Justification Document for the Selection of a CoRAP Substance

Group Name:	Iron complexes with N,N'-1,2-ethanediylbis{N-[(2-hydroxyphenyl)methyl]glycine} derivatives
EC Numbers:	938-828-8, 283-041-9, 283-044-5, 405-420-1, 214-625-3
CAS Numbers:	-, 84539-53-7, 84539-55-9, -, 1170-02-1
Authority:	Swedish Chemicals Agency
Date:	20/03/2018

Cover Note

This document has been prepared by the evaluating Member State given in the CoRAP update.

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1 IDENTITY OF THE SUBSTANCES

1.1 Identifiers of the substances within the group

EC/List number	CAS number	Public Substance Name	Index number in Annex VI of the CLP Regulation	Type of substance (mono-, multi-consituent, uvcb)
938-828-8	-	Reaction product of phenol, formaldehyde, ethylenediamine diacetic acid, iron chloride and potassium hydroxide	-	UVCB
283-041-9	84539-53-7	Acetic acid, oxo-, sodium salt, reaction products with cresol and ethylenediamine, iron sodium salts	-	UVCB
283-044-5	84539-55-9	Acetic acid, oxo-, sodium salt, reaction products with ethylenediamine and phenol, iron sodium salts	-	UVCB
405-420-1	-	It is a NONS. Identified by its registered trivial name "EDDHMAFEK" (the potassium salt?)	-	UVCB
214-625-3	1170-02-1	Registered intermediate. The organic part of the iron complex EC No. 240-505-5.	-	UVCB

Type of substance ☐ Mono-constituent ☐ Multi-constituent ☒ UVCB

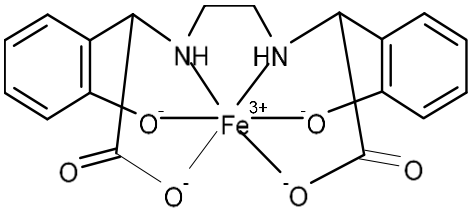
1.2 Similar substances/grouping possibilities

There is a read-across justification in the registrations for the *"reaction products of acetic acid, oxo-, sodium salt, ethylenediamine, iron sodium salt with either cresol or phenol"* substance category.

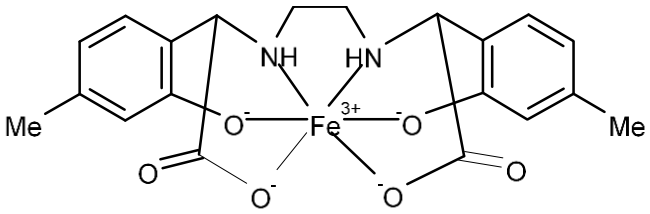
Read-across basis:
The substances are structural analogues and seem to have similar physiochemical properties and toxicity profiles. Target organs are the hematopoetic system, kidney, liver and adrenal glands. The substances are predicted to have similar toxicokinetics and mode of action for toxicity (mainly through metal-ion chelation). However, there are some differences in toxicity between the substances. It can not be excluded that the methyl groups present in the source substance (EC 283-041-9) can influence the uptake from the GI-tract and/or the strength of metal-ion chelation. In addition, the constituents in these UVCB substances are partly different.

Structural formula:

NaFe-o,o-EDDHA, EC 240-505-5 (structure below) is the main constituent of acetic acid, oxo-, sodium salt, reaction products with ethylenediamine and phenol, iron sodium salts, EC 283-044-5 (target substance).



NaFe-o,o-EDDHMA, (EC 408-108-6) is the main constituent of acetic acid, oxo-, sodium salt, reaction products with cresol and ethylenediamine, iron sodium salts, EC 283-041-9 (Source substance).



