

The Test Methods and Judgment Criteria Concerning the Judgment etc. for assignment to the Monitoring Chemical Substances

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In preparation for advisory councils to be held jointly by the Ministry of Health, Labour and Welfare, the Ministry of Economy, Trade and Industry, and the Ministry of the Environment, concerning evaluation of chemical substances pursuant to the Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc., the current judgment criteria concerning test results of tests necessary for the judgment of assignment to Type I, Type II and Type III Monitoring Chemical Substances are specified as follows.

The judgment for assignment to individual Monitoring Chemical Substances will be made based on the following criteria and taking into consideration the expertise of the advisory councils.

Account

I. Testing methods

- (1) The judgment as to whether a new chemical substance or an existing chemical substance are to be assigned to a Monitoring Chemical Substance is to be made based on the results of the following tests pursuant to the provisions of paragraph (1) to (3) of the Article 2 and the Article 2-2 of "Ministerial Ordinance Specifying Items Concerning the Testing of New Chemical Substances and the Study of the Hazardous Properties of Type I Monitoring Chemical Substances and Type II Monitoring Chemical Substances", and on existing information on the chemical substances.

- (i) Biodegradation test of a chemical substance using a microorganism etc. (Biodegradation test)
 - (ii) Bioaccumulation test of a chemical substance in fish or shellfish (Bioaccumulation test) or a measurement of the partition coefficient between 1-octanol and water (Pow measurement test)
 - (iii) Repeated dose 28-day toxicity study in rodents (Repeated dose 28-day toxicity study) or repeated dose 90-day toxicity study in rodents (Repeated dose 90-day toxicity study)
 - (iv) Bacteria reverse mutation test and in vitro mammalian chromosome aberration test or mouse lymphoma TK assay (Mutagenicity test)
(Hereafter (iii) and (iv) are referred to as the "Screening toxicity test")
 - (v) Alga, growth inhibition test, daphnia acute immobilization test and fish, acute toxicity test (Ecotoxicity test)
- (2) Although the above tests are specified to be carried out, in principle, in accordance with “the Notice On the Test Method Concerning New Chemical Substances (November 21, 2003, No. 1121002, Pharmaceutical and Food Safety Bureau, MHLW, No.2, Manufacturing Industries Bureau, METI, No. 031121002, Environmental Policy Bureau, MOE)” (hereafter referred to as the "Notice"), the results obtained pursuant to other test methods (OECD test guideline, etc.) may be used for judgment in the case where they are considered to be treated as the equivalents of the methods described in (1) and reliability of the test results are recognized to have been assured.

II. Judgment criteria concerning test results

In the case where judgment is to be made pursuant to the test results of the tests listed in I. (1), the judgment in principle will be made in accordance with the following criteria.

(1) Biodegradation test

(i) Ready biodegradable

- The biodegradability based on BOD testing is 60 percent or more in two or more of three test vessels, and the average biodegradability of the three test vessels is 60 percent or more.
: In addition to the above criterion, it should be confirmed that no degradation products are observed by direct analysis (HPLC, GC, etc.).
: In the case where the results under the testing methods specified in the Notice do not meet the criteria described above, wherein it is suggested that continued biodegradation even after completion of the tests is indicated from BOD curves, etc. (upward tendency, etc), judgment can be made based on the test results under the OECD Test Guideline 302C.

(ii) Non-biodegradable

- Properties of not being ready biodegradable

(2) Bioconcentration test or Pow measurement test

(i) Highly bioaccumulative

- A bioconcentration factor of 5000 or greater

(ii) Not highly bioaccumulative

Any of the followings:

- A bioconcentration factor of less than 1000
 - The logarithm of the partition coefficient between 1-octanol and water (Pow) of less than 3.5. However, this is not applied to surface-active substances, mixtures with molecular weight distribution, organometallic compounds, low-purity substances (excluding HPLC method) or inorganic compounds.
- (iii) In the case where the bioconcentration factor is 1000 or more and less than 5000, judgment is to be made comprehensively taking into account of the followings:
- Elimination test
 - Bioconcentration factors for different parts of the fish body (edible parts)

In addition, when the judgment described above is to be made, steady-state bioconcentration factors are to be used in principle. In the case where they are not available, the judgment is to be made comprehensively. Also, in the case where the concentration-dependence is observed on the bioconcentration factors, tests may be carried out in a range of lower concentrations if necessary, and the judgment will be made by taking into account of the test results.

