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SCIENTIFIC OPINION

Guidance on the assessment of the safety of feed additives for the users

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Abstract

This guidance document is intended to assist the applicant in the preparation and the presentation of an application, as foreseen in Article 7.6 of Regulation (EC) No 1831/2003, for the authorisation of additives for use in animal nutrition. It specifically covers the assessment of the safety for the users.

KEYWORDS

feed additives, guidance, safety, user

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1 | INTRODUCTION

1.1 | Background and Terms of Reference

Regulation (EC) No 1831/2003 establishes the rules governing the Community authorisation of additives for use in animal nutrition. Moreover, Regulation (EC) No 429/2008 provides detailed rules for the implementation of Regulation (EC) No 1831/2003 as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives.

The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) has adopted a series of Guidance documents which aim at complementing Regulation (EC) No 429/2008 to help the applicants in the preparation and submission of technical dossiers for the authorisation of additives for use in animal nutrition according to Regulation (EC) No 1831/2003.

At the plenary meeting in September 2021, the FEEDAP Panel identified the following Guidance documents and statement for revision:

- the Guidance on user safety, considering recent scientific developments and the Panel's experience gained during the last years while working under the provisions of Regulation (EC) No 429/2008,
- the Guidance on the assessment of the efficacy of feed additives, making it complementary to the revised Regulation (EC) No 1831/2003 by stimulating innovation and sustainability in particular for additives that are beneficial for the environment and animal welfare, as outlined in the Green Deal,
- the Guidance on the characterisation of microorganisms used as feed additives or as production organisms, harmonising it with related EFSA Guidance documents, and
- the EFSA Statement on the requirements for whole genome sequence analysis of microorganisms intentionally used in the food chain, keeping track of the fast development in this field.

In view of the above, the European Food Safety Authority (EFSA) asked its FEEDAP Panel to:

1. Analyse for the identified Guidance documents which aspects are most relevant to be updated based on the scientific developments and stakeholder perspective;
2. Update the identified Guidance documents, focussing on the most relevant aspects and taking into account the comments received during public and/or targeted consultations.

This output addresses the two terms of reference as they relate to the assessment of the user safety.

In line with EFSA's policy on openness and transparency, and for EFSA to receive comments from the scientific community and stakeholders, a draft of the Guidance was released for public consultation.[1] The outcome of the public consultation is described in a technical report published as Annex A[2] to this Guidance.

1.2 | Scope of the guidance

This guidance document is an update of the EFSA FEEDAP Panel Guidance on user safety published in 2012 (EFSA FEEDAP Panel, 2012) which it replaces. Like the previous version, it is intended to assist the applicant in the preparation and the presentation of an application for authorisation of a feed additive, as foreseen in Article 7.6 of Regulation (EC) No 1831/2003, concerning the safety for the users. This document does not substitute for the obligation of an applicant to comply with the requirements of Regulation (EC) No 1831/2003 and its implementing rules (Regulation (EC) No 429/2008). Applicants should justify the omission from the dossier of any data or any deviations from the requirements detailed in this guidance.

The authorisation process foresees the need for the assessment of the safety of an additive for people who may come into contact with it in the workplace. This definition is restricted to those workers who may be exposed to the additive while handling it, when incorporating it into premixtures, feed materials or compound feeds or using a premix or feedingstuff supplemented with the additive. The guidance does not cover human accidental exposure (e.g. ingestion) or the use of an additive at home (e.g. pet owners). The assessment as proposed in this Guidance refers to the 'unprotected' user.

A hazard assessment relevant to users should be included in the application dossier, based on studies relevant to the nature of the additive. Experience in the manufacturing plant may be an important source of information in evaluating the risks to users from exposure to the additive itself by both airborne and topical routes. Information from other uses of the additives (e.g. as a food additive, pharmaceuticals or cosmetics) and other routes of exposure (e.g. oral exposure) could be considered. This guidance considers possible local and systemic hazards for relevant routes and timelines of working place exposures during the use/handling of feed additives.

[1] https://connect.efsa.europa.eu/RM/s/publicconsultation

[2] Annex A can be found in the online version of this output (in the 'Supporting information' section).

