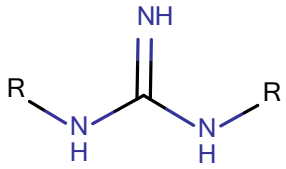
Assessment of regulatory needs

Authority: European Chemicals Agency (ECHA)

Group Name: Guanidylureas, cyanoguanidines and biguanides

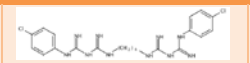
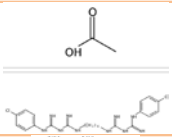
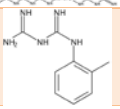
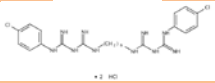
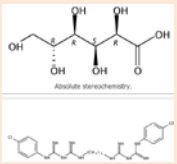
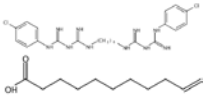
General structure:



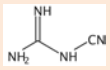
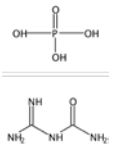
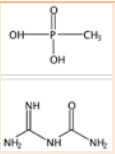
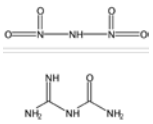
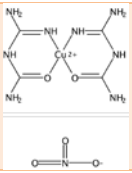
Revision history

Version	*Date*	*Description*
1.0	10 December 2021	

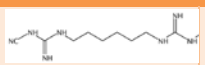
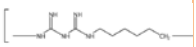
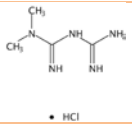
Substances within this group:

	EC / List number	CAS number	Substance name	Chemical structure	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
Aromatic biguanides	200-238-7	55-56-1	Chlorhexidine		TII/OSII, not (publicly) available
	200-302-4	56-95-1	Chlorhexidine di(acetate)		Not registered
	202-268-6	93-69-6	1-o-tolylbiguanide		Full, not (publicly) available
	223-026-6	3697-42-5	Chlorhexidine dihydrochloride		Full, not (publicly) available
	242-354-0	18472-51-0	D-gluconic acid, compound with N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecane diamidine (2:1)		Full, 10-100
	813-944-0	1884575-91-0	N,N'-bis{N-[N-(4-chloro phenyl)carbamimidoyl] carbamimidoyl}hexane-1,6-bis(aminium) diundec-10-enoate		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	Chemical structure	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [2]
Guanidylureas and cyanoguanidines	207-312-8	461-58-5	Cyanoguanidine		Full, > 1000
	241-659-6	17675-60-4	Amidinourea phosphate		Full, not (publicly) available
	282-758-4	84402-58-4	Methylphosphonic acid, compound with amidinourea (1:1)		Full, not (publicly) available
	451-590-5		1-carbamimidoylurea - (nitroamino)(oxo)azane oxide (1:1)		NONS, not (publicly) available
	800-038-5	1071838-81-7	Copper(2+), bis[N-[amino(imino-.kappa.N) methyl]urea-.kappa.O]-, nitrate (1:2)		Full, not (publicly) available

[2] 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	Chemical structure	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [3]
Aliphatic dicyanogyanidine, their biguanide derivatives	240-032-4	15894-70-9	N,N'''-1,6-hexanediylbis [N'-cyanoguanidine]		Full, not (publicly) available
	608-042-7	27083-27-8	PHMB		Not registered
	608-723-9	32289-58-0	PHMB; polyhexa methylene biguanide hydrochloride		
	618-745-0	91403-50-8	Poly(hexamethylene biguanid)-hydrochlorid		
	687-569-4	32289-58-0	Poly(iminoimidocarbonyl iminoimidocarbonylimino hexamethylene), hydrochloride (8CI)		
	214-230-6	1115-70-4	Metformin hydrochloride		Full, not (publicly) available

This table does not contain group members that are only notified under the CLP Regulation. 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.

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

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[4].

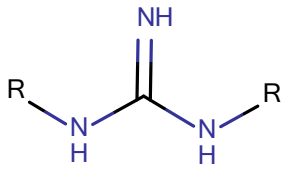
[4] https://echa.europa.eu/understanding-assessment-regulatory-needs

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 the guanidyl moiety shown in the figure below.



