Reliability Assessments of Hazard Data on Ecological Impacts in Light of the Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture etc. (Japanese Chemical Substances Control Act)

Introduction

With the Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture etc. (hereinafter referred to as "Japanese Chemical Substances Control Act") revised, assessments (hereinafter referred to as "screening assessment") were conducted in fiscal 2010 to designate priority assessment chemical substances for Type II/III monitoring chemical substances. Furthermore, the screening assessments have been in place since fiscal 2011 for general chemical substances and newly registered chemical substances.

As for hazard data required for the screening assessments, the three ministries' joint council is expected to review the results of toxicity tests imposed on businesses for newly registered chemical substances. With regard to general chemical substances, however, toxicity tests are not mandatory and there are a great number of chemical substances, making it difficult to conduct case-by-case examinations like those conducted for newly registered chemical substances. The reliability of relevant hazard data, therefore, should be assessed to make the most existing information and according to the examination standards for newly registered chemical substances for streamlining purposes.

This document provides the concepts and procedures for assessing the reliability of hazard data (existing information or information presented by businesses) required for screening assessments with respect to ecological impacts.

As for substances designated as a priority assessment chemical substances based on screening assessments, the reliability of additional information obtained until initial risk assessments (assessment I) must also be assessed according to this document.

1. Principles of handling hazard data on ecological impacts

1) The reliability should not deviate significantly from that of hazard data derived from examinations of newly registered chemical substances under Japanese Chemical Substances Control Act.
2) The test method and organism species should be based on those specified in the testing methods of Japanese Chemical Substances Control Act, the OECD test guidelines and others (designated test methods, as described in Annex 1). An endpoint refers to NOEC (No Observed Effect Concentration) for chronic toxicity and to LC50 (50% Lethal Concentration or median lethal concentration) and EC50 (50% Effective Concentration or median effective concentration) for acute toxicity. In the case not to be available for NOEC in chronic toxicity, it can be substituted either by EC10 (10% Effective Concentration) or by MATC (Maximum Acceptable Toxicant Concentration) and others.
3) The reliability of hazard data is assessed based on the assumptions mentioned above, followed by categorization as "Rank 1 (reliable without restrictions)", "Rank 2 (reliable with restrictions)", "Rank 3 (not reliable)" and "Rank 4 (not assignable)" (reliability assessment).
4) Hazard data available for screening assessments is categorized either as Rank 1 or Rank 2 (standards for the validity of use).
5) In general, toxicity values obtained from chronic toxicity tests are used first for each trophic level. In the case of the toxicity category (acute toxicity and chronic toxicity) being the same, toxicity values with higher reliability levels shall be adopted. Likewise, in the case of the

reliability level being the same, lower toxicity values shall be adopted (key study selection rule).

6) The same applies to cases where the reliability of toxicity values differs from trophic level to trophic level.
7) Experts' judgement should be adopted as for the case being difficult to judge by the above rule.

2. Reliability ranking

Based on the concept described in the preceding section and in accordance with reliability assessments in the OECD Manual for Investigation of HPV Chemicals (Reference 1) and with ranking standards in the "assessment of the reliability of the use of public data for the establishment of standards for registration suspension of agrochemicals to prevent impacts on aquatic flora and fauna" provided by the Agrochemicals Subcommittee under the Soil and Agricultural Chemicals Committee of the Central Environment Council (Reference 2), the reliability of hazard data is categorized into the following four ranks as mentioned in Section 3, with the test methods and recommended species (described in Section 1-2) verified.

[Rank 1: Reliable without restrictions]

- Tests are conducted in accordance with GLP (Good Laboratory Practice), using designated test methods, and
- With basic information about test substances (purity, ingredients, etc.) specified, ingredients such as impurities are considered to have no impact on their toxicity, which also applies to test substances with a purity of 95% or more.

  For example, the hazard data described in Section 3.1-2) [Rank 1: Reliable without restrictions] is categorized as Rank 1.

[Rank 2: Reliable with restrictions]

- Although there are uncertainties and some deviations from designated test methods, it is generally considered reliable, and
- With basic information about test substances (purity, ingredients, etc.) specified, ingredients such as impurities are considered to have no impact on their toxicity, which also applies to test substances with a purity of 95% or more.

  For example, the hazard data described in Section 3.1-2) [Rank 2: Reliable with restrictions] is categorized as Rank 2.

[Rank 3: Not reliable]

- Test methods deviate significantly from designated test methods, with their compatibility with the test standards is unknown, or
- Basic information about test substances (purity, ingredients, etc.) is specified, but impurities could have impacts on their toxicity.

  For example, the hazard data described in Section 3.1-2) [Rank 3: Not reliable] is categorized as Rank 3.

[Rank 4: Not assignable]

- Test methods involve many uncertainties and their compatibility with the test standards is unknown, or
- Basic information about test substances (purity, ingredients, etc.) is not specified and their validity is unknown.

  For example, the hazard data described in Section 3.1-2) [Rank 4: Not assignable] is categorized as Rank 4.

3. Procedures for assessing the reliability of hazard data with respect to ecological impacts

Figure 1 shows the procedures for selecting toxicity values (key study) used for calculating PNEC (Predicted No-effect Concentration) based on hazard data reliability assessments.

