SCIENTIFIC OPINION

Scientific Opinion on safety and efficacy of zinc compounds (E6) as feed additive for all species: zinc sulphate monohydrate, based on a dossier submitted by Grillo-Werke AG/EMFEMA[1]

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Zinc sulphate monohydrate is considered as a safe source of zinc for all animal species, regarding the maximum contents for total zinc in feedingstuffs set by the EU. Based on data on consumer exposure and the tolerable upper intake level determined for zinc, no concerns for consumer safety are expected from the use of zinc sulphate monohydrate in animal nutrition. The hazards associated with handling of zinc sulphate monohydrate are well recognised and documented. In particular, zinc sulphate monohydrate is considered as a severe irritant to eyes. The zinc sulphate monohydrate under application is considered a compound with high dusting potential, which may result in exposure of users by inhalation. In the view of the FEEDAP Panel, it would be prudent to take measures to avoid exposure by inhalation. The use of zinc-containing feed additives does not pose a direct environmental concern for agricultural soils, but the available data were not sufficient to exclude any risk related to drainage and the run-off of zinc to surface water. The use of zinc-containing additives in aquaculture up to maximum authorised zinc level in feeds is not expected to pose an appreciable risk to the environment. Zinc sulphate monohydrate is an efficacious source of zinc in meeting animal requirements.

KEY WORDS

Nutritional additive, compounds of trace elements, zinc sulphate monohydrate, safety, environment, efficacy

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1 On request from the European Commission, Question No EFSA-Q-2011-00842 adopted on 23 May 2012.
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3 Acknowledgement: The Panel wishes to thank the members of the Working Group on Trace Elements, including Reinhard Kroker, for the preparatory work on this scientific opinion.

Suggested citation: EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP); Scientific Opinion on safety and efficacy of zinc compounds (E6) as feed additive for all species: zinc sulphate monohydrate, based on a dossier submitted by Grillo-Werke AG/EMFEMA. EFSA Journal 2012;10(6):2734. [23 pp.] doi:10.2903/j.efsa.2012.2734. Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety and efficacy of zinc sulphate monohydrate when used as feed additive for all animal species.

Zinc is the second most abundant trace element, after iron, in most vertebrates. It is required for a variety of basic biological processes, including metabolism of proteins, nucleic acids, carbohydrates and lipids, and is also involved in more complex processes, such as the immune response, neurotransmission and cell signalling. It is an integral component of many proteins, in which it contributes to tertiary structure or catalytic activity.

The FEEDAP Panel concludes that zinc sulphate monohydrate is a safe source of zinc for all animal species, considering the maximum contents for total zinc in feedingstuffs set by the EU.

Based on data on consumer exposure and the tolerable upper intake level determined for zinc, no concerns for consumer safety are expected from the use of zinc sulphate monohydrate in animal nutrition.

The hazards associated with handling of zinc sulphate monohydrate are well recognised and documented. In particular, zinc sulphate monohydrate is considered as a severe irritant to eyes. The zinc sulphate monohydrate under application is considered a compound with high dusting potential, which may result in exposure of users by inhalation. In the view of the FEEDAP Panel, it would be prudent to take measures to avoid exposure by inhalation.

The use of zinc-containing feed additives does not pose a direct concern for the agricultural soil compartment. However, there is a potential environmental concern related to drainage and the run-off of zinc to surface water. Acid sandy soils are most vulnerable to these processes. In order to draw a final conclusion, some further refinement to the assessment of zinc-based feed additives in livestock needs to be considered, for which additional data would be required. The use of zinc-containing additives in aquaculture up to maximum authorised zinc level in feeds is not expected to pose an appreciable risk to the environment.

Zinc sulphate monohydrate is an efficacious source of zinc in meeting animal requirements.

The FEEDAP Panel made a recommendation concerning the specification of the additive.

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BACKGROUND

Regulation (EC) No 1831/2003[4] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 10(2) of that Regulation also specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, at the latest one year before the expiry date of the authorisation given pursuant to Directive 70/524/EEC for additives with a limited authorisation period, and within a maximum of seven years after the entry into force of this Regulation for additives authorised without a time limit or pursuant to Directive 82/471/EEC.

The European Commission received a request from Grillo-Werke AG/EMFEMA[5] for re-evaluation of authorisation, of the zinc-containing additive *zinc sulphate monohydrate*, when used as feed additive for all animal species (category: Nutritional additives; functional group: compounds of trace elements).

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicants the technical dossiers in support of this application.[6] According to Article 8 of that Regulation, 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. The particulars and documents in support of the application were considered valid by EFSA as of 2 August 2011.

The additive zinc sulphate monohydrate had been authorised in the European Union (EU) under the element Zinc-Zn for all animal species "Without a time limit" (Commission Regulation (EC) No 1334/2003)[7] and amendments. Following the provisions of Article 10(1) of Regulation (EC) No 1831/2003 the compound was included in the EU Register of Feed Additives under the category "Nutritional additives" and the functional group "Compounds of trace elements".[8]

The Scientific Committee on Animal Nutrition (SCAN) issued an opinion on the use of zinc in feedingstuffs (EC, 2003a). EFSA issued opinions on the safety of the chelated forms of zinc with synthetic feed grade glycine (EFSA, 2005) and on the safety and efficacy of a zinc chelate of hydroxy analogue of zinc (Mintrex®Zn) (EFSA, 2008a; EFSA, 2009a; EFSA, 2009b), of zinc sulphate monohydrate (EFSA, 2012a), of zinc sulphate of aminoacids hydrate (EFSA, 2012b), and of tetra-basic zinc chloride (EFSA, 2012c) as feed additives.

