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Safety of a feed additive consisting of sodium saccharin for suckling and weaned piglets, fattening pigs, calves for rearing and for fattening (FEFANA asbl)

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety of sodium saccharin as a sensory feed additive (flavouring compound) for suckling and weaned piglets, fattening pigs, calves for rearing and for fattening. In a previous assessment, the Panel on Additives and Products or substances used in Animal Feed (FEEDAP Panel) could not conclude on the safety of the additive for the environment because concentrations of the additive or its degradation product 4-hydroxysaccharin in groundwater above 0.1 μg/L were likely to occur. In addition, regarding user safety, sodium saccharin was considered to be potentially harmful by inhalation or by contact to skin and eyes. In the current opinion, the applicant restricted the use to suckling and weaned piglets and up to a use level of 5 mg/kg complete feed. In relation to the user safety, the additive was neither a skin or eye irritant, nor a dermal sensitiser. In the absence of data, the FEEDAP Panel could not conclude on the potential of the additive to be toxic by inhalation. Regarding the safety of the additive for the environment, the new conditions of use describe a maximum use level of 5 mg sodium saccharin/kg feed. The applicant indicated that a restriction to a lower use level due to environmental safety would be accepted and submitted an environment risk assessment based on a use level of 1.13 mg sodium saccharin/kg feed. This use level cannot be considered safe. The estimated use level that would result in a concentration in groundwater below 0.1 μg/L is of 0.022 mg sodium saccharin/kg feed. The available data do not allow to conclude on the potential effect of the degradation product 4-hydroxysaccharin in ground water.

Keywords: sensory additives, flavouring compounds, sodium saccharin, piglets, safety

Requestor: European Commission

Question number: EFSA-Q-2021-00528

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 9 defines the terms of the authorisation by the Commission. The applicant, FEFANA ASBL, is seeking a Community authorisation of sodium saccharin as a feed additive to be used as a flavouring compound for suckling and weaned piglets (Table 1).

Table 1: Description of the substance

Category of additive	Sensory additives
Functional group of the additive	Flavouring compounds
Description	Sodium saccharin
Target animal category	Suckling and weaned piglets
Applicant	FEFANA ASBL
Type of request	New opinion

On 21 February 2018, the Panel on Additives and Products or Substances used in Animal Feed for the European Food Safety Authority ("Authority"), in its opinion on the safety and efficacy of the product, could not conclude on the safety of sodium saccharin: "Sodium saccharin is considered to be potentially harmful by inhalation or by contact to skin and eyes. The high mobility and relative persistence of saccharin and the high persistency of its degradation product 4-hydroxysaccharin indicate that groundwater contamination above 0.1 μg/L is likely to occur".

During the discussion with the Member States at a meeting in the Standing Committee on Plants, Animals, Food and Feed (Animal Nutrition section), it was suggested to check for the possibility to demonstrate the safety of the additive for workers and for the environment. The Commission gave the possibility to the applicant to submit supplementary information and data in order to complete the assessment and to allow a revision of the EFSA's opinion. The new data has been received on 07 April 2021 and the applicant has been requested to transmit them to EFSA as well.

In view of the above the Commission asks the Authority to deliver a new opinion on sodium saccharin on the safety for the worker and for the environment as a feed additive for suckling and weaned piglets based on the additional data submitted by the applicant, in accordance with Article 29(1)(a) of Regulation (EC) No 178/2002.

1.2. Additional information

Sodium saccharin is listed in the EU Register of Feed Additives on the basis of the notification procedure and thus authorised for use in feed in the EU. It is authorised for piglets as aromatic and appetiser (Commission Directive 91/248/EEC)[2] up to 4 months of age at a maximum level of 150 mg sodium saccharin/kg feed.

