SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

EDDHA-FeNa and HBED-FeK

(Iron complexes with N,N'-1,2-ethanediylbis{N-[(2-hydroxyphenyl)methyl]glycine} derivatives)

EC numbers 283-044-5, 938-828-8

CAS RNs 84539-55-9, 1463474-95-4

Evaluating Member State(s): Sweden

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2021

The evaluating member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The group of "Iron complexes with N,N'-1,2-ethanediylbis{N-[(2-hydroxyphenyl) methyl]glycine} derivatives", here referred to as "Fe-complexes", consists of three "Unknown or variable composition, complex reaction products or of biological materials" (UVCB) substances:

- EDDHA-FeNa (EC number 283-044-5)
- HBED-FeK (EC number 938-828-8)
- EDDHMA-FeK (EC number 405-420-1)

The substances were included in the Community Rolling Action Plan (CoRAP) for Substance Evaluation (SEv) in 2021, by the competent authority of Sweden.

The group of three substances was originally selected for substance evaluation in order to clarify concerns about:

- Suspected reproductive toxicity
- Potential endocrine disruptor
- Suspected sensitiser
- Wide dispersive use, consumer use
- Exposure of workers
- Exposure of environment

During the evaluation no other concern was identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Compliance check (CCH) was started in 2021 and is currently ongoing for EDDHA-FeNa and HBED-FeK.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

The concern for reproductive toxicity, specifically for development and developmental neuro- and immunotoxicity, was substantiated during the SEv for all the substances in the group. The evaluating MSCA concluded that further information was needed to conclude on the concern and for proper risk management.

However, as data gaps for standard information requirements, including data on reproductive toxicity were identified, the group was handed over to ECHA to request the information under CCH.

Also, information on skin sensitisation was identified as a standard information requirement to be addressed under CCH.

CCH was started in 2021 and is currently ongoing for EDDHA-FeNa and HBED-FeK. The third substances in the group, EDDHMA-FeK is a former notified substance (NONS). Based on its registration status, this substance could not be addressed under CCH (separate SEv conclusion document).

Further, in March 2021, the Registrant(s) of EDDHA-FeNa and HBED-FeK informed the evaluating MSCA that reproductive toxicity screening studies, according to the OECD TG 422, were planned to be started in 2021 with these substances. After the conclusion of SEv, in January 2022, these Registrant(s) submitted dossier updates, including preliminary findings of the OECD 422 study, as well as an updated read-across justification.

Based on the upcoming data, the evaluating MSCA may consider regulatory follow-up action for these substances.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	
Clarification of hazard properties/exposure	
Actions by the registrants to ensure safety, as reflected in the registration	
Currently, no need for regulatory follow-up at EU-level. Reproductive toxicity was the main concern under SEv. The evaluating MSCA concluded that further information is needed to clarify the concern. Conclusion on possible regulatory follow-up awaits the upcoming results.	X

Based on the upcoming data, the evaluating MSCA may consider submitting proposals for harmonised classification for these substances.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The group of "Iron complexes with N,N'-1,2-ethanediylbis{N-[(2-hydroxyphenyl) methyl]glycine} derivatives", here referred to as "Fe-complexes", consists of three "Unknown or variable composition, complex reaction products or of biological materials" (UVCB) substances:

- EDDHA-FeNa (EC number 283-044-5)
- HBED-FeK (EC number 938-828-8)
- EDDHMA-FeK (EC number 405-420-1)

The substances were included in the Community Rolling Action Plan (CoRAP) for Substance Evaluation (SEv) in 2021, by the competent authority of Sweden.

The group of three substances was originally selected for substance evaluation in order to clarify concerns about:

- Suspected reproductive toxicity
- Potential endocrine disruptor
- Suspected sensitiser
- Wide dispersive use, consumer use
- Exposure of workers
- Exposure of environment

During the evaluation no other concern was identified.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Reproductive toxicity Fertility and development	Concern unresolved. Pending data generated via CCH or by the registrants.
Endocrine disruption Human health	Concern unresolved. Pending data generated via CCH or by the registrants.
Suspected sensitiser	Concern unresolved. Pending data generated via CCH.
Wide dispersive use, consumer use	Concern refuted based on the existing data.
Exposure of workers	Concern refuted based on the existing data.
Exposure of environment	Concern refuted based on the existing data.

7.2. Procedure

The group of Fe-complexes, consisting of the three "Unknown or variable composition, complex reaction products or of biological materials" (UVCB) substances: EDDHA-FeNa (EC number 283-044-5), HBED-FeK (EC number 938-828-8) and EDDHMA-FeK (EC number 405-420-1), was included in the Community Rolling Action Plan (CoRAP) for Substance Evaluation (SEv) in 2021, by the competent authority of Sweden. The scope of the evaluation was human health, targeted to the concern for reproductive toxicity and potential endocrine disrupting properties.

The concern for reproductive toxicity, specifically for development and developmental neuro- and immunotoxicity was substantiated for the substances in the group, based on read across to the available data for the similar substance EDDHMA-FeNa (EC number 283-041-9) and/or publicly available information. However, existing data was not sufficient to conclude on the concern and for appropriate regulatory risk management, i.e. harmonised classification.

The evaluating MSCA concluded that further information on reproductive toxicity, namely an Extended one-generation reproductive toxicity study (EOGRTS) with the developmental neuro- and immunotoxicity cohorts was needed to clarify the concern for reproductive toxicity. However, as this information is a standard data requirement for the Registrants of the substances at Annex IX, the group was handed over to ECHA for compliance check (CCH).

In 2021, CCH was initiated for EDDHA-FeNa and HBED-FeK.