(3) Screening toxicity tests

(i) Bacterial reverse mutation test

a) Positive

- The number of revertant colonies increases by more than twice the solvent control in any of the test systems, and reproducibility or dose-dependency is observed in the effect.
- The substance is judged highly positive in principle in the case where a relative mutagenic activity of approximately 1000 rev/mg or more is observed.
- The substance is judged slightly positive in principle in the case where positive results are obtained and reproducibility or dose-dependency is insignificant.

b) Negative

- Test results are not positive.

(ii) In vitro mammalian chromosome aberration test or mouse lymphoma TK assay

a) In vitro mammalian chromosome aberration test

[1] Positive

- The incidence of chromosomal aberrations is approximately 10 percent or more as compared with the negative control, and reproducibility or dose-dependency is observed in the effect.
- The substance is judged highly positive in principle in the case where the D_{20} value is 10^{-2} mg/ml or less.
- The substance is judged slightly positive in principle in the case where positive results are obtained with insignificant reproducibility or dose-dependency, or in the case where positive reactions are observed only in a range of concentrations at which the cell growth is inhibited by approximately 50 percent or more, or the like.

[2] Negative

- Test results are not positive.

b) Mouse lymphoma TK assay

[1] Positive

- There is a statistically significant increase in mutagenic frequency in any of the test

systems, and reproducibility or dose-dependency is observed in the effect.

- The substance is judged highly positive in principle in the case where mutation frequently increases more than four times that of the negative control or more than $400 * 10^{-6}$ of the negative test systems.
- The substance is judged slightly positive in principle in the case where positive results are obtained and reproducibility or dose-dependency is insignificant, or in the case where mutation frequency increase less than twice that of the negative control, or in the case where positive reactions are observed only in a range of concentrations at which cytotoxicity of approximately 80 percent or more is observed, or the like.

[2] Negative

- Test results are not positive.

(iii) Repeated dose 28-day toxicity study (hereinafter, including tests conducted in accordance with the methods specified in OECD Test Guideline 422) or Repeated dose 90-day toxicity study

a) Depending on the degree of NOEL and observed toxicity, a chemical substance is classified into the following three categories:

- [1]:
- a chemical substance with a NOEL of less than 25 mg/kg/day (excluding the cases in which only slight toxicological changes are observed such as non-specific changes in the estimation criteria of NOEL, etc.);
 - a chemical substance with a NOEL of approximately 25 mg/kg/day or more but less than 250 mg/kg/day, where the toxicologically significant changes such as neurobehavioral toxicity, severe histopathological effects, etc. in the estimation criteria of NOEL or other observed toxicity in the test (concerning the effects in the convalescent phase, see b) A or B));
- [2]: a chemical substance with a NOEL of approximately less than 250 mg/kg/day (excluding those assigned to category [1]); and
- [3]: a chemical substance with a NOEL of approximately 250 mg/kg/day or more.

In addition, in the repeated dose 90-day toxicity study, the judgment should be made taking into consideration the longer administration period etc. compared with the repeated dose 28-day toxicity study.

b) Depending on degree of the effect observed in the recovery test, a chemical substance is classified into the following three categories. In addition, at the classification, consideration should be given to the degree of reversibility, persistence of toxicity in the convalescent phase, presence of delayed toxicity, and presence of biochemical effects caused by histological changes, etc.

