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Sammanfattning

Kemikalieinspektionen har inom ramen för det svenska miljömålsarbetet flera åtaganden. Ett av dem är att utreda begreppet gruppering och visa på hur grupper av kemiska ämnen kan hanteras i lagar och regler. I den här rapporten granskar vi hur gruppering av ämnen kan göras och vilka möjligheter det finns att reglera grupper av ämnen i två olika europeiska regelverk, Reach-förordningen och CLP-förordningen. Uppdraget redovisas med hänsyn till de slutsatser som framkom i ett tidigare regeringsuppdrag om att utveckla Reach,”Utveckla och effektivisera Reach – en handlingsplan” (Kemikalieinspektionen, 2014a).

Kemiska ämnen kan grupperas på många olika sätt, till exempel efter kemisk struktur, (eko)toxikologiska egenskaper, funktion eller användningsområde. Hur grupperingen görs beror på vad den ska användas till. I kemikaliekontrollarbetet utnyttjas gruppering bland annat för att effektivisera arbetet och för att förhindra att ett ämne med oönskade egenskaper byts ut mot ett annat ämne med liknande egenskaper.

Gruppering av ämnen görs redan idag inom ramen för Reach och CLP. Till exempel kan dataluckor i ämnesregistreringar i Reach fyllas med information från ämnen inom samma grupp. Metoden definieras av en hög grad av vetenskaplighet och förutsätter en god kunskap om ämnesidentiteter. Gruppvis hantering av ämnen sker även i ett vidare perspektiv inom Reach, från val av enstaka ämnen för vidare analys till reglering av hela ämnesgrupper med specifika inneboende egenskaper.

Kemikalieinspektionen arbetar med gruppering av ämnen på flera nivåer, både i prioriteringen av ämnen som kan bli föremål för reglering i Reach eller CLP, men även inom kemikaliekontrollarbetet i stort. I det löpande arbetet på Kemikalieinspektionen sker en kontinuerlig utveckling av grupperingsmetodiken allteftersom nya åtgärdsförslag förs fram inom ramen för Reach och CLP. Möjligheterna till att hantera flera ämnen i grupp avgörs från fall till fall och beror på syftet med grupperingen.

Glossary and key terms

CAS No.	Chemicals Abstracts Service Number. Identification number for chemical substances.
The CLP Regulation	Classification, Labelling and Packaging. EU Regulation (EC No 1272/2008) on classification, labelling, and packaging of substances and mixtures.
CMR	Carcinogenic, Mutagenic, toxic for Reproduction. Substances that can induce cancer, or harm genetic material or reproductive capacity.
CoRAP	Community Rolling Action Plan. EU's ongoing action plan for substance evaluation.
ECHA	European Chemicals Agency.
EC No.	Numeric identifier for substances in the EC Inventories.
ELoC	Equivalent Level of Concern.
ERC	Environmental Release Category. A category of use descriptors that are applied to describe the use and exposure of a substance.
IUCLID	International Uniform Chemical Information Database. Software application that is used for e.g. REACH registrations.
IUPAC	International Union of Pure and Applied Chemistry. International federation representing chemists.
MSC	Member State Committee (at ECHA).
OECD	Organisation for Economic Co-operation and Development. OECD is an organisation of 35 countries (European countries, USA, Australia, Japan and others.).
Regrettable substitution	Regrettable substitution pertains to the problem of substances with undesirable properties being replaced by structurally similar substances with comparable properties.
PBT	Persistent, Bioaccumulative, Toxic. Used for substances categorized as persistent, bioaccumulative and toxic.
PC	Product Category. The product category describes the type of mixture in which the substance is incorporated. A category of use descriptors that are applied to describe the use and exposure of a substance.
PetCo	Petroleum and Coal stream substances.
PFAS	Per- and polyFluorinated Alkyl Substances.
PFCA	Perfluorinated Carboxylic Acids. A subset of PFAS.
PROC	Process Category. The process category describes the process in which the substance is used. A category of use descriptors that are applied to describe the use and exposure of a substance.
(Q)SAR	Qualitative and Quantitative Structure-Activity Relationship. Models or relationships based on the chemical structure to predict a substance's properties, e.g. endocrine disruptor properties.
RAAF	Read-Across Assessment Framework. ECHA's framework for evaluating read-across.
RAC	Committee for Risk Assessment (at ECHA).
RCR	Risk Characterization Ratio.
The REACH Regulation	EU regulation (EC No 1907/2006) on the Registration, Evaluation, Authorisation and Restriction of Chemicals.
Read-across	Method used to predict the properties of a (target) substance using relevant information on similar (source) substances.
RMOA	Risk Management Option Analysis. Evaluation of risk management activities.
SEAC	Committee for Socio-Economic Analysis (at ECHA).