EFSA issued an opinion on the safety and efficacy of sodium saccharin when used as a feed flavour in feed for piglets, pigs for fattening, calves for rearing and calves for fattening (EFSA FEEDAP Panel, 2018). In the previous opinion the conclusions on the safety for the user were based on information of the safety data sheet of the additive. As regards the safety for the environment, it was indicated that groundwater concentrations above 0.1 μg/L are likely to occur because of the high mobility and relative persistence of saccharin and the high persistency of its degradation product 4-hydroxysaccharin.

EFSA published an external scientific report on a Review and synthesis of data on the potential environmental impact of artificial sweeteners (Lewis and Tzilivakis, 2021).

The applicant has submitted complementary information to address aspects related to the safety for the user and the environment.

[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] Commission Directive of 12 April 1991 amending the Annexes to Council Directive 70/524/EEC concerning additives in feedingstuffs. OJ 18.5.91, L 124/1–42.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of supplementary information[3] to a previous application on the same product.[4]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of sodium saccharin is in line with the principles laid down in Regulation (EC) No 429/2008[5] and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2007) and Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019).

3. Assessment

This assessment considers the data newly submitted by the applicant to address aspects regarding the safety for the user and the environment of sodium saccharin when used as a feed additive.

3.1. Characterisation

The additive sodium saccharin (≥ 98%; CAS No 128-44-9) was fully characterised in terms of composition, purity and physicochemical properties in the previous opinion of the FEEDAP Panel (2018). No new information has been provided regarding the characterisation of the additive.

Sodium saccharin is intended to be used as a sensory additive (functional group: flavouring compounds). The application[6] was originally submitted to cover the use of the additive in feed and water for piglets (suckling and weaned), pigs for fattening, calves for rearing up to 4 months, and calves for fattening up to 6 months, with use levels up to 150 mg/kg. The applicant has withdrawn the request for the use in feed and water for pigs for fattening, calves for rearing and calves for fattening, and has also modified the previous use levels: sodium saccharin is intended for use in flavouring mixtures for piglets (suckling and weaned) at levels up to 5 mg/kg complete feed.[7]

3.2. Safety

3.2.1. Safety for the user

In the previous opinion (EFSA FEEDAP Panel, 2018), no data were provided on user safety other than particle size and dusting potential. The particle size distribution (up to 60% (v/v) of the particles had < 50 μm diameter) and the dusting potential (up to 5.5 g/m^3)[8] indicated a likelihood of exposure by respiratory route. The safety data sheet submitted by the applicant regarded saccharin as being potentially harmful to users exposed by inhalation or by contact with skin or eyes. Based on that information, the Panel concluded that 'sodium saccharin is considered to be potentially harmful by inhalation or by contact to skin and eyes'.

For the current assessment, the applicant conducted a literature search to support the safety of the additive for the user.[7]

The databases searched were the European Chemicals Agency (ECHA), the EPA CompTox Chemicals Dashboard, the Cosmetic Ingredient Review, and the Scientific Committee on Consumer Safety and related opinions. The applicant provided a skin irritation study and an eye irritation study made with sodium saccharin of a different origin. In addition, some publications relevant to the skin sensitization potential of the additive were made available.

[3] FEED dossier reference: EFSA-Q-2021-00528.
[4] FEED dossier reference: FAD-2010-0157.
[5] 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.
[6] FAD-2010-0157.
[7] Technical dossier/Supplementary information July 2022/22–07-05 Supplementary information 040322 Sodium saccharin final.
[8] Technical dossier/Supplementary information July 2022/20–07-05 Supplementary information 040322 Sodium saccharin final.

3.2.1.1. Effects in the respiratory system

Considering that the dusting potential is up to 5.5 g/m^3 (EFSA FEEDAP Panel, 2018), the Panel considered that the exposure through inhalation is likely. The applicant submitted a calculation of the exposure of the user by inhalation that assumed a low concentration of sodium saccharin in the additive (3.4% vs 98% of the specification) and it was not considered further in the assessment.[9] In absence of an inhalation toxicity study, it is not possible to conclude on the inhalation toxicity potential of the additive under assessment.

