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Safety and efficacy of a feed additive consisting of potassium ferrocyanide for all animal species (K + S KALI GmbH)*

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Mojca Durjava, Maryline Kouba, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Gabriele Aquilina, Georges Bories, Carlo Nebbia, Jürgen Gropp, Jaume Galobart, Maria Vittoria Vettori, Montserrat Anguita, Jordi Ortuño Casanova, Angelica Amaduzzi and Matteo Lorenzo Innocenti

Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of potassium ferrocyanide as a technological feed additive, functional group anticaking agents, for all animal species. The additive potassium ferrocyanide is intended to be used in potassium chloride with a maximum content of 150 mg ferrocyanide anion/kg salt. The use of potassium ferrocyanide is safe, when added to potassium chloride at a maximum content of 150 mg ferrocyanide anions (anhydrous)/kg for: pigs for fattening and lactating sows, sheep, goats, salmon and dogs. In the absence of a margin of safety, the use of potassium chloride according to the proposed conditions of use is not considered to be safe for chickens for fattening, laying hens, turkeys, piglets, veal calf, cattle for fattening, dairy cows, horse, rabbit and cats. In the absence of information on the use of potassium chloride in the diets for any other animal species, no conclusion on a potentially safe level of potassium chloride, supplemented with 150 mg ferrocyanide/kg, can be made. The use of potassium ferrocyanide in animal nutrition is of no concern for consumer safety. The results of *in vivo* studies showed that potassium ferrocyanide is not irritant to skin and eye and is not a skin sensitiser. However, due to the presence of nickel, the additive should be considered as a respiratory and dermal sensitiser. The available data do not allow the FEEDAP Panel to conclude on the safety of the additive for the soil and the marine environment, while the use of the additive in land-based aquaculture according to the proposed conditions of use is considered of no concern. Potassium ferrocyanide is considered to be efficacious as an anticaking agent when included in potassium chloride at the proposed use levels.

Keywords: technological additives, anticaking agents, potassium ferrocyanide, safety, efficacy

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Correspondence: feedap@efsa.europa.eu

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Panel members: Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Mojca Durjava, Maryline Kouba, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa and Ruud Woutersen.

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from K + S KALI GmbH[2] for authorisation of the product potassium ferrocyanide (E536), when used as a feed additive for all animal species (category: technological additive; functional group: anti-caking agents).

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 4(1) (authorisation of a feed additive or new use of a feed additive). The particulars and documents in support of the application were considered valid by EFSA as of 27 November 2013.

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 potassium ferrocyanide, when used under the proposed conditions of use (see **Section 3.1.3**).

1.2. Additional information

Potassium ferrocyanide is currently authorised as a feed additive,[3] with a maximum content of 80 mg/kg NaCl (calculated as ferrocyanide anion).

Potassium ferrocyanide is currently authorised as a food additive in accordance with Annex II to Regulation (EC) No 1333/2008[4], to be used in salt and salt substitutes. Specific purity criteria on potassium ferrocyanide have been defined in Commission Regulation (EU) No 231/2012[5].

Potassium ferrocyanide has not been previously assessed by EFSA as feed additive.

The Scientific Committee for Animal Nutrition (SCAN) has already delivered an opinion on Potassium ferrocyanide as anticaking agents (European Commission, 2001).

Potassium ferrocyanide was assessed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1970a,b, 1974a,b,c, 1975) and by the Scientific Committee for food (SCF) (European Commission, 1991). The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) delivered an opinion on the safety of potassium ferrocyanide (E536) (EFSA ANS Panel, 2018). Potassium ferrocyanide has not been previously assessed by EFSA as feed additive.

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[6] in support of the authorisation request for the use of potassium ferrocyanide as feed additive.

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, to deliver the present output.

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the potassium ferrocyanide in animal feed.

[1] 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.

[2] K + S KALI GmbH, Bertha-von-Suttner-Straße, 7, 34131, Kassel, Germany.

[3] Commission Regulation (EC) No 1810/2005 of 4 November 2005 concerning a new authorisation for 10 years of an additive in feedingstuffs, the permanent authorisation of certain additives in feedingstuffs and the provisional authorisation of new uses of certain additives already authorised in feedingstuffs. OJ L291, 5.11.2005, p. 5.

[4] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16.

[5] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p. 1–295.

[6] FEED dossier reference: FAD-2013-0016.

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of potassium ferrocyanide is in line with the principles laid down in Regulation (EC) No 429/2008[7] and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEEDAP Panel, 2017a), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018) and Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019).

3. Assessment

The present assessment is related to an additive consisting of potassium hexacyanoferrate. It is intended to be used as a technological additive (functional group: anticaking agents) in potassium chloride for all animal species.

3.1. Characterisation

3.1.1. Manufacturing process

The additive is produced by chemical synthesis and can be manufactured following two production processes. In the first one, calcium hexacyanoferrate is prepared from the reaction of hydrogen cyanide (HCN), iron (II) chloride ($FeCl_2$) and calcium hydroxide $Ca(OH)_2$. After filtration, the solution is concentrated by evaporation under reduced pressure, and the calcium hexacyanoferrate crystallises with 11 molecules of water. Two methods are used for the conversion of calcium hexacyanoferrate to the potassium salt, either the formation of a double potassium/calcium salt following the addition of stoichiometric amounts of potassium chloride, which is further treated with calcium carbonate to release the potassium salt, or the preparation of iron hexacyanoferrate by the addition of iron chloride followed by the addition of stoichiometric amounts of potassium cyanide.