2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

other processes	RMOA	REACH process			Authorisation		Restriction	h C&L	process under other EU legislation		previous legislation		Stockholm convention	other processes EU legislation
EC entries		CCH	TPE	SEV	candidate list	Annex XIV	Annex XVII	Annex VI (CLP)	PPP	BPR	NONS	RAR	POPs	
Substance 938-828-8														
Constituent 203-632-7	PACT			x				x						
Constituent 200-001-8				x				x						

other processes	RMOA	REACH process			Authorisation		Restriction	h C&L	process under other EU legislation		previous legislation		Stockholm convention	other processes EU legislation
EC entries		CCH	TPE	SEV	candidate list	Annex XIV	Annex XVII	Annex VI (CLP)	PPP	BPR	NONS	RAR	POPs	
Substance 283-041-9														
Constituent 203-577-9				x					x					
Constituent 203-468-6								x						
Constituent 203-468-6	PACT				x			x						

other processes	RMOA	REACH process			Authorisation		Restriction	h C&L	process under other EU legislation		previous legislation		Stockholm convention	other processes EU legislation
EC entries		CCH	TPE	SEV	candidate list	Annex XIV	Annex XVII	Annex VI (CLP)	PPP	BPR	NONS	RAR	POPs	
Substance 283-044-5														
Constituent 203-577-9				x					x					
Constituent 203-468-6								x						
Constituent 203-468-6	PACT				x			x						

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

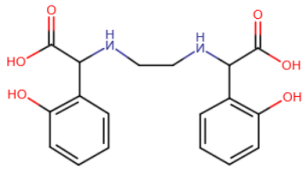
No harmonised classification for the group including members.

3.1.2 Self classification

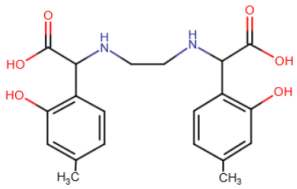
- In the registration:
  - None for EC 938-828-8 and EC 283-041-9
  - Skin Sens. 1 for EC 283-044-5

3.2 Environmental hazard assessment/PBT assessment

The organic part of these iron complexes was identified to be:



A: CAS No 1170-02-1/EC No 214-625-3



B: CAS No ?/EC No ?

Substance A is probably a raw material for both EC No. 938-828-8 and EC No. 283-044-45 and substance B is probably a raw material for EC No. 283-041-9. According to the EPIsuite QSAR model these chelating agernts are not expected to be P, B or T. Lowest predicted aquatric toxicity is acut toxicity for Daphnia with a 48h LC50 of 139 mg/l for the chelating agent A and 91 mg/l for the chelating agent B.

3.3 Human Health hazard assessment

Group seed (EC 938-828-8)

Repeated-dose toxicity
No repeated dose toxicity studies with the substance are provided in the registration.
Read across to 28-day and 90-day oral studies with the substances EC 283-044-5 and EC 283-041-9 is provided. In the 28-day study increased adrenal weight, epidermal hyperkeratosis and centritubular hypertrophy of hepatocytes were reported.

Reproduction toxicity
No reproduction toxicity study with the substance is provided in the registration. Read-across to a One-Generation Reproductive Toxicity study, OECD 415, (1997) with EC 283-041-9 is provided. In this study animals were treated with 0, 50, 200 and 750 mg/kg bw/day. The study showed reduced body weight gain and food consumption (200 mg/kg bw/day) and mortality (750 mg/kg bw/day) in the parental generation. At 750 mg/kg bw/day reproductive toxicity was observed: decrease in the conception indicies and delay in precoital time. Developmental NOAEL was set to 50 mg/kg bw/day based on increased mortality at 200 and 750 mg/kg bw/day) and reduced body weight during lactation at 750 mg/kg bw/day.

Hormonal parameters (estrous cyclicity and sperm parameters), F1 sexual maturation, F1 histopathology and organ weghits (P and F1) were not examined in this study.

Developmental toxicity
No developmental toxicity study with the substance is provided. Read-across to Prenatal Developmetal Toxicity studies, OECD 414, with EC 283-041-9 (1997) and EC 283-041-9 (1995) is used. Both studies indicated maternal toxicity shown by reduced body weight and food intake (Maternal NOAEL=100 mg/kg bw/day). No adverse effects on foetal parameters were reported.

Group member: FeNa-EDDHMA (EC 283-041-9)

Repeated-dose toxicity
28-days oral OECD 407 (1996) and 21/28-days dermal OECD 410 (1996) repeated dose toxicity studies with the substance are provided in the registration. Increase in adrenal weight, epidermal hyperkeratosis and centritubular hypertrophy of hepatocytes were reported. In the 90-day study (1998) the NOAEL was set to 10 mg/kg bw/day, based on transient normochromic anemia at higher doses. A supporting study showed that the haematopoetic system and at higher dose levels the kidney represent the target organs following oral exposure.

