

Kihatsu No. 603
September 16, 1988

To Directors of Prefectural Labour Bureaus

Director-General
Labour Standards Bureau of the Ministry of Labour

Application of the Standards of Investigation of Toxicity and the Standards to be Provided at the Test
Facilities Carrying out Investigation of Toxicity

The standards (Notification No. 77 of the Ministry of Labour in 1988; hereinafter referred to as the "Standards of Investigation of the Toxicity"), specified by the Minister of Labour based on the provisions of Article 57-2, paragraph (1) of the Industrial Safety and Health Act (Act No. 57 of 1972; hereinafter referred to as the "Act") and the standards to be provided at the test facilities carrying out investigation of toxicity (Notification No. 76 of the Ministry of Labour in 1988; hereinafter referred to as the "Standards to be Provided at the Test Facilities Carrying out Investigation of Toxicity") based upon the provisions of Article 34-3, paragraph (2) of the Ordinance on Industrial Safety and Health (Ordinance of the Ministry of Labour No. 32 of 1972; hereinafter referred to as the "Ordinance") were promulgated on September 1, 1988 and were applied from October 1, 1988, respectively.

We expect you to pay attention to the following matters without omissions of their operation.

No. 1. Purpose of enactment

The OECD (Organisation for Economic Co-operation and Development) ensures the reliability of the chemical safety testing procedures, and it aims to ensure mutual use of the test results among countries, using standard testing methods (hereinafter referred to as "Test Guidelines") and Good Laboratory Practice (hereinafter referred to as the "GLP"), and recommends that each Member Country should adopt these test results. It has been decided that Member Countries shall mutually accept the results of the tests conducted at the test facilities, which meet the OECD Principles of GLP in compliance with to the OECD Test Guidelines.

In regards to the investigation of toxicity of new chemical substances under the provisions of Article 57-2, paragraph (1) of the Act, we have developed standards for the mutagenicity test using microorganisms and the standards to be provided at the test facilities carrying out the mutagenicity

test, and provided guidance to related entities in accordance with the "Standard of the Mutagenicity Test Using Microorganisms" based on the Notification of Director-General, Kihatsu No. 261 dated May 18, 1985 (hereinafter referred to as the "Director-General Notification Kihatsu No. 261"). In the context of such international trends, legislations have been amended with the aim of legally securing the reliability of the investigation, and two standards were enacted as Notifications of the Labour Ministry, providing guidelines for investigating the toxicity levels of new chemical substances, which shall be tested in accordance with the standards of investigation of toxicity (Test Guidelines), and the investigation of toxicity shall be provided at the test facilities that meet the necessary standards to carry out investigations concerning the levels of toxicity.

No. 2. Standards of investigation of toxicity

1. General matters

(1) The investigation of toxicity under the provisions of Article 57-2, paragraph (1) of the Act shall be conducted pursuant to the provisions of Article 34-3, paragraph (1), item (i) of the Ordinance, where the intended test is conducted using the mutagenicity test, which is a form of test from which information equivalent to the present test or better than that obtainable from a mutagenicity test or the carcinogenicity tests is used, to carry out any one of these tests. Among these test details, the mutagenicity test using microorganisms shall be conducted according to these standards.

(2) These standards shall be equivalent to the "Standard of the Mutagenicity Test Using Microorganisms" as shown in Appendix 1 of Notification No. 261.

(3) When the employer intends to file a notification under the provisions of Article 57-2, paragraph (1) of the Act and conducts a test for investigation of toxicity other than the mutagenicity test using microorganisms, it shall be instructed that the employer shall have a discussion beforehand with the Chemical Substance Investigation Division, Industrial Safety and Health Department, Labour Standards Bureau, Ministry of Labour.

2. Details

(1) Article 2 related matters

A. In principle, the test shall be conducted by pre-incubation method or plate method.

B. The "metabolic activation system" stipulated referred to paragraph (2) shall be the same as what is usually called "S9 Mix."

(2) Article 3 related matters

"In view of the nature of the test item, if it is deemed necessary to conduct a mutagenicity test

using new strains other than these existing ones," and when it shows negative value to all five strains shown in this Article, the test item shall have two or more reactive bonding groups in its chemical structure and may have crosslinking between DNA strands. In this case, strains to be added shall include *S. Typhimurium TA 92* and *TA 94*.

(3) Article 4 related matters

A. When mutagenicity is observed in the concentration setting test, appropriate dose shall be applied in this test so that dose-response relationship is obtained.

B. The provisions of the proviso of item (i), the highest dose when "growth inhibition is recognized" shall be the dose at which growth inhibition is first observed when the dose of the test item is gradually increased.

(4) Article 7 related matters

In principle, regarding a test item showing particularly strong inhibition of growth at a low dose, the number of mutagenesis and viable bacteria shall be counted for the washed microorganisms, and the mutagenicity frequency shall be determined after applying the test item.

