Provisional translation

Adapted on 1st June, 2018
Expert Committee on Veterinary Medicinal Products
The Food Safety Commission

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Assessment guide for veterinary medicinal products with endocrinological activities

1. Background

In 2016, the Expert Committee on Veterinary Medicinal Products (ECVMP) conducted a risk assessment of melengestrol acetate (MGA), which had been used as a growth promotor, from foods. By that time, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) had already established an ADI. In contrast, EU had delivered the statement that an ADI establishment had not been realistic due to the lack of whole spectrum of data about growth-promoting hormones (natural and synthetic forms, including MGA) by using quantitative analysis. After JECFA and EU decisions, at the Food Safety Commission of Japan (FSCJ), ECVMP has organized their key principles of thinking, then conducted s risk assessment.

It is clear that each international organization has different way of deliberating its assessment about growth–promoting hormonal product, other than MGA, therefore, the FSCJ-ECVMP must organize its assessment guide regarding process of such veterinary medicinal products with endocrinological activities (hormonal products), in order to consistently carry risk assessments in this category.

2. Basic principles

(1) The assessment should be conducted to clarify the risk of human health effects via consumption of foods derived from livestock that were given veterinary hormonal products, to see the indirect effect of those hormonal products to human. This is different from assessing the direct effect of those hormones ingestion by human. Therefore, the assessment process also should include discussion on oral exposure of human to those products via animal products.

(2) Assessment based on toxicological test should acknowledge and consider the following points:

a) Negative effects by direct ingestion

b) Negative effects of indirect intake via foods

(3) Detailed consideration might be omitted over the residual information of those products, in case their probability to negatively affect human health is highly unlikely by the look of chemical structures among those proteins and peptides.

(4) For the moment, the detailed discussion, indicated below, needs to be done on hormonal products, if their assessment principles vary among international organizations.

3. Assessment methods

(1) Direct negative effects by the use of hormonal products

a) Genotoxicity

The hormonal product to be assessed should be judged whether it has the kind of genotoxicity that might raise concerns over human health. The degree of genotoxicity to human health should be clarified for the assessment of hormone products. If genotoxicity is negligible, it is thought possible to set NOAEL and LOAEL to obtain the toxicological ADI.

b) Endpoints

It is necessary to consider the possibility of species' susceptibility differences for the targeted hormonal product at the assessment. If susceptibility gap among species are acknowledged based on toxicological studies, the endpoints should be determined inclusive of such factors for human relevance.

c) Epigenetic effects, the regulatory effect of gene expressions caused indirectly by chemical modifications on to genetic materials including DNA and histone proteins

Regarding the effect of hormonal products on chemical modification of DNA, in such case as human ingestion of livestock products, the comprehensive consideration and confirmation are essential to judge whether actual concerning insight exists over the assessed hormonal substance. The most sensitive period of DNA duplication for such chemical modification is known to be at the stage of spermatogenesis. Thus, when the actual insight is found to exist, the discussion should be comprehensive, especially make sure to include whether to have reproductive toxicity test results as endpoints.

d) Sensitivity difference by exposure timing

It should be made sure whether certain age-wise data of human health effects exist regarding the assessed substance ingestion via livestock products. The timing instances

include prenatal, perinatal, prepubertal or menopausal periods in life. In case there is an insight exists, follow the same steps as in ‘c) Epigenetic endpoints’ above. There needs to be a consideration about whether to include reproductive toxicological test results as an endpoint.

(2) Indirect effect of hormones

a) Endogenous hormones to be taken into account

Make sure to check if there are different types of endogenous hormones in increase after usage of the hormonal product in livestock.

b) Concerning levels of endogenous hormones

If the increase in endogenous hormones by the hormonal products is found, as in ‘a) Endogenous hormones’, further investigate if this gap is over the physiological fluctuation range in the livestock.

c) Effect on human

After ‘b) Concerning levels of endogenous hormone gap’ is checked and confirmed to be more than the physiological fluctuation range, comprehensive review should be given to the oral absorption rate and physiological fluctuation range of the given hormone in human, in order to consider the negative effects on human health.

d) Others

Regarding the other factors, such as varying sensitivity by exposure duration, or altered gene expressions by regulatory mechanisms indirectly brought about by chemical modifications on DNA and histone proteins, additional discussion should be given after implementing above items a) through c).