Of hazard data on target chemical substances, hazard information provided by businesses is checked to determine if it corresponds to data proven by organizations such as government agencies at home and abroad (described in Section 3.1-1)), thus requiring no detailed reliability assessments. If not, the information is considered hazard data whose reliability should be assessed according to Section 3.2-1). Of hazard data that requires no detailed reliability assessments described in Section 3.1-1), Test methods, recommended species and hazard data corresponding to endpoints for the principles of handling hazard data for ecological impacts should be collected, with the ranking of the collected hazard data determined according to the procedures described in Section 3.1-2) (reliability assessment). Specifically, toxicity values categorized as Rank 1 or Rank 2 are candidates for those (key studies) used for calculating PNEC (standards for the validity of use). In the case where toxicity values categorized as Rank 1 or Rank 2 are not available, the reliability of hazard data that requires detailed reliability assessments described in Section 3.2-1) is assessed according to the procedures described in Section 3.2-2), while hazard data categorized as Rank 1 or Rank 2 are adopted as candidates for key studies used for calculating PNEC. If toxicity values categorized as Rank 1 or Rank 2 cannot be obtained through these procedures, it is considered “toxicity values not available.”

Finally, key studies used for calculating PNEC are selected for each trophic level from among the above-mentioned toxicity values categorized as Rank 1 or Rank 2 according to the principles of handling hazard data for ecological impacts.

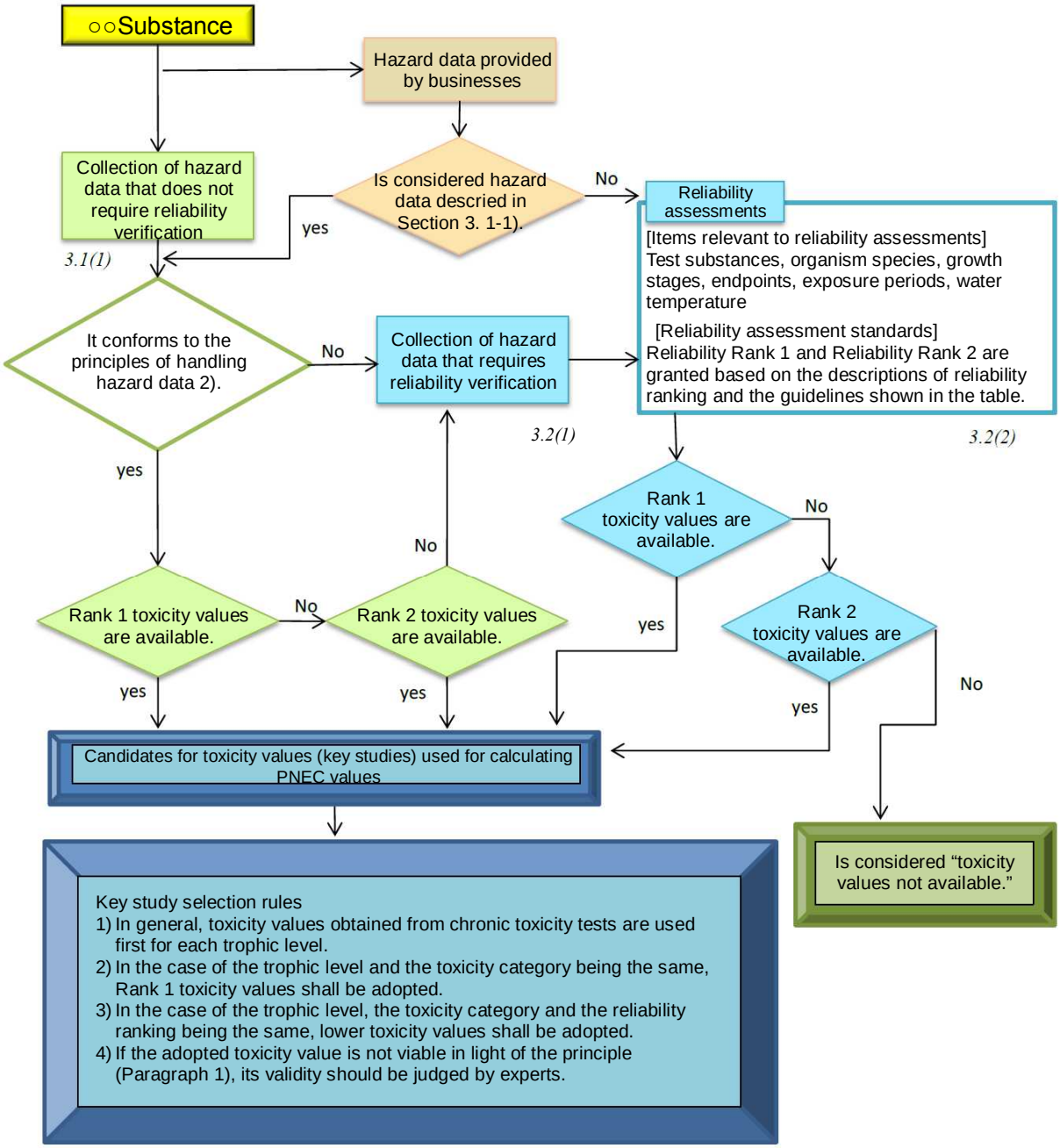

Figure 1 From Reliability Assessment of Hazard Data to Selection of Toxicity Values (Key Studies) Used for Calculating PNEC Values

