Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

tetrairon tris(pyrophosphate);
ferric pyrophosphate

EC Number: 233-190-0
CAS Number: 10058-44-3

CLH-O-0000007280-81-01/F

Adopted

16 March 2023

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16 March 2023

CLH-O-0000007280-81-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **tetrairon tris(pyrophosphate); ferric pyrophosphate**

EC Number: **233-190-0**

CAS Number: **10058-44-3**

The proposal was submitted by **Poland** and received by RAC on **11 February 2022.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Poland has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **21 March 2022**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **20 May 2022**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Mihaela Pribu**

Co-Rapporteur, appointed by RAC: **Irina Karadjova**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

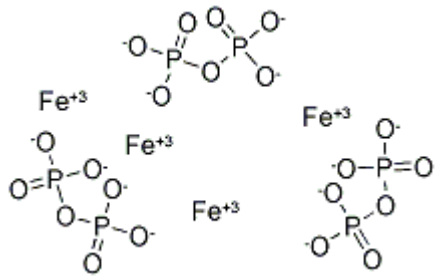
The RAC opinion on the proposed harmonised classification and labelling was adopted on **16 March 2023** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	tetrairon tris(pyrophosphate); ferric pyrophosphate	233-190-0	10058-44-3	Eye Irrit. 2	H319	GHS07 Wng	H319			
RAC opinion	TBD	tetrairon tris(pyrophosphate); ferric pyrophosphate	233-190-0	10058-44-3	Eye Irrit. 2	H319	GHS07 Wng	H319			
Resulting Annex VI entry if agreed by COM	TBD	tetrairon tris(pyrophosphate); ferric pyrophosphate	233-190-0	10058-44-3	Eye Irrit. 2	H319	GHS07 Wng	H319			

RAC general comment

About this substance



$Fe_4(P_2O_7)_3$; iron (III) pyrophosphate

Tetrairon tris (pyrophosphate); ferric pyrophosphate is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area at ≥ 100 to < 1000 tonnes per annum.

This substance is used by consumers and professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing of several products such as coating products, plasters, inks, pest control products, food products and food supplements. It is also a pesticidal active substance under (EC) 1107/2009.

Dossier Submitter's classification proposal

According to Annex VI, part 2 of the CLP Regulation, the information provided in the REACH Registration dossier was included in the CLH report and considered in this opinion.

This RAC opinion is mainly based on the available data from the CLH report which were included in the Renewal Assessment Report developed in accordance with the Commission Regulation (EC) No. 844/2012.

Ferric pyrophosphate is characterised by a low bioavailability following oral administration. Due to the poor solubility in water and lipids the absorption in the body is low, and it does not accumulate in the organism. A low level of iron excretion is observed under normal physiological conditions.

Given the prevalence in nature of iron and phosphorus, and the potential absorption of ferric pyrophosphate from water, exposure to this substance will not increase significantly as a result of its use in plant protection products. Exposure related to absorption of pyrophosphate in other ways is not expected as the substance is non-volatile and the product has a form of non-dusty granules.

Data on exposure cited from acknowledged scientific sources combined with low toxicity evidenced in the studies presented indicate that further toxicological studies are not yet necessary.

Regarding the completeness of the data in the CLH report, RAC concludes that the applicant submitted a limited data package with the ferric pyrophosphate including acute oral and inhalation toxicity, eye and skin irritation studies, a genotoxicity test battery and short-term oral toxicity studies in rats.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

Ferric pyrophosphate is a solid inorganic substance, therefore only hazard classes relevant for solids were open for consultation. The DS proposed no classification for all the relevant hazard classes based on the chemical structure (explosives, self-reactive substances, oxidising solids, organic peroxides, and corrosive to metals), on experience (pyrophoric solids, and substances which in contact with water emit flammable gases), or based on study results (flammable solids, and self-heating substances).

Comments received during consultation

No comments were received

Assessment and comparison with the classification criteria

RAC notes that the screening procedure for explosives or self-reactive substances based on the chemical structure is applicable for organic substances only, while ferric pyrophosphate is an inorganic compound. RAC concludes on no classification for explosives and self-reactive substances due to lack of data.

For oxidising solids, the screening procedure is applicable to inorganic substance which do not contain oxygen or halogen atoms. Ferric pyrophosphate does contain oxygen atoms, thus the screening procedure is not applicable and the UN RTG O.1 test should have been conducted. RAC concludes on **no classification for oxidising solids due to lack of data.**

RAC notes that based on the structure the hazard class "organic peroxide" is not relevant for an inorganic substance.

RAC agrees with the DS on **no classification based on experience for pyrophoric solids and substances which in contact with water emit flammable gases**.

RAC agrees with the DS on **no classification as flammable solids** based on a negative EU A.10 test (not highly flammable, see Table 9 of the CLH report).

RAC agrees with the DS on **no classification for self-heating substances** based on a negative EU A.16 test method.

RAC agrees with the DS, that ferric **pyrophosphate should not be classified as corrosive to metals.**

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute toxicity - oral route

Two studies performed according with GLP and guideline compliant (OECD TG 420) with ferric pyrophosphate are available, both on rats (see Table 12 of the CLH report). The acute oral LD_{50} was > 2000 mg/kg bw in both of them.

The DS proposed no classification for acute toxicity based on the LD_{50} values > 2000 mg/kg bw.

Acute toxicity - dermal route

Because the acute oral LD_{50} value for ferric pyrophosphate is above 2000 mg/kg bw, the acute dermal toxicity study is not necessary according to Commission Regulation (EU) No. 283/2013. Consequently, there is not acute dermal study in the CLH report, and the DS proposed no classification for acute dermal toxicity for ferric pyrophosphate due to lack of data.

Acute toxicity - inhalation route

Two studies on acute inhalation toxicity (4h, nose-only) using ferric pyrophosphate were performed according with GLP on Wistar rats. The LC_{50} was above the stated maximum attainable concentrations of 2.69 mg/L for the first study (OECD TG 403), and of 5.19 mg/L for the second one (OECD TG 436) (see Table 13 of the CLP report).
The DS proposed no classification for ferric pyrophosphate with respect the trigger for acute toxicity – inhalation.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

Acute oral toxicity

Study 1, Anonymous 1, 2013

The test substance was ferric pyrophosphate (purity 101.73%), and was administered to 6 female Wistar rats (age: 9-11 weeks), at 300 and 2000 mg/kg bw during 14-days of exposure. The study followed the OECD TG 420 with a deviation regarding the relative air humidity which was lower than 30% a few times, but this had no influence on the results. Air humidity was recorded to vary between 5 to 60%, due to the regulation of the air-conditioning device at that time. Water was available for the animals all the time. The test item in the form of a suspension in 0.5% carboxymethylcellulose in a volume of 0.5 mL/100 g bw was administered using a metal stomach tube. No mortalities or clinical signs were observed in the study, and the gross examinations of the animals did not reveal any pathological changes. The acute oral LD_{50} was found to be > 2000 mg/kg bw in all 5 Wistar rats female.

Study 2, Anonymous 2, 2012a

A single dose of 2000 mg/kg bw Ferric pyrophosphate was administered by the oral route to 5 female Wistar rats . The test item in the form of a suspension in 0.5% carboxymethylcellulose in a volume of 0.5 mL/100 g bw was administered using a metal stomach tube. No mortalities or clinical signs were noted in exposed animals; the animals increased their body weight during the observation period and no pathological changes were observed at necropsy. The acute oral LD_{50} was found to be > 2000 mg/kg bw.

