REGULATED PRODUCTS SAFETY ASSESSMENT

Safety Assessment on the Safety and Efficacy of an Additive of Dicopper Chloride Trihydroxide (IntelliBond® C) as a Feed Additive for Use in All Animal Species (RP812)

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An application was submitted to the Foods Standard Agency in March 2021 from Trouw Nutrition GB ('the Applicant') for the renewal and modification of an additive (IntelliBond® C) containing dicopper chloride trihydroxide, under the category of 'nutritional additives' and functional group 'compounds of trace elements'. The additive is proposed to be used in all animal species. The Advisory Committee on Animal Feedings (ACAF) was asked to review the dossier and the supplementary information submitted by the Applicant, and to advise the Food Standards Agency and Food Standards Scotland (FSA/FSS) in evaluating the dossier. The FSA/FSS concluded, based on the ACAF's evidence, that the additive was fully identified and characterised, and no further concerns were raised for this section of the dossier. The use of the additive at recommended levels of incorporation into feed can continue to be considered safe for the target species and the consumer. Regarding user safety, the additive was determined to be non-corrosive and is not a skin sensitiser, however, is a skin irritant and should be regarded as a potential eye irritant. Following a request for a Phase I environmental risk assessment, the ACAF concluded that the additive poses an acceptable risk to the environment when used at the proposed levels for terrestrial species and land-based aquaculture systems. However, the safety of the additive for marine sediment when used in sea cages could not be concluded upon. It was concluded that the proposed minor modifications to the specifications and other provisions would not affect efficacy and therefore efficacy could be extrapolated from the original authorisation to the modified authorisation. The views of ACAF have been taken into account in this safety assessment which represents the opinion of the FSA/FSS.

1. Introduction

The FSA/FSS have undertaken a safety assessment for a feed additive (IntelliBond® C, Trouw Nutrition GB, Blenheim House, Bleinheim Road, Ashbourne, Derbyshire, United Kingdom) consisting of dicopper chloride trihydroxide, under Assimilated Regulation (EC) Nº 1831/2003 for a renewal and modification of authorisation under the category 'nutritional additives', functional group 'compounds of trace elements' for use in all animal species. To support the safety assessment, the ACAF provided advice to the FSA/FSS as outlined in this document.

In line with Article 8 of 1831/2003, the assessment has considered whether the feed additive complies with the conditions laid down in Article 5, including: safety considerations for human, animal and environmental health; efficacy of the additive for its intended effect; potential impairment of the distinctive features of animal products. This, and the guidance put in place by the European Food Safety Authority (EFSA) for the evaluation of feed additive applications, has formed the basis and structure for the assessment.

The dossier was initially evaluated by the Advisory Committee on Animal Feedingstuffs (ACAF) at their February 2023 meeting, after which a request was sent to a specialist to provide a report on environmental safety. The Committee formed conclusions based on this report and a request for further information was communicated to the applicant. The applicant's response to this request by ACAF was reviewed at the September 2023 meeting and a further response reviewed at the December 2023 meeting.

This document sets out the findings of the Committee's assessment on the safety and efficacy of the feed additive, on which the FSA/FSS have made their opinion for the request of a renewal and modification of an authorisation.

Table 1. Table showing products included in this assessment

Title	Product type	Intended use/s	Intended species or categories of animals
Dicopper chloride trihydroxide (IntelliBond® C)	Feed additive	Nutritional additive	Bovines, ovines, caprines, piglets, crustaceans, other animals.

2. Assessment

2.1. Section II: Identity, characterisation and conditions of use

The additive is a preparation containing dicopper chloride trihydroxide (min. 90%) and a small amount of starch or other food-grade binding agent *(ca.* 5%). The existing authorisation describes the additive as being comprised of two polymorphs atacamite and paratacamite, however powder x-ray diffraction techniques have subsequently identified the additive as being comprised of atacamite and clinoatacamite. As part of the renewal, the applicant proposed an update to the nomenclature, as well as a proposal that the specification continues to state the minimum alpha-crystal content (min. 95%), specifying that this is the sum of atacamite and clinoatacamite crystalline forms.

The applicant provided data from five batches supporting the specification values and supporting the physico-chemical properties and purity given below in Table 2. Testing for microbiological impurities are not required for mineral substances.

