

# Assessment of the feed additives betaine anhydrous (3a920) and betaine hydrochloride (3a925) for all animal species for the renewal of their authorisations (Orffa Additives B.V.)

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) |

Roberto Edoardo Villa | Giovanna Azimonti | Eleftherios Bonos | Henrik Christensen |

Mojca Durjava | Birgit Dusemund | Ronette Gehring | Boet Glandorf | Maryline Kouba |

Marta López-Alonso | Francesca Marcon | Carlo Nebbia | Alena Pechová |

Miguel Prieto-Maradona | Ilén Röhe | Katerina Theodoridou | Stefania Fusani |

Jaume Galobart | Paola Manini | Alberto Navarro-Villa | Fabiola Pizzo |

Maria Vittoria Vettori | Orsolya Holczknecht

Correspondence: [feedap@efsa.europa.eu](mailto:feedap@efsa.europa.eu)

The declarations of interest of all scientific experts active in EFSA's work are available at <https://open.efsa.europa.eu/experts>

## Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of betaine anhydrous and betaine hydrochloride for the renewal of its authorisation. The applicant provided evidence that the additives betaine anhydrous (solid form) and betaine hydrochloride (solid form) both produced by chemical synthesis currently on the market comply with the existing conditions of authorisation. The use of betaine anhydrous and betaine hydrochloride as feed additives in animal nutrition remains safe for target species, consumers and the environment under the current authorised conditions. Regarding user safety, betaine anhydrous and betaine hydrochloride are irritant to skin and eyes. Betaine hydrochloride is also a dermal and respiratory sensitiser. Any exposure to these additives is considered a risk. These conclusions apply, in principle, to any preparations containing the active substances. There is no need for assessing the efficacy of the additives in the context of this renewal of the authorisation.

## KEYWORDS

betaine anhydrous, betaine hydrochloride, efficacy, nutritional additives, safety, vitamins

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## 1 | INTRODUCTION

### 1.1 | Background and Terms of Reference

Regulation (EC) No 1831/2003<sup>1</sup> establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 14(1) of that Regulation lays down that an application for renewal shall be sent to the Commission at the latest one year before the expiry date of the authorisation.

The European Commission received a request from Orffa Additives B.V.<sup>2</sup> for the renewal of the authorisation of the additives betaine anhydrous (3a920) and betaine hydrochloride (3a925), when used as feed additives for all animal species (category: nutritional additive; functional group: vitamins, pro-vitamins and chemically well-defined substances having a similar effect).

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 14(1) (renewal of the authorisation). The dossier was received on 19 June 2024 and the general information and supporting documentation are available at <https://open.efsa.europa.eu/questions/EFSA-Q-2024-00408>. The particulars and documents in support of the application were considered valid by EFSA as of 25 September 2024.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user, and the environment and on the efficacy of the feed additive consisting of betaine anhydrous-3a920 betaine hydrochloride-3a925 when used under the proposed conditions of use (see Section 3.1.3).

### 1.2 | Additional information

The additives betaine anhydrous and betaine hydrochloride are currently authorised for use in feed for all animal species (3a920, 3a925).<sup>3</sup>

The FEEDAP Panel adopted one opinion on the safety and efficacy of betaine anhydrous and betaine hydrochloride for all animal species (EFSA FEEDAP Panel, 2013a) and three other opinions on the safety and efficacy of betaine anhydrous (EFSA FEEDAP Panel, 2013b, 2013c, 2018).

## 2 | DATA AND METHODOLOGIES

### 2.1 | Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier<sup>4</sup> in support of the authorisation request for the use of betaine anhydrous and betaine hydrochloride as a feed additive.

The confidential version of the technical dossier was subject to a target consultation of the interested Member States from 30 September to 30 December 2024; the comments received were considered for the assessment.

In accordance with Article 38 of the Regulation (EC) No 178/2002<sup>5</sup> and taking into account the protection of confidential information and of personal data in accordance with Articles 39 to 39e of the same Regulation, and of the Decision of EFSA's Executive Director laying down practical arrangements concerning transparency and confidentiality,<sup>6</sup> a non-confidential version of the dossier has been published on Open.EFSA.

According to Article 32c(2) of Regulation (EC) No 178/2002 and to the Decision of EFSA's Executive Director laying down the practical arrangements on the pre-submission phase and public consultations, EFSA carried out a public consultation on the non-confidential version of the technical dossier from 3 to 24 January 2025, for which no comments were received.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports and experts' (elicitation) knowledge, to deliver the present output.

