Assessment of regulatory needs

Authority: European Chemicals Agency (ECHA)

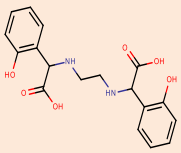
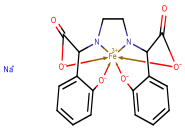
Group Name: 2-hydroxyphenyl- and 2-hydroxybenzyl-glycine derivatives (chelates)

General structure: -

Revision history

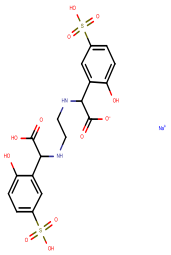
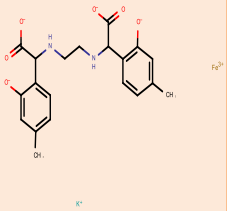
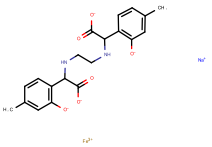
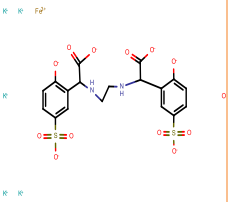
Version	*Date*	*Description*
1.0	2 May 2023	

Substances within this group:

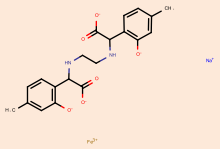
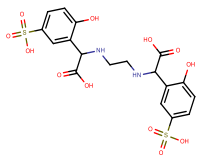
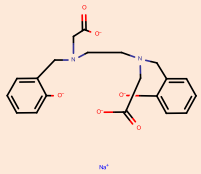
EC/List number	CAS number	Substance name and acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
214-625-3	1170-02-1	Ethylenediamine-N,N'-bis((2-hydroxyphenyl)acetic acid) EDDHA		OSII or TII
240-505-5*	16455-61-1	Sodium [[α,α'-(ethylenediimino)bis[2-hydroxybenzene-1-acetato]](4-)]ferrate(1-) EDDHA-FeNa		Full, not (publicly) available
283-041-9	84539-53-7	Acetic acid, oxo-, sodium salt, reaction products with cresol and ethylenediamine, iron sodium salts EDDHMA-FeNa		Cease manufacture
283-042-4	84539-54-8	Acetic acid, oxo-, sodium salt, reaction products with ethylenediamine and hydroxybenzenesulfonic acid monosodium salt, iron sodium salts EDDHSA-FeNa		Full, 100-1000
283-044-5*	84539-55-9	Acetic acid, oxo-, sodium salt, reaction products with ethylenediamine and phenol, iron sodium salts	Not available	Full, > 1000

[1] Note that the total aggregated tonnage band may be available on ECHA's webpage at https://echa.europa.eu/information-on-chemicals/registered-substances

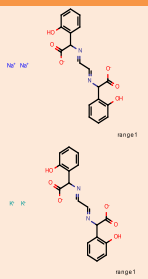
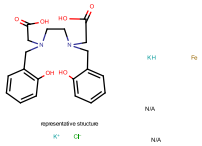
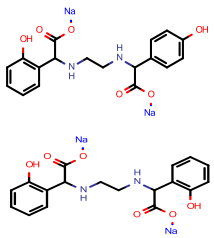
[*] Based on substance identity information included in submission dossiers, in this Group the following are considered duplicate entries: EC 240-505-5 and 283-044-5

EC/List number	CAS number	Substance name and acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
		EDDHA-FeNa		
290-809-7	90247-45-3	Tetrasodium α,α'.-(ethylenediimino)bis[(2-hydroxy-5-sulphonatophenyl)acetate] EDDHSA-Na		OSII or TII
405-420-1	-	No public or meaningful name is available EDDHMA-FeK		NONS
408-180-6**	149057-66-9	Sodium (ethylenediiminobis((2-hydroxy-4-tolyl)acetato))ferrate(1-) EDDHMA-FeNa		NONS
450-300-4	-	No public or meaningful name is available EDDHSA-FeNa	Not available	NONS
462-490-6	-	Acetic acid, oxo-, potassium salt, reaction products with ethylenediamine and para-hydroxybenzenesulfonic acid potassium salt, iron potassium salts EDDHSA-FeK		Full, not (publicly) available

** When a dossier is submitted without EC number, REACH-IT automatically assigns a List number to the dossier. Sometimes, due to IT technical limitations, duplicate List numbers are created. In this group the following are considered duplicate entries: EC 408-180-6 and List nr 604-672-1. In general EC numbers take precedence over List numbers.