The Committee found the identity and characterisation section for the additive to be well-described. The applicant wished to update the additive name to include the term 'granulated' and noted that a substantial amount of product was not meeting the previous specification, which was for less than 1% w/w of the particles to be 50 µm or less in diameter. Particle size was found to vary with production site; therefore, the applicant proposed a modification in the specification for less than 5% of the particles to be less than 50 µm. The Committee deemed both requests to be reasonable.

The manufacturing process was found to be well-detailed and there were no other concerns with the identity and characterisation section.

The proposed conditions of use of the additive are described in Table 3.

2.1.1. Conclusions on Section II

The ACAF concluded that the additive was fully identified and characterised. No further concerns were raised for Section II of this dossier.

2.2. Section III: Safety

2.2.1. Safety for the target species

The applicant provided a well-documented literature search encompassing ninety-four relevant papers to demonstrate the safety of dicopper chloride trihydroxide as a source of dietary copper for all animal species. These

Table 2. Identity table for the additive dicopper chloride trihydroxide

Composition	
Mineral composition	
Atacamite	12.5 – 18.8%
Clinoatacamite	80.0 – 85.6%
Botallackite	0.0 – 1.2%
Tenorite (copper oxide)	0.2 – 2.5%
Alpha-crystals (sum of atacamite and clinoatacamite)	97.4 – 98.9%
Additive composition	
Moisture	0.2 – 0.4%
Copper	≥ 53.0%
Purity	≥ 90.0%
Binding agent	*ca.* 5%
Appearance	
Green crystalline powder	
Physico-chemical specifications	
Bulk density, loose Bulk density, tapped	862 – 1088 kg/m^3 909 – 1137 kg/m^3
Dusting potential	0.22 – 0.30 g/m^3
Particle size (measured by laser diffraction)	188 – 218 µm Less than 5% w/w of particles of diameter ≤50 µm
Impurities	
Arsenic	<1.0 – 1.36 mg/kg
Lead	17.6 – 33.4 mg/kg
Cadmium	<0.4 mg/kg
Mercury	<0.01 mg/kg
Dioxins	0.088 – 0.170 ng/kg
Sum of dioxins and dioxin-like PCBs	0.14 – 0.21 ng/kg
Non-dioxin-like PCBs	<0.41 – 0.52 µg/kg

studies were published between 31 December 2010 and 6 January 2021. No safety concerns were observed in any of the species tested. In addition, over 280 tonnes of the product were sold in the EU in 2020 alone with no adverse effects reported. The ACAF concluded that the literature search was comprehensive and that the additive remains safe for the target species under the recommended conditions of use.

2.2.2. Safety for the consumer

Several studies in the literature search compared the bioavailability of dicopper chloride trihydroxide to copper sulphate when used as a source of copper in the feed of animals. No substantial differences in metabolic behaviour were observed between the sources of copper. Therefore, it

Table 3. Proposed conditions of use of the additive dicopper chloride trihydroxide

Proposed mode of use in animal nutrition			
Additive	Dicopper chloride trihydroxide		
Registration number/ EC No/No	Not available		
Category(-ies) of additive	3. Nutritional additives		
Functional group(s) of additive	b. Compounds of trace elements		
Description			
Description	**Chemical formula**	**Purity criteria**	**Method of analysis**
A preparation of dicopper chloride trihydroxide (min. 90%) and binding agent (*ca.* 5%)	$Cu_2(OH)_3Cl$	Min. 90% Min. Cu content 53%	ICP-AES: EN 15510 or CEN/TS 15621
Trade name (if appropriate)	IntelliBond C®		
Conditions of use			
Species or category of animal	**Min. content (mg/kg complete feedingstuff with moisture content of 12%)**	**Max. content (mg/kg complete feedingstuff with moisture content of 12%)**	
Bovines	-	Bovines before the start of rumination: 15 (total) Other bovines: 30 (total)	
Ovines	-	15 (total)	
Caprines	-	35 (total)	
Piglets	-	Sucking and weaned up to 4 weeks after weaning: 150 (total) From 5th week after weaning up to 8 weeks after weaning: 100 (total)	
Crustaceans	-	50 (total)	
Other animals	-	25 (total)	
Other provisions 1. Dicopper chloride trihydroxide may be placed on the market and used as an additive consisting of a preparation. 2. The additive shall be incorporated into feed in the form of a premixture. 3. For user safety: breathing protection, safety glasses and gloves should be worn during handling. 4. The following words shall be included in the labelling: ◦ For feed for sheep if the level of copper in the feed exceeds 10 mg/kg: ◦ The level of copper in this feed may cause poisoning in certain breeds of sheep ◦ For feed for bovines after the start of rumination if the level of copper in the feed is less than 20 mg/kg: ◦ The level of copper in this feed may cause copper deficiencies in cattle grazing pastures with high contents of molybdenum or sulphur			

is expected that the deposition of copper in edible tissues and products would not differ significantly. The Committee were satisfied that dicopper chloride trihydroxide continues to not present a risk for the consumer.