2 Introduction

There are many reasons for choosing to combine two or more individual chemical substances in one larger group. The term grouping is thus used in many different contexts, and is not clearly defined. Because grouping can have different meanings in different contexts, it is always necessary to define what is meant in each case. The purpose of this report is to explain and provide examples of the various ways in which the term grouping can be used with regard to chemicals and chemicals legislation. Examples of grouping of chemical substances in the work of the Swedish Chemicals Agency are presented in Annex 1.

2.1 Why group chemical substances

The number of chemical substances present in the market is estimated to be around 100,000. Between 30,000 - 40,000 substances are estimated to be manufactured or imported into the EU in quantities above 1 tonne; these must be registered in accordance with REACH. Grouping of substances with similar chemical structure, (eco)toxicological properties, function and/or areas of use, has therefore become a necessary strategy if we are to process and prioritize substances for chemicals management and safety. There are also practical and efficiency reasons for using grouping in the day-to-day work. Electing to work with a group of substances, such as cadmium compounds, phthalates or highly fluorinated substances (PFAS), generates more detailed knowledge on the group. This can subsequently be applied when drawing up new proposals for additional group members in one or more legislative processes. Furthermore, knowledge on individual substances in a group of substances with similar structures, can provide a more coherent picture of the properties of all the substances in the group.

Chemicals legislation, including REACH and CLP, focuses to a large extent on regulation of individual chemicals. However, where the legislation permits, group regulation can also be an efficient method to rationalise legislation and avert regrettable substitution. When a substance is restricted or banned, the substance tends to be replaced by a structurally similar substance with the same or comparable properties. This is because chemically similar substances often have the same technical function. However, they will also have the same undesirable properties affecting health and/or the environment. It should be possible to overcome these problems in part if substances in groups are regulated together.

Grouping substances based on structural similarity, intrinsic properties or areas of use have been identified as important measures and placed on the political agenda. The government and parliament of Sweden have set 16 environmental quality objectives, one of which is *A Non-Toxic Environment*. The goal is that by 2020, conditions will be in place for protecting people's health and the environment from hazardous chemicals. The government has decided that on the road to achieving the environmental objectives, there will be eight milestones within the framework of hazardous substances, with a particular emphasis on grouping of substances. The milestone *Development and application of the EU*'s *chemical rules* states that:

> REACH and other relevant EU regulations are to be applied by 2020 at the latest or revised if necessary so that:
>
> - It will to a greater extent become possible to assess and test groups of substances with similar intrinsic properties, chemical structures or areas of use.

To improve the conditions for achieving the environmental quality objectives, the government presented a strategy in 2013 for a non-toxic environment, the chemicals bill (2013/14:39)

"Towards a toxin-free everyday environment – a platform for chemicals policy"[6]. The strategy is comprised of the eight milestones and additional instruments. The bill develops the need for evaluation and regulation of groups of chemicals in order to rationalise chemicals management:

> To facilitate the evaluation and restriction of substances of very high concern it should be possible to process substances in groups based on chemical structure, properties or area of use. Such a development would lead to a substantial rationalisation of chemicals management.
>
> (The author's translation)

2.2 Grouping of substances in chemicals management

Grouping of substances is used in a number of ways in chemicals management. Among other, grouping is used when selecting substances that could be the subject of various proposed measures, such as adaptation of regulations (classification in accordance with CLP, restriction in accordance with REACH, inspection, other legislation, etc.) or other instruments (economic instruments, industry dialogues, information activities, etc.) (Figure 1). Whether the selected substances can be managed as a group in chemicals management is decided case by case and depends on the purpose of the grouping, and what options are available for managing the substances as a group. For example, a high scientific level is necessary for grouping in REACH and CLP where the purpose is to predict (eco)toxicology data from one substance to another substance within the group (so called read-across), and for which comprehensive international guidance has been produced. Substances can also be grouped on the basis of their intrinsic properties (for example, CMR substances), by a specific function, or by an area of use. Such grouping of substances is already utilized in the REACH framework (and in part in CLP) and in several other regulations. It is important to note that an initial grouping of substances can progress depending on which stage of chemicals management is involved; for example, from an initial wide selection of substances to one or a few substances in a final proposed measure.