The potential risks following skin/eye and/or inhalation exposure associated with the presence of nanoparticles[3] could not be fully assessed, because generally accepted methods covering all possible hazards from the relevant routes of exposure for the safety for the user for this type of additives are presently not available.[4] Until such methods are developed, the assessment should follow the requirements set in the present Guidance. Data generated following other recognised guidances on the safety of nanomaterials may be submitted and will be assessed on a case-by-case basis.

The guidance does not propose specific mitigation measures (e.g. gloves, masks, glasses, room ventilation) intended to reduce the exposure of users to an additive or its components, as these are a risk management issue.

Regarding animal welfare, data requirements and testing strategies are in line with the principle of the replacement, reduction and refinement of experiments involving live animals (3 Rs).[5] In the interest of sound science and animal welfare, it is important to avoid unnecessary use of animals and to minimise any testing that is likely to produce severe responses in animals. In accordance with the objective of more efficient use of resources, the assessments are carried out taking into account and seeking harmonisation with existing assessments and classifications of other EU institutions and agencies (e.g. European Chemical Agency – ECHA, European Medicines Agency – EMA).[6]

The guidance is divided into three sections: the first deals with the hazard assessment for skin, eyes, respiratory tract and systemic toxicity and describes the criteria used to identify the need for experimental data. The second section considers exposure via skin, eyes, and/or inhalation routes, and the third, risk assessment.

2 | HAZARD ASSESSMENT

As general rule, all available data on physical/chemical properties and toxicity of the feed additive and/or of its components should be used to assess the potential local and systemic toxicity of all the forms of the final product(s) for which the application has been submitted. For non-holder-specific additives,[7] toxicological evidence/data may be provided for the active substance(s)/agent(s) only. For complex mixtures (e.g. botanical additives), existing information on physical/chemical properties and on the toxicological profile of the components of the mixture should be provided.

The assessment of user safety should also consider potential contaminants/impurities present in the active substance/agent or in the additive.[8]

To avoid unnecessary testing, the FEEDAP Panel has developed an approach for the assessment of potential sensitisation and irritation after skin, eye and inhalation exposure. If a hazard has been identified for one or more endpoints, no further testing for the same or other relevant exposure route(s) is considered necessary since mitigation measures are expected to be put in place.

2.1 | Data sources

All existing information on an active substance/agent or on the additive relevant to its toxicological potential should be evaluated prior to considering *in vivo* testing and should be made available to EFSA.

It is recommended that a weight-of-evidence analysis should be used to evaluate the existing information to determine whether (i) additional studies are needed to fully characterise the toxicological potential and (ii) studies other than *in vivo* could be used.

As a general principle, when the available information (as listed below) indicates a hazard, this should not be further investigated. The absence of a hazard, instead, should be supported by analytical/experimental evidence and the original studies should be provided.

1. Non-testing data

   a. Physical–chemical properties of an active substance/agent or of the additive (e.g. pH)
   b. In silico approaches (grouping, (Quantitative) Structure Activity Relationship ((Q)SARs) and read-across) (ECHA, 2016a; ECHA, 2017)

2. Existing evaluation/classification

   a. Harmonised Classification and Labelling (CLH)[9]

[3]Including engineered nanomaterials (as set out in Regulation (EU) No 2015/2283) or substances that do not meet the definition of engineered nanomaterial but may include particles at the nanoscale (EFSA SC, 2021a, 2021b).

[4]The currently available EFSA Guidance on the nano risk assessment (EFSA SC, 2021a, 2021b) focuses mainly on oral exposure.

[5]Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. OJ L 276, 20.10.2010, p. 47.

[6]https://research-and-innovation.ec.europa.eu/news/all-research-and-innovation-news/recommendation-safe-and-sustainable-chemicals-published-2022-12-08_en

[7]As defined by Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 22.9.2003, p. 15.

[8]Data to establish the presence of contaminants/impurities should be provided using analytical methods with adequate characteristics of selectivity, sensitivity, accuracy and precision.