2.2.3. Safety for the user

The applicant presented the following tests to evaluate the safety of the additive for the user/worker:

- *In vitro* human three-dimensional model (EPISKIN-SM; OECD TG 439) to assess skin irritation
- Skin corrosion study performed following OECD 431 protocol
- *In vitro* reconstituted human model (EpiOcular; OECD TG 492) to assess eye irritation
- Bovine corneal opacity and permeability (BCOP) test performed following OECD 437

It was noted that the change in the specification permitted the presence of more particles of diameter ≤50 µm that could deposit in the lungs of workers if inhaled as part of a dust. The Committee considered that harmful levels of exposure to users via inhalation are unlikely, due to the low dusting potential of the additive (mean 0.26 airborne dust g/m^3). The Committee concluded that further inhalation toxicity studies are not necessary.

The applicant referred to five unpublished skin irritation studies, stating that four of the five studies showed no signs of skin irritation. However, members had no access to these studies and therefore requested they be provided. In response, the applicant provided skin irritation and skin corrosion testing performed using the final product according to the OECD 439 and 431 guidelines. After reviewing these studies, the Committee concluded that the additive is irritant to the skin and is non-corrosive to skin.

The Committee originally could not conclude on eye irritation as they were unable to access the original studies. Upon request for further information, the applicant provided an eye irritancy study for the final product that was conducted following the relevant OECD guidelines (OECD 492). As a prediction on classification was not possible with this study, the applicant consequently performed a bovine corneal opacity and permeability test (OECD 437), resulting in adverse reactions in both of these end-points. However, as before, no prediction on classification of eye irritancy could be made. The Committee concluded that, as no conclusion can be drawn from either of the tests provided for eye irritancy, and as they did not see the remaining two studies referred to by the applicant, the additive dicopper chloride trihydroxide should be regarded as a potential eye irritant.

Two unpublished studies evaluating the skin sensitisation potential of dicopper chloride trihydroxide were identified. Upon reviewing these studies, members concluded that the additive is not a skin sensitiser.

2.2.4. Safety for the environment

In the environment dicopper chloride trihydroxide will dissociate into its component ions, all of which are naturally present in the environment. Members discussed the potential for the copper to reach locally toxic levels, as the REACH registration states it is very toxic to aquatic life with long-lasting effects. The Committee concluded that an independent expert should be contacted to provide their expertise regarding safety for the environment. Therefore, the Secretariat requested the input of Dr. Chris Sinclair, a member of the Register of Specialists of the FSA. Members requested a Phase I assessment from the applicant after reviewing the report prepared by the specialist. Upon receiving the environmental risk assessment report for Phase I assessment along with the calculated Predicted Environmental Concentrations for terrestrial animals, the Committee concluded the additive poses an acceptable risk when used at the proposed use levels for terrestrial species and land-based aquaculture systems. However, they could not conclude on the safety of the additive for marine sediment when used in sea cages.

2.2.5. Conclusions on safety

The ACAF concluded that the additive can continue to be considered safe for the target species and consumers under the recommended conditions of use.

The ACAF concluded that the additive is irritant (but not corrosive) to skin and should be considered as a potential eye irritant. The additive is not a skin sensitiser. An unacceptably high level of exposure to users via inhalation is not expected due to the low dusting potential of the additive.

The ACAF concluded that the additive poses an acceptable risk to the environment when used at the proposed levels for terrestrial species and land-based aquaculture systems. However, they could not conclude on the safety of the additive for marine sediment when used in sea cages.