The second production process consists in the reaction of hydrocyanic acid, potassium hydroxide and iron as starting materials. After reaction and filtration, potassium ferrocyanide is crystallised and dried to obtain the additive.

3.1.2. Characterisation of the additive

The additive is composed only of the active substance potassium ferrocyanide (potassium hexacyanoferrate(II) trihydrate, (chemical formula: $K_4 [Fe(CN)_6]·3H_2O$)), identified by the CAS number 14459–95-1 and EINECS number 237–722-2. The additive is a lemon-yellow coloured, fine crystallised and odourless powder. It has a molecular weight of 422.4 g/mol, its solubility in water is 289 g/L (at 20°C) and it has a density of 1,850 kg/m^3.

The additive is specified to contain potassium ferrocyanide $\geq$ 99%, moisture $\leq$ 1%, water insoluble matter $\leq$ 0.03%, chloride (Cl) $\leq$ 0.2%, sulphate (SO_4) $\leq$ 0.1%, lead $\leq$ 5 mg/kg, free cyanide not detectable and ferricyanide not detectable.

Analytical data were provided for five batches of the additive (no details on the manufacturing process followed were available),[8] showing the following average values: 8.78% (1.9–11.1) loss of drying, 53.2% (47–59) hexacyanoferrate(II), corresponding to calculated 106.4% (94–118) potassium ferrocyanide.

The same five batches were analysed for impurities and for dioxins and dioxins like polychlorinated biphenyls. Cadmium, lead, mercury, arsenic and nickel concentrations showed the following values: < 0.01–0.09 mg cadmium/kg, 0.31–1.2 mg lead/kg, < 0.005–< 0.01 mg mercury/kg, < 0.1–1.8 mg arsenic/kg and < 0.5–2 mg nickel/kg.[9]

7 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.

8 Technical dossier/Supplementary Information_Aug_2014/CoA Batch no. 11588, CoA Batch no. 14289, CoA Batch no. 16361, CoA Batch no. 20130731, CoA Batch no. 20140218.

9 '<' refers to the limit of quantification (LOQ).

Polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and coplanar dioxin-like polychlorinated biphenyls (Co-planar PCBs) were analysed in the same five batches. The calculated (upper bound) levels of dioxins and the sum of dioxins and dioxin-like-PCBs were 0.08 ng WHO-PCDD/F-TEQ/kg and 0.12 ng WHO-PCDD/F-PCB-TEQ/kg, respectively.

The results regarding impurities do not raise safety concerns.

The dusting potential of potassium ferrocyanide was measured in one batch[10] according to DIN 33897–2 and to EN 15051, method B 'continuous drop'. The test showed respirable dustiness mass fraction (WR) of 13.6 mg/kg and inhalable dustiness mass fraction (WI) of 1,259 mg/kg, corresponding to concentration of WR of 2.5 mg/m^3 and of WI 237 mg/m^3. The laser diffraction analysis of one batch of the additive showed that 20% of the particles had a diameter < 405 μm, 1.12% < 100 μm, 0.17% < 10 and no particles were < 3.15 μm.[11]

3.1.3. Conditions of use

The additive potassium ferrocyanide is intended to be used as an anticaking agent. It is used in potassium chloride at a proposed maximum concentration of 150 mg ferrocyanide anion (anhydrous) from potassium ferrocyanide trihydrate/kg potassium chloride.[12] No specific maximum levels for complete feed are included.

The feed material potassium chloride supplemented with potassium ferrocyanide is intended to be used in feed for all animal species.

3.2. Safety

No specific studies done for the current application were provided. The safety for use in food of ferrocyanides (sodium-, potassium- and calcium-) was assessed by JECFA (JECFA, 1969, 1973, 1975) and by EFSA (EFSA ANS Panel, 2018). To support the safety of the additive the applicant referred to the conclusions reached in these evaluations and submitted the relevant studies. The main results of the previous assessments are summarised below, in the respective sections.

In addition, the applicant conducted an extensive literature search (ELS) to identify data which could support the safety of the additive.[13] The ELS done using PubMed/Medline, Scopus, CAB Direct, Science Direct and Google Scholar as database platform, covering the period between years 1990 and 2021, and using as keywords ferrocyanide (and relevant synonyms) and toxicology related terms.

3.2.1. Absorption, distribution, metabolism and excretion (ADME)

A study (Nielsen et al., 1990a) performed in rat administered orally a single dose (10 mg) of labelled $K_4[^{59}Fe(^{14}CN)_6]$ indicated that: (i) ^{59}Fe was absorbed at a limited extent (up to 2.6%), most (about 95%) being recovered in the faeces and about 2.5% in the urine (^{14}C in urine amounting to about 2.8% of the administered dose) after 7 days; the limited absorption may be compared to the 0.22% absorption measured in humans administered 500 mg (Nielsen et al., 1990b); (ii) $K_4[^{59}Fe(^{14}CN)_6]$ was excreted essentially unchanged in the faeces, while in the urine up to 1.5% was unchanged and the rest appeared as Fe(II), cyanide and its main metabolite thiocyanate; exposure to free cyanide amounted to 0.06 mg/kg body weight (bw); (iii) the ^{14}C activity (related to the cyanide moiety) found in the urine was significantly higher compared to the excretion of $^{59}Fe(II)$, indicating that a fraction of the hexacyanoferrate(II) anion must have been hydrolysed either in the intestinal tract prior to the absorption of ferrous iron and cyanide or dissociated in the body after absorption of the anion; (iv) the $^{59}Fe/^{14}C$-ratios in the liver and kidney are close to 1.0, indicating that residues are likely non-dissociated $[Fe(CN)_6]^4$.