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

5 Grillo-Werke AG/EMFEMA. Weseler Straße, 1. 47169-Duisburg. Germany. This application involves two companies, which have been nominated in the text as follows: (A) Grillo and (B) Eco-Zinder.

6 EFSA Dossier reference: FAD-2010-0059.

7 Commission Regulation (EC) No 1334/2003 of 25 July 2003 amending the conditions for authorisation of a number of additives in feedingstuffs belonging to the group of trace elements. OJ L 187, 26.7.2003, p. 11.

8 European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. http://ec.europa.eu/food/food/animalnutrition/feedadditives/comm_register_feed_additives_1831-03.pdf

TERMS OF REFERENCE

According to Article 8 of Regulation (EC) No 1831/2003, EFSA shall 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 the efficacy of the zinc sulphate monohydrate, when used under the conditions described in Table 1.

Table 1: Description and conditions of use of the additive as proposed by the applicant

Additive	Zinc sulphate, monohydrate
Registration number/EC No/No (if appropriate)	231–793–3
Category(-ies) of additive	3. Nutritional additives
Functional group(s) of additive	b. Compounds of trace elements

Description			
Composition, description	Chemical formula	Purity criteria (if appropriate)	Method of analysis (if appropriate)
	ZnSO4 H2O	Complies with EU law on undesirable substances	ICP-AES

Trade name (if appropriate)	Zinc sulphate, monohydrate
Name of the holder of authorisation (if appropriate)	

Conditions of use				
Species or category of animal	Maximum Age	Minimum content	Maximum content	Withdrawal period (if appropriate)
		mg/kg of complete feedingstuffs		
all species			Pet animals: 250 (total) Fish: 200 (total) Milk replacers: 200 (total) Other species: 150 (total)	Not relevant

Other provisions and additional requirements for the labelling	
Specific conditions or restrictions for use (if appropriate)	Can only be used through a premixture (Article 13, point 1, Council directive 96/51/EC of 23 July 1996 amending Directive 70/524/EEC concerning additives in feedingstuffs)
Specific conditions or restrictions for handling (if appropriate)	Hazardous material: Wear personal protective clothing If handled uncovered, arrangements with local exhaust ventilation should be used if possible. When using do not eat, drink, smoke, sniff. Avoid: Generation of dust. Depositing of dust. Protect drains and sewers from entry of the product. Provide for retaining containers, eg. floor pan without outflow. Keep in locked storage or only make accessible to specialists or their authorised assistants. Containers have to be labelled clearly and permanently. Keep

	container tightly closed in a cool, well-ventilated place.
Post-market monitoring (if appropriate)	There is no need for specific requirements of post-market monitoring. It is recommend to conduct post marketing monitoring in compliance with EU law on feed hygiene, namely by use of HACCP and tracebility systems, and formal monitoring of customer feedback through product or service complaints.
Specific conditions for use in complementary feedingstuffs (if appropriate)	To supply Zn in final feeds within EU legal limits for each species.

Maximum Residue Limit (MRL) (if appropriate)			
Marker residue	Species or category of animal	Target tissue(s) or food products	Maximum content in tissues
-	-	-	-

ASSESSMENT

This opinion is based in part on data provided by an applicant representing two companies involved in the production/distribution of zinc sulphate monohydrate. It should be recognised that this data covers only a fraction of existing zinc sulphate monohydrate additives.

1. Introduction

The transition metal zinc is essential to all living organisms. It is an integral component of an estimated 10 % of all proteins, in which it contributes to tertiary structure or catalytic activity covering all enzyme classes. It is also a signalling substance in that it functions as second messenger and synaptic neuromodulator. The biological functions of zinc are numerous and diverse and include glucose and lipid metabolism, cell proliferation, embryogenesis and those related with the nervous and immune systems. The roles of zinc, its deficiency and toxicity symptoms in farm animals have been described in a previous opinion of the Scientific Committee on Animal Nutrition (EC, 2003a), and a brief update on normal functions and toxicity of zinc is given in Appendix B. To the knowledge of the FEEDAP Panel, there is no additional relevant information that may lead to reconsideration of that opinion.

The additive under assessment is zinc sulphate monohydrate for use in feed for all animal species/categories. This compound is already authorised in the European Union (EU) as a nutritional feed additive and foreseen for re-evaluation.

A compilation of risk assessments carried out on zinc and its compounds, including opinions from EFSA Panels other than the FEEDAP Panel, is in Appendix C. A list of authorisations of zinc compounds in the EU, other than as feed additive, is reported in Appendix D.

The EFSA commissioned the University of Gent (Belgium) to carry out a study of selected trace and ultratrace elements, including zinc. The findings were submitted to the EFSA in the form of a technical report (Van Paemel et al., 2010). Another report on the environmental impact of zinc and copper used in animal nutrition has been provided to EFSA following a call for tender (Monteiro et al., 2010). Information from these reports has been used in this opinion.

This application involves two companies, which have been mentioned in the text as follows: (A) Grillo and (B) Eco-Zinder.

2. Zinc sulphate monohydrate

For compounds of trace elements, the element itself is considered the active substance.

2.1. Characterisation and identity

Zinc sulphate monohydrate (Chemical Abstracts Service (CAS) no 7446-19-7) has the chemical formula $ZnSO_4{\cdot}H_2O$ (molecular weight 179.45 g/mol, theoretical maximum zinc content 36.5 %).