3.1 Collection scope and reliability assessment of hazard data that requires no detailed reliability assessments

1. Collection scope of hazard data
   1) Hazard data examined according to Japanese Chemical Substances Control Act (newly registered and existing chemical substances)
   2) Of the results of ecological impact tests conducted by the Ministry (Agency) of the Environment and other government agencies, those that are proven for their reliability (e.g., hazard data proven for its reliability through initial ecological risk assessments)

3) Of the hazard data used for setting the Standards for Registration Suspension of Agrochemicals to Prevent Impacts on Aquatic Flora and Fauna under the Agricultural Chemicals Regulation Law, those that meet the conditions of designated test methods
4) Hazard data registered on the Pesticide Ecotoxicity Database of the US Environmental Protection Agency (US EPA) (Reference 3)
5) Hazard data assessed in the OECD's Screening Information Data Set (SIDS) initial assessment report
6) Hazard data registered on the EU's International Union Chemical Information Database (IUCLID)
7) Hazard data registered on the database of EU-ECHA (European Chemicals Agency)
8) Toxicity values that are proven for their reliability through environmental risk assessments of chemical substances (initial ecological risk assessments) of the Ministry of the Environment
9) Hazard data that are proven for their reliability through the EU Risk Assessment Report of EU-ECB (European Chemicals Bureau)
10) Hazard data adopted by the National Institute of Technology and Evaluation for their initial risk or hazard assessments of chemical substances
11) Hazard data registered with the Aquatic Toxicity Database of ECETOC (ECETOC Aquatic Toxicity：EAT)
12) Hazard data adopted by WHO/IPCS (International Programme on Chemical Safety) for Environmental Health Criteria (EHC)
13) Hazard data adopted by WHO/IPCS for the Concise International Chemical Assessment Documents (CICAD)
14) Hazard data collected through the Japan Challenge Program

2. Reliability assessments

As for those based on the information sources described in Section 3.1-1), the reliability ranking corresponding to Section 2 is granted, following assessments to determine whether they conform to the test methods, recommended species and endpoints for the principles of handling hazard data for ecological impacts described in Section 1-2), while the detailed reliability assessments described in Section 3.2 for individual hazard data are not conducted – i.e., respective reliability ranking is granted where the following descriptions listed by information source are verified. If the reliability ranking with the same hazard data differs depending on available information, a value with a higher ranking (ranking with lower reliability) is granted, while other reliability ranking is used for Rank 4 (not assignable).

[Rank 1: Reliable without restrictions]

1) The hazard data examined according to Japanese Chemical Substances Control Act
2) Of the results of ecological impact tests conducted by the Ministry (Agency) of the Environment and other government agencies, those whose reliability is ranked "A" by initial ecological risk assessments or whose reliability is considered identical to that of newly registered chemical substances by experts
3) Of the hazard data used for setting the Standards for Registration Suspension of Agrochemicals to Prevent Impacts on Aquatic Flora and Fauna under the Agricultural Chemicals Regulation Law, those corresponding to concentrations lower than the solubility limit and those involving the use of surfactant dispersants at concentrations lower than those specified in Japanese Chemical Substances Control Act.

4) Of the hazard data corresponding to Category C (Core) of the US-EPA's Pesticide Ecotoxicity Database, those obtained from tests that are identical to those specified in Japanese Chemical Substances Control Act
5) Of the hazard data with Reliability Level 1 (according to the OECD's SIDS) and obtained according to GLP, those obtained from tests that are identical to those specified in Japanese Chemical Substances Control Act
6) Of the hazard data collected through the Japan Challenge Program, those obtained according to GLP

[Rank 2: Reliable with restrictions]

1) Of the results of ecological impact tests conducted by the Ministry (Agency) of the Environment and other government agencies, those whose reliability is ranked "B" by initial ecological risk assessments
2) US-EPA's Pesticide Ecotoxicity Database – Category "S (Supplemental)"
3) EU's IUCLID: Reliability 1 or 2
4) ECHA Database: Reliability 1 or 2
5) OECD's SIDS: Reliability 1 (excluding those categorized as Rank 1) or 2
6) Initial ecological risk assessments of chemical substances by the Ministry of the Environment: Hazard data reliability "A" or "B"
7) Hazard data that is assessed "Valid" in the EU Risk Assessment Report
8) Hazard data adopted by the National Institute of Technology and Evaluation for its initial risk assessments of chemical substances
9) Hazard data registered on the Aquatic Toxicity Database (ECETOC Aquatic Toxicity: EAT) of ECETOC
10) Hazard data adopted by WHO/IPCS for the Environmental Health Criteria (EHC)
11) Hazard data adopted by WHO/IPCS for the Concise International Chemical Assessment Documents (CICAD)
12) Of the hazard data collected through the Japan Challenge Program, those of Non-GLP

[Rank 3: Not reliable]