The ADME of ammonium ferric [^{14}C]hexacyanoferrate (AFCF) was studied in the cow (Arnaud et al., 1988) and previously assessed by EFSA FEEDAP Panel (2021). The results are summarised as follows: (i) *in vitro* incubation with rumen fluid showed that 9% of the compound was dissociated/metabolised to [^{14}C]hexacyanoferrate (89%) and thiocyanate (11%), (ii) most of the radioactivity orally administered (single dose of about 1.7 g) *in vivo* (two animals) was recovered after 9 days in the faeces (92 and 96%, respectively) with 0.5–0.2% in the urine and 0.07–0.07% in the milk. [^{14}C]

[10] Technical dossier/Supplementary Information_Feb_2015/A 7828–14 engl_analysis report dusting potential and Ldf_7January2015_Dusting potential g-m3.

[11] Technical dossier/confidential parts 061113/Annex_II_3_AnalRep111870-2.

[12] Technical dossier/FAD-2011-0047_FAD-2011-0048_FAD-2013-0016_SIn_Oct18/Sin_Na_K_FCN_18–06-12.docx.

[13] Technical dossier/FAD-2011-2013-0016_Supplementary Information September 2021/Annex_SIn_ELS_Ferrocyanide_21–08-25.

hexacyanoferrate was identified as one of the main AFCF dissociation products/metabolites in the faeces (16%), which is consistent with the *in vitro* study, and in the urine (89%); (iii) average concentration of total radioactivity in milk was 300 Bq/L, equivalent to 0.025 mg/L; due to the very low levels of radioactivity, no direct identification of [^{14}C]hexacyanoferrate was possible; (iv) very low amounts of radioactivity ($\leq$ 6 Bq/kg above the background level, equivalent to 0.0005 mg/kg) were measured in the edible tissues analysed (i.e. liver and muscle) after 9-day withdrawal. The results of this experiment, done with a single oral dose about 10–12 times higher than the level of the additive proposed for use, cannot be retained for a quantitative evaluation of the transfer of hexacyanoferrate to milk. However, they confirm the very limited absorption of this compound and its limited excretion in milk.

3.2.2. Toxicological studies

Ferrocyanides were evaluated by JECFA in 1969 (JECFA, 1969), which established a temporary acceptance of 0–0.00125 mg/kg bw per day. Subsequently a temporary acceptable daily intake (ADI) of 0–0.025 mg/kg bw per day (calculated as sodium ferrocyanide) was established by JECFA (1973), and confirmed in 1974 (JECFA, 1975).

The EFSA ANS Panel (EFSA ANS Panel, 2018) assessed the available information on ferrocyanides, in the context of the re-evaluation of ferrocyanides as food additives; in its assessment, the EFSA ANS Panel reviewed sub-chronic toxicity studies, genotoxicity studies and chronic toxicity studies, briefly summarised below.

The ANS Panel evaluated two sub-chronic toxicity studies, one in rat and one in dog; treatment related effects on kidney (higher kidney weight, tubular damage and granular and calcified deposits) were observed in rats fed 450 or 4,500 mg sodium ferrocyanide/kg bw per day for 13 weeks, while no effects were observed in dogs receiving up to 25 mg sodium ferrocyanide/kg bw per day for 13 weeks.

With regards to genotoxicity, potassium ferrocyanide was negative in two Rec-assay system with *Bacillus subtilis* strains H17 and M45, in a SOS Chromotest with *Escherichia coli* strains PQ37 and PQ35, with or without metabolic activation. In an *in vitro* Comet assay in human lymphocyte cells, sodium ferrocyanide did not induce DNA damage, while potassium ferrocyanide significantly increased DNA damage at high concentrations. The ANS Panel noted 'that the effect may be related to an indirect mechanism, such as reactive oxygen species (ROS) generation under *in vitro* conditions which is based on the evidence that in food systems potassium ferrocyanide promotes lipid oxidation' and concluded that ferrocyanides are not of genotoxic concern. The FEEDAP Panel noted that in mammalian cells only an in vitro Comet assay is reported, a test not validated for regulatory purposes, while no studies on chromosomal aberrations are available. However, the Panel considered that the proposed mechanism is expected to be expressed at rather high exposure levels and is unlikely to be of concern in the proposed conditions of use of the feed additive. Therefore, integrating the available information, the FEEDAP Panel supports the conclusion reached by the ANS Panel.

In two chronic toxicity studies, rats were fed 0, 50, 500 or 5,000 mg/kg sodium ferrocyanide in the diet (corresponding to 0, 4.4, 45 and 450.7 mg/kg bw per day for males and 0, 6.2, 62.5 and 630.1 mg/kg bw per day for females) for either 49 weeks or 2 years. No carcinogenic effects were observed and none of the non-neoplastic findings observed was considered to be of toxicological relevance. However, in the 2-year study, rats fed the mid and high doses frequently showed higher cell excretion rate in 2-h urine samples. The ANS Panel considered 'the increased cell excretion rate indicative for occasional, transient kidney toxicity' and therefore, identified from this study a no observed adverse effect level (NOAEL) of 4.4 mg/kg bw per day in male rats and 6.2 mg/kg bw per day in female rats.

In one prenatal developmental toxicity study in rats, the highest dose tested of 1,000 mg sodium ferrocyanide/kg bw per day was considered to be the NOAEL.