<sup>1</sup>Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

<sup>2</sup>Orffa Additives B.V. Minervum 7032 4817 ZL Breda – The Netherlands.

<sup>3</sup>COMMISSION IMPLEMENTING REGULATION (EU) 2015/1060 of 2 July 2015 concerning the authorisation of betaine anhydrous and betaine hydrochloride as feed additives for all animal species. OJ L 174, 03.07.2015, p. 3.

<sup>4</sup>Dossier reference: FEED-2024-27132.

<sup>5</sup>Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–48.

<sup>6</sup>Decision available at: <https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements>.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment regarding the methods used for the control of the betaine anhydrous and betaine hydrochloride are valid and applicable for the current application.<sup>7</sup>

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of betaine anhydrous and betaine hydrochloride is in line with the principles laid down in Regulation (EC) No 429/2008<sup>8</sup> and the relevant guidance documents: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2021).

3 | ASSESSMENT

The additives betaine anhydrous (produced by chemical synthesis or by extraction from sugar beet molasses or vinasses by-products of sugar production, solid and liquid form) and betaine hydrochloride (produced by chemical synthesis, solid form) are currently authorised as nutritional feed additives (functional group: vitamins, pro-vitamins and chemically well-defined substances having similar effect) for use in feed and water for all animal species. The present application for renewal covers only betaine anhydrous and betaine hydrochloride, both in solid form and produced by chemical synthesis.

3.1 | Characterisation

3.1.1 | Characterisation of the active substances

**Betaine anhydrous** (IUPAC name: 2-trimethylammonioethanoate) is identified by the CAS number 107-43-7 and the EINECS number 203-490-6. The molecular formula of betaine anhydrous is  $C_5H_{11}NO_2$  and its molecular weight is 117.15 g/mol. It is an off-white to white powder with a characteristic odour, very soluble<sup>9</sup> in water.

According to the authorising regulation, the active substance is produced by either chemical synthesis or by extraction from sugar beet molasses or vinasses, by-products of sugar production. The authorisation also sets a minimum content of betaine anhydrous of 97% (on anhydrous basis) for the solid form and 47% of betaine anhydrous in liquid form. The applicant is requesting the renewal only for betaine anhydrous in solid form and produced by chemical synthesis. The applicant declared that no changes to that manufacturing process have been made since the previous authorisation.<sup>10</sup>

**Betaine hydrochloride** (IUPAC name: 2-(trimethylazaniumyl) acetate hydrochloride) is identified by the CAS number 590-46-5 and the EINECS number 209-683-1. The molecular formula is  $C_5H_{11}NO_2 \cdot HCl$  and its molecular weight is 153.62 g/mol. It is an off-white to white crystalline powder with a characteristic odour, freely soluble in water.

According to the authorising regulation, betaine hydrochloride is in solid form and is produced by chemical synthesis, and it has a purity of at least 98% betaine hydrochloride on anhydrous basis. The applicant stated that no changes in the chemical production process have been introduced since the last authorisation.<sup>11</sup>

Data from five batches of betaine anhydrous and betaine hydrochloride were analysed to demonstrate compliance with the specifications (Table 1).<sup>12</sup>

**TABLE 1** Data on the batch-to-batch variation of the betaine anhydrous and betaine hydrochloride. The data presented are average values and (range) based on five batches.

Parameter	Betaine anhydrous		Betaine hydrochloride	
	Specification	Analytical results	Specification	Analytical results
Assay (%) <sup>(1)</sup>	≥ 97	99.68 (99.58–99.82)	≥ 98	99.33 (99.25–99.49)
Loss on drying (%)	≤ 2	0.82 (0.75–0.92)	≤ 2	0.55 (0.47–0.65)

<sup>(1)</sup>Specifications set in Regulation (EU) No 669/2014.

Results showed compliance with the specifications set by Regulation (EU) No 669/2014.

<sup>7</sup>Evaluation report available on the EU Science Hub [https://joint-research-centre.ec.europa.eu/eurl-fa-eurl-feed-additives/eurl-fa-authorisation/eurl-fa-evaluation-reports\\_en](https://joint-research-centre.ec.europa.eu/eurl-fa-eurl-feed-additives/eurl-fa-authorisation/eurl-fa-evaluation-reports_en).

<sup>8</sup>Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

<sup>9</sup>For solubility terms, see Table 2 of the EFSA Scientific Committee Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles (EFSA Scientific Committee, 2021).

