Asiantaeth Safonau Bwyd
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Cyngor i ymgeiswyr ar gynnal asesiad risg i'w gyflwyno i gefnogi cais am dreial bwyd anifeiliaid yn y DU ar gyfer ychwanegyn bwyd anifeiliaid heb ei gymeradwyo

Dylai ymgeiswyr gyflwyno asesiad risg sy'n ymwneud â'r treial bwyd anifeiliaid arfaethedig. Oherwydd eu natur technegol ac yn unol â'n rhwymedigaethau, mae'r canllawiau hyn ar gael yn Saesneg yn unig.

Applicants should submit a risk assessment relating to the intended trial, using any evidence already held in relation to:

- Safety for the consumer
- Safety for the target species
- Safety for the environment
- Safety for the worker

It is understood that feed additives to be trialled will be at different stages of the R&D pipeline, and that a trial application will not contain all the final safety data required for a complete feed additive dossier. However, enough safety data should be provided, along with a relevant risk assessment, to address any concerns relating to safety for the target species, consumers, environment and workers, relevant for this trial application.

Safety for the consumer

Safety for the consumer applies if it is the intention to have subsequent animal products going into the food chain from trial animals exposed to the test item during the trial. In short, the applicant's risk assessment should consider the fate of the additive in the animal system, the toxicity of the additive and any relevant metabolites, the exposure of food consumers to these from consumption of the animal products, and the characterisation of the risk.

In cases where the active compound is present in a fermentation product, the whole fermentation formulation should be assessed, which should be identical to the product intended for the market.

If an additive has several active compounds, the safety of each should be assessed, and a discussion provided on potential combined effects. Residue studies should be undertaken on the final form of the product, including the combination of active compounds, to account for any metabolic interactions. For mixtures where potential active compounds cannot be each characterised, the combined mixture should be evaluated.

The risk assessment should evaluate consumer exposure following EFSA's guidance on the safety of feed additives for the consumers (Section 4). This should include establishment of a toxicological health-based guidance value (HBGV), such as an acceptable daily intake (ADI), an exposure assessment based on residue data in the edible animal products, and comparison of

exposure to the HBG.

In certain cases, safety, ADME and residue studies are not required as outlined in Section 3 of EFSA's guidance on the safety of feed additives for the consumers.

In summary, studies that could be provided as evidence alongside the applicant's risk assessment include:

- An ADME study following Organisation for Economic C-operation and Development (OECD) Test Guideline (TG) No. 417. To show the metabolism of the test item(s) in laboratory animals and the intended target species as a basis for its toxicological evaluation. This study(s) should also establish the metabolism kinetics of the test item, e.g. major metabolites as potential marker residues.
- A baseline set of data to evaluate genotoxicity from a reverse mutation (OECD TG 471) and a micronucleus assay (OECD TG 487). These should then be complemented if appropriate by further studies to evaluate if the observed genotoxic result occurs in vivo. For example, a mammalian erythrocyte micronucleus test (OECD TG 474), a transgenic rodent somatic and germ cell gene mutation assay (OECD TG 488) and/or an in vivo Comet assay (OECD TG 489), as appropriate.
- (In order to reduce the number of test animals, a single study combining the analysis of different endpoints (e.g. micronucleus and comet assay) should be considered).
- A sub-chronic oral toxicity study (OECD TG 408).
- An in-vivo chronic oral toxicity study (OECD TG 452), if considered required based on the results of the sub-chronic toxicity study.
- A carcinogenicity study (OECD TG 451) or combined with a chronic toxicity study as per OECD TG 453), if there are indications for any potential carcinogenic effect.
- In-vivo reproductive and prenatal developmental toxicity studies if there are any indications for a potential effect on reproduction and/or development (OECD TG 416, a two-generation reproduction study or OECD TG 443, an extended one-generation reproductive toxicity study, and OECD TG 414, a test guideline for prenatal developmental toxicity studies.
- Other toxicology studies if there are potential adverse effects not adequately addressed by the above studies.
- Residue studies providing data for the relevant animal products to enter the food chain, using the highest inclusion concentration intended for the feed trial. A total and/or marker residue study should be undertaken following EFSA's guidance on the safety of feed additives for the consumer (Section 2.1.2). If relevant the marker residue should be derived from the ADME data and the established ratio of marker to total residues should be provided for the appropriate animal products.
- A literature review covering past published safety evaluations of the additive to complement the studies above or provide evidence that a new study is not required. Reviews should be undertaken and reported following the EFSA guidance by Glanville et al. (2014) .

