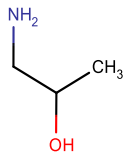
Assessment of regulatory needs

Authority: European Chemicals Agency (ECHA)

Group Name: Isopropanolamines

General structure:



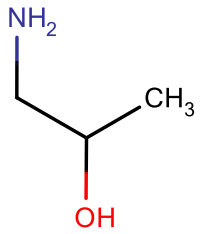
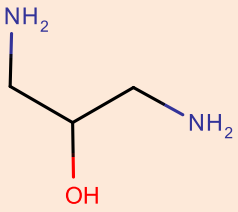
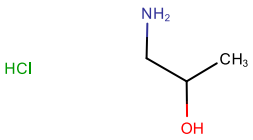
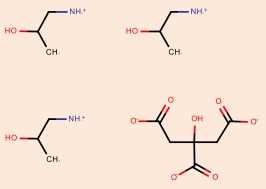
isopropanolamine

Revision history

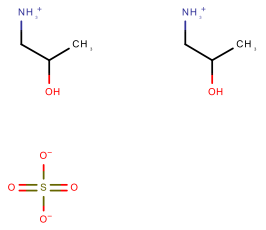
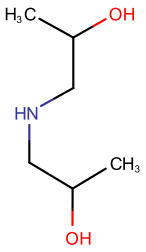
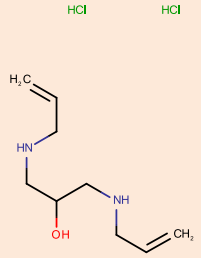
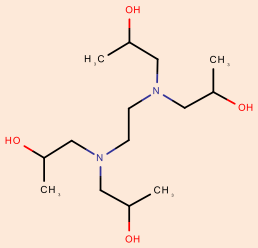
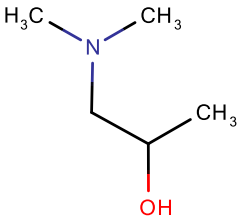
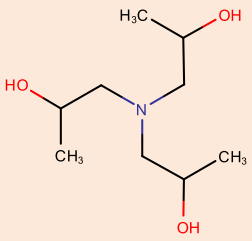
Version	*Date*	*Description*
1.0	3 January 2024	

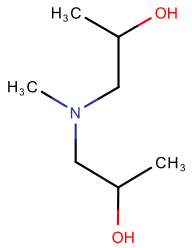
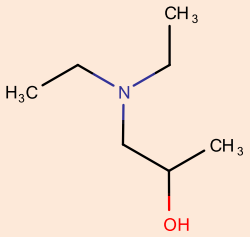
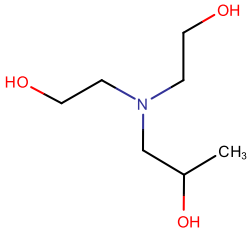
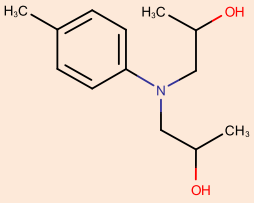
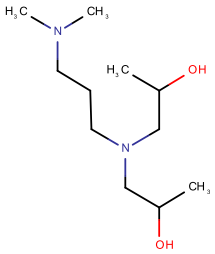
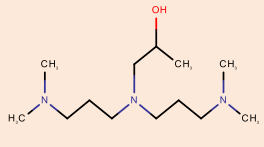
Substances within this group:

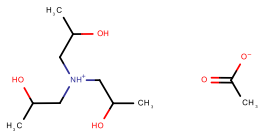
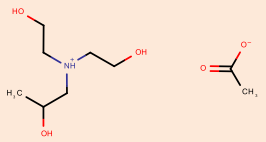
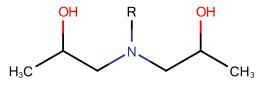
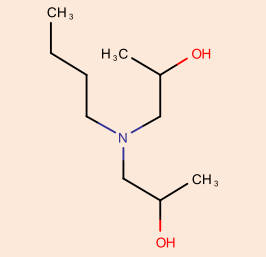
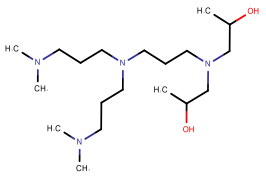
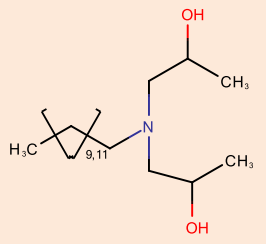
The substances in this group were subdivided in sub-groups based on whether they are primary, secondary or tertiary amines and their respective salts. The table below illustrates this subdivision.

EC/List no	CAS no	Substance name (acronyms)	Chemical structures	Registration type (full, OSII or TII, NONS, cease manufacture), highest tonnage band among all the registrations (t/y) [1]
Primary isopropanolamines and their salts				
201-162-7	78-96-6	1-aminopropan-2-ol **(MIPA)**		Full, >1000
210-474-2	616-29-5	1,3-diaminopropan-2-ol		OSII or TII
231-948-5	7780-04-3	1-aminopropan-2-ol hydrochloride		C&L notification
250-342-1	30798-32-4	(2-hydroxypropyl)ammonium citrate		Full, not (publicly) available

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

946-381-5		2-hydroxypropan-1-aminium sulfate		Full, not (publicly) available
Secondary isopropanolamines and their salts				
203-820-9	110-97-4	1,1'-iminodipropan-2-ol **(DIPA)**		Full, >1000
692-156-7	1101184-94-4	2-Propanol, 1,3-bis(2-propen-1-ylamino)-, hydrochloride (1:2)		OSII or TII
Tertiary isopropanolamines and their salts				
203-041-4	102-60-3	1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol		Full, >1000
203-556-4	108-16-7	1-(dimethylamino)propan-2-ol		Full, not (publicly) available
204-528-4	122-20-3	1,1',1''-nitrilotripropan-2-ol **(TIPA)**		Full, >1000