1) Of the results of ecological impact tests conducted by the Ministry (Agency) of the Environment and other government agencies, those whose reliability is ranked "C" by initial ecological risk assessments
2) US-EPA's Pesticide Ecotoxicity Database – Category "IN (Invalid)"
3) EU's IUCLID: Reliability 3
4) OECD's SIDS: Reliability 3
5) Initial ecological risk assessments of chemical substances by the Ministry of the Environment: Hazard data reliability "C"
6) Hazard data that is assessed "Invalid" in the EU Risk Assessment Report

[Rank 4: Not assignable]

1) EU's IUCLID: Reliability 4

2) OECD's SIDS: Reliability 4
3) Initial ecological risk assessments of chemical substances by the Ministry of the Environment: Hazard data reliability "D"

3.2 Collection scope and reliability assessments of hazard data that requires detailed reliability assessments

1) Collection scope of hazard data

The following are scientific papers and others that are required assessing in detail the reliability of hazard data. Those proven to be unreliable are not used.

1. Hazard data reported by businesses (actual measured data or data sourced from scientific papers, etc.)

   (*Excluding those applicable to Section 3.1-1))

2. Ecological impact tests are being conducted by government agencies, etc. at home and abroad, but reliability assessments are yet to be implemented.

   - Hazard data whose reliability has not been verified yet through ecological impact tests by the Ministry of the Environment
   - Hazard data derived from preliminary bioconcentration tests
   - Hazard data that has yet to be subjected to the existing chemicals examination by Japan governments

3. Hazard data is opened by government agencies, etc. at home and abroad, but reliability assessments are yet to be done or the completion of such assessments is unknown.

   - Environment/Health Canada: Priority Substance Assessment Reports
   - Australia NICNAS Priority Existing Chemical Assessment Reports
   - WHO/FAO Pesticide Data Sheets (PDSs)
   - BUA Report

4. Hazard data sourced from scientific papers, etc. obtained from the following ecotoxicity databases and others

   - The US-EPA's Ecotoxicity database: AQUIRE (AQuatic Toxicity Information Retrieval)
   - An ecotoxicity database contained in OECD QSAR Toolbox: Aquatic OASIS

2) Detailed reliability assessments

[Items relevant to reliability assessments]

GLP tests should be examined for the validity of the test methods on hazard data. Because the detailed data of the other reference data is hardly obtainable for detail data such as GLP tests, the reliability ranking (or reliability assessment) can be conducted using parameters such as the purity of test substances, organism species, growth stages, endpoints, exposure periods, water temperature and others.

[Reliability assessment standards]

The descriptions of the reliability ranking and the indications shown in Table 1 and 2 are used to grant Rank 1 and Rank 2.

Table 1 Indications of for Rank 1 and Rank 2 (Chronic Toxicity Values)

Reliability ranking	Item/organism	Fish	Daphnia	Algae
Rank 1 and 2	Test organisms	Species recommended by OECDTG210 (Rainbow trout, fat head minnow, zebra fish, killifish)	Daphnia magna recommended by OECDTG211	Species recommended by Japanese Chemical Substances Control Act TG or OECD TG *Pseudokirchneriella subcapitata: Desmodesmus subspicatus Navicula pelliculosa* *Anabaena flos-aquae 1* *Synechococcus leopoliensis* *Chlorella vulgaris* (OECD TG201,1984)
Rank 1 (Japanese Chemical Substances Control Act TG and OECD TG)	Growth stage	From the embryonic stage (before blastocyst division or the stage close to it) to the stage where all fish in the batch start to feed	Hatchlings (less than 24 hours old and the second generation and beyond)	The exponential growth phase should be maintained.
	Endpoint	NOEC for the following: Cumulative mortality, the number of healthy fish at completion of the test, the start/completion time of hatching, the number of hatchlings, the body length and weight of survived fish, the number of malformed fish, the number of fish exhibiting unusual behavior	NOEC for breeding The number of hatchlings per female Daphnia or the concentration where more than 20% of the parents die	NOEC for growth inhibition
	Exposure period	Rainbow trout: Two weeks after the control group starts to feed (or 60 days after hatching) Fat head minnow: 32 days after the start of the test (or 28 days after hatching) Zebra fish: 30 days after hatching Japanese killifish: 30 days after hatching	21 days	In general, 72 hours
	Test condition (water temperature)	Rainbow trout: Embryos (10±2°C), larval and young fish (12±2°C) Fat head minnow: 25±2 °C Zebra fish: 25±2 °C Japanese killifish: Embryos (24±1°C), larval and young fish (23±2°C)	18-22 °C Temperature range: ±2 °C	21-24 °C Temperature range: ±2 °C

Reliability ranking	Item/organism	Fish	Daphnia	Algae
Rank 2	Growth stage	From embryos to young fish	Hatchlings (less than 24 hours old and the second generation and beyond)	The exponential growth phase should be maintained
	Endpoint	NOEC for the following: Cumulative mortality, the number of healthy fish at completion of the test, the start/completion time of hatching, the number of hatchlings, the body length and weight of survived fish, the number of malformed fish, the number of fish exhibiting unusual behavior	NOEC for breeding The number of hatchlings per female Daphnia or the concentration where more than 20% of the parents die	NOEC for growth inhibition
	Exposure period	Growth period from embryos to young fish	21 days	Within ±24 hours from the period specified in the test guidelines of Japanese Chemical Substances Control Act Algae: 48-96 hours
	Test condition (water temperature)	Temperature ranges for chronic toxicity tests and acute toxicity tests Rainbow trout: 10-15 °C Fat head minnow: 21-25 °C Zebra fish: 21-25 °C Japanese killifish: 21-25 °C	18-22°C Temperature range: ±2 °C	Water temperature range: Within ±3°C from the range specified in the test guidelines of Japanese Chemical Substances Control Act 18-27°C