The product is a solid, white to cream-coloured, odourless powder with solubility in water of 400 g/L at 20 °C. It has a density of 3.2 g/cm^3 at 20 °C and a bulk density of 1400–1600 kg/m^3.

Zinc sulphate monohydrate is manufactured by the reaction of zinc-containing materials (e.g. zinc oxide) and sulphuric acid. After subsequent purification and evaporation steps, zinc sulphate hexahydrate and zinc sulphate heptahydrate are dehydrated to produce zinc sulphate monohydrate.

Analysis of ten batches of the additive (five batches per company) showed 35.3–35.7 % zinc.[9] Data were provided for heavy metals (Pb and Cd (five batches per company)), As, dioxins and the sum of

[9] Technical Dossier/Section II/Annexes II_07 and II_08 (for zinc, heavy metals and arsenic content).

dioxins and dioxin-like polychlorinated biphenyls (PCBs) (five batches from company A and one batch from company B). All these data were in compliance with EU legislation.[10]

Data for particle size of zinc sulphate monohydrate have been provided for three batches from each company.[11] The fraction < 50 µm particle size, which is critical for inhalation exposure, was 1.7 % in product from company A and 42 % in that from company B. Dusting potential was measured on three batches from company A and averaged 2.5 g/m^3 (range 2.33–2.67 g/m^3).[12] Company B provided data from measurement of dusting potential from a single batch and reported a value of 0.65 g/m^3.[13]

2.2. Stability and homogeneity

Stability data are not required for inorganic compounds of trace elements. The applicant claimed a shelf-life of one year when stored under cool, dry conditions in closed, original packaging.

Evidence for homogeneity of the additive from one of the two companies (A) was provided by showing the coefficient of variation (CV) for zinc concentrations determined in ten samples of a mineral premixture, a compound feedingstuff for horses and a dry dog food (one batch each). The CV for zinc in these feed products was 3.0, 16.1 and 12.9 % respectively.[14]

2.3. Physico-chemical incompatibilities in feed

According to the current knowledge, incompatibilities resulting from the use of zinc sulphate monohydrate in compound feed are not expected.

2.4. Conditions of use

The zinc compound under application, zinc sulphate monohydrate, is intended to supply zinc in final feed for all species up to a total content of 150 mg Zn/kg complete feed, except for the following: pet animals, 250 mg Zn/kg complete feed; calves, 200 mg Zn/kg milk replacer; and fish, 200 mg Zn/kg complete feed.

2.5. Evaluation of the analytical methods by the European Union Reference Laboratory (EURL)

The EFSA has verified the EURL report as it relates to the methods used for the control of zinc (seven compounds, including zinc sulphate monohydrate) in animal feed. The Executive Summary of the EURL report is in Appendix A.

3. Safety

3.1. Safety for the target species

Zinc is recognised to be of low to moderate oral toxicity in farm animals. The National Research Council (NRC, 2005) evaluated the maximum tolerable zinc concentration in several animal species and found this to be 250 mg/kg for fish, 300 mg/kg for sheep, 500 mg/kg for cattle and poultry and 1 000 mg/kg for pigs. By interspecies extrapolation, the NRC derived maximum tolerable concentrations of 500 mg/kg for equine species and rodents. The few data available for pets allow only a conservative approximation of the maximum tolerable dietary level, which may be 500 mg/kg diet. Consequently, the margin of safety (maximum tolerable concentration/maximum content of zinc authorised in feed) varies between species: 1.25 for fish, 2 for sheep, 3.3 for cattle and poultry and 6.7 for pigs. For the species with incomplete datasets the margin of safety is about 3 for equine species and rodents and about 2 for pets. Regarding the tolerance level for fish, the FEEDAP Panel notes that values reported in literature are markedly different for different species, i.e. < 100 mg/kg for tilapia

[10] Technical Dossier/ Section II/Annexes II_09, II_10 and II_11. Supplementary information/Annexes 03 and 04.
[11] Technical Dossier/Section II. Supplementary information/Annex 02.
[12] Supplementary Information/Annex 05.
[13] Supplementary Information/Annex 06.
[14] Supplementary Information/Annex 07.

(*Oreochromis niloticus*) and > 2000 mg/kg for carp (several species) and rainbow trout (*Oncorhynchus mykiss*) (Clearwater et al., 2002).

3.1.1. Conclusions on the safety for the target species

The FEEDAP Panel concludes that the zinc sulphate monohydrate is a safe source of zinc for all animal species, considering the maximum contents for total zinc in feedingstuffs set by the EU.

3.2. Safety for the consumer

The Scientific Committee on Food (SCF) derived a tolerable upper intake level (UL) of 25 mg/day for adults and 13 mg/day for children aged 7–10 years (EC, 2003b). The UL was based on a depressed copper uptake and an altered lipid profile in humans. An uncertainty factor of 2 is applied owing to the small number of subjects included in relatively short-term studies but acknowledging the rigidly controlled metabolic experimental conditions employed.