224-536-1	4402-30-6	1,1'-(methylimino)dipropan-2-ol		Full, not (publicly) available
224-537-7	4402-32-8	1-diethylaminopropan-2-ol		Full, not (publicly) available
229-764-5*	6712-98-7	1-(N,N-bis(2-hydroxyethyl)amino)propan-2-ol (DEIPA)		Full, >1000
254-075-1*	38668-48-3	1,1'-(p-tolylimino)dipropan-2-ol		Full, 100-1000
264-261-4	63469-23-8	1,1'-[[3-(dimethylamino)propyl]imino]bispropan-2-ol		Full, >1000
266-587-2*	67151-63-7	1-[bis[3-(dimethylamino)propyl]amino]propan-2-ol		Full, not (publicly) available

427-360-5		2-Propanol, 1,1',1''-nitrilotris, acetate		Full, not (publicly) available
444-360-0	191617-13-7	bis(2-hydroxyethyl)-(2-hydroxypropyl)ammonium acetate		NONS
695-977-9*	1309955-79-0	Propanol, iminobis-, N-(C16-18 and C18-unsatd. alkyl) derivs.		Full, not (publicly) available
814-434-0	4402-34-0	1-[butyl(2-hydroxypropyl)amino]propan-2-ol		OSII or TII
816-324-8*	2044770-20-7	1,1'-[(3-{bis[3-(dimethylamino)propyl]amino}propyl)imino]dipropan-2-ol		Full, not (publicly) available
911-174-0		1,1'-(dodecylimino)dipropan-2-ol + 1,1'-(tetradecylimino)dipropan-2-ol		OSII or TII

* Substances considered outliers from their subgroup.

This table contains also group members that are only notified under the CLP Regulation. However, the list is currently non-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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Foreword

The assessment of regulatory needs of a group of substances is an iterative, informal process to help authorities consider the most appropriate way to address an identified concern for a group of substances or a single substance and decide whether further regulatory risk management activities are necessary.

The grouping is mainly based on structural similarity and associations made by the registrants between substances through read-across and category approaches as well as category associations from external sources (e.g. OECD categories)[2]. These methods are different from grouping as defined in Section 1.5 of Annex XI to REACH because the scope and intended use of ECHA's grouping is different. Thus, in this context, grouping does not aim to validate read-across and category approaches according to the Annex XI requirements but rather to support a faster and more consistent approach for regulating chemicals and avoid regrettable substitution.

The focus of the assessment is largely based on information available in the registration dossiers and on properties requiring regulatory risk management action at EU level[3]. The information reported on uses is from the registration dossiers (IUCLID) and is used as a proxy for assessing how widespread uses are and whether potential for exposure to humans and releases to the environment can be expected. The chemical safety reports are not necessarily consulted and no quantitative exposure assessment is performed at this stage.

The outcome of these assessments are proposals for immediate (the first action) and subsequent regulatory action(s), including the foreseen ultimate regulatory action (last foreseen regulatory action) to address the identified concern(s) in case the potential hazards are confirmed. For example, further data generation through compliance check is suggested as a first action, to confirm the identified hazard.

Where hazards are confirmed, regulatory risk management actions could be considered for the whole group, for a subgroup or for individual substances within the group. The robustness of the group depends on the stage of assessment and the level of certainty this stage requires. For example, the needs for grouping under restriction may differ from the needs for grouping for the purpose of harmonised classification. Group membership is reconsidered accordingly throughout the iterative assessment of regulatory needs, for example, after further information is generated and the hazard has been clarified or when new insights on uses and risks are available.

The assessment of regulatory needs in itself does not represent a regulatory action, but rather a preparatory step to consider further possible regulatory actions at the level of individual substances or groups/subgroups of substances.

[2] Working with Groups - ECHA (europa.eu)

[3] Regarding hazard properties the focus is for instance 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 report. This does not mean that the substances do not have other known or potential hazards. In some specific cases, ECHA may consider additional hazards (e.g. neurotoxicity, STOT RE).

Publication of ARNs makes it easier for companies to follow the latest status of their substances of interest, anticipate potential regulatory actions and make strategic choices in their chemicals portfolio.

For more information on assessments of regulatory needs please consult ECHA's website[4].

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

Glossary

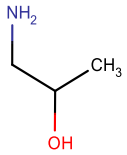
ARN	Assessment of Regulatory Needs
CCH	Compliance Check
CLH	Harmonised classification and labelling
CMR	Carcinogenic, mutagenic and/or toxic to reproduction
DEv	Dossier evaluation
ED	Endocrine disruptor
NONS	Notified new substances
OEL	Occupational exposure limit
OSII or TII	On-site isolated intermediate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

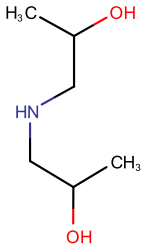
Explanations on the scope of this assessment is available in the foreword to this document. Please read it carefully before going through the report.

ECHA has grouped together structurally similar substances. The group can be described as isopropanolamines containing various functional groups and their salts.

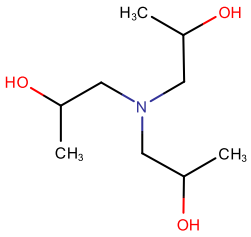
Depending on the number of hydrogen atoms displaced, they can be classified as *primary* (RNH2), *secondary* (R2NH) or *tertiary* (R3N) isopropanolamines. This element has been used for subgrouping.



primary isopropanolamine



secondary isopropanaolamine



tertiary isopropanolamine

It may be noted however that some substances from different sub-groups share close structural similarities.

According to the nature and number of substituents on the nitrogen the substances can be classified as aliphatic (e.g. alkylamines, ethylenediamines, fatty amines) or aromatic (p-toluidine). The hazard data shows a number of outliers from the sub-grouping which may possibly be due to the presence of structural moieties (such as the p-toluidine, fatty acid, diethanolamine) which may impact the toxicokinetic or toxicodynamic properties of the substances.

The group consists of 22 substances. Fifteen substances have at least one active Article 10 registration(s); four substances have intermediate registration(s) only (ECs/Lists 692-156-7, 814-434-0, 210-474-2, 911-174-0); two substances are NONS (ECs 444-360-0 and 427-360-5); one substance is only notified under the CLP Regulation (EC 231-948-5).

Most of the substances are mono-constituent substances. Two are multi-constituents and two are UVCBs (EC/Lists 254-075-1 and 695-977-9).