Table 2 Guidelines for Rank 1 and Rank 2 (Acuter Toxicity Values)

Reliability ranking	Item/organism	Fish	Daphnia	Algae
Rank 1 and 2	Test organism	Species recommended by Japanese Chemical Substances Control Act TG and OECD TG		
Rank 1 Japanese Chemical Substances Control Act TG	Growth stage	Zebra fish: 2.0±1.0 cm Fat head minnow: 2.0±1.0 cm Carp: 4.0±2.0cm Japanese killifish: 2.3±1.2 cm Guppy: 2.0±1.0 cm	Hatchlings: Less than 24 hours old	The exponential growth phase should be maintained

Reliability ranking	Item/organism	Fish	Daphnia	Algae
		Bluegill: 2.0±1.0 cm Rainbow trout: 5.0±1.0 cm		
	Endpoint	LC50	EC 50 for immobilization	EC50 for growth inhibition
	Exposure period	96 hours	48 hours	In general, 72 hours
	Test condition (water temperature)	Zebra fish: 21-25 °C Fat head minnow: 21-25 °C Carp: 20-24 °C Japanese killifish: 21-25 °C Guppy: 21-25 °C Bluegill: 21-25 °C Rainbow trout: 13-17 °C（±2 °C)	18-22 °C (±1 °C)	21-24 °C (±2 °C)
Rank 1 (OECDTG)	Growth stage	Zebra fish: 2.0±1.0 cm Fat head minnow: 2.0±1.0 cm Carp: 3.0±1.0cm Japanese killifish: 2.0±1.0 cm Guppy: 2.0±1.0 cm Bluegill: 2.0±1.0 cm Rainbow trout: 5.0±1.0 cm	Hatchlings: Less than 24 hours old	e.g., *Pseudokirchneriella subcapitata*: 5×10^3-10^4cells/mL
	Endpoint	LC50	EC 50 for immobilization	EC50 for growth inhibition
	Exposure period	96 hours	48 hours	In general, 72 hours
	Test condition (water temperature)	Zebra fish: 21-25 °C Fat head minnow: 21-25 °C Carp: 20-24 °C Japanese killifish: 21-25 °C Guppy: 21-25 °C Bluegill: 21-25 °C Rainbow trout: 13-17 °C	18-22 °C	21-24 °C

Reliability ranking	Item/organism	Fish	Daphnia	Algae
Rank 2	Growth stage	Total length of test fish: From half to twice the average length specified in the test guidelines of Japanese Chemical Substances Control Act and OECD TG・ Zebra fish: 1.0-4.0 cm Fat head minnow: 1.0-4.0 cm Carp: 1.5-8.0 cm Japanese killifish: 1.0-4.6 cm Guppy: 1.0-4.0 cm Bluegill: 1.0-4.0 cm Rainbow trout: 2.5-10 cm	Hatchlings: Less than 24 hours from hatching	
	Endpoint	LC50	EC50 or LC50 for immobilization	EC50 for growth inhibition
	Exposure period	Within ±24 hours from the period specified in the test guidelines of Japanese Chemical Substances Control Act・ Fish: 72-120 hours	Within ±24 hours from the period specified in the test guidelines of Japanese Chemical Substances Control Act・ Daphnia: 24-72 hours	Within ±24 hours from the period specified in the test guidelines of Japanese Chemical Substances Control Act・ Algae: 48-96 hours
	Test condition (water temperature)	Water temperature: Within ±3°C from the temperature specified in the test guidelines of Japanese Chemical Substances Control Act・ Zebra fish: 18-28°C Fat head minnow: 18-28°C Carp: 17-27°C Japanese killifish: 18-28°C Guppy: 18-28°C Bluegill: 18-28°C Rainbow trout: 10-20°C	Water temperature: Within ±3°C from the temperature specified in the test guidelines of Japanese Chemical Substances Control Act・ 15-25°C	Water temperature: Within ±3°C from the temperature specified in the test guidelines of Japanese Chemical Substances Control Act 18-27°C

Annex 1 Test methods equivalent to those specified in Japanese Chemical Substances Control Act (designated test methods)

1) Organisation for Economic Co-operation and Development (OECD)

1. OECD TG 201: Freshwater Alga and Cyanobacteria, Growth Inhibition Test
2. OECD TG 202: Daphnia sp., Acute Immobilisation Test
3. OECD TG 203: Fish, Acute Toxicity Test
4. OECD TG 210: Fish, Early-life Stage toxicity Test
5. OECD TG 211: Daphnia magna Reproduction Test

2) International Organization for Standardization (ISO)

6. ISO 6341: Water quality - Determination of the inhibition of the mobility of *Daphnia magna* Straus (*Cladocera, Crustacea*) - Acute toxicity test
7. ISO 7346: Water quality -- Determination of the acute lethal toxicity of substances to a freshwater fish [*Brachydanio rerio* Hamilton-Buchanan (Teleostei, Cyprinidae)]
8. ISO 8692: Water quality - Freshwater algal growth inhibition test with unicellular green algae
9. ISO 10706: Water quality - Determination of long term toxicity of substances to *Daphnia magna* Straus (*Cladocera, Crustacea*)
10. ISO 12890: Water quality - Determination of toxicity to embryos and larvae of freshwater fish - Semi-static method

3) Agricultural Chemicals Regulation Law
* Special attention should be paid for the use of auxiliary agents.