The ANS Panel used the lowest NOAEL identified in the chronic toxicity study in rat (4.4 mg sodium ferrocyanide/kg bw per day for male rats) to derive an ADI of 0.044 mg sodium ferrocyanide/kg bw per day. Based on the assumption that the toxicity of sodium ferrocyanide is due to the ferrocyanide ion only, the ANS Panel established a group ADI for sodium, potassium and calcium ferrocyanide of 0.03 mg/kg bw per day expressed as ferrocyanide ion.

The FEEDAP Panel, having reviewed the relevant studies, supports the conclusions reached by the EFSA ANS Panel in 2018 and considers the ADI of 0.03 mg ferrocyanide ion/kg bw per day as adequate for the present assessment.

3.2.3. Safety for the target species

No specific studies aimed to demonstrate the safety of the additive for the target species were made available. The maximum safe concentration of the additive in complete feed can be derived using the results of the toxicological studies (EFSA FEEDAP Panel, 2017a,b,c). From the results of the toxicological studies available (see Section 3.2.2), the FEEDAP Panel considers that the NOAEL of 4.4 mg sodium ferrocyanide/kg bw and day (corresponding to 3 mg ferrocyanide ion/kg bw per day) in the chronic (2-year) toxicity study in rats is the appropriate value to calculate the safe level in feed for the target species. The NOAEL for ferrocyanide anion was used to calculate the maximum safe dose for the different target species as per guidance. From the values obtained the maximum safe levels for the feed material containing the additive were calculated. The results are shown in Table 1.

The maximum safe level of ferrocyanide ions from potassium ferrocyanide in complete feed corresponds to: 0.45 mg/kg for turkey for fattening; 0.33 mg/kg chickens for fattening and other poultry species for fattening or reared for laying/breeding; 0.50 mg/kg for laying hens and other laying/breeding birds; 0.60 mg/kg for piglets; 0.72 mg/kg for pigs for fattening and minor porcine species for fattening; 0.88 mg/kg for sows and minor porcine species for reproduction/breeding; 1.40 mg/kg for veal calves (milk replacer); 0.86 mg/kg for dairy cows and other dairy ruminants (except for sheep/goats); 1.32 mg/kg for cattle for fattening and other ruminants for fattening or for rearing, sheep/goats and horses; 0.53 mg/kg for rabbits; 1.51 mg/kg for salmonids and other fin fish; 1.58 mg/kg for dogs; 1.32 mg/kg for cats and 5.87 mg/kg for ornamental fish.

The maximum safe level of potassium chloride containing the additive requires comparison with the levels of KCl used in the diets in order to establish a margin of safety. To this aim, the applicant was requested to provide practical data on the inclusion level of KCl in complete feeds. The applicant submitted several publications concerning requirements/ allowances/recommendations of K for the relevant animal species/categories listed in the FEEDAP guidance on the safety of the feed additive for the target species (EFSA FEEDAP Panel, 2017a,b,c) and proposed to assume that all the required K is supplemented by KCl, notwithstanding the contribution from the natural K-content of feed materials. The FEEDAP Panel considered this proposal as a reasonable and conservative estimate of KCl addition to complete feed. The data sources including the conversion of the different K-dimensions used in the publications to a KCl concentration in complete feed are listed in the Appendix A (Table A.1), and the proposed maximum KCl supplementation levels are reported in Table 1.

Table 1: Maximum safe concentration of ferrocyanide anion in complete feed and of ferrocyanide-supplemented KCl for different target animals

Animal category	Default values		Maximum safe concentration in complete feed[(1)]		Proposed maximum KCl supplementation in complete feed (%)	Margin of safety[(2)]
	Body weight (kg)	Feed intake (g DM per day)	ferrocyanide (mg/kg)	KCl (%)		
Chicken for fattening	2	158	0.33	0.22	0.38	None
Laying hen	2	106	0.50	0.33	0.36	None
Turkey for fattening	3	176	0.45	0.30	0.32	None
Piglet	20	880	0.60	0.40	0.48	None
Pig for fattening	60	2,200	0.72	0.48	0.36	1.3
Sow lactating	175	5,280	0.88	0.58	0.38	1.5
Veal calf (milk replacer)	100	1,890	1.40	1.00	1.16	None
Cattle for fattening	400	8,000	1.32	0.88	1.73	None
Dairy cow	650	20,000	0.86	0.57	1.01	None
Sheep	60	1,200	1.32	0.88	0.76	1.2
Goat	60	1,200	1.32	0.88	0.82	1.1
Horse	400	8,000	1.32	0.88	1.18	None
Rabbit	2	100	0.53	0.35	1.14	None
Salmon	0.12	2.1	1.51	1.01	0.86	1.2

Animal category	Default values		Maximum safe concentration in complete feed[(1)]		Proposed maximum KCl supplementation in complete feed (%)	Margin of safety[(2)]
	Body weight (kg)	Feed intake (g DM per day)	ferrocyanide (mg/kg)	KCl (%)		
Dog	15	250	1.58	1.06	0.97	1.2
Cat	3	60	1.32	0.88	1.33	None
Ornamental fish	0.012	0.054	5.87	3.91	–	–

(1): Complete feed dry matter (DM) = 88%, milk replacer DM = 94.5%.
(2): Margin of safety calculated as the ratio between the proposed maximum KCl supplementation and the maximum safe KCl (containing the additive) level in complete feed.

When considering (i) the proposed conditions of use (150 mg ferrocyanide anions/kg potassium chloride), (ii) the default values used in Table 1 and (iii) the conservative assumption provided by the applicant on high potassium chloride salt supplementation of complete feed, the margin of safety denotes that the use of sodium ferrocyanide and potassium ferrocyanide is safe for: pigs for fattening and lactating sows, sheep, goats, salmon and dogs. In the absence of a margin of safety, the use of potassium chloride according to the proposed conditions of use is not considered to be safe for chickens for fattening, laying hens, turkeys, piglets, veal calf, cattle for fattening, dairy cows, horse, rabbit and cats. In the absence of information on the use of potassium chloride in the diets for any other animal species, no conclusion on a potentially safe level of potassium chloride, supplemented with 150 mg ferrocyanide/kg, can be made.