EC/List number	CAS number	Substance name and acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
604-672-1**	149057-66-9	Ferrate(1-), [[α,α'-[1,2-ethanediyldi(imino-κN)]bis[2-(hydroxy-κO)-4-methylbenzeneacetato-κO]](4-)]-, sodium EDDHMA-FeNa		Not registered
611-514-5	57368-07-7	Benzeneacetic acid, .alpha.,.alpha.'-(1,2-ethanediyldiimino)bis[2-hydroxy-5-sulfo- EDDHSA		OSII or TII
700-327-5	1061328-86-6	Ferrate(1-), [[N,N'-1,2-ethanediylbis[N-[[2-(hydroxy-.kappa.O)phenyl]methyl]glycinato-.kappa.N,.kappa.O]](4-)]-, sodium (1:1), (OC-6-13)- HBED-FeNa		Full, not (publicly) available
828-479-9	2088841-41-0	Acetic acid, 2-oxo-, reaction products with ethylenediamine, iron chloride (FeCl3) and phenol, potassium salts EDDHA-FeK	Not available	Full, not (publicly) available

** When a dossier is submitted without EC number, REACH-IT automatically assigns a List number to the dossier. Sometimes, due to IT technical limitations, duplicate List numbers are created. In this group the following are considered duplicate entries: EC 408-180-6 and List nr 604-672-1. In general EC numbers take precedence over List numbers.

EC/List number	CAS number	Substance name and acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
928-813-4	1179904-58-5	Acetic acid, 2-oxo-, reaction products with ethylenediamine, phenol, potassium hydroxide and sodium hydroxide EDDHA-NaK		C&L notification
938-828-8	1463474-95-4	Glycine, N,N'-1,2-ethanediylbis-, reaction products with formaldehyde, iron chloride (FeCl3) and phenol, potassium salts HBED-FeKFe		Full, not (publicly) available
941-679-1	-	Reaction mass of disodium [2,2'-(ethane-1,2-diylbis{[2-(hydroxy-kO)benzyl]imino-kN})diacetato-kO(4-)]zinc(2-) and sodium chloride HBED-ZnNa	Not available	Full, not (publicly) available
946-857-2	-	Reaction mass of disodium [(2-{[carboxylato(2-hydroxyphenyl)methyl]amino}ethyl)amino](4-hydroxyphenyl)acetate and disodium 2,2'-(ethane-1,2-diyldiimino)bis[(2-hydroxyphenyl)acetate] EDDHA-Na		OSII or TII
948-113-2	-	isliFe MEAHA-FeNa	Not available	Cease manufacture
951-575-8	-	Acetic acid, oxo-, sodium salt, reaction products with 2-aminoethanol, phenol, and sodium hydroxide	Not available	Cease manufacture

EC/List number	CAS number	Substance name and acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
		MEAHA-Na		
953-735-2	-	Acetic acid, oxo-, sodium salt, reaction products with ethylenediamine and phenol, manganese sodium salts EDDHA-MnNa	Not available	Full, not (publicly) available
953-736-8	-	Acetic acid, oxo-, sodium salt, reaction products with ethylenediamine and phenol, zinc sodium salts EDDHA-ZnNa	Not available	Full, not (publicly) available
954-272-9	-	Condensation products of ethylenediamine, glyoxylic acid and 4-hydroxybenzensulfonic acid, sodium and potassium salts EDDHSA-NaK	Not available	OSII or TII

This table contains also group members that are only notified under the CLP Regulation. However, the list is not necessarily exhaustive. Should further regulatory risk management action on one or more substances in the group be considered, ECHA may make an additional search for related C&L notified substances to be included in the group and develop an assessment of regulatory needs for them.

Contents

DISCLAIMER

The author does not accept any liability with regard to the use that may be made of the information contained in this document. Usage of the information remains under the sole responsibility of the user. Statements made or information contained in the document are without prejudice to any further regulatory work that ECHA, the Member States or other regulatory agencies may initiate at a later stage. Assessment of regulatory needs and their conclusions are compiled on the basis of available information and may change in light of newly available information or further assessment.

Foreword

The purpose of the assessment of regulatory needs of a group of substances is to help authorities conclude on the most appropriate way to address the identified concerns for a group of substances or a single substance, i.e. the combination of the regulatory risk management instruments to be used and any intermediate steps, such as data generation, needed to initiate and introduce these regulatory measures.

An assessment of regulatory needs can conclude that regulatory risk management at EU level is required for a (group of) substance(s) (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. While the assessment is done for a group of substances, the (no) need for regulatory action can be identified for the whole group, a subgroup or for single substance(s).

The assessment of regulatory needs is an important step under ECHA's Integrated Regulatory Strategy. However, it is not part of the formal processes defined in the legislation but aims to support them.

The assessment of regulatory needs can be applied to any group of substances or single substance, i.e., any type of hazards or uses and regardless of the previous regulatory history or lack of such. It can be done based on a different level of information. A Member State or ECHA can carry out this case-by-case analysis. The starting point is available information in the REACH registrations and any other REACH and CLP information. However, a more extensive set of information can be available, e.g. assessment done under REACH/CLP or other EU legislation, or can be generated in some cases (e.g. further hazard information under dossier evaluation). Uncertainties associated to the level of information used should be reflected in the documentation. It will be revisited when necessary. For example, after further information is generated and the hazard has been clarified or when new insights on uses are available. It can be revisited by the same or another authority.

The responsibility for the content of this assessment rests with the authority that developed it. It is possible that other authorities do not have the same view and may develop further assessment of regulatory needs. The assessment of regulatory needs does not yet initiate any regulatory process but any authority can consequently do so and should indicate this by appropriate means, such as the Registry of Intentions.