11. Fish acute toxicity tests
12. Daphnia acute immobilization tests
13. Daphnia reproduction tests
14. Algae growth inhibition tests

(Reference 1)

Reliability defined by the OECD Manual for Investigation of HPV Chemicals

Klimisch Code, adopted for assessment of the reliability of hazard data in the OECD HPV (High Production Volume) Chemicals Programme and the REACH regulations, was developed by Klimisch et al. (1997) to rank the reliability of tests. It consists of four ranks: 1. Reliable without restrictions, 2. Reliable with restrictions, 3. Not reliable and 4. Not assignable.

Rank 1 = reliable without restrictions: "studies or data generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline, or in which all parameters described are closely related/comparable to a guideline testing method."

Rank 2 = reliable with restrictions: "studies or data (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable."

Rank 3 = not reliable: "studies or data in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment."

Rank 4 = not assignable: "studies or data which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)."

Klimisch, H.J., Andreae, E., Tillmann, U. (1997) A systematic approach for evaluating the quality of experimental and ecotoxicological data., Reg. Toxcol. Pharm. 25, 1-5.

(Reference 2)

The Agrochemicals Subcommittee under the Soil and Agricultural Chemicals Committee of the Central Environment Council
(9th) Reference 5 dated June 3, 2008

Assessments of the reliability of the use of public data for the establishment of standards for registration suspension of agrochemicals to prevent impacts on aquatic flora and fauna

Assessments of the reliability of the use of public data for the establishment of standards for registration suspension of agrochemicals to prevent impacts on aquatic flora and fauna

In setting standards for registration suspension of agrochemicals to prevent impacts on aquatic flora and fauna, a report prepared by the 2004 Investigative Commission on Standards for Registration Suspension of Agrochemicals to Prevent Impacts on Aquatic Flora and Fauna (May 2005) stipulates that public data on the toxicity of agrochemicals on aquatic organisms be collected, compliance of relevant data with agrochemical test guidelines be verified, and those that are verified by experts be adopted for setting standards for registration suspension.

Accordingly, the Ministry of the Environment collects public data on the toxicity of agrochemicals, while the investigative commission and the subcommittee verify compliance of those data with agrochemical test guidelines, with verified data adopted for setting standard values.

The Ministry of the Environment, moreover, provides guidelines on the reliability assessment for an availability of public data, based on its experience in setting various environmental standards (see attachment).

Attachment

Guidelines of reliability Assessment for the availability of Pubic Data

1. Principle

Toxicity data, whose test methods are not in full compliance with the guidelines but the deviation is not expected to affect the reliability of the methods, can be adopted for setting standard values. On the other hand, there may be cases where several toxicity data (including test results and public data) provided by applicants are considered reliable for the same type of tests (same organism species, test of test methods), but their reliability varies in view of the compatibility with test guidelines and the purity of test substances. In such cases, it is recommended that more reliable toxicity data shall be selected from among those derived from the same type of tests.

2. Concept of reliability assessments

The reliability is assessed in stages according to the compatibility with test guidelines and the purity of test substances, etc., the details of which are described below.

Reliability Rank 1 (highly reliable)

1) The test method is in compliance with the test guidelines specified in the Agricultural Chemicals Regulation Law or in the OECD test guidelines (hereinafter referred collectively to as “the test guidelines).
2) The test substance is the same as those used by applicants or has a higher purity with the percentage of isomers being almost the same.

Reliability Rank 2 (reliable)

1) The test method deviates slightly from the test guidelines with some uncertainties, but is generally considered reliable.
2) The test substance is not so different from those used by applicants in terms of purity and the percentage of isomers.

Reliability Rank 3 (not reliable)

1) The test method deviates significantly from the test guidelines and it is not fully reliable.
2) The test substance is so different from those used by applicants in terms of purity and the percentage of isomers.

Reliability Rank 4 (not assignable)

1) The test method involves many uncertainties with the compatibility with the test guidelines unknown.
2) Both the purity of the test substance and the percentage of isomers are unknown.

From the reliability assessment, data with Reliability Rank 1 and 2 can be used to set standard values. In the case where several toxicity data (including test results and public data) provided by applicants are categorized as Rank 1 or Rank 2 for the same type of tests (same organism species, test of test methods), Rank 1 toxicity data is used to set standard values. In the case of the reliability ranking being the same, meanwhile, data involving lower toxicity value is preferentially used.

In addition, standard tests and additional tests are used to derive data required for setting standard

values as a different test.