Reproduction toxicity
A one-generation reproductive toxicity study OECD 415, (1997) with the substance is provided (summerised above). A justification for data waiving for 2-generation study is provided in the registration.

Developmental toxicity
A Prenatal Developmetal Toxicity study, OECD 414 (1996) with the substance is provided in the registration. No adverse effects on foetal parameters were reported.

Group member: FeNa-EDDHA (EC 283-044-5)

Repeated-dose toxicity
28-day oral, 90-day oral and 28-day dermal repeated dose studies with the substance are provided in the registration. The studies show kidney and liver as target organs. Also an increase in adrenal weight is shown.
In the 90-day oral key study (1998) the NOAEL was set to 10 mg/kg bw/day based on normochromic anemia seen at higher doses. A supporting study showed that the haematopoetic system and at higher dose levels the kidney represent the target organs following oral exposure. In the 28-day dermal study an increased adrenal weight in males was observed.

Reproduction toxicity
No reproduction toxicity study with the substance is provided in the registration. The information is waived with read-across to a one-generation reproductive toxicity study to EC 283-041-9 (summerised above).

Developmental toxicity
A Prenatal Developmetal Toxicity study, OECD 414 (1995) with the substance is provided in the registration. No developmental effects were reported.

Skin sensitization

There is a Maximisation Test of Magnusson and Kligman (GPMT) in guinea pigs OECD 406, (1994) for the substance. 20 and 55% of the animals showed skin reactions 24 and 48 hours after removing the dressings, respectively. The substance was considered therefore a weak sensitizer. A Local Lymph Node Assay (LLNA), OECD 429, (2010) with the substance is also available. In this study, Stimulation Indices of 1.59, 2.89, and 2.00 were determined at concentrations of 5, 10 and 25 % in dimethylformamide, respectively. A statistically significant increase in DPM/animal and in lymph node weights was observed in all treated groups in comparison to the vehicle control group (p=0.008).
The registrant concludes that the results of the in vivo skin sensitisation tests for EDDHA-Fe were ambiguous: "It is most likely that the ambiguous results in the available animal studies were induced by an intrinsic impurity, ethylenediamine (EDA), that has skin sensitising potential. The concentration of EDA was 0.2% in the LLNA study inducing a borderline positive result for "FeNaEDDHA containing >=0.2% EDA as intrinsic impurity". Therefore, FeNaEDDHA is concluded as non-sensitiser, but if skin sensitising intrinsic impurities, such as 0.2% ethylenediamine, are included in FeNaEDDHA classification of "FeNaEDDHA including >=0.2% ethylenediamine as intrinsic impurity" as skin sensitizer is warranted." This point could be addressed by performing SID analysis.

Exposure assessment and risk characterisation
DNELs for human health effects:
No DNELs for short-term systemic or local effects or for long-term local effects were derived.
Worker DNELs for Long-term systemic effects were set to:
0.83 mg/kg bw/day for Dermal exposure (NOAEL=100 mg/kg bw/day)
1.76 mg/kg bw/day for inhalation exposure (oral NOAEL=10 mg/kg bw/day)

Exposure assessment
No exposure assessment or RCR calculation for the human health or the environment has been provided in the CSR. The registrant states that no risk characterisation is required as the substance is not classified as toxic or harmfull.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[1]

4.1 Tonnage and registration status

Table: Tonnage and registration status

EC number	Registration status	Tonnage band (Nr. of registrations)	Total tonnage band
938-828-8	Full (Joint submission)	100-1000 T(1)	
283-041-9	Full (Joint submission) INAKTIVE	100-1000 T(1)	
283-044-5	Full (Joint submission)	1000T+ (6) 10-100T (2) 100-1000T(2)	10 000-100 000

[1] *The dissemination site was accessed in August 2017*

4.2 Overview of uses

Table: Uses

Part 1:

☒ Manufacture	☒ Formulation	☐ Industrial use	☒ Professional use	☒ Consumer use	☐ Article service life	☐ Closed system

Group member: EC 283-041-9

☒ Manufacture	☒ Formulation	☐ Industrial use	☒ Professional use	☒ Consumer use	☐ Article service life	☐ Closed system