A: a chemical substance causing histopathological changes that are not recoverable within the recovery test period, or a chemical substance causing delayed toxicity

B: a chemical substance causing biochemical changes that are not recoverable within the recovery test period

C: a chemical substance with reversible changes that are indicated to be recoverable or in the process of recovery in the recovery test period

(4) Ecotoxicity test

Depending on the alga, growth inhibition test, daphnia acute immobilization test, and fish, acute toxicity test, a chemical substance is classified into the following three categories (The values of the EC50 and the NOEC under the alga, growth inhibition test are, in

principle, those which calculated by the growth rates of algae.):

- [1]: a chemical substance with a minimum L(E)C50 value of approximately 1 mg/l or less from the results of three types of tests
- [2]: a chemical substance with a minimum L(E)C50 value of approximately more than 1 mg/l up to 10 mg/l from the results of three types of tests (excluding those assigned to category [1])
- [3]: a chemical substance with a minimum L(E)C50 value of approximately more than 10 mg/l from the results of three types of tests

(5) The judgment of Type I Monitoring Chemical Substances

For an existing chemical substance, the one which is judged to be non-biodegradable in (1) and highly bioaccumulative in (2) and is uncertain as to the long-term toxicity in either humans or animals at the top of the food chain (higher predators) is to be judged as a Type I Monitoring Chemical Substance.

(6) The judgment of Type II Monitoring Chemical Substances

A chemical substances which is judged to be non-biodegradable in (1) and not highly bioaccumulative in (2) is to be judged as a Type II Monitoring Chemical Substance, in the case where the results of (3) correspond to any of the followings:

- (i) a chemical substance for which severe toxicity is suggested in the repeated dose 28-day toxicity study or the repeated dose 90-day toxicity study (hereinafter referred to as the, "repeated-dose toxicity test") (i.e. corresponding to (3) (iii) [1])
- (ii) a chemical substance for which highly positive results are suggested in the mutagenicity test (i.e. corresponding to (3) either (i) or (ii) is highly positive)
- (iii) a chemical substance for which moderate toxicity is observed in the repeated-dose toxicity test etc., and results are positive albeit not highly positive in the mutagenicity test (classified to (3) (iii) and [2], and corresponding to (3) either (i) or (ii) being positive (excluding the slightly positive cases)).

However, in the case where toxicologically important effects such as death, cancer, prolonged disorder, effects on reproduction and future generations are observed in chronic toxicity study, reproduction/developmental toxicity test, prenatal developmental toxicity study, mutagenicity test (micronucleus test etc.), carcinogenicity study, toxicokinetics, pharmacology study, or tests having effects equivalent to these tests as specified in the Notice, chemical substances by taking into consideration the test results of these tests if necessary.

(7) The judgment of Type III Monitoring Chemical Substances

A chemical substance which is judged to be non-biodegradable in (1), not to be a Class I specified chemical substance, is to be judged as a Type III Monitoring Chemical Substance, in the case where correspond to a Type III Monitoring Chemical Substance from the following [1] or [2].

[1] The judgment will be made as follows from the results of (4).

- (i) a chemical substance with a minimum L(E)C50 value of approximately less than 1 mg/l from the results of three types of tests (i.e. (4) [1]) is judged to be a Type III Monitoring Chemical Substance
- (ii) a chemical substance with a minimum L(E)C50 value of approximately more than 1 mg/l but not exceeding 10 mg/l from the results of three types of tests (i.e. (4) [2]) is judged as

follows. In addition, the one which is assigned to two or more of the following a) to c) categories and the one which is divided over the judgment of a Type III Monitoring Chemical Substance, is judged as a Type III Monitoring Chemical Substance.