2.3. Section IV: Efficacy

Efficacy studies are not required for the renewal of the authorisation of feed additives unless an amendment is proposed that may have an impact on the efficacy of the additive. The applicant has proposed minor modifications to the specifications and other provisions of dicopper chloride trihydroxide, as outlined in section 2.1, however they do not feel that these impact the efficacy of the additive as a source of dietary copper. In addition, the applicant evaluated the impact of the atacamite and clinoatacamite ratios on the solubility of the additive in an acetate buffered aqueous solution at pH 4.7 under ambient conditions. Members expressed concerns that the additive presented in this application appears to be

more soluble than that of the original application due to the proposed modification. Upon receiving a justification from the applicant explaining why this change in solubility would not have a physiological effect, the Committee were able to extrapolate the efficacy data from the original authorisation to the modified authorisation. Therefore, the additive continues to be considered efficacious under the proposed conditions of use for all animal species.

3. Analytical methods evaluation

Conclusions on the analytical methods are presented here as an extract from the Evaluation Report of the European Union Reference Laboratory (EURL) for Feed Additives on the Method(s) of the Analysis of dicopper chloride trihydroxide, also called tribasic copper chloride (TBCC) (EURL-FA, 2011):

> "For the identification of TBCC in the feed additive, the Applicant submitted an X-ray diffraction (XRD) method to confirm the crystal forms of TBCC.
>
> For the determination of total copper in the feed additive, premixtures and feedingstuffs the Applicant submitted the internationally recognised ring trial validated method EN 15510, based on inductively coupled plasma atomic emission spectroscopy (ICP-AES). The following performance characteristics were reported: a relative standard deviation of repeatability (RSD_r) ranging from 2.9 to 12 %; a relative standard deviation for reproducibility (RSD_R) ranging from 8 to 22 %; and a limit of quantification of 3 mg/kg.
>
> The EURL identified an alternative CEN ring-trial validated method (CEN/TS 15621) based on ICP-AES after pressure digestion, for the determination of total copper in the feed additive, premixtures and feedingstuffs. The total copper concentration is determined using external calibration or standard addition technique. The following performance characteristics were reported for a feed for pigs, and for sheep, a rock phosphate, a mineral premix and a mineral mix, where the total copper content ranged from 7.3 to 470 mg/kg: RSD_r ranging from 2.6 to 6.8 %; RSD_R ranging from 3.8 to 12; and LOQ = 1 mg/kg feedingstuffs.
>
> Furthermore, a Community method is available for the determination of total copper in feedingstuffs, but no performance characteristics for the method were provided. The UK Food Standards Agency recently reported results of a

> ring-trial based on the above mentioned Community method, and reported precisions (RSD_r and RSD_R) for feedingstuffs ranging from 2.4 to 9.2 %.
>
> Based on these acceptable method performance characteristics the EURL recommends for official control the CEN methods EN 15510 or CEN/TS 15621 to determine total copper content by ICP-AES in the feed additive and premixtures. As for the determination of total copper content in feedingstuffs, the EURL recommends for official control the Community method based on AAS and the above mentioned CEN methods (EN 15510 or CEN/TS 15621).
>
> Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005) is not considered necessary."

FSA/FSS accepts the EURL analytical method evaluation reports. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

4. Conclusions

The FSA/FSS have considered and agree with the conclusions reached by the ACAF on the safety and efficacy of the feed additive.

The ACAF found the identity, characterisation and manufacturing sections to be detailed and well-described. No causes of concern were raised for the identity section.

The ACAF concluded that the additive can continue to be considered safe for the target animal species and the consumer under the recommended conditions of use. Regarding user safety, the additive is non-corrosive to skin and is not a skin sensitiser, however it is a skin irritant and should be considered as a potential eye irritant. Significant exposure to users via inhalation is not expected due to the low dusting potential of the additive. The ACAF concluded that the additive poses an acceptable risk to the environment when used at the proposed levels for terrestrial species and land-based aquaculture systems. However, they could not conclude on the safety of the additive for marine sediment when used in sea cages.

Although the applicant proposed minor modifications to the specifications and other provisions, the ACAF concluded these would not impact efficacy and so efficacy could be extrapolated from the original authorisation to this modified authorisation.

The FSA/FSS agree with the conclusions reached by ACAF. FSA/FSS accepts the EURL analytical method evaluation reports. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

Abbreviations

Acronym	Definition
ACAF	Advisory Committee on Animal Feedingstuffs
BCOP	Bovine corneal opacity and permeability
EC	European Commission
EURL	European Union Reference Laboratory
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
LOQ	Limit of quantification
RSDR	Relative standard deviation for reproducibility
RSDr	Relative standard deviation of repeatability
TBCC	Tribasic copper chloride
XRD	X-ray diffraction

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