In both studies, the LD_{50} was above the cut-off value of 2000 mg/kg bw for classification in Category 4. RAC agrees with the DS proposal of **no classification for acute oral toxicity**.

Acute toxicity - dermal route

No acute dermal study is included in the CLH report, therefore RAC considers that **no classification for acute dermal toxicity is warranted due to lack of data**.

Acute toxicity - inhalation route

Study 1, Anonymous 3, 2013
Ferric pyrophosphate, purity 101.73%, was administered by inhalation for 4 hours, nose-only, to 3 male and 3 female Wistar rats. The maximum attainable concentration was of 2.69 mg /L. No mortalities were observed during the study, and no abnormalities were detected in any of the animals on necropsy at the end of observation period. The study is reliable, and the LC_{50} was estimated to be > 2.69 mg/L air.

Study 2, Anonymous 4, 2012
Ferric pyrophosphate, purity 101.73%, was administrated by inhalation to 3 male and 3 female Wistar rats at a concentration of 5.19 mg/L, for 4 hours, nose-only. No mortalities were recorded during the study, and no abnormalities were detected in any of the animals on necropsy at the end of observation period. The study is reliable, and the LC_{50} was estimated to be > 5.19 mg/L air.

The acute inhalation LC_{50} of a dust aerosol of ferric pyrophosphate was higher than both the tested concentrations of 2.69 and 5.19 mg/L.
In the CLP Regulation, the cut-off criteria for classification in Category 4 for acute inhalation (dust/mist) is $1 < LC_{50} \leq 5$ mg/L). In the second study (Anonymous 4, 2012), the tested concentration of 5.19 mg/L is above the classification criteria and no mortalities were observed. In the other study (Anonymous 3, 2013), the LC_{50} was above the highest technically attainable concentration of 2.69 mg/L; also in this study no mortalities (or significant changes in the animals) were observed. RAC agrees with the DS proposal of **no classification for acute inhalation toxicity**.

Conclusion on classification and labelling for acute toxicity

RAC considers that no classification is warranted for acute toxicity via all routes of exposure.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

Ferric pyrophosphate was investigated in a number of acute studies by the oral and inhalation routes (see section 10.1-10.3 of CLH report). There was no indication that ferric pyrophosphate caused specific toxicity to any organ after a single exposure. There was no evidence of narcotic effects from any toxicological study. No signs of respiratory irritation were observed in the acute inhalation study.
The DS did not consider a classification for specific target organ toxicity – single exposure (STOT SE) for ferric pyrophosphate appropriate based on the findings from the acute toxicity studies.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

During the acute oral toxicity study the animals were examined for clinical changes in areas such as: locomotor system, behaviour, reactions to stimuli, skin and hair, eyes and eyelids, respiratory system, digestive system, urinary system, reproductive system, whereas in the acute inhalation study observations included, but were not be limited to: changes in the skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous system, somatomotor (pertaining to movements of the body) activity and behaviour pattern. Attention was directed to observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep, coma and rectal temperature.

Non-lethal effects were not reported after acute exposure to ferric pyrophosphate via oral or inhalation route, including clinical signs, influence on behaviour, and effects on body weight gain or changes in macroscopic examination. It is not anticipated that ferric pyrophosphate has specific target organ toxicity, under single-dose exposure.

No known mechanisms of narcotic effects are expected to occur in case of ferric pyrophosphate based on its molecular structure, solubility.

Ferric pyrophosphate has been used as food additive for many years, even in small children. In accordance with Regulation (EU) No. 609/2013 of the European Parliament and of the Council of 12 June 2013, it was approved for use in baby food for infants and young children, processed cereal-based foods, food for children, for special medical purposes, and as total diet replacement. In principle, ferric pyrophosphate could cause respiratory tract irritation (RTI) through a physical/mechanical irritation mode of action following dust inhalation. However, no evidence of irritation was observed in the acute toxicity study. Furthermore, no narcotic effects nor cause-related RTI have been reported following extensive experience with the substance.

Conclusion on classification and labelling for STOT SE

No single dose toxicity studies other than acute limit tests were submitted to enable the assessment of non-lethal toxic effects. Despite all the studies, even at the limit dose, no signs which could indicate specific effects on target organs were reported.

Overall, RAC concludes that **no classification for STOT SE is warranted** for ferric pyrophosphate.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

Ferric pyrophosphate was tested in three studies for skin irritation/corrosion effects.
One of the studies was carried out on rabbits according to test method B.4 in compliance with GLP.
The other two studies were carried out using a reconstituted human epidermis model with ferric pyrophosphate according to OECD TG 439 and OECD TG 431, both GLP compliant.
The skin corrosion/irritation findings did not meet the criteria for classification in any of the studies. Consequently, the DS proposed no classification for skin corrosion/irritation.

Comments received during consultation

No comments were received

Assessment and comparison with the classification criteria

Skin corrosion/irritation studies available are described in the table 14 of the CLH report.

Study 1, Anonymous 5, 2013

Ferric pyrophosphate was administrated to 3 adult female New Zealand White (NZW) rabbits. The concentration of ferric pyrophosphate was of 0.5 g for 4 hours applied onto clipped skin using a semi-occlusive dressing. The study is reliable, conducted according to Method B.4 and GLP compliant.

At first, the test substance was applied on the skin of one rabbit for 4 hours. Skin reactions were investigated 3 minutes, 1 hour and 4 hours after patch removal. No evidence of skin irritation or corrosion were observed. In the confirmatory test, no skin reactions were observed on the two additional rabbits. No other signs of intoxication were observed. Overall, no skin reactions on NZW rabbit were observed after 4h exposure to ferric pyrophosphate.

Study 2, Anonymous 6, 2012a

Ferric pyrophosphate was tested in an *in vitro* GLP compliant study performed according to OECD TG 439, and reliable. The test item was applied for 15 minutes onto the reconstituted human skin, followed by 42 hours post-exposure incubation. The average tissue viability was 110%, which is above the 50% criteria for no classification.

Study 3, Anonymous 6, 2012b

A second GLP compliant *in vitro* study was performed according to OECD TG 431 and reliable. Ferric pyrophosphate was applied directly to the reconstructed epidermis surface for 3, 60 or 240 minutes. The viability after 240 minutes was 79.5% which fulfils the prediction model for no classification (≥ 35%).

Conclusion on classification and labelling for skin corrosion/irritation

RAC agrees with the DS that **classification for skin irritancy is not warranted** for ferric pyrophosphate.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

Ferric pyrophosphate was tested in three studies for acute eye irritation, two *in vivo* studies (EU B.5 and EU B.5/OECD TG 405) and one *ex vivo* BCOP (OECD TG 437), all of which were GLP compliant. In the first *in vivo* study (Anonymous 7, 2013), an average score of 2 for conjunctival redness was observed in all 3 male of NZW rabbits. The effects were reversible within 6 days after exposure. In the second *in vivo* study (Anonymous 2, 2012b), the maximum chemosis score of 0.33 was observed in one out of 2 NZW rabbits but this adverse effect was fully reversible within 48 hours (animal no 1) and within the 72 hours (animal no 2). In the *in vitro* study (Anonymous 6, 2021c), on bovine eye, the IVIS score was 25.3 which is in the "no prediction can be made" zone, as defined in OECD TG 437 for scores between 3 < IVIS ≤55.

Based on the results of the first *in vivo* study, the DS proposed to classify ferric pyrophosphate as Eye Irrit. 2; H319, causes serious eye irritation.

Comments received during consultation

One MSCA commented on the available studies, pointing out that conjunctival redness was not investigated in Anonymous 2 (2012b), and they agreed with the DS proposal (Eye Irrit. 2; H319) based on the results of Anonymous 7 (2013).