In March 2021, the Registrant(s) of EDDHA-FeNa and HBED-FeK informed the evaluating MSCA that reproductive toxicity screening studies, according to the OECD TG 422, were planned with the substances. In January 2022, these Registrants submitted dossier updates, including preliminary findings from the extended OECD 422 studies, as well as an updated read-across justification.

7.3. Identity of the substances

Table 4

EDDHA-FeNa: SUBSTANCE IDENTITY	
Public name:	Acetic acid, oxo-, sodium salt, reaction products with ethylenediamine and phenol, iron sodium salts
EC number:	283-044-5
CAS number:	84539-55-9
Index number in Annex VI of the CLP Regulation:	_
Molecular formula:	n.a.
Molecular weight range:	n.a.
Synonyms:	EDDHA-FeNa Fe EDDHA Iron (III) EDDHA chelate sodium salt

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

Structural formula: n.a.

Table 5

EDDHA-FeNa constituents (not a complete list)	EC Number
[[Alpha,alpha'-[1,2-ethanediyldiimino]bis[2-(hydroxy-benzeneacetic acid]] (4-)] ferrate(1-), sodium salt	240-505-5
Alpha-[[2-[[carboxy(4-hydroxyphenyl)methyl]amino]ethyl]amino]-2-hydroxy-benzeneacetic acid (4-) ferrate(1-), sodium salt	-
Phenol	203-632-7

Ethylenediamine	203-468-6

Table 6

HBED-FeK: SUBSTANCE IDENTITY	
Public name	Iron(III) chloride, complex with reaction products of 2,2'-(ethane-1,2-diyldiimino)diacetic acid, formaldehyde, phenol and potassium hydroxide
EC number	938-828-8
CAS number	1463474-95-4
Index number in Annex VI of the CLP Regulation	_
Molecular formula	_
Molecular weight range	_
Synonyms:	HBED-Fe Reaction product of phenol, formaldehyde, ethylenediamine, diacetic acid, iron chloride and potassium hydroxide Glycine, N,N'-1,2-ethanediylbis-, reaction products with formaldehyde, iron chloride (FeCl3) and phenol, potassium salts

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

Structural formula: n.a

Table 7

HBED-FeK constituents (not a complete list)	EC / CAS
bis(2-hydroxybenzyl)ethylenediamine diacetic acid, ferric potassium complex, HBED-KFe(III),	CAS 74877-84-2
Potassium chloride (KCl)	231-211-8
Phenol	203-632-7
Formaldehyde	200-001-8

7.3.1. Grouping and read-across

7.3.1.1. Group description

The three UVCB substances, EDDHA-FeNa, HBED-FeK and EDDHMA-FeK, subject to this group evaluation are chelating agents for iron (Fe) and used mainly as fertilizers.

The organic part of the substance EDDHA-FeNa consists of ethylenediamine-N,N′-bis(2-hydroxyphenyl) acetic acid (EDDHA). EDDHA is generally produced by the multicomponent reaction of phenol, glyoxalic acid and ethylenediamine. It binds metal ions as a hexadentate ligand, using two amines, two phenolate centres and two carboxylates as the six binding sites. The complex is anionic and forms salts with positive ions, such as Na or K. EDDHA-FeNa and EDDHMA-FeNa consist of the same reaction products except cresol (EC number 203-577-9) versus phenol (EC number 203-468-6) in the composition.

The main constituents of EDDHA-FeNa and EDDHMA-FeNa are the ortho-isomers. These are manufactured as UVCB substances, containing the ortho, ortho- and ortho, para-isomers as the main components. It is suggested that both isomers have the same functionality, i.e. mono- and multivalent metal-ion binding.

The organic part of HBED-FeK consists of N,N'-Bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED). HBED is produced by reaction of ethylenediamine, diacetic acid, formaldehyde and phenol. The main constituents of HBED-FeK are HBED isomers (range 10-25%). Other constituents in these UVCBs including phenol and ethylene diamine (EC number 203-468-6) are present at lower concentrations.

Table 8

Overview: EDDHA, EDDHMA and HBED derivatives		
UVCB abbreviation (Main constituent)	**EC number**	**CAS RN**
EDDHA	214-625-3	1170-02-1
EDDHA-Fe	240-505-5	16455-61-1
EDDHA-FeNa* # (EDDHA-FeNa)	283-044-5 (240-505-5)	84539-55-9 16455-61-1
EDDHMA-FeNa # (EDDHMA-FeNa)	283-041-9 (408-108-6)	84539-53-7
EDDHMA-FeK*	405-420-1	-
EDDHSA-Fe	283-042-4	84539-54-8
EDDHSA-FeK	462-490-6	-
HBED	700-327-5	1061328-86-6
HBED-FeK* # (HBED-FeK)	938-828-8 (616-154-2)	1463474-95-4 74877-84-2

* Substances in the group evaluated under SEv in 2021.

Substances tested in OECD TG 422 studies. EDDHMA-FeNa (EC number 283-041-9), has currently no active registration, but was included in the OECD TG 422 study with EDDHA-FeNa as a high dose group for read-across purposes (see 7.3.1.2).

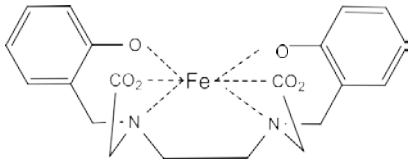
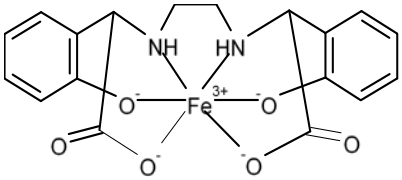
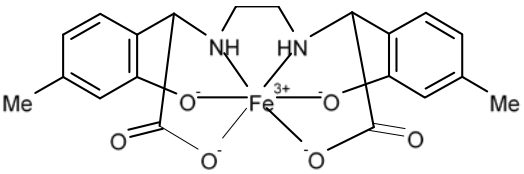
These chelates have structural and functional similarity to the members of the aminocarboxylic acid (ethylenediamine-based) chelates category, including Ethylenediamine tetraacetic acid (EDTA). All members have a molecular structure with an ethylenediamine backbone, which has 2-4 acetic acid or hydroxy functional groups attached to the nitrogens. The ethylenediamine backbone together with multiple functional groups on the amine provides chelates their unique metal ion binding properties.