3.2.1. Metabolic and residue studies

The metabolic behaviour of zinc has been discussed in detail by the SCF (EC, 2003b) and it has been briefly described, including zinc tissue distribution, by the EFSA's FEEDAP Panel (EFSA, 2008a): "Within the range of homeostatic regulation, tissue storage of zinc increases only slightly as dietary zinc increases, this not being the case in the presence of excessive amounts of the metal (NRC, 1980). In general, the zinc content of liver, kidney and muscles remains low when zinc is used about requirement levels; however, with additional zinc intake within authorised levels, zinc content in liver and kidney is increased while muscle zinc remains essentially unchanged (Jenkins and Hidiroglou, 1991)." To the knowledge of the FEEDAP Panel, no new data that would modify that statement have become available.

3.2.2. Toxicological studies

The toxicological properties of zinc have been discussed in detail by the SCF (EC, 2003b). It exerts low oral acute toxicity resulting in gastrointestinal distress with clinical signs of nausea, vomiting, abdominal cramps and diarrhoea (at 2–8 mg/kg body weight per day in different species). Some positive results in genotoxicity tests were observed. In the view of the SCF, "The weight of evidence from the *in vitro* and *in vivo* genotoxicity tests supports the conclusion that zinc, notwithstanding some positive findings at chromosome levels at elevated doses, has no biologically relevant genotoxicity activity (reviewed by the World Heath Organization, 2001)." This conclusion is supported by US Agency for Toxic Substances and Disease Registry (ATSDR, 2005).

One of the most sensitive and well-described effects of chronic excess zinc intake is a depressed copper uptake with associated copper deficiency effects (reviewed by Maret and Sandstead, 2006). This effect is reflected in the UL set by the SCF (EC, 2003b) of 25 mg Zn/day.

3.2.3. Consumer exposure assessment

The SCF described the mean zinc intake of the European population as between 7.5 and 12 mg Zn/day, based on nutritional surveys (EC, 2003b). The 97.5th percentile in some countries (Austria, Ireland) was estimated to be higher than 20 mg and close to the UL, but this was not considered a matter of concern by the SCF. The SCF data, although collected in the 1990s, appear to describe a currently valid scenario when compared with more recent data (Flynn et al., 2009; Rubio et al., 2009; Turconi et al., 2009).

A 2008 German consumption survey (Bundesministerium für Ernährung, Landwirtschaft und Verbraucherschutz, 2008) found that the median daily zinc intake of zinc among adult Germans was 11.6 and 9.1 mg in men and women, respectively. The corresponding 95th percentiles were 20.2 and 15.1 mg. Data for zinc intake in children (6–11 years) were taken from the KIGGS Modul EsKiMo (Mensink et al., 2007). The median zinc daily intake of boys aged 6–11 years was 7.4–8.7 mg and that for girls of the same age group 7.1–8.3 mg. The upper 95th percentiles were 13.1 and 12.6 mg for boys and girls, respectively.

In all consumer groups tissues and products of animal origin contributed to about 40–50 % of total zinc intake. Since the supplementation of animal feed with zinc-containing compounds has not essentially changed during the last decade, it is reasonable to assume that food of animal origin recorded in the above-mentioned consumption surveys originated from food derived of animals fed zinc-supplemented diets. Since zinc sulphate is considered as a kind of standard for other zinc-containing compounds, the continued use of zinc sulphate monohydrate in animal nutrition would not modify consumer exposure to zinc.

3.2.4. Conclusions on consumer safety

No concerns for consumer safety are expected from the use of zinc sulphate monohydrate in animal nutrition.

3.3. Safety for the users/workers

The hazards associated with handling of zinc sulphate monohydrate are well recognised and documented. In particular, zinc sulphate monohydrate is considered as a severe irritant to eyes.

The zinc sulphate monohydrate under application is considered a compound with high dusting potential, which may result in exposure by inhalation. In the view of the FEEDAP Panel it would be prudent to take measures to avoid exposure by inhalation.

3.4. Safety for the environment

During the use of zinc-containing feed additives, zinc is unavoidably released into the environment. When used in livestock feed, zinc excreted in the faeces will enter the soil environment when the faeces are applied as a fertiliser to land, in the form of manure, slurry or litter. This may present two main potential risks:

zinc accumulation within the topsoil to concentrations posing potential toxic risks to soil organisms;

leaching of zinc from soil to surface waters in concentrations posing potential toxic risks to organisms resident in the water column and bottom sediments.

When used in aquaculture, trace elements such as zinc may be released directly to the broader aquatic environment around an aquaculture facility or be taken up by fish and then excreted into the environment. As stated in the EFSA technical guidance (EFSA, 2008b), the compartment of concern for fish farmed in cages is assumed to be the sediment, whereas for fish farmed in land-based systems the effluent flowing to surface water is considered to pose the main environmental risk.

EFSA commissioned a study on the environmental impact of zinc and copper used in animal nutrition (Monteiro et al., 2010). The results of this study were used as the basis for the present opinion.

To assess the potential risks associated with the use of zinc as an additive in feed for terrestrial animals, a model was used that integrates the physico-chemical and hydrological processes that determine the accumulation and leaching of metals in soil. Input rates of metals resulting from the use of feed additives and the spreading of animal manure on the land were based on the maximum allowable metal contents of feed additives for different livestock types based on maximum allowable rates of nitrogen input of 170 kg/ha per annum. Calculation of concentrations in surface water (as dissolved metal) and sediment (as total sediment metal) was done based upon the Forum for the Coordination of Pesticide Fate Models and Their Use (FOCUS) scenario methodology and taking into consideration the speciation in the environment. More specific information on the parameterisation and assumption made is given in the report.

The predicted no-effect concentrations (PNECs) for the different compartments were calculated following the same methodologies as presented in the EU risk assessment report for zinc by correcting for bioavailability based on the assumed soil and water chemistry of the different scenarios. Likewise, it was decided to use the added PNEC approach for zinc.