<sup>10</sup>Sect\_2.3\_Manufacturing process v3.

<sup>11</sup>Sect\_2.3\_Manufacturing process v3.

<sup>12</sup>Annex 2.1.3 COAs Betaine anhydrous; Annex 2.1.6 COAs Betaine hydrochloride.

### 3.1.2 | Characterisation of betaine anhydrous and betaine hydrochloride preparations

The current authorisation states that both products may be placed on the market and used as an additive consisting of a preparation. The applicant reported that typical preparations of betaine anhydrous contain 2% anti-caking agent (e.g. calcium stearate) and have a betaine anhydrous content of 96% (on anhydrous basis); typical preparations of betaine hydrochloride contain 3% anti-caking agent (e.g. silicon dioxide (E551)<sup>13</sup>) and have a betaine hydrochloride content of 95% (on anhydrous basis).<sup>14</sup> The applicant provided information for one example preparation for each additive. The results of the analysis of the batch-to-batch variation,<sup>15</sup> impurities,<sup>16</sup> and physical properties<sup>17</sup> of these preparations are included in Table 2.

**TABLE 2** Data on the batch-to-batch variation, impurities and physical properties of preparations containing betaine anhydrous and betaine hydrochloride. The data presented are average values and (range) for batch-to-batch variation and ranges for all other parameters. The number of batches analysed for each group of parameters is indicated in [].

	Betaine anhydrous preparation	Betaine hydrochloride preparation
<b>Specifications</b>		
Active substance (%)	≥ 96	≥ 95
Loss on drying (%)	≤ 2	≤ 2
<b>Batch to batch variation</b>		
Active substance (%)	[8] 96.83 (96.72–96.95)	[8] 95.67 (95.49–95.96)
Loss on drying (%)	0.78 (0.59–0.99)	0.37 (0.23–0.49)
Residue on ignition (%)	2.28–2.61	4.03–4.88
<b>Impurities</b>		
Lead (mg/kg)	[3] 0.01–0.03	[3] < 0.005
Mercury (mg/kg)	< 0.0015	< 0.0015–0.011
Cadmium (mg/kg)	< 0.005	< 0.0025
Arsenic (mg/kg)	0.007–0.010	< 0.0025
Trimethylamine (TMA) (mg/kg) <sup>(1)</sup>	13–28	21–39
<b>Physical properties</b>		
Bulk density (kg/m <sup>3</sup> )	[3] 6000–7500	[3] 6500–8000
Tap density (kg/m <sup>3</sup> )	7000–8500	7000–8500
Dusting potential (Stauber-Heubach) (mg/m <sup>3</sup> )	1732–1979	4375–4875
Particle size distribution (laser diffraction) (% of particles below, v/v)		
100 µm	19.9–21.6	4.7–7.5
50 µm	3.5–5.9	1.8–3.2
10 µm	0.0–0.9	0.3–0.6
<b>Homogeneity in complete feed</b>		
Coefficient of variation (%) of 10 subsamples	2.2	5.0

Note: < below the limit of detection (LOD) except for cadmium for betaine anhydrous, which is limit of quantification (LOQ).

<sup>(1)</sup>TMA was analysed in five batches.

The Panel considers that the levels of the impurities analysed in these preparations are of no concern.

In the former opinion, the FEEDAP Panel described the data on stability and homogeneity obtained from studies with one preparation of each form of betaine (EFSA FEEDAP Panel, 2013a). Considering that their composition is essentially the same as the ones described in this application, the Panel considers that these data are still valid. The applicant provided new data on the outcome of homogeneity tests with the same preparations of each form of betaine (Table 2).

<sup>13</sup>Currently under re-evaluation as feed additive.

<sup>14</sup>Sect\_2.1–2.2\_Detailed identification and characterisation v10 PS.

<sup>15</sup>Annex 2.1.4 COAs Betaine anhydrous preparation v2 PS; Annex 2.1.7 COAs Betaine hydrochloride preparation v2 PS.

<sup>16</sup>Annex 2.1.10 B Heavy metals analysis Betaine anhydrous, Annex 2.1.11 B Heavy metals analysis Betaine hydrochloride.

<sup>17</sup>Annex 2.1.12 Density Betaine anhydrous, Annex 2.1.14 Particle size distribution betaine anhydrous, Annex 2.1.14 B Calculations particle size distribution; Annex 2.1.15 Dusting potential betaine anhydrous, Annex 2.1.16 Density Betaine hydrochloride, Annex Annex 2.1.17 Particle size distribution betaine hydrochloride, 2.1.18 Dusting potential betaine hydrochloride; Annex 2.4.8 Homogeneity Betaine anhydrous; Annex 2.4.9 Homogeneity Betaine hydrochloride.