7.3.1.2. Read-across basis

In the registration(s) read-across between these substances has been proposed for the (eco)toxicity endpoints. According to the justifications provided, the read-across is based on similarities in structure, physiochemical properties and toxicity profiles. Moreover, data from the similar substances EDDHSA-FeNa and EDDHSA-FeK is taken into account as supporting source substances.

Specifically, justification is provided for read-across:
-From EDDHMA-FeNa (source) to EDDHA-FeNa (target)
-From EDDHMA-FeNa (source) and EDDHA-FeNa (source) to HBED-FeK (target)

Table 9

Structure of the main constituents in the UVCBs	
UVCB Substance (abbreviation) **Main constituent**	**Structure of the main constituent**
HBED-FeK, EC number 938-828-8 Bis(2-hydroxybenzyl) ethylenediamine diacetic acid, ferric potassium complex EC 616-154-2	
EDDHA-FeNa, EC number 283-044-5 Sodium [[α,α'-(ethylenediimino)bis[2-hydroxybenzene-1-acetato]](4-)] ferrate(1-) EC 240-505-5	
EDDHMA-FeNa, EC Number 283-041-9 Sodium (ethylenediiminobis((2-hydroxy-4-tolyl)acetato)) ferrate(1-), EC 408-180-6	

The source substance EDDHMA-FeNa (currently no active registration) is the methylated form of EDDHA-FeNa. The substances consist of the same reaction products and differ only in the cresol versus phenol group in the composition. As a result, EDDHMA-FeNa is methylated EDDHA-FeNa (Table 9). According to the read across justification, as methyl groups are considered to be stable and to possess limited reactivity, it is proposed that no significant differences in toxicological properties are to be expected between EDDHA-FeNa and EDDHMA-FeNa. EDDHMA-FeNa has also been proposed as the source substance for read across to HBED-FeK. In HBED-FeK the carboxylic arms of the molecule are attached to the amine groups, whereas in EDDHMA-FeNa these are attached to a benzoyl position. This results in tertiary amines in HBED-FeK and secondary amines in EDDHMA-FeNa at the iron binding sites.

Available data indicate that these substances have similar physiochemical properties, including high water solubility, low octanol-water partition coefficient (Pow), no hydrolysis in water and low vapour pressure. These substances are thus expected to behave similarly in aqueous solutions. No toxicokinetics studies are available in the registration(s) for the substances. Instead, predictions of the toxicokinetics behaviour, based on the physicochemical properties and toxicity data of the substances and/or their structurally related substances has been provided (see section 7.9.1).

The available information on toxicity is mainly from the repeated dose toxicity studies with EDDHMA-FeNa and EDDHA-FeNa, including 28-day and 90-day repeated dose toxicity studies. Based on these studies the hematopoietic system (shown by anaemia) and kidneys are identified as the main target organs (see section 7.9.4).

No repeated dose toxicity study is provided for HBED-FeK. Thus, no bridging study is available to support the read-across. According to the ECHA guidance (2017), bridging studies, i.e. comparable studies on the source and target substance, allow side-by-side comparison of the substances for a particular property. Bridging studies may demonstrate that two UVCBs have similar properties for a particular endpoint and play a key role in a read-across justification. In the absence of such an empirical demonstration, read-across may be difficult to justify for complex compositions.

In March 2021, the Registrants of EDDHA-FeNa and HBED-FeK informed the evaluating MSCA that OECD TG 422 studies were planned with these substances with the aim to provide further information on reproductive toxicity and to support the proposed read-across (bridging) between substances EDDHMA-FeNa, EDDHA-FeNa and HBED-FeK. The study with EDDHA-FeNa was planned to include an additional high dose group animals, treated with EDDHMA-FeNa to support the read-across.

After conclusion of the SEv, in December 2021, dossier updates including preliminary results from the OECD TG 422 studies and an updated read-across justification were provided by the Registrant(s).

7.3.1.2.1. Mode-of-Action for toxicity

Limited/no toxicity data is available for HBED-FeK. Available studies with EDDHA-FeNa and its similar substances indicate adverse effects, primarily on the hematopoietic system and kidneys. The Mode-of-Action (MoA) for toxicity seems to be iron chelation, consistent with the intrinsic property of the substances. However, there is not sufficient experimental evidence to support a MoA.

Based on the observed toxicity, EDDHA-FeNa and EDDHMA-FeNa seem to be absorbed systemically. It is likely that toxicity is due to disruption of iron homeostasis. Anaemia symptoms suggest that chelates are de-complexed in the body. After de-complexation, chelators free of iron sequester systemically available iron leading to anaemia. The anaemia symptoms, i.e. reduced red blood cells, haemoglobin and haematocrit and findings in kidneys suggest that absorbed chelates compete for the internal pool of iron, complex this iron and are either excreted or redistribute iron to other organs. Similar pathways has been reported for other chelators (Heimbach et al., 2000). It is possible that exposure to these substances could induce a condition similar to thalassemia. Thalassemia patients have reduced blood cell levels, together with hepatic iron overload as the result of frequent blood transfusion or high absorption of dietary iron (Herschko, 2010). Such a condition could be mimicked by high amounts of iron absorbed in from EDDHA-FeNa and EDDHMA-FeNa. In case these substances, when de-complexed in the body compete with e.g. transferrin, excess iron will be redistributed to organs, while released chelators would bind further iron. Thus, the toxicity pattern suggests that when these chelates enter the body they likely become de-complexed from Fe, and then sequester further iron, competing with the endogenous iron-regulating proteins.

Regarding potential binding to metal ions other than iron, it has been shown that EDTA forms complexes with different metals dependent on their affinity constant, pH and concentration of competing metals and/or ligands in the gastrointestinal tract (Heimbach et al., 2000). EDDHA-Fe and EDDHMA-Fe seem to be more stable compounds and thus not expected to bind to other metals as the affinity to iron is very high. No substitution of iron by other metals was shown experimentally, suggesting that these substances have such a high affinity to iron that other metal levels are left unaffected (Lopez-Rayo et al., 2009).

Regarding the MoA for toxicity, the evaluating MSCA concludes that the anaemia and kidney toxicity findings in the available repeated dose toxicity studies with EDDHA-FeNa and EDDHMA-FeNa suggest impaired iron balance as a result of exposure to these substances. However, the specific mechanisms leading to toxicity are not clear.

Taken together, the evaluating MSCA concludes that read across between EDDHMA-FeNa and EDDHA-FeNa is plausible. However, further supporting information (i.e. “bridging information”) would be needed to confirm similar effects. Read-across from EDDHA-FeNa and EDDHMA-FeNa to HBED-FeK cannot be justified as no bridging study is currently available and because of the differences in structure between these substances.

7.4. Physico-chemical properties

Table 10

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES: EDDHA-FeNa , EC number 283-044-5	
Physical state at 20°C and 101.3 kPa	Fine grained, free flowing, homogeneous solid
Vapour pressure	0 hPa at 25°C
Water solubility	150-203 g/L at 23°C
Partition coefficient n-octanol/water (Log Kow)	-4.2 at 23° C
Flammability	Non flammable
Explosive properties	Non explosive
Oxidising properties	No

Table 11

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES: HBED-FeK, EC number 938-828-8	
Physical state at 20°C and 101.3 kPa	Solid, odourless, dark red-brown, microgranules
Vapour pressure	0 hPa at 25°C (read-across EDDHA-FeNA)
Water solubility	40 g/L at 20°C
Partition coefficient n-octanol/water (Log Kow)	-8.97
Flammability	Non flammable
Explosive properties	Non explosive
Oxidising properties	No

7.5. Manufacture and uses

7.5.1. Quantities

Table 12

EC NUMBER 283-044-5, AGGREGATED TONNAGE (PER YEAR): 10 000-100 000				
☒ 1 – 10 t	☒ 10 – 100 t	☒ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential
EC NUMBER 938-828-8, AGGREGATED TONNAGE (PER YEAR): 10 000-100 000				
☐ 1 – 10 t	☐ 10 – 100 t	☒ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

All three substances are used mainly as fertilisers or micronutrients.

Table 13

USES: EC NUMBER 283-044-5	
Formulation	Formulation of powder and liquid
Uses at industrial sites	Inclusion into/onto article
Uses by professional workers	End-use of liquid or powder in field or glasshouse Liquid in hydroponic cultures Trace element fertiliser by farmers Direct application in water solutions
Consumer Uses	Fertiliser
USES: EC NUMBER 938-828-8	
Formulation	Liquid and solid formulations Agricultural use
Uses by professional workers	Agriculture, forestry, fishing Research and development
Consumer Uses	Fertiliser

Information was collected from the ECHA dissemination site on 2021-09-20.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

None.

7.6.2. Self-classification

In the registration(s): none

The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

EC number 283-044-5 Skin Sens 1 and Skin Sens 1B

7.7. Environmental fate properties

Not assessed.

7.8. Environmental hazard assessment

Not assessed.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

No toxicokinetics studies are available in the registrations for these substances. Predictions of the toxicokinetics behaviour have been provided for EDDHA-FeNa and HBED-FeK.

7.9.1.1. Absorption and distribution

Prediction of the absorption and distribution behaviour of the substances is based mainly on the results of the repeated dose toxicity studies with EDDHA-FeNa (EC number 283-044-5) and EDDHMA-FeNa (EC number 283-041-9).

In vitro studies with EDDHA and its derivatives in solutions with trivalent metal ions at different pH values show that iron forms stable complexes with EDDHA, even at pH 2 with no free metal present in solutions. The stability constants (logK) for EDDHA-Fe and EDDHMA-Fe as mixtures of meso- and rac- isomers were reported to be about 37. In comparison, the log stability constant for EDTA-Fe is 25. Consistently, it has been shown that EDTA-Fe in solution de-complexes at the pH range 6-8, releasing iron, while EDDHA-Fe remains complexed until pH 12 (registration).

The stability of these chelate complexes *in vivo* e.g., in the gastrointestinal (GI) tract is expected to influence their absorption and fate under physiological conditions. According to the information in the registration(s) EDDHA-Fe is a highly stable Fe chelate in a wide pH range. However, based on the observed toxicity, EDDHA-FeNa and EDDHMA-FeNa seem to be de-complexed from iron and absorbed systemically. It is not known whether the intact EDDHA-Fe is absorbed in the small intestine with the subsequent distribution to organs or if the complex is dissociating before absorption and then the separate components (iron and chelator) are absorbed. It is also possible that the complexed EDDHA-Fe is absorbed and then de-complexed in the liver, contributing to the iron load in the liver, while still being able to bind iron from serum or the GI tract following release from the liver.

7.9.1.2. Metabolism and excretion

No studies of metabolism or excretion of these substances is available. According to the information in the registration(s), based on the structures of the substances metabolism in humans will mainly consist of phase-II metabolising steps, leading to a higher water solubility for excretion. Based on the water solubility and the log Pow values, excretion via urine is likely. As substances have a molecular weight range above 300 g/mol excretion via the bile is also possible, especially if phase-II conjugation takes place e.g., with formation of glucuronide derivates.

In conclusion, the evaluating MSCA notes that the toxicokinetics behaviour of these substances is not known. It is not clear how these UVCBs are absorbed or distributed in the body. Toxicity observed after oral exposure suggests that dissociation of the chelate complexes can take place. Release of Fe from these complexes could occur before uptake in the gut or after uptake in the blood.

7.9.2. Acute toxicity and Corrosion / Irritation

Not assessed.

7.9.3. Sensitisation

Not assessed.

Information on skin sensitisation is a standard information requirement for these substances and needs to be addressed under CCH.

7.9.4. Repeated dose toxicity

Repeated dose toxicity (RDT) studies with EDDHA-FeNa and EDDHMA-FeNa are available in the registration(s). These studies pre-date the current test guidelines.

No RDT studies have been provided for HBED-FeK. Instead, read-across to EDDHA-FeNa and EDDHMA-FeNa has been proposed by the registrants.

7.9.4.1. Subacute toxicity

7.9.4.1.1. Subacute toxicity of EDDHA-FeNa (EC number 283-044-5)

In a 28-day oral gavage study (range-finding for a 90-day study) rats were treated with 50, 200 or 1000 mg/kg bw/d EDDHA-FeNa (1996). Decreased mean body weight and body weight gain was observed at ≥200 mg/kg bw/d. Absolute and relative organ weight changes were reported. Relative kidney weights were increased in males (12%) at 200 mg/kg bw/d and (51%) 1000 mg/kg bw/d and in females (31%) at 1000 mg/kg bw/d. Relative adrenal weights were increased in males dose dependently (11%, 13% and 28%, respectively). Relative spleen weights were increased in females (24%) at 1000 mg/kg bw/d.
Anaemia without erythropoietic response was reported at ≥50 mg/kg bw/d in males and females. Males in the high-dose group had lower levels of white blood cells, predominantly lymphocytes and basophils. Blood chemistry examination showed increased plasma creatinine and cholesterol levels in males and females. Kidney was identified as the main target, based on increased weight, microscopical changes (i.e. cytoplasmic vacuolisation of cortical tubules) and changes in blood chemistry. NOAEL was set to 50 mg/kg bw/d.

A 28-day dermal toxicity study (OECD TG 410) with EDDHA-FeNa is also available (1996). In this study rats were treated with 10, 100 or 1000 mg/kg bw/d EDDHA-FeNa. Body weight loss was observed at 1000 mg/kg bw/d. Epidermal hyperkeratosis, increased adrenal weight and centritubular hypertrophy of hepatocytes was observed at 1000 mg/kg bw/d. NOAEL was set to 100 mg/kg bw/d.

7.9.4.1.2. Subacute toxicity of EDDHMA-FeNa (EC number 283-041-9)

A 28-day study is available with EDDHMA-FeNa. EDDHMA-FeNa was administered by oral gavage to rats for 4 weeks at 40, 200 or 1000 mg/kg bw/d. Mean body weights and body weight gain were decreased at 1000 mg/kg bw/d. Hematology examinations showed a decrease in the red blood cells and hemoglobin in males and females. Hematocrit values were decreased in the mid- and high-dose animals. High-dose males and females showed an increased blood content and a corresponding increase of erythrocytes in urine. Predominantly, in the high-dose males an increased content of leukocytes was found. Increased urea and plasma creatinine levels was observed in males and females.

Organ weight changes were observed in the liver, spleen and kidney. At the high-dose, relative kidney and spleen weights were increased in males and females. In the kidneys slight fatty degenerations of tubular cells was observed at 200 mg/kg bw/day. High-dose animals showed hydropic and fatty degenerations, associated with necrotic changes of tubular epithelial cells in individual animals. The NOAEL was set to 20 mg/kg bw/day.

7.9.4.2. Subchronic toxicity

7.9.4.2.1. Subchronic toxicity of EDDHA-FeNa (EC number 283-044-5)

A 90-day study with EDDHA-FeNa is available (1998). In this study rats were treated at 5, 50 or 200 mg/kg bw/d. A 4-week recovery period was included in the study. No mortality was reported. Decreased body weight gain in males (21%) and females (9%) was reported at 200 mg/kg bw/d. During the recovery period, body weight gain in treated animals was higher compared to controls. Organ weight examination showed changes in the relative weights in kidneys and adrenals (no statistical significance).

Normochromic anaemia with decreased erythrocyte count, haemoglobin concentration and haematocrit values was observed in females at 200 mg/kg bw/d and in males at ≥50 mg/kg bw/d. A higher reticulocyte count associated with higher Mean Corpuscular Volume (MCV)

and Mean Corpuscular Hemoglobin (MCH) values was observed in males at 200 mg/kg bw/d. Reduced values for white blood cell, basophil, lymphocyte and monocyte counts were reported in males at 200 mg/kg bw/d. A higher platelet count for males at ≥50 mg/kg bw/d and a higher prothrombin activity for males and females at 200 mg/kg bw/d was observed. These effects were reversible after the recovery period. Several clinical chemistry parameters including plasma creatinine, urea, protein, globulin, cholesterol and sodium concentration were increased at 50 and/or 200 mg/kg bw/d. The authors estimated a NOAEL of 10 mg/kg bw/d from the LOAEL of 50 mg/kg bw/d applying an assessment factor of 5 with the argument that only slight adverse effects (anaemia) were observed at 50 mg/kg bw/d.

7.9.4.2.2. Subchronic toxicity of EDDHMA-FeNa (EC number 283-041-9)

A 90-day study with EDDHMA-FeNa, according to the OECD TG 408 is also available (1996). In this study Wistar rats were treated via oral gavage with 20, 100 or 500 mg/kg bw/d. No mortality was reported. Body weights and body weight gain were decreased in males and females and clinical signs were lethargy, hunched posture and piloerection at 500 mg/kg bw/d. Red blood cell count, haemoglobin and haematocrit values of males and females were decreased at 500 mg/kg bw/d and in males at 100 mg/kg bw/d. Cholesterol, creatinine and urea levels were increased at the high dose. Organ weight examination showed increased absolute and relative kidney weights at ≥100 mg/kg bw/d in males and at 500 mg/kg bw/d in females. Degenerative changes in the kidneys, i.e. cortical tubular cell vacuolisation was reported at 500 mg/kg bw/d. Increased creatinine and kidney weight, as well as nephrosis and cortical tubular cell vacuolation point to an adaptive response of kidney. The NOAEL was set to 20 mg/kg bw/d.

In conclusion, the evaluating MSCA notes that the available subchronic and chronic repeated dose toxicity studies with EDDHA-FeNa and EDDHMA-FeNa show that these substances have a similar toxicity profile. Available data consistently show toxicity to the haematopoietic system (primarily anaemia) and kidneys. Altered blood chemistry with increased levels of creatinine and urea support kidney toxicity. Considering the toxicity profile together with the iron-binding properties of the substances, data is indicative of disturbed iron balance as a result of exposure to these substances (Pari et al., 2015; Rishi and Subramaniam, 2017).

7.9.5. Mutagenicity

Not assessed.

7.9.6. Carcinogenicity

Not assessed.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

No reproductive toxicity study is provided in the registration(s) for EDDHA-FeNa. Read-across from EDDHMA-FeNa (source) to EDDHA-FeNa and HBED-FeK is proposed. According to the ECHA dissemination site (April 2021) and communication with the Registrants for the substances EDDHA-FeNa and HBED-FeK OECD TG 422 studies were planned to be performed in 2021 with the aim to provide further information on toxicity and to support the read-across (bridging) between EDDHMA-FeNa, EDDHA-FeNa and HBED-FeK.

A One-generation reproductive toxicity study (OECD TG 415) with EDDHMA-FeNa is available (1996): Wistar rats were treated by oral gavage at 50, 200 and 750 mg/kg bw/d. Treatment started ten weeks prior to mating in males and two weeks prior to mating in females. Mortality was reported in one female in the control group and in one male and four females (of total 28) at 750 mg/kg bw/d. No possible cause for mortality was provided. Parental mean body weight and body weight gain was decreased in males and females at

750 mg/kg bw/d during the treatment period. In males decreased body weight was also observed at 200 mg/kg bw/d. During the lactation period, significantly increased body weights compared to the controls was observed in females. Other signs of general toxicity reported at 750 mg/kg bw/d were lethargy, hunched posture, and piloerection.

Table 14

FERTILITY PARAMETERS				
Dose (mg/kg bw/d)	**0**	**50**	**200**	**750**
Mean precoital time	1.9	2,6	2,3	2,7
Gestation index	95,8	100	100	100
Fertility index	85,7	96,4	92,9	67,9
Conception index	85,7	96,4	92,9	67,9
Gestation index = (number of females with living pups / number of females pregnant) X100 Fertility index = (number of pregnant females / females paired) X100 Conception index = (number of pregnant females / females mated) X100				

Effects were also observed on the parental reproductive parameters. These included increased precoital time at ≥50 mg/kg bw/d and decreased fertility and conception indices at 750 mg/kg bw/d (Table 14). Adverse effects were also observed in the offspring. At the first litter check number of dead pups was higher in the control group, as one dam lost 13 pups. A dose-dependent increase in mortality was reported as increased postnatal loss on PND 0-4 in all treatment groups. The pup viability index showed a dose-dependent decrease. Furthermore, pup mean body weights were decreased from PND 4 in both males and females (Table 15).

Table 15

DEVELOPMENTAL/PUP PARAMETERS				
Dose (mg/kg bw/d)	**0**	**50**	**200**	**750**
Dead pups at first litter check (litters affected)	19 (5)	3 (3)	5 (3)	3 (1)
Live birth index	94,7	99,3	98,8	99,9
Viability index	99,4	94,9**	90,4**	85,4**
Number of litters	24	27	26	19
Number of postnatal loss day 0-4	2	21**	39**	39**
Postnatal loss day 0-4 (litters affected)	0,6 (1)	5,1 (7*)	9,6 (7*)	14,6 (6*)
Mean pup body weight PND 4 (m+f)	10,5	9,8	10,0	9,2#
Mean pup body weight PND 14 (m+f)	38,7	38,1	36,7	33,7##
Mean pup body weight PND 21 (m+f)	61,3	59,9	58,0	54,6##
Live birth index = (number of alive pups on PND 4 / number of pups born alive) X 100 Viability index = (number of alive pups at the first litter check / number of pups born) X 100 Postnatal loss = % of living pups Fishers´s Exact test significant at 5% (*) or 1% (**) T-test pooled variant significant at 5% (#) or 1% (##)				

The evaluating MSCA notes that the study has limitations hampering the interpretation of the data and reaching a conclusion on reproductive toxicity. Higher pup death was observed at the first litter check in the controls, compared to the treated animals. Also,

fertility index was lower in the controls compared to the low- and mid- but not high-dose animals. Further, the study was performed according to the OECD TG 415 and a number of critical parameters such as parental organ weights, oestrous cyclicity, sperm parameters, pup anogenital distance (AGD), nipple retention and sexual maturation were not examined.

7.9.7.1. Publicly available information relevant for reproductive toxicity

It is well-established that maintenance of iron homeostasis is critical for health during all life-stages (Anderson and Frazer, 2017; Pantopoulos et al., 2012). Consistently, iron levels are regulated through multiple elaborate mechanisms at the systemic and cellular level to maintain homeostasis. Insufficient iron supply results in a range of adverse effects, while excess iron can lead to organ dysfunction. In particular, publicly available information on the effects of iron imbalance on reproduction further strengthen the concern for developmental toxicity of these substances. Available data show that Fe homeostasis is crucial for the proper course of pregnancy and has significant impact on the development of the fetus and health of the newborn (Grzeszczak et al., 2020; Killip et al., 2007). Proper concentration of iron during pregnancy reduces the risk of e.g., low pup weight and other postnatal complications. The developmental effects observed in the available one-generation reproductive toxicity study with EDDHMA-FeNa are consistent with these reports.

The evaluating MSCA concludes that the available data is limited on the reproductive toxicity potential of these substances. Adverse effects on reproductive performance and fertility caused by EDDHMA-FeNa were observed. Decreased fertility and conception indices were reported at 750 mg/kg bw/d. Also, developmental effects, primarily an increased post-natal pup mortality and decreased pup growth was observed, starting at the lowest dose tested (50 mg/kg bw/d). Thus, no NOAEL for reproductive toxicity could be established.

7.9.7.2. Developmental neuro- and immunotoxicity

A concern for developmental neuro- and immunotoxicity of the substances is also identified, based on the effects observed in the repeated dose toxicity studies, indicating disruption of Fe homeostasis. Maintenance of iron homeostasis has been shown to be critical and iron imbalance has been shown to be toxic for both development and function of the nervous and the immune system.

The concern for developmental neurotoxicity is based on suspected effects of the substances on iron homeostasis. Publicly available studies show that iron levels and distribution in brain is crucial for maintaining normal physiological functions and that imbalance causes the onset and progression of neurodegenerative disorders. During development disrupted distribution of iron in different brain regions has been shown to induce oxidative stress and thereby impact multiple cellular pathways (Michael and Georgieff, 2008; Salvador et al., 2011).

The concern for developmental immunotoxicity is based on reported changes in the weight of the immune organ (spleen), levels of white blood cells and plasma globulin following repeated exposure to the substances. In addition, iron deficiency has been indicated to prevent the development of T-lymphocytes and to be associated with reduced phagocytic activity. Conversely, excess iron has been shown to promote formation of intracellular free radicals, which can cause oxidative damage in immune cells. Iron levels impact production of key cytokines and can thereby inhibit phagocytic function. Iron overload affects the balance between helper and cytotoxic T-cells and impairs proliferative responses (Aly et al., 2018; Cronin et al., 2019; Cunningham-Rundles et al., 2000).

The evaluating MSCA concludes that the available information is not sufficient to conclude on the potential reproductive toxicity hazard. Further information is needed on possible reproductive toxicity, including neuro- and immunotoxicity effects of these substances.

7.9.7.3. Prenatal development

Prenatal developmental toxicity studies are available for EDDHMA-FeNa and EDDHA-FeNa in the rats.

In a prenatal developmental toxicity (PNDT) study EDDHMA-FeNa was administered to mated female rats by oral gavage at 50, 200 or 1000 mg/kg bw/d (1996). In dams, there were no treatment-related clinical signs or mortality. Body weight gain and food intake was reduced at 1000 mg/kg bw/d. No adverse effects on pregnancy and no embryo-/foetotoxic effects were observed. The NOAEL was 200 mg/kg bw/d for maternal toxicity and 1000 mg/kg bw/d for developmental toxicity. In another PNDT study EDDHA-Fe was administered to Sprague-Dawley rats by oral gavage at 5, 100 or 500 mg/kg bw/d (1995). In dams, there were no treatment-related clinical signs or mortality. The body weight gain and food consumption were reduced at 500 mg/kg bw/d. No adverse effects on pregnancy and no embryotoxic effects were observed. The NOEL was 100 mg/kg bw/d for maternal toxicity and 500 mg/kg bw/d for developmental toxicity and teratogenicity.

The evaluating MSCA notes that EDDHMA-FeNa and EDDHA-FeNa caused no prenatal developmental toxicity or teratogenicity at up to 1000 mg/kg bw/d in the available studies.

7.9.8. Hazard assessment of physico-chemical properties

Not assessed.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

7.9.9.1. Short-term local and systemic DNELs

No short-term DNELs were derived for EDDHA-FeNa (EC number 283-044-5). According to the information in the CSR, EDDHA-FeNa displays low acute toxicity as evidenced by LD_{50}>2000 mg/kg bw for the oral and the dermal route and LC_{50}>4200 mg/m³ for the inhalation route in rats. Therefore, EDDHA-FeNa is not subject to classification for acute toxicity according to Regulation (EC) No 1272/2008 and consequently the derivation of worker DNELs for short-term systemic effects is not required. Further, in the current CSR it is indicated that based on the available data, EDDHA-FeNa is not subject to classification for skin, eye and/or respiratory irritation and skin sensitisation and thus no DNELs for local effects were derived.

In the CSR no short-term DNELs were derived for HBED-FeK (EC number 283-044-5), based on the available data for the similar substances EDDHA-FeNa and EDDHMA-FeNa.

The evaluating MSCA notes that once new data for these substances is available e.g. following CCH, the DNELs for short-term local and systemic effects may need to be revised.

7.9.9.2. Long-term systemic DNELs

For EDDHA-FeNa DNELs for the long-term systemic effects for workers and the general population for the oral and inhalation route were derived based on the NOAEL=10 mg/kg bw/d from an oral subchronic toxicity study. Anaemia was observed at 50 mg/kg bw/d.

For HBED-FeK DNELs for long-term systemic effects were derived from the NOAEL=50mg/kg bw/day from a subchronic oral study with the similar substance EDDHMA-FeNa (1996). According to the information in the CSR, in the available one-generation reproductive toxicity study with EDDHMA-FeNa a parental NOAEL of 50 mg/kg was established. The NOAEL in an oral 4 week study with EDDHMA-Fe (1988) was 200 mg/kg bw. In an oral 4-week study with EDDHMA-FeNa the NOAEL was 20 mg/kg bw/d, based on fatty degenerations of renal tubular epithelial cells reported at 200 mg/kg bw/d.

The evaluating MSCA notes that once new data on reproductive toxicity for these substances is available the DNELs for long-term systemic effects may need to be revised.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

According to the information in the registrations(s) the evaluated Fe-complex substances have no irritating or sensitising properties and are thus not classified for these endpoints.

In the available repeated dose toxicity studies, anaemia and kidney toxicity are the predominant effects. According to the registration(s), there is no other evidence of chronic toxicity or specific target organ toxicity after repeated exposure and thus the substances are not classified (as STOT RE category 1 or 2).

Reproductive/developmental toxicity is observed in the available studies. However, data are currently inconclusive.

Upcoming information from the CCH and/or ongoing studies should be used to determine the need for classification of these substances.

7.10. Assessment of endocrine disrupting (ED) properties

The substances were put on CoRAP also with a concern for potential ED properties for human health. The ED concern was based on (i) the observed adverse effects on reproduction, seen in the available One-generation reproductive toxicity study with the similar substance EDDHMA-FeNa and (ii) suspected ED properties of the constituents in the UVCBs.

7.10.1. Data on the UVCBs

No Quantitative Structure-Activity Relationship (QSAR), *in-vitro* or mechanistic *in-vivo* data on potential ED properties is available in the registration(s) for these UVCBs and/or for their structurally similar substances.

The observed adverse effects on reproduction, i.e. (possible) reduced fertility and increased early post-natal pup mortality can be regarded as ED-sensitive, but not diagnostic effects. The observed effects are from a One-generation reproductive toxicity study with the similar substance EDDHMA-FeNa (1996). In addition to several unreliabilities which hinder concluding on the effects on e.g., fertility (see section 7.9.7) this study lacks analysis of the ED relevant endpoints such as sperm parameters, oestrous cyclicity, AGD, nipple retention and sexual maturation. Therefore, it is not possible to conclude on potential ED properties of these substances based on the study.

Toxicity observed in the available repeated dose subacute and subchronic studies is primarily targeted to the haematopoietic system and kidneys. No adverse effects on the endocrine or reproductive organs were reported in the available 28-day or 90-day studies with EDDHA-FeNa and EDDHMA-FeNa. It should be noted that these studies predated the current test guidelines and thus several relevant parameters, including hormone levels were not examined.

The evaluating MSCA notes that although the Mode-of-Action for toxicity caused by these substances is not clarified, considering the main property of the substances, namely binding iron and the pattern of toxicity they induce, it is likely that the observed reproductive toxicity effects are caused by disruption of the iron homeostasis rather than an endocrine MoA.

7.10.2. Data on the constituents

The constituents with suspected endocrine disrupting properties in these UVCBs are phenol (EC number 203-632-7), formaldehyde (CAS RN 50-00-0) and cresol (p-cresol, EC number

106-44-5). Phenol is present in EDDHA-FeNa at <1% (w/w) and in HBED-FeNa at <0,3% (w/w). Formaldehyde is present in HBED-FeNa at <0,1% (w/w). The indicated concentrations of these constituents in the UVCBs are below the limit for classification for CMR properties.

Phenol, formaldehyde and cresol are included as potential endocrine disruptors in the Endocrine Disruption Exchange list (TEDX) and/or show positive results in *in-vitro* tests for endocrine activity. The TEDX database lists potential endocrine disruptor based on publicly available literature and peer-reviewed research showing effects on endocrine signalling.

A detailed assessment of the potential ED properties of these constituents was out of the scope of the current SEv. Both phenol and p-cresol have been evaluated under SEv. However, ED properties were not investigated under SEv for Phenol. For p-cresol it was concluded under SEv that it does not fulfil the WHO criteria for ED. After a review of the currently available information regarding the ED properties on these suspected ED substances the evaluating MSCA noted that ED properties for these substances are currently not confirmed.

Taken together, the evaluating MSCA notes that limited data is available to conclude on possible endocrine disrupting properties of these UVCB substances. Assessment of the available data did not confirm a concern for endocrine disruption for these substances.

7.11. PBT and VPVB assessment

Not assessed.

7.12. Exposure assessment

Not assessed.

The evaluating MSCA did not assess exposure, due to inconclusive information on the initial hazard concerns.

7.13. Risk characterisation

Not assessed.

7.14. References

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7.15. Abbreviations

AGD	Anogenital distance
CAS	Chemical abstracts service
CCH	Compliance check
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR	Carcinogenic, Mutagenic or Reprotoxic
CoRAP	Community Rolling Action Plan
CSR	Chemical safety report
DIT	Developmental immunotoxicity
DNEL	Derived no effect level
DNT	Developmental neurotoxicity
ECHA	European Chemicals Agency
ED	Endocrine Disruptor
EDDHA	Ethylenediamine-N,N′-bis(2-hydroxyphenyl) acetic acid
EDTA	Ethylenediaminetetra acetic acid
eMSCA	Evaluating Member State Competent Authority
EOGRTS	Extended one-generation reproductive toxicity study
GI	Gastrointestinal
HBED	Hydroxybenzyl ethylene diamine
Kow	n-Octanol/Water Partition Coefficient
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MSC	Member State Committee
MSCA	Member State Competent Authority
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative, Toxic
PNDT	Prenatal developmental toxicity
QSAR	Quantitative structure-activity relationship
RAAF	Read-Across Assessment Framework
RAC	Risk Assessment Committee
RDT	Repeated Dose Toxicity
TEDX	The Endocrine Disruption Exchange
UVCB	Unknown or variable composition, complex reaction products or of biological materials