[9]https://echa.europa.eu/regulations/clp/harmonised-classification-and-labelling

b. Occupational limits: when available, Occupational Exposure Limits (OEL) and Derived No Effect Levels (DNEL), Predicted No Effect Concentrations (PNEC) and Threshold Limit Values (TLV) should be provided

3. Prior knowledge

a. Classification, labelling and packaging (CLP) notifications[10]
b. Safety data sheets (SDS)
c. Publications (including case reports and human studies)
d. Existing *in vivo* and *in vitro* data
e. Experience in manufacturing plants

4. Specific experimental data with the active substance/agent or with the additive under assessment

2.2 | Skin and respiratory sensitisation

A skin sensitiser refers to a substance that will lead to an allergic response following skin exposure (UN GHS, 2023). A respiratory sensitiser is a substance or agent that will lead to hypersensitivity of the airways following inhalation exposure (UN GHS, 2023). At present, sensitisation as a consequence of respiratory exposure lacks any validated *in vitro* or *in vivo* assays and, at best, can only be extrapolated from a dermal response (Chary et al., 2017) or human data. Consequently, conclusions on respiratory sensitisation will be based on the nature of the additive and/or on any data on skin sensitisation. For an additive or its components concluded to be a skin sensitiser, in the absence of other information, it should be also considered as a respiratory sensitiser.

Due to the absence of validated methods to assess the sensitisation potential of microorganisms, microbial-based products should be considered as potential skin and respiratory sensitisers.

If the presence of a well-known sensitising substance or agent is demonstrated (e.g. nickel) in the additive, it should be considered as a skin and respiratory sensitiser[11] without the need to perform further studies.

If the additive or its components are proteinaceous in nature (e.g. enzymes), then it is assumed to be a respiratory sensitiser.

If an additive is a skin irritant and/or skin sensitiser, any exposure to skin is considered a risk.

In case experimental data are needed, mechanistically based *in chemico* and *in vitro* cell-based systems, such as those described in OECD Testing Guideline (TG) 442 C, D and E (for which the application of a 'two out of three approaches' is recommended), OECD 497 (Defined approaches on skin sensitisation) are applicable. In case *in vitro* methods are not appropriate, the *in vivo* study according to OECD TG 429 (Skin Sensitisation - Local Lymph-Node assay) should be conducted.[12] In case the local lymph node assay is not appropriate to assess the potential sensitisation of the additive, the Guinea pig maximisation test (OECD TG 406) can be used, if properly justified.

2.3 | Skin and eye irritation

Skin irritation refers to the production of reversible damage to the skin occurring after exposure to a substance or mixture (UN GHS, 2023). Eye irritation refers to the production of changes in the eye, occurring after exposure to a substance or a mixture which are fully reversible (UN GHS, 2023).

Skin corrosion refers to the production of irreversible damage to the skin manifested as visible necrosis through the epidermis and into the dermis, following the application of a test chemical (UN GHS, 2023). Similarly, serious eye damage is the production of irreversible tissue damage in the eye (UN GHS, 2023).

Prior to undertaking de novo testing, all available information (see Section 2.1), including existing data of *in vivo* tests, should be assessed. In addition, OECD TG 404 ('A sequential testing strategy for dermal irritation and corrosion') should be consulted to determine the need for such tests. According to Regulation (EC) No 429/2008, corrosion is not a default requirement for the assessment of feed additives for the user. If the additive is composed of, or contains, a strong acid or base (pH of the additive ≤ 2 or pH ≥ 11.5), the additive should be considered corrosive to the skin and the eye and further testing is not needed (ECHA, 2016b).

If an additive or its components are considered a skin sensitiser (see Section 2.2), the FEEDAP Panel considers that any exposure to skin is a risk, thus further testing for skin irritation would not be needed. However, the eye irritation potential should be assessed. Available test results for skin irritation will be considered and included in the assessment, if relevant.

[10]It is the responsibility of applicants to ensure that they have the necessary rights in order to use any information which they include in support of their applications to EFSA. EFSA shall not be held liable for any unlawful use by applicants of proprietary data to support applications submitted to EFSA.

[11]Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. 16.3.2022, OJ 88/1.

[12]Any updated version or new OECD TG made available after the publication of this Guidance, might be considered relevant for the assessment of user safety in the context of the safety evaluation of feed additives.

For additives for which specific studies on skin irritation are needed, these should be carried out before eye irritation tests, and only if the former gives negative results, the eye irritation should be evaluated.