The processes in REACH (registration, evaluation, authorisation and restriction) and CLP permit a group approach to a certain extent. Grouping of substances is prioritised by ECHA. ECHA recently compiled a draft report on grouping in REACH and CLP as documentation for cooperation between ECHA and competent authorities in the EU (ECHA, 2016a). The Swedish Chemicals Agency has previously highlighted the need for managing groups of substances in REACH and CLP; increased options for grouping substances can result in more effective legislation (The Swedish Chemicals Agency, 2014a).

[6] Kemikaliepropositionen (2013/14:39), "På väg mot en giftfri vardag – plattform för kemikaliepolitiken". https://data.riksdagen.se/fil/524DA9CB-B9E4-48B8-800F-48308883CA09.

Particle size:

- Inhalable
- Respirable

3.3 Use and emission, exposure

3.3.1 Technical function

The description of the technical function may be used in the grouping of substances. The technical function indicates how a substance is used, which is linked to the degree of exposure. In connection with the regulation of substances, it can be strategic to have identified groups of substances on the market that have the same technical function. This can predict potential substitutes in case of future restrictions. The Swedish Chemicals Agency's product register includes data that allows grouping of substances that have similar technical function, such as softeners, pigments, preservatives, etc.

Frequently, there is a link between technical function and hazard. For example, the chemical structure that makes the substance usable as a hardener (i.e. function) may also induce allergy (e.g. electrophilic acrylates).

Grouping according to technical function is common in a number of environmental labelling systems and, recently, also in the chemical tax evaluation (SOU 2015:30) in relation to certain electronics. In regard to the latter, all additive flame retardants containing bromine, chlorine or phosphorus have been grouped together; if certain concentration limits are met, they may be entitled to a reduction for taxable articles.

The Danish Environmental Protection Agency recently published a report on a group of 61 structurally similar flame retardants (brominated linear and branched alkyl alcohols). (Q)SAR predictions indicate carcinogenic effects for all substances. One of the long-term objectives is to regulate flame retardants as a group (The Danish Environmental Protection Agency, 2016).

3.3.2 Type of products

Substances can be grouped based on their use in various types of products. Product type, like technical function, can be used for exposure evaluation. In addition to estimating the degree of emission, the product type can often indicate the target groups for exposure. For example, substances in shampoo can be linked to exposure of consumers of all ages, while substances in cement would indicate occupational exposure of adults.

Certain types of products/articles are regulated by specific regulatory frameworks. The legislations (which do not contain only chemical requirements) regulate both individual substances and groups of substances. Examples of such regulations are:

- Electronics (The RoHS Directive 2011/65/EU)
- Batteries (The Battery Directive 2006/66/EC)
- Toys (The Toy Safety Directive 2009/48/EC)
- Hygiene products (The Regulation on Cosmetic Products (EC) 1223/2009)

3.3.3 Target groups

Substances can be grouped according to who uses them, for example:

- Age: children/adolescents/adults/elderly
- Gender: male/female

4 Grouping of substances in REACH and CLP

Grouping of substances in REACH and CLP is used in a number of ways. In a regulatory context, substances can be grouped based on their intrinsic properties as in REACH Article 57 in which SVHC substances (Substances of Very High Concern) are identified as substances with CMR (categories 1A/1B) properties (57a-c), PBT properties (57d), vPvB properties (57e) or substances with equivalent level of concern to CMR or PBT/vPvB (57f). According to CLP Article 36, substances that are respiratory sensitisers (category 1) or meet the criteria for CMR (categories 1A/1B/2) shall be covered by harmonised classification. To facilitate and rationalise risk management, substances are also grouped for different purposes based on their structural similarity, or according to use patterns. An overview of the processes in REACH and CLP is presented below, and is followed by a more detailed description of the possibilities and challenges with grouping of substances in the various processes.

4.1 Overview of REACH and CLP processes[9]

Manufacturers or importers of chemical substances in volumes of at least one tonne per year must register them in accordance with REACH. Registration includes test documentation, self-classification of the hazardous properties and information on the intended use throughout its entire life cycle. The larger the volume of substance produced or imported, the more information must be included in the registration. For substances that meet a classification criterion and are manufactured or imported in volumes greater than 10 tonnes per year, the registration must also include a safety assessment.