Based on information reported in the REACH registration dossiers, isopropanolamines substances are used in many applications. They are known to be used for their reactive properties e.g. reducing properties, pH regulating properties and/or cross-linking properties. Based on information reported in the REACH registration dossiers, main applications include use in polymers, adhesives, coatings and inks, use in construction chemicals (cements), use in textile, paper and leather processing, use in lubricants and fuels, use in washing and cleaning products, cosmetics, biocides, use in gas and water treatment and intermediate uses.

Potential for exposure to human health and releases to environment cannot be ruled out for most substances in the group, considering their professional uses and/or consumer uses, their potential presence in articles, their uses in processes potentially generating fumes or dust (e.g. lubrication, cement grinding) or in

products with potential high release in the environment (down the drain products such as e.g. washing and cleaning products, cosmetics, biocides). Few substances are registered for intermediate use only, leading to assumed more limited exposure/release potential.

Interchangeability/substitution among substances within the group or sub-groups is considered plausible, to a certain extent. Depending on their properties (e.g. molecular weight, physical form at ambient temperature) some substances appear however better suited than others for some applications.

2 Conclusions and proposed actions

The conclusions and actions proposed in the table below are based mainly on the REACH and CLP information available at the time of the assessment by ECHA. The conclusions are preliminary suggestions from a screening-level assessment done by ECHA with the aim to propose the next steps for further work (e.g., strengthening of the hazard conclusions, clarification of the uses and/or potential for exposure). 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 may be updated, and conclusions and actions revisited.

Subgroup name, EC/List no, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Suggested regulatory actions
EC 254-075-1 **EC 266-587-2** **EC 695-977-9** **EC 816-324-8** ***(Outliers of the tertiary isopropanolamines subgroup)***	Known or potential hazard for Repr for all substances in this subgroup and combined with STOT SE1 (nervous system) for EC 254-075-1.	Known or potential hazard for Aquatic toxicity for all substances in this subgroup.	Professional uses e.g. in various formulations used in the building and construction sector, potentially leading to inclusion in articles For List 816-324-8: Industrial use only, but potential for substitution with other hazardous substances in the group used by professional workers	**First step:** CCH for ECs 254-075-1 and 266-587-2. Await the outcome of ongoing data generation process for List 695-977-9. **Potential next steps (if hazard confirmed after data generation):** CLH (as a minimum for the Repr. and STOT SE (nervous system) hazards). **Potential last action:** **Restriction** with main focus on professional uses triggered by Repr. 1B / Repr. 2 for all 4 substances + by STOT SE1 (nervous system) for EC 254-075-1. Justification: professional uses likely to happen at many sites, indoor and outdoor, involve many users (including self-

				employed workers not covered by OSH), present limited possibilities for automation or engineering controls and lead to frequent exposure. Consumers co-exposure not excluded. For List 816-324-8: potential for substitution with other hazardous substances in the group used by professional workers.
Remaining members of the tertiary isopropanolamines subgroup	Inconclusive hazard for Repr. and ED	Inconclusive hazard for PBT/vPvB, PMT and aquatic toxicity for List 911-174-0 Inconclusive hazard for PMT for EC 203-041-4 Known or potential hazard for Aquatic toxicity for ECs 224-537-7, 266-587-2, 427-360-5, 444-360-0.	-	**First step**: new CCH for EC 264-261-4 Await the outcome of ongoing data generation on ECs 204-528-4, 264-261-4 203-041-4. Await for DEA classification. If DEA hazard confirmed, check that registrants apply the appropriate self-classification for EC 229-764-5 based on composition. **Currently not possible to assess the regulatory needs** Justification: Data is missing to conclude on Repr. and ED for all members Furthermore, for EC 203-041-4 and List 911-174-0 specifically: Data is missing to conclude on PBT/vPvB and /or PMT

All members of the primary and secondary isopropanolamines subgroups	No hazard or unlikely hazard	No hazard or unlikely hazard	-	Await the outcome of ongoing data generation (dossier evaluations decisions) for EC 201-162-7 (MIPA) **Currently no need for EU RRM**

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

Tertiary isopropanolamines and their salts

The chemical structure, hazard and use profile of substances belonging to the tertiary isopropanolamines and salts sub-group (hereafter referred to as tertiary isopropanolamines) presents some variability, leading to different regulatory strategies depending on the substances.

Based on currently available information, there is a need for (further) EU regulatory risk management – Restriction targeting mainly widespread uses (professional uses and possibly uses in articles) triggered by potential Repr. 1B combined with STOT SE1 (nervous system) hazard for EC 254-075-1, by potential Repr. 1B for EC 816-324-8, and by potential Repr. 2 for ECs 266-587-2 and 695-977-9. These substances present a chemical structure diverging from the other substances in the sub-group of tertiary isopropanolamines (*i.e.* structural outliers).

Based on ECHA's assessment of currently available hazard information, potential reproductive toxicity hazards were identified for all 4 substances. For EC 254-075-1, males showed reduced fertility index in an OECD TG 422 at all doses (2.5 to 40 mg/kg bw/day). This substance differs structurally from all the other isopropanolamines as it contains a p-toluidine substituent. In the case of EC 816-324-8, a dose-related decrease in pup weight, viability and increased mortality (at 60 and 200 mg/kg bw/day) was found in an OECD TG 421 study with limitations in the reporting of the study. For EC 266-587-2, adverse effects on development in the rat were observed in an OECD TG 422 (reductions in litter size, pup viability/survival with possible relation to maternal toxicity) and in an OECD TG 414 (increased skeletal variations in the absence of maternal toxicity). No adverse development was observed in an OECD TG 414 in rabbit. In the case of EC 695-977-9 there is a diethanolamine related moiety which raises a possible alert for reproductive toxicity. Further data has been requested on this substance in the context of a group of structurally analogous substances outside of this GMT to allow conclusion on the hazard.

It is noted that no consistent pattern emerges from the available information on these substances: there is a need for new compliance check for substance EC 254-075-1 and to await the outcome of the ongoing data generation process on the substance EC 695-977-9 to clarify the reproductive toxicity hazard.