The environmental risks resulting from the use of zinc in aquaculture were assessed using the exposure models recommended in the technical guidance (EFSA, 2008b). The estimated concentrations in surface water resulting from the use of zinc as a feed additive for different fish species farmed in raceways, ponds, tanks and recirculation systems and the estimated concentration in sediment arising from the use of feed additives in sea cage were all below the PNEC and therefore do not give rise to concern.

Concerning terrestrial environment, the predicted environmental concentrations (PECs) in soil simulated over period of 50 years of manure application did not exceed the PNEC for terrestrial species in any model scenario developed. This is in accordance to the finding of De Vries et al. (2004), who calculated future zinc concentration after 100 years based on geo-referenced data on zinc inputs and calculated uptake and leaching.

For the water compartment, a potential risk was identified for one drainage scenario and two run-off scenarios. Two of these scenarios represent acidic soil types (i.e. an acidic sandy soil and acidic sandy loam). For these scenarios, the surface water PNEC is predicted to be exceeded by a factor of 3 after ten years of continuous application of any manure type, and by a factor of up to 5 after 50 years.

Predicted concentrations in the sediments of receiving waters, derived from erosion of metal-enriched particles and transport in drainage and run-off, responded dramatically to increases in zinc inputs due to manure application. Potential risks were predicted after ten years' continuous application for all FOCUS scenarios identified in the EFSA Guidance (EFSA, 2008b) and all manure types. In most cases, the PNEC is exceeded by a factor of more than 10, especially in the case of acidic soil types. In the view of the FEEDAP Panel, these findings should be treated with caution as further refinements are feasible, e.g. by taking into account the surface water chemistry of the locations of the FOCUS scenarios, more updated bioavailability models, resuspension and washout of deposited sediment and chemical transformation of trace elements in the sediment following deposition (i.e. formation of acid-volatile sulphides and metal sulphides).

The FEEDAP Panel is also aware that the environmental impact of zinc is also under scrutiny within the EU framework on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).[15] Therefore, additional data submitted to the European Chemicals Agency (ECHA) may support further refinement of PNECs for the different environmental compartments for the assessment of zinc in animal nutrition.

3.4.1. Conclusions

Based on the assessment above, the use of zinc as a feed additive does not pose a direct concern for the agricultural soil compartment. However, there is a potential environmental concern related to drainage and the runoff of zinc to surface water. Acid sandy soils are most vulnerable to these processes. In order to draw a final conclusion, some further refinement to the assessment of zinc-based feed additives in livestock needs to be considered, for which additional data would be required.

The use of zinc-containing feed additives in aquaculture up to maximum authorised zinc level in feeds is not expected to pose an appreciable risk to the environment.

[15] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. OJ L 396, 30.12.2006, p. 1.

4. Efficacy

The use of zinc sulphate monohydrate in animal nutrition is extensively documented in scientific literature. It is recognised as an efficacious source of zinc in meeting animal requirements.

5. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation[16] and Good Manufacturing Practice.

CONCLUSIONS AND RECOMMENDATION

CONCLUSIONS

The FEEDAP Panel concludes that zinc sulphate monohydrate is a safe source of zinc for all animal species, considering the maximum contents for total zinc in feedingstuffs set by the EU.

No concerns for consumer safety are expected from the use of zinc sulphate monohydrate in animal nutrition.

The hazards associated with handling of zinc sulphate monohydrate are well recognised and documented. In particular, zinc sulphate monohydrate is considered as a severe irritant to eyes. The zinc sulphate monohydrate under application is considered a compound with high dusting potential, which may result in exposure of users by inhalation.

The use of zinc as a feed additive does not pose a direct concern for the agricultural soil compartment. However, there is a potential environmental concern related to drainage and the run-off of zinc to surface water. Acid sandy soils are most vulnerable to these processes. In order to draw a final conclusion, some further refinement to the assessment of zinc-based feed additives in livestock needs to be considered, for which additional data would be required. The use of zinc-containing additives in aquaculture up to maximum authorised zinc level in feeds is not expected to pose an appreciable risk to the environment.

Zinc sulphate monohydrate is an efficacious source of zinc in meeting animal requirements.

RECOMMENDATION

A specification of zinc sulphate monohydrate should include a minimum zinc content. Based on the analytical values this could be 35 %.

GENERAL REMARKS

Current knowledge on the zinc requirements of animals indicate the potential to considerably reduce the current maximum content for dietary zinc without affecting animal health and welfare or the productivity of animal husbandry. A reduction in the maximum zinc content would decrease the zinc load in the environment. The simultaneous use of phytases opens further possibilities for the reduction of dietary zinc in animal nutrition. A new assessment of the zinc requirements/allowances of animals would provide the basis to react if a need for action will arise from another relevant field like ecology.

The FEEDAP Panel notes that problems of high zinc concentrations in drainflow and run-off, once established, would be difficult to remediate; it is recommended to assess soil sensitivity before setting policies on manure application.

[16] Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier Zinc sulphate monohydrate for all animal species. June 2010. Submitted by Grillo-Werke AG/EMFEMA.

2. Dossier Zinc sulphate monohydrate for all animal species. Supplementary information. February 2012. Submitted by Grillo-Werke AG/EMFEMA.

3. Evaluation report of the European Union Reference Laboratory for Feed Additives on the methods(s) of analysis for Zinc (E6).