The DS responded that additional information on the conjunctival redness results in study Anonymous 2, 2012b could be found in the REACH registration dossier (https://echa.europa.eu/registration-dossier/-/registered-dossier/12264/7/4/3): conjunctiva redness was 0.33 in two animals fully reversible within 48 and 72 hours, respectively. According to the study protocol, "if the second animal revealed corrosive or severe irritant effects, the test is not continued" and "additional animals may be needed to confirm weak or moderate irritant responses". Therefore, the results of the study by Anonymous 2 (2012b) could not be considered to be conclusive data.

A company manufacturer considered the results of the study performed by the EU REACH Registrant to be GLP and OECD TG compliant, reliable and that they clearly fulfilled the criteria for no classification. In their comment, the discrepancy between the study in the PPP review (fulfilling the criteria for Cat. 2) and these included in the REACH registration dossier could be due to a different composition, thus promoting the re-assessment of all studies based in light with accurate information on the composition. They considered the information on the EU REACH registrants did not support a harmonised classification for this endpoint.

The DS responded that the results of the *ex vivo* study (BCOP, Anonymous 6, 2012c) was 25.3 which is above the "< 3" criteria for no classification and that the other study in the REACH registration dossier could not be considered to be conclusive as only 2 animals were tested instead of 3 (Anonymous 2, 2012b). Thus, the classification is based on the results of Anonymous 7 (2013).

Assessment and comparison with the classification criteria

Study 1, Anonymous 7, 2013
Ferric pyrophosphate was administrated by instillation directly on the eyes of 3 male NZW rabbit, for 4 hours. The study was conducted accordingly to Method B.5 and was GLP compliant, and is considered reliable. One hour after instillation, chemosis and conjunctivae were observed in all rabbits, see table below. Chemosis of grade 2 was observed in all rabbits at 24, 48 and 72h after instillation, and it was completely reversible in 2 animals by day 5 and by day 6 in the third rabbit.

***Table**: CA B 6.2-4 (from RAR, 2019) Result of reaction of treated eye (grades)*

Animal No.	Ocular lesions	Time interval of examination							
		1h	24h	48h	72h	4th day	5th day	6th day	7th day
16	Cornea	0	0	0	0	0	0	0	0
	Iris	0	0	0	0	0	0	0	0
	Conjunctivae	2	**2**	**2**	**2**	1	1	0	0
	Chemosis	1	0	0	0	0	0	0	0
17	Cornea	0	0	0	0	0	0	0	-
	Iris	0	0	0	0	0	0	0	-

	Conjunctivae Chemosis	3 2	**2** 0	**2** 0	**2** 0	1 0	0 0	0 0	- -
18	Cornea Iris Conjunctivae Chemosis	0 0 3 2	0 0 **2** 0	0 0 **2** 0	0 0 **2** 0	0 0 1 0	0 0 0 0	0 0 0 0	- - - -

The mean scores of conjunctivae redness following grading at 24, 48 and 72 hours after installation were: 2, 2, 2, therefore the classification criteria for eyes irritation in Category 2 are met.

Study 2, Anonymous 2, 2012b

Ferric pyrophosphate (0.1 mL or 98 mg) was administrated by instillation directly onto the eyes on 2 male NZW rabbits for 72 hours. The study was conducted accordingly to Method B.5 and GLP compliant, and it is considered reliable.

The mean scores over time were 0.33, 0 for chemosis, and 0.33, 1 for redness. No other signs of eye irritation/corrosion were observed during the experiment.

Study 3, Anonymous 6, 2012c

Ferric pyrophosphate (20% diluted with 0.9% w/v sodium chloride solution) was applied directly to the epithelial surface of the cornea of bovine eye for 240 min (4 hours). The study was performed according to OECD TG 437, was GLP compliant, and is considered reliable.

The study irritation score was 25.3 which is in the "no stand-alone prediction can be made" range of scores ($3 < IVIS \leq 55$).

Conclusion on classification and labelling for serious eye damage/eye irritation

Based on the result of study 1, the criteria for classification as eye irritant in Category 2 are fulfilled, therefore RAC considers **classification as Eye Irrit. 2; H319 is warranted** for ferric pyrophosphate.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

DS proposed no classification for respiratory sensitisation for ferric pyrophosphate.

Comments received during consultation

No comments were received

Assessment and comparison with the classification criteria

No data are available to assess respiratory sensitisation.

Conclusion on classification and labelling for respiratory sensitisation

RAC proposes **no classification for respiratory sensitisation**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Due to lack of skin sensitisation studies for ferric pyrophosphate, the data on ferric orthophosphate were used. Both substances are relatively insoluble inorganic ferric (Fe^{3+}) compounds. In these conditions, ionisation to the Fe cation and the orthophosphate cation (iron orthophosphate) or pyrophosphate cation (tetrairon tris(pyrophosphate)) will occur. In biological systems (i.e. in the presence of alkaline phosphatase) the pyrophosphate will be broken down into orthophosphate. It is considered that the Fe^{3+} cation is of most relevance when considering the sensitisation potential and as iron orthophosphate is slightly more soluble, this substance is a good candidate for read-across. Pyrophosphate itself is not considered to be a sensitiser, in addition, the breakdown product of pyrophosphate (orthophosphate) is a natural component of blood and cellular fluids.

As ferric pyrophosphate has a lower water solubility than iron orthophosphate, it is considered to be less bioavailable and therefore iron orthophosphate is considered to be a worst case for sensitisation potential of ferric pyrophosphate. The study reports that iron orthophosphate is a non-sensitiser (Anonymous 2, 2011).

DS proposed no classification regarding to skin sensitisation for ferric pyrophosphate.

Comments received during consultation

No comments were received

Assessment and comparison with the classification criteria

The available study on skin sensitisation is described in Table 16 of the CLH report.

Study 1, Anonymous 2, 2011
Iron orthophosphate was administrated to female (CBA/Ca (CBA/CaOlaHsd)) mice at concentrations of 50%, 25% or 10% w/w in dimethyl formamide by direct application to calculate the Stimulation Index (SI). The LLNA study was performed according to OECD TG 429 and was GLP compliant and reliable. No mortalities or adverse effects were observed. At a 50% concentration, a value of SI = 2 was derived for iron orthophosphate, therefore the test is considered negative.

Conclusion on classification and labelling for skin sensitisation

RAC proposes **no classification as skin sensitiser** for tetrairon tris(pyrophosphate) based on the negative LLNA study conducted on the read-across substance iron orthophosphate.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

Two studies were performed on Han Wistar or Wistar rats according to OECD TG 407 and OECD TG 408, respectively, with deviations. Tetrairon tris(pyrophosphate) was administrated by

feeding for 28 days or 90 days. The scope of these studies was to identify the long-term effects during repeated exposure on animals.

The DS did not propose to classify ferric pyrophosphate as STOT RE either in category 1 or 2.

Comments received during consultation

No comments were received

Assessment and comparison with the classification criteria

The studies are presented in Table 18 of CLH report.

Study 1, Anonymous 11, 2013

Ferric pyrophosphate was administered by gavage to Han Wistar rats in concentrations of 0, 100, 500, 1000 mg/kg bw/d as a suspension in 0.5% methylcellulose solution, in the same volume (1 mL), for 28 days (7 days/week). The was performed according to OECD TG 407, GLP compliant and reliable.