In case *in vitro* testing is needed, the protocols used should comply with relevant OECD TGs: 439 (In vitro skin irritation), 437 (Bovine Corneal Opacity and Permeability Test), 438 (Isolated Chicken Eye test), 467 (Defined Approaches for Serious Eye Damage and Eye Irritation), 491 (Short Time Exposure *In Vitro* Test Method for Identifying (i) Chemicals Inducing Serious Eye Damage and (ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage), 492 (In vitro eye irritation or serious eye damage) and 492B (Reconstructed Human Cornea-like Epithelium (RHCE) Test Method for Eye Hazard Identification).[13] If tests for corrosivity are negative, information on irritancy is still needed.

2.4 | Respiratory tract irritation

Respiratory tract irritation is addressed under the CLP Regulation as 'transient target organ effects'. Respiratory irritant effects (characterised by localised redness, oedema, pruritis and/or pain) are defined as those effects that impair function with symptoms such as coughing, pain, choking and breathing difficulties included (Regulation (EC) No 1272/2008).

Exposure to vapours from volatile substances and to aerosols (dusts, fumes, mists) may result in irritation and other disorders of the respiratory organs. The effects are partly determined by the site of deposition of inhaled particles or droplets in the respiratory tract. For particulate substances, effects depend on the size, mass, shape, chemical composition, biopersistence and solubility of the particles.

There are currently no validated *in vitro* or *in vivo* tests that deal specifically with respiratory tract irritation and it is not a requirement under Regulation (EC) No 429/2008. An assessment of this endpoint will be considered on a case-by-case basis.

If an additive is shown to be a skin irritant and/or an eye irritant, it should be considered as a respiratory irritant.

[13] Any updated version or new OECD TG made available after the publication of this Guidance, might be considered relevant for the assessment of user safety in the context of the safety evaluation of feed additives.

The approach for the assessment of the user safety as described in Sections 2.2, 2.3 and 2.4 is illustrated in Figure 1.