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APPENDICES

APPENDIX A

Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for Zinc (E6)[0]

In the current application authorisation is sought under articles 4(1) and 10(2) for zinc acetate dihydrate[1], zinc chloride anhydrous[1], zinc oxide[1, 5], zinc sulphate heptahydrate[1], zinc sulphate monohydrate[1, 2, 3], zinc chelate of amino acids hydrate[1, 4] and zinc chelate of glycine hydrate[1] under the category/functional group 3(b) of "nutritional additives"/"compounds of trace elements", according to the classification system of Annex I of Regulation (EC) No 1831/2003.

According to the Applicants: - *zinc acetate dihydrate* is white solid with a minimum content of 29.6 % total zinc; - *zinc chloride anhydrous* is white to slightly coloured solid with a minimum content of 46 % total zinc; - *zinc oxide* is white to dark green or beige brownish solid with a minimum content of 72 % total zinc; - *zinc sulphate heptahydrate* is a white solid with a minimum content of 22 % total zinc; - *zinc sulphate monohydrate* is a white to cream coloured solid with a minimum content of 34 % total zinc; - *zinc chelate of amino acid hydrate* is beige to dark tanned solid with a minimum content of 10% total zinc; and - *zinc chelate of glycine hydrate* is white to cream coloured solid with a minimum content of 24 % total zinc. Specifically, authorisation is sought for the use of these *feed additives* for all categories and species.

For the identification and quantification of the inorganic zinc compounds (i.e. zinc acetate dihydrate, zinc chloride anhydrous, zinc oxide, zinc sulphate heptahydrate and zinc sulphate monohydrate) in the feed additive, the EURL recommends for official control the relevant European Pharmacopoeia Monograph (1482, 0110, 0252, 0111 and 2159) methods, based on complexometric titration with 0.1 M sodium EDTA using xylenol orange triturate as indicator.

For the quantification of "amino" content in the amino zinc chelates (i.e. z*inc chelate of glycine hydrate* and *zinc chelate amino acids hydrate*), the Applicant proposed - upon request from the EURL - the Community method based on High Performance Liquid Chromatography (HPLC) combined with post-column derivatisation using ninhydrin as derivatisation agent and photometric detection at 570 nm. The EURL considers the Community method suitable for the characterisation of the amino compounds in the frame of official control.

For the *determination* of total zinc in all the *feed additives*, *premixtures* and *feedingstuffs* the Applicant submitted the CEN 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 1.7 to 8.8 %; - a relative standard deviation for *reproducibility* (RSD_R) ranging from 5.0 to 19 %; and - a limit of quantification (LOQ) of 3 mg/kg. Furthermore, the Applicant identified an alternative CEN ring-trial validated method (CEN/TS 15621) based on ICP-AES after pressure digestion, for the determination of total zinc in the *feed additive*, *premixtures* and *feedingstuffs*. 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 zinc content ranged from 26.6 to 3618 mg/kg: - RSD_r ranging from 1.5 to 5.4 %; - RSD_R ranging from 2.7 to 22%; and - LOQ = 1 mg/kg *feedingstuffs*. Finally, the Applicant suggested the Community method for the determination of total zinc in *feedingstuffs*, with limited method performance characteristics provided. However, the UK Food Standards Agency organised a comparative trial based on the above mentioned Community method and reported precisions (RSD_r and RSD_R) for *feedingstuffs* ranging from 1.0 to 9.5 %.

[0] The full report is available on the EURL website: http://irmm.jrc.ec.europa.eu/SiteCollectionDocuments/FinRep-SANCO-Zinc.pdf

[1] FAD-2010-0142; [2] FAD-2010-0228; [3] FAD-2010-0059; [4] FAD-2010-0063; [5]FAD-2010-0072

Based on these acceptable method performance characteristics the EURL recommends for official control the ICP-AES CEN methods (EN 15510 and CEN/TS 15621) to determine total zinc content by in the *feed additive* and *premixtures.* As for the determination of total zinc content in *feedingstuffs*, the EURL recommends for official control the Community method based on AAS together with the above mentioned ICP-AES CEN methods.

For the quantification of total zinc in *water* the Applicant[2] submitted the ring trial validated method EN ISO 11885, based on ICP-AES. The following performance characteristics are reported: - RSD_r ranging from 1.5 to 2.4 %; - RSD_R ranging from 4.9 to 5.9 %; and LOQ = 1 µg/L. Based on these acceptable method performance characteristics the EURL recommends for official control the CEN methods (EN ISO 11885) to quantify total zinc content by ICP-AES in the *water.*

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.

APPENDIX B

Update on the biological role and toxicity of zinc

Zinc is a trace element that is essential to all known organisms, and it is the second most abundant trace element, after iron, in most vertebrates. Zinc is required for a variety of basic biological processes, including metabolism of proteins, nucleic acids, carbohydrates and lipids, and it is also involved in more complex processes, such as the immune response, neurotransmission and cell signalling (Coleman, 1992; Beyersmann, 2002; Murakami and Hirano, 2008). It has been estimated that there are approximately 3 000 zinc-containing proteins in humans (Passerini et al., 2007). Almost all of the zinc in cells is bound to proteins, peptides and amino acids, but there is a minute fluctuating pool of labile cytosolic Zn^{2+}, which is involved in cell signalling pathways (Murakami and Hirano, 2008; Haase and Rink, 2009; Hogstrand et al., 2009). One of the mechanisms by which Zn^{2+} transduces intracellular signals is by inhibition of protein tyrosine phosphatases; for example, this is believed to be the molecular mechanism behind its insulin-mimetic effect (Haase and Maret, 2003; Miranda and Dey, 2004; Wong et al., 2006). Uptake of zinc, as well as its compartmentalisation between tissues and within cells, is managed principally by two large and biologically ubiquitous families of zinc transporters, the ZnT (SLC30A) family and the ZIP (SLC39A) family, which between them have 24 paralogues in most mammals (Feeney et al., 2005). The distinct distribution and activities of these transporters determine the distribution of zinc within cells and animals. However, cellular zinc influx may also occur via various Ca^{2+} channels and probably through some amino acid transporters.