The FEEDAP Panel notes that the above assessment is based on the assumption that potassium chloride is the only dietary source of ferrocyanide anions, since safety estimate for maximum content of supplemented potassium chloride is derived from the ferrocyanide safety. Any other source of ferrocyanide would reduce the margin of safety given for the use of supplemented potassium chloride in the different animal species/categories. The only figure which is independent from the use of any other feed material containing or supplemented with ferrocyanide is the maximum dietary concentration of ferrocyanide in complete feed.

3.2.3.1. Conclusions on the safety for the target species

The maximum safe concentration of ferrocyanide ions from potassium ferrocyanide in complete feed corresponds to: 0.45 mg/kg for turkey for fattening; 0.33 mg/kg chickens for fattening and other poultry species for fattening or reared for laying/breeding; 0.50 mg/kg for laying hens and other laying/breeding birds; 0.60 mg/kg for piglets; 0.72 mg/kg for pigs for fattening and minor porcine species for fattening; 0.88 mg/kg for sows and minor porcine species for reproduction/breeding; 1.40 mg/kg for veal calves (milk replacer); 0.86 mg/kg for dairy cows and other dairy ruminants (except for sheep/goats); 1.32 mg/kg for cattle for fattening and other ruminants for fattening or for rearing, sheep/goats and horses; 0.53 mg/kg for rabbits; 1.51 mg/kg for salmonids and other fin fish, 1.58 mg/kg for dogs; 1.32 mg/kg for cats and 5.87 mg/kg for ornamental fish.

The use of potassium ferrocyanide is safe, when added to potassium chloride at a maximum content of 150 mg ferrocyanide anions (anhydrous)/kg for: pigs for fattening and lactating sows, sheep, goats, salmon and dogs.

In the absence of a margin of safety, the use of potassium chloride according to the proposed conditions of use is not considered to be safe for chickens for fattening, laying hens, turkeys, piglets, veal calf, cattle for fattening, dairy cows, horse, rabbit and cats. In the absence of information on the use of potassium chloride in the diets for any other animal species, no conclusion on a potentially safe level of potassium chloride, supplemented with 150 mg ferrocyanide/kg, can be made.

3.2.4. Safety for the consumer

3.2.4.1. Assessment of consumer exposure and consumer safety

No residue data in tissues and products resulting from the use of potassium ferrocyanide incorporated in KCl in the target species were submitted by the applicant.

The applicant proposed instead to estimate consumer exposure on the basis of a theoretical worst-case model applied to dairy cows, the only target species for which ADME data are known for a similar additive (AFCF, see Section 3.2.1). The study of Arnaud et al. (1988) showed that ferrocyanide did not accumulate in edible tissues (e.g. liver and muscle) of dairy cows and that the small amount absorbed could be found in urine and milk. Consequently, it appears reasonable to base a consumer exposure model on the intake of cow's milk as the only source of ferrocyanide applying highly conservative uncertainties factors (UFs) at the different steps of the calculation. The FEEDAP Panel agreed to this proposal.

Default settings of the model were (i) ferrocyanide is considered as the residue of concern, since the ADI is related to that anion of the salts under assessment, (ii) all ingested ferrocyanide is absorbed in the intestine and fully bioavailable (from the available information, less than 10% of the ingested ferrocyanides are absorbed (see Section 3.2.1), (iii) 10% of the ingested ferrocyanide is excreted unchanged via milk (published data on ferrocyanides show excretion of ferric ammonium hexacyanoferrate via milk of less than 0.1% of the total dose administered) (see Section 3.2.1). The FEEDAP Panel considered the proposal of the applicant as acceptable. However, the Panel considered that to have a realistic estimate of the consumer exposure, data on the intake of dairy cows of ferrocyanide ions from the supplemented KCl would be necessary. At the proposed conditions of use (KCl 1.01% complete feed (see Table 1)), the additive is not considered to be safe for dairy cows (see Section 3.2.3). Therefore, for consumer exposure, the highest calculated safe level of KCl in complete feed (0.57%) for dairy cows (see Table 1), instead, is used.

The FEEDAP Panel added other proposals by settings default values for (iv) maximum safe level in feed of KCl supplemented with 150 mg ferrocyanide/kg salt is 0.57% KCl in complete feed and (v) feed intake data and milk yield of dairy cows are based on equations derived from feeding studies with individual cows (assumptions: Simmental, 2nd lactation, 670 kg bw, 160 days in milk, 6.2 MJ NEL/kg forage DM, concentrate 6.7 MJ NEL/kg).[14]

The calculations were made considering the above settings for milk yields between 20 and 36 L/cow/day, corresponding to a dry matter intake of 16.7 to 23.3 kg/cow/day, and assuming that 10% of ingested ferrocyanide is excreted via milk (calculations reported in Appendix B). The highest concentration of ferrocyanide in milk (0.071 mg/L) resulted from cows with the lowest performance (20 L milk/day, 16.7 kg dry matter intake).

The FEEDAP Panel performed an exposure assessment following the methodology described in the Guidance on consumer safety (EFSA FEEDAP Panel, 2017a,b,c) (Appendix C), using the estimated residue data in milk from dairy cows.