Studies involving animals should respect the rules on animal welfare laid down by EU legislation (see Directive 63/2010/EU). Studies should not be repeated if data are already available.

Safety for the target species

All applications should address the safety implications for the target species within the risk assessment, following EFSA's guidance on the assessment of the safety of feed additives for the target species.

This should cover the intended inclusion concentration(s) for the trial and use data from toxicity data from repeated dose studies in laboratory animals and/or relevant tolerance studies if available. This should include studies from the published literature in the first instance. Reviews should be undertaken and reported following the EFSA guidance by Glanville et al. (2014).

Interspecies extrapolation of data can be used within the applicant's risk assessment if this extrapolation is between physiologically similar species (see Table 3 in EFSA's guidance on the assessment of the safety of feed additives for the target species4) and the margin of safety (the ratio of tolerated to maximum proposed use level) is established as ? 10 for the species used for the extrapolation. This extrapolation margin of safety criteria may be lower for certain additives such as e.g. organic acids, certain coccidiostats.

Any known interactions of the test item with other relevant feed ingredients, other additives or veterinary products should be described within the application.

In certain cases, safety studies are not required as outlined in Section 2 of EFSA's guidance on the assessment of the safety of feed additives for the target species.

If the application does not fully address the above guidance the applicant should indicate what monitoring and controls are in place to quickly identify and manage any adverse effects that occur during the trial.

Safety for the environment

All applications should consider and discuss risks to the environment regarding the trial. Please see EFSA guidance on safety for the environment. The FSA may use an external contractor to support the evaluation of this assessment.

Safety for the worker

All applications should consider and discuss risks to the worker regarding the trial. Please see EFSA guidance on safety for the users. The FSA may use an external contractor to support the evaluation of this assessment.

Other considerations for the risk assessment

The efficacy trial should be designed following recommendations laid out in FSA/FSS Guidance on the assessment of the efficacy of feed additives. The risk assessment should indicate whether the trial design complies with the relevant animal welfare regulations (e.g., (England) Reg 2007/2078, (Wales) Reg 2007/3070, (Scotland) 2010/388, (Northern Ireland) 2011/16 and 2012/156, EC Dir 2010/63, EC Dir 98/58, EC Dir 1999/74, EC Dir 2007/43, EC Dir 2008/119 and EC Dir 2008/120). A trial that is not shown to comply with these requirements will not be accepted as part of the application dossier.

Where an application contains an additive produced from a production microorganism the applicant should provide as much information as possible on the production processes. Furthermore, safety data should be provided relating to this process where relevant. For example, data to show absence of the host production organism and/or fermentation products in the final product. If the host production organism has previously shown to be safe, for example on the EFSA list of QPS recommended biological agents, but is genetically modified, then it should be shown in supporting evidence that the molecular characterisation of the genetic modification does not give rise to concern.

Where an application relates to a microorganism, for example a probiotic strain, or uses a production microorganism, molecular characterisation and phenotypic testing for antimicrobial resistance (AMR) should be provided. The molecular characterisation should include taxonomic identification, genotypic screening for AMR genes, and an assessment of antimicrobial production, toxigenicity and pathogenicity. Results should be interpreted in-line with EFSA guidance.

All supporting studies provided as evidence within the feed trial application should be undertaken and documented according to appropriate quality standards and should respect the rules on animal welfare laid down by retained EU legislation, particularly those listed in retained EU Directive 63/2010/EU. Studies should be compliant with the criteria established by a recognised, externally audited, quality assurance scheme (e.g. good laboratory practice (GLP) in accordance with retained EU Directive 2004/10/EC).

Where a trial uses a different or modified form of a test item cited in the referenced studies, equivalence of the trial test item to the test item in the studies cited should be demonstrated and the specific differences described.

We encourage the continuing development of new approach methodologies (NAMs) and Integrated Approaches to Testing and Assessment (IATA) including high throughput screening, omics and in silico computer modelling strategies (e.g. Artificial Intelligence (AI) and machine learning) for the evaluation of hazard and exposure towards safety to complement required toxicological data. This also advocates the Replacement, Reduction and Refinement (3Rs) of animals.

All information provided to the FSA/FSS in relation to an application will remain confidential.