Based on ECHA's assessment of currently available hazard information, single exposure toxicity hazard (nervous system) was identified for EC 254-075-1, there are indications of neurotoxicity (clinical signs such as tonic-clonic convulsions and mortality after one or several exposures) observed at 40/80 mg/kg bw/day in a study with repeated oral exposure in rat.

Furthermore, based on ECHA's assessment of currently available hazard information, repeated dose toxicity hazard was identified for EC/Lists 266-587-2 (STOT RE2, liver) and 695-977-9. For EC 266-587-2 the liver is a target organ for toxicity following repeated oral exposure. Adverse effects in the liver (single cell

necrosis from 25 mg/kg bw/day and liver fibrosis at 250 mg/kg bw/day) and also changes in haematology parameters were reported in rat following repeated dosing for 90 days. The registrant applies a self-classification of STOT RE2. For List 695-977-9, it is a fatty amine and there is a structural alert for diethanolamine which as a substance shows multiple target organ toxicities in animals[5]. As mentioned above, this substance and structurally related substances has been under data generation in the context of a group of structurally analogous substances outside of this GMT and the data are still being assessed.

The first step of the regulatory risk management action proposed is the confirmation of the potential Repr. and STOT SE1 (nervous system) hazards **via harmonised classification (CLH).** The harmonised classification will strengthen company level risk management measures for workers. In this context, the further hazards associated to the substances may be formally confirmed i.e. in addition to potential Repr. 1B or Repr. 2 for the substances EC/Lists 254-075-1, 266-587-2, 695-977-9, 816-324-8 and STOT SE1 (nervous system) for EC 254-075-1 the following further classifications could be confirmed after data generation:

- STOT RE for EC/Lists 266-587-2 and 695-977-9;
- Aquatic toxicity for EC/Lists 816-324-8 as well as 266-587-2 and 254-075-1 (after a compliance check is conducted) (see further information on environmental hazards below).

A restriction is suggested after harmonised classification. For the substances EC/Lists 254-075-1, 266-587-2, 695-977-9 and 816-324-8 the restriction appears to be justified based on the potential Repr. 1B or 2 hazard associated with widespread types of uses. Registered professional uses include (with some variation among substances) use of various products typically used in building and construction work e.g cement/concrete/mortar, road-marking materials, adhesives/sealants, different types of coatings, polyurethane foams and elastomers- potentially leading to the presence of the substances in articles, as well as professional uses in metal working fluids and lubricants. These types of uses are likely to happen at many sites, indoor and outdoor, involved many users, present limited possibilities for automation or engineering controls and lead to frequent exposure. Consumers may be co-exposed to the substances used by professionals[6]. In addition, professional users using these types of products may be self-employed and therefore not covered by occupational safety and health (OSH) legislation.

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.

Furthermore, the use of the most harmful substances by professional workers has been recognised as an area of concern under the European Commission's Chemicals

[5] Substance Evaluation Conclusion and Evaluation report. 2,2'Iminodiethanol (EC 203-868-0) available at https://echa.europa.eu

[6] It is noted that no 'consumer use' is reported in registrations. However, the extent to which the products formulated can be limited to strict use by professional workers and do not reach the general public is to a certain extent questionable.

Strategy for Sustainability[7] which aims to extend to professional users under REACH the level of protection granted to consumers.

The substance List 816-324-8 is reported to be used in lower tonnage and for flexible foams production at industrial sites only. Still, that substance is considered for harmonised classification and restriction together with the other three substances listed above, as it is deemed plausible that the substance could be used as part of substitution solution package for the other substances in the group. Furthermore, article service-life cannot be excluded based on the information currently available.

Potential exposure from articles needs further investigation. The need for restricting substances in articles (assumed to be potentially relevant for all 4 substances, though not always explicitly reported in registrations) should be considered in the context of the restriction of professional uses. All new information on presence of the substances in articles should be re-considered in the next iteration of this assessment and during the restriction dossier preparation. During the restriction dossier preparation, it should also be assessed whether regulatory risk management measure beyond harmonised classification would be needed to address risk from industrial uses.

The substance List 695-977-9 is in addition potentially PBT but no definite conclusion can be reached yet (i.e. PBT hazard is inconclusive). The substance is considered in this regard as an outlier from the tertiary isopropanolamines sub-group as it has much lower water solubility than the rest of the group and a higher Log Kow. It is a UVCB and therefore its properties will actually span a range of values. New information on biodegradation has been requested in a compliance check decision and is still being assessed and information on bioaccumulation may need to be requested. The substance is Aquatic toxic based on the long-term aquatic toxicity data which leads to self-classification Aquatic Acute 1 (M factor 10), Aquatic Chronic 1.

The substances EC/Lists 254-075-1, 266-587-2 and 816-324-8 are not readily biodegradable (potentially P/vP) and are expected to be very mobile in the environment and potentially toxic. Their bioaccumulation potential is not known but based on their structures and physico-chemical properties it is not expected that they will be bioaccumulative and thus PBT/vPvB. Compliance check is proposed for the Annex IX substances (ECs 254-075-1 and 266-587-2) to clarify their potential persistency, bioaccumulation potential and Koc. A degradation simulation test for EC 266-587-2 will also provide useful information for the substance List 816-324-8 which is structurally similar. The persistent, mobile and toxic properties of the substances shall be taken into consideration when progressing the regulatory action on these substances.

The substances ECs 254-075-1 and 266-587-2 (for which compliance check is recommended) and EC 816-324-8 are known or likely to have aquatic toxicity. A CLH proposal is proposed on these substances triggered by the Repr. hazard (see above). The aquatic toxicity hazard may possibly be considered for harmonisation in that context. However, in the meantime, it is expected that registrants would adequately self-classify the substances and implement necessary RMMs to ensure safe use. List 816-324-8 is already self-classified as Aquatic Chronic 3. Based on the available data, Aquatic Chronic 2 should be applied. We recommend that the

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

registrants apply the stricter classification. EC 254-075-1 is self-classified Aquatic chronic 3, although long-term fish and long-term Daphnia toxicity data are missing. These data should be requested in a compliance check to ensure that the most appropriate environmental classification is applied.