The exposure of the consumer to ferrocyanide was calculated on the basis of the highest reliable percentile (HRP) of food consumption (raw agricultural food commodities), expressed in mg/kg bw per day for the different population categories and compared with the ADI established by EFSA ANS Panel (2018)). The highest concentration of ferrocyanide in milk of dairy cows (0.081 mg/L) was used to estimate the exposure of the consumer.

The results of the dietary exposure to ferrocyanide for the different population categories are reported in Table 2.

Table 2: Chronic human dietary exposure to ferrocyanide anion from milk of dairy cows fed with the additive potassium ferrocyanide. Maximum highest reliable percentile expressed in mg/kg bw per day

Population class	Number of surveys	Maximum highest reliable percentile	% ADI*
Infants	6	0.0101	34
Toddlers	10	0.0099	33
Other children	18	0.0130	43
Adolescents	17	0.0048	16
Adults	17	0.0027	9
Elderly	14	0.0023	8
Very elderly	12	0.0026	9

*: ADI: Acceptable daily intake: 0.03 mg/kg body weight and day.

[14] Futteraufnahme bei der Milchkuh, Bayerische Landesanstalt für Landwirtschaft (2006). https://www.lfl.bayern.de/mam/cms07/ite/dateien/zuteilungstabellen_fleckvieh_braunvieh.pdf

The calculated exposure resulted in values (maximum HRP) between 0.0023 and 0.0130 mg (kg bw per day for the different population classes, which corresponds to 8 and 43% of the ADI (0.03 mg ferrocyanide anion/kg bw (EFSA ANS Panel, 2018)). The highest exposure, with a maximum HRP of 0.0130 mg/kg bw per day, was observed for 'other children', the maximum HRP for adults was 0.0027 mg/kg bw per day.

The FEEDAP Panel notes that potassium ferrocyanide, as well as sodium ferrocyanide, are currently authorised for use in sodium chloride at a maximum inclusion level of 80 mg ferrocyanide anion/kg salt. It is noted that the safety of the use of sodium chloride and potassium chloride both supplemented with ferrocyanides at the maximum authorised or maximum recommended level was not assessed in the current evaluation.

In this context, it is noted that potassium ferrocyanide can also be used as food additive. The EFSA ANS Panel (2018)) estimated the exposure to ferrocyanides resulting from its use in food. The highest exposure to ferrocyanides (calculated based on regulatory maximum permitted level) was up to 0.009 mg/kg bw per day in children and adolescents. The ANS Panel considered that the uncertainties identified indicate an overestimation of the exposure to ferrocyanides. The exposure of consumers to ferrocyanides from the simultaneous use of potassium ferrocyanide as food and feed additives would not exceed the ADI.

3.2.4.2. Conclusions on the safety for the consumer

The FEEDAP Panel concludes that the use of the feed additive potassium ferrocyanide in incorporated in potassium chloride (providing a maximum of 150 mg ferrocyanide/kg KCl) does not raise concerns on the safety for the consumers.

3.2.5. Safety for the user

No specific information on the inhalation toxicity of potassium ferrocyanide was provided. The dusting potential of potassium ferrocyanide (237 mg/m^3) makes exposure by inhalation likely.

The highest nickel content analysed in the additive was 2 mg/kg. The dusting potential of the product was 237 mg/m^3, corresponding to about 0.0005 mg Ni/m^3. This value would not exceed the transitional limit value of 0.1 mg Ni/m^3 for the inhalable fraction and 8 h time-weighted average (8 h TWA) exposure established in Directive (EU) 2022/431.[15] However, due to the presence of nickel, the additive should be considered as a respiratory and dermal sensitiser.

To test the irritation potential to skin and eye and the skin sensitisation potential, the applicant has submitted studies done with sodium ferrocyanide.

The skin irritation potential of sodium ferrocyanide was tested in a study performed according to the OECD Guideline 404, which showed that it is not a skin irritant.[16]

The eye irritation potential of sodium ferrocyanide was tested in a study performed according to OECD Guideline 405, which showed that it is not a skin irritant.[17]

A local lymph node assay was performed to assess the skin sensitisation potential of sodium ferrocyanide, in line with the OECD Guideline 429[18] and the Method B42 Skin sensitization of Commission Regulation (EC) No 440/2008.[19] The results showed that sodium ferrocyanide is not a skin sensitiser.

The FEEDAP Panel notes that, since (i) the sodium salt and the potassium salt of ferrocyanide will dissociate to sodium and potassium ions and ferrocyanide anions when in contact with water, (ii) the additive has a high purity and (iii) that the toxicity of sodium and potassium ferrocyanide could be attributed to the ferrocyanide anion only, the FEEDAP Panel considered that the results of the above studies obtained with sodium ferrocyanide could be used to conclude also on the safety of potassium ferrocyanide.

3.2.5.1. Conclusions on safety for the user

In vivo studies showed that potassium ferrocyanide is not irritant to skin and eye and is not a skin sensitiser. However, due to the presence of nickel, the additive should be considered as a respiratory and dermal sensitiser.