Dietary zinc has low toxicity to vertebrates (Clearwater et al., 2002; van Paemel et al., 2010). Some of the most sensitive effects of zinc toxicity are impairment of copper and iron uptake with knock-on effects on systems depending on these metals (Eid and Ghonim, 1994; Balesaria et al., 2010). There are also effects on lipid metabolism and the immune system as zinc is a natural regulator of processes involved in these functions. Water-breathing organisms are sensitive to waterborne zinc, with acute toxicity concentrations typically being higher than those for metals such as silver, cadmium and copper but lower than those for manganese and nickel (McDonald and Wood, 1993). The relatively high risk of zinc toxicity to aquatic life has led to its inclusion as a “priority pollutant” by the US Environmental Protection Agency (USEPA, 2002).

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APPENDIX C

List of Risk Assessment Reports on zinc and zinc compounds

Besides the reports cited in the Background section, risk assessments from other EU bodies and Institutions have been carried out. Bodar et al. (2005) summarised the process and facts of the EU risk assessment of zinc and zinc compounds.

1. EU Risk Assessment Reports (RARs)

Zinc metal (CAS No. 7440–66–6). Available online at:
http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/15064/1/lbna24587enn.pdf

Zinc oxide (CAS No. 1314–13–2). Available online at:
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Zinc chloride (CAS No. 7646–85–7). Available online at:
http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/SUMMARY/zincchlorideENVsum075.pdf

Zinc distearate (CAS No 557–05–1/91051–01–3). Available online at:
http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/REPORT/zincdistearatereport074.pdf

Zinc sulphate (CAS No. 7733–02–0). Available online at:
http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/SUMMARY/zincsulphateENVsum076.pdf

Trizinc bis(orthophosphate) (CAS No. 7779–90–0). Available online at :
http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/REPORT/zincphosphatereport077.pdf

2. EC Health and Consumers Scientific Committees Opinions

The Scientific Committee on Health and Environmental Risk (SCHER) opinion on the RARs on Zn. (http://ec.europa.eu/health/ph_risk/committees/04_scher/docs/scher_o_069.pdf)

3. EFSA-ANS Panel Opinions

Chromium picolinate, zinc picolinate and zinc picolinate dihydrate added for nutritional purposes in food supplements (http://www.efsa.europa.eu/en/efsajournal/pub/1113.htm)

Magnesium aspartate, potassium aspartate, magnesium potassium aspartate, calcium aspartate, zinc aspartate, and copper aspartate as sources for magnesium, potassium, calcium, zinc, and copper added for nutritional purposes to food supplements—Scientific Panel on Food Additives and Nutrient Sources added to food (http://www.efsa.europa.eu/en/efsajournal/pub/883.htm)

Calcium L-methionate, magnesium L-methionate and zinc mono-L-methionine sulphate added for nutritional purposes to food supplements - Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food (http://www.efsa.europa.eu/en/efsajournal/pub/924.htm)

Calcium ascorbate, magnesium ascorbate and zinc ascorbate added for nutritional purposes in food supplements http://www.efsa.europa.eu/en/efsajournal/pub/994.htm

4. EFSA-AFC Panel Opinions

Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to Calcium, Magnesium and Zinc Malate added for nutritional purposes to food supplements as sources for Calcium, Magnesium and Zinc and to Calcium Malate added for nutritional purposes to foods for particular nutritional uses and foods intended for the general population as source for Calcium (http://www.efsa.europa.eu/en/efsajournal/pub/391a.htm)

Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to Calcium, iron, magnesium, potassium and zinc L-pidolate as sources for calcium, iron, magnesium, potassium and zinc added for nutritional purposes to food supplements and to foods intended for particular nutritional uses (http://www.efsa.europa.eu/en/efsajournal/pub/495.htm)

Magnesium L-lysinate, calcium L-lysinate, zinc L-lysinate as sources for magnesium, calcium and zinc added for nutritional purposes in food supplements—Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (http://www.efsa.europa.eu/en/efsajournal/pub/761.htm)

Opinion on certain bisglycinates as sources of copper, zinc, calcium, magnesium and glycinate nicotinate as source of chromium in foods intended for the general population (including food supplements) and foods for particular nutritional uses—Scientific Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (http://www.efsa.europa.eu/en/efsajournal/pub/718.htm)

5. EFSA-NDA Panel Opinions

Scientific Opinion on the substantiation of health claims related to zinc and maintenance of normal skin (ID 293), DNA synthesis and cell division (ID 293), contribution to normal protein synthesis (ID 293, 4293), maintenance of normal serum testosterone concentrations (ID 301), “normal growth” (ID 303), reduction of tiredness and fatigue (ID 304), contribution to normal carbohydrate metabolism (ID 382), maintenance of normal hair (ID 412), maintenance of normal nails (ID 412) and contribution to normal macronutrient metabolism (ID 2890) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 (http://www.efsa.europa.eu/en/efsajournal/pub/1819.htm)