This group on 'Guanidylureas, cyanoguanidines and biguanides' is a subset of groups around the guanidyl moiety, which either are part of future ECHA group assessments or are part of a different assessment framework.[5]

This group consists in total of 14 substances. One substance is only registered as intermediate (chlorhexidine, EC 200-238-7) and two are not registered under REACH:

- A C&L notified substance Chlorhexidine di(acetate) (EC 200-302-4); and
- One approved as active substance for use in biocides in the EU (Polyaminopropyl Biguanide (PHMB) identified by four list numbers: List 608-042-7 / 608-723-9 / 618-745-0 / 687-569-4)[6] with harmonised classifications for skin sensitisation (Skin Sens. 1B), carcinogenicity (Carc. 2), repeated exposure target organ toxicity (STOT RE 1) and aquatic toxicity (Aquatic Acute 1 and Chronic 1).

Based on information reported in the REACH registration dossiers, six of the substances are used as preservatives for their biocidal, antiseptic and antimicrobial properties. This is the case for chlorhexidine, the four salts of chlorhexidine included in the group (EC 200-302-4, 223-026-6, 242-354-0 and List 813-944-0) as well as the approved biocide PHMB[7]. All of these six substances are used as preservatives in industrial, professional and consumer uses including in clinical uses, personal care products but also washing and cleaning products. Exposure and release potential to these preservatives is therefore expected to be high including for consumers and professionals. One of the four salts (EC 242-354-0) is currently evaluated for its use as active substance in biocides including in products for human hygiene. Next to the Biocidal Products Regulation, many of these preservatives are also subject to the Cosmetics Products Regulation, Medical Products Regulation and Medical Devices Regulation.

[5] These groups are a) Guanidine and simple guanidinium salts, b) aromatic guanidines, c) non-aromatic guanidines and d) aminoureas, aminoguanidines and nitroguanidines.

[6] List numbers 618-745-0 and 687-569-4 were created in error and are linked to no longer existing CAS numbers (91403-50-8 and 322895-80-). The two remaining list numbers 608-042-7 and 608-723-9 are both valid and link to two separate CAS numbers (27083-27-8 and 32289-58-0). The former describes PHMB in terms of its monomers and the latter as the resulting polymer.

[7] Approval was denied among others for use in human hygiene products.

Although not used as a preservative on its own, the monomer of the approved biocide PHMB (EC 240-032-4) is also included in the group, mainly to clarify whether hazards of the approved biocide may also apply to this substance.

A further six substances in the group are used as propellants (Copper(2+), bis[N-[amino(imino-.kappa.N) methyl]urea-.kappa.O]-, nitrate (1:2), List 800-038-5 and 1-carbamimidoylurea - (nitroamino)(oxo)azane oxide (1:1), EC 451-590-5), as flame retardants for example in textiles (Methylphosphonic acid, compound with amidinourea (1:1), EC 282-758-4 and Amidinourea phosphate, EC 241-659-6) and as binding agents (Cyanoguanidine, EC 207-312-8 and 1-o-tolylbiguanide, EC 202-268-6). While exposure and release potential are expected to be low for the flame retardants and propellants, there may be significant worker exposure to the binding agents and in particular for EC 202-268-6. There is also a high release potential for EC 207-312-8 given its use in fertilisers.

Metformin hydrochloride (EC 214-230-6) is used in pharmaceuticals, as a laboratory chemical and intermediate and there is potential for releases into the environment due to widespread uses in medical products.

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 endocrine disrupting effects in the environment and potential for exposure for the substances in the biguanides group namely for chlorhexidine (EC 200-238-7) and its four salts (EC 200-302-4, 223-026-6, 242-354-0 and 813-944-0) as well as 1-o-tolylbiguanide (EC 202-268-6). For metformin hydrochloride (EC 214-230-6) only SVHC identification is suggested.

Data from the scientific literature indicates that metformin hydrochloride (EC 214-230-6) may be an endocrine disruptor in the environment. One hypothesis could be that endocrine disrupting effects may be associated with the biguanide structure in metformin hydrochloride and this hazard therefore has the potential to also be relevant for the other biguanides in the group. Metformin hydrochloride is an active pharmaceutical ingredient approved by the European Medicines Agency (EMA) for a variety of drugs that treat type 2 diabetes[8]. Approval by EMA for many of these drugs however dates back to before 2005[9], when market authorisations became conditional on an environmental risk assessment. Potential ED hazards to the environment were thus not considered at the time of approval for many of the drugs. REACH registration data further suggests metformin hydrochloride is used as an intermediate and laboratory chemical. Its presence in wastewater (see e.g. Lee et al., 2019) suggests that there may be significant releases into the environment.