Based on currently available information, it is not possible to assess the need for regulatory risk management for substances in the tertiary isopropanolamines and their salts sub-group not covered above as information on hazard is not sufficient to conclude on reproductive toxicity and ED hazards. Furthermore, for EC/Lists 911-170-0 and 203-041-1 based on currently available information, it is also not possible to assess the need for regulatory risk management as information on hazard is not sufficient to conclude on PBT and/or PMT hazards.

This is the largest sub-group and comprises greater structural diversity in relation to the number of amine and alcohol substituents. The data currently available on these tertiary isopropanolamines do not show a consistent indication of reproductive toxicity, ED, and PBT/vPvB[8] hazards. These conclusions are based on the following data. As to reproductive and developmental toxicity, there is some inconsistency in the findings. A one generation reproductive toxicity study (TG 415 equivalent) by the dietary route of TIPA (EC 204-528-4) did not show reproductive toxicity (up to equivalent oral dose of 609 and 700 (mg/kg bw/day) in females and males, respectively). Reproductive toxicity screening studies (ECs 264-261-4 (2012), EC 203-556-4 (2019, with investigation of ED parameters)) and pre-natal developmental toxicity studies in rat (ECs 204-528-4), all conducted with oral gavage, did not show toxicologically significant adverse effects on reproductive or pre-natal developmental toxicity. A TG 414 in rat of EC 264-261-4 showed skeletal variation (incomplete ossification 6th sternabrae) in the presence of limited maternal toxicity[9]. Conversely, a one generation fertility study (TG 415 equivalent) with oral gavage of EC 427-360-5 (acetate salt of TIPA) showed an increase in post-implantation loss and a decrease in birth index (86.5 versus 96% in controls) at the highest tested dose (1000 mg/kg bw/day; TIPA equivalent oral dose 762 mg/kg bw/day) in the presence of limited parental toxicity. The acetate is not expected to contribute to the toxicity. In the case of EC 229-764-5 reduced ossification of in skull bones did not appear due to a general developmental delay as no effect on foetal bodyweight and only slight maternal toxicity was observed. Such a discrete effect was not observed in a second species as once tested in the rabbit (OECD 414, 2018) the development NOAEL was at the top dose of 1000 mg/kg which showed reduced maternal feed consumption; at this dose a slightly raised incidence of malformation types also seen in controls was observed. In addition, there are some limitations in the data coverage for this largest sub-group as there is a lack of adequate and reliable reproductive (e.g. OECD 416/443 in rat) and only a single pre-natal developmental toxicity study (TG 414) is available in non-rodent species (EC 229-764-5); the TIPA registration included a weight of evidence approach relied on a pre-natal developmental toxicity in rabbit conducted with the picrolam salt of TIPA was rejected by ECHA. No data on reproductive and developmental toxicity conducted with the registered substance are available for several substances with Annex VII data requirements. Further data are needed to confirm the reproductive and developmental toxicity hazard profile within this sub-

[8] See the specific remarks on PBT / PMT conclusions for the substances ECs 203-041-4 and 911-174-0 below.

[9] Data pending assessment under Follow-up Procedure

group (see data generation below). The reproductive and developmental toxicity data generation may also allow further confirmation on the ED conclusion.

Based on ECHA's assessment of currently available hazard information, no potential hazards requiring EU RRM were identified for the other human health hazards: The substances are not mutagenic and therefore a genotoxic mode of action for carcinogenicity is unlikely. The available mutagenicity data on isopropanolamines group as a whole mainly covers the required *in vitro* genotoxicity test battery and results are consistently negative. An adequate in vivo genotoxicity study (TG 474) for EC 264-261-4, showed a negative result. A study with limitations (small number of animals, single dose level) of EC 204-528-4 did not show evidence of carcinogenicity. Some indications of potential systemic toxicity following single and repeated dosing in animals (e.g., anaemia, liver) were identified but these adverse effects are mostly seen at relatively high doses. For EC 203-041-4, a reproductive screening study (TG 422, 2009) showed evidence of neurotoxicity of the CNS (vacuolation of epithelial cells of the lateral ventricles of the brain) in all animals at 1000 mg/kg bw/day (NOAEL 300 mg/kg bw/day) which needs to be investigated further under data generation (see below).

The provided *in vivo/vitro* skin sensitisation studies are negative or this endpoint or the requirement has been waived based on corrosivity. Based on structural similarity the conclusions from the toxicity studies are tentatively extrapolated to the substances in this sub-group where there is limited information for these endpoints.

Some of these substances are under data generation due to dossier evaluation decisions:

- EC 203-041-4 request of in vitro mutagenicity, 90d RDT and PNDT in two species, EOGRT (data generation still ongoing).
- EC 204-528-4 (TIPA) request of PNDT in non-rodent species – under enforcement.
- EC 264-261-4 A Testing Proposal evaluation for Extended One Generation Reproductive Toxicity study and pre-natal developmental toxicity study (second species) is ongoing.

The further data generated may allow confirmation of the conclusions on mutagenicity, repeated dose toxicity, reproductive toxicity and ED.

It is noted that the substance **EC 229-764-5** contains DEA as an impurity. The impurity DEA (EC 203-868-0) is reported in the joint submission's boundary composition and is also reported in several legal entity compositions. DEA underwent a substance evaluation which was recently concluded with a CLH proposal expected for Repr. 1B/Carc 2. If this classification is adopted and DEA is present in EC 229-764-5 above any agreed (generic or specific concentration limits) this will impact the human health classification of some grades of EC 229-764-5. EU regulatory risk management for this substance is however currently not proposed on this basis as the hazard of DEA needs first to be confirmed. To the extent the Repr. 1B/Carc2 for DEA would be confirmed, we expect that companies will take into account this information and self-classify EC 229-764-5 accordingly and implement the necessary risk management measures to ensure safe use of the substance (e.g. through minimisation of the presence of DEA as impurity, or cease the uses). These changes are expected to be reflected in registration updates. Currently registered uses of the substance include industrial and professional use in lubricants, metal working fluids and cements. Changes in the use pattern and substance composition will be assessed in the next iteration to this assessment.

All substances in this sub-group except List 911-174-0 are no or unlikely PBT/vPvB. All substances in this sub-group except EC/Lists 203-041-4 and 911-174-0 are unlikely PMT.