- a) In the case where the result under the fish, acute toxicity test is assigned to the above mentioned value range, the chemical substance is judged as a Type III Monitoring Chemical Substance.
 - b) In the case where the result under the daphnia acute immobilization test is assigned to the above mentioned range, the chemical substance is judged individually based on the chemical structure of the substance, etc.
 - c) In the case where the result under the alga, growth inhibition test is assigned to the above mentioned value range, the judgment will be made as follows.
 - 1] A chemical substance with an EC50 value of more than 1 mg/l up to 2 mg/l is judged as a Type III Monitoring Chemical Substance.
 - 2] A chemical substance with an EC50 value of more than 2 mg/l up to 10 mg/l is not be judged as a Type III Monitoring Chemical Substance.
- (iii) a chemical substance with a minimum L(E)C50 value of approximately more than 10 mg/l from the results of three types of tests (i.e. (4) [3]) is not judged to be a Type III Monitoring Chemical Substance.
- [2] In the case where the values of NOEC as the test results under the alga, growth inhibition test, daphnia reproduction test and fish, early-life stage toxicity test prescribed in the Notice On the Test Method Concerning the study of the Hazardous Properties of Type III Monitoring Chemical Substances (March 25, 2004, No.6, Manufacturing Industries Bureau, METI, No. 040325004, Environmental Policy Bureau, MOE) are at least 0.1 mg/l or less, a chemical substance with the NOEC is judged as a Type III Monitoring Chemical Substance. In addition, a chemical substance for which test results except for above mentioned are suggested in chronic toxicity of aquatic animals, is individually judged.

In addition, for a chemical substance that is difficult to be judged based on the above criteria, it is judged from the standpoint of safety side, by taking into consideration the examples of assessment and judgment of analogous substances.

III. Judgment based on the flow scheme for polymers

The judgment based on the flow scheme for polymers involves the following criteria in principle:

- (1) A chemical substance is judged to be non-biodegradable and not highly bioaccumulative in the case where it meets the criteria of the following tests:
 - (i) Stability test
 - Criterion for weight change
: No changes in the weight before and after the test. (Changes of 2 percent or less are not counted)
 - Criterion for DOC change
: No changes in DOC before and after the test. (Changes of 5 ppm or less are not counted.)
 - Criterion for IR spectra
: No changes in IR spectra before and after the test.
 - Criterion for molecular weight change

: No changes in the molecular weight before and after the test.

(ii) Solubility test

- a) A chemical substance which is insoluble in any of the following nine solvents, and has specific structural characteristics (cross-linked structure, high crystallinity, etc.) or is insoluble in acids or alkalis.
water, n-octanol, n-heptane, toluene, 1,2-dichloroethane, isopropyl alcohol, tetrahydrofuran (THF), methyl isobutylketone (MIBK), and dimethyl formamide (DMF)
- b) For a chemical substance other than a), the content of components with the molecular weight of less than 1000 is 1 percent or less.

In addition, as for a chemical substance that does not meet the criteria (i) and (ii), the results of the biodegradation test, the bioconcentration test, the screening toxicity test, and the ecotoxicity test are to be used for the judgment.

(2) A chemical substance that meets the criteria III (1) (i) and (ii) is judged as follows.

- a) in the case where the chemical substance does not contain heavy metals and there is no suggestion that it has long-term toxicity to humans judging from other information on the relationship between the chemical structures and long-term toxicity, it is judged to be not a Type II Monitoring Chemical Substance.
- b) A chemical substance other than a) is judged for the assignment to a Type II Monitoring Chemical Substance, based on the results of the screening toxicity test.
- c) Any chemical substance meeting the following requirements is judged to be not a Type III Monitoring Chemical Substance.
 - (i) in the case where the chemical substance does not contain heavy metals and the solubility in water, acid and alkali is not confirmed, and falls in one of the following categories:
 - auto dispersiveness* in water is not confirmed
 - auto dispersiveness in water is confirmed, but without cationic properties* a chemical substance dispersive properties under conditions without a dispersant
 - (ii) in the case where the chemical substance does not contain heavy metals and does not exhibit cationic properties if solubility in water, acid and alkali is confirmed; and there is no suggestion that the chemical substance has possible adverse effects on inhabitation or growth of flora and fauna judging based on the information on the relationship between toxicity in flora and fauna and the chemical structure
- d) A chemical substance other than c) is judged for the assignment to a Type III Monitoring Chemical Substance based on the results of the ecotoxicity test.