3.2.1.2. Effects in skin and eyes

The acute skin irritation potential of sodium saccharin of a different source (93% purity) was tested in accordance with the OECD testing guideline (TG) 404, in a good laboratory practice (GLP) compliant study.[10] The test item did not produce any skin reaction or clinical signs of toxicity.

The acute eye irritation potential of sodium saccharin of a different source (93% purity) was tested in accordance with the OECD TG 405 in a GLP-compliant study.[11] The test item was considered no irritant to eyes.

The potential for skin sensitisation of saccharin was reviewed using the results of a local lymph node assay in mice (Warbrick et al., 2001) following a method described by Kimber and Basketter (1992), demonstrating that saccharin has no sensitisation potential.

3.2.1.3. Conclusions on the safety for the user

The additive is not a skin or eye irritant, and it is not a skin sensitiser. Users may be exposed by inhalation. In the absence of data, the FEEDAP Panel cannot conclude on the potential of the additive to be toxic by inhalation.

3.2.2. Safety for the environment

In the previous opinion (EFSA FEEDAP Panel, 2018), the FEEDAP Panel concluded that the use of sodium saccharin at the dose considered safe for target species (150 mg/kg feed corresponding to 134 mg saccharin/kg feed) is unlikely to have detrimental effects on the terrestrial and freshwater compartments. The high mobility and relative persistence of saccharin and the high persistency of its degradation product 4-hydroxysaccharin indicate that groundwater concentrations above 0.1 μg/L are likely to occur.

The applicant has provided new information to support the safety of the additive for the environment. This information included: a lysimeter study according to OECD TG 22, and a proposal for predicted environmental concentrations (PECs, soil and groundwater) refinement based on real farm conditions and inverse FOCUS modelling.

3.2.2.1. Fate and degradation in soil

Although there is no experimental guidance to assess the leaching of feed additives to groundwater, it is noted that the use of saccharine in feed is comparable to the pathways of the veterinary medicines. Therefore, in order to quantify the levels of saccharin reaching groundwater following its use as feed additive for piglets, the applicant performed a study in line with OECD TG 22 (out-door monolith lysimeter study), recommended in the Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMA, 2016). Manure and soil were considered the appropriate media. The objective of the study was to evaluate the concentration of the additive in manure, plants, soil and leaching to groundwater; radio-labelled ^{14}C sodium saccharin was used. Considering that there are data available (Buerge et al., 2011) (liquid manure) showing that sodium saccharin does not degrade under anaerobic conditions, performing a test OECD 308 was not considered appropriate since this test is for degradation of compounds in surface water instead of groundwater.

The study submitted analysed the fate of sodium saccharin and its metabolites in soil (e.g. 4-hydroxysaccharin) when applied via manure to soil under outdoor conditions.[12] Just one application was performed; the study started in autumn 2017 and went on for about 2 years. A mixture of [^{14}C]-

[9] Technical dossier/Supplementary information July 2022/Annex 5.16 user safety exposure.
[10] Technical dossier/Supplementary information July 2022/Annex Sin 5.4.
[11] Technical dossier/Supplementary information July 2022/Annex Sin 5.5.
[12] Technical dossier/Annexes/Annexes 1 and 2, and supplementary information July 2022.

sodium saccharin and non-labelled sodium saccharin was applied to 1.5 kg pig slurry in two replicates to obtain a total sodium saccharin concentration in the slurry of approx. 200 mg per 1.5 kg (133 mg/kg). After 3 months of incubation, the pig slurry was applied to two different monolith lysimeters. Immediately after sowing of winter barley, the slurry was spread between the seed rows and incorporated into the upper 5 cm. Sampling of leachates was performed in coordination with precipitation (rain) events. The volume of the leachates, the total radioactivity, the amount of sodium saccharin and the main metabolite 4-hydroxysaccharin were determined. At the end of the vegetation periods, plant samples were analysed to determine radioactivity in plant material. When dismantled, the two monolith lysimeters were disassembled by dividing the soil cores into horizontal strata of 10 cm height. A total of nine samples were obtained from each layer and analysed for total radioactivity.