It is proposed to open compliance check on ECs 264-261-4 to confirm the PBT and PMT hazard conclusion.

The substance List 911-174-0 is inconclusive for PBT and PMT. It is an outlier from this subgroup as it is a multi-constituent substance, it has much longer alkyl chains than the other tertiary isopropanolamines and it can be expected to be more lipophilic and therefore to have a higher bioaccumulation potential. There are no experimental data for this substance therefore no conclusion can be reached. The substance is registered as transported isolated intermediate only.
The substance 203-041-4 is inconclusive for PMT. It is not readily biodegradable so may fulfil the P/vP criteria, and is expected to be mobile in the environment. The substance may have long-term toxicity to aquatic organisms and data generation is ongoing.

The following substances are known or likely to have aquatic toxicity: ECs 224-537-7, 266-587-2, 427-360-5, 444-360-0 (with harmonised classification Aquatic Chronic 3) . It is expected that following data generation for aquatic toxicity registrants would adequately self-classify the substances and implement necessary RMMs to ensure safe use. Therefore, it is proposed that there is currently no need for EU-wide regulatory risk management on the basis of this hazard. All remaining substances except EC 911-174-0 have no or unlikely aquatic toxicity hazard. List 911-174-0 is inconclusive due to lack of data but no further action is suggested for the time being.

Primary and secondary isopropanolamines and their salts

Based on currently available information, there is no need for (further) EU regulatory risk management for all substances in the subgroups primary isopropanolamines and secondary isopropanolamines, and their salts.

Based on ECHA's assessment of currently available hazard information, no potential hazards requiring EU-wide regulatory action were identified for human health or environment. The data currently available does not show indication of hazards for C/M/R, ED, skin sens, PBT/vPvB, aquatic toxicity, ED hazards and other environmental hazards.

These conclusions are based on the following data. The main source of human health data comes from two registrations which include higher tier data whereas the 4 remaining registered substances (mainly simple salts) have lower registration requirements and few higher tier data. In the case of the primary isopropanolamine (201-162-7) an oral route repeat dose toxicity study (TG 422) conducted with its structurally analogous hydrochloride salt showed "mild" anemia at the top dose (equivalent to 673 isopropanolamine mg/kgbw/day) in male parental rats. The repeat dose toxicity studies for EC 203-820-9 (DIPA, a secondary isoproanolamine) showed effects (e.g. kidney weight) at relatively high doses with NOAELs at 100 mg/kg/day or greater. The available mutagenicity data on the isopropanolamines group as a whole mainly covers the required *in vitro* genotoxicity test battery and results are consistently negative. The substances are not mutagenic and therefore

a genotoxic mode of action for carcinogenicity is unlikely. Studies with limitations (low number of animals, single dose level) for EC 203-820-9 (DIPA) did not show evidence of carcinogenicity. The currently available reproductive and developmental toxicity data available do not show reproductive or developmental toxicity hazards or ED adversities. In the case of the primary isopropanolamine 201-162-7 (MIPA or its hydrochloride salt), no evidence of reproductive/developmental toxicity or ED was observed in rat in a reproductive screening study (OECD TG 422; 2008 without investigation of ED parameters) or a pre-natal developmental toxicity study in rat. However, adequate and reliable information to assess toxicity to the offspring is not available. In the case of the secondary isopropanolamine 203-820-9 (DIPA), the registration indicates no adverse effect in pre-natal developmental toxicity in rat conducted up to a limit dose. To address developmental toxicity in a non-rodent species and reproductive toxicity of DIPA the registrants use information from the structural analogues MIPA (201-162-7), TIPA (204-528-4) and a picrolam salt of TIPA (these two latter substances are further discussed in the sections on tertiary isopropanolamines). In line with a substance evaluation of DIPA[10], while the concern for reproductive toxicity at that time was considered addressed, there are some uncertainties with such read-across approach in respect of hazard identification for reproductive toxicity as, for example, the available one generation study with the proposed source substance TIPA does not address all parameters of the Annex X standard information requirement for reproductive toxicity. In addition, there is currently no adequate and reliable information to address pre-natal developmental toxicity in non-rodent species on primary or secondary isopropanolamines. The provided *in vivo/vitro* skin sensitisation studies are negative or this endpoint has been correctly waived based on corrosivity. Based on structural similarity the conclusions from the toxicity studies are extrapolated to the substances where there is limited information for these endpoints. Dossier Evaluation decisions for EC 201-162-7 (MIPA) requested EOGRT and long-term toxicity tests on fish and Daphnia (deadline 24 June 2024) which will allow confirmation on the conclusion of unlikely hazard for reproductive toxicity, ED and aquatic toxicity for that substance.

The substances in these subgroups are unlikely to fulfil the PBT/vPvB screening criteria, because they are readily biodegradable. All substances are unlikely PMTs for the same reason. All substances in these sub-groups are unlikely to have aquatic toxicity hazard based on the available short-term toxicity data. Based on structural similarity the conclusions from the ecotoxicity and environmental fate studies are extrapolated to the substances where there is limited information for these endpoints.

Further general remark

Although the substances as such seem not to have carcinogenic potential, the potential formation of carcinogenic nitrosamines cannot be excluded [11,12] . This generic issue requires a wider assessment of the hazardous properties of **tertiary and/or secondary alkyl amines substances** in general and has not been

[10] ECHA CoRAP Substance Evaluation Report 203-820-9.

[11] Final report on the Safety Assessment of Diisopropanolamine, Triisoproanolamine, Isopropanolamine, and mixed Isopropanolamine. Journal of American College of Toxicology. Volume 6, (1). (1987).

[12] Scientific Committee on Consumer Safety. Opinion on Nitrosamines and Secondary Amines in Cosmetic products (2011).

explored further for the individual substances in the group in this assessment. Provisionally, a concern for carcinogenicity is identified without follow up regulatory action. It is expected that a common approach will be developed regarding substances with potential to form nitrosamines as part of co-exposure with nitrosating agents and that potential regulatory measures will be discussed in this context, where relevant.