No mortalities or clinical signs of toxicity were noted. Haematological parameters and serum biochemistry either did not show statistically significant differences between the exposed groups and the control, or were within the reference values. No signs of toxicity related to elevated enzymes and potassium level were noted. Gross pathology findings did not indicate systemic toxicity of ferric pyrophosphate up to 1000 mg/kg bw/d.

Study 2, Anonymous 12, 2014

Ferric pyrophosphate was administrated by gavage to 15/sex Wistar rats for 90 days, at a concentration of 1000 mg/kg bw/d, suspended in 0.5% methylcellulose solution seven days a week. Concurrently, control group (8 males/females) received the vehicle (0.5% methyl cellulose solution) at the same volume as the test material, and a satellite group (8 males/females) received the test material at a dose of 1000 mg/kg bw/d.

The study is considered reliable, was performed according to OECD TG 408 and was GLP compliant. The study deviates from the original planned study because a different rat strain was used in this study than in 28 day oral study, the coagulation parameters were not evaluated for all animals.

No mortalities or clinical signs of toxicity were noted and the body weight, food and water consumption, and pathology were normal. From the 11th week, behavioural tests were carried out and on the last exposure day the animals underwent neurological examination.

The statistically significant changes in haematological and biochemical parameters in the exposed animals were within reference values provided by the applicant for rats, and they do not constitute evidence of severe adverse effects caused by ferric pyrophosphate.

Results

Blood analysis

Statistically significant haematological findings were increased red blood cell count and haematocrit value in male and female tested group (1000 mg/kg bw/d) in comparison with the control group, while leukocytes and reticulocytes were increased in females only. These findings did not exceed the reference values and did not correlate with other clinical symptoms.

Plasma and serum analysis

Statistically significant differences in females were increased unsaturated iron binding capacity, phosphorous, triglycerides, urea, albumin and total protein level, and decreased glucose and total cholesterol levels. In males, statistically significant changes were as follows: increased magnesium, iron, urea, creatinine, alanine aminotransferase, alkaline phosphatase and amylase levels. In addition, statistically significant decreased phosphorous levels, as well as unsaturated and total iron binding capacities were reported in males. These statistically significant biochemical differences were within the available reference values and did not correlate with other clinical symptoms. Pathologic discharge from reproductive organs was not included in the CLH dossier.

Conclusion on classification and labelling for STOT RE

No significant organ damage was observed in rats up to 1000 mg/kg bw/d. Consequently, RAC agrees with the DS's proposal for **no classification**.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The mutagenic potential of ferric pyrophosphate was investigated in three *in vitro* assays (bacterial mutagenicity assay, mutagenicity test in mouse lymphoma and mutagenicity test in human peripheral blood lymphocytes) and one *in vivo* assay (rat bone marrow micronucleus test). All studies were performed according to the relevant OECD TG and were GLP compliant. All results were negative, therefore ferric pyrophosphate is not considered to be genotoxic or mutagenic, consequently the DS proposed no classification for germ cell mutagenicity.

Comments received during consultation

No comments were received

Assessment and comparison with the classification criteria

All the studies regarding the mutagenicity/genotoxicity effects are summarised in the table 16 of the CLH report.

Study 1, Sathe, 2014

The GLP compliant study, performed according to OECD TG 471, is considered reliable. Ferric pyrophosphate was not mutagenic to any of the five *Salmonella* tester strains of TA98, TA100, TA1535, TA1537 and TA102 when tested at 5000 µg/plate in the presence as well as in the absence of metabolic activation (10% v/v S9 Mix).

Study 2, Anonymous 8, 2014

The GLP compliant study, performed according to OECD TG 476, is considered reliable. Due to the low solubility, the highest dose was limited by the precipitation of ferric pyrophosphate in DMSO (1250 µg/mL). No cytotoxicity and only slight precipitation were reported at this concentration. Ferric pyrophosphate did not induce any increase in the mutant frequency when tested at up to 1250 µg/mL, with or without metabolic activation, during the short or long periods of treatment; thus, it is considered not mutagenic in this system.

Study 3, Anonymous 9, 2013

The GLP compliant study, performed according to OECD TG 487, is considered reliable. The lymphocytes were isolated from two healthy, non-smoking donors.
Ferric pyrophosphate at the concentrations used (0.05 mg/mL, 0.0158 mg/mL, 0.005 mg/mL, 0.00158 mg/mL), both after 3h exposure (with or without metabolic activation system) and after 24h exposure (without metabolic activation system) did not induce any statistically significant increase in the frequency of micronuclei in exposed cell cultures compared to control cultures.

Study 4, Anonymous 10, 2014

The GLP compliant study, performed according to OECD TG 474, is considered reliable. The incidence of micronucleated erythrocytes was observed in 2000 immature erythrocytes and 2000 mature erythrocytes from the bone marrow and peripheral blood. The proportion of immature erythrocytes among mature erythrocytes of peripheral blood and bone marrow were scored and evaluated, concluding that ferric pyrophosphate does not cause cytogenetic damage which stimulates micronucleus formation in the immature erythrocytes *in vivo* in mammals.

Ferric pyrophosphate did not induce a positive response in the *in vivo* micronucleus test.

Conclusion on classification and labelling for germ cell mutagenicity

All available studies were negative, consequently, RAC proposes **no classification for ferric pyrophosphate as a germ cell mutagen**.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

DS proposed no classification of ferric pyrophosphate as a carcinogen.

Ferric pyrophosphate has been used as food additive for many years, even in small children. In accordance with Regulation (EU) No. 609/2013, it was approved for use in baby foods for infants and young children, processed cereal-based foods and food for children, food for special medical purposes, and in total diet replacement.

Results of epidemiological studies suggest that there might be a correlation between the increased iron supply (total or haeme iron) and increased risk of colorectal and duodenal cancer (Nelson, 2001; Torti and Torti, 2013), however these differences were not statistically significant. These study results did not provide conclusive evidence that considerable iron overload and increased ferritin concentration might contribute to cancer development. Heterozygosity in haemochromatosis might be related to this phenomenon but this relationship has also not proved to be statistically significant. Thus, it is not possible to draw definitive conclusions. Results of studies on red meat consumption, which is a source of haeme iron, invariably pointed to an increase in the risk of colorectal and duodenal cancer. However, these studies do not exclude the role of confounding variables such as environmental factors or e.g. lifestyle of the patients. It is not possible to determine the dose-response relationship and the threshold value of the amount of consumed and processed red meat.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

No carcinogenicity study was included in the CLH report for ferric pyrophosphate. The epidemiological evidence of a direct correlation between increased iron supply and colorectal and duodenal cancer is not sufficient for classification.

Conclusion on classification and labelling for carcinogenicity

RAC proposes **no classification due to lack of data**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

DS proposed no classification for reproductive toxicity of ferric pyrophosphate.

During pregnancy, iron demand is significantly increased and dietary fortification or supplementation are indicated. Ferric pyrophosphate is one of iron sources approved in the European Union for food fortification and dietary supplement.

A WHO report[1] cites the results of studies on the influence of iron and its compounds on reproduction, which show that no maternal toxicity or teratogenic effects were observed for doses up to 160 mg/kg bw/d in mice and rats (ferric sodium pyrophosphate).

Despite this, some studies describe potential correlation of iron overload with birth and infant adverse health outcomes including growth retardation, foetal malformations or preterm births. The level of evidence is, however, rather low due to the limited sample size[2]. In another study, patients with beta-thalassemia experienced iron overload and impaired fertility[3]. In these patients sexual maturation was delayed and they had hypogonadism and sperm DNA damage. This could be due to the potential for iron to increase ROS production, decrease antioxidant levels, enhance the lipid peroxidation of the cell membrane, cause apoptosis, and contribute to the oxidative damage of DNA[4,2].

Comments received during consultation

No comments were received

Assessment and comparison with the classification criteria

No reproductive toxicity study has been submitted for ferric pyrophosphate.

The available epidemiological information does not indicate adverse effects of ferric phosphate on reproductive hazard for humans or mammals.

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1 Joint FAO/WHO Expert Committee on Food Additives. Toxicological evaluation of certain food additives and food contaminants. WHO Food Additives Series, No. 18, 571. Iron; 1983

2 Brannon and Taylor. Iron Supplementation during Pregnancy and Infancy: Uncertainties and Implications for Research and Policy, Nutrients; 2017, 9, 1327

3 Golub (ed) (2006) Metals, fertility, and reproductive toxicity. Taylor and Francis, Boca Raton

4 Pizent *et al.* Reproductive toxicity of metals in men, Arh Hig Rada Toksikol; 2012; 63

Conclusion on classification and labelling for reproductive toxicity

RAC proposes **no classification due to lack of data**.

RAC evaluation of aspiration toxicity

Summary of the Dossier Submitter's proposal

DS proposed no classification warranted for aspiration toxicity.

Ferric pyrophosphate is not a hydrocarbon and is not known to cause human aspiration toxicity hazards.

Comments received during consultation

No comments were received

Assessment and comparison with the classification criteria

RAC agrees with the DS assessment of aspiration toxicity.

Conclusion on classification and labelling for aspiration toxicity

RAC proposes **no classification**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Ferric pyrophosphate is considered as insoluble metal compound. The DS proposed for ferric pyrophosphate no classification for acute aquatic toxicity and no classification for chronic aquatic toxicity. The conclusion was based on calculated acute ERV value of 4.30 mg/L and calculated chronic ERV value of 1.87 mg/L.

Degradation

Ferric pyrophosphate is an inorganic substance. Since the substance is inorganic the biodegradation concept does not apply.

Environmental transformation of metals or inorganic metals compounds

The DS presented ferric pyrophosphate as a stable non-volatile inorganic salt, virtually insoluble in water. Iron, the main component of ferric pyrophosphate, is a chemical element which composes about 5% of the Earth's crust and is found in the form of minerals such as: hematite, magnetite, siderite or pyrite. Generally, iron is found in two oxidation states - reduced, as ferrous ion Fe^{2+}, or oxidized, as ferric ion Fe^{3+}. Fe^{2+} is more physiologically important for plants, however Fe^{3+} is more stable and represents the main ion distributed in the environment. Iron is an essential element for plants and its availability for plants is increased by various mechanism.

Phosphorus, the other main component of ferric pyrophosphate, is also an essential element important for the functioning of every cell. Phosphorus compounds in soil display great diversity both in terms of chemical forms and the strength of bonding with the solid phase. The DS presented extended discussion on iron and phosphorus behaviour in soils and fertilizers as sources for both elements.

Data from transformation/dissolution test for ferric pyrophosphate according to the OECD TG 29 is not available. The DS proposed the analysis of transformation/dissolution to be based on the read-across data for iron orthophosphate, taking into account the similar structure, physical-chemical properties, environmental fate properties and ecotoxicological profile of the substances. The study to determine the transformation/dissolution of the test items iron(III)orthophosphate anhydrous (CAS 10045-86-0) and iron (III) orthophosphate dihydrate (CAS 14567-75-0) was conducted according to the OECD TG 29 (2001) and GLP, at both pH 6 and 8 to cover acidic as well as basic conditions in environment. As requested, the test was conducted with a loading of 100 mg/L of both test items over 24 hours and one sampling after one day. The maximum amount of iron in the screening test was quantified at pH 6 applying iron(III)orthophosphate (CAS 10045-86-0 [anhydrous]). Therefore, the full test had been subsequently conducted with iron(III)orthophosphate (CAS 10045-86-0) at pH 6. Solution pH, oxygen concentrations and total dissolved iron concentrations were measured at each sampling time. Iron(III)orthophosphate (CAS 10045-86-0 [anhydrous]) at pH 6 exhibited the highest dissolved Fe concentration in the screening after 24 h with 11.229 ± 4.544 µg Fe/L. The mean dissolved amount of Fe after 168 h of testing at pH 6 with a loading of 100 mg/L was 21.062 ± 9.214 µg Fe/L. This corresponds to a calculated solubility of 58.506 ± 25.594 µg test item/L. At the loadings of 10 and 100 mg test item/L the dissolved Fe concentrations decreases over time. This is probably due to formation of hydroxides and subsequent precipitation.

Bioaccumulation

The DS concluded that since ferric pyrophosphate is insoluble in water, octanol/water partition coefficient cannot be established. Essentiality of both elements iron and phosphorus ruled out bioconcentration of ferric pyrophosphate in organisms. The DS concluded there is a low potential for bioaccumulation of ferric pyrophosphate in aquatic organism.

Acute aquatic hazard

The summary of the acute aquatic toxicity studies of ferric pyrophosphate is reported in Table below. Only information considered adequate, reliable and relevant for the classification proposal has been included.

***Table**: Summary of relevant information on acute aquatic toxicity*

Method	Species	Test material	Results	Remarks	Reference
Acute toxicity to rainbow trout OECD TG 203	rainbow trout (*Oncorhynchus mykiss*)	Ferric pyrophosphate Batch 120327086	LC_{50} > 0.134 mg/L (measured concentration; solubility limit) – LC_{50} > 100 mg/L (nominal concentration)	Exposure: 96h, static Measured and nominal concentration 14,40°C - 16,10°C pH 8,5	Anonymous 13, 2013; Report No. 0003/0024/E
Aquatic invertebrates short-term toxicity	*Daphnia magna*	Ferric pyrophosphate Batch 120327086	48h EC_{50} > 0.092 mg/L (measured concentration, solubility limit) 48h EC_{50} >100 mg/L	Exposure: 48h, static Measured and nominal concentration	Ziółkowska, Wickiel, 2013; Report No. 0003/0022/E

Method	Species	Test material	Results	Remarks	Reference
OECD TG 202			(nominal concentration)	20 ± 2°C pH 7.24-7.63	
Growth inhibition test on algae OECD TG 201	*Pseudokirchneriella subcapitata*	Ferric pyrophosphate Batch 120327086	E_rLR_{50} ≥ 0.0212 mg/L (measured concentration) E_yLR_{50} ≥ 0.0212 mg/L (measured concentration) E_rLR_{50} > 100 mg/L (nominal concentration) E_yLR_{50} > 100 mg/L (nominal concentration)	Exposure: 72 h Measured and nominal concentration 23.5-23.8°C pH 7.0-7.5	Heisterkamp, 2015; Report No. 1040

Acute (short-term) toxicity to fish

The acute toxicity of ferric pyrophosphate toward rainbow trout (*Oncorhynchus mykiss*) was studied, according to OECD TG 203 (Anonymous 13, 2013), for an exposure period of 96 hours. The iron content in the test solution was measured by the inductively coupled plasma optical emission spectrometry (ICP-OES). The ferric pyrophosphate was found non-toxic at concentration of 134 µg/L, being its solubility limit, corresponding to nominal concentration of 100 mg/L. The 96h LC_{50} greater than 134 µg/L was defined.

Acute (short-term) toxicity to aquatic invertebrates

The acute toxicity of ferric pyrophosphate toward Daphnia sp. (*Daphnia magna*) was studied in an immobilization test, conducted according to OECD TG 202, for an exposure period of 48 hours (Ziółkowska and Wickiel, 2013). The iron content in the test solution was measured by the inductively coupled plasma optical emission spectrometry (ICP-OES). The ferric pyrophosphate was non-toxic at a concentration of 92 µg/L, being its solubility limit, and corresponding to nominal concentration of 100 mg/L. The 48h EC_{50} greater than 92 µg/L was defined.

Acute (short-term) toxicity to algae or other aquatic plants

A growth inhibition test with *Pseudokirchneriella subcapitata* was conducted according to OECD TG 201 (Heisterkamp, 2015). The test vessels were prepared in three replicates and the control vessels were prepared in six replicates with five nominal loading rates (LR) between 6.25 mg/L and 100 mg/L. The specific growth rate, yield and their percent inhibition compared to the controls were calculated for each replicate after 72 *hours* based on iron concentration measurement. Exposure of *Pseudokirchneriella subcapitata* to ferric pyrophosphate at a nominal concentration of 100 mg/L (0.0212 mg/L measured) did not show any significant effects on growth rate or biomass over 72 hours. The E_rLR_{50} and E_yLR_{50} were calculated to be > 100 mg/L, the NOELR was ≥ 100 mg/L.

Acute aquatic hazard

Ferric pyrophosphate hydrolyses in aqueous solution releasing Fe^{3+} ions and pyrophosphate ions which further dissociate to orthophosphate ions.

For classification purposes, the DS considered the toxicity values of calcium hydrogenorthophosphate for justification of the toxicity of the non-metallic ion PO_4^{3-}.

Ecotoxicological data for three trophic levels are available for non-metallic ion PO_4^{3-}, obtained from registration report for the iron (III) orthophosphate, available at the following link:

https://echa.europa.eu/da/registration-dossier/-/registered-dossier/13292/6/2/1

Table: *Acute ecotoxicological data for $CaHPO_4$*

Test substance	pH	Test organism	Test duration	Effect [mg/L]	Reference
FISH					
$CaHPO_4$	7.18-7.97	*Oryzias latipes*	acute 96h	LC_{50} > 13.5_{mm} LC_{50} > 100_{nom}	Kim *et al.*, 2013
DAPHNIDS AND OTHER INVERTEBRATES					
$CaHPO_4$	7.73-8.18	*Daphnia magna*	acute 48h	EC_{50} > 2.75_{mm} EC50 > 100_{nom}	Kim *et al.*, 2013
AQUATIC ALGAE					
$CaHPO_4$	Control: 9.06 - 8.36 0.3 mg/L: 8.83 - 8.39 1.0 mg/L: 8.84 - 8.37 3.1 mg/L: 8.87 - 8.35 9.8 mg/L: 8.89 - 8.30 31.3 mg/L: 8.79 - 8.32 100.0 mg/L: 8.57 - 8.44	*Pseudokirchneriella subcapitata*	acute 72h	ErC_{50}> 4.4_{m} ErC_{50} > 100_{nom}	Kim *et al.*, 2013

nom – nominal test substance concentrations
m -measured test concentrations
mm - mean measured concentration

For the classification of Fe^{3+}, reliable data (LC_{50}/EC_{50} for acute toxicity of dissolved iron compound $FeCl_3$) has been taken into account from the EURAS critical review (Vangheluwe & Versonnen, 2004), obtained with $FeCl_3 \cdot 6H_2O$ and $FeSO_4 \cdot 7H_2O$, available at the following link:

https://echa.europa.eu/pl/registration-dossier/-/registered-dossier/16109/6/2/7

Table*: Acute ecotoxicological data for Fe^{3+} ion from the EURAS critical review (Vangheluwe & Versonnen, 2004)*

Test substance	Test Conditions	Test organism	Test duration	Endpoint Nominal/ Measured	Effect [mg Fe/L]	Reference
FISH						
$FeCl_3 \cdot 6H_2O$	pH: 6.3; T: 22; H: 100; Alk: 24 Test medium: Reconstituted ASTM water	*Lepomis macrochirus*	96h	Survival total Fe measured	LC_{50} = 20.3	Birge *et al.*, 1985
$FeCl_3 \cdot 6H_2O$	pH: 6.7; T: 22; H: 100; Alk: 30 Test medium: Reconstituted ASTM water	*Pimephales promelas*	96h	Survival total Fe measured	LC_{50} = 21.8	Birge *et al.*, 1985
$FeSO_4 \cdot 6H_2O$	pH: 6.0-7.1; H: 56-60; Alk: 32, a Test medium: Dechlorinated / carbon filtered tap water	*Oncorhynchus mykiss*	96h	Survival total dissolved Fe, measured, filtered 0.2 µm filter	LC_{50} = 16.6	Mattock, 2002a
$FeSO_4 \cdot 6H_2O$	pH: 6.9-7.0; T: 13-15; H: 64-97 Test medium: Dechlorinated / carbon filtered tap water	*Oncorhynchus mykiss*	96h	Survival total dissolved Fe, measured, c	LC_{50} > 27.9	Mattock, 2002b

$FeSO_4$	pH: 5.5 pH: 6 pH: 7 Test medium: Carbon filtered river water	*Salvelinus fontinalis*	96h	Survival total and total dissolved Fe, measured	pH 5.5 LC_{50} = 0.41 pH 6 LC_{50} = 0.48 pH 7 LC_{50} = 1.75	Decker & Menendez, 1974
$FeSO_4$	pH: 7.1; small carp pH 7.1; large carp Test medium: not reported	*Cyprinus carpio*	96h	Survival nominal	LC_{50} = 0.83 LC_{50} = 1.62	Alam & Maugham, 1992
$FeSO_4 \cdot 6H_2O$	pH: 5; T: 25; H:40 pH: 7; T: 25; H: 40 pH: 9; T: 25; H: 40 Test medium: Aerated, aged tap water	*Danio rerio*	48h	Survival nominal	LOEC > 32 LOEC > 32 LOEC > 32	Dave, 1985
DAPHNIDS AND OTHER INVERTEBRATES						
$FeCl_3 \cdot 6H_2O$	pH: 6.1; T: 20; H: 96; Alk: 28 Test medium: Reconstituted ASTM water	*Daphnia pulex*	48h	Immobility measured	EC_{50} = 12.9	Birge *et al.,* 1985
$FeCl_3 \cdot 6H_2O$	pH: 7.7; T: 18; (room T); static Test medium: Lake Superior water	*Daphnia magna*	48h	Immobility total Fe measured	EC_{50} = 9.6	Biesinger & Christensen, 1972
$FeSO_4 \cdot 7H_2O$	pH: 6.0; T: 21.6-22 Test medium: Reconstituted water	*Daphnia magna*	48h	Immobility total dissolved Fe, measured	EC_{50} = 1.29	LISEC study no. WE-01-225. Draft
$FeSO_4$	pH: 7.6 Test medium: Standard reference water	*Daphnia magna*	24h	Immobility nominal	EC_{50} = 5.25	Lilius *et al.,* 1995
$FeSO_4$	pH: 7.6 Test medium: Standard reference water	*Daphnia pulex*	24h	Immobility nominal	EC_{50} = 36.9	Lilius *et al.,* 1995
$FeSO_4$	SOP Test medium: Reconstituted water	*Daphnia magna*	24h	Immobility nominal	EC_{50} = 17	Calleja *et al.,* 1994
$FeSO_4$	SOP Test medium: ASTM E1440-91	*Brachionus calycifloru, Rotifer*	24h	Survival nominal	LC_{50} = 12	Calleja *et al.,* 1994
$FeSO_4 \cdot 7H_2O$	pH: 7.6; T: 13; H: 240; Alk: 400 Test Medium: Filtered, aerated tubewell water	*Daphnia magna*	48h	Immobility nominal	EC_{50} = 7.2	Khangarot & Ray, 1989
$FeCl_3$	pH: 8.2-8.4 Test medium: Lake Eria water	*Daphnia magna*	64h	Immobility nominal	'threshold' < 6.1	Anderson, 1950
AQUATIC PLANTS						
Fe^{3+}	pH: 7.5, T: 27; Test medium: deionized water	*Lemna minor*	4 days	growth nominal	EC_{50} = 3.7	Wang, 1986

Finally, the DS calculated for each pH range the acute $ERV_{compound}$ taking into account molecular weights of iron salts and compound stoichiometry:

Acute $ERV_{ferric\ pyrophosphate}$ = 3.7 x (745.21/223.36) = 12.34 mg/L (around pH 8)

Acute $ERV_{ferric\ pyrophosphate}$ = 16.6 x (745.21/223.36) = 55.38 mg/L (around pH 7)

Acute $ERV_{ferric\ pyrophosphate}$ = 1.29 x (745.21/223.36) = 4.30 mg/L (around pH 6)

The DS considered as a next step solubility of ferric pyrophosphate, assessed based on the read-across data for iron orthophosphate.

The results of the 24 hours Dissolution Screening test for the iron orthophosphate have been obtained from REACH registration dossier.

DS concluded that highest dissolution value at pH 6, 11.23 µg/L < acute ERV of the soluble ion being 4.3 mg/L (at pH 6) thus confirming that ferric pyrophosphate is an insoluble metal compound.

The dissolution of orthophosphate at pH 8 was not reported in REACH registration dossier, however, it was emphasized that the highest dissolved Fe concentration in the screening test was determined at pH 6. This clearly showed that solubility at pH 8 was lower than 11.23 µg/L. Therefore, it can be concluded that acute ERV of the soluble ion being 12.34 mg/L (around at pH 8) is much higher than the solubility at pH 8.

Long-term aquatic hazard

Chronic toxicity studies with ferric pyrophosphate toward fish species and *Daphnia* were not available. The chronic toxicity studies toward Zebrafish *Danio rerio* and *Daphnia magna* were conducted with plant protection product containing 3% ferric pyrophosphate (BW01 GB formulation).

The DS noted that these studies can be used to obtain ecotoxicological endpoint acceptable for classification purposes.

The summary of the chronic aquatic toxicity studies is reported in Table below. Only information considered adequate, reliable and relevant for the classification proposal has been included.

***Table**: Summary of relevant information on chronic aquatic toxicity*

Method	Species	Test material	Results	Remarks	Reference
Long-term and chronic toxicity to fish OECD TG 210	Zebrafish *Danio rerio*	BW01 GB Batch: 032014-P82 Content of active substance: 3% of iron pyrophosphate	**NOEC = 0.138 mg a.s./L** NOEC = 4.6 mg product/L - measured concentration (10 mg product/L nom)	Exposure: 30-days 26.20°C- 27.50°C pH 8.10-8.16	Anonymous 14, 2014; Report No. 0001/0109/E
Daphnia reproduction test OECD TG 211	*Daphnia magna*	BW01 GB Batch: 032014-P82 Content of active substance: 3% of iron pyrophosphate	**$NOEC_{reproduction}$ = 3 mg a.s./L nom** $NOEC_{reproduction}$ = 100 mg product/L nom (Concentrations were measured only for the lowest (6.4 mg/L) and the highest (250 mg/L) nominal test item concentrations. Mean measured concentrations of	Exposure: 21-days, 20 ± 2 °C pH 7.4-8.01	Winkler, 2014; Report No. 0001/0111/E

Method	Species	Test material	Results	Remarks	Reference
			test item in medium was 4 mg/L for both - the lowest and the highest - nominal concentrations)		
Growth inhibition test on algae OECD TG 201	*Pseudokirchneriella subcapitata*	Ferric pyrophosphate Batch 120327086	**$NOEL_R$ ≥ 100 mg/L** (nominal concentration) $NOEL_R$ ≥ 0.0212 mg/L (measured concentration)	Exposure: 72 h 23.5-23.8 °C pH 7.0-7.5	Heisterkamp, 2015; Report No. 1040

Chronic toxicity to fish

The Fish Early Life Stage test was conducted with Zebrafish (*Danio rerio*) according to OECD TG 210 using the BW01 GB formulation (plant protection product containing ferric pyrophosphate) as test item (Anonymous 14, 2014). The iron content during the test was determined by ICP-OES. Obtained results indicated that test material BW01 GB at the concentration of 4.6 mg product/L (corresponding to 0.138 mg a.s./L) has no effect on the percentage hatching, the survival or growth of organisms (expressed as weight and length change).

Chronic toxicity to aquatic invertebrates

Daphnia magna reproduction test was conducted according to OECD TG 211 with BW01 GB formulation (plant protection product containing ferric pyrophosphate) (Winkler, 2014). The recommended test medium M4 or M7 contains Na_2EDTA and was replaced in this case with ISO medium, recommended by the OECD TG 202. The validity criteria for the minimum number of produced offspring at the end of the experiment was passed and results accepted as valid for OECD TG 211. Obtained results demonstrate no toxic effects on *Daphnia magna* reproduction and development up to concentration 100 mg product/L (corresponding to 3 mg a.s./L).

Chronic toxicity to algae or other aquatic plants

Please refer to data presented in section on acute aquatic toxicity where the toxicity tests with the substance on algae are included.

The DS used the ecotoxicological data (NOEC and EC_{50}) for long-term toxicity of dissolved iron compound $FeCl_3$ to read across for chronic toxicity data.

Ecotoxicological data for three trophic levels were obtained from the EURAS critical review (Vangheluwe & Versonnen, 2004) for the $FeCl_3$ available at the following link:

https://echa.europa.eu/pl/registration-dossier/-/registered-dossier/16109/6/2/7

***Table**: Long term ecotoxicological data for FeCl3 from the EURAS critical review (Vangheluwe & Versonnen, 2004)*

Test substance	Test conditions	Test organism	Test duration	Nominal/Measured	Endpoints	Effect [mg Fe/L]	Reference
FISH							
$FeCl_3$	pH: 7.7; TºC: 25; Hardness: 103; Alkalinity: 56	*Pimephales promelas*	33d	total Fe measured; total dissolved Fe, measured; total Fe(II) ion measured	Length	**NOEC = 1.00**	Birge et al. 1985
					Weight	**NOEC = 1.61**	

	Test medium: reconstituted ASTM water						
$Fe(OH)_3$	pH: 8.1; TºC: 11; Hardness: 159-180 Test medium:	*Oncorhynchus kisutch*	30d	total Fe measured; total dissolved Fe, measured; total Fe(II) ion measured	Survival	NOEC = 2.81	Smith & Sykora 1976
$FeSO_4.7H_2O$	pH: 7.7-7.9; TºC: 15.7 – 22.6	*Cyprinus carpio*	2 weeks	total Fe measured	Cortisol level	NOEC = 0.52	van Anholt *et al.,* 2002
DAPHNIDS AND OTHER INVERTEBRATES							
$FeCl_3$	pH: 7.6; TºC: 20; Hardness: 94; Alkalinity: 48 Test medium: Reconstituted ASTM water	*Daphnia pulex*	chronic 21d	total Fe measured; total dissolved Fe, measured; total Fe(II) ion measured	Immobility	NOEC = 2.51	Birge *et al.*, 1985
					Total offspring	**NOEC = 0.63**	
					Brood size	NOEC = 0.63	
					Aborted eggs	NOEC = 1.26	
					Length	NOEC = 1.26	
$FeCl_3 \cdot 6H_2O$	pH: 7.7; TºC: 18 (room TºC); static renewal Test medium: Lake Superior water	*Daphnia magna*	chronic 3 weeks	total Fe measured	Immobility, reproduction	$EC_{50\ immobility}$ = 5.9	Biesinger & Christensen, 1972
						$EC_{50\ reproduction}$= 5.2	
						EC_{16} reproduction = 4.4	
$FeSO_4 \cdot 7H_2O$	pH: 7.7-7.9; TºC: 15.7-22.6 Test medium: River water	*Daphnia magna*	2 weeks	total Fe measured	Reproduction	NOEC = 0.52	Van Anholt *et al.*, 2002
MACROPHYTES							
$FeCl_3$	pH: 7.5	*Spirodela polyrhiza*	Chronic 14 days	Measured total iron	Growth effects	NOEC < 0.56	Sinha *et al.*, 1994 Long-term aquatic toxicity data on Macrophyte from the OECD (2007)

Finally, the DS calculated for each pH range chronic $ERV_{compound}$ taking into account molecular weights of iron salts and compound stoichiometry:

Chronic $ERV_{ferric\ pyrophosphate}$ = 0.56 x (745.21/223.36) = 1.87 mg/L

Chronic $ERV_{ferric\ pyrophosphate}$ = 5.2 x (745.21/223.36) = 17.35 mg/L

Comparison with the CLP criteria

Following the CLP guidance: *„Where the acute ERV for the metal ions of concern corrected for the molecular weight of the compound (further called as acute $ERV_{compound}$) is greater than 1 mg/L, the metal compounds need not to be considered further in the classification scheme for acute hazard*."

The DS, based on calculated acute $ERV_{\text{ferric pyrophosphate}}$ values, concluded that lowest one (4.3 mg/L) is above 1 mg/L and warrants no classification for ferric phosphate for acute aquatic hazard.

Following the CLP guidance: "*Where the chronic ERV for the metal ions of concern corrected for the molecular weight of the compound (further called as chronic $ERV_{compound}$) is greater than 1 mg/L, the metal compounds need not to be considered further in the classification scheme for long-term hazard*."

The DS, based on calculated chronic $ERV_{\text{ferric pyrophosphate}}$ values, concluded that lowest one (1.87 mg/L) is above 1 mg/L and warrants no classification for ferric phosphate for chronic aquatic hazard.

Conclusion on classification and labelling for environmental hazards

The DS concluded on the classification of ferric pyrophosphate for environmental aquatic hazard according to CLP Regulation.

Ferric pyrophosphate is considered an insoluble metal compound.

The calculated acute $ERV_{\text{ferric pyrophosphate}}$ value of 4.30 mg/L is greater than 1 mg/L.

The calculated chronic $ERV_{\text{ferric pyrophosphate}}$ value is 1.87 mg/L is greater than 1 mg/L.

According to CLP-Regulation both values warrant no classification for ferric phosphate for aquatic hazards.

Comments received during consultation

One comment was received from one MSCA demonstrating agreement with the proposed approach and outcome for ferric pyrophosphate classification. The MSCA required more detailed information about the toxicity data presented for read across.

The DS clarified reliability of some studies and presented additional toxicity studies for soluble iron salts.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS's proposal to consider that ferric pyrophosphate is an inorganic substance that hydrolyse but do not degrade.

Bioaccumulation

RAC is of the opinion that iron ions and orthophosphate ions are essential for aquatic species and potential for bioaccumulation is not expected.

Environmental transformation of metals or inorganic metals compounds

Ferric pyrophosphate is insoluble compound which presents iron complex with pyrophosphate anion. In aqueous solution it slowly hydrolyses to iron(III) and orthophosphate ions. Iron is one

of the basic metals occurring in the aquatic environment and it is considered a microelement with regard to live organisms. This metal has a broad range of applications that, together with factors conditioning its chemical transitions, results in the occurrence of many iron species in surface waters. The most common oxidation states of iron in water are the ferrous (Fe^{2+}) and the ferric (Fe^{3+}) ions, although other forms may be present in organic and inorganic complexes. In surface waters, iron is generally present in the ferric state; in reducing waters, the ferrous form can persist. Iron (Fe) is an essential micronutrient for marine organisms, and it is now well established that low Fe availability controls phytoplankton productivity, community structure, and ecosystem functioning in vast regions of oceans. The biogeochemical cycle of Fe involves complex interactions between lithogenic inputs (atmospheric, continental, or hydrothermal), dissolution, precipitation, scavenging, biological uptake, remineralization, and sedimentation processes. Each of these aspects of Fe biogeochemical cycling is likely influenced by organic Fe-binding ligands, which complex more than 99% of dissolved Fe. Orthophosphate is essential micronutrient ensuring functioning and biodiversity of aquatic species. Increased orthophosphate concentrations are responsible for algal blooms and dissolved oxygen depletion.

Aquatic toxicity

Ferric pyrophosphate hydrolyses in aqueous solution releasing Fe^{3+} ions and pyrophosphate ions which further dissociate to orthophosphate ions.

Experimental toxicity studies are available for all three trophic levels for ferric pyrophosphate and results showed that for all levels acute toxicity LC_{50}/EC_{50} values are above its solubility in aqueous solution. For chronic toxicity, experimental results are available for fish and invertebrates for plant protection product containing 3% ferric pyrophosphate (BW01 GB formulation). Obtained results indicate chronic toxicity above solubility values.

RAC supports the DS proposal to classify ferric pyrophosphate using weight of evidence approach and read across data from suitable iron and phosphate compounds. The acute and chronic toxicity of released PO_4^{3-} is based on the toxicity data available for $CaHPO_4$ and acute and chronic toxicity for Fe^{3+} toxicity is based on data available for soluble iron salts ($FeCl_3.6H_2O$ and $FeSO_4.7H_2O$).

RAC agrees with the DS calculation of acute ERVs:

Acute $ERV_{\text{ferric pyrophosphate}}$ = 3.7 x (745.21/223.36) = 12.34 mg/L (around pH 8)

Acute $ERV_{\text{ferric pyrophosphate}}$ = 16.6 x (745.21/223.36) = 55.38 mg/L (around pH 7)

Acute $ERV_{\text{ferric pyrophosphate}}$ = 1.29 x (745.21/223.36) = 4.30 mg/L (around pH 6)

RAC agrees with the DS calculation of chronic ERVs:

Chronic $ERV_{\text{ferric pyrophosphate}}$ = 0.56 x (745.21/223.36) = 1.87 mg/L

Chronic $ERV_{\text{ferric pyrophosphate}}$ = 5.2 x (745.21/223.36) = 17.35 mg/L

All calculated ERVs are above 1 mg/L. Following the CLP guidance, RAC agrees with the DS that ferric pyrophosphate **does not warrant classification for acute and chronic aquatic hazards**.

RAC evaluation of hazards to the ozone layer

Summary of the Dossier Submitter's proposal

The DS concluded that ferric pyrophosphate highly unlikely depletes the stratospheric ozone layer due to its low volatility.

Comments received during consultation

No comments were received during consultation.

Assessment and comparison with the classification criteria

RAC agrees with the DS that, on the basis of the properties of ferric pyrophosphate, there is no indication of it posing a hazard to the structure and/or the functioning of the stratospheric ozone layer.

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ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).