For more information on Assessment of regulatory needs please consult ECHA website[2].

[2] https://echa.europa.eu/understanding-assessment-regulatory-needs

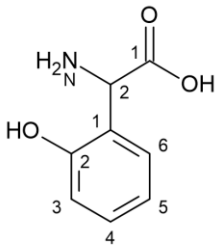
Glossary

ARN	Assessment of Regulatory Needs
CCH	Compliance Check
CLH	Harmonised classification and labelling
CMR	Carcinogenic, mutagenic and/or toxic to reproduction
DEv	Dossier evaluation
ED	Endocrine disruptor
NONS	Notified new substances
OEL	Occupational exposure limit
OSII or TII	On-site isolated intermediate or transported isolated intermediate
PBT/vPvB	Persistent, bioaccumulative and toxic/very persistent and very bioaccumulative
PMT/vPvM	Persistent, mobile and toxic/very persistent and very mobile
RMOA	Regulatory management options analysis
RRM	Regulatory risk management
SEv	Substance evaluation
STOT RE	Specific target organ toxicity, repeated exposure
SVHC	Substance of very high concern

1 Overview of the group

The present group is composed of substances structurally similar to the 2-hydroxyphenyl- and 2-hydroxybenzyl- glycine moieties (cf. the figure below). These structures are able to effectively chelate metal ions. The group consists of 23 substances, out of which 10 have a full registration, 5 are intermediates, 3 are non-updated NONS and 5 aren't registered or have inactive registrations (including 3 substances with ceased manufacturing).

2-(2-hydroxyphenyl)glycine



N-(2-hydroxybenzyl)glycine

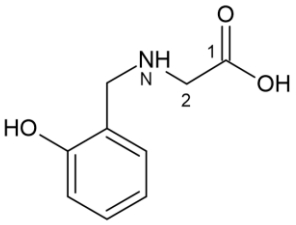
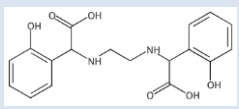
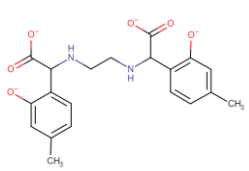


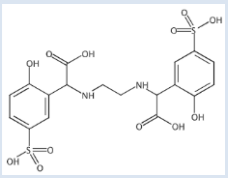
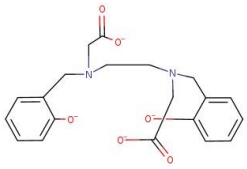
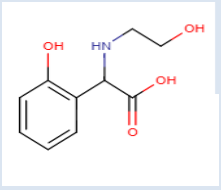
Figure 1: Structures of (2-hydroxyphenyl)- and 2-hydroxybenzyl- glycine.

The group has been divided into the following sub-groups based on the core structure:

- EDDHA: ethylenediamine-N,N'-bis(2-**hydroxypheny**l)acetic acid)
- EDDHMA: (ethylenediamino)bis[(2-hydroxy-4-**methyl**phenyl)acetic acid]
- EDDHSA: (ethylenediimino)bis[(2-hydroxy-5-**sulphonato**phenyl)acetic acid]
- HBED: (ethylenediamino)bis[(2-**hydroxybenzyl**)acetic acid]
- MEAHA: [(2-hydroxyethyl)**amino**](2-hydroxy-phenyl) acetic acid

Table 1: Overview of type of chelates covered in this group

Acronym (group)	EC/List number, substance-specific acronym			
	unchelated	Fe-chelate	Zn-chelate	Mn-chelate
EDDHA 	214-625-3 EDDHA, 928-813-4 EDDHA-NaK, 946-857-2 EDDHA-Na	240-505-5 EDDHA-FeNa, 283-044-5 EDDHA-FeNa, 828-479-9 EDDHA-FeK	953-735-2 EDDHA-MnNa	953-736-8 EDDHA-ZnNa
EDDHMA 	-	405-420-1 EDDHMA-FeK, 408-180-6 EDDHMA-FeNa, 283-041-9 EDDHMA-FeNa, 604-672-1 EDDHMA-FeNa	-	-

Acronym (group)	EC/List number, substance-specific acronym			
	unchelated	Fe-chelate	Zn-chelate	Mn-chelate
EDDHSA 	290-809-7 EDDHSA-Na, 611-514-5 EDDHSA, 954-272-9 EDDHSA-NaK	283-042-4 EDDHSA-FeNa, 462-490-6 EDDHSA-FeK, 450-300-4 EDDHSA-FeNa	-	-
HBED 	-	700-327-5 HBED-FeNa, 938-828-8 HBED-FeK	941-679-1 HBED-ZnNa	-
MEAHA 	951-575-8 MEAHA-Na	948-113-2 MEAHA-FeNa	-	-

The registered substances are in majority identified as UVCB substances. The substances are either unchelated or chelated with iron; few substances are also chelated with zinc or manganese (see

Table 1).