[15] 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. OJ L 88, 16.3.2022, p. 1–14.
[16] Technical dossier/ FAD-2013-0016 Supplementary Information September 2022/Annex_SIN_2–3.
[17] Technical dossier/ FAD-2013-0016 Supplementary Information September 2022/Annex_SIN_2–4.
[18] Technical dossier/ FAD-2013-0016_SIn_Oct18/Annex_SIN_3–3.
[19] Available online: https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf

3.2.6. Safety for the environment

To assess the safety for the ferrocyanide ions for the environment, the maximum proposed inclusion levels in the diets of potassium chloride (see Table 1), supplemented with the maximum content of 150 mg ferrocyanide/kg KCl, should be used. However, at the proposed conditions of use (see Table 1), the additive is not considered to be safe for the majority of the target species. Therefore, for pigs for fattening and lactating sows, sheep, goats, and salmon, the proposed maximum KCl supplementation in complete feed is used, while for the other species (for which the proposed use level is not considered safe), the highest calculated safe level of KCl in complete feed (see Table 1) is used as a worst case scenario to calculate the predicted environmental concentration (PEC) of ferrocyanide in the different environmental compartments, in line with the FEEDAP Guidance on the evaluation of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019).

The use of the additive under these conditions results in concentrations of ferrocyanide in soil above the trigger value of 10 μg/kg for most of the terrestrial target species. The predicted environmental concentration in freshwater is below the trigger value and considered safe for land-based aquaculture. For marine aquaculture, the PEC sediment is above the trigger value.

The available data do not allow the FEEDAP Panel to conclude on the safety of the additive for the soil and the marine environment, while the use of the additive in land-based aquaculture according to the proposed conditions of use is considered of no concern.

3.3. Efficacy

Potassium ferrocyanide is used as a food additive as an anticaking agent in salt and salt substitutes. It is reasonable to expect that the effect seen in food will be observed in feed when this additive is used in potassium chloride used in animal nutrition.

The applicant provided an *in vitro* test, [redacted][20] [redacted] The results showed a dose dependent effect in improving flowability, which supports the above assumption.

4. Conclusions

The use of potassium ferrocyanide is safe, when added to potassium chloride at a maximum content of 150 mg ferrocyanide anions (anhydrous)/kg for: pigs for fattening and lactating sows, sheep, goats, salmon and dogs.

In the absence of a margin of safety, the use of potassium chloride according to the proposed conditions of use is not considered to be safe for chickens for fattening, laying hens, turkeys, piglets, veal calf, cattle for fattening, dairy cows, horse, rabbit and cats. In the absence of information on the use of potassium chloride in the diets for any other animal species, no conclusion on a potentially safe level of potassium chloride, supplemented with 150 mg ferrocyanide/kg, can be made.

The use of potassium ferrocyanide in animal nutrition is of no concern for consumer safety.

The results of *in vivo* studies showed that potassium ferrocyanide is not irritant to skin and eye and is not a skin sensitiser. However, due to the presence of nickel, the additive should be considered as a respiratory and dermal sensitiser.

The available data do not allow the FEEDAP Panel to conclude on the safety of the additive for the soil and the marine environment, while the use of the additive in land-based aquaculture according to the proposed conditions of use is considered of no concern.

Potassium ferrocyanide is considered to be efficacious as an anticaking agent when included in potassium chloride at the proposed use levels.

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Abbreviations

ADI	acceptable daily intake
AFC	EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
ANS	EFSA Scientific Panel on Additives and Nutrient Sources added to Food
BW	body weight
CD	Commission Decision
DM	dry matter
ECHA	European Chemicals Agency
EINECS	European Inventory of Existing Chemical Substances
EMA	European Medicines Agency
EURL	European Union Reference Laboratory
FAO	Food Agricultural Organization
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
FFAC	Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FLAVIS	The EU Flavour Information System
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOQ	limit of quantification
MW	molecular weight
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development

Appendix A – Potassium chloride supplementation in complete feedingstuffs

Table A.1: Potassium-requirements/allowances/recommendations for target species

Target species	Source	Data-type	Dimension	K requirement	K (%) in complete feed(1)	KCl (%) in complete feed
Chicken for fattening	NRC (1994)	Requirements	% complete feed (90% DM(2))	0.20	0.20	0.38
Laying hen				0.19	0.19	0.36
Turkey for fattening				0.17	0.17	0.32
Piglet	NRC (2012)	Requirements	% complete feed (90% DM)	0.26	0.25	0.48
Pig for fattening				0.19	0.19	0.36
Sow				0.20	0.20	0.38
Calf (milk replacer)	NRC (2001)	Recommendation	% in DM	0.65	0.61	1.16
Dairy cow	NRC (2001)	Requirements derived from model diets	% in DM	1.03	0.91	1.73
Cattle for fattening	NRC (2016)	Requirements	% in DM	0.60	0.53	1.01
Sheep	NRC (2007)	Requirements	% in DM	0.45	0.40	0.76
Goat				0.49	0.43	0.82
Horse, work	FND (2016)	Exemplary ration	g/day	62	0.62	1.18
Rabbit	NRC (1977)	Adequate level	% in diet	0.6	0.6	1.14
Salmonids	Philip et al. (2022)	Trouw premix composition	% in diet	0.45	0.45	0.86
Dog	FEDIAF (2019)	Recommendation	g/100 g DM	0,58	0.51	0.97
Cat				0,80	0.70	1.33

(1): Complete feed with 88% DM (milk replacer 94.5%).
(2): DM: dry matter.