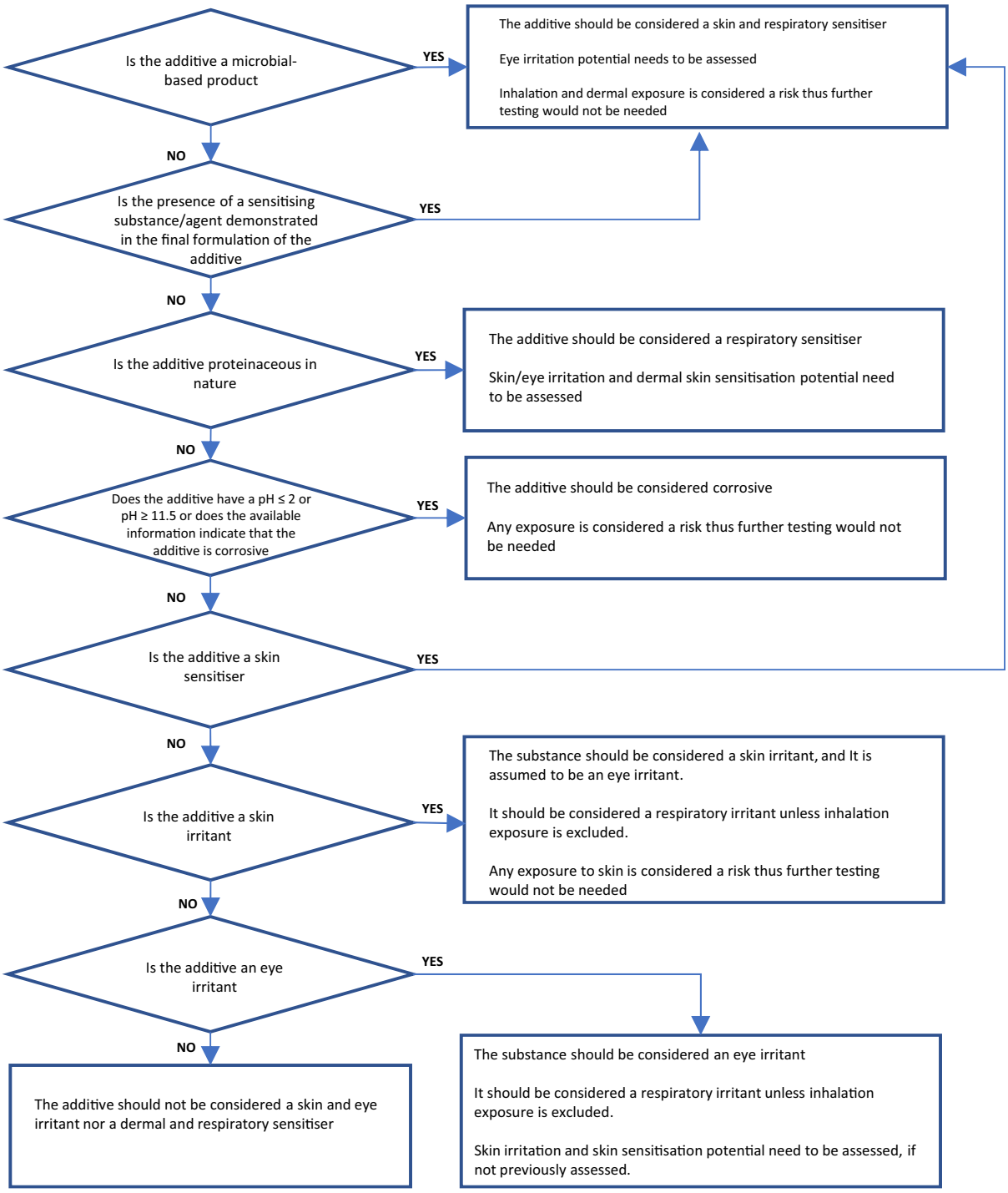

FIGURE 1 Approach for the assessment of skin/eye/respiratory irritation and skin and respiratory sensitisation using all available information.

2.5 | Local and systemic toxicity after repeated exposure

If in the context of the safety assessment of an active substance/agent or on the additive for the consumer and/or for the target species (in the context of data compilation as described in Section 2.1 and EFSA FEEDAP Panel, 2017a, 2017b), a potential for serious local or systemic adverse effects (including genotoxicity and carcinogenicity) is identified, this should be taken into account in the assessment of the safety for the users.

Depending on structural alerts or other toxicological information, (geno)toxicological data may be required, if not provided elsewhere in the application. This could be achieved by reference to published studies (Section 2.1).

3 | EXPOSURE ASSESSMENT

Exposure assessment primarily focuses on the users exposed at the working place through skin/eyes and inhalation routes.

In the majority of cases, an exposure assessment is not considered necessary based upon the following criteria:

1. When the only identified hazard concerns skin and/or eye irritation, skin and/or respiratory sensitisation, it is assumed that any exposure will be a risk and no quantification of exposure is needed;
2. When a hazard without a threshold has been identified from the background toxicity data of the active substance/agent or the additive (e.g. a component or impurity with a genotoxic potential), it is assumed that any exposure will be a risk and no quantification of exposure is needed;
3. When an occupational exposure limit (e.g. OEL, DNEL) exists, there is the legal responsibility of the operator to ensure compliance with the legal limits;
4. When the physico-chemical properties of the active substance/agent or of the additive exclude the possibility of exposure to substances of toxicological relevance (e.g. encapsulation, dust-free formulations).

In all other cases, an exposure assessment is required, for example, for additives for which a toxicological threshold has been identified (e.g. health-based guidance value – HBGV exists) and when the total consumer exposure (all sources) is close to the HBGV. In such cases, the purpose of an exposure assessment would be to establish whether any exposure in the workplace would result in the HBGV being exceeded. When required, an estimation of the exposure assessment should be made by the applicant with an appropriate justification of the scenario chosen and considering the proposed use of the additive.

4 | RISK ASSESSMENT

In the majority of cases, the assessment of user safety is restricted to hazard assessment. There are only a few cases in which a complete risk assessment based on exposure data is needed as described in Section 3.

ABBREVIATIONS

CLH	Harmonised Classification and Labelling
CLP	Classification, Labelling and Packaging
DNEL	Derived No Effect Level
ECHA	European Chemicals Agency
EMA	European Medicines Agency
HBGV	Health-based Guidance Value
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
(Q)SAR	(Quantitative) Structure Activity Relationship
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
PNEC	Predicted No-Effect Concentration
SDS	Safety Data Sheet
TLV	Threshold Limit Value
TWA	Time Weighted Average
TG	Testing Guideline
UN-GHS	United Nations -Globally Harmonized System of Classification and Labelling of Chemicals

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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