SVHC listing of metformin hydrochloride could trigger further regulatory action under the EU Medicinal Products Regulation at EMA. Such synergies seem to resonate with the aims of the current EU Chemicals Strategy for Sustainability and support a "One substance - one assessment"[10] approach, as well as with the EU Strategic Approach to Pharmaceuticals in the Environment. In addition, SVHC identification could trigger voluntary action to limit emissions into the environment on behalf of the pharmaceutical industry. A REACH restriction could nonetheless be an option in the future in case risks to the environment from medicinal products are not sufficiently addressed. REACH authorisation for metformin hydrochloride is not an option given the uses as active pharmaceutical ingredients and existing EMA approvals.

Chlorhexidine and its salts are used as preservatives in consumer products, medical products and devices as well as cosmetics. They are used for their biocidal, antiseptic and antimicrobial properties and there is also an application for approval as active biocidal substance for 242-354-0. Industrial, professional and consumer uses are widespread and exposure as well as release potentials are high. They are used by professionals and consumers in a range of products such as eye drops, mouth washes and air care products. The substitution potential between the four salts in particular is high. 1-o-tolylbiguanide is used as binding agent/hardener in polymers and textile dyes. There is potential for worker exposure and environmental releases for it due to at least some manual application in powder form with PPE only.

As a first step metformin hydrochloride (EC 214-230-6) is proposed to be added onto the Community rolling action plan (CoRAP) to initiate substance evaluation to clarify the environmental ED properties. In addition, CCH is proposed to be done in parallel with the SEv to request further aquatic toxicity data for the other registered non-intermediate biguanides. If the outcome of SEv supports the environmental ED concern the need for further data generation for the other registered non-

[8] An estimated 1 200 tonnes of metformin hydrochloride alone were prescribed in Germany in 2011 to treat type 2 diabetes (Brandmayr et al., 2015). The drug is also used to treat other common conditions (e.g. Lashen, 2010).

[9] E.g. for Glucophage: https://www.ema.europa.eu/en/documents/referral/summary-information-referral-opinion-following-arbitration-pursuant-article-11-council-directive-75/319/eec-amended-glucophage/glucophage-forte/risidon/dianben-international-non-proprietary-name_en.pdf

[10] See e.g. https://www.echa.europa.eu/documents/10162/21877836/efsa-echa-position-paper-osoa_en.pdf/74b1ae31-290b-a608-85e9-05b340840b34

intermediate biguanides under SEV will be considered. If substance evaluation is eventually initiated for environmental ED for metformin hydrochloride, it could also be considered to clarify the ED hazard to human health for metformin as well as the other six biguanides.

All seven biguanides[11]**Error! Bookmark not defined.** in the group are also potentially very persistent, very mobile and (potentially) aquatic toxic. Compliance check and if needed substance evaluation is suggested to clarify persistency and mobility.

The first step of the regulatory risk management action proposed, should the hazard exist, is the confirmation of hazard via SVHC identification[12] and inclusion of all the substances on the Candidate List as ED ENV.

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, (ii) responding to consumer requests within 45 days and (iii) notifying ECHA if the article they produce contains the substance above regulatory threshold.

Confirmation of the hazard properties via SVHC identification is not considered sufficient to minimise potential releases of the substances in the environment. A restriction is seen as the most appropriate option as potential for exposure is expected from their uses as preservatives in consumer products such as personal care, washing/cleaning, polishes/waxes and air care products, medical products and devices as well as cosmetics.

Releases to the environment from consumer uses cannot be avoided. Widespread professional uses are typically non-contained and non-automated leading to releases to the environment. Therefore, a restriction of the substances as such or in mixtures (concentration limit in mixtures) used by consumers, professional workers and industrial workers, is suggested after SVHC identification, with the aim to minimise exposures and emissions to humans and the environment. The use of ED substances by consumers and professional workers has been recognised as an area of concern under the European Commission's Chemicals Strategy for Sustainability[13].

Potential PMT properties should be considered in the restriction if clarified after generation of data.

In addition, chlorhexidine and its salts are known or likely aquatic toxic but are currently not consistently self-classified as such and there is some uncertainty regarding long-term aquatic toxicity. Compliance check is therefore recommended on all substances proposed for inclusion in CoRAP It is expected that after compliance check, registrants would adequately self-classify the substances and implement the relevant RMM which would be sufficient to ensure safe use in accordance with environmental legislation.