Scientific Opinion on the substantiation of health claims related to zinc and function of the immune system (ID 291, 1757), DNA synthesis and cell division (ID 292, 1759), protection of DNA, proteins and lipids from oxidative damage (ID 294, 1758), maintenance of bone (ID 295, 1756), cognitive function (ID 296), fertility and reproduction (ID 297, 300), reproductive development (ID 298), muscle function (ID 299), metabolism of fatty acids (ID 302), maintenance of joints (ID 305), function of the heart and blood vessels (ID 306), prostate function (ID 307), thyroid function (ID 308), acid-base metabolism (ID 360), vitamin A metabolism (ID 361) and maintenance of vision (ID 361) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 (http://www.efsa.europa.eu/en/efsajournal/pub/1229.htm)

Scientific Opinion on the substantiation of a health claim related to zinc and “the prevention of bad breath by neutralising of volatile sulphur compounds in the mouth and oral cavity” pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (http://www.efsa.europa.eu/en/efsajournal/pub/2169.htm)

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APPENDIX D

List of authorisations of zinc compounds other than feed additive

The following zinc compounds are authorised for use in food (Regulation (EC) No 1170/2009):[1] zinc acetate, zinc chloride, zinc oxide, zinc sulphate, zinc bisglycinate, zinc l-Lysinate (which may be used in the manufacture of food supplements); zinc acetate, zinc chloride, zinc oxide, zinc sulphate, zinc bisglycinate, which may be added to food. Zinc acetate (E-650) is authorised as food additive for its use in chewing gum at the maximum level of 1000 mg/kg (European Parliament and Council Directive No 95/2/EC).[2]

The following zinc compounds can be used for the manufacturing of dietetic foods (Commission Regulation (EC) No 953/2009):[3] zinc acetate, zinc chloride, zinc citrate, zinc gluconate, zinc lactate, zinc oxide, zinc carbonate, zinc sulphate and zinc bisglycinate.

The following zinc compounds can be used for the manufacturing of processed cereal-based foods and baby foods for infants and young children (Commission Directive 2006/125/EC):[4] zinc, zinc acetate, zinc citrate, zinc lactate, zinc sulphate, zinc oxide and zinc gluconate.

The following zinc compounds are listed in Table 1 of the Annex of Regulation 37/2010[5] as *Allowed substances, no MRL required*: zinc acetate, zinc aspartate, zinc choride, zinc gluconate, zinc oleate, zinc oxide, zinc stearate, zinc sulphate.

The following zinc compound is listed in Annex of Commission Implementing Regulation (EU) No 540/2011[6] as "Active substances approved for use in plant protection products": trizinc diphosphide (zinc phosphide).

The following type of fertilisers for zinc as *Fertilisers containing only one micro-nutrient* are listed in Annex I of Regulation (EC) No 2003/2003 of the European Parliament and of the Council:[7] (a) zinc salt (chemically obtained product and having as its essential ingredient a mineral salt of zinc), (b) zinc chelate (water-soluble product obtained by combining zinc chemically with a chelating agent), (c) zinc oxide (chemically obtained product and having as its essential ingredient zinc oxide), (d) zinc-based fertiliser (product obtained by mixing types "a" and "c"), zinc-based fertiliser solution (product obtained by dissolving types '"a" and/or one of type "b" in water).

The following zinc compounds can be used for cosmetic purposes (Regulation (EC) No 1223/2009 of the European Parliament and of the Council):[8] zinc acetate, zinc chloride, zinc gluconate, zinc glutamate, zinc phenolsulfonate, zinc oxide, zinc stearate, zinc pyrithione, zinc peroxide.

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1 Commission Regulation (EC) No 1170/2009 of 30 November 2009 amending Directive 2002/46/EC of the European Parliament and of Council and Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards the lists of vitamin and minerals and their forms that can be added to foods, including food supplements. OJ L 314, 1.12.2009, p. 36.

2 European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners. OJ L 61, 18.3.1995, p. 1.

3 Commission Regulation (EC) No 953/2009 of 13 October 2009 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses. OJ L 269, 14.10.2009, p. 9.

4 Commission Directive 2006/125/EC of 5 December 2006 on processed cereal-based foods and baby foods for infants and young children. OJ L 339, 6.12.2006, p. 16.

5 Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. OJ L 15, 20.1.2010, p. 1

6 Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 1.

7 Regulation (EC) No 2003/2003 of the European Parliament and of the Council of 13 October 2003 relating to fertilisers. OJ L 304, 21.11.2003, p. 1.

8 Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. OJ L 342, 22.12.2009, p. 59.

ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
As	arsenic
CAS	Chemical Abstracts Service
Cd	cadmium
CV	coefficient of variation
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EsKiMo	Ernährungsstudie als KIGGS-Modul
EU	European Union
EURL	European Union Reference Laboratory
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
FOCUS	Forum for the Coordination of Pesticide Fate Models and Their Use
Hg	mercury
MRL	maximum residue limit
NRC	National Research Council
Pb	lead
PCB	polychlorinated biphenyl
PEC	predicted environmental concentration
PNEC	predicted no effect concentration
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCAN	Scientific Committee on Animal Nutrition
SCF	Scientific Committee on Food
UL	tolerable upper intake level
WHO	World Health Organization
Zn	zinc