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**NATIONAL STANDARD OF THE
PEOPLE'S REPUBLIC OF CHINA**

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National food safety standard -- Chronic toxicity test

食品安全国家标准 慢性毒性试验

(English Translation)

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1 Scope

This standard specifies the basic technical requirements and test methods for chronic toxicity tests.

This standard applies to the evaluation of the chronic toxicity of the test substance.

2.1 Chronic toxicity

Experimental animals after long-term toxic effects of repeated administration of the test substance caused.

2.2 No observed adverse effect level

Through animal experiments, the existing technical means and detection index was not observed any of the test substance-related toxic effects maximum dose.

2.3 Minimum observed adverse effect level

Under specified conditions, the test substance causing a minimal effect dose animal tissue morphology, function, growth and development, and other harmful effects.

2.4 Target organ

Organ by the test substance caused significant toxic effects of experimental animals.

2.5 Satellite Group

Toxicity of the design and implementation of the additional group of animals, animal handling and feeding conditions and its main research similar to the test medium or Test convalescence observation and testing can also be used to observe and testing does not include other indicators and parameters in the main study.

3 Test purposes and principles

Animal experiments to determine the long-term oral chronic toxic effects of repeated administration of the test substance caused understand the test substance dose - response relationship and toxic effects with the target organ, determined not observed adverse effect level (NOAEL) and the minimum observed adverse effect level (LOAEL), the predicted population Chronic exposure to the toxic effects of the test substance and determine the health guidance values provide the basis.

4.1 Instruments and equipment

Anatomy of commonly used laboratory equipment, animal scales, electronic scales, biological microscope, biochemical analyzer, hematology analyzer, blood coagulation analyzer Instrument, urine analyzers, centrifuges, slicing machines.

4.2 Reagents

Formaldehyde, xylene, ethanol, hematoxylin-eosin, paraffin, blood dilution, chemical and biological reagents, analytical reagents coagulation, urinalysis reagent.

5.1 Test substance

The test substance should be used in the original sample, if it can not use the original sample, the test should be treated in accordance with the principles of the test substance

for proper disposal. will Test was incorporated into feed, drinking water or gavage administration.

5.2.1 Animal selection

Experimental animals should be selected in line with national standards and regulations (GB 14923, GB 14922.1, GB 14922.2). First rodents Selected from the rats, rodents, dogs preferred. Recommended-week-old rats 6 weeks to 8 weeks, at the beginning of each test gender differences in animal weight should not exceed $\pm 20\%$ of average weight. At least 40 the number of animals per group, male and female, should be non-parous female Rat, non-pregnant rats. If you plan to test the mid-sectional Experimental observation of the subject or the end of the recovery period to do (for satellite), should increase the number of animals (n = interim necropsy at least 20, male and female; for satellite communication Often only increased in the control group and high-dose groups of at least 20, male and female). Dogs should be used no more than nine months of age puppies (usually monthly Selected age 4 months to 6 months), at the beginning of each test gender differences in animal weight should not exceed the average weight of $\pm 20\%$, the number of animals per group at least eight, male and female, dogs should be non-parous dog, non-pregnant dogs. If you plan to test the mid or end of the test do necropsy convalescent observation should Increase the number of animals (control and high dose groups each increased by 4, male and female). Sex and number of animals in the control group should be the same group with a test substance.

5.2.2 Animal Preparation

Before the test, animals in the experimental animal room should be at least 3d ~ 5d (dogs 7d ~ 14d) acclimatization and quarantine observation.

5.2.3 Animal Feeding

Animal feeding conditions, drinking water, feed should be in line with national standards and regulations (GB 14925, GB 5749, GB 14924.1, GB 14924.2, GB 14924.3). During the test animals free access to water and food, according to the component group sex feeding cage, cage number of animals (per general Rats with no more than three) shall meet the minimum space required for experimental animals in order not to affect the free movement of animals and the animals were observed for signs appropriate. test During non-animal test each test shall be less than 10% of mortality, dying animal blood biochemical tests should be carried out as far as possible, Gross Anatomy and histopathological examination, each biological samples loss rate should be less than 10%.

Dose group and 5.3

5.3.1 Test subjects were set up at least three groups, a negative (vehicle) control group, the control group except that no administration of the test substance, the rest were treated by

the same Trial was set. If necessary, additional untreated control group.

5.3.2 should be based on 90 days of high-dose oral toxicity test shall be so determined the animals appear more obvious toxicity in principle, but does not cause too High mortality; low dose does not cause any toxic effects; the dose should be between high-dose and low-dose, toxicity can cause mild to Obtained dose - response relationship, NOAEL and (or) LOAEL. General dose group spacing of 2 to 4 times is appropriate, not more than 10 times.

5.4 Test period

The trial period for at least 12 months. Any toxic change reversibility satellite group monitored by the test substance caused persistent or delayed for with stop after the observation period to the test substance is not less than 28d, more than 1/3 of the test period.

5.5 Test procedure and outcome measures

5.5.1

The test is administered 5.5.1.1 according to the characteristics of the test substance and test purposes, select the test was incorporated into feed, water or orally administered. If the test was its driving Was palatability, should be given orally.

5.5.1.2

test was orally administered to the test substance is dissolved or suspended in a suitable vehicle, the preferred solvent is water, water-insoluble test substance You can use vegetable oils (such as olive oil, corn oil, etc.), do not dissolve in water or oil test substance may be used as carboxymethyl cellulose, starch, etc. dubbed suspension or paste like. The test substance should now use the existing, data show that except for its storage solution or suspension stabilizer. Taking into account the use of solvent Media may test substance by the body absorption, distribution, metabolism and accumulation; on the test of physical and chemical properties and toxicity resulting therefrom Impact characteristics; impact on animal food intake or water intake or nutritional status. To ensure that the test substance concentration in vivo stability, daily Same period gavage once (weekly gavage 6d), during the test, weighed twice a week for 4 weeks before 5th week to 13th week weekly weigh 1, then every 4 weeks weighed 1, weight-adjusted volume of gavage. Rodent gavage volume of generally not more than 10mL/kg of body weight, Dog 15mL/kg body weight; as an oily liquid, orally should not exceed the volume of 4mL/kg body weight. Each group was given the volume of the same.

5.5.1.3

incorporated into feed or drinking water test substance administered to the test substance and feed (or water) and mixed well to ensure the stability of the test substance formulation Qualitative and uniformity, without affecting the animal feeding, nutrition and water balance