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90-day Oral Toxicity Test

90天经口毒性试验方法

National Medical Products Administration

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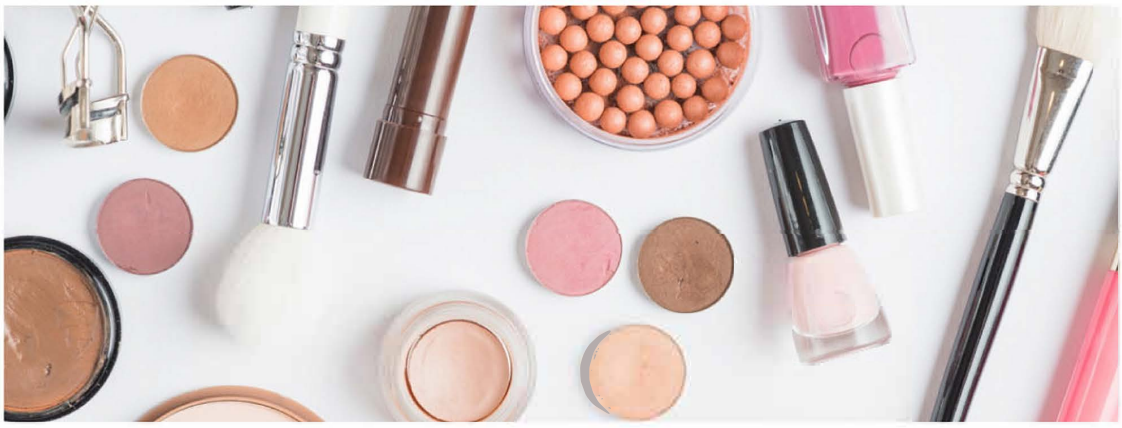
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Attachment 8

90-Day Oral Toxicity Test

1 Scope

This method specifies the basic principles, requirements, and methods for conducting a 90-day oral toxicity test in rodents.

This method applies to the evaluation of the 90-day oral toxicity of cosmetic ingredients.

2 Test Objectives

This test is designed to obtain information on the potential health hazards resulting from repeated oral exposure to a test substance over a defined period, helping to identify the target organ, dose-response relationship, reversibility and potential for accumulation of toxic effects, and estimate the no observed adverse effect level (NOAEL) and/or lowest observed adverse effect level (LOAEL), thereby providing a basis for selecting doses, observation indicators, and toxicity endpoints for chronic toxicity tests, as well as for establishing safe thresholds for human exposure.

3 Definitions

3.1 No Observed Adverse Effect Level (NOAEL)

The highest dose at which no toxic effects related to the test substance are observed using available technical means or testing indicators under specified test conditions.

3.2 Lowest Observed Adverse Effect Level (LOAEL)

The lowest dose at which the test substance induces adverse effects on the histomorphology, function, growth and development of experimental animals under specified test conditions.

3.3 Target Organ

The organ of experimental animals exhibiting significant toxic effects caused by the test substance.

3.4 Cumulative Toxicity

The capacity of the test substance to cause functional or organic damage in organisms following repeated exposure at doses below the acute toxicity threshold, due either to progressive accumulation (absorption exceeding elimination) or to cumulative toxic effects.

4 Basic Test Principles

The test substance is administered orally to each group of experimental animals at different doses on a daily basis for a continuous period of at least 90 days. At least three dose groups and one control group shall be set up, with each provided with a single dose level. Through comprehensive clinical observations, clinical examinations, gross necropsy, and histopathological examinations, the target organ and dose-response relationship are systematically identified, and ultimately the NOAEL and/or LOAEL are determined, which provide(s) key safety basis for chronic toxicity studies and human risk assessments.

5 Test Methods

5.1 Preparation of the Test Substance

When the test substance needs to be prepared into a solution or suspension with a vehicle, water shall be the first-choice vehicle, followed by vegetable oils (e.g., olive oil, corn oil). For test substances that are insoluble in water or oil, they may be prepared into a suspension or paste with carboxymethyl cellulose, starch, *etc.* If other vehicles are employed, their toxic characteristics must be learned before use, and the reasons for their use shall be provided.

5.2 Experimental Animals and Housing Environment

5.2.1 Selection of Animal Strain

Rodents, preferably rats, shall be used. Generally, SPF-grade rats aged 6~8 weeks shall be selected. At the start of the test, the body weights of the animals shall not differ by more than ±20% from the average weight. If this test serves as a preliminary test for a chronic test, the same animal strain shall be used in both tests.

