

**Committee for Risk Assessment**  
**RAC**

Annex 2  
**Response to comments document (RCOM)**  
to the 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**

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TETRAIRON TRIS(PYROPHOSPHATE); FERRIC PYROPHOSPHATE**

**COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION**

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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**Substance name: tetrairon tris(pyrophosphate); ferric pyrophosphate**  
**EC number: 233-190-0**  
**CAS number: 10058-44-3**  
**Dossier submitter: Poland**

**GENERAL COMMENTS**

Date	Country	Organisation	Type of Organisation	Comment number
18.05.2022	Germany		MemberState	1
Comment received				
In section 1.1, table 1 the "Degree of purity (%)" (if relevant for the entry in Annex VI)" of tetrairon tris(pyrophosphate) is given. If not relevant for the entry in Annex VI, the given purity should be deleted.				
Dossier Submitter's Response				
Thank you for your comment, we agree with it, the given degree of purity may be removed.				
RAC's response				
Thank you for you comments.				

**OTHER HAZARDS AND ENDPOINTS – Eye Hazard**

Date	Country	Organisation	Type of Organisation	Comment number
18.05.2022	Germany		MemberState	2
Comment received				
An in vitro test (OECD 437: Bovine corneal opacity and permeability) yielded an overall irritation score (IVIS) of 25.3, which implies that no stand-alone prediction can be made based on this result. An eye irritation study in rabbits (EU method B.5) revealed no effects except chemosis (score: 0.33) in one animal, but conjunctival redness was apparently not an investigated parameter (Anonymous 2, 2012b). A second eye irritation study in rabbits (EU method B.5) showed conjunctival redness, which was scored as 2 at all times of observation (24, 48 and 72 h) in each animal (Anonymous 7, 2013). A classification as Eye Irrit. 2 is foreseen, if in at least 2 of 3 tested animals a conjunctival redness $\geq 2$ is detected. The severity of conjunctival redness (score: 2) is just sufficient for a classification as Eye Irrit. 2 (H319). The proposed classification corresponds to the conclusions drawn in the EU pesticide peer review process and is supported.				

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<p><b>Dossier Submitter's Response</b></p> <p>Thank you for comments and support a classification of ferric pyrophosphate as Eye Irrit. 2 (H319). Additional information on conjunctival redness results in study Anonymous 2, 2012b: Based on data provided in REACH registration dossier (<a href="https://echa.europa.eu/registration-dossier/-/registered-dossier/12264/7/4/3">https://echa.europa.eu/registration-dossier/-/registered-dossier/12264/7/4/3</a>) Average score for each animal (mean: 24, 48, 72 h) of conjunctiva redness was 0.33 fully reversible within: 48 hours (animal no 1), 1 (animal no 2) fully reversible within: 72 hours. However above information does not change conclusion on eye irritation potential of ferric pyrophosphate. It should be noted that only 2 animals were tested, in total, and third animal should be tested to exclude eye irritation potential of tested item. According to description of the test method B.5 "if a corrosive effect is not observed in the initial test (using one animal), the irritant or negative response should be confirmed using up to two additional animals." (...) "if the second animal reveals corrosive or severe irritant effects, the test is not continued" and "additional animals may be needed to confirm weak or moderate irritant responses" Therefore study by Anonymous 2, 2012b, could not be considered as conclusive data.</p>
<p><b>RAC's response</b></p> <p>Thank you for the comment. RAC notes the interpretation of study results from the comments and agrees with the DS that classification of ferric pyrophosphate as Eye Irrit. 2 (H319) is warranted.</p> <p>Three studies are available addressing eye irritation effect on ferric pyrophosphate.</p> <p>The <i>in vitro</i> test (OECD 437: Bovine corneal opacity and permeability) had a score (IVIS) of 25.3 after 240 minutes. This value is in the "no prediction can be made" range, therefore it is not possible to conclude on the classification based on this study.</p> <p>The second study was performed on 2 Male New Zealand White rabbits, time of exposure was 72 hours and the observations were performed after 1 hour and 24, 48 and 72 hours following the period of application of the test material. The study followed the EU Method B.5 (Acute Toxicity: Eye Irritation / Corrosion), OECD TG 405 (Acute Eye Irritation / Corrosion) and the author is Anonymous 2 (2012b). The study was conducted in 2 instead of 3 animals and the recovery period after period of exposure was short. Therefore, the study is not conclusive for classification.</p> <p>The third study (Anonymous 7, 2013) was conducted on 3 New Zealand albino male rabbits, according to EU method B.5 and was GLP compliant. The average scores after 24, 48 and 72 hours were 0 for chemosis, iris and cornea in all animals and 2 for conjunctiva in all animals. The effects were reversible by the 6<sup>th</sup> day. The study is reliable and a conjunctival redness (score: 2) fulfils the criteria for a classification as Eye Irrit. 2 (H319).</p> <p>The classification criteria for Cat. 2 are: "<i>Substances that produces in at least 2 of 3 tested animals a positive response of: corneal opacity <math>\geq</math> 1 and/or iritis <math>\geq</math> 1, and/or conjunctival redness <math>\geq</math> 2 conjunctival oedema (chemosis) <math>\geq</math> 2 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of normally 21 days.</i>"</p>

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Date	Country	Organisation	Type of Organisation	Comment number
11.04.2022	United Kingdom	<confidential>	Company-Manufacturer	3

**Comment received**

The EU REACH Registrants performed an ex vivo followed by an in vivo study to assess the eye irritancy of tetrairon tris(pyrophosphate). This study was performed in accordance with an appropriate OECD TG and under the conditions of GLP and as such we believe the results (not classified) to be reflective of the registered substance. It is noted that data submitted under the PPP suggests that the substance is classified. It is our opinion that the results should be reviewed alongside the compositional information of both the substance registered under PPP and the substance registered under EU REACH to determine if in fact a classification is appropriate. Further information is required to assess the adequacy of the data submitted under PPP. In conclusion a classification for eye irritancy will not be reflected in the dossier submitted under EU REACH and the EU REACH registrants do not support a harmonised classification for this endpoint.

**Dossier Submitter's Response**

Thank you for your comments.  
 In a study using bovine cornea the irritation score (IVIS) was 25.3 thus below of 55 which is defined as: "no prediction can be made". Lack of classification for eye effects can be considered for IVIS<3 according to criteria of OECD 437 test method.  
 The Bovine Corneal Opacity and Permeability (BCOP) test (OECD TG 437) is recommended for use as part of a tiered-testing strategy for regulatory classification and labelling. Based on this strategy only if the irritancy potential of a test chemical can be assigned based on the existing information, no additional testing is required. If the irritancy potential of a test chemical cannot be assigned based on the existing information, a step-wise sequential animal testing procedure is performed until an unequivocal classification can be made.  
 In study by Anonymous 2, 2012b only 2 animals were tested, in total, and third animal should be tested to exclude eye irritation potential of tested item.  
 According to description of the test method B.5 "if a corrosive effect is not observed in the initial test (using one animal), the irritant or negative response should be confirmed using up to two additional animals." (...) "if the second animal reveals corrosive or severe irritant effects, the test is not continued" and "additional animals may be needed to confirm weak or moderate irritant responses" Therefore results of this study could not be considered as conclusive.  
 In reliable, GLP, study (Anonymous 7, 2013) the severity of conjunctival redness (score: 2) is sufficient for a classification as Eye Irrit. 2 (H319). Therefore, the classification of ferric pyrophosphate for eye irritation is fully justified using tiered testing strategy.

**RAC's response**

Thank you for the comments. RAC agrees with the DS's explanation and notes that Anonymous 7 (2013) is a GLP study, with a conclusive result. The conjunctival redness (score: 2) supports a classification as Eye Irrit. 2 (H319).

**OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment**

Date	Country	Organisation	Type of Organisation	Comment number
18.05.2022	Germany		MemberState	4

**Comment received**

The classification is based on derived ERV from toxicity data for the non-metallic ion PO43- and the Fe3+ ion. This approach is agreed on. However, more detailed information about

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the toxicity data is not given. The information provided in the REACH dossier especially regarding the Fe<sup>3+</sup> ion is sparse and partly ambiguous. Two examples: (i) the endpoint for aquatic macrophytes left censored and (ii) for the long-term toxicity for aquatic invertebrates Johnson et al., a study which is cited in the REACH dossier of FeCl<sub>3</sub>, derived a NOEC of 0.16 mg/L as the relevant endpoint. No further information is given in the CLH-report on the size of the effects seen at the left-censored endpoint or why the NOEC of 0.16 mg/L is less reliable and not considered for classification purposes. We would appreciate if further information on the available studies and their reliability would be provided.

**Dossier Submitter's Response**

Thank you for comments and support to classification approach. According to the REACH dossier for FeCl<sub>3</sub>, the effects of ferric or ferrous salt on aquatic organisms were assessed based on the literature reviews: Vangheluwe & Versonnen (2004), Johnson et al. (2007) and OECD (2007). The results of the studies were selected as "reliable" by the respective authors. Nonetheless the studies must be rated as "not reliable" (Klimisch 3) according to the Klimisch et al. (1997) scale due to methodological objections. The mentioned above long-term toxicity study results value NOEC=0.16 mg/L for aquatic invertebrates (Johnson et a. 2007) was reliable with restrictions according to the authors but according to the Klimisch scale was corrected to 3 "not reliable".

Notwithstanding the methodological objections, the toxicity data from the EURAS critical review (Vangheluwe & Versonnen 2004), were used for classification purpose in ECHA Guidance on the Application of the CLP Criteria Version 5.0(2017, Example D. p.622). Therefore these data with higher authors's reliability were used for classification.

The toxicity data for Fe<sup>3+</sup> should be completed as follow:

**Table 24: Acute ecotoxicological data for Fe<sup>3+</sup> 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	Author's Reliability
FISH								
Short-term exposure								
FeCl <sub>3</sub> .6H <sub>2</sub> O	pH: 6.3; T: 22; H: 100; Alk: 24  Test medium: Reconstituted ASTM water	<i>Lepomis macrochirus</i>	96h	Survival	To	LC <sub>50</sub> = 20.3 (measured To)	Birge et al. 1985	R1
FeCl <sub>3</sub> .6H <sub>2</sub> O	pH: 6.7; T: 22; H: 100; Alk: 30  Test medium: Reconstituted ASTM water	<i>Pimephales promelas</i>	96h	Survival	To	LC <sub>50</sub> = 21.8 (measured To)	Birge et al. 1985	R1

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FeSO <sub>4</sub> .6H <sub>2</sub> O	pH: 6.0-7.1; H: 56-60; Alk: 32, a  Test medium: Dechlorinated / carbon filtered tap water	<i>Oncorhynchus mykiss</i>	96h	Survival	TD, c	LC <sub>50</sub> = 16.6	Mattock 2002a	R1
FeSO <sub>4</sub> .6H <sub>2</sub> O	pH: 6.9-7.0; T: 13-15; H: 64-97  Test medium: Dechlorinated / carbon filtered tap water	<i>Oncorhynchus mykiss</i>	96h	Survival	TD, c	LC <sub>50</sub> >27.9	Mattock 2002b	R1
FeSO <sub>4</sub>	pH: 5.5 pH: 6 pH: 7  Test medium: Carbon filtered river water	<i>Salvelinus fontinalis</i>	96h	Survival	To, TD	pH 5.5 LC <sub>50</sub> = 0.41 (measured dissolved)  pH 6 LC <sub>50</sub> = 0.48 (measured dissolved)  pH 7 LC <sub>50</sub> = 1.75 (measured dissolved)	Decker & Menendez 1974	R2
FeSO <sub>4</sub>	pH: 7.1; small carp pH 7.1; large carp  Test medium: not reported	<i>Cyprinus carpio</i>	96h	Survival	N	LC <sub>50</sub> = 0.83  LC <sub>50</sub> = 1.62	Alam & Maugham 1992	R2
FeSO <sub>4</sub> .6H <sub>2</sub> O	pH: 5; T: 25; H:40  pH: 7; T: 25; H: 40  pH: 9; T: 25; H: 40  Test medium: Aerated,	<i>Danio rerio</i>	48h	Survival	N	LOEC > 32  LOEC > 32  LOEC > 32	Dave 1985	R2

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	aged tap water								
DAPHNIDS AND OTHER INVERTEBRATES									
Short-term exposure									
FeCl <sub>3</sub> .6H <sub>2</sub> O	pH: 6.1; T: 20; H: 96; Alk: 28  Test medium: Reconstituted ASTM water	<i>Daphnia pulex</i>	48h	Immobility	N	EC <sub>50</sub> = 12.9 (measured)	Birge et al. 1985	R1	
FeCl <sub>3</sub> .6H <sub>2</sub> O	pH: 7.7; T: 18; (room T); static  Test medium: Lake Superior water	<i>Daphnia magna</i>	48h	Immobility	To	EC <sub>50</sub> = 9.6	Biesinger & Christensen 1972	R1	
FeSO <sub>4</sub> .7H <sub>2</sub> O	pH: 6.0; T: 21.6-22  Test medium: Reconstituted water	<i>Daphnia magna</i>	48h	Immobility	TD	EC <sub>50</sub> = 1.29	LISEC study no. WE-01-225. Draft	R1	
FeSO <sub>4</sub>	pH: 7.6  Test medium: Standard reference water	<i>Daphnia magna</i>	24h	Immobility	N	EC <sub>50</sub> = 5.25	Lilius et al. 1995	R1	
FeSO <sub>4</sub>	pH: 7.6  Test medium: Standard reference water	<i>Daphnia pulex</i>	24h	Immobility	N	EC <sub>50</sub> = 36.9	Lilius et al. 1995	R1	
FeSO <sub>4</sub>	SOP  Test medium: Reconstituted water	<i>Daphnia magna</i>	24h	Immobility	N	EC <sub>50</sub> = 17	Calleja et al. 1994	R1	
FeSO <sub>4</sub>	SOP  Test medium: ASTM E1440-91	<i>Brachionus calycifloru</i> , <i>Rotifer</i>	24h	Survival	N	LC <sub>50</sub> = 12	Calleja et al. 1994	R1	
FeSO <sub>4</sub> .7H <sub>2</sub> O	pH: 7.6; T: 13; H: 240; Alk: 400  Test Medium: Filtered,	<i>Daphnia magna</i>	48h	Immobility	N	EC <sub>50</sub> = 7.2	Khargarot & Ray 1989	R2	

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	aerated tubewell water							
FeCl <sub>3</sub>	pH: 8.2-8.4 Test medium: Lake Eria water	<i>Daphnia magna</i>	64h	Immobility	N	'threshold' < 6.1	Anderson 1950	R3
AQUATIC PLANTS								
Short-term exposure								
Fe <sup>3+</sup>	pH: 7.5, T: 27; Test medium: deionized water	<i>Lemna minor</i>	4 days	growth	N	EC <sub>50</sub> =3.7	Wang 1986	R3

a: only measured prior to testing

Alk: alkalinity [mg/L CaCO<sub>3</sub>]

c: samples were filtered over a 0.2 µm filter

H: hardness [mg/L CaCO<sub>3</sub>]

N: Nominal concentration

R1, R2: Reliable without restriction according to the scheme of the authors, corrected to Klimisch 3 "not reliable" as discussed above.

R3: Not reliable according to the authors

T: temperature [°C]

TD: dissolved total Fe measured

To: total Fe measured

**Table 24: Long term ecotoxicological data for FeCl<sub>3</sub> from the EURAS critical review (Vangheluwe & Versonnen 2004)**

Test substance	Test conditions	Test organism	Test duration	Nominal/Measured	Endpoints	Effect [mg Fe/L]	Reference	Author's Reliability
FISH								
Long-term exposure								
FeCl <sub>3</sub>	pH: 7.7; T: 25; H: 103; Alk: 56 Test medium: reconstituted ASTM water	<i>Pimephales promelas</i>	33d	To, TD, T2	Length Weight	NOEC = 1.00 (measured To) NOEC = 1.61	Birge et al. 1985	R1
Fe(OH) <sub>3</sub>	pH: 8.1; T: 11; H: 159-180 Test medium:	<i>Oncorhynchus kisutch</i>	30d	To, TD, T2	Survival	NOEC = 2.81 (measured To)	Smith & Sykora 1976	R1
FeSO <sub>4</sub> ·7H <sub>2</sub> O	pH: 7.7-7.9; T: 15.7 – 22.6	<i>Cyprinus carpio</i>	2 weeks	To	Cortisol level	NOEC = 0.52	van Anholt et al. 2002	R2
DAPHNIDS AND OTHER INVERTEBRATES								

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		Long-term exposure						
FeCl3	pH: 7.6; T: 20; H: 94; Alk: 48  Test medium: Reconstituted ASTM water	<i>Daphnia pulex</i>	chronic 21d	To, TD, T2	Immobility	NOEC = 2.51	Birge et al. 1985	R1
					Total offspring	NOEC = 0.63		
					Brood size	NOEC = 0.63		
					Aborted eggs	NOEC = 1.26		
					Length	NOEC = 1.26		
FeCl3.6H2O	pH: 7.7; T: 18 (room T); static renewal  Test medium: Lake Superior water	<i>Daphnia magna</i>	chronic 3 weeks	To	Immobility, reproduction	EC50 immobility: = 5.9	Biesinger & Christensen 1972	R1
						EC50 reproduction = 5.2		
						EC16 reproduction = 4.4		
FeSO4.7H2O	pH: 7.7-7.9; T: 15.7-22.6  Test medium: River water	<i>Daphnia magna</i>	2 weeks	To	Reproduction	NOEC = 0.52	van Anholt et al. 2002	R2
		Long-term exposure						
FeCl3	7.5 <sup>a</sup>	<i>Spirodela polyrrhiza</i>	Chronic 14 days	Measured total iron	Growth effects	NOEC < 0.56	Sinha et al 1994	R2  Long-term aquatic toxicity data on Macrophyta from the OECD (2007)

a: only measured prior to testing

Alk: alkalinity [mg/L CaCO<sub>3</sub>]

c: samples were filtered over a 0.2 µm filter

H: hardness [mg/L CaCO<sub>3</sub>]

N: Nominal concentration

R1, R2: Reliable without restriction according to the scheme of the authors, corrected to Klimisch 3 "not reliable" as discussed above.

R3: Not reliable according to the authors

T: temperature [°C]

TD: dissolved total Fe measured

To: total Fe measured

T2: total Fe(II) ion measured

**RAC's response**

RAC agrees with the DS on presenting additional information on Fe toxicity and to include reliability scores of the studies in response to the comment of the MSCA.

RAC included the updated information in the Opinion.