### 3.1.3 | Conditions of use

The additives betaine anhydrous and betaine hydrochloride are currently authorised for use in complete feed and in water for all animal species and categories without a minimum or maximum content.

Under other provisions of the authorisation, it is specified that:

1. Betaine anhydrous/hydrochloride may be placed on the market and used as an additive consisting of a preparation.
2. In the directions for use of the additive and premixtures, indicate the storage and stability conditions.
3. The additive may be used in water for drinking.
4. Recommended not to exceed supplemental levels of: 2000 mg of betaine/kg of complete feed (with a moisture content of 12%) or 1000 mg of betaine/L of water for drinking for poultry, 700 mg of betaine/L of water for drinking for pigs and 250 mg of betaine/L of water for drinking for calves for rearing.
5. In case of simultaneous use of betaine supplementation in feed and water for drinking, caution should be exercised not to exceed overall recommended levels, taking into account inherent levels in the feed.
6. For user safety: breathing protection, safety glasses and gloves should be worn during handling.

The applicant did not request any change in the current conditions of the authorisation.

## 3.2 | Safety

In its previous opinion, the FEEDAP Panel (EFSA FEEDAP Panel, 2013a) concluded that betaine is safe for all animal species and categories. The Panel also concluded that the use of betaine anhydrous and betaine hydrochloride as feed additives up to a supplementation rate of 2000 mg betaine/kg complete feed is unlikely to pose concerns for consumer safety. Moreover, in the absence of data, the Panel concluded that the additives should be considered as a hazard by inhalation and irritant to skin, eyes and mucous membranes and skin sensitisers. Finally, the supplementation of these additives does not pose a risk to the environment.

The applicant declared that no adverse effects for the target species, consumers, users and the environment, including accidents (previously unknown effects, severe effects of any type, increased incidence of known effects) have been reported to them during the last 10 years of authorisation period.<sup>18</sup>

The applicant conducted an extensive literature search (ELS) to demonstrate that the additive remains safe for the target species, consumers, users and the environment since the first authorisation. The search covered the period from 2015 to 2024, and two databases (Medline/PubMed and Google Scholar) were used. The search strategy was provided, and the search terms were related to the active substance in combination with terms relevant to the safety of the target animals, consumers, users and the environment.<sup>19</sup> The FEEDAP Panel assessed the papers and concluded that none of them identified new information that would lead to reconsider its previous conclusions.

### 3.2.1 | Safety for the target species, consumers and the environment

In its previous opinion, the FEEDAP Panel concluded that betaine is safe for piglets at the maximum supplementation rate of 2000 mg/kg complete feed with a margin of safety below 5. This conclusion was extended to all pigs and extrapolated to all animal species and categories. None of the papers identified in the ELS provided relevant data that would lead the Panel to modify its previous conclusions on the safety for the target animals, the consumers or the environment. Considering that the composition and the production process<sup>20</sup> have not been modified and in the absence of any new evidence indicating adverse effects from the use of betaine anhydrous and betaine hydrochloride in animal nutrition, the FEEDAP Panel concludes that the additives remain safe for the target animals, the consumers and the environment under the current conditions of the authorisation.

The Panel reiterates its previous recommendation that supplemental levels of betaine should not exceed 2000 mg/kg of complete feed (with a moisture content of 12%) or 1000 mg/L of water for drinking for poultry, 700 mg/L of water for drinking for pigs and 250 mg/L of water for drinking for calves for rearing should be maintained.

<sup>18</sup> Annex 3.1.1 Statement No adverse effects\_TargetAnimals, Annex 3.2.1 Statement No adverse effects\_Consumer, Annex 3.3.1 Statement No adverse effects\_Users-workers, Annex 3.4.1 Statement No adverse effects\_Environment.

<sup>19</sup> Annex 3.1.2 Literature Review Target animal safety v4 PS, Annex 3.2.2 Literature Review Consumer Safety v6 PS, Annex 3.3.2 Literature Review Users-Workers safety v5 PS, Annex 3.4.2 Literature Review Safety for the environment v3 PS.

<sup>20</sup> The application covers only betaine anhydrous produced by chemical synthesis and the solid form only.