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[11] metformin hydrochloride (214-230-6), chlorhexidine (200-238-7) and its four salts (200-302-4, 223-026-6, 242-354-0 and 813-944-0) as well as 1-o-tolylbiguanide (202-268-6)

[12] 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.

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

Based on information available in the registration dossiers there is no indication of systemic toxicity or mutagenicity. For substance EC 242-354-0 two carcinogenicity studies from 1981/1983 are available in rat and mouse indicating no enhanced tumour activity. Chlorhexidine and its salts are not fetotoxic or toxic to reproduction. No effects on fertility and no effects in reproductive or endocrine system organs. The compliance check will further assess the absence of CMR/ED (for human health) potential and/or the need for related data generation.

Chlorhexidine and its salts and 1-o-tolylbiguanide are known or potential skin sensitisers. For 1-o-tolylbiguanide, self-classification for skin sensitisation hazard is incomplete: While REACH registrants classify for Skin Sens. 1, only about 60% of the C&L notifications include this hazard. It is recommended that the compliance check also clarifies whether the hazard is category 1A or 1B. For chlorhexidine and its salts, compliance check could then also confirm existing data on skin sensitisation and possibly generate additional data, also because many of the hazard endpoints currently rely on read-across to data for D-gluconic acid, compound with N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetra decane diamidine (2:1) (EC 242-354-0). This should then result in proper and complete self-classification by all registrants.

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

Adequate product labelling should then in principle also provide consumers with sufficient information to manage risks arising from the use of mixtures containing chlorhexidine and its salts.

However, there is a concern related to skin sensitisers (potentially) present in consumer mixtures and the need to 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.

Currently no need for (further) EU regulatory risk management for the remaining substances in the group.

Based on ECHA’s assessment of hazard information currently available in the registration dossiers and considerations of structural similarity of the substances, the aromatic biguanides, guanidylureas and cyanoguanides do not seem to have CMR, ED HH or STOT RE hazards excluding substance Copper(2+), bis[N-[amino(imino-.kappa.N)methyl]urea-.kappa.O]-, nitrate (1:2) (List 800-038-5) which has a known hazard for mutagenicity and STOT RE.

For 1-carbamimidoylurea - (nitroamino)(oxo)azane oxide (1:1) (EC 451-590-5) there is remaining uncertainty for reproductive toxicity, in particular developmental toxicity, due to the presence of nitro moieties within the composition for this substance and is not linked to the guanidine moiety. There is no specific reproductive toxicity data for this substance, however, based on CLH intention for nitroalkenes (nitromethane and nitroethane), the potential for developmental toxicity from the nitro moiety present in the substance cannot be excluded.

All substances in the subgroups ‘aromatic biguanides’ and ‘aliphatic dicyanogyanidine, their biguanide derivatives’ as well as substance ‘Copper(2+),

bis[N-[amino(imino-.kappa.N)methyl]urea-.kappa.O]-, nitrate (1:2)' (List 800-038-5) are potential or known skin sensitisers. The data available in the registration dossiers of substances in subgroup 'guanidylureas and cyanoguanidines' does not indicate potential for skin sensitisation (negative results for EC 282-758-4, 241-659-6, and 207-312-8). However, there is remaining uncertainty taking into account the skin sensitisation potential identified for substances in other subgroups and, therefore, further data generation via CCH is needed to confirm the presence or absence of this hazard.

Polyhexanide biguanide (PHMB; List 608-042-7 / 608-723-9 / 618-745-0 / 687-569-4) has been found to be repeated dose toxic (STOT RE 1 via inhalation), carcinogenic (Carc. 2), skin sensitising (Skin Sens. 1B) and aquatic toxic (Aquatic Acute 1 and Aquatic Chronic 1). It is used as preservative in consumer products, medical products and devices as well as cosmetics. As such, it is used in a range of products including in cosmetics, beer brewing, farm operations, animal care and so on. The substance is already subject to a harmonised classification for all the above hazards. PHMB is also subject to the EU Biocidal Products Regulation and was not approved for use as active biocidal substance in human hygiene products, drinking water, preservatives and fibres due to the associated risks. In addition, it may not be used in cosmetics products above a concentration of 0.1% as per Annex V of the EU Cosmetic Products Regulation. No follow-up action is proposed. Further investigations (e.g. with respect to endocrine disrupting properties) regarding this substance would need to take place under BPR.

N,N'''-1,6-hexanediylbis [N'-cyanoguanidine] (EC 240-032-4), as the monomer of PHMB, is expected to be repeated dose toxic (STOT RE 1 via inhalation), carcinogenic (Carc. 2), skin sensitising (Skin Sens. 1B) and aquatic toxic (Aquatic Acute 1 and Aquatic Chronic 1) similar to PHMB. This substance is however only used as intermediate and laboratory chemical and exposure and release potentials are currently low and no EU regulatory risk management is foreseen at this point. Compliance check for the substance is nonetheless recommended to address current data gaps in the dossier for reproductive and developmental toxicity and for long term aquatic toxicity and mobility.

Copper(2+), bis[N-[amino(imino-.kappa.N) methyl]urea-.kappa.O]-, nitrate (1:2) (List 800-038-5) is self-classified as mutagenic (Muta. 2), repeated dose toxic (STOT RE 2), skin sensitising (Skin Sens. 1B) and aquatic toxic (Aquatic Acute 1 and Aquatic Chronic 1). No additional hazards were identified during the screening at hand. The use of this substance appears to currently be limited to the production of gas generators by two registrants only and most of the activities on-site appear to be automated. Exposure and release potential of this substance are therefore low. Self-classification applies to the limited industrial uses currently registered. It is therefore assumed that risk management measures in line with existing worker protection legislation adequately control risks. Compliance check is nonetheless proposed to clarify the level of mutagenicity hazard, developmental toxicity and confirm persistence, mobility and long-term aquatic toxicity.

1-carbamimidoylurea - (nitroamino)(oxo)azane oxide (1:1) (EC 451-590-5) is an unclaimed NONS with a low registered tonnage band. Based on the information available and owing to the low level of use in only industrial settings and the associated low exposure and release potential no further regulatory actions are planned currently.

Methylphosphonic acid, compound with amidinourea (1:1) (EC 282-758-4) and Amidinourea phosphate (EC 241-659-6) are both used as flame retardants for example in paper and board treatment products but also in non-washable textiles. They are potential substitutes for one another. There are no known or potential

hazards to human health for either of them while only Methylphosphonic acid, compound with amidinourea (1:1) has a lower-level aquatic toxicity (Aquatic Chronic 3). Compliance check is nonetheless proposed for it to clarify mobility.

Cyanoguanidine (EC 207-312-8) is used as binding agent in surface treatment, in polymers, paints and textile dyes. The substance has the highest tonnage band among the entire group and widespread industrial and professional uses including application as a nitrification inhibitor for fertiliser by farmers. This substance is potentially P/vP and is expected to be mobile in the environment. Since this is an Annex X substance with high release potential to surface waters, soil and ground water due to the use as fertiliser, compliance check is proposed to clarify the potential persistency and mobility of the substance. However, for the time being no EU regulatory risk management is proposed for this substance until confirmation of the hazard properties.

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 number, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
214-230-6 Metformin hydrochloride **Chlorhexidine and salts** **200-238-7** Chlorhexidine **200-302-4** Chlorhexidine di(acetate) **223-026-6** Chlorhexidine dihydrochloride **242-354-0** D-gluconic acid, compound with N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecane diamidine (2:1)	**Metformin hydrochloride** No hazard or unlikely hazard **Chlorhexidine and salts and 1-o-tolylbiguanide** Known or potential hazard for skin sensitisation	Known or potential hazard for aquatic toxicity for P/vP and mobility for ED ENV	**Metformin hydrochloride** Widespread industrial use in pharmaceuticals with high potential for releases **Chlorhexidine and salts** Widespread I, P, C, A uses as preservative with high potential for exposure and release **1-o-tolylbiguanide** Widespread industrial uses only including in textiles; uncertain exposure and release	**Need for EU RRM: Restriction** For Metformin hydrochloride a REACH restriction could be an option in the future in case risks to the environment from medicinal products are not sufficiently addressed.	**First step:** CCH, except for 214-230-6 200-302-4 200-238-7 Substance evaluation for 214-230-6 **Next steps (if hazard confirmed):** SVHC identification Restriction (for Chlorhexidine and salts and 1-o-tolylbiguanide)

Subgroup name, EC number, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
813-944-0 N,N'-bis{N-[N-(4-chloro phenyl)carbamimidoyl] carbamimidoyl}hexane-1,6-bis(aminium) diundec-10-enoate **202-268-6** 1-o-tolylbiguanide			potential but likely not high.		
PHMB **608-042-7** **608-723-9** **618-745-0** **687-569-4**	Known or potential hazard for skin sensitisation for STOT RE for carcinogenicity (Carc. 2)	Known or potential hazard for aquatic toxicity for P/vP and mobility	No registered use (approved as biocide under BPR)	Currently no need for EU RRM Justification: No uses other than the biocidal active substance	No action
240-032-4 N,N'''-1,6-hexanediylbis [N'-cyanoguanidine]			Currently not widespread, Industrial and intermediate only	Currently no need for EU RRM Justification: Only industrial and intermediate uses	**First step:** CCH
800-038-5 **Copper(2+), bis[N-[amino(imino-.kappa.N)**	Known or potential hazard for skin sensitisation for STOT RE		Only limited industrial use as propellant in the production of gas	Currently no need for EU RRM Justification:	

Subgroup name, EC number, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
methyl]urea-.kappa.O]-, nitrate (1:2)	for mutagenicity		generators. Low exposure and release potential.	Low exposure and release potential from limited industrial uses	
207-312-8 Cyanoguanidine **241-659-6** Amidinourea phosphate **282-758-4** Methylphosphonic acid, compound with amidinourea (1:1) **451-590-5** 1-carbamimidoylurea - (nitroamino)(oxo)azane oxide (1:1)	No hazard or unlikely hazard	Known or potential hazard for P/vP and mobility for aquatic toxicity Except 207-312-8	Industrial uses 207-312-8: Professional use in fertilisers	Currently no need for EU RRM Justification: The need for EU RRM will be further investigated once the hazard properties will be clarified after data generation.	**First step:** CCH for 207-312-8 282-758-4

Annex 1: Overview of classifications

Data extracted on 18 November 2022

EC/ List No	CAS No	Substance name	Harmonised classification	Classification in registrations
200-238-7	55-56-1	Chlorhexidine	-	Aquatic Chronic 1 H410, M-factor: 10.00 Eye Damage 1 H318 Aquatic Acute 1 H400, M-factor: 10.00
200-302-4	56-95-1	Chlorhexidine di(acetate)	-	-
202-268-6	93-69-6	1-o-tolylbiguanide	-	Eye Irrit. 2 H319 Skin Sens. 1 H317 Aquatic Chronic 3 H412
207-312-8	461-58-5	Cyanoguanidine	-	-
214-230-6	1115-70-4	Metformin hydrochloride	-	Acute Tox. 4 H302 Eye Irrit. 2 H319
223-026-6	3697-42-5	Chlorhexidine dihydrochloride	-	Eye Irrit. 2 H319 Aquatic Acute 1 H400, M-factor: 10.00 Aquatic Chronic 1 H410
240-032-4	15894-70-9	N,N'''-1,6-hexanediylbis[N'-cyanoguanidine]	-	-
241-659-6	17675-60-4	Amidinourea phosphate	-	Acute Tox. 4 H302
242-354-0	18472-51-0	D-gluconic acid, compound with N,N''-bis(4-chlorophenyl)-3,12-	-	Eye Damage 1 H318 Aquatic Acute 1 H400, M-factor:

EC/ List No	CAS No	Substance name	Harmonised classification	Classification in registrations
		diimino-2,4,11,13-tetraazatetradecanediamidine (2:1)		10.00 Aquatic Chronic 1 H410
282-758-4	84402-58-4	Methylphosphonic acid, compound with amidinourea (1:1)	-	-
451-590-5	217464-38-5	1-carbamimidoylurea - (nitroamino)(oxo)azane oxide (1:1)	-	Expl. Div. 1.4 H204 Flam. Solid 2 H228
608-042-7	27083-27-8	Poly(hexamethylene biguanid)-hydrochlorid	Index number: 616-207-00-X Acute Tox. 4 Hazard Statement: H302 STOT RE 1 Hazard Statement: H372 [respiratory tract; inhalation] Hazard Category: Eye Dam. 1 Hazard Statement: H318 Carc. 2 Hazard Statement: H351 Acute Tox. 2 Hazard Statement: H330 Aquatic Acute 1 Statement: H400 Aquatic Chronic 1 Statement: H410 Skin Sens. 1B Statement: H317 10 M-Factor (chronic); 10 M-Factor (acute)	-
608-723-9	32289-58-0	PHMB;polyhexamethylenebiguanide hydrochloride	Index number: 616-207-00-X Acute Tox. 4 Hazard Statement: H302 STOT RE 1 Hazard Statement: H372 [respiratory tract; inhalation] Hazard Category: Eye Dam. 1 Hazard Statement: H318 Carc. 2 Hazard Statement: H351 Acute Tox. 2 Hazard Statement: H330 Aquatic Acute 1 Statement: H400 Aquatic Chronic 1 Statement: H410 Skin Sens. 1B Statement: H317	-

EC/ List No	CAS No	Substance name	Harmonised classification	Classification in registrations
			10 M-Factor (chronic); 10 M-Factor (acute)	
618-745-0	91403-50-8	PHMB	-	-
687-569-4 Error! Bookmark not defined.	322895-80-0	Poly(iminoimidocarbonyliminoimidocarbonyliminohexamethylene),hydrochloride (8CI)	-	-
800-038-5	1071838-81-7	Copper(2+), bis[N-[amino(imino-.kappa.N)methyl]urea-.kappa.O]-, nitrate (1:2)	-	Muta. 2 H341 Acute Tox. 4 H302 Skin Irrit. 2 H315 Eye Damage 1 H318 Skin Sens. 1B H317 STOT Rep. Exp. 2 H373 Aquatic Acute 1 H400, M-factor: 10.00 Aquatic Chronic 1 H410
813-944-0	1884575-91-0	N,N'-bis{N-[N-(4-chlorophenyl)carbamimidoyl]carbamimidoyl}hexane-1,6-bis(aminium) diundec-10-enoate	-	-

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

Data extracted on 20 May 2021

Main types of applications structured by product or article types	EC/List	800-038-5	451-590-5	282-758-4	241-659-6	207-312-8	242-354-0	223-026-6	813-944-0	202-268-6	200-238-7	200-302-4	608-042-7	240-032-4	214-230-6
PC 11: Explosives			I												
PC 12: Fertilisers						F, **P**									
PC 4: Anti-freeze and de-icing products						F									
PC 35: Washing and cleaning products		I					F, I, **P**, **C**	F, I, **P**, **C**							
PC 8: Biocidal products (e.g. disinfectants, pest control)		I					F, I, **P**, **C**	**C**							
PC 28: Perfumes, fragrances							F, I, **P**, **C**	F, I, **P**, **C**							
PC 3: Air care products							F, I, **C**	**C**							
PC 39: Cosmetics, personal care products						F	F, I, **P**, **C**, **A**	F, I, **P**, **C**, **A**	**C**	F					
PC 29: Pharmaceuticals							**C**		**C**		I				I

Main types of applications structured by product or article types	EC/List	800-038-5	451-590-5	282-758-4	241-659-6	207-312-8	242-354-0	223-026-6	813-944-0	202-268-6	200-238-7	200-302-4	608-042-7	240-032-4	214-230-6
PC 31: Polishes and wax blends							F, I, **C**	**C**							
PC 15: Non-metal-surface treatment products					F, I	F, I, **P**									
PC 32: Polymer preparations and compounds		I				F, I, **P**				F, I					
PC 1: Adhesives, sealants						F, I, **P**									
PC 9b: Fillers, putties, plasters, modelling clay						F, I, **P**									
PC 9a: Coatings and paints, thinners, paint removes						F, I, **P**			**C**	I					
PC 26: Paper and board treatment products				I, **A**			**P**			F					
PC 34: Textile dyes, and impregnating products				F, I, **A**		F, I, **P**				I					
PC 23: Leather treatment products						F, I, **A**									
PC 38: Welding and soldering products, flux products		I													
PC 21: Laboratory chemicals						F	F							I	I
PC 19: Intermediate						I					I			I	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

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

Data extracted on 29 April 2021

EC / List number	RMOA	Authorisation		Restriction*	CLH	Actions not under REACH / CLP
		Candidate list	Annex XIV	Annex XVII	Annex VI (CLP)	
200-238-7						Subject to Cosmetics Regulation Annex V
200-302-4						Subject to Cosmetics Regulation Annex V
223-026-6						Subject to Cosmetics Regulation Annex V
242-354-0						Application for approval as biocide evaluated by PT. Decision outstanding. Subject to Cosmetics Regulation Annex V
608-042-7					YES	Approved biocide (excludes product types with high human exposure)
608-723-9					YES	
618-745-0					YES	
687-569-4					YES	

*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.