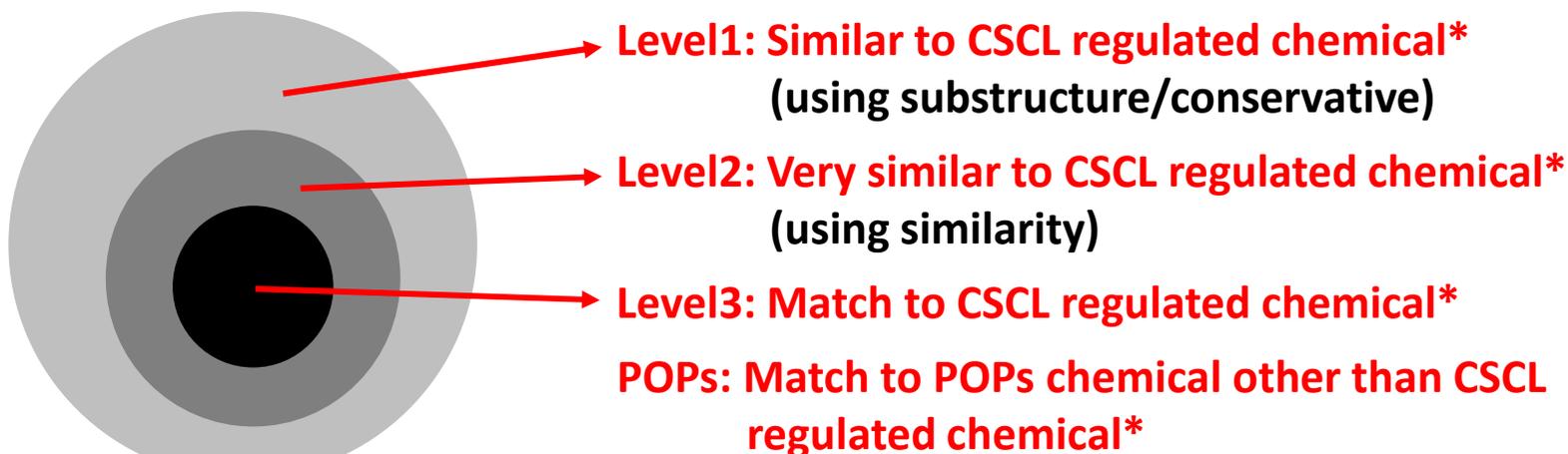
Read-across assessment

Prioritized list with support information

Final decision

A. Screening Tool for Identifying Analogues of Regulated Chemicals

Custom profiles for the QSAR Toolbox



A. Screening Tool for Identifying Analogues of Regulated Chemicals

Level3 profiler

List of regulated chemicals under CSCL

Structural definition by CSCL

The screenshot displays the Level3 Profiler software interface. On the left, a list of regulated chemicals is shown, with 'Class_I_02_Polychlorinated naphthalenes (only those containing 2 or more chlorine atoms in the molecule)' highlighted in red. A red arrow points from this text to the same text in the 'List of regulated chemicals under CSCL' label. In the center, a 'Category tree' shows '[43] Class_I_02_Polychlorinated naphthalenes (only those containing 2 or more chlorine atoms in the molecule)' with a red circle around a puzzle piece icon. A red arrow points from this icon to the 'Structural definition by CSCL' label. Below, the 'Query details' section shows a 'Structure Query' with the SMILES string [c](>-1)[c](>-1)[c](>-1)[c](>-1)[c]2[c](>-1)[c](>-1) and a chemical structure diagram with atoms marked with '(1)'. A red arrow points from the SMILES string to the 'Structural definition by CSCL' label. The interface also includes buttons for 'Save Scheme', 'Export Scheme', 'Save Tests', 'View Tests', and 'Run All Tests' at the top, and a 'Left click on any marked atom to explore' instruction at the bottom.