### 3.2.2 | Safety for the user

In its previous opinion, the FEEDAP Panel concluded that it would be prudent to assume that inhalation of dust from betaine anhydrous and betaine hydrochloride presents a health hazard to workers. In the absence of data, both additives should be considered irritants to skin, eyes and mucous membranes and skin sensitisers (EFSA FEEDAP Panel, 2013a).

Based on the highest dusting potential measured in the preparations (see Table 2), the FEEDAP Panel considers that the exposure of users through inhalation is likely.

Based on the classification, labelling and packaging (CLP) notifications,<sup>21</sup> betaine anhydrous should be considered a skin and eye irritant and may cause respiratory irritation. Based on the information present in the SDS, betaine hydrochloride preparation is considered an irritant to the skin and eye and is a dermal and respiratory sensitiser.<sup>22</sup>

Based on the above information, betaine anhydrous and betaine hydrochloride are irritants to skin, eyes and mucous membranes. Betaine hydrochloride is also a dermal and respiratory sensitiser. Any exposure to these additives is considered a risk. These conclusions would apply, in principle, to any preparation containing the active substances.

## 3.3 | Efficacy

The present application for renewal of the authorisation does not include a proposal for amending or supplementing the conditions of the original authorisation that would have an impact on the efficacy of the additives. Therefore, there is no need for assessing the efficacy of the additive in the context of this renewal of the authorisation.

## 4 | CONCLUSIONS

The applicant provided evidence that the additives betaine anhydrous produced by chemical synthesis (solid form) and betaine hydrochloride (solid form) currently in the market comply with the existing conditions of authorisation.

The use of betaine anhydrous and betaine hydrochloride as feed additives in animal nutrition remains safe for target species, consumers and the environment under the current authorised conditions.

Regarding user safety, betaine anhydrous and betaine hydrochloride are irritants to skin and eyes. Betaine hydrochloride is also a dermal and respiratory sensitiser. Any exposure to these additives is considered a risk. These conclusions would apply, in principle, to any preparation containing the active substances.

There is no need for assessing the efficacy of the additives in the context of this renewal of the authorisation.

## 5 | RECOMMENDATIONS

The Panel notes that, in its previous opinion, it strongly recommended the introduction of maximum levels in feed (2000 mg/kg of complete feed) and water (1000 mg/L for poultry, 700 mg/L for pigs and 250 mg/L for calves for rearing). This was incorporated in the authorising regulation as a recommendation under 'other provisions'. In the absence of data supporting the safety of higher use levels, the Panel considers that these levels should be set as maximum content and not as a recommendation in the regulation.

### ABBREVIATIONS

BW	body weight
CAS	Chemical Abstracts Service
ECHA	European Chemicals Agency
EINECS	European Inventory of Existing Chemical Substances
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
IUPAC	International Union of Pure and Applied Chemistry
LOD	limit of detection
LOQ	limit of quantification

### ACKNOWLEDGEMENTS

The Panel wishes to thank the following for the support provided to this scientific output (in alphabetical order of the last name): Montserrat Anguita Freixa, Matteo Lorenzo Innocenti, Jordi Tarrés-Call.

### REQUESTOR

European Commission

<sup>21</sup><https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/33607>.

<sup>22</sup>Annex 2.5.2 MSDS Betaine hydrochloride.

## QUESTION NUMBER

EFSA-Q-2024-00408

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## PANEL MEMBERS

Roberto Edoardo Villa, Giovanna Azimonti, Eleftherios Bonos, Henrik Christensen, Mojca Durjava, Birgit Dusemund, Ronette Gehring, Boet Glandorf, Maryline Kouba, Marta López-Alonso, Francesca Marcon, Carlo Nebbia, Alena Pechová, Miguel Prieto-Maradona, Ilén Röhe, Katerina Theodoridou.

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**How to cite this article:** EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Villa, R. E., Azimonti, G., Bonos, E., Christensen, H., Durjava, M., Dusemund, B., Gehring, R., Glandorf, B., Kouba, M., López-Alonso, M., Marcon, F., Nebbia, C., Pechová, A., Prieto-Maradona, M., Röhe, I., Theodoridou, K., Fusani, S., Galobart, J., ... Holczknecht, O. (2025). Assessment of the feed additives betaine anhydrous (3a920) and betaine hydrochloride (3a925) for all animal species for the renewal of their authorisations (Orffa Additives B.V.). *EFSA Journal*, 23(4), e9355. <https://doi.org/10.2903/j.efsa.2025.9355>