The applicant acknowledged that there was an error in applying radioactivity in monolith lysimeter 1 (about 5 times lower compared with lysimeter 2) and proposed not to use the data from lysimeter 1 in the assessment. However, the FEEDAP Panel considered the data to be still relevant considering the new use level proposed.

Minor losses of radioactivity were seen during the period of storage of pig slurry in form of $^{14}CO_2$. The measured radioactivity in leachates increased rapidly and reached a maximum in both lysimeters at the beginning of January 2018. A dry spring and summer made that no leachate could be recovered up to December 2018 despite additional irrigation.

Radioactivity in plant materials was observed in small amounts only in the first harvest of 2018 (7 and 24 KBq in lysimeters 1 and 2, respectively).

In lysimeter 1, about 14% of the initial radioactivity was still determined in the soil at the end of the study. Most of the radioactivity was in the top 10 cm of the soil. Only about 3% of the radioactivity was extractable. The remaining 11% was not extractable.

In lysimeter 2, only 4.5% of the original radioactivity was detected. The distribution pattern followed the one described above. Only 0.5% of the applied radioactivity was extractable, being the no extractable fraction of about 90% of the total radioactivity detectable in soil. The results for both lysimeters are reported in Table 2.

Table 2: Results of the monolith lysimeter out-door study

Parameter	Monolith lysimeter 1	Monolith lysimeter 2
Applied amount	33 mg/m^2 equals to 0.33 kg/ha	182.54 mg/m^2 equals to 1.82 kg/ha
% Recovered radio activity (RA)	42	68
% RA in leachate	28	63
% RA in soil	14	5
% RA in plants	0.02	0.03
% 4-OH-saccharin in leachates	Negligible, only in 2nd year	Negligible, only in 2nd year
Annual mean Na saccharin concentration in leachate in 1st year (μg/L)	15	225
Annual mean Na saccharin concentration in leachate in 2nd year (μg/L)	0.1	0.1

In total, 27.9% and 62.5% of the applied sodium saccharin was found in the leachates of lysimeter 1 and lysimeter 2, respectively. Most of the applied sodium saccharin leached in the first year after application resulting in high concentrations in the leachates of 16.4 μg/L in lysimeter 1 and 251.8 μg/L in lysimeter 2. Considering the molar masses of sodium saccharin (205.17 g/mol) and saccharin (183.19 g/mol), this results in mean saccharin concentrations of 14.6 μg/L and 224.8 μg/L for lysimeters 1 and 2, respectively in the first year. In the second year, when no application occurred, the average concentrations were below 0.1 μg/L in both lysimeters.

The high concentrations of 4-hydroxysaccharin predicted by the FOCUS PEARL modelling submitted for the previous evaluation[13] were not confirmed in the lysimeter study. For this reason, transformation products were not considered further by the applicant in the inverse modelling study.

[13] FAD-2010-0157.

The FEEDAP Panel considers that the outdoor monolith lysimeter study can be regarded as reliable, even if some inconsistencies were identified (i.e. manure was not analysed before application and just radioactivity was considered; one soil had been previously treated with a pesticide forming saccharin as a metabolite; being saccharin applied just once, no consideration on the possible formation and leaching of the more persistent metabolite can be performed). The results of the studies show that the additive leaches to groundwater, confirming that saccharin can reach the groundwater compartment.