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Appendix B – Calculated ferrocyanide content in milk

Table B.1: Ferrocyanide anion (FC) intake and content in milk of dairy cows at different yielding stages when fed complete feed containing 0.57% KCl, supplemented with 150 mg ferrocyanide from potassium ferrocyanide, with the assumption that 10% of ingested FC is excreted via milk

FC in KCl (mg/kg)	KCl in feed (g/kg)	DM intake (kg/day)	Feed intake (kg/day)	KCl intake (g/day)	FC intake (mg/day)	Milk yield (L/day)	FC in milk (mg/L)
150	5.7	16.7	19.0	108	16.2	20	0.081
150	5.7	18.6	21.1	120	18.0	24	0.075
150	5.7	20.5	23.3	133	19.9	28	0.071
150	5.7	22.4	25.5	145	21.8	32	0.068
150	5.7	23.3	27.6	157	23.6	36	0.066

Appendix C – Detailed results of chronic exposure calculation

Table C.1: Chronic dietary exposure of consumers to residues of ferrocyanide anion per population class, country and survey (mg/kg body weight per day) based on residue data

Population class	Survey's country	Number of subjects	Highest Reliable Percentile value	Highest Reliable Percentile description
Infants	Bulgaria	523	0.01005	95th
Infants	Germany	142	0.00547	95th
Infants	Denmark	799	0.00770	95th
Infants	Finland	427	0.00629	95th
Infants	Italy	9	0.00266	50th
Infants	United Kingdom	1,251	0.00480	95th
Toddlers	Belgium	36	0.00832	90th
Toddlers	Bulgaria	428	0.00801	95th
Toddlers	Germany	348	0.00780	95th
Toddlers	Denmark	917	0.00836	95th
Toddlers	Spain	17	0.00469	75th
Toddlers	Finland	500	0.00991	95th
Toddlers	Italy	36	0.00624	90th
Toddlers	Netherlands	322	0.00730	95th
Toddlers	United Kingdom	1,314	0.00810	95th
Toddlers	United Kingdom	185	0.00786	95th
Other children	Austria	128	0.01304	95th
Other children	Belgium	625	0.00724	95th
Other children	Bulgaria	433	0.00644	95th
Other children	Germany	293	0.00649	95th
Other children	Germany	835	0.00466	95th
Other children	Denmark	298	0.00624	95th
Other children	Spain	399	0.00475	95th
Other children	Spain	156	0.00513	95th
Other children	Finland	750	0.00714	95th
Other children	France	482	0.00663	95th
Other children	Greece	838	0.00648	95th
Other children	Italy	193	0.00507	95th
Other children	Latvia	187	0.00467	95th
Other children	Netherlands	957	0.00594	95th
Other children	Netherlands	447	0.00489	95th
Other children	Sweden	1,473	0.00574	95th
Other children	Czechia	389	0.00719	95th
Other children	United Kingdom	651	0.00508	95th
Adolescents	Austria	237	0.00347	95th
Adolescents	Belgium	576	0.00255	95th
Adolescents	Cyprus	303	0.00211	95th
Adolescents	Germany	393	0.00344	95th
Adolescents	Germany	1,011	0.00260	95th
Adolescents	Denmark	377	0.00299	95th
Adolescents	Spain	651	0.00262	95th
Adolescents	Spain	209	0.00291	95th

Population class	Survey's country	Number of subjects	Highest Reliable Percentile value	Highest Reliable Percentile description
Adolescents	Spain	86	0.00207	95th
Adolescents	Finland	306	0.00342	95th
Adolescents	France	973	0.00338	95th
Adolescents	Italy	247	0.00290	95th
Adolescents	Latvia	453	0.00304	95th
Adolescents	Netherlands	1,142	0.00315	95th
Adolescents	Sweden	1,018	0.00344	95th
Adolescents	Czechia	298	0.00475	95th
Adolescents	United Kingdom	666	0.00243	95th
Adults	Austria	308	0.00245	95th
Adults	Belgium	1,292	0.00219	95th
Adults	Germany	10,419	0.00228	95th
Adults	Denmark	1,739	0.00198	95th
Adults	Spain	981	0.00204	95th
Adults	Spain	410	0.00203	95th
Adults	Finland	1,295	0.00265	95th
Adults	France	2,276	0.00223	95th
Adults	Hungary	1,074	0.00175	95th
Adults	Ireland	1,274	0.00172	95th
Adults	Italy	2,313	0.00181	95th
Adults	Latvia	1,271	0.00189	95th
Adults	Netherlands	2,055	0.00218	95th
Adults	Romania	1,254	0.00159	95th
Adults	Sweden	1,430	0.00202	95th
Adults	Czechia	1,666	0.00229	95th
Adults	United Kingdom	1,265	0.00165	95th
Elderly	Austria	67	0.00177	95th
Elderly	Belgium	511	0.00235	95th
Elderly	Germany	2,006	0.00217	95th
Elderly	Denmark	274	0.00193	95th
Elderly	Finland	413	0.00228	95th
Elderly	France	264	0.00190	95th
Elderly	Hungary	206	0.00173	95th
Elderly	Ireland	149	0.00200	95th
Elderly	Italy	289	0.00155	95th
Elderly	Netherlands	173	0.00200	95th
Elderly	Netherlands	289	0.00191	95th
Elderly	Romania	83	0.00132	95th
Elderly	Sweden	295	0.00200	95th
Elderly	United Kingdom	166	0.00182	95th
Very elderly	Austria	25	0.00129	75th
Very elderly	Belgium	704	0.00265	95th
Very elderly	Germany	490	0.00233	95th
Very elderly	Denmark	12	0.00120	75th
Very elderly	France	84	0.00179	95th
Very elderly	Hungary	80	0.00205	95th

Population class	Survey's country	Number of subjects	Highest Reliable Percentile value	Highest Reliable Percentile description
Very elderly	Ireland	77	0.00175	95th
Very elderly	Italy	228	0.00170	95th
Very elderly	Netherlands	450	0.00198	95th
Very elderly	Romania	45	0.00141	90th
Very elderly	Sweden	72	0.00232	95th
Very elderly	United Kingdom	139	0.00214	95th