European Food Safety Authority

Genotoxicity
Guidance on Food Additives

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Genotoxicity

RATIONALE

Genetic damage in somatic or germ cells is associated with serious detrimental health effects, including cancer, heritable diseases and degenerative conditions. These effects can in principle be induced by genotoxic substances also at low doses.

Consequently EFSA considers that genotoxic substances should not be deliberately added to food at any dose level (EFSA, 2005)

Genotoxicity

OBJECTIVE

Objective of genotoxicity testing of food additives and other food ingredients is the genotoxic hazard identification, with the purpose of mimimizing the health risk for consumers through the primary prevention of the exposure to genotoxic substances.

Genotoxicity testing - general considerations

End-points to be considered:

- gene mutation
- structural and numerical (aneuploidy) chromosomal alterations

All three end-points need to be considered for an adequate genotoxicity assessment of chemical substances, as all of them have detrimental health effects.

Test strategy:

No single test system can detect all three end-points, thus a battery of complementary tests is necessary.

Genotoxicity testing – the EFSA approach

The recommended approach for genotoxicity testing of food additives is based on the recent **Scientific Committee Guidance on Genotoxicity Testing Strategy** (EFSA, 2011)

A harmonized and simplified scheme for genotoxicity testing is proposed, based on the step-wise (tiered) application of in vitro (Tier 1) and in vivo (Tier 2) tests, driven by test results (rather than by exposure scenarios).

The new EFSA guidance document on food additives (2012) presents some relevant changes [new] in the recommended test batteries compared to the SCF Guidelines of 2001.

Genotoxicity - Tiered approach

Tier 1 (mandatory for all new food additives)

In vitro genotoxicity testing*

- Recommended test battery: *new*
  - Bacterial reverse mutation assay (OECD TG 471)
  - In vitro mammalian cell micronucleus test (OECD 487)

Outcomes of *in vitro* genotoxicity

Negative: no further testing

Positive: further *in vivo* testing required (Tier 2)

* In vivo assays are not considered necessary in Tier 1, unless available information indicate the inadequacy of in vitro systems

Genotoxicity - Tiered approach

Tier 2 (follow-up of *in vitro* positives)

In vivo genotoxicity testing

- Recommended tests*: **new**
- *In vivo* micronucleus test (OECD TG 474)
- *In vivo* comet assay (OECD TG in preparation)
- Transgenic rodent mutagenicity assay (OECD TG 488)

*to be selected case-by-case based on in vitro test results, SAR, metabolic and toxicokinetic considerations...

Outcomes of *in vivo* genotoxicity testing:

Negative**: no further testing

Positive: genotoxic hazard to humans

** with evidence of target cells exposure

Genotoxicity - Tiered approach

Tier 3 testing

(Follow-up from Tier 2 positives with germ cells or carcinogenicity studies)

Normally there is no Tier 3 genotoxicity testing

- Substances positive in tests in somatic cells are assumed to reach germ cells and to be germ cell mutagens too;

- Even in presence of negative carcinogenicity data, genotoxicity in vivo in somatic cells is considered an adverse effects *per se*.