A. Screening Tool for Identifying Analogues of Regulated Chemicals

POPs profiler

The screenshot shows the 'POPs (Custom) - Profiling Scheme Browser' application. The interface includes a menu bar with 'Save Scheme', 'Export Scheme', 'Save Tests', 'View Tests', and 'Run All Tests'. Below the menu is a 'Categories' panel on the left with a filter and a tree view showing 'POPs' expanded to include 'PCDD', 'PCDF', 'PFOA', and 'PFOA?'. The main workspace is titled 'Category tree' and shows a logical flowchart for 'PFOA'. The flowchart starts with a root node '1' (a house icon) which branches into several 'NOT' nodes, which then converge into an 'AND' node. A red circle highlights one of the 'NOT' nodes. To the right of the flowchart are buttons for 'ADD', 'DEL', 'AND', 'OR', 'NOT', and 'Copy'. Below the flowchart is the 'Query details' section, which has tabs for 'Structure Query' and 'Metabolism'. The 'Structure Query' tab is active, showing a 'Contents' panel with 'Queries' and 'Masks' sections. Below this are buttons for 'Add Query', 'Add Mask', and 'Remove'. There are also checkboxes for 'Exact connectivity', 'Ignore stereo information', and 'Exact match', and a dropdown for 'Queries execution mode' set to 'All'. At the bottom, there is a 'Mapping' section with a checked 'Unique mappings' checkbox and a 'Max maps' field set to '1000'. The 'SMARTS' field contains the query: C(=O)([O,F,Cl,Br,I])\$[\$[CHOROX4]][8..,\$[F]{17..}]{.;x}. Below the SMARTS field is a 'View mode' dropdown set to 'Facade' and a 'Navigation mode' dropdown set to 'Cascade'. The chemical structure of PFOA is shown in a central window, with atoms 1 and 2 marked. Atom 1 is the carbonyl carbon, and atom 2 is the terminal carbon of the perfluorinated chain. A red arrow points from the highlighted 'NOT' node in the flowchart to the SMARTS query field.

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])\$[\$[CHOROX4]][8..,\$[F]{17..}]{.;x}

A. Screening Tool for Identifying Analogues of Regulated Chemicals

Profiling 1 [target] 2 3 4

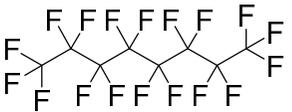
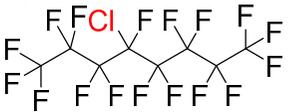
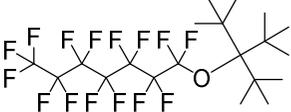
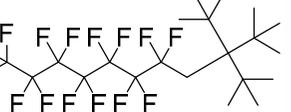
Structure

Structure info

Profiling

Custom

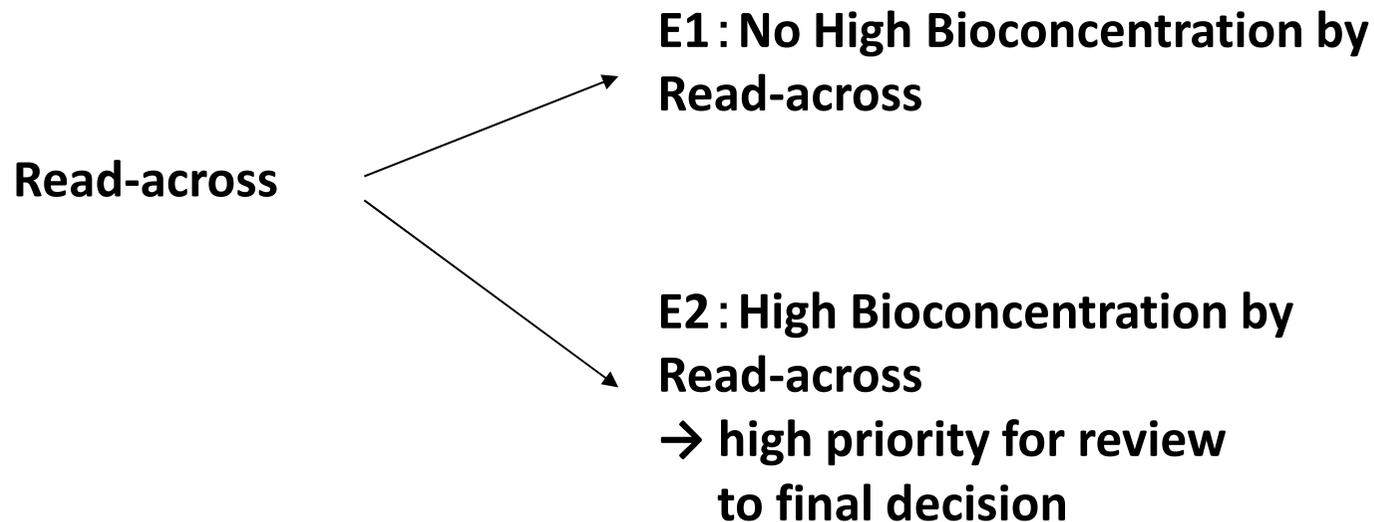
- Level1
- Level2
- Level3
- POPs

			
14A	14A	14A	14A
Class_I_17_Perfluoro(octane-1-sulf...	Class_I_17_Perfluoro(octane-1-sulfo...	(N/A)	(N/A)
Class_I_18_Perfluoro(octane-1-sulf...	Class_I_18_Perfluoro(octane-1-sulfo...		
Monitoring_27_Perfluoro(1,2-dime...	Monitoring_27_Perfluoro(1,2-dimeth...		
Monitoring_35_Perfluorooctane	Monitoring_35_Perfluorooctane		
Monitoring_36_2,2,3,3,4,4,5-Heptaf...	Monitoring_36_2,2,3,3,4,4,5-Heptafl...		
Monitoring_35_Perfluorooctane	(N/A)	(N/A)	(N/A)
(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.