Annex 1: Overview of classifications

Data extracted on 1 March 2021

EC/List No	Substance name	Self-classification		
		Harmonised classification	**Self-classification in registration dossier***	**Additional classification in C&L notifications****
Primary isopropanolamines and their salts				
201-162-7	1-aminopropan-2-ol (MIPA)	**Skin Corr. 1B**	Acute Tox. 4 H312 Skin Corr. 1B H314 Eye Damage 1 H318	Aquatic Chronic 3 H412 Acute Tox. 4 H302 Flam. Liquid 4 H227 Met. Corr. 1 H290
210-474-2	1,3-diaminopropan-2-o	**-**	Skin Corr. 1B H314 Acute Tox. 4 H302 Skin Sens. 1 H317	STOT Single Exp. 3 H335 Skin Corr. 1C H314 Eye Irrit. 2 H319 Skin Irrit. 2 H315 Eye Damage 1 H318
231-948-5	1-aminopropan-2-ol hydrochloride	-	-	-
250-342-1	(2-hydroxypropyl)ammonium citrate	-	-	-
946-381-5	2-hydroxypropan-1-aminium sulfate	-	-	-
Secondary isopropanolamines and their salts				
203-820-9	1,1'-iminodipropan-2-ol **(DIPA)**	Eye Irrit. 2	Eye Irrit. 2 H319	Eye Damage 1 H318
692-156-7	2-Propanol, 1,3-bis(2-propen-1-ylamino)-, hydrochloride (1:2)	-	Eye Irrit. 2 H319 Skin Irrit. 2 H315 STOT Single Exp. 3 H335, affected organs: Respiratory system	-
Tertiary isopropanolamines and their salts				
203-041-4	1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol	-	Eye Irrit. 2 H319	STOT Single Exp. 3 H336, affected organs: organs STOT Single Exp. 3 H335, affected organs: Respiratory tract irritation Skin Irrit. 2 H315

				STOT Single Exp. 3 H335, affected organs: not identified Carc. 2 H351 Skin Sens. 1 H317 STOT Single Exp. 3 H335, affected organs: Respiratory tract and lungs Repr. 2 H361 Eye Damage 1 H318
203-556-4	1-(dimethylamino)propan-2-ol	Acute Oral Tox. 4 Skin Corr 1B H314	Flam. Liquid 3 H226 Acute Tox. 4 H302 Acute Tox. 4 H312 Skin Corr. 1B H314 Eye Damage 1 H318	Acute Tox. 3 H331
204-528-4	1,1’,1’’-nitrilotripropan-2-ol **(TIPA)**	-	Eye Damage 1 H318 Eye Irrit. 2 H319	STOT Single Exp. 3 H335, affected organs: RTI Skin Corr. 1B H314 Aquatic Chronic 1 H410
224-536-1	1,1'-(methylimino)dipropan-2-ol	-	Skin Corr. 1B H314	Eye Damage 1 H318
224-537-7	1-diethylaminopropan-2-ol	-	Eye Damage 1 H318	Acute Tox. 4 H302 Eye Irrit. 2 H319 Skin Corr. 1B H314 STOT Single Exp. 3 H335 Eye Damage 1 H318 Skin Irrit. 2 H315
229-764-5	1-(N,N-bis(2-hydroxyethyl)amino)propan-2-ol (DEIPA)	-	Eye Irrit. 2 H319	Repr. 2 H361 Skin Irrit. 2 H315
254-075-1	1,1’-(p-tolylimino)dipropan-2-ol	-	Acute Tox. 2 H300 Eye Irrit. 2 H319 Aquatic Chronic 3 H412	Eye Damage 1 H318 Acute Tox. 3 H301
264-261-4	1,1'-[[3-(dimethylamino)propyl]imino]bispropan-2-ol	-	Skin Corr. 1C H314 Eye Damage 1 H318	Skin Irrit. 2 H315 Skin Corr. 1B H314 Aquatic Chronic 3 H412
266-587-2	1-[bis[3-(dimethylamino)propyl]amino]propan-2-ol	-	Acute Tox. 4 H302 Skin Corr. 1C H314 Eye Damage 1 H318	STOT Rep. Exp. 1 H372, affected organs: Affected Organs Aquatic Chronic 3 H412 Skin Corr. 1B H314 Acute Tox. 4 H332 Skin Corr. 1A H314 STOT Rep. Exp. 1 H372, affected organs: Skin and digestive Acute Tox. 4 H312

427-360-5	2-Propanol, 1,1',1'',-nitrilotris, acetate	-	-	-
444-360-0	bis(2-hydroxyethyl)-(2-hydroxypropyl)ammonium acetate	-	-	-
695-977-9	Propanol, iminobis-, N-(C16-18 and C18-unsatd. alkyl) derivs.	-	Acute Tox. 4 H302 Skin Corr. 1C H314 Eye Damage 1 H318 Aquatic Acute 1 H400, M-factor: 10.0000000000 Aquatic Chronic 2 H411	-
814-434-0	1-[butyl(2-hydroxypropyl)amino]propan-2-ol	-	Skin Corr. 1B H314	-
816-324-8	1,1'-[(3-{bis[3-(dimethylamino)propyl]amino}propyl)imino]dipropan-2-ol	-	-	-
911-174-0	1,1’-(dodecylimino)dipropan-2-ol + 1,1’-(tetradecylimino)dipropan-2-ol	-	-	-

* The column gives the classifications in registrations received under REACH. Additional classifications in intermediate and in inactive registrations (if any) are annotated and displayed last. For each classification the table includes information on the hazard category, the hazard statement and any available information on specific effects (relevant for reproductive toxicity), specific concentration limits, M-Factors and affected organs. Two classifications differing in any of these aspects are considered different and are repeated in the table. The columns "Classifications in registrations" and "Classifications in C&L notifications" are empty if there are no Registrations/C&L notifications (hazard is unknown). The value '-' is displayed on the same columns when there are (relevant) submissions but they do not contain self-classifications (substance is not hazardous).

** The column gives the additional classifications not found in registrations but found in active or inactive C&L notifications (without distinguishing them). For each classification this column also provides the number of C&L notifications that contain the classification out of the total number of C&L notifications received for the substance. A single C&L notification file submitted by a group of notifiers is only counted once. Therefore, the numbers may differ from the dissemination site which counts number of notifiers.