3.2.2.2. PEC refinement based on real farm conditions

The applicant provided a report on real farm conditions in Europe, considering the use of the additive restricted to piglets (suckling and weaned) and reducing the use levels to 1 mg saccharin/kg feed (corresponding to 1.13 mg additive, 4.4 times less than the maximum recommended dose).[14]

Considering that (i) piglets usually live in the same farm with mother sows (sows do not receive the additive) until weaning, (ii) after weaning piglets may move to the fattening site (from weaning to slaughter) or can be reared for the weaner period in 'isowean' farms, the applicant assumed that the possible release of saccharin to the environment needs to take into consideration that the saccharin contained in the manure of piglet is 'diluted' by the mixing with manure of sows fed with no saccharin at all. To take into account this dilution, the applicant proposes a value of about 40% of the calculated PECs. This refinement, which is considered acceptable by the FEEDAP Panel for farms in which piglets live with the sows, calculated at the reduced use level of 1 mg saccharin/kg feed, results in a PEC_{soil} of 7 μg/kg (corresponding to an application rate of 5.25 g/ha) and PEC_{gw} of 6 μg/L.[15]

3.2.2.3. Refinement with modelling

The sorption and degradation data for sodium saccharin, as determined in the lysimeter study, were analysed using the inverse modelling technique according to the recommendations made by FOCUS (2009).[16]

The parameters (K_{oc} = 0.009 mL/g; DT_{50} = 28.7 days) were then used to perform FOCUS PEARL simulations considering an application rate of 2 kg/ha.

The inverse modelling study based on the lysimeter experiment confirms high concentrations in the percolate even above the previous simulations performed with standard parameters.

In order to address the high percolate concentration in the FOCUS PEARL simulation, a second calculation was performed considering a reduced application rate of only 5.25 g/ha. This rate was based on an initial PEC_{soil} of 7 μg/kg over 5 cm, which is the 'diluted PEC_{soil}' obtained considering real farm application and just 1 mg saccharin/kg feed. The results for these simulations are shown in Table 3.

Table 3: The 80th percentile of annual leaching concentration for saccharin (as μg/L) modelled using FOCUS PEARL using the optimised parameters(1) together with a reduced rate of 5.25 g/ha (corresponding to 1 mg/kg feed – 'diluted')

Computer model	**FOCUS PEARL**		
Application	Winter cereals, 5.25 g/ha, soil incorporation		
Target animal	swine		
K_{oc}	0.009 mL/g		
DT_{50}	28.7 days		
Scenario	JOKIOINEN	PIACENZA	SEVILLA
80th percentile of concentration in leachate (μg saccharin/L)	2.164	0.464	0.137

Even with this lowered dose (1 mg/kg) and considering the 'dilution' of manure, the concern for groundwater remains.

[14] Technical dossier/Annexes/Annex 3 FFAC 2021 real farm conditions CONF.
[15] Technical dossier/Annexes/Annex 4 ERA calc sacch 134 ppm EFSA 2019 FA mixed manure CONF.
[16] Technical dossier/Annexes/Annexes 5 to 7 and supplementary information July 2022.

Finally, with an inverse modelling exercise ('try and error' technique), the maximum application rate in g/ha that respects the trigger of 0.1 μg/L in the percolate was calculated for the FOCUS scenario Jokioinen (the worst-case scenario). This application rate corresponds to 0.24 g/ha. This low application rate would result in a concentration in the groundwater of 0.099 μg/L. The respective initial PEC_{soil} related to this application rate would be 0.323 μg/kg, which corresponds to a value of 0.020 mg saccharin/kg feed corresponding to 0.022 mg sodium saccharin/kg feed.

The applicant noted that in the environmental risk assessment of veterinary medical products, as regards groundwater, a risk quotient approach is allowed for the risk characterisation in cases where PEC_{gw} is > 0.1 μg/L.[17] In addition, sodium saccharin is a feed additive but saccharin is also a degradation product of some pesticides. In pesticide regulatory arena, saccharin was identified as a non-toxicological relevant metabolite (see e.g. Peer review of the pesticide risk assessment of the active substance propoxycarbazone [EFSA, 2016]), whose trigger value in groundwater may arrive up to 10 μg/L. The default value in Regulation 429/2008, however, is set at 0.1 μg/L and the FEEDAP Panel retains this later value as the relevant for the assessment.