With the exception of MEAHA, the substances are structurally based on ethylenediamine backbone and have two 2-hydroxyphenyl (EDDHA, EDDHMA, EDDHSA) or two 2-hydroxybenzyl (HBED) moieties attached to the glycine-based part of the structure. The group members are widely reported as metal ion chelating agents, in particular for iron Fe^{3+}. Given their structure, they are characterised by hexa-coordination capacity for metal chelation (cf. Fig.2). Complexation of iron ions is well documented and reported with the complex stability constant (K_{stab}) of around 35 for EDDHA, EDDHMA and EDDHSA[3,4]. HBED exhibits higher iron chelation capacity with a K_{stab} of 40. For comparison, EDTA being a well-known chelating agent has a K_{stab} of 25, in relevant conditions. MEAHA is an exception to this group and is expected to have the lowest chelating capacity within the group. Having a structure based on monoamine, it would require two molecules of water to provide hexa-coordination capacity typical for EDTA and members of this group. The

[3] F.Yunta et al.: Chelating Agents Related to Ethylenediamine Bis(2-hydroxyphenyl)acetic Acid (EDDHA): Synthesis, Characterization, and Equilibrium Studies of the Free Ligands and Their Mg2+, Ca2+, Cu2+, and Fe3+ Chelates; Inorg. Chem. 2003, 42, 5412-5421.

[4] P.Nadal et al.: Evaluation of Fe-N,N'-Bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetate (HBED/Fe3+) as Fe carrier for soybean (Glycine max) plants grown in calcareous soil; Plant Soil, 2012.

reported chelating agents form strong complexes with iron which remain stable in aqueous solution and physiologically relevant pH over long periods of time.

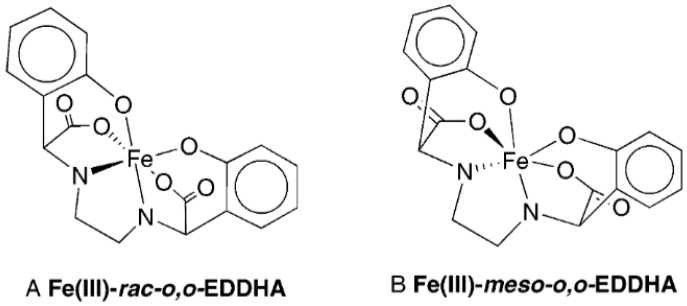


Figure 2: Hexa-coordination capacity of EDDHA for iron chelation (adopted from F.Yunta et al.[5])

Based on information reported in the REACH registration dossiers, the metal chelates are used as fertilisers (soil amendment) by professionals and most also by consumers. The unchelated salts are used as intermediates. For EDDHA-FeK (List 828-479-9) use in biocidal products is indicated, however, the substance is not an approved biocidal substance.

A Substance Evaluation (SEv) conclusion document has been published in 2022 for EDDHA-FeNa (EC 283-044-5) and HBED-FeK (List 938-828-8)[6] that was prepared by the Swedish Member State Competent Authority (SE MSCA). For EDDHMA-FeK (EC 405-420-1)[7] a separate SEv conclusion document was prepared because this is a former notified substance (NONs) for which no further regulatory action (including SEv) can be taken.

[5] F.Yunta et al.: Chelating Agents Related to Ethylenediamine Bis(2-hydroxyphenyl)acetic Acid (EDDHA): Synthesis, Characterization, and Equilibrium Studies of the Free Ligands and Their Mg2+, Ca2+, Cu2+, and Fe3+ Chelates; Inorg. Chem. 2003, 42, 5412-5421.

[6] https://echa.europa.eu/documents/10162/f0a21c19-9f5c-7c96-b902-a73b44e1e0e8

[7] Template_SEV_conclusion_and_report (europa.eu)

Note on the scope of ECHA's assessment of regulatory needs

Regarding hazards, the focus of ECHA's assessment is on CMR (carcinogenic, mutagenic and/or toxic to reproduction), sensitiser, ED (endocrine disruptor), PBT/vPvB or equivalent (e.g. substances being persistent, mobile and toxic), aquatic toxicity hazard endpoints and therefore only those are reflected in the table in section 3. This does not mean that the substances do not have other known or potential hazards. In some specific cases, where ECHA identifies a need for regulatory risk management action at EU level for other hazards (e.g. neurotoxicity, STOT RE), such additional hazards may be addressed in the assessment. An overview of classification is presented in Annex 1.

On the exposure side, ECHA is mainly using the information on uses reported in the registration dossiers (IUCLID) as a proxy for assessing the potential for exposure to humans and releases to the environment. The potential for release / exposure is generally considered high for "widespread" uses, i.e. professional and consumer uses and uses in articles. For these uses, normally happening at many places, the expected level of control is *à priori* considered limited. The chemical safety reports are not necessarily consulted and no quantitative exposure assessment is performed at this stage.

2 Justification for the need for regulatory risk management action at EU level

Based on currently available information, there is a need for (further) EU regulatory risk management – restriction - for reproductive toxicity and PMT/vPvM due to the potential for release/ exposure of **EDDHA-Fe** and **EDDHMA-Fe** salts used as fertilizers.

Environmental hazards

All substances in the group are potentially persistent or very persistent (*P/vP)* and are expected to be mobile or *very mobile in the environment (M/vM)*. The P/vP hazard was identified based on results from ready biodegradability tests available for four of the substances within the group (EDDHA-FeNa, EDDHSA-FeK, Fe(III)HBED-FeNa and HBED-FeKFe). In addition, there is a potential for mobility in the environment based on the high water solubility of the substances and the limited available organic carbon normalized adsorption coefficient (logKoc) data. Data on logKoc are available for three substances (EDDHA-FeNa, Fe(III)HBED-FeNa and HBED-FeKFe) with values ranging from negative to close to zero. A read-across approach amongst the complexed and the empty chelates of the group can be considered plausible for persistency and mobility. Since these substances have high release potential to surface waters, soil and ground water due to their use as *fertiliser*, a number of compliance checks are proposed to clarify the potential persistency and mobility of these substances.

Additionally, all EDDHA-Fe and EDDHMA-Fe salts in the group are also **potentially toxic** (i.e. they may fulfil the 'T' criterion as they may meet the criteria for classification as STOT RE 2 and Repro 1A or 2) in additional to the potential **persistence and mobility properties.** Compliance check and if needed substance

evaluation are proposed to clarify persistency, mobility and toxicity for potential future regulatory action.

Reproductive toxicity and repeated dose toxicity

In the SEV conclusion document for EDDHA-FeNa and HBED-FeK (2022[8]), the evaluating MSCA noted that "*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). […] The developmental effects observed in the available one-generation reproductive toxicity study with EDDHMA-FeNa are consistent with these reports. […] Adverse effects on reproductive performance and fertility caused by EDDHMA-FeNa were observed. Decreased fertility and conception indices were reported.*" The recently submitted OECD 422 study (2022) with extended premating period (with total 13 weeks exposure) performed with EDDHA-FeNa and EDDHMA-FeNa (testing at the high dose only) confirms the concern for effects on parturition and for anaemia for both substances.

It is suggested to await the results of an extended one-generation reproductive toxicity study that is being requested with EDDHA-FeNa (EC 283-044-5) to have a solid basis for a harmonised classification with regards to reproductive toxicity.

The mode of action for the observed reproductive effects and anaemia (disturbance of iron homeostasis by EDDHA-Fe and EDDHMA-Fe salts) seems to be different compared to the mode of action for EDTA (zinc depletion).

Based on ECHA's assessment, the hazards – repeated dose toxicity, reproductive toxicity – identified based on data for EDDHA-FeNa and EDDHMA-FeNa are extrapolated only to other salts of the same metal chelate (e.g., extrapolation from EDDHA-FeNa to EDDHA-FeK). This extrapolation was also considered plausible by the evaluating MSCA in SEv. In contrast, the limited data provided for EDDHSA-Fe indicate the absence of such effects. No effects were seen in a 28-day study with EDDHSA-Fe (NOAEL 1000 mg/kg bw/d) whereas a 28-day study with EDDHA-Fe has a NOAEL of 10 mg/kg bw/d based on anaemia at the next dose level. Further data generation is intended to confirm the absence of such effects for EDDHSA-Fe.

The limited data available for the whole group does not allow to conclude on the ED hazard for human health.

Harmonised classification and labelling

None of the EDDHA-Fe and EDDHMA-Fe salts have a self- or a harmonised classification for Repro 1B or 2 or STOT RE 2. The first step of the regulatory risk management action proposed, should the hazard exist, is the confirmation of hazard via harmonised classification (CLH) as STOT RE 2 and Repro 1B or 2.

CLH Repro 1B i) will require company level risk management measures (RMM) under the OSH legislation for workers, to be in place, ii) is needed or highly recommended for further regulatory processes under REACH and iii) is a prerequisite to restrict the presence of the substances in consumer mixtures, by means of the restriction entry 30.

[8] https://echa.europa.eu/documents/10162/f0a21c19-9f5c-7c96-b902-a73b44e1e0e8

CLH will also support regulatory action under other regulations. For instance, in this specific case:

- harmonised classification as CMR cat. 1 will trigger regulatory action under the biocidal product regulation (EU) 528/2012, which does not allow the use by the general public of a product containing substances above the concentration limit leading to classification of the mixture as CMR cat 1.

CLH Repro 2 i) will require company level risk management measures (RMM) under the OSH legislation for workers to be in place, ii) require that the necessary safety measures are in place for specific sensitive workers, i.e. pregnant women in accordance with Directive 92/85/EEC and young people in accordance with Directive 94/33/EC.

SVHC identification

All substances identified in the current group are potentially persistent and mobile in the environment and EDDHA-Fe and EDDHMA-Fe salts most likely be identified as toxic (STOT RE 2 and/or Repro 1B or 2). Substances from several subgroups (EDDHA, EDDHSA, HBED) are registered at the higher tonnage bands, with high release potential to surface waters, soil and ground water, expected. Due to the use as fertiliser, compliance check is proposed to clarify the potential persistency and mobility of the substances.

Should the hazard for EDDHA-Fe and EDDHMA-Fe be confirmed by CLH for STOT RE 2 and/or Repro 1B or 2, SVHC identification[9] and possible inclusion on the Candidate List as PMT could be proposed for EDDHA-Fe and EDDHMA-Fe.

SVHC identification is highly recommended as a step prior to restriction. In addition, SVHC identification brings immediate obligations for suppliers of the substances such as (i) supplying a safety data sheet and communicating on the safe use of the substances and (ii) responding to consumer requests within 45 days.

Restriction

The following professional and consumer uses – fertiliser (soil amendment) – are expected to be widespread (at many sites and by many users). Professional use of fertilisers (in e.g. agriculture, horticulture) is widespread with relatively low levels of operational controls and risk management measures. Releases to the environment are direct and exposures of workers may be frequent and with a long duration. In addition, professional users may be self-employed and therefore not covered by occupational safety and health (OSH) legislation. For consumer uses there are no effective operational controls and risk management measures.

Regulation (EU) 2019/1009 of the European Parliament and of the Council of 5 June 2019 laying down rules on the making available on the market of EU fertilising products and amending Regulations (EC) No 1069/2009 and (EC) No 1107/2009

[9] Note that the Commission published the proposal for introducing new hazard classes in CLP (PBT/vPvB, PMT/vPvM, ED): CLP Delegated Act (europa.eu). Therefore, if/when these hazard classes will be implemented in CLP, instead of SVHC identification under REACH, these hazards may be confirmed under the CLP.

and repealing Regulation (EC) No 2003/2003. The regulation will apply in full from 16 July 2022.[10]

The fertilisers regulation (EU 2019/1009) does not seem to be sufficient to address the hazards of its constituent substances. The regulation does not contain a specific clause that would prevent the use of Repro Tox or vPvM/PMT substances in fertilisers and it states that the safety of its constituent substances for use in fertilisers should be established through REACH registration.

Therefore, a **restriction of the substance as such or in mixtures (concentration limit in mixtures) used by professionals and consumers** could be suggested after CLH in case a risk for professionals could be demonstrated.

Restriction of professional uses is usually preferred over authorisation as it is considered to be more efficient and effective to introduce controls at the level of placing on the market rather than at the level of uses.

In addition, the use of the most harmful substances by professional workers has been recognised as an area of concern under the European Commission's Chemicals Strategy for Sustainability[11] which aims to extend to professional users under REACH the level of protection granted to consumers.

Based on currently available information, it is not possible to assess the need for regulatory risk management; even if there is a potential for vPvM, the information on hazard is not sufficient to conclude on reproductive toxicity, STOT RE hazards for EDDHA-Mn and EDDHA-Zn sodium salts.

These two substances are potentially vPvM and they are substances with high release potential to surface waters, soil and ground water due to the use as fertiliser. However, since these substances are low tonnage, simulation studies cannot be requested under compliance check. Compliance check is proposed for the EDDHA-Zn and this will clarify also the mobility potential of the substance. However, for the time being no EU regulatory risk management is proposed for these substances until confirmation of the hazard properties which should help identifying what the main protection goals are for these specific substances.

It is not possible to assess the needs for regulatory risk management for EDDHA-MnNa (List 953-735-2) and EDDHA-ZnNa (List 953-736-8) as information on hazard is not sufficient to conclude on reproductive and STOT RE hazards. The needs for regulatory risk management actions will be assessed once generation of data is completed (CCH).

Based on currently available information, there is no need for (further) EU regulatory risk management for EDDHA, EDDHA-salts, EDDHSA, EDDHSA salts and EDDHSA-Fe salts and HBED-Fe and HBED-Zn salts and MEAHA and MEAHA-Fe salts.

It is not possible to clarify the potential hazards of those substances due to the **use as intermediates or because they are not registered** [EDDHA (EC 214-625-3); EDDHA-NaK (List 928-813-4), EDDHA-Na (List 946-857-2); EDDHSA-Na (EC 290-809-7), EDDHSA (List 611-514-5), EDDHSA-NaK (List 954-272-9)] or

[10] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R1009&from=EN

[11] European Commission, *Chemical Strategy for Sustainability Towards a Toxic-Free Environment*, available at https://ec.europa.eu/environment/pdf/chemicals/2020/10/Strategy.pdf

due to **cease of manufacture** [(MEAHA-Na (List 951-575-8) and MEAHA-FeNa (948-113-2)]. Therefore, no EU regulatory risk management action is currently proposed for any of the aforementioned substances due to low exposure potential. It is worth noting however that the strategy may need to be revisited and need for further regulatory action reconsidered if there is a change in the registration status or reported uses for any of these substances.

Based on ECHA's assessment of currently available hazard information, **no potential hazards were identified for human health** for EDDHSA-FeK (EC 462-490-6). This conclusion is based on a sub-acute toxicity study with EDDHSA-FeK indicating no toxicity up to 1 000 mg/kg bw/day (see also above). Therefore, it is proposed that there is currently no need for EU RRM action on this substance. Following data generation, potentially follow up actions will be re-considered when the assessment will be revisited.

Based on ECHA's assessment of currently available hazard information, a potential hazard was identified for human health. The available information indicates **potential for skin sensitisation** due to findings in skin sensitisation tests (OECD 406) with HBED-FeNa (List 700-327-5) and HBED-ZnNa (List 941-679-1). For those substances self-classification is applied. This hazard is extrapolated to HBED-FeK (List 938-828-8), that does not have a self-classification, but for which data generation was already requested. No further extrapolation is performed to other groups of substances because such data were negative or evaluated in a weight of evidence as negative with the exception of a specific registration for a EDDHA-FeNa salt that is classified due to an impurity (ethylenediamine > 0.2 %).

For industrial and professional uses, sufficient and consistent self-classification by registrants for skin sensitisation should require adequate risk management measures to be in place according to workplace legislation.

Adequate product labelling should in principle provide consumers with sufficient information to manage risks arising from the use of mixtures containing substance HBED-Fe or HBED-Zn.

However, there is a concern related to skin sensitisers (potentially) present in consumer mixtures and the need to further investigate whether further regulatory actions are needed and what would be the best options to address this concern.

Such concern has already been identified in other groups of substances and was brought for further discussion to Member States. Work is ongoing on this generic issue by both Member States and ECHA which may affect the regulatory actions on substances in this group.

Therefore, it is proposed that there is currently no need for EU-wide regulatory risk management.

Based on ECHA's assessment, the hazard – chronic **aquatic toxicity** – is identified for metal chelates containing zinc, i.e., EDDHA-ZnNa and HBED-ZnNa and is expected for un-chelated substances (e.g., EDDHSA,). Chelates of Fe- and Mn-, and are not likely to be toxic to the aquatic environment; the metal ion for this chelates are intrinsically not toxic for the aquatic environment.

EDDHA-ZnNa and HBED-ZnNa are already self-classified for aquatic toxicity and necessary RMMs should be implemented to ensure safe use. The un-chelated substances are either not registered or used as intermediates. Therefore, it is proposed that there is currently no need for EU-wide regulatory risk management.

3 Conclusions and actions

The conclusions and actions proposed in the table below are based on the REACH and CLP information available at the time of the assessment by ECHA. The main source of information is the registration dossiers. Relevant public assessments may also be considered. When new information (e.g. on hazards through evaluation processes, or on uses) will become available, the document will be updated and conclusions and actions revisited.

Subgroup name, EC/List number, acronym	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
EDDHA and EDDHMA 240-505-5 EDDHA-FeNa 283-044-5 EDDHA-FeNa 828-479-9 EDDHA-FeK	Known or potential hazard for STOT RE for reproductive toxicity	Known or potential hazard for PMT/vPvM	Use as fertiliser by professionals and consumers	**Need for EU RRM: Restriction** <u>Justification:</u> The harmonised classification as Repro 1B would trigger the restriction entry 30 and by that ensure that the substances are not included in consumer mixtures above the limits specified in that entry. The reported professional uses are widespread (at many sites and many users) with relatively low levels of operational controls and risk management measures but with often frequent exposures with a long duration. Restriction of professional uses is preferred over authorisation as it is considered to be more efficient and effective to introduce controls at the level of placing on the market rather than at the level of uses.	**First step:** CCH EC 240-505-5 EC 828-479-9 **Next steps (if hazard confirmed):** CLH SVHC identification Restriction
405-420-1 EDDHMA-FeK 408-180-6 EDDHMA-FeNa			Uses not reported (NONs)		
283-041-9 EDDHMA-Fe 604-672-1 EDDHMA-FeNa			No relevant uses (cease of manufacture EC 283-041-9; not registered EC 604-672-1)		

Subgroup name, EC/List number, acronym	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
				SVHC might be required for PMT substances used as fertiliser	
953-735-2 EDDHA-MnNa 953-736-8 EDDHA-ZnNa	Inconclusive hazard for STOT RE for reproductive toxicity	Known or potential hazard for • vPvM • Aquatic toxicity (List 953-736-8)	Use as fertiliser by professionals	**Currently not possible to assess the regulatory needs** Justification: The need for EU RRM will be assessed if the results from data generation confirm the PMT properties.	**First step:** CCH EC 953-735-2 EC 953-736-8 **Next steps (if hazard confirmed):** No action
214-625-3 EDDHA 928-813-4 EDDHA-NaK 946-857-2 EDDHA-Na	Inconclusive hazard for STOT RE for reproductive toxicity		Only TII/OSII use.	**Currently no need for EU RRM** <u>Justification:</u> Low potential for release is expected. Actions may be re-considered when the assessment will be revisited.	**First step:** No action **Next steps (if hazard confirmed):** No action
EDDHSA 283-042-4 EDDHSA-FeNa 462-490-6 EDDHSA-FeK	No hazard or unlikely hazard	Known or potential hazard for vPvM	Use as fertiliser by professionals and consumers	**Currently no need for EU RRM** <u>Justification:</u> The available data indicate no relevant effects that would require classification for HH	**First step:** CCH EC 462-490-6 **Next steps (if hazard confirmed):** No action
450-300-4 EDDHSA-FeNa			uses not reported (NONs)		
290-809-7 EDDHSA-Na 611-514-5 EDDHSA 954-272-9 EDDHSA-NaK		Known or potential hazard for: • vPvM • aquatic toxicity	Only TII/OSII use		
HBED	Known or potential hazard	Known or potential hazard for vPvM	Use as fertiliser by professionals and consumers	**Currently no need for EU RRM** <u>Justification:</u>	**First step:** CCH EC 938-828-8

Subgroup name, EC/List number, acronym	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
700-327-5 HBED-FeNa 938-828-8 HBED-FeK	for skin sensitisation			Appropriate self-classification should be sufficient to ensure safe use	**Next steps (if hazard confirmed):** No action
941-679-1 HBED-ZnNa		Known or potential hazard for: • vPvM • aquatic toxicity			
MEAHA 948-113-2 MEAHA-FeNa 951-575-8 MEAHA-Na	Inconclusive hazard for STOT RE for reproductive toxicity	Known or potential hazard for: • vPvM • aquatic toxicity (List 951-575-8)	Currently no relevant uses (cease manufacture)	**Currently no need for EU RRM** Justification: Currently no relevant uses	**First step:** No action **Next steps (if hazard confirmed):** No action

Annex 1: Overview of classifications

Data extracted on 8 December 2022

EC/ List No	CAS No	Acronym	Harmonised classification	Classification in registrations	Classification in C&L notifications (*)
214-625-3	1170-02-1	**EDDHA**	-	-	-
240-505-5	16455-61-1	EDDHA-FeNa	-	-	STOT Single Exp. 3 H335 [3 out of 12] Skin Irrit. 2 H315 [3 out of 12] Eye Irrit. 2 H319 [3 out of 12] Acute Tox. 4 H302 [3 out of 12]
283-044-5	84539-55-9	EDDHA-FeNa	-	- (with impurity ethylenediamine < 0.2%) Skin Sens. 1B H317 (with impurity ethylenediamine > 0.2%)	Skin Sens. 1 H317 [3 out of 9]
828-479-9	2088841-41-0	EDDHA-FeK	-	-	-
928-813-4	-	EDDHA-NaK	-	-	-
946-857-2	-	EDDHA-Na	-	-	-
953-735-2	-	EDDHA-MnNa	-	Eye Damage 1 H318	-
953-736-8	-	EDDHA-ZnNa	-	Skin Irrit. 2 H315 Eye Damage 1 H318 Aquatic Chronic 3 H412	-
283-041-9	84539-53-7	**EDDHMA**-Fe	-	-	-

EC/ List No	CAS No	Acronym	Harmonised classification	Classification in registrations	Classification in C&L notifications (*)
283-042-4	84539-54-8	**EDDHSA**-FeNa	-	-	Eye Irrit. 2 H319 [1 out of 1] Aquatic Chronic 3 H412 [1 out of 1]
290-809-7	90247-45-3	EDDHSA-Na	-	-	Eye Irrit. 2 H319 [1 out of 5] Aquatic Chronic 3 H412 [1 out of 5]
462-490-6	-	EDDHSA-FeK	-	-	-
611-514-5	57368-07-7	EDDHSA	-	Eye Damage 1 H318 [intermediate (active)] Skin Irrit. 2 H315 [intermediate (active)]	-
954-272-9	-	EDDHSA-NaK	-	-	-
700-327-5	1061328-86-6	HBED-FeNa	-	Skin Sens. 1 H317	-
938-828-8	-	HBED-FeK	-	-	-
941-679-1	-	HBED-ZnNa	-	Eye Irrit. 2 H319 Skin Sens. 1B H317 Aquatic Chronic 3 H412	-
948-113-2	-	MEAHA-FeNa	-	Eye Irrit. 2 H319 [Article 10 (inactive)]	-
951-575-8	-	MEAHA-Na	-	-	-

(*) the number in brackets indicates the number of notifications received. Each notification can represent a group of notifiers, therefore the number may differ from the C&L inventory which displays number of notifiers.

Annex 2: Overview of uses based on information available in registration dossiers

Data extracted on 8 December 2022

Main types of applications structured by product or article types	214-625-3	240-505-5	283-041-9	283-042-4	283-044-5	290-809-7	462-490-6	611-514-5	700-327-5	828-479-9	938-828-8	941-679-1	946-857-2	948-113-2	951-575-8	953-735-2	953-736-8	954-272-9
PC 12: Fertilisers	I,	F, P, C,	F, P, C,	F, P, C,	F, P, C,		F, P, C,		F, P, C,	F, P, C,	F, P, C,	F, P,		F, I, P,	I,	F, P,	F, P,	
PC 8: Biocidal products										F, P,								
PC 9a: Coatings and paints, thinners, paint removers																F[1)]	F[1)]	
PC 21: Laboratory chemicals			F, P,							F, P,								
PC 19: Intermediate	I,							I,		F, P,			I,		I,			F, I,

F: formulation, I: industrial use, P: professional use, C: consumer use, A: article service life; P, C and A are highlighted in red to indicate widespread use with potential for exposure/release

[1)] There is uncertainty about the indicated uses of List numbers 953-735-2 and 953-736-8 for formulation for PC 9a; registrants to clarify

Annex 3: Overview of completed or ongoing regulatory risk management activities

There are no relevant completed or ongoing regulatory risk management activities for any of the substances.