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

Data extracted on 1 March 2021

	Primary isopropanolamines and their salts				Secondary isopropanolamines and their salts	
Main types of applications	**201-162-7 (MIPA)**	**210-474-2**	**250-342-1**	**946-381-5**	**203-820-9 (DIPA)**	**692-156-7**
PC 24: Lubricants, greases, release products	F, I, **P**				**P**	
PC 25: Metal working fluids	I, **P**				**P**	
PC 17: Hydraulic fluids	I, **P**				F, I, **P**	
PC 13: Fuels	F, I, **P**, **C**				F, **P**	
PC 32: Polymer preparations and compounds	I, ***(A)***				I, **P**, ***(A)***	
PC 1: Adhesives, sealants	I, **P**, ***(A)***				I, **P**, ***(A)***	
PC 9b: Fillers, putties, plasters, modelling clay *(construction chemicals)*	**P**, **C**, **A**				**P**, **A**	
PC 9a: Coatings and paints, thinners, paint removes	I, **P**, ***(A)***				I, **P**, ***(A)***	
PC 18: Ink and toners	I, **P**, ***(A)***					
PC 26: Paper and board treatment products	I, **P**				I	
PC 34: Textile dyes, and impregnating products	I, **P**				I	
PC 23: Leather treatment products	I, **P**				I	
PC 14: Metal surface treatment products	I			I		
PC 20: Products such as ph-regulators, flocculants, precipitants, neutralisation agents	I, **P**					
PC 35: Washing and cleaning products	I, **P**, **C**			I, **P**, **C**	I, **P**, **C**	
PC 8: Biocidal products (e.g. disinfectants, pest control)	I, **C**					
PC 39: Cosmetics, personal care products	**C**		F, **P**, **C**	**P**, **C**	**C**	
PC 29: Pharmaceuticals				**P**		
PC 37: Water treatment chemicals	I					
PC other: gas treatment					I	

PC 21: Laboratory chemicals	I, **P**				I, **P**		
PC 19: Intermediate	I	I			I	I	

	Tertiary isopropanolamines and their salts													
Main types of applications	**203-041-4**	**203-556-4**	**204-528-4 (TIPA)**	**224-536-1**	**224-537-7**	**229-764-5**	**254-075-1**	**264-261-4**	**266-587-2**	**427-360-5**	**695-977-9**	**814-434-0**	**816-324-8**	**911-174-0**
PC 24: Lubricants, greases, release products			I, **P**	F		I, **P**		F, I, **P**	I, **P**					
PC 25: Metal working fluids			I, **P**			I, **P**		F, I, **P**	F, I, **P**					
PC 16: Heat transfer fluids								F, I, **P**						
PC 17: Hydraulic fluids				F, I, **P**				F, I, **P**						
PC 13: Fuels			F, I, **P**, **C**											
PC 32: Polymer preparations and compounds	F, I, **P**, **A**	F, I, **P**, ***(A)***	I, **C**, **A**	F, I	I		F, I, **P**, ***(A)***	I, **P**, ***(A)***	F, I, **P**, ***(A)***				I, ***(A)***	
PC 1: Adhesives, sealants	F, I, **P**, **C**, ***(A)***	F, I, **P**, ***(A)***	**P**, ***(A)***				F, I, **P**, ***(A)***	F, I, **P**, ***(A)***	F, I, **P**, ***(A)***					
PC 9b: Fillers, putties, plasters, modelling clay *(construction chemicals)*	F, (I), **(P)**, **(C)**, **(A)**		I, **P**, **C**, **A**			F, I, **P**, **A**	F, **P**, ***(A)***	F, I, ***(A)***	F, I, **P**, ***(A)***	F, I, **P**	F, **P**, ***(A)***			
PC 9a: Coatings and paints, thinners, paint removes	F, I, **P**, **C**, ***(A)***	F, I, **P**, ***(A)***	**P**, ***(A)***				F, I, **P**, ***(A)***	F, I, **P**, ***(A)***	F, I, **P**, ***(A)***					
PC 18: Ink and toners		I, **P**, ***(A)***	F, I, **P**, **C**, ***(A)***				I, **P**, ***(A)***							
PC 26: Paper and board treatment products			I, **P**											

	Tertiary isopropanolamines and their salts													
Main types of applications	**203-041-4**	**203-556-4**	**204-528-4 (TIPA)**	**224-536-1**	**224-537-7**	**229-764-5**	**254-075-1**	**264-261-4**	**266-587-2**	**427-360-5**	**695-977-9**	**814-434-0**	**816-324-8**	**911-174-0**
PC 34: Textile dyes, and impregnating products			I, **P**					F, I, **P**						
PC 23: Leather treatment products			I, **P**											
PC 4: Anti-freeze and de-icing products	F													
PC 35: Washing and cleaning products	**C**		**P**, **C**					F, I, **P**						
PC 8: Biocidal products (e.g. disinfectants, pest control)	F		I, **C**					F, I						
PC 28: Perfumes, fragrances								**P**						
PC 3: Air care products	F							F, I, **P**						
PC 39: Cosmetics, personal care products	**C**		**C**											
PC 31: Polishes and wax blends								F, I						
PC 15: Non-metal-surface treatment products	F						F, **P**							
PC 14: Metal surface treatment products						I, **P**		F, I, **P**						
PC 7: Base metals and alloys	F													
PC 2: Adsorbents	F													
PC 21: Laboratory chemicals		I, **P**	I, **P**	F, I			F		F, I, **P**					
PC 19: Intermediate		I	I	I	I	I		I	I			I		I

Legend:
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;
In bracket and italic, the life-cycle stages not explicitly reported in registrations but assumed to be potentially relevant based on information available

Notes:
-No information on uses could be compiled for substance EC 444-360-0 from the tertiary isopropanolamine subgroup.
-No information on uses is presented for substance EC 231-948-5. The substance is not registered.

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

Data consulted on 18/03/2021

EC/ List number	RMOA	Authorisation		Restriction*	CLH
		Candidate List	Annex XIV	Annex XVII	Annex VI (CLP)
204-528-4					YES[13]

*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 substances not listed in the table.

[13] A harmonised classification of Eye Irrit. 2; H319 was adopted. Further information on the CLH process can be found here: https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e180a13947