To a large extent, the total data for the substance registrations forms the basis for regulation of substances in REACH and CLP, which is primarily coordinated through ECHA. The content and quality of the registrations are therefore critical for management of the substances in the various processes. In accordance with REACH Articles 40-41, ECHA shall evaluate whether the company's registration satisfies the requirements in REACH in regard to standard information, safety assessment and risk management measures. If the registration does not satisfy the legislated requirements, ECHA will produce a proposal for a decision on required supplementary information. From the large number of registered substances, some are selected for substance evaluation or regulatory risk management through harmonised classification, inclusion in the so called Candidate List and the authorisation list (REACH Annex XIV), or restriction (REACH Annex XVII). The various processes are interdependent and should be viewed as a whole. In most cases, before an authority produces a proposal to regulate a substance through REACH, a risk management option analysis (RMOA) is performed to investigate which process is most suitable. The result of an RMOA can be that a substance should be included on the Candidate List or be regulated via a restriction, but the authority may also propose that the substance is to undergo harmonised classification or substance evaluation. The analysis can also result in the authorities concluding that there is no need for further regulatory action, or that other legislation is more suitable for regulation. Figure 4 presents an overview of the various processes and how they are interrelated.

[9] This section is a condensed version of the corresponding section in the Swedish Chemicals Agency internal report "Prioritering av ämnen för ämnesutvärdering och åtgärdsförslag enligt REACH och CLP" (2015).

Screening is divided into two phases (Figure 5). Initially, there is an automated IT screening of ECHA's database which generates a selection of substances for the "Short List"[13]. Thereafter, the Member States' competent authorities select a number of substances from the Short List for evaluation (manual screening) which results in a recommendation for further measures for each substance. Substances that are identified as candidates for SVHC at manual screening move forward to RMOA and substances that are identified as candidates for substance evaluation move forward to the Community Rolling Action Plan (CoRAP). Other potential proposed measures include harmonised classification or dossier evaluation (compliance check).

Substances on the Short List are grouped according to identified (potential) regulatory measures and structural similarity. To achieve maximum efficiency, Member States are recommended, as far as possible, to process all substances in the same group in the manual screening. Worth noting is that grouping on the Short List by structural similarity is on a general level, and other substances on the Short List could be included in a potential group if the review was more detailed. When all (relevant) substances and any measures have been identified, high efficiency can be achieved by managing the entire group of substances in the next process. For example, in a few cases ECHA has initiated dossier evaluation for groups of substances where several structurally similar substances are evaluated in parallel (ECHA, 2016a).

In 2017, ECHA has further developed the group approach for IT screening of substances by identifying additional structurally similar substances in *both* the registration database and the Classification and Labelling Inventory (ECHA, 2017c)[14]. The Swedish Chemicals Agency participated in the manual screening of four groups of substances. One advantage of this wider screening is that it enables identification of substances that may be used to replace an original (problematic) substance, and which should therefore be included in a proposed regulatory measure.

[13] Screening scenarios are compiled annually by ECHA and include both hazard-based criteria and exposure-based criteria.

[14] Substances belonging to a specific group have also been identified from read-across/category argument in the REACH registrations (IUCLID dossiers) and other categories (e.g. OECD categories).

4.2.3 Grouping in risk management option analysis (RMOA)

In RMOA work, substances can be grouped according to structural similarity (and/or (eco)toxicological properties) and use patterns (Figure 6). Substances with similar uses, and thus exposure patterns, can be managed together for any subsequent risk management.

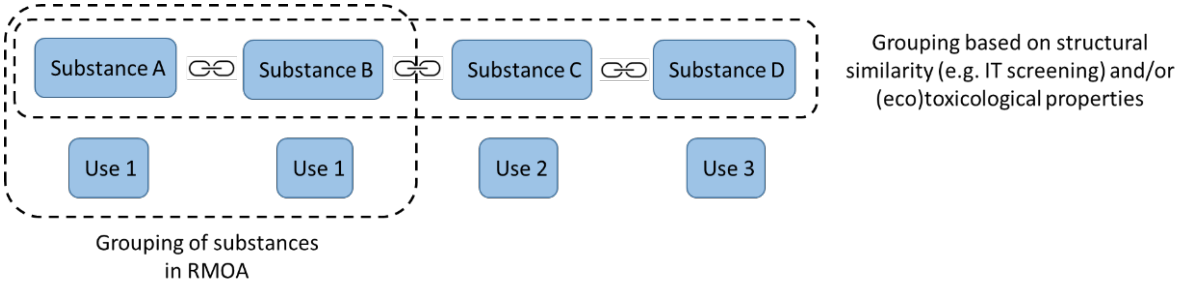

Figure 6. Grouping in RMOA at two levels, structural similarity (and/or intrinsic properties) and use pattern (∞relates to substance relationships).

For example, in 2017 the Swedish Chemicals Agency presented an RMOA for skin sensitisers in textiles (Annex 1). The substances were grouped according to intrinsic toxicological properties (skin sensitisers) and use pattern (presence in textiles). Substances that could potentially be covered included dispersion colorants, formaldehyde, flame retardants and odorants. Thus, the substances did not need to be structurally similar but were grouped based solely on their intrinsic properties and uses[16].

4.3 REACH – Registration

Grouping structurally similar substances and read-across of data are used widely by registrants in order to satisfy the information requirements in REACH. Many registrations that use read-across of data are, however, poor with unfounded or insufficiently justified groupings. The Swedish Chemicals Agency has previously addressed these shortcomings and proposed various measures (Swedish Chemicals Agency, 2014a). As part of the work with expanded support for registrants, ECHA has published several detailed and well-described examples of grouping of substances. Recently, ECHA's framework for evaluating read-across and grouping of structurally similar substances in regard to health or the environment (RAAF) has been developed (ECHA, 2017a). The purpose of RAAF is to ensure that important scientific aspects of grouping and read-across of data are evaluated in a consistent manner, but RAAF is also an aid for registrants to obtain acceptable scientific data.

To achieve general high-quality registrations in REACH, ECHA has initiated sector-specific activities in which the registrations for groups of substances are reviewed; for example, substances in the petroleum and coal stream sector that are reviewed in dialogue with relevant stakeholders (PetCo). Another initiative is the Collaborative Approach in which smaller groups of substances are assessed in consultation between ECHA, selected Member States' competent authorities and registrants. The Swedish Chemicals Agency participates in both of these activities. ECHA also plans additional initiatives for sector-specific substance groups during 2017/2018. The purpose of the initiatives is to improve the registrations without having to use the formal regulatory processes for dossier and/or substance evaluation.

[16] A similar grouping is also used in the EU Commission restriction proposal for CMR substances in textiles in accordance with REACH Article 68.2. The proposal has been discussed by the REACH Committee during 2017.

Table 1. Structurally similar substances in the CoRAP update 2015–2017.

Year	Member State	EC No.	CAS No.	Substance name	Initial grounds for concern*	Source
2015	Finland	264-848-5 (S6)	64365-17-9	Resin acids and rosin acids, hydrogenated, esters with pentaerythritol (HRPE)	Environment/suspected PBT/ vPvB; exposure/wide dispersive use, exposure of environment, consumer use, high (aggregated) tonnage	Already in CoRAP
		266-042-9 (S6)	65997-13-9	Resin acids and rosin acids, hydrogenated, esters with glycerol (HRGE)		
2015	France	215-477-2 (S1)	1327-41-9	Aluminium chloride basic	Human health/ suspected CMR; high (aggregated) tonnage	Already in CoRAP
		231-208-1 (S1)	7446-70-0	Aluminium chloride	Human health/ suspected CMR; exposure/high RCR; exposure of workers; high (aggregated) tonnage	
		233-135-0 (S1)	10043-01-3	Aluminium sulphate	Human health/ suspected CMR; suspected sensitiser; exposure/wide dispersive use, consumer use, high RCR, high (aggregated) tonnage	
2015	Germany	202-422-2 (S2)	95-47-6	o-Xylene	Human health/suspected CMR, suspected sensitiser; exposure/wide dispersive use, consumer use, cumulative exposure, high RCR, high (aggregated) tonnage	Already in CoRAP
		203-396-5 (S2)	106-42-3	p-Xylene		
		203-576-3 (S2)	108-38-3	m-Xylene		
2015	Germany	231-511-9 (S4)	7601-89-0	Sodium perchlorate	Suspected C, potential endocrine disruptor, other hazard, wide dispersive use, exposure of workers	New
		232-235-1 (S4)	7790-98-9	Ammonium perchlorate	Suspected C, potential endocrine disruptor, other hazard, wide dispersive use, exposure of workers, high RCR	
2016	Germany	218-407-9 (S3)	2144-53-8	3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl methacrylate	Suspected PBT/vPvB, other hazard, wide dispersive use, exposure of environment	New
		241-527-8 (S3)	17527-29-6	3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl acrylate		
2017	Germany	215-535-7 (S5)	1330-20-7	Xylene	Human health/ suspected CMR, suspected sensitiser; exposure/wide dispersive use, consumer use, cumulative exposure, high RCR, high (aggregated) tonnage	Already in CoRAP
		905-562-9 (S5)	n.a.	Reaction mass of ethylbenzene and m-xylene and p-xylene	Suspected R, suspected sensitiser, other: neurotoxicant, wide dispersive use, consumer use, exposure of sensitive populations, high RCR, high (aggregated) tonnage	New
		905-588-0 (S5)	n.a.	Reaction mass of ethylbenzene and xylene		

** Further concerns may be identified during the substance evaluation process.*

4.5 CLP – Classification

Grouping substances based on structural similarity can be used for classification in accordance with CLP, both in regard to read-across of data in a category as support in the evaluation of one substance, and in regard to group classifications (group entries). It can also be advantageous to process several structurally similar substances in a group sequentially to achieve greater work efficiency, even if each substance is processed individually in regard to regulations. The substance for which there is the most data should be evaluated first.

In accordance with Annex I to CLP (section 1.1.1.3) all available information must be used in a classification of a substance to determine the hazards using a weight of evidence determination, including "[…] information from the application of the category approach (grouping, read-across*)* […]". In several cases, the Swedish Chemicals Agency has used grouping and read-across of data from other structurally similar substances as part of the weight of evidence determination when preparing classification dossiers. For example, for the classification of perfluorodecanoic acid (PFDA) an analogue approach was used. Here, data from perfluoroctanoic acid (PFOA) and its ammonium salt (APFO) were used for read-across of data in relation to its carcinogenicity and reproductive toxicity. Data for other homologous perfluoroalkyl acids have also been used to support the evaluation. In a classification proposal for a metalorganic dialkyltin compound, dibutylbis(pentane-2,4-dionato-O,O´)tin, read-across of data was performed in a category comprised of several structurally similar dialkyltin compounds (Annex 1).

There are several group entries with harmonised classification in Annex VI to CLP[17]. A majority of these group entries are, however, classifications decided in accordance with the Council Directive 67/548/EEC which has been implemented within the framework of CLP. One example is lead compounds with index number 082-001-00-6, "lead compounds with the exception of those specified elsewhere in this Annex" where a wide approach has been applied to cover a large number of substances containing the (eco)toxic lead ion.

A few group approaches have also been processed within the CLP framework. A review of classification proposals in accordance with CLP on ECHA's website[18] gives the following summary of group entries (Table 2). Classifications that include several CAS No./EC No. but which can still be considered to be identical substances in accordance with REACH (for example isomer mixtures resulting from a manufacturing process, various hydrated forms, etc.) have not been included in Table 2. UVCB substances (for example reaction products) which are considered as individual substances in accordance with REACH have not been included.

[17] http://www.echa.europa.eu/sv/web/guest/information-on-chemicals/cl-inventory-database.

[18] The list includes substances/groups of substances that have been for public consultation (332 entries, February 2018). http://echa.europa.eu/harmonised-classification-and-labelling-previous-consultations.

Table 2. Examples of group entries processed under CLP.

Substance name	EC No.	CAS No.	Index number	Reason for group entry
White spirits The dossier originally included 5 substances, but 2 were excluded during the process. Also previous classification, therefore different index numbers.	232-489-3 265-185-4 265-191-7	8052-41-3 64742-82-1 64742-88-7	649-345-00-4 649-330-00-2 649-405-00-X	Belong to the same category, 80-85% identical hydrocarbons with similar physico-chemical properties
Perfluorononan-1-oic acid (and Na+/NH4+ salts) (PFNA)	206-801-3	375-95-1 21049-39-8 4149-60-4	607-718-00-9	Occur in the same form at relevant pH
Nonadecafluorodecanoic acid (and Na+/NH4+ salts) (PFDA)	206-400-3 221-470-5	335-76-2 3108-42-7 3830-45-3	607-720-00-X	Occur in the same form at relevant pH
Isoeugenol, (E)-2-Methoxy-4-(prop-1-enyl)phenol (Z)-2-Methoxy-4-(prop-1-enyl)phenol	202-590-7 227-678-2 227-633-7	97-54-1 5932-68-3 5912-86-7	Not available	Stereoisomers with similar properties
Carvone, 5-Isopropenyl-2-methylcyclohex-2-en-1-one (d/l) Carvone (d) Carvone (l)	202-759-5 218-827-2 229-352-5	99-49-0 2244-16-8 6485-40-1	606-148-00-8	Stereoisomers with similar properties
Tributyltin compounds Dossier for Repr. 1B, previous group entry in accordance with 67/548/EEC	-	-	050-008-00-3	Form the same metabolite under physiologically relevant conditions

The classifications above primarily cover groups of substances where the group members have been specifically defined (specific CAS No./EC No.). The group members are structurally related to each other, for example through chain length (white spirits), or the substances are mixtures of isomers (isoeugenol), or acids and their salts. The group entry for tributyltin compounds which was adopted under a previous directive (67/548/EEC) is distinct in that the members of the group are undefined. Nonetheless, common to all group entries is that the members are processed as a group based on the specific endpoint that is indicated.

In summary, there are several examples of undefined (wide) group entries in Annex VI to CLP which were adopted under the previous Council Directive 67/548/EEC. Similar (new) group entries have not yet been processed by RAC. One can, however, note that the substances can be, and to a certain extent have been, processed in groups with the intention of classification under CLP, but that the number of new group entries is limited. It can generally be concluded that there is no universal solution as to which approach should be chosen for harmonised classification of a group of substances, and that the decision on strategy is decided case by case.

4.6 REACH – Candidate List and authorisation

Grouping substances based on structural similarity is also used to a limited extent in the authorisation process. Read-across of data from a source substance(s) to a target substance has been utilised for SVHC identification (for example for PBT identification of perfluorononan-

1-oic acid (PFNA) proposed by the Swedish Chemicals Agency), and some group entries are also to be found on the Candidate List and in Annex XIV. In exactly the same way as for classification, several structurally similar substances can be processed advantageously in succession to achieve higher efficiency, even if each substance is processed individually. Obviously, efficiency would be even greater if the same/similar substance recurred in several different REACH/CLP processes.

A review of the Candidate List on ECHA's website[19] revealed about twenty group entries, a few examples of which are given in Table 3. Four group entries, namely HBCDD, chromic acid, ethoxylated 4-nonylphenol (branched and linear) and ethoxylated 4-(1,1,3,3-tetramethylbutyl)phenol can also be found in Annex XIV in REACH[20]. Entries with several CAS No./EC No. that can be considered as identical substances are not considered to be group entries (see above).

Group entries apply to both defined groups where specific substances are listed and undefined groups where specific substances are missing. The latter, however, cover structurally similar substances for which example lists of substances that are included in the groups have often been indicated in the documentation for SVHC identification. In some cases, for example for PFNA, the group is the same as that for the applicable classification (same index number) which demonstrates the importance of defining the group early in the REACH/CLP processes.

Table 3. Examples of group entries on the Candidate List.

Substance name	EC No.	CAS No.	Reason for inclusion (Art. 57)	Reason for group entry	Included in Annex XIV
Perfluorohexane-1-sulphonic acid and its salts (many substances listed in an example list) (PFHxS)	-	-	vPvB (57e)	Occur in the same form at relevant pH	-
1,2-Benzenedicarboxylic acid, di-C6-10 alkyl esters or mixed decyl and hexyl and octyl diesters, with ≥ 0.3% of dihexyl phthalate (EC No. 201-559-5)	271-094-0 272-013-1	68515-51-5 68648-93-1	Repro. (57c)	272-013-1 (C6/C8/C10) is covered by 271-094-0 (C6-C10)	-
Perfluorononan-1-oic acid (and Na+/NH4+ salts) (PFNA)	206-801-3	375-95-1 21049-39-8 4149-60-4	Repro. (57c) PBT (57d)	Occur in the same form at relevant pH	-
Nonadecafluorodecanoic acid (and Na+/NH4+ salts) (PFDA)	206-400-3 221-470-5	335-76-2 3830-45-3 3108-42-7	Repro. (57c) PBT (57d)	Occur in the same form at relevant pH	-
5-sec-Butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [1], 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [2] covering any of the individual stereoisomers of [1] and [2] or any combination thereof (2 substances specified)	-	-	vPvB (57e)	Isomers with similar properties	-

[19] http://echa.europa.eu/web/guest/candidate-list-table (181 entries, February 2018).
[20] https://echa.europa.eu/sv/authorisation-list (43 entries, February 2018).

4-Nonylphenol, branched and linear, ethoxylated (includes all substances with linear/branched C9 in position 4 to phenol, ethoxylated, incl. polymers, etc.)	-	-	ELoC (57f)	Degrade to analogous nonylphenols	-
4-Nonylphenol, branched and linear (includes all substances with linear/branched C9 in position 4 to phenol, incl. polymers, etc.)	-	-	ELoC (57f)	Analogous nonylphenols	-
Acids generated from chromium trioxide and their oligomers (3 substances specified)	.	.	Carc. (57a)	Related via equilibria in aqueous environments	Yes
Hexabromocyclododecane (HBCDD) and all major diastereoisomers identified (5 substances specified)	-	-	PBT (57d)	Stereoisomers with similar properties	Yes

Undefined, wide group entries on the Candidate List would potentially result in (many) more substances being subject to the information requirements for articles and, after inclusion in Annex XIV in REACH, that more substances are subject to authorisation. A potential approach that has been discussed in recent years to identify SVHC substances is the "Substances in Substances" method, SiS (Figure 7). SiS means a non-specific group entry on the Candidate List that includes all substances Y which contain a constituent/impurity X that has been identified as an SVHC substance. An analysis of this type of approach (ECHA, 2012) indicated that it could be implemented but that it would require a different working method than that currently used, in particular for prioritisation of substances for Annex XIV. Prioritisation from the Candidate List to Annex XIV in REACH must be performed in accordance with the criteria in Article 58.3, i.e. substances with PBT/vPvB properties, widespread use or large volumes are prioritised. Substances identified as SVHC using the SiS method can have widely varying volumes and uses, which must be delineated in the prioritisation rather than in connection with RMOA and SVHC identification. The work load of the authorities will therefore probably not be less overall. The analysis also revealed that industry faces a problem in regard to information requirements, as it can be difficult to know if one is covered by a group entry or not. There are also a number of uncertainties from a legal perspective.

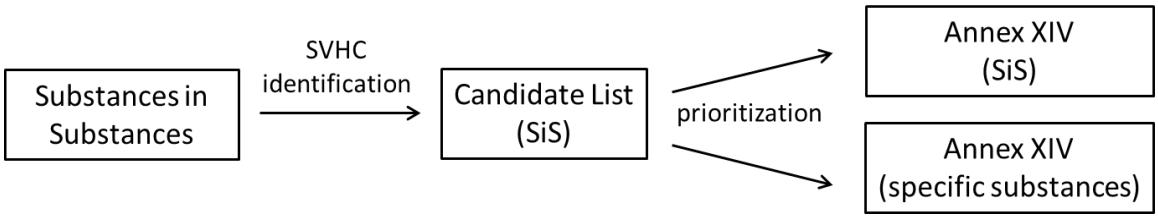

Figure 7. Approach for the SiS method. A potential prioritisation to Annex XIV of the entire non-specific group or specific substances from the group has been discussed.

The Candidate List thus contains both defined and partially (un)defined group entries. However, prioritisation of substances to Annex XIV in REACH can cause problems with group entries that are too wide. To prevent regrettable substitution, individual substances on the Candidate List can also be processed in groups when prioritising substances to Annex XIV (ECHA, 2014a). The purpose of prioritising groups of substances is that substances on Annex XIV shall not be substituted with other substances on the Candidate List with similar SVHC properties.

When applying for authorisation in accordance with REACH Article 62.3, it may be appropriate to group substances:

> Applications may be made for one or several substances that meet the definition of a group of substances in Section 1.5 of Annex XI, and for one or several uses.

In practice, a group of substances (several entries on Annex XIV) can therefore be covered by the same authorisation application.

4.7 REACH – Restriction

Group entries are common for restrictions, as shown in the example list (Table 4) covering various substances and uses. A complete list of existing group entries can be found in Annex 2.

The restrictions primarily comprise groups with defined group members (for example no. 50 which lists eight substances in the group) but also groups for which the members are not specifically defined (for example no. 20).

Table 4. Examples of group entries in REACH Annex XVII.

No.	Designation of the substance, of the group of substances or of the mixture
20	Organostannic compounds
43	Azocolourants and azodyes
50	Polycyclic aromatic hydrocarbons a) Benzo[a]pyrene (BaP), CAS No. 50-32-8 b) Benzo[e]pyrene (BeP); CAS No. 192-97-2 c) Benzo[a]anthracene (BaA); CAS No. 56-55-3 d) Chrysen (CHR), CAS No. 218-01-9 e) Benzo[b]fluoranthene (BbFA), CAS No. 205-99-2 f) Benzo[j]fluoranthene (BjFA); CAS No. 205-82-3 g) Benzo[k]fluoranthene (BkFA), CAS No. 207-08-9 h) Dibenzo[a,h]anthