Assessment of regulatory needs

Authority: European Chemicals Agency (ECHA)

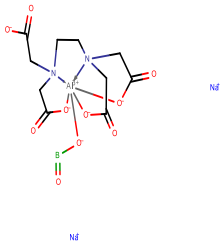
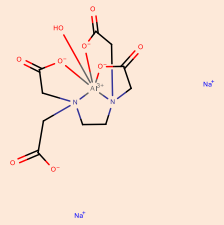
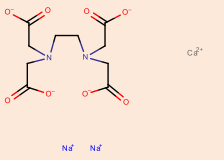
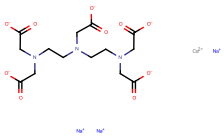
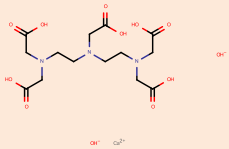
Group Name: (Hydroxy)carboxylic acid amine chelates

General structure: See table 1 on p. 16.

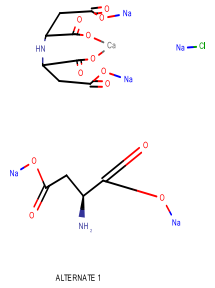
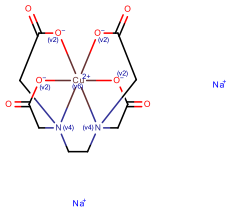
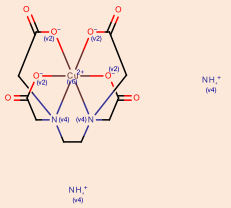
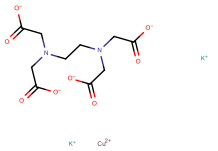
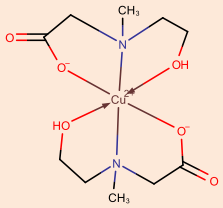
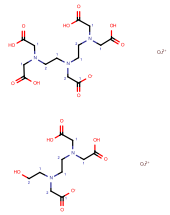
Revision history

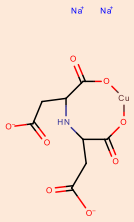
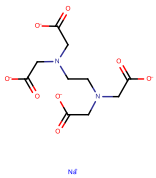
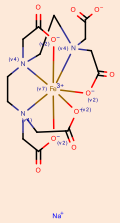
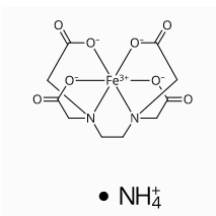
Version	*Date*	*Description*
1.0	27 March 2023	

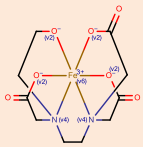
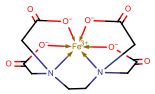
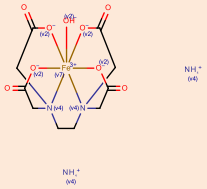
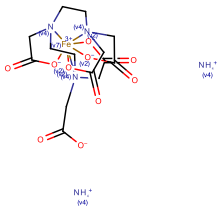
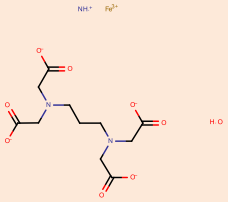
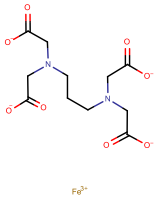
Substances within this group:

EC/List number	CAS number	Substance name; acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
Al-chelates				
934-405-7		Aluminate(2-),[[N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON] (oxidoborate-μ-oxido)(-1),disodium; **EDTA-AlBNa2**		Full Not (publicly) available
934-407-8		Aluminate(2),[[N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON]hydroxy-,disodium; **EDTA-AlNa2**		Full Not (publicly) available
Ca-chelates				
200-529-9	62-33-9	sodium calcium edetate; **EDTA-CaNa2**		Full 100-1000
235-169-1	12111-24-9	Calcium trisodium pentetate; **DTPA-CaNa3**		Not registered
902-532-7		Reaction mass of N-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid) and calcium dihydroxide; **DTPA-Ca2**		Full Not (publicly) available

[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

EC/List number	CAS number	Substance name; acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
944-341-1		Reaction mass of disodium [2,2'-(imino-?N)dibutanedioato-?2O1,O4(4-)]calcium(2-), sodium chloride and disodium L-aspartate; **IDHA-Ca**		Full Not (publicly) available
Cu-chelates				
237-864-5 (686-516-2)	14025-15-1	disodium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']cuprate(2-); **EDTA-CuNa2**		Full 100-1000 (C&L notification)
268-018-3	67989-88-2	diammonium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']cuprate(2-); **EDTA-Cu(NH4)2**		Full 100-1000
277-749-7	74181-84-3	dipotassium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']cuprate(2-); **EDTA-CuK2**		Full Not (publicly) available
300-491-4	93940-93-3	bis[N-(2-hydroxyethyl)-N-methylglycinato-N,O,ON]copper		Full Not (publicly) available
915-008-8		Reaction mass of [N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]cuprate(3-) and diammonium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']cuprate(2-) and dipotassium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-		Full Not (publicly) available

EC/List number	CAS number	Substance name; acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
		)-N,N',O,O',ON,ON']cuprate(2-) and sodium [N-[2-[bis(carboxymethyl)amino]ethyl]-N-(hydroxymethyl)glycinato(3-)]cuprate(1-); **DTPA-Cu, HEDTA-Cu**		
938-868-6		disodium [2,2'-(imino-κN)disuccinato-κ2O1,O4(4-)]cuprate(2-) **IDHA-CuNa2**		Full Not (publicly) available
Fe-chelates				
235-627-0	12389-75-2	sodium hydrogen [N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]ferrate(2-); **DTPA-FeNa**		Full 100-1000
239-802-2 (803-202-4, 927-442-5)	15708-41-5	sodium feredetate; **EDTA-FeNa2**		Full >1000
243-136-8	19529-38-5	disodium [N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]ferrate(2-); **DTPA-FeNa2**		Full 100-1000
244-302-2	21265-50-9	ammonium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']ferrate(1-); **EDEDTA-Fe(NH4)**		C&L notifications

EC/List number	CAS number	Substance name; acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
257-036-7	51181-50-1	sodium [N-[2-[bis(carboxymethyl)amino]ethyl]-N-(2-hydroxyethyl)glycinato(4-)]ferrate(1-); **HEDTA-FeNa**		Full 100-1000
259-411-0	54959-35-2	potassium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']ferrate(1-)' **ETDA-FeK**		Full Not (publicly) available
270-232-7	68413-60-5	diammonium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']hydroxyferrate(2-); **EDTA-Fe(NH4)2(OH)**		Full >1000
289-064-0	85959-68-8	diammonium [N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]ferrate(2-); **DTPA-Fe(NH4)2**		Full >1000
400-660-3	-	ammonium iron(III) trimethylenediaminetetraacetate hemihydrate; Ammonium-Iron-PDTA; **PDTA-FeNH4**		NONS
405-680-6	148434-01-9	potassium iron(III) 1,3-propanediamine-N,N,N',N'-tetraacetate hemihydrate; **PDTA-FeK**		NONS

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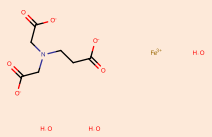
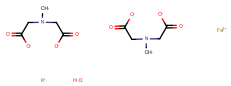
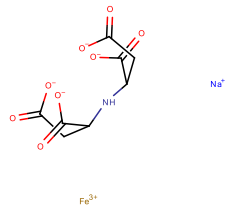
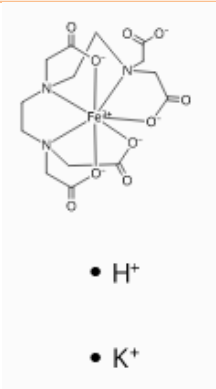
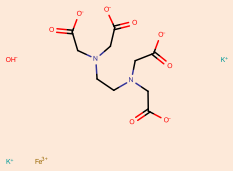
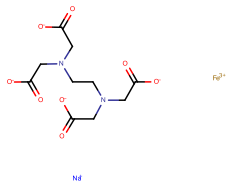
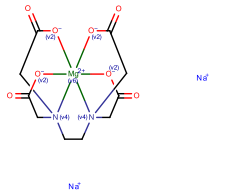
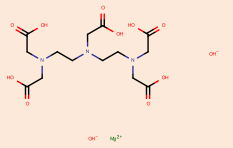
406-173-2	-	iron(III) N,N-bis(carboxymethyl)-beta-alaninate trihydrate		NONS
411-640-9	153352-59-1	potassium bis(N-carboxymethyl)-N-methyl-glycinato-(2-)N,O,O,N)-ferrate-(1-) monohydrate		NONS Ceased manufacture
422-080-1	-	NX-12	Not (publicly) available	NONS
433-620-9	-	NX-15	Not (publicly) available	NONS Ceased Manufacture
438-890-1	-	RC-0018	Not (publicly) available	NONS
476-670-7	-	Reaction mass of iron chelate of sodium salt N-[1,2 dicarboxyethyl] D,L aspartic acid and sodium chloride; **IDHA-FeNa**		Full Not (publicly) available
803-202-4 (239-802-2)	18154-32-0 (15708-41-5)	Not (publicly) available	Not (publicly) available	C&L notification
813-880-3	2055396-18-2	potassium [N-(2-{bis[(carboxy-κO)methyl]amino-κN}ethyl)-N-(2-{(carboxymethyl)[(carboxy-κO)methyl]amino-κN}ethyl)glycinato(4-)-κN]ferrate(1-); **DTPA-FeK**		Full Not (publicly) available

EC/List number	CAS number	Substance name; acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
824-774-1	148124-40-7	Dipotassium [2,2',2'',2'''-(ethane-1,2-diyldinitrilo-k2N,N')tetra(acetato-kO)]hydroxidoferrate(2-); **EDTA-FeK2**		Full Not (publicly) available
927-442-5 (239-802-2)	15651-72-6	Ethylendiaminetetraacetic acid ferrous sodium; **EDTA-FeNa2**		Full Not (publicly) available
Mg-chelates				
238-372-3	14402-88-1	disodium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']magnesate(2-); **EDTA-MgNa2**		Full 100-1000
902-533-2		Reaction mass of ammonium;potassium;sodium;2-[2-[bis(carboxymethyl)amino]ethyl-(carboxymethyl)amino]acetate;magnesium, ammonium;potassium;sodium;2-[bis[2-[bis(carboxymethyl)amino]ethyl]amino]acetate;magnesium and ammonium;potassium;sodium;2-[2-[bis(carboxymethyl)amino]ethyl-(2-hydroxyethyl)amino]acetate; magnesium; **DTPA-Mg, EDTA-Mg, HEDTA-Mg**		Full Not (publicly) available

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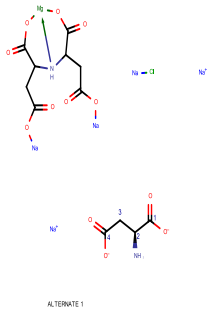
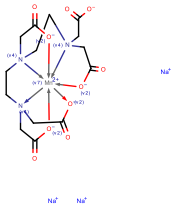
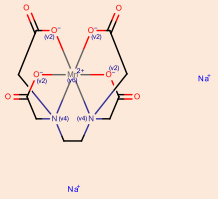
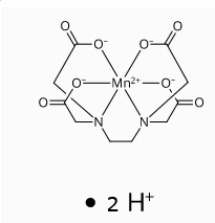
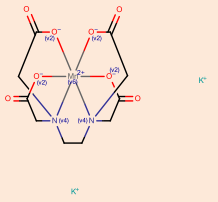
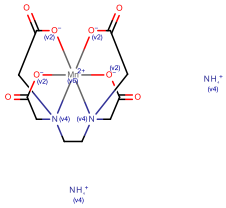
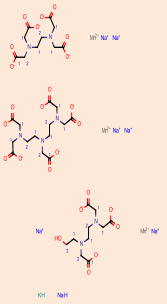
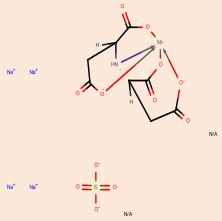
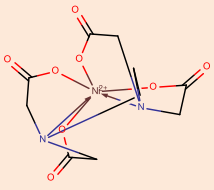
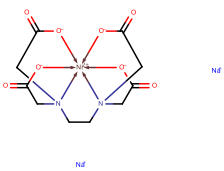
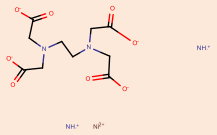
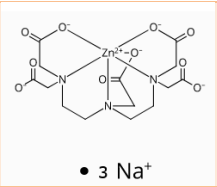
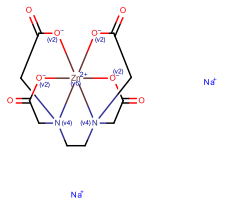
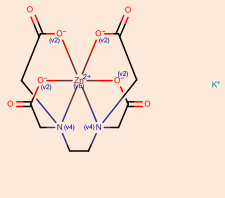
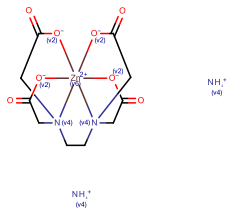
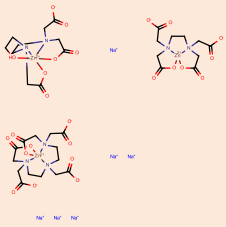
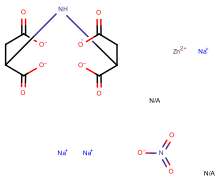
946-985-9		Reaction mass of disodium [2,2'-(imino-kN)dibutanedioato-k2O1,O4(4-)]magnesium(2-), sodium chloride and disodium L-aspartate; **IDHA-MgNa**		Full Not (publicly) available
Mn-chelates				
234-282-3	11065-74-0	trisodium [N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]manganate(3-); **DTPA-MnNa3**		Full Not (publicly) available
239-407-5	15375-84-5	disodium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']manganate(2-); **EDTA-MnNa2**		Full >1000
259-645-3	55448-20-9	dihydrogen [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']manganate(2-); **ETDA-Mn**		Not registered
268-144-9	68015-77-0	dipotassium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']manganate(2-); **EDTA-MnK2**		Full 100-1000
304-037-6	94233-07-5	diammonium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']manganate(2-) **EDTA-Mn(NH4)2**		Full Not (publicly) available

EC/List number	CAS number	Substance name; acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
915-009-3		Reaction mass of diammonium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']manganate(2-) and dipotassium [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']manganate(2-) and sodium [N-[2-[bis(carboxymethyl)amino]ethyl]-N-(2-hydroxyethyl)glycinato(3-)]manganate(1-) and trisodium [N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]manganate(3-); **DTPA-Mn, EDTA-Mn, HEDTA-Mn**		Full Not (publicly) available
924-348-6	-	Manganese DTPA chelate; **DTPA-Mn**	Not (publicly) available	Not registered
939-867-3		Reaction mass of disodium [2,2'-(imino-kappaN)dibutanedioato-kappa2O1,O4]manganate(2-) and sodium sulphate; **IDHA-Mn**		Full Not (publicly) available
Ni-chelates				
247-019-2	25481-21-4	dihydrogen [[N,N'-ethylenebis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']nickelate(2-); **EDTA-Ni**		Full Not (publicly) available
692-065-2	15708-55-1	Disodium {2,2',2'',2'''-[ethane-1,2-diyldi(nitrilo-kN)]tetra(acetato-kO)(4-)}nickelate(2-); **ETDA-NiNa2**		Full Not (publicly) available

EC/List number	CAS number	Substance name; acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
947-740-9		Nickel(2+) diammonium 2,2',2'',2'''-(ethane-1,2-dinitrilo)tetraacetate; **EDTA-Ni(NH4)2**		Full Not (publicly) available
Zn-chelates				
234-305-7	11082-38-5	trisodium [N,N-bis[2-[bis(carboxylatomethyl)amino]ethyl]glycinato(5-)]zincate(3-); **DTPA-ZnNa3**		C&L notifications
237-865-0	14025-21-9	disodium [[N,N'-ethylenediylbis[N-(carboxylatomethyl)glycinato]](4-)-N,N',O,O',ON,ON']zincate(2-); **EDTA-ZnNa2**		Full >1000
238-729-3	14689-29-3	dipotassium [[N,N'-ethylenebis[N-(carboxylatomethyl)glycinato]](4-)-N,N',O,O',ON,ON']zincate(2-); **EDTA-ZnK2**		Full 100-1000
267-400-7	67859-51-2	diammonium [[N,N'-ethylenebis[N-(carboxylatomethyl)glycinato]](4-)-N,N',O,O',ON,ON']zincate(2-); **EDTA-Zn(NH4)2**		Full 100-1000
275-554-1	71501-24-1	sodium [N-[2-[bis(carboxylatomethyl)amino]ethyl]-N-(2-hydroxyethyl)glycinato(3-)]zincate(1-); **DTPA-Zn, EDTA-Zn, HEDTA-Zn**		Full Not (publicly) available

EC/List number	CAS number	Substance name; acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
700-366-8		Reaction mass of disodium [2,2'-(imino-κN)dibutanedioato-κ2O1,O4(4-)]zincate(2-) and sodium nitrate		Not registered
931-053-6		Not (publicly) available	Not (publicly) available	Full Not (publicly) available

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

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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

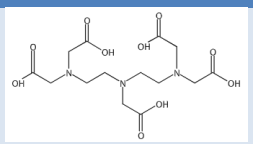
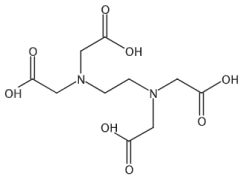
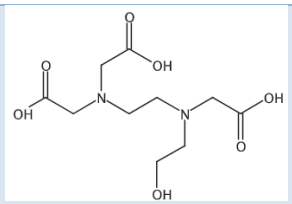
ARN	Assessment of Regulatory Needs
CCH	Compliance Check
CLH	Harmonised classification and labelling
CMR	Carcinogenic, mutagenic and/or toxic to reproduction
Dev	Dossier evaluation
ED	Endocrine disruptor
NONS	Notified new substances
OEL	Occupational exposure limit
OSII or TII	On-site isolated intermediate or transported isolated intermediate
PBT/vPvB	Persistent, bioaccumulative and toxic/very persistent and very bioaccumulative
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

ECHA has grouped together structurally similar substances based on the presence of polycarboxylic acid monoamines, hydroxy derivatives and their salts with multivalent cations.

The present group is composed of substances with structural relation to ethylenediaminetetraacetic acid (EDTA), a well-known chelating agent. In Table 1 the most frequently observed chemical structures of EDTA-like ligands covered by this group with full registrations are presented in the form of their acids. EDTA-like substances as their acids or ammonium, sodium or potassium salts ('empty' chelates) are addressed in the ARN report 'EDTA-related acids and salts'. The current group assessment covers EDTA-like substances that are complexed with metal ions such as iron (Fe), calcium (Ca), magnesium (Mg), copper (Cu), manganese (Mn) or zinc (Zn), and a few with aluminium (Al), boron (B) or nickel (Ni). The metal complexing of EDTA leading to an EDTA metal complex is shown in Figure 1.

Table 1: Most frequent ligand types of chelates with full registrations and their chemical structure (presented in the form of their acid) covered by this group

Acronym	Chemical name of the acid used as basis for the acronym	Chemical structure of the ligand	Chelation capacity for metals	Stability constant for Zn(II) [3,4]
DTPA	diethylenetriamine-pentaacetic acid		8	18.40, 18.75
EDTA	ethylenediamine-tetraacetic acid		6	16.50
HEDTA	(2-hydroxyethyl)ethylenediamine-triacetic acid		5	14.50, 14.70

The work on this group is related to the one performed for the COLLA project dealing with EDTA derivatives. The COLLA project report is publicly available on the ECHA website[5]. In Appendix 1 of the COLLA project report the included substances

[3] Based on: Hart et al., 2012 *Ethylenediaminetetraacetic Acid and Related Chelating Agents,* Ullmann's Encyclopedia of Industrial Chemistry, 2012

[4] https://www.dojindo.eu.com/images/Product%20Photo/Chelate_Table_of_Stability_Constants.pdf

[5] Collaborative approach pilot projects. March 2017 – March 2018. Final report: https://echa.europa.eu/documents/10162/13628/colla_pilot_project_report_en.pdf/0ba58a2e-675f-387e-4827-05aba076a0e0

are described. The COLLA assessment dealt with 'empty' EDTA derivatives e.g. EDTA, DTPA, PDTA and HEDTA chelates (which are the focus of the ARN report 'EDTA-related acids and salts') and with EDTA derivatives complexed with metal ions (such as Cu^{2+}, Fe^{2+}; Mn^{2+}, Zn^{2+}), which are in the scope of the current group assessment.

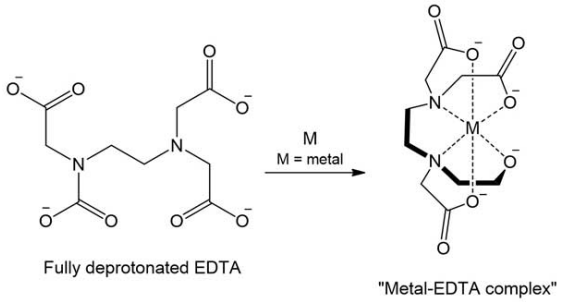


Figure 1: Hexa-coordination capacity of EDTA for metal chelation. Typically, a metal-EDTA complex with octahedral geometry is generated.

The EDTA-like structures of these substances show multiple complexing sites enabling one molecule to interact with all the reactive centres of a metal ion (in red and blue in Figure 2). These ligands include both oxygen and nitrogen atoms, taking advantage of the fact that some metals bond more strongly to nitrogen and others prefer oxygen. The chelation capacity of the substances depends inter alia on the availability of electron donor atoms such as nitrogen from amines and oxygen in carboxyl groups: EDTA-like substances have a hexavalent complexation capacity, DTPA-like substances a higher, octavalent complexation capacity, while HEDTA-like substances have a lower complexation capacity compared to EDTA (Figure 2).

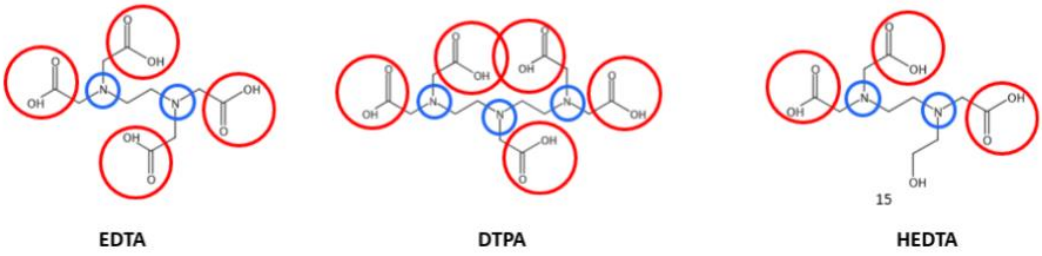


Figure 2: EDTA-like acids and salts have a structural symmetry and availability of electron donor atoms (nitrogen from amines and oxygen in COOH moieties)

The stability of the organic complexes with metals is very difficult to predict because of the complexity of the organic compounds.

The chelation capacity is given as stability constant K_{stab} of such complexes with metals. With regards to complexation of zinc (Zn^{2+}), the metal relevant for the reproductive effects due to zinc depletion, the stability constants were reported with 18.40 for DTPA, 16.50 for EDTA, and 14.70 for HEDTA[6]. In another source, the stability constant for HEDTA was indicated with 14.50, for CDTA with 18.67, for DTPA with 18.75, the two last ones being higher compared to EDTA reported with 16.50[7].

[6] Based on: Hart et al., 2012 *Ethylenediaminetetraacetic Acid and Related Chelating Agents,* Ullmann's Encyclopedia of Industrial Chemistry, 2012

[7] https://www.dojindo.eu.com/images/Product%20Photo/Chelate_Table_of_Stability_Constants.pdf

The constants of affinity of EDTA and DTPA for different metal ions is listed in Table 2. It shows that for Fe^{3+} and Cu^{2+} the affinity is higher than for Zn^{2+}, whereas it is lower for Fe^{2+}, Mn^{2+}, Ca^{2+}, and Mn^{2+}.

Table 2: Constants of affinity of EDTA and DTPA chelants for different ions (RAC opinion on CLH proposal for DTPA 2017)

	Constants of affinity (Log K values)	
Ion	**EDTA**	**DTPA**
Mg^{2+}	8.8	9.3
Ca^{2+}	10.7	10.8
Mn^{2+}	13.9	15.2
Fe^{2+}	14.3	16.2
Zn^{2+}	16.5	18.2
Cu^{2+}	18.8	21.2
Fe^{3+}	25.1	28.8

All substances are well-defined with a few being multi-constituent substances (EC numbers 422-080-1; 433-620-9; 438-890-1; 476-670-7; 700-366-8; 902-532-7; 902-533-2; 915-008-8; 915-009-3; 931-053-6; 939-867-3; 944-341-1; 946-9859;). All the other substances are mono-constituent substances.

The data were analysed taking into account the chelation capacity of the ligands and the type of metal.

Several substances in this group are included in a read-across category approach performed by the registrants of EDTA (EC 200-449-4), EDTA-Na4 (EC 200-573-9), EDTA-Na2 (EC 205-358-3) and EDTA-(NH4)2 (EC 244-063-4). Another read-across category is provided in the registration for DTPA-Na5 (EC 205-391-3). The read-across approaches are using DTPA, EDTA and HEDTA with different metals such as:

- **DTPA**-based chelates including
  - DTPA-**Fe**Na (EC 235-627-0), DTPA-FeNa2 (EC 243-136-8), DTPA-Fe(NH4)2 (EC 259-411-0)
- **EDTA**-based chelates including
  - EDTA-**Ca**Na2 (EC 200-529-9),
  - EDTA-**Cu**Na2 EC 237-864-5, EC 686-516-2, EC 920-959-7), EDTA-Cu(NH4)2 (EC 268-018-3), EDTA-CuK2 (EC 277-749-7),
  - EDTA-**Fe**Na2 (EC 239-802-2, EC 803-202-4, EC 927-442-5), EDTA-FeK (EC 259-411-0), EDTA-Fe(NH4)2(OH) (EC 270-232-7)
  - EDTA-**Mg**Na2 (EC 238-372-3)
  - EDTA-**Mn**Na2 (EC 239-407-5), EDTA-MnK2 (EC 268-144-9), EDTA-Mn(NH4)2 (EC 304-037-6)
  - EDTA-**Zn**Na4 (EC 237-865-0), EDTA-ZnK2 (238-729-3), EDTA-Zn(NH4)2 (EC 267-400-7),
- **HEDTA**-based chelates including
  - HEDTA-**Fe**Na (EC 257-036-7)

Based on information reported in the REACH registration dossiers, the main uses of substances chelated with Ca, Cu, Fe, Mg, Mn, Ni, and Zn are (other than laboratory chemicals) **synthetic fertilizers for soil amendment to enhance plant growth**. The complexation of the metal ion with the chelate enhances the solubility and the bioavailability of the complexed ion to the plants. Complexed ions can then be taken up by the plants. Free metal ions in soil solution tend to precipitate quickly, rendering them not bioavailable to the plants.

Several iron EDTA or HEDTA complexes (EC 239-802-2 = EC 927-442-5, EC 257-036-7, EC 270-232-7), one calcium EDTA complex (EC 200-529-9) and one zinc EDTA complex (EC 237-865-0) are indicated to have multiple (up to 38) other uses by consumers and/or professionals (in addition to the use as fertiliser) such as water softener, washing and cleaning, biocidal products, perfume, air care products, pharmaceuticals, polishes and waxes, lubricants, hydraulic fluids, fuels, adhesive sealants, coatings and paints, ink an toner, textiles and dyes, intermediates, or photochemicals.

In some registrations uses other than fertiliser are specified, such as pharmaceutical (EDTA complex with aluminium and boron; EC 934-405-7), textile dying (complex with copper; EC 300-491-4), and as trace element additive for the production of biogas (EDTA complex with nickel; EC 692-065-2, EC 947-740-9). For two substances neither uses nor technical function are specified (EDTA complex with aluminium (EC 934-407-8) and PDTA complex with iron (EC 400-660-3). For all registered substances of this group potential exposure of consumers and/or professionals are expected to occur.

EDTA (EC 200-449-4) is listed in Regulation (EU) No. 10/2011, hence this substance and all salts can be used for plastics with food contact. There is no specific migration limit. However, the maximum overall migration is set to 60 mg/kg food.

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

Considerations for the justification of regulatory needs for the current group of EDTA-like metal complexes are linked to the group 'EDTA related acids and salts' (un-complexed or 'empty' chelates) and are used as the starting point for this group evaluation.

Based on currently available information, there is a need for (further) EU regulatory risk management (CLH, restriction) for reproductive (developmental and/or fertility) toxicity hazards for all metal chelates except for Zn-chelates.

Reproductive toxicity

Un-complexed EDTA-like substances (see ARN 'EDTA related acids and salts') are complexing and sequestering (binding or confining) metal ions such as Fe^{3+}, Cu^{2+}, Zn^{2+}, Fe^{2+}, Mn^{2+}, Ca^{2+} and Mg^{2+}. The complexation of zinc and consequent zinc depletion is the main **human health concern** for those substances leading to zinc depletion and in animals to an impact on male fertility (e.g., gonadal dysfunction, decreased testicular weight, diminished seminiferous tubules, and defects in spermatozoa), female fertility (e.g., disruption of the oestrous cycle with prolonged gestation, stillbirths, and difficulty in parturition), and the offspring (increased foetal resorption rates, reduced or inhibited foetal growth, and high incidences of congenital malformations; see NTP TR592)[8]. DTPA (EC 200-652-8), DTPA-Na5 (EC 205-391-3), and DTPA-K5 (EC 404-290-3) have a harmonised classification Repr. 1B; H360D due to malformations observed in prenatal developmental toxicity studies (Note that an application for annulment of the annex VI entry for the three DTPAs is under processing in the General Court in Luxemburg). Since all substances in this group have the potential for zinc depletion, all substances were considered to have a potential for developmental toxicity, albeit the potency might vary depending e.g., on the chelation potency (DTPA > EDTA > HEDTA), the route of administration (teratogenic effects at lower doses observed with dietary administration compared to gavage administration) and the highest dose administered (with substances of lower potency, effects might occur only at doses higher than 1 000 mg/kg bw/day). Effects on fertility may also be expected for these substances, however, no reliable studies regarding fertility were available.

EDTA-like metal complexes dissociate in the gastrointestinal tract to a bioavailable form of the metal and an EDTA salt and metal ions are freely exchanged. Accordingly, the various EDTA salt forms are expected to have essentially similar properties in the body regardless of the EDTA-metal complex to which exposure occurred (Heimbach et al., 2000). However, it is expected that some metals could modify the effects observed with 'empty' chelates. For example, Zn complexes provide supplementary zinc and are therefore expected not to lead to zinc depletion in the same severity as similar complexes without Zn. Furthermore, some metal might add a specific toxicity such as nickel (Skin Sens 1, Carc 2, STOT RE 1) and manganese (potential neurotoxicity).

In addition, subtle differences in the toxicity of these chemicals are due to differences in affinity towards different metals. This determines whether the chelant

[8] https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr592_508.pdf?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tr592

alters the ion balance of the organism either by releasing ions through dissociation from the EDTA or DTPA salts or removing such ions through chelation (RAC opinion on CLH proposal for DTPA 2017).

As summarised in Table 2, the affinities for Fe^{3+} and Cu^{2+} are higher compared to Zn^{2+}, whereas the affinity for the other metal ions listed above is lower. Therefore, effects related to zinc depletion might be expected to occur at higher doses with Fe^{3+} and Cu^{2+} EDTA compared to the other EDTA metal complexes. However, the available data are insufficient to demonstrate this assumption.

It is also noted that although the order of affinities for different ions is the same between EDTA and DTPA, the affinity of DTPA is always higher than the affinity of EDTA for a specific ion. This can be explained by considering that the affinities increase with the number of functional groups. (RAC opinion on CLH proposal for DTPA 2017).

None of the EDTA-like metal complexes have a harmonised or a self-classification with regards to reproductive toxicity.

Data density with regards to studies on reproductive toxicity is very low. Therefore, it is not possible to make firm conclusions on differences in the potency of the reproductive hazard of the substances. The available data indicate that:

- The route of oral administration is important for identification of a reproductive hazard: with dietary administration (which is more relevant to humans), malformations were detected at lower EDTA doses compared to gavage administration and without maternal toxicity (e.g., Kimmel, 1977). However, most reproductive toxicity studies were performed following gavage administration.

- 'Empty' chelates: DTPA (but not EDTA) induced malformations in a PNDT study following gavage administration of 1 000 mg/kg bw/day. However, with dietary administration of similar doses, malformations were also observed with EDTA (Kimmel, 1977, Swenerton 1971).

- Metal chelates: in OECD 422 screening studies performed with gavage administration of metal chelates, the highest doses tested of 1 500 mg/kg bw/day resulted in sperm effects (DTPA-FeNa), offspring mortality (EDTA-CuNa2) and sperm effects as well as offspring mortality (EDTA-MnNa2). The next lower doses (500 mg/kg bw/day) did not show such effects. A screening study performed with gavage administration of a Reaction mass of DTPA-Mn, EDTA-Mn, HEDTA-Mn did not show any clear effects at 1 000 mg/kg bw/day.

- Zinc chelates seem to prevent/reduce zinc depletion based on non-guideline studies.

In conclusion, similarly to un-complexed EDTA-like ('empty') chelates the metal complexes are considered to have a potential for reproductive toxicity related to developmental toxicity and possible effects on fertility, albeit the potency might vary.

However, Zn-complexes may be considered to have a lower potency to lead to zinc depletion and reproductive toxicity that may not require a harmonised classification for reproductive toxicity.

Damage to the respiratory tract following inhalation

Since metal chelates are already complexed with a metal, effects on the respiratory tract might be expected to be less severe compared to 'empty' chelates for which damage to the respiratory tract was leading to a proposal for a harmonised STOT RE 2 classification (for 'empty' DTPA chelates). This assumption is supported by an old inhalation study on DTPA-CaNa3 (EC 235-169-1) with limited exposure duration. The observed effects (slight histocytosis) might not fulfil the criteria for STOT RE classification and anyway histocytosis was only observed at concentration level, which is above the guidance value for classification.

Repeated dose, mutagenic, carcinogenic, skin sensitising or ED properties

Based on the data in the registration dossiers, the substances are unlikely to be mutagenic, carcinogenic, skin sensitising or having ED properties with the following exceptions:

- Nickel is classified for Skin Sens 1 (H317), STOT RE 1, and Carc 2 (H351); the classifications for STOT RE 1 and Carc 2 are related to inhalation exposure. EDTA-NiNa2 (List No 692-065-2) and EDTA-(NH4)2 (List No 947-740-0) are self-classified as Skin Sens 1 (H317). Following inhalation exposure, it is not expected that nickel would dissociate in the respiratory tract in a relevant amount. Therefore, the potential for the STOT RE and carcinogenicity properties of the EDTA-Ni chelates is expected to be lower compared to nickel.

- In addition, the following substances are self-classified for Skin Sens 1 based on available data:
    - EC 300-491-4 (bis[N-(2-hydroxyethyl)-N-methylglycinato-N,O,ON]copper)
    - EC 476-670-7 (Reaction mass of iron chelate of sodium salt N-[1,2 dicarboxyethyl] D,L aspartic acid and sodium chloride)

No extrapolation of such results to other metal chelates of this group seems to be justified.

Action for human health endpoints

CCHs to be opened will include all substances of the registrant's categories; the read-across performed will be assessed in this context. In addition, CCH will be opened for the following substances with potential incompliances:

- EC/List No 902-532-7 (DTPA-KCa)
- EC/List No 931-053-6 (IDHA-Zn)

Environmental hazard

Data density for all environmental endpoints is low. All substances in the group are potentially persistent and mobile in the environment. Metal complexed chelates are relatively stable under environmental conditions and release of the metal ion is expected to be limited, depending on the complexation capacity of the substance.

Chelates of Ca-, Fe-, Mn-, and Mg- are not likely to be aquatic toxic; the metal ion for this chelates are intrinsically not toxic.

Chelates of Al-, Cu-, Ni-, and Zn- are potential chronically toxic to the aquatic environment, due to the potential release of the metal. One Cu-chelate (EC 300-

491-4) is properly classified Aquatic acute and Chronic 1 based on data on the substance. The high aquatic toxicity for this substance is likely caused by the release of the copper ion under environmental conditions and this is likely due to the lower capacity of the chelate to form coordinate covalent bonds (tetravalent complexation capacity). Metal complexed chelates of higher complexation capacity are more stable under environmental conditions and release of the metal ion is expected to be limited. Some chelates of Al-, Cu-, Ni-, and Zn- are self-classified as Aquatic chronic 3; however, several Cu-, Ni-, and Zn-chelates are not self-classified.

Data generation would provide the data for clarifying on the persistency and mobility of the substances of this group. A read-across approach from the empty chelates might be considered plausible for persistency, mobility and bioaccumulation.

Compliance checks to be opened for all substances included in registrant's categories. Regarding the aquatic toxicity there is a need for data generation for classification purposes for following the following chelates:

- Ni-chelates:
    - EC/List No 247-019-2 (not included in the registrant's category)
- Cu-chelates
    - EC/List No 237-864-5 (included in registrant's category),
    - EC/List No 268-018-3 (included in registrant's category)
    - EC/List No 277-749-7 (included in registrant's category)

In case of appropriate self-classification for aquatic toxicity, no further risk management measures would be required.

Harmonised classification and labelling

The first step of the regulatory risk management, should the hazard exist, is the confirmation of hazard via harmonised classification (CLH) as reproductive toxicity (development and/or fertility) hazards for all EDTA-like metal chelates of this group, except EDTA-like Zn-chelates. However, based on the lower reproductive potency of EDTA-like substances with lower chelating potency compared to DTPA, and the further expected lower potency for Fe^{3+} and Cu^{2+} EDTA-complexes, the priority for preparing CLH proposal(s) might be considered. When preparing the proposals, it may be considered what would be the best way to develop them, for instance whether to make a proposal for the group of substances, to submit them individually or jointly.

A harmonised classification 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.

In addition, substances that are mutagenic, carcinogenic or toxic to reproduction should not be used in food contact materials or articles without previous authorisation (Regulation (EU) No 10/2011).

Uses

Professional uses such as fertiliser (soil amendments) are reported for 34 of the 40 registered substances and for four of those substances also multiple uses. The uses

as fertiliser and the mentioned multiple uses are expected to be widespread (at many sites and by many users). Professional use is often widespread with relatively low levels of operational controls and risk management measures but with often frequent exposures with a long duration. In addition, professional users may be self-employed and therefore not covered by occupational safety and health (OSH) legislation.

Consumers may be co-exposed to the substances used by professionals as fertilisers; the widespread uses mentioned for professionals are usually also uses for consumers.

Ferric sodium EDTA (EC 239-802-2) is authorised as a novel food ingredient used as a source of iron. The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) evaluated 2018 the use of ferric sodium EDTA as an ingredient in the context of Regulation (EC) 258/97 on novel foods and Regulation (EU) 609/2013 on food intended for infants and young children, food for special medical purposes and total diet replacement for weight control. The Panel concluded that there is no sound scientific justification to increase the current ADI for EDTA of 1.9 mg/kg body weight per day and recommended that additional toxicological data should be provided to address the shortcomings in the available toxicity database prior to the re-evaluation of calcium disodium EDTA[9].

Restriction

A restriction of the substances from the whole group (excluding Zn-chelates) as such or in mixtures (concentration limit in mixtures) used by professionals may be suggested after considering CLH.

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.

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[10] which aims to extend to professional users under REACH the level of protection granted to consumers.

To prevent regrettable substitution, the further need for EU regulatory risk management for the substances of the current group should not be limited to substances registered under REACH but to all substances of this group.

Taken together, a restriction of professional uses seems to be the most appropriate regulatory risk management option for this group of EDTA-related metal chelates (possibly excluding Zn-chelates) in case risk(s) related to reproductive (developmental) toxicity would be identified.

Based on currently available information, there is no need for (further) EU regulatory risk management for Zn-chelates.

Human health hazards

As explained above, the complexation of zinc and consequent zinc depletion is the main human health concern for substances leading to zinc depletion and in animals to an impact on male fertility, female fertility, and on the offspring. EDTA-like metal

[9] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5369

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

complexes dissociate in the gastrointestinal tract to a bioavailable form of the metal and an EDTA salt and metal ions are freely exchanged. Zn-complexes provide supplementary zinc and are therefore expected not to lead to zinc depletion in the same severity as similar complexes without Zn. Several non-guideline studies in experimental animals support this assumption.

Therefore, Zn-complexes may be considered to have a lower potency to lead to zinc depletion and reproductive toxicity that may not require a harmonised classification for reproductive toxicity and consequently a restriction.

Environmental hazards

As explained above, Zn-chelates included in the group with penta- to octavalent chelation capacity are relatively stable under environmental conditions and release of the metal ion is expected to be limited. One Zn-chelate (EC 275-554-1) has a self-classification Aquatic chronic 3. However, other Zn-chelates (ECs 237-865-0, 238-729-3, 267-400-7, 931-053-6) are not self-classified.

Regarding the aquatic toxicity there is a need for data generation for classification purposes for following the following chelates:

- Zn-chelates:
    - EC/List No 237-865-0 (included in registrant's category),
    - EC/List No 238-729-3 (included in registrant's category),
    - EC/List No 267-400-7 (included in registrant's category)
    - EC/List No 931-053-6 (not included in the registrant's category).

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.

Metal	EC number	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
Fe	235-627-0* 239-802-2* 243-136-8* 244-302-2 257-036-7* 259-411-0* 270-232-7* 289-064-0* 400-660-3 405-680-6 406-173-2 411-640-9 422-080-1 433-620-9 438-890-1 476-670-7 803-202-4 813-880-3 824-774-1 927-442-5 * Registrants' category	Known or potential hazard for reproductive toxicity	Known or potential hazard for persistency and mobility	For registered substances: - Fertiliser - multiple uses (similar to 'empty' chelates: ECs, 239-802-2, 257-036-7, 270-232-7, 927-442-5)	**Need for EU RRM: Restriction** If risk(s) identified. Justification: Restriction could address potential risks related to reproductive toxicity (e.g., use by professionals)	**First step:** CCH: 235-627-0* 239-802-2* =927-442-5 243-136-8* 257-036-7* 259-411-0* 270-232-7* 289-064-0* **Next steps (if hazards and risks confirmed):** CLH (group) Restriction (group)

Metal	EC number	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
Ca	200-529-9* 235-169-1 902-532-7 944-341-1 * Registrants' category					**First step:** CCH: 200-529-9* 902-532-7 **Next steps (if hazards and risks confirmed):** CLH (group) Restriction (group)
Mg	238-372-3* 902-533-2 946-985-9 * Registrants' category					**First step:** CCH: 238-372-3* **Next steps (if hazards and risks confirmed):** CLH (group) Restriction (group)
Mn	234-282-3 239-407-5* 259-645-3 268-144-9* 304-037-6* 915-009-3 939-867-3 * Registrants' category					**First step:** CCH: 239-407-5* 268-144-9* 304-037-6* **Next steps (if hazards and risks confirmed):** CLH (group) Restriction (group)

Metal	EC number	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
Al, B	934-407-8 934-405-7		Known or potential hazard for aquatic toxicity for persistency and mobility	- Unknown (EC 934-407-8), - Pharmaceutical (EC 934-405-7)		**First step:** CCH: None **Next steps (if hazards and risks confirmed):** CLH (group) Restriction (group)
Cu	237-864-5* 268-018-3* 277-749-7* 300-491-4 686-516-2 915-008-8 938-868-6 * Registrants' category			- Fertiliser or - Textile colourant (only EC 300-491-4)		**First step:** CCH: 237-864-5* 268-018-3* 277-749-7* **Next steps (if hazards and risks confirmed):** CLH (group) Restriction (group)
Ni	247-019-2 692-065-2 947-740-9	Known or potential hazard for reproductive toxicity for skin sensitisation for carcinogenicity		- Fertiliser (EC 247-019-2) - Slow-release nickel source for biogas production (EC 692-065-2, 947-740-9)		**First step:** CCH: 247-019-2 **Next steps (if hazards and risks confirmed):** CLH (group) Restriction (group)

Metal	EC number	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
Zn	237-865-0* 238-729-3* 234-305-7 267-400-7* 275-554-1 700-366-8 931-053-6	No hazard or unlikely hazard		- Fertiliser, laboratory agent, intermediate - Multiple uses similar to 'empty' chelates (EC 237-865-0)	**Currently no need for EU RRM**	**First step:** CCH: 237-865-0* 238-729-3* 267-400-7* 931-053-6 **Next steps (if low hazards and risks confirmed):** No action

Annex 1: Overview of classifications

Data extracted on 29/08/2022

EC Number	CAS Number	Metal	Harmonised classification	Classification in registrations	Classification in C&L notifications (*)
934-405-7	-	**Al** **B**	-	Aquatic Chronic 3 H412	-
934-407-8	-	**Al**	-	Aquatic Chronic 3 H412	-
200-529-9	62-33-9	**Ca**	-	-	STOT Single Exp. 3 H335, affected organs: Respiratory tract. STOT Single Exp. 3 H335, affected organs: lungs Eye Damage 1 H318 Eye Irrit. 2 H319 Skin Irrit. 2 H315
902-532-7	-	**Ca**	-	-	-
944-341-1	-	**Ca**	-	-	-
237-864-5 686-516-2 920-959-7	14025-15-1	**Cu**	-	Acute Tox. 4 H302 Eye Irrit. 2 H319	Aquatic Chronic 3 H412 Skin Irrit. 2 H315
268-018-3	67989-88-2	**Cu**	-	Acute Tox. 4 H302 Skin Irrit. 2 H315	Eye Irrit. 2 H319
277-749-7	74181-84-3	**Cu**	-	Acute Tox. 4 H302 Skin Irrit. 2 H315 Eye Irrit. 2 H319	-
300-491-4	93940-93-3	**Cu**	-	Acute Tox. 4 H302 Skin Irrit. 2 H315 Eye Irrit. 2 H319 Skin Sens. 1 H317 Aquatic Acute 1 H400, M-factor: 10.00 Aquatic Chronic 1 H410	-
686-516-2	14025-15-1	**Cu**	-	-	-
915-008-8	-	**Cu**	-	Skin Irrit. 2 H315 Eye Irrit. 2 H319 Aquatic Chronic 3 H412	-
938-868-6	-	**Cu**	-	Acute Tox. 4 H302 Aquatic Chronic 3 H412	-
235-627-0	12389-75-2	Fe	-	-	Eye Irrit. 2 H319
239-802-2	15708-41-5	Fe	-	-	STOT Single Exp. 3 H335 Eye Irrit. 2 H319 Skin Irrit. 2 H315 Acute Tox. 4 H302 STOT Single Exp. 3 H335, affected organs: Respiratory tract
243-136-8	19529-38-5	Fe	-	-	-
244-302-2	21265-50-9	Fe	-	-	Eye Irrit. 2 H319
257-036-7	51181-50-1	Fe	-	-	-
259-411-0	54959-35-2	Fe	-	-	-
270-232-7	68413-60-5	Fe	-	-	-
289-064-0	85959-68-8	Fe	-	-	-
304-037-6	94233-07-5	Fe	-	-	-
400-660-3	-	Fe	-	-	-
405-680-6	-	Fe	-	-	-
476-670-7	-	Fe	-	Skin Sens. 1B H317	-

EC Number	CAS Number	Metal	Harmonised classification	Classification in registrations	Classification in C&L notifications (*)
803-202-4	18154-32-0	Fe	-	-	Eye Irrit. 2 H319 Skin Irrit. 2 H315 STOT Single Exp. 3 H335, affected organs: lungs
813-880-3	2055396-18-2	Fe	-	-	-
824-774-1	148124-40-7	Fe	-	-	-
927-442-5	-	Fe	-	-	-
238-372-3	14402-88-1	Mg	-	-	Eye Damage 1 H318
902-533-2	-	Mg	-	-	-
946-985-9	-	Mg	-	-	-
234-282-3	11065-74-0	Mn	-	-	-
239-407-5	15375-84-5	Mn	-	-	Eye Irrit. 2 H319
268-144-9	68015-77-0	Mn	-	-	-
915-009-3	-	Mn	-	-	-
939-867-3	-	Mn	-	-	-
247-019-2	25481-21-4	Ni	-	-	Acute Tox. 4 H302 Carc. 2 H351 Skin Sens. 1 H317 Aquatic Chronic 2 H411
692-065-2	15708-55-1	Ni	-	Acute Tox. 4 H302 Eye Irrit. 2 H319 Skin Sens. 1 H317 Aquatic Chronic 3 H412	Carc. 2 H351
947-740-9	-	Ni	-	Acute Tox. 4 H302 Eye Irrit. 2 H319 Skin Sens. 1 H317 Aquatic Chronic 3 H412	-
234-305-7	11082-38-5	Zn	-	-	-
237-865-0	14025-21-9	Zn	-	-	Acute Tox. 4 H302 Eye Irrit. 2 H319
238-729-3	14689-29-3	Zn	-	-	-
267-400-7	67859-51-2	Zn	-	-	-
275-554-1	71501-24-1	Zn	-	Aquatic Chronic 3 H412	-
931-053-6	-	Zn	-	Acute Tox. 5 H303	-

(*)Each notification can represent a group of notifiers,

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

Table 3: Overview of main uses sorted by increasing EC number (1/2)

EC number	200-529-9	234-282-3	235-627-0	237-864-5	237-865-0	238-372-3	238-729-3	239-407-5	239-802-2	243-136-8	247-019-2	257-036-7	259-411-0	267-400-7	268-018-3	268-144-9	270-232-7	275-554-1	277-749-7	289-064-0
Metal	**Ca**	**Mn**	**Fe**	**Cu**	**Zn**	**Mg**	**Zn**	**Mn**	**Fe**	**Fe**	**Ni**	**Fe**	**Fe**	**Zn**	**Cu**	**Mn**	**Fe**	**Zn**	**Cu**	**Fe**
PC 20: Products such as ph-regulators, flocculants, precipitants, neutralisation agents	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 36: Water softeners	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 37: Water treatment chemicals	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 2: Adsorbents					F, I, **P**				F, I, **P**								F, I, **P**			
PC 11: Explosives			**P**		F, I, **P**				F, I, **P**								F, I, **P**			
PC 12: Fertilisers	F, I, **P**, **C**	F, **P**	F, I, **P**, **C**	F, I, **P**, **C**	F, I, **P**, **C**	F, **P**, **C**	F, I, **P**, **C**	F, I, **P**, **C**	F, I, **P**, **C**	F, I, **P**, **C**	F, **P**, **C**	F, **P**, **C**	F, **P**, **C**	F, I, **P**, **C**	F, I, **P**, **C**	F, I, **P**, **C**	F, I, **P**, **C**	F, **P**, **C**	F, **P**, **C**	F, **P**, **C**
PC 27: Plant protection products				I, **P**	F, I, **P**				F, I, **P**								F, I, **P**			
PC 4: Anti-freeze and de-icing products					F, I, **P**				F, I, **P**								F, I, **P**			
PC 35: Washing and cleaning Products	**C**			F, **P**	F, I, **P**, **C**				F, I, **P**, **C**			**C**			F, **P**		F, I, **P**, **C**			
PC 8: Biocidal products (e.g.	**C**				F, I, **P**, **C**			F, **P**	F, I, **P**, **C**		I	**C**					F, I, **P**, **C**			

EC number	200-529-9	234-282-3	235-627-0	237-864-5	237-865-0	238-372-3	238-729-3	239-407-5	239-802-2	243-136-8	247-019-2	257-036-7	259-411-0	267-400-7	268-018-3	268-144-9	270-232-7	275-554-1	277-749-7	289-064-0
Metal	**Ca**	**Mn**	**Fe**	**Cu**	**Zn**	**Mg**	**Zn**	**Mn**	**Fe**	**Fe**	**Ni**	**Fe**	**Fe**	**Zn**	**Cu**	**Mn**	**Fe**	**Zn**	**Cu**	**Fe**
disinfectants, pest control)																				
PC 28: Perfumes, fragrances	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 3: Air care Products					F, I, **P**				F, I, **P**								F, I, **P**			
PC 39: Cosmetics, Personal care products	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 29: Pharmaceuticals	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 31: Polishes and wax blends	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 15: Non-metal-surface treatment products	**C**			I	F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 24: Lubricants, greases, release products	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 25: Metal working fluids					F, I, **P**				F, I, **P**								F, I, **P**			
PC 16: Heat transfer fluids					F, I, **P**				F, I, **P**								F, I, **P**			
PC 17: Hydraulic fluids					F, I, **P**				F, I, **P**								F, I, **P**			
PC 13: Fuels					F, I, **P**				F, I, **P**								F, I, **P**			
PC 32: Polymer	**C**				F, I, **P**, **C**				F, I, **P**, **C**			I, **C**					F, I, **P**, **C**			

EC number	200-529-9	234-282-3	235-627-0	237-864-5	237-865-0	238-372-3	238-729-3	239-407-5	239-802-2	243-136-8	247-019-2	257-036-7	259-411-0	267-400-7	268-018-3	268-144-9	270-232-7	275-554-1	277-749-7	289-064-0
Metal	**Ca**	**Mn**	**Fe**	**Cu**	**Zn**	**Mg**	**Zn**	**Mn**	**Fe**	**Fe**	**Ni**	**Fe**	**Fe**	**Zn**	**Cu**	**Mn**	**Fe**	**Zn**	**Cu**	**Fe**
preparations and compounds																				
PC 1: Adhesives, sealants	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 9C: Finger paint	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 9b: Fillers, putties, plasters, modelling clay	**C**			F, I, **P**, **C**	F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 9A: Coatings and paints, thinners, paint removes	F, **C**			F, I, **P**, **C**	F, I, **P**, **C**	F		F	F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 18: Ink and toners	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 26: Paper and board treatment products	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 34: Textile dyes, and impregnating products	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 23: Leather treatment products	**C**				F, I, **P**, **C**				F, I, **P**, **C**			**C**					F, I, **P**, **C**			
PC 14: Metal surface treatment products	**C**			F, I	F, I, **P**, **C**				F, I, **P**, **C**			**C**			F, I		F, I, **P**, **C**			
PC 38: Welding and soldering					F, I, **P**				F, I, **P**								F, I, **P**			

EC number	200-529-9	234-282-3	235-627-0	237-864-5	237-865-0	238-372-3	238-729-3	239-407-5	239-802-2	243-136-8	247-019-2	257-036-7	259-411-0	267-400-7	268-018-3	268-144-9	270-232-7	275-554-1	277-749-7	289-064-0
Metal	**Ca**	**Mn**	**Fe**	**Cu**	**Zn**	**Mg**	**Zn**	**Mn**	**Fe**	**Fe**	**Ni**	**Fe**	**Fe**	**Zn**	**Cu**	**Mn**	**Fe**	**Zn**	**Cu**	**Fe**
products, flux products																				
PC 7: Base metals and alloys					F, I, **P**				F, I, **P**								F, I, **P**			
PC 33: Semiconductors					F, I, **P**				F, I, **P**								F, I, **P**			
PC 21: Laboratory chemicals	F, I, **P**		F, **P**	F, **P**	F, I, **P**	F, **P**	F, I, **P**	F, I, **P**	F, I, **P**	F, I, **P**		F, **P**	F, **P**	F, I, **P**	F, **P**	F, **P**	F, I, **P**		F, **P**	F, **P**
PC 19: Intermediate				I	F, I, **P**			F, **P**	F, I, **P**								F, I, **P**			
PC 40: Extraction agents					F, I, **P**				F, I, **P**								F, I, **P**			
PC41: Oil and gas exploration or production products					I, **P**															
PC42: Electrolytes for batteries					I, **P**															
PC 30: Photo-chemicals	**C**				F, I, **P, C**				F, I, **P, C**			**C**					F, I, **P, C**			

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

Table 4: Overview of main uses sorted by increasing EC number (2/2)

EC number	300-491-4	304-037-6	400-660-3	476-670-7	692-065-2	813-880-3	824-774-1	902-532-7	902-533-2	915-008-8	915-009-3	927-442-5	931-053-6	934-405-7	934-407-8	938-868-6	939-867-3	944-341-1	946-985-9	947-740-9
Metal	**Cu**	**Mn**	**Fe**	**Fe**	**Ni**	**Fe**	**Fe**	**Ca**	**Mg**	**Cu**	**Mn**	**Fe**	**Zn**	**Al**	**Al**	**Cu**	**Mn**	**Ca**	**Mg**	**Ni**
PC 20: Products such as Ph-regulators, flocculants, precipitants, neutralisation agents												F, I, **P**, **C**		F	F					
PC 36: Water softeners												F, I, **P**, **C**								
PC 37: Water treatment chemicals												F, I, **P**, **C**								
PC 2: Adsorbents												F, I, **P**								
PC 11: Explosives												F, I, **P**								
PC 12: Fertilisers		F, **P**, **C**		F, **P**, **C**		F, **P**	F, **P**, **C**	F, **P**, **C**	F, **P**, **C**	F, **P**, **C**	F, **P**, **C**	F, I, **P**, **C**	**P**, **C**			F, **P**	F, **P**, **C**	F, **P**	F, **P**	
PC 27: Plant protection products												F, I, **P**								
PC 4: Anti-freeze and de-icing products												F, I, **P**								
PC 35: Washing and cleaning products												F, I, **P**, **C**								
PC 8: Biocidal products (e.g. disinfectants, pest control)												F, I, **P**, **C**								

EC number	300-491-4	304-037-6	400-660-3	476-670-7	692-065-2	813-880-3	824-774-1	902-532-7	902-533-2	915-008-8	915-009-3	927-442-5	931-053-6	934-405-7	934-407-8	938-868-6	939-867-3	944-341-1	946-985-9	947-740-9
Metal	**Cu**	**Mn**	**Fe**	**Fe**	**Ni**	**Fe**	**Fe**	**Ca**	**Mg**	**Cu**	**Mn**	**Fe**	**Zn**	**Al**	**Al**	**Cu**	**Mn**	**Ca**	**Mg**	**Ni**
PC 28: Perfumes, fragrances												F, I, **P**, **C**								
PC 3: Air care products												F, I, **P**								
PC 39: Cosmetics, personal care products												F, I, **P**, **C**								
PC 29: Pharmaceuticals												F, I, **P**, **C**		F, **P**						
PC 31: Polishes and wax blends												F, I, **P**, **C**								
PC 15: Non-metal-surface treatment products												F, I, **P**, **C**								
PC 24: Lubricants, greases, release products												F, I, **P**, **C**								
PC 25: Metal working fluids												F, I, **P**								
PC 16: Heat transfer fluids												F, I, **P**								
PC 17: Hydraulic fluids												F, I, **P**								
PC 13: Fuels												F, I, **P**								
PC 32: Polymer Preparations and compounds												F, I, **P**, **C**								

EC number	300-491-4	304-037-6	400-660-3	476-670-7	692-065-2	813-880-3	824-774-1	902-532-7	902-533-2	915-008-8	915-009-3	927-442-5	931-053-6	934-405-7	934-407-8	938-868-6	939-867-3	944-341-1	946-985-9	947-740-9
Metal	**Cu**	**Mn**	**Fe**	**Fe**	**Ni**	**Fe**	**Fe**	**Ca**	**Mg**	**Cu**	**Mn**	**Fe**	**Zn**	**Al**	**Al**	**Cu**	**Mn**	**Ca**	**Mg**	**Ni**
PC 1: Adhesives, sealants												F, I, **P**, **C**								
PC 9C: Finger paint												F, I, **P**, **C**								
PC 9b: Fillers, putties, plasters, modelling clay												F, I, **P**, **C**								
PC 9A: Coatings and paints, thinners, paint removes												F, I, **P**, **C**								
PC 18: Ink and toners												F, I, **P**, **C**								
PC 26: Paper and board treatment products												F, I, **P**, **C**								
PC 34: Textile dyes, and impregnating products	I, **A**											F, I, **P**, **C**								
PC 23: Leather treatment products												F, I, **P**, **C**								
PC 14: Metal surface treatment products												F, I, **P**, **C**								
PC 38: Welding and soldering products, flux products												F, I, **P**								

EC number	300-491-4	304-037-6	400-660-3	476-670-7	692-065-2	813-880-3	824-774-1	902-532-7	902-533-2	915-008-8	915-009-3	927-442-5	931-053-6	934-405-7	934-407-8	938-868-6	939-867-3	944-341-1	946-985-9	947-740-9
Metal	**Cu**	**Mn**	**Fe**	**Fe**	**Ni**	**Fe**	**Fe**	**Ca**	**Mg**	**Cu**	**Mn**	**Fe**	**Zn**	**Al**	**Al**	**Cu**	**Mn**	**Ca**	**Mg**	**Ni**
PC 7: Base metals and alloys												F, I, **P**								
PC 33: Semiconductors												F, I, **P**								
PC 21: Laboratory chemicals		F, **P**		**P**			F, **P**					F, I, **P**				F, **P**				
PC 19: Intermediate												F, I, **P**								
PC 40: Extraction agents												F, I, **P**								
PC41: Oil and gas exploration or production products																				
PC42: Electrolytes for batteries																				
PC 30: Photo-chemicals												F, I, **P**, **C**								

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

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

Data extracted on 01/09/2022

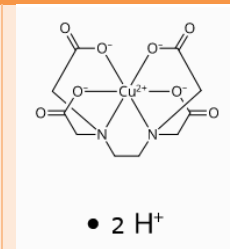
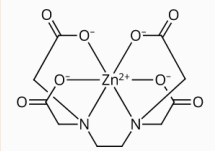
EC entries	RMOA	Authorisation		Restriction	CLH	Actions not under REACH/ CLP*
		Candidate List	Annex XIV	Annex XVII	Annex VI (CLP)	
411-640-9					YES	NONS

*Some of the broad restriction entries in the Annex XVII of REACH are not represented in the overview, e.g. when the scope of the restriction is defined by its classification or the substance identification is broad (e.g. entries 3, 28-30 and 40).

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

Annex 4: Non exhaustive list of substances in the C&L inventory that may fall into the group definition

The following substances and group entry were found but not yet selected for inclusion of this group as they were not mentioned for read-across.

EC/List number	CAS number	Substance name; acronym	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [11]
259-169-6	54453-03-1	Dihydrogen [[N,N'-ethylenebis [N-(carboxymethyl)glycinato]] (4-)-N,N',O,O',ON,ON'] cuprate(2-); **EDTA-Cu**		C&L notifications
290-989-7	90294-99-8	Copper, EDTA complexes (group entry)		Not registered
922-432-7	12519-36-7	[[*N*,*N*′-1,2-ethanediylbis[*N*-[(carboxy-κ*O*)methyl]glycinato-κ*N*,κ*O*]](4-)] zincate(2-); **EDTA-Zn**		Not registered

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