3. Categorization as Rank 1 and Rank 2

Tentatively, the Secretariat of the Ministry of the Environment is expected to do the screening while the Investigative Commission on Standards for Registration Suspension of Agrochemicals to Prevent Impacts on Aquatic Flora and Fauna and the Agrochemicals Subcommittee under the Soil and Agricultural Chemicals Committee of the Central Environment Council are responsible for the reliability categorization (Rank 1 or Rank 2) based on the below-mentioned standards, which will be revised as needed by the accumulation of case studies.

1) Guidelines for identity of test substances

Reliability Rank 1: Both the purity and the percentage of isomers are in compliance with those of substances provided by applicants.
(Note: The standard values and the normal values are in the purity and the percentage of isomers. The standard values are used here.)

Reliability Rank 2: Both of the following a) and b) must be met.
a) The purity is more than 90% of the lower limit of substances provided by applicants.
b) The percentage of isomers deviates less than 10% from those of substances provided by applicants (which does not apply to cases where there is no significant difference in toxicity between isomers, meaning that data with a deviation of more than 10% can be used).
(Ex. Applicable when the purity is more than 95×0.9 = 85.5%, with the standard purity of substances provided by applicants of 95% and over, or when the ratio of isomers ranges from 25:75 to 60:40 with those of substances provided by applicants ranging from 35:65 to 50:50)

2) Guidelines for compliance with test guidelines

Reliability Rank 1: The test method is in compliance with the test guidelines, while it is recommended that the test be conducted according to GLP.

Reliability Rank 2: The test method deviates slightly from the test guidelines with some uncertainties, but is generally considered reliable.

The attached table shows the guidelines for each item relevant to screening of toxicity data that can be categorized as Reliability Rank 2.

4. Example of setting standard values through reliability assessments

1) Case 1

Where the following toxicity data is obtained:
Data A (acute toxicity tests on Japanese killifish, data provided by applicants, Reliability Rank 1, LC50 = 10μg/L)
Data B (acute toxicity tests on Japanese killifish, public data, Reliability Rank 2, LC50 = 5μg/L)
→ As for Japanese killifish, the toxicity value is lower in Data B than in Data A, but the latter is adopted as its reliability is categorized as Rank 1. As a result, the following is obtained:

AECf=Data A/UF

2) Case 2

Where the following toxicity data is obtained:
Data A (acute toxicity tests on carp, data provided by applicants, Reliability Rank 1, LC50 = 10μg/L)
Data B (acute toxicity tests on Japanese killifish, public data, Reliability Rank 2, LC50 = 5μg/L)
→ As for Japanese killifish, data with Reliability Rank 2 is adopted as no other data is available. As a result, the following is obtained:
AECf=Min (Data A, Data B)/UF

3) Case 3

Where the following toxicity data is obtained:
Data A (acute toxicity tests on carp, data provided by applicants, Reliability Rank 1, LC50 = 10μg/L)
Data B (acute toxicity tests on Japanese killifish, public data, Reliability Rank 1, LC50 = 10μg/L)
Data C (acute toxicity tests on Japanese killifish, public data, Reliability Rank 1, LC50 = 8μg/L)
Data D (acute toxicity tests on Japanese killifish, public data, Reliability Rank 2, LC50 = 5μg/L)
Data E (toxicity tests on hatchlings of Japanese killifish, public data, Reliability Rank 2, LC50 = 3μg/L)
Data F (acute toxicity tests on rainbow trout, public data, Reliability Rank 2, LC50 = 2μg/L)
→ As for acute toxicity tests on Japanese killifish, data with Reliability Rank 1 is prioritized over other data, while Data C with a lower toxicity value is selected from two sets of data with Reliability Rank 1.

With respect to Japanese killifish, meanwhile, there is Data E with Reliability Rank 2, which concerns toxicity tests on hatchlings (i.e., tests on a different growth stage). In addition, lower toxicity values are adopted for tests on fish with different growth stages, where Data E is adopted based on comparison between Data C and Data E.

As for species other than Japanese killifish, Data A with Reliability Rank 1 is available for carp, as is Data F with Reliability Rank 2 for rainbow trout. With these data adopted and Data E incorporated, the following is obtained:
AECf=Min (Data A, Data E, Data F)/UF

(Attached Table)

Guidelines for screening toxicity data that can be categorized as Reliability Rank 2

Organism	Item	Draft guidelines	Definition by Agrochemicals TG	Definition by OECD TG
Fish	Growth level (total length of test fish)	From half to twice the median total length specified in the test guidelines Carp: 1.5-8.0 cm Japanese killifish: 1.0-4.6 cm Bluegill: 1.0-4.0 cm Rainbow trout: 2.5-10 cm Guppy: 1.0-4.0cm Zebra Danio: 1.0-4.0 cm Fat head minnow: 1.0-4.0 cm	Carp: 4.0±2.0 cm Japanese killifish: 2.3±1.2 cm Bluegill: 2.0±1.0 cm Rainbow trout: 5.0±1.0 cm Guppy: 2.0±1.0cm Zebra Danio: 2.0±1.0 cm Fat head minnow: 2.0±1.0 cm	Carp: 3.0±1.0 cm Japanese killifish: 2.0±1.0 cm Bluegill: 2.0±1.0 cm Rainbow trout: 5.0±1.0 cm Guppy: 2.0±1.0cm Zebra Danio: 2.0±1.0 cm Fat head minnow: 2.0±1.0 cm
	Density	Possible when the concentration of a test substance does not decrease and DO levels can be maintained without aeration	<1g/L (higher densities are possible under running water)	<1g/L(higher densities are possible under running water)
	Exposure period	Within 24 hours from the period specified in the test guidelines Fish: 72-120 hours	Fish: 96 hours	Fish: 96 hours
	Test condition (water temperature)	The water temperature falls within the range of ±3°C from the range specified in the test guidelines. Carp: 17-27°C Japanese killifish: 18-28°C Bluegill: 18-28°C Rainbow trout: 10-20°C Guppy: 18-28°C Zebra Danio: 18-28°C Fat head minnow: 18-28°C	Carp: 20-24°C Japanese killifish: 21-25°C Bluegill: 21-25°C Rainbow trout: 13-17°C Guppy: 21-25°C Zebra Danio: 21-25°C Fat head minnow: 21-25°C	Carp: 20-24°C Japanese killifish: 21-25°C Bluegill: 21-25°C Rainbow trout: 13-17°C Guppy: 21-25°C Zebra Danio: 21-25°C Fat head minnow: 21-25°C
	Concentration setting (geometric ratio)	On a case-by-case basis with dose-response effects taken into account	The geometric ratio is recommended to be less than 2.2.	The geometric ratio is recommended to be less than 2.2.
	Stability of concentrations (chemical analysis)	1) The result is calculated based on actual values measured at completion of the test. 2) Calculation based on default values is possible for substances whose concentrations can be maintained.	The concentrations of test substance are measured at the star and completion of exposure as well as before and after the exchange of water. It is recommended to be 80% and more of the setting concentrations during the exposure period.	At least 80% of the setting concentrations must be maintained. Actual measuring values are used for calculation where the concentration changes by more than 20%.
	Dose-Response	The toxicity value must be obtained through interpolation. Others are determined based on reaction curves.		

Crustacea	Growth stage	Hatchlings: Less than 24 hours old Adults: In a growth stage without breeding during the exposure period	Hatchlings: Less than 24 hours old Adults: 7 days old	Hatchlings: Less than 24 hours old
	Density	Hatchlings:less than one/2mL、Adults:less than one/4mL	less than one/5mL	less than one/2mL
	Endpoint	Including death	Immobilization	Immobilization
	Exposure period	Within ±24 hours from the period specified in the test guidelines Daphnia: 24-72 hours	Daphnia: 48 hours	Daphnia: 48 hours
	Test condition (water temperature)	The water temperature falls within the range of ±3°C from the range specified in the test guidelines. Daphnia: 15-25°C	Daphnia: 20°C	Daphnia: 18-22°C
	Concentration setting (geometric ratio)	Same as fish	Same as fish	Same as fish
	Stability of concentrations (chemical analysis)	Same as fish	Same as fish	Actual measuring values are used for calculation where the concentration changes by more than 20%.
	Dose-Response	Same as fish		
Algae	Exposure period	Within ±24 hours from the period specified in the test guidelines Algae: 48-96 hours	Algae: 72 hours	Algae: 72 hours
	Test condition (water temperature)	The water temperature falls within the range of ±3°C from the range specified in the test guidelines. Algae: 18-27°C	Algae: 21-24°C	Algae: 21-24°C
	Concentration setting (geometric ratio)	Same as fish	The geometric ratio is recommended to be less than 3.2.	The geometric ratio is recommended to be less than 3.2.
	Stability of concentrations (chemical analysis)	Same as fish	The concentrations of test substance are measured at the start and completion of exposure. It is recommended to be 80% and more of the setting concentrations at the start of exposure.	Actual measuring values are used for calculation where the concentration changes by more than 20%.
	Dose-Response	Same as fish		

Note: These guidelines for screening toxicity data that can be categorized as Reliability Rank 2 are designed to help the Secretariat of the Ministry of the Environment screen public data including those that deviate slightly from the test guidelines. Eventually, the Investigative Commission on Standards for Registration Suspension of Agrochemicals to Prevent Impacts on Aquatic Flora and Fauna and the Agrochemicals Subcommittee under the Soil and Agricultural Chemicals Committee of the Central Environment Council are responsible for determining the reliability of each piece of public data.

(Reference 3)

Categories in the Pesticide Ecotoxicity Database of the US Environmental Protection Agency

Core (C): Information included in this category meets the basic requirements of the FIFRA guidelines and therefore can be used for risk assessments pertaining to registration of agrochemicals.

Supplement (S): Information included in this category is scientifically valid. Although the results do not meet the requirements of the guidelines, with tests being conducted under conditions that deviate significantly from recommended protocols, they may be of help in conducting risk assessments.

Invalid (IN): Information included in this category is not considered useful and may not be scientifically valid. With tests being conducted under conditions that deviate significantly from recommended protocols, moreover, the results are inappropriate for use in risk assessments. In addition, the purity of test substances is unknown and hence the test results may be categorized as “invalid.”