Group member: EC 283-044-5

☒ Manufacture	☒ Formulation	☐ Industrial use	☒ Professional use	☒ Consumer use	☐ Article service life	☐ Closed system

Part 2:

Description of use	**Technical function**	**Use by**	**Portion of fully registered substances with this use**
Fertilizer (Agriculture, forestry and fishing)	Keeping the nutrient iron in solution	Professional workers Consumer	Dominating
Laboratory chemical		Workers	Minor

Part 3: There is high potential for exposure of

☒ Humans	☒ Environment

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1. Legal basis for the proposal

☒ Article 44(2) (refined prioritisation criteria for substance evaluation)

☐ Article 45(5) (Member State priority)

5.2. Selection criteria met (why the substance qualifies for being in CoRAP)

☒ Fulfils criteria as CMR/ Suspected CMR

☒ Fulfils criteria as Sensitiser/ Suspected sensitiser

☐ Fulfils criteria as potential endocrine disrupter

☐ Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB

☐ Fulfils criteria high (aggregated) tonnage (*tpa > 1000*)

☒ Fulfils exposure criteria

☐ Fulfils MS's (national) priorities

5.3. Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR ☐ C ☐ M ☐ R	Suspected CMR[1] ☐ C ☐ M ☒ R	☒ Potential endocrine disruptor
☐ Sensitiser	☒ Suspected Sensitiser[2]	
☐ PBT/vPvB	☐ Suspected PBT/vPvB[1]	☐ Other (please specify below)
Exposure/risk based concerns		
☒ Wide dispersive use	☒ Consumer use	☐ Exposure of sensitive populations
☒ Exposure of environment	☒ Exposure of workers	☐ Cumulative exposure
☐ High RCR	☐ High (aggregated) tonnage	☐ Other (please specify below)

[2] CMR/Sensitiser: known carcinogenic and/or mutagenic and/or reprotoxic properties/known sensitising properties (according to CLP harmonized or registrant self-classification or CLP Inventory)
Suspected CMR/Suspected sensitiser: suspected carcinogenic and/or mutagenic and/or reprotoxic properties/suspected sensitising properties (not classified according to CLP harmonized or registrant self-classification)
Suspected PBT: Potentially Persistent, Bioaccumulative and Toxic

There are concerns for reproductive toxicity, ED and skin sensitization for this group of substances.

The concern for reproductive toxicity and ED is based on the effects on fertility and development noted in an available one-generation study with one substance within the group and possible ED properties of the constituents. The one-generation study indicates reproductive toxicity shown by decrease in the conception indices and delay in precoital time and developmental toxicity, shown by a dose-related increase in mortality and reduced body weights during lactation of the F1 pups (PND 0-4). Hormonal parameters (estrous cyclicity and sperm parameters), F1 sexual maturation, F1 histopathology and organ weights (P and F1) were not examined in this study (see also chapter 3.3, human health assessment).

The concern for possible skin sensitization is based on the available positive/ambiguous in vivo tests. For the substance EC 283-044-5 an "intrinsic impurity"/constituent (ethylenediamine) is a classified skin sensitiser (See section 3.3, Skin sensitisation).

5.4. Preliminary indication of information that may need to be requested to clarify the concern

☒ Information on toxicological properties	☐ Information on physico-chemical properties
☐ Information on fate and behaviour	☐ Information on exposure
☐ Information on ecotoxicological properties	☐ Information on uses
☒ Information ED potential	☐ Other (provide further details below)

An extended one-generation reproductive toxicity study (OECD 443), may need to be requested to clarify the concern for reproductive toxicity and ED. The concern is based on the effects on fertility and development seen in an available one-generation study with one substance within the group and possible ED properties of the constituents.

Additional information on the toxicokinetics and stability of the chelat-Fe-complex may be needed to conclude on the concern for reproductive toxicity due to metal-ion balance disruption.

Also, further information to reach a conclusion on the possible skin sensitization potential of the substance EC 283-044-5 may be requested.

5.5. Potential follow-up and link to risk management

☒ Harmonised C&L	☐ Restriction	☐ Authorisation	☒ Other (provide further details)

Information from the reproductive toxicity study and skin sensitisation may lead to harmonized classification of the substance.

In addition, DNEL values for proper risk characterization and risk management can be derived.