No. 3. Standards to be provided at the test facilities providing investigation of toxicity

1. General matters

(1) When conducting a mutagenicity test, which is included in the investigations of toxicity under the provisions of Article 57-2, paragraph (1) of the Act, the test shall be conducted on test facilities equipped with these standards concerning organization, equipment, etc.

(2) These standards shall be determined in consideration of consistency with the OECD principles of GDP and the other domestic laws and regulations regarding GDP based on the "standards to be provided at the test facilities providing a mutagenicity test" as specified in Annex 3 of Notification of the Directive-General, Kihatsu No. 261.

(3) When the employer who attempts to make a notification under the provisions of Article 57-2, paragraph (1) of the Act, which is included in the investigation of toxicity, conducts a test other than a mutagenicity test, it shall be instructed that the employer shall have a discussion with the Chemical Substance Investigation Division, Industrial Safety and Health Department, Labour Standards Bureau, Ministry of Labour.

2. Details

(1) Article 2 related matters

A. A "person who submits the results of the test to the Minister of Labour" referred to item (i) means the one who submits the results of the toxicity test conducted by others to the Minister of Labour other than those who outsource the testing to test facilities. The purpose of applying these standards to the above case is that, even when a person who did not outsource a test at the time of testing, that person could later submit the results of the test to the Minister of Labour.

B. The word "etc." of the "magnetic tapes, etc." referred to item (iv) shall include photographs and charts. Also, the word "etc." of the "original observation results, etc." referred to the same item shall include work records.

(2) Article 3 related matters

A. The purpose of paragraph (1), "conducting the following matters," also means that not only the Test Facility Management does it by himself/herself, but also lets proxy conduct the matters and check the results therefrom.

B. In the case of "nomination" referred to the provisions of paragraph (1), item (i), when it is difficult for a Study Director to fulfill the duties stipulated in Article 4, this person shall be immediately replaced. In this case, the date and reason for the change shall be recorded.

C. The purpose of "(excluding staff pertaining to the test)" referred to paragraph (1), item (v) is that, in order to ensure the neutrality of quality assurance work, a person engaged in quality assurance operations shall not participate in the implementation of the test subject to the quality assurance work. Also, for the same purpose, the Test Facility Management shall not concurrently serve as the person responsible for the quality assurance.

D. In the case of the "nomination" referred to the provisions of paragraph (1), item (v), and when it is difficult for the Quality Assurance Personnel to fulfill the duties stipulated in Article 5, this person shall be immediately replaced. In this case, the date and reason for the change shall be recorded.

E. The purpose of paragraph (1), item (v), and the phrase "may be substituted for the nomination" is that the sponsor may nominate a Quality Assurance Personnel concerning the consigned test following confirmation by the Test Facility Management.

F. When creating the "quality assurance program" referred to paragraph (1), item (vii), the date shall be included in the quality assurance program. Also, when the quality assurance program is changed, the reason for and date of such change shall be included in the quality assurance program.

G. In the case of the "nomination" referred to paragraph (1), item (viii), and when it is difficult for the Archive Director to fulfill the duties stipulated in Article 7, this person shall be immediately replaced. In this case, the date and reason for the change shall be recorded.

H. When creating the "standard operating procedures" referred to paragraph (1), item (ix), the date shall be included in the standard operating procedures. Also, when the standard operating procedures are changed, the reason for and date of such change shall be included in the standard operating procedures.

(3) Article 4 related matters

A. In the case of foreign test facilities, only "signature" may be acceptable to meet the "signature and seal" referred to item (i). The same shall apply to the handling of "signature and seal" in each of the following articles.

B. When receiving the "approval" referred to item (i), a document stating to that effect shall be prepared and attached to the study plan document upon receipt of a signature and seal of the Test Facility Manager or the sponsor.

C. When correction or addition is to be made to the final report after receiving the audit under the provisions of Article 5, item (v), it shall be as follows:

① When correction or addition is to be made; it shall be in a manner that does not obscure the statement before correction or addition.

② When correction or addition is to be made; the date thereof and reason therefor shall be included in the final report, signed and sealed.

③ The Quality Assurance Personnel shall again audit the final report to which such corrections or additions were made.

(4) Article 5 related matters

Item (vi) specifies that, following the amendment of the system, the certificate of quality assurance prescribed by the Notification No. 261 was abolished, and therefore the inspection records shall be prepared.

(5) Article 8 related matters

The "archive equipment" may be acceptable in replacement of the "archive facility" referred to paragraph (1), item (iv).

(6) Article 13 related matters

The "dissolution, etc." in item (vii) shall include suspension and dilution.

(7) Article 15 related matters

The provisions of paragraph (3) mean that the sponsors shall be obliged to store the archives.

No. 4 Others

The application of the standards of investigation of toxicity and the standards to be provided at the test facilities carrying out investigation of toxicity shall abolish the Director-General Notification Kihatsu No. 261.