5.2.2 Sex and Number of Animals

Each dose group shall include at least 20 experimental animals (half male and half female), and the females shall be non-pregnant and nulliparous. The number of animals at the end

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附件 8

90 天经口毒性试验方法
90-day Oral Toxicity Test

1 范围

本方法规定了啮齿类动物 90 天经口毒性试验的基本原则、要求和方法。

本方法适用于评价化妆品原料的 90 天经口毒性。

2 试验目的

通过本试验可获得在一定时期内经口重复暴露受试物可能产生的健康危害的信息，了解其作用靶器官、剂量-反应关系、可逆性以及蓄积的可能性，并估计未观察到有害作用水平（NOAEL）和/或观察到有害作用最低水平（LOAEL），为慢性毒性试验剂量、观察指标、毒性终点的选择及建立人体暴露的安全阈值提供依据。

3 定义

3.1 未观察到有害作用水平 no observed adverse effect level（NOAEL）

在规定的试验条件下，用现有的技术手段或检测指标未观察到任何与受试物有关的毒性作用的最大剂量。

3.2 观察到有害作用最低水平 lowest observed adverse effect level（LOAEL）

在规定的试验条件下，受试物引起实验动物组织形态、功能、生长发育等有害效应的最低剂量。

3.3 靶器官 target organ

实验动物出现由受试物引起的明显毒性作用的器官。

3.4 蓄积毒性 cumulative toxicity

机体以低于急性中毒阈值的剂量反复接触受试物，吸收量大于排出量逐渐累积或毒作用累加，引起功能性或器质性损害的能力。

4 试验的基本原则

受试物以不同剂量每日经口给予各组实验动物，至少设立 3 个剂量组和 1 个对照组，每组 1 个剂量水平，连续给予至少 90 d。通过全面的临床观察、临床检查、大体解剖和组织病理学检查，系统性地确定靶器官、剂量-反应关系，并最终确定 NOAEL 和/或 LOAEL，为慢性毒性研究和人类风险评估提供关键安全性依据。

5 试验方法

5.1 受试物制备

当受试物需使用溶媒配制成溶液或混悬液时，溶媒首选水，其次为植物油（如橄榄油、玉米油等），不溶于水或油的受试物亦可使用羧甲基纤维素、淀粉等配成混悬液或糊状物。如果使用其他溶媒时，必须先了解其毒性特点并说明理由。

5.2 实验动物和饲养环境

5.2.1 动物种系的选择

啮齿类动物，首选大鼠。一般选用 6 ~ 8 周龄 SPF 级大鼠，试验开始时动物体重差异不应超过平均体重的±20%。若该试验为慢性试验的预备试验，则在两个试验中所用的动物品系应当相同。

5.2.2 动物的性别和数量

每一剂量组实验动物至少应有 20 只（雌雄各半），雌性应为未妊娠和未经生产的动物。试验结束时的动物数需达到能够有效评价受试物毒性作用的数量。应至少在对照组和最高剂量组各增加 10 只动物（雌雄各半），作为恢复期卫星组。若试验计划包含中期剖检，则应至少在对照组和最高剂量组再分别增加 10 只动物（雌雄各半）。

5.2.3 动物饲养

实验动物及动物试验环境、饲料、饮水应符合国家相应规定。试验期间，动物自由饮水和摄食。动物按组别、性别分笼饲养，每笼动物数量应满足动物最低需要的空间，不影响动物自由活动和观察动物的体征为宜。

5.3 剂量设计

试验剂量的设计可参考 28 天重复剂量经口毒性试验结果和/或急性经口毒性试验 LD_{50} 剂量，也可开展剂量范围探索研究。试验时至少设 3 个剂量组和 1 个对照组。除不接触受试物外，对照组的其他条件均与试验组相同。最高剂量的设计应在引起毒性效应的前提下又不致造成动物死亡或严重反应，否则将会影响结果的评价。低剂量水平应不出现任何毒性作用。若掌握人群接触水平，则最低剂量不低于人群的实际接触水平。中间剂量可引起较轻的可观察到的毒性作用。若设置多个中间剂量组，则各组的剂量应引起不同程度毒性作用。各剂量的组间距以 2 ~ 4 倍为宜，一般不超过 10 倍。

5.4 限值试验

在本项试验中，如在一个不低于 1000mg/kg BW/d 的剂量组未产生可观测到的



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