For the metabolite 4-hydroxysaccharin, the available PEC_{GW} modelling suggests potential leaching above the trigger value of 0.1 μg/L while in the outdoor monolith lysimeter study the metabolite was detected only at trace levels. It should be noted though, that the lysimeter data represents the formation, degradation and adsorption of this metabolite in a single soil only and that based on the fairly strong adsorption of the metabolite (K_{oc} = 1,711 ml/g) the duration of the lysimeter study may have been too short for the compound to reach the bottom of the soil column.

3.2.2.4. Conclusions on safety for the environment

Although the new conditions of use describe a maximum use level of 5 mg sodium saccharin/kg feed, the applicant indicated that a restriction to a lower use level due to environmental safety would be accepted.[18] The environmental assessment submitted by the applicant was based on a use level of 1 mg saccharin/kg feed, corresponding to 1.13 mg sodium saccharin/kg. No safe use can be identified at 1.13 mg sodium saccharin/kg feed. The estimated use level that would result in a concentration in groundwater below 0.1 μg/L is of 0.022 mg sodium saccharin/kg feed. The available data do not allow to conclude on the potential effect of the degradation product 4-hydroxysaccharin in ground water.

4. Conclusions

The additive is not a skin or eye irritant, and it is not a dermal sensitiser. Users may be exposed by inhalation. In the absence of data, the FEEDAP Panel cannot conclude on the potential of the additive to be toxic by inhalation.

As regards the safety of the additive for the environment, 1.13 mg sodium saccharin/kg feed cannot be considered safe. The estimated use level that would result in a concentration in groundwater below 0.1 μg/L is of 0.022 mg sodium saccharin/kg feed. The available data do not allow to conclude on the potential effect of the degradation product 4-hydroxysaccharin in ground water.

5. Documentation provided to EFSA/Chronology

Date	Event
07/04/2021	Dossier received by EFSA. Follow-up opinion linked to EFSA-Q-2010-01228 - Sodium saccharin for piglets, pigs for fattening, calves for rearing and calves for fattening. Submitted by FFAC - Feed Flavouring Authorisation Consortium
13/07/2021	Reception mandate from the European Commission
01/10/2021	Application validated by EFSA – Start of the scientific assessment

[17] Cases in which PECgw is above the trigger value, and there is available data on ecotoxicity in surface water species. A risk quotient RQgw = PECgroundwater/(PNECsurfacewater/10) is applied, considering the PNECsw of the most sensitive species. See EMA CVMP guidance on environmental impact of veterinary medicines on groundwater (EMA, 2018).For saccharin, a PNECgw of 10 μg/kg is extrapolated by applying an additional assessment factor of 10 to the PNECsw of 100 μg/kg for algae, the most sensitive species (EFSA FEEDAP Panel, 2018). When considering the refined PECgw of 6 μg/L calculated at the proposed use level of 1 mg/kg (see section 3.2.2.2), a RQqw of 0.6 is calculated. or better: When considering the concentration from the FOCUS scenario of 0.137–2.164, a RQgw ≤ 0.22 is calculated.

[18] Technical dossier/Supplementary information July 2022/22–07–05 Supplementary information 040322 Sodium saccharin final, reply to question 1.

Date	Event
03/04/2022	Request of supplementary information to the applicant in line with Article 7(3) of Commission Regulation (EC) No 1304/2003– Scientific assessment suspended. *Issues: Conditions of use/ safety for the user/Safety for the environment*.
05/07/2022	Reception of supplementary information from the applicant - Scientific assessment re-started
22/11/2022	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviations

CAS	chemical abstracts service
DT_{50}	time to degradation of 50% of the original concentration of the compound in the tested soil
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)
FOCUS	forum for the coordination of pesticide fate models and their use
K_{oc}	organic carbon-water partitioning coefficient

OECD	organisation for Economic Co-operation and Development
PEARL	pesticide emission assessment at regional and local scales
PEC	predicted environmental concentration
VICH	trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration