

ICS 67.020
CCS C 53



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

GB 15193.25-2014

**National food safety standard -- Reproductive and
developmental toxicity test**

食品安全国家标准 生殖发育毒性试验

(English Translation)

Issued on: December 1, 2014

Implemented on: May 1, 2015

**Issued by: National Health and Family Planning Commission of the
People's Republic of China**

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1 Scope

This standard specifies the reproductive and developmental toxicity test basic test methods and technical requirements.

This standard applies to the evaluation of the test substance Reproductive and developmental toxicity.

2.1 Reproductive toxicity

Damage and harmful effects on male and female reproductive function or capability of future generations. Reproductive toxicity can occur in females during pregnancy, but also it can occur in pre-pregnancy and lactation. It showed the impact of exogenous chemicals on the reproductive process, such as changes in the reproductive organs and the endocrine system, for the impact of the cycle and sexual behavior, and the impact on fertility and pregnancy outcomes like.

2.2 Developmental Toxicity

Individuals prenatal exposure to the test substance, and development before becoming adult (including embryo, fetal and postnatal) harmful effects occur, table Now the development of the organism structural abnormalities, altered growth, dysfunction and death.

2.3 Maternal toxicity

Effects of test substances cause health damage, direct or indirect parent females pregnant animals, expressed as weight reduction, dysfunction, and signs of poisoning, and even death.

2.4 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.

2.5 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.

3 Test purposes and principles

The trial included three generations (F0, F1 and F2). F0 and F1 generation of administration of the test substance, reproductive toxicity was observed, F2 generation of developmental toxicity was observed features Sex. Provide information on the test substance to the female reproductive development and function of male animals. such as gonadal function, mating behavior, pregnancy, childbirth, breast-feeding, broken Milk and offspring growth and neurobehavioral and so on. The main toxic effects include progeny born after the death of increased growth and development of Change, functional defects offspring (including neural behavior, physical development) and reproductive abnormalities.

Test Method 4

4.1 Test substance

The test substance should first use 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 at the appropriate Management. The test was incorporated into the feed, drinking water or gavage administration.

4.2.1 Animal selection

Experimental animals should be selected in line with the relevant provisions of GB GB 14922.2 and 14922.1 of. Select has been documented on the test substance sensitive Animal species and strains, generally preferred rodent rat, avoid using low reproductive or developmental defects high incidence of strains. For positive Accurately assess the impact of the test substance on animal reproductive and developmental capacity of animals of both sexes should be used. The selected animal species should be indicated, product

Department, sex, weight and weeks of age. Experiment with sex between an individual animal weight difference does not exceed the average weight of $\pm 20\%$. Parental choice (F0 generation) should be non-parous female Rat, non-pregnant rats.

4.2.2 Number of experimental animals

In order to obtain basic experimental data with statistical requirements, the correct evaluation of the test substance on animal reproductive process development (including the F0 move Was reproductive, pregnancy and feeding process, first generation (F1 generation) animals from birth to maturity in the process of breast growth and development, as well as son and two Generation (F2 generation) the animals from birth to weaning growth and development related indicators) may cause toxic effects, the need to ensure that each test substance group and Control access to at least 20 pregnant rats. Usually at the beginning of the test both sexes in each group needs 30 (F0 generation), follow-up tests Used to mate the animals of each sex in each group needs 25 (F1 generation) (at least one from each litter male and female, most male and female from each litter

4.2.3 Animal Preparation

Before the test, animals in the experimental animal room should be at least 3d ~ 5d acclimatization and quarantine observation, reproductive and developmental toxicity can be carried out test.

4.2.4 Animal breeding environment

Animal feeding conditions, drinking water, feed should be consistent with GB 14924, the relevant provisions of GB 14925, GB 5749's. Press experimental animals Single cage or caged by sex, free food and water. When pregnant rats approaching childbirth, in childbirth should be kept separate cages, cage placement made when needed Nest litter.

Dose group and 4.3

Animals were randomly grouped experimental design was tested at least three groups and one control group. If a solvent is used the test substance, the control group should be given We use the maximum amount of the solvent. If the test substance causes animal food intake and decreased utilization, then the test and control animals needs Pair fed animals. High-dose group was designed to test some of the test substance should consider its impact on the balance of nutrients for non-nutrient Test substance dose should not exceed 5% of the feed.

In a test of physical and biological characteristics of the conditions allowed, the highest dose should be F0 and F1 generation animals significant toxicity, but Do not cause animal death; intermediate doses can cause mild toxicity; of low dose should not be any cause parental animals and offspring of anti should. If the toxicity of the test substance is low,

1000mg/kg bw has not seen the development of the reproductive process have any side effects, then Limit test may be used, that is no longer considered experimental test substance added another dose group. If the pre-test the effect of high doses of the drug to clear the parent Role, but had no effect on fertility, it can also be used a limited test.

4.4 Test procedure

4.4.1

The test is administered

4.4.1.1

During the test, all animals should be used in the same manner to give the test substance; such as oral administration of the test substance by gavage frequency per day 1, 7 days a week administration of the test substance. Each rat was tested dose administered (administered by the animal weight, mg/kg body weight or g/kg body Weight), the same feed and water.

4.4.1.2

according to the characteristics of the test substance or test purposes, the test substance may be incorporated into the feed, water or oral administration. Preferred incorporation of feed, if that is Test was added to the feed or drinking water affect animal palatability, oral administration of the test substance should be selected.

4.4.1.3

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 can also make use of the test substance carboxymethyl cellulose, starch, etc. dubbed suspended Liquid or paste and the like. The test substance should now use the existing, data show that except for its storage solution or suspension stabilizer. Should at the same time daily Gavage once weighed twice weekly intragastric volume weight adjustment. Gavage volume of generally not more than 10mL/kg body weight, such as a water-soluble when the liquid, the maximum volume of fed up 20mL/kg body weight; as an oily liquid, orally should not exceed the volume of 4mL/kg body weight; each group was given Consistent volume.

4.4.1.4

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, nutritional balance and water intake to the principle of the test substance incorporated into feed ratio is generally less than the mass fraction 5%, while if more than 5% (maximum not more than 10%), the control diet was adjusted nutrient levels (when the test substance no heat or nutrients, and