European Commission

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Ferric pyrophosphate

Volume 3 – B.2 (AS)

Rapporteur Member State: Poland

Co-Rapporteur Member State:

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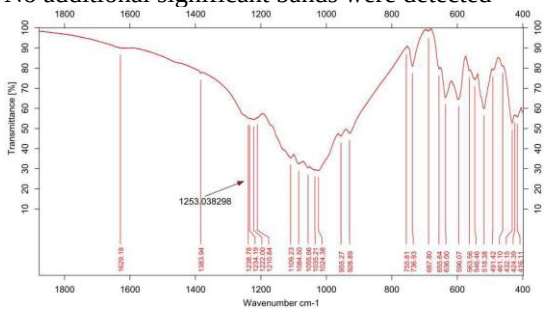
B.2. PHYSICAL AND CHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE

Test or study annex point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
B.2.1. MELTING POINT AND BOILING POINT						
Melting, freezing or solidification point B.2.1/01	EU A1	Batch No: 120327086 Purity: 101,73%	Melting point > 360°C	Acceptable	Y	M. Włodarczak 2015; 0001/0164/FA
Boiling point B.2.1/02	-	-	Boling point – Pursuant to Column II of Annex VII to Commission Regulation (EC) No 1907/2006 the study does not need to be conducted for gases or for substances which decompose before boiling, or melt above 300°C. On this basis testing is not required because melting point for ferric pyrophosphate is above 360°C. Applicant's explanation: *Since the active substance is a solid we measured the melting point and it turned out that it does not melt or decompose up to 360°C. According to Regulation (EU) 283/2013 measurement has to be performed up to 360°C.*	Acceptable	-	M. Włodarczak 2015; 0001/0164/FA
Decomposition/ Sublimation temperature B.2.1/03	-	-	Decomposition was not observed to 360°C	Acceptable	-	M. Włodarczak 2015; 0001/0164/FA
B.2.2. VAPOUR PRESSURE, VOLATILITY						
Vapour pressure B.2.2/01	-	-	Pursuant to Column II of Annex VII to Commission Regulation (EC) No 1907/2006 the study does not need to be conducted if the melting point is above 300 °C.	Acceptable	-	M. Włodarczak 2015; 0001/0164/FA

Test or study annex point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
			On this basis testing is not required because melting point for ferric pyrophosphate is above 360°C Applicant's explanation: *Vapour pressure and Henry's Law constant (volatility) - it cannot be measured since according to Regulation 283/2013 it has to be calculated or measured based on the water solubility. We have tested water solubility and it is insoluble, therefore this measurement will not be scientifically feasible or accurate.*			
Volatility (Henry's Law constant) **B.2.2/02**	-	-	Pursuant to Column II of Annex VII to Commission Regulation (EC) No 1907/2006 the study does not need to be conducted if the melting point is above 300 °C. On this basis testing is not required because melting point for ferric pyrophosphate is above 360°C Applicant's explanation: *Vapour pressure and Henry's Law constant (volatility) - it cannot be measured since according to Regulation 283/2013 it has to be calculated or measured based on the water solubility. We have tested water solubility and it is insoluble, therefore this measurement will not be scientifically feasible or accurate.*	Acceptable	-	M. Włodarczak 2015; 0001/0164/FA
B.2.3. APPEARANCE (PHYSICAL STATE, COLOUR)						
Physical state and colour **B.2.3/01**	OPPTS 830.6302 OPPTS 830.6303 Polish Pharma-copoeia VI	Batch No: 120327086 Purity: 101,73%	PHYSICAL STATE: solid, fine powder COLOR: very light shade of beige, outside the Munsell scale system	Acceptable	Y	M. Włodarczak 2015; 0001/0164/FA
Odour **B.2.3/02**	EPA/OPPTS 830.6304	Batch No: 120327086	ODOUR: a delicate, slightly noticeable characteristic odour	Acceptable	Y	M. Włodarczak 2015;

Test or study annex point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
	Polish Pharma-copoeia VI	Purity: 101,73%				0001/0164/FA
B.2.4. SPECTRA (UV/VIS, IR, NMR, MS), MOLAR EXTINCTION AT RELEVANT WAVELENGTHS, OPTICAL PURITY						
Ultraviolet/visible (UV/VIS) B.2.4/01	-	-	UV/VIS spectrum – is technically not possible to supply (item 1.5. Commission Regulation (EU) No 283/2013) UV/VIS spectrum was not presented due to very low solubility of the substance in water and in organic solvents. Molar extinction – is technically not possible to supply (item 1.5. Commission Regulation (EU) No 283/2013) due to very low solubility of the substance in water and organic solvents.	Acceptable	-	M. Włodarczak 2015; 0001/0164/FA
Infrared (IR) B.2.4/02	-	Batch No: 120327086 Purity: 101,73%	IR – FT-IR spectrum The recorded spectrum showed absorption bands in accordance (both band position, shape and intensity) with the reference spectrum. No additional significant bands were detected  FTIR spectrum of Ferric pyrophosphate (KBr pellet, range: 1800 – 400 cm-^{1}) List of recorded bands in comparison with reference spectrum **Reference [cm^{-1}] | Recorded [cm^{-1}]**	Acceptable		E.Steger, B.Kasner, Spectrochimica Acta vol. 24A, pp. 447-456 (1968).

Test or study annex point	Guideline and method	Test material purity and specification	Used methods / Results	Comments (Acceptable / Non acceptable)	GLP	Reference
			1253 / 1253 1220 / 1222 1213 / 1211 1166 / Shoulder 1109 / 1109 1084 / 1084 1054 / 1056 1039 / 1035 1019 / 1024 (broad diffused) 954 / 955 930 / 929 821 / Shoulder 735 / 737 655 / 656 599 / 596 550 / 546 519 / 518 458 / 461 414 / 416			

Nuclear magnetic resonance (NMR) B.2.4/03	-	-	NMR spectrum - is not scientifically necessary (item 1.5. Commission Regulation (EU) No 283/2013) Despite the fact that in case of ferric pyrophosphate is technically possible to carried out the study of 31P NMR, the result would only be a confirmation of phosphorus presence in the test item. NMR method is also not suitable for determination of iron component in ferric pyrophosphate. That information is not sufficient to detailed specification of the test item. According to this fact, data will not be provided, because there are other methods more appropriate to inorganic compounds, providing higher level of accuracy of analytical and structural data, compared to data obtained from NMR method.	Acceptable	-	-
Mass spectra (MS) B.2.4/04	-	-	MS spectrum - is technically not possible to supply (item 1.5. Commission Regulation (EU) No 283/2013) Methods based on mass spectroscopy are not recommended to investigate inorganic compounds, because they do not provide any useful data. Ferric pyrophosphate is non-volatile and conjunction with ionic structure makes ionization by using the standard techniques impossible According to this fact, data will be not provided, because there are other methods more appropriate to inorganic compounds, providing higher level of accuracy of analytical and structural data, compared to the data obtained from spectrometric methods.	Acceptable	-	-
Spectra for impurities B.2.4/05	-	-	Ferric pyrophosphate does not contain relevant impurities	-	-	-
Spectra for purified active substance Optical purity B.2.4/06	-	-	Optical purity is not scientifically necessary (item 1.5. Commission Regulation (EU) No 283/2013). Ferric pyrophosphate is the ionic solid and is not optically active.	Acceptable	-	-

B.2.5. SOLUBILITY IN WATER						
Solubility in water B.2.5/01	OECD 105	Batch No: 120327086 Purity: 101,73%	Temperature 20±0,5°C pH 4 (24h – 140,3 µg/l; 48h – 164.8 µg/l; 72h – 141,7 µg/l) pH 7 (24h – 41,2 µg/l; 48h – 41,6 µg/l; 72h – 39,0 µg/l) pH 9 (24h – 135,9 µg/l; 48h – 113,1 µg/l; 72h – 112,3 µg/l)	Acceptable	Y	M. Włodarczak 2015; 0001/0164/FA
B.2.6. SOLUBILITY IN ORGANIC SOLVENTS						
Solubility in organic solvents B.2.6/01	CIPAC MT 181	Batch No: 120327086 Purity: 101,73%	Inorganic salts of iron are virtually insoluble in organic solvents e.g. ferric phosphate is not soluble in organic solvents. n-heptane < 10 [g/dm^3] p-xylene < 10 [g/dm^3] 1,2-dichloroethane < 10 [g/dm^3] methanol < 10 [g/dm^3] acetone < 10 [g/dm^3] ethyl acetate < 10 [g/dm^3]	Acceptable	Y	M. Włodarczak 2015; 0001/0164/FA
B.2.7. PARTITION COEFFICIENT N-OCTANOL/WATER						
Partition coefficient n-octanol/water B.2.7/01	-	-	In accordance with information set out in Commission Communication in the framework of the implementation of Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, to determine partition coefficient n-octanol/water 'Shake Flask Method' based on OECD Guideline (OECD Test Guideline 107) should be used. Precise description of the method is set out in the Council Regulation (EC) No 440/2008 of 30 May 2008. In case, when substance is an inorganic compound, study is not required. On the basis of above information, determination of partition coefficient n-octanol /water for ferric pyrophosphate as inorganic compound, was not carried out.	Acceptable	-	-

B.2.8. DISSOCIATION IN WATER						
Dissociation constant B.2.8/01	-	-	In accordance with information set out in Commission Communication in the framework of the implementation of Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, to determine dissociation constant in water, test based on the method described in OECD Guidelines (OECD Test Guideline 112) should be performed. For the tested substance – ferric pyrophosphate experimental determination of dissociation constant in water was not carried out. Result obtained from the study performed according to test procedures proposed in OECD Guidelines No 112 would provide only dissociation constant for the anion derived from the starting compound, for which literature data are available. Following data were assumed for the assessment of the pyrophosphate acid [1]: pKa1 = 0,91 (25ºC) pKa2 = 2,10 (25ºC) pKa3 = 6,70 (25ºC) pKa4 = 9,32 (25ºC)	Acceptable	-	CRC Handbook of Chemistry and Physics, 93rd Ed., pp 5-93
B.2.9. FLAMMABILITY AND SHELF-HEATING						
Flammability B.2.9/01	EU A.10.	Batch No: 120327086 Purity: 101,73%	Not highly flammable Not self-ignitable.	Acceptable	Y	M. Włodarczak 2015; 0001/0164/FA
Self heating B.2.9/02	EC A.16	Batch No: 120327086 Purity: 101,73%	Not self-~~heating~~ ignitable.	Acceptable	Y	M. Włodarczak 2015; 0001/0164/FA

B.2.10. FLASH POINT						
Flash point B.2.10/01	-	-	In accordance with Commission Regulation (EU) No 283/2013 flash point should be determined and reported for active substance with a melting point below 40 °C. On this basis testing is not required because melting point for ferric pyrophosphate is above 360°C (please refer to Section CA 2.1)	Acceptable	-	-
B.2.11. EXPLOSIVE PROPERTIES						
Explosive properties B.2.11/01	-	-	In accordance with Commission Regulation (EU) No 283/2013 for determination of explosive properties criteria set out in Appendix 6 of the United Nations 'Recommendations on the Transport of Dangerous Goods Manual of Tests and Criteria' are appropriate. Explosive properties are associated with the presence of certain chemical groups in a molecule, which can react to produce very rapid increases in temperature or pressure. Examples of groups indicating explosive properties in materials could be: C-C unsaturations (acetylenes, acetylides, 1,2-dienes); C-Metal (Grignard reagents, organo-lithium compounds); N-N (azides, aliphatic azo compounds, diazonium salts, hydrazines)' O-O (peroxides, ozonides); N-O (hydroxylamines, nitrates, citro compounds, nitroso compounds); N-halogen (chloramines, fluoroamines)' O-halogen (chlorates, perchlorates, iodosyl compounds). Ferric pyrophosphate do not contain any of the mentioned group, therefore pursuant to the existing guidelines testing of explosive properties is not required.	Acceptable	-	-
B.2.12. SURFACE TENSION						
Surface tension B.2.12/01	-	-	In accordance with Commission Regulation (EU) No 283/2013, to determine surface tension study based on Method A.5. set out in Commission Regulation (EC) NR 440/2008 should be performed. According to the method A.5 testing is not required to the substances with solubility below 1 mg/l. Testing was not carried out, because solubility of the ferric pyrophosphate was determined below 1 mg/l.	Acceptable	-	M. Włodarczak 2015; 0001/0164/FA

B.2.13. OXIDISING PROPERTIES						
Oxidizing properties B.2.13/01	-	-	In accordance with Commission Regulation (EU) No 283/2013 for determination of oxidizing properties criteria set out in Appendix 6 of the United Nations 'Recommendations on the Transport of Dangerous Goods Manual of Tests and Criteria' are appropriate. The study does not need to be conducted if the substance is incapable of reacting exothermically with combustible materials, on the basis of the chemical structure. Pyrophosphate is non-oxidizing ion (originate from non-oxidizing acid). Disconnection of the oxygen from the pyrophosphate group is very difficult due to phosphorus high affinity to oxygen. Phosphorus is one of the strongest reducers (phosphorus seeks to the highest oxidation state, where it is stable). Phosphorous when bound to oxygen is in a stable state and reducing it to elemental P is very difficult, requiring extreme conditions and very strong reducing agents. extreme conditions and very strong reducing agents. In accordance with ECHA official opinion, ferric pyrophosphate was not classified as oxidizing under REACH Regulation, as well as tetrasodium pyrophosphate, which proves lack of the oxidizing properties for pyrophosphates.	Acceptable	-	-
B.2.14. OTHER STUDIES						
	-	-	-	-	-	-

Ferric pyrophoshate is a stable, very light shade of beige fine powder that melting above 360 °C. It is non-volatile and characterised by very low solubility in water. Ferric pyrophosphate is insoluble in organic solvents. It is non-flammable, contains no explosive compounds and does not flash.

B.2.15. REFERENCES RELIED ON

The only relevant scientific publications for the section physical and chemical properties selected by the applicant are: Steger E. et al. 1968 and Haynes W.M. et al. 2012-2013.

Reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant) Published or not	Vertebrate Y/ N	Data Protection Claimed Y / N	Justification if data protection is claimed	Owner
CA 2.1 ~~also:~~ ~~CA 2.3~~ ~~CA 2.4~~ ~~CA 2.5~~ ~~CA 2.6~~ ~~CA 2.9~~ ~~CA 2.10~~ ~~CA 2.12~~	Włodarczak M.	2015	Determination of physico-chemical properties of test material Ferric pyrophosphate; SORBO Research Laboratory, Study code: 0001/0164/FA GLP / Unpublished	N	Y	New study	BROS
CA 2.3 ~~also:~~ ~~CA 2.1~~ ~~CA 2.4~~ ~~CA 2.5~~ ~~CA 2.6~~ ~~CA 2.9~~ ~~CA 2.10~~ ~~CA 2.12~~	Włodarczak M.	2015	Determination of physico-chemical properties of test material Ferric pyrophosphate; SORBO Research Laboratory, Study code: 0001/0164/FA GLP / Unpublished	N	Y	New study	BROS
CA 2.4 ~~also:~~ ~~CA 2.1~~ ~~CA 2.3~~ ~~CA 2.5~~ ~~CA 2.6~~ ~~CA 2.9~~ ~~CA 2.10~~ ~~CA 2.12~~	Włodarczak M.	2015	Determination of physico-chemical properties of test material Ferric pyrophosphate; SORBO Research Laboratory, Study code: 0001/0164/FA GLP / Unpublished	N	Y	New study	BROS

Reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant) Published or not	Vertebrate Y/ N	Data Protection Claimed Y / N	Justification if data protection is claimed	Owner
CA 2.4	Steger E., et al.	1968	Die Infarotspektren von wasserfreien Schwermetall-Diphosphaten Spectrochimica Acta vol. 24A, p. 447-456 (1968). nGLP / Published	N	N	New study	Public
CA 2.5 ~~also:~~ ~~CA 2.1~~ ~~CA 2.3~~ ~~CA 2.4~~ ~~CA 2.6~~ ~~CA 2.9~~ ~~CA 2.10~~ ~~CA 2.12~~	Włodarczak M.	2015	Determination of physico-chemical properties of test material Ferric pyrophosphate; SORBO Research Laboratory, Study code: 0001/0164/FA GLP / Unpublished	N	Y	New study	BROS
CA 2.6 ~~also:~~ ~~CA 2.1~~ ~~CA 2.3~~ ~~CA 2.4~~ ~~CA 2.5~~ ~~CA 2.9~~ ~~CA 2.10~~ ~~CA 2.12~~	Włodarczak M.	2015	Determination of physico-chemical properties of test material Ferric pyrophosphate; SORBO Research Laboratory, Study code: 0001/0164/FA GLP / Unpublished	N	Y	New study	BROS
CA 2.8	Haynes W.M. et al.	2012-2013	CRC Handbook of Chemistry and Physics, 93th Ed., pp 5-93, nGLP/Published	N	N	New study	Public
CA 2.9 ~~also:~~ ~~CA 2.1~~ ~~CA 2.3~~ ~~CA 2.4~~ ~~CA 2.5~~ ~~CA 2.6~~ ~~CA 2.10~~ ~~CA 2.12~~	Włodarczak M.	2015	Determination of physico-chemical properties of test material Ferric pyrophosphate; SORBO Research Laboratory, Study code: 0001/0164/FA GLP / Unpublished		Y	New study	BROS

Reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant) Published or not	Vertebrate Y/ N	Data Protection Claimed Y / N	Justification if data protection is claimed	Owner
CA 2.10 ~~also:~~ ~~CA 2.1~~ ~~CA 2.3~~ ~~CA 2.4~~ ~~CA 2.5~~ ~~CA 2.6~~ ~~CA 2.9~~ ~~CA 2.12~~	Włodarczak M.	2015	Determination of physico-chemical properties of test material Ferric pyrophosphate; SORBO Research Laboratory, Study code: 0001/0164/FA GLP / Unpublished	N	Y	New study	BROS
CA 2.12 ~~also:~~ ~~CA 2.1~~ ~~CA 2.3~~ ~~CA 2.4~~ ~~CA 2.5~~ ~~CA 2.6~~ ~~CA 2.9~~ ~~CA 2.10~~	Włodarczak M.	2015	Determination of physico-chemical properties of test material Ferric pyrophosphate; SORBO Research Laboratory, Study code: 0001/0164/FA GLP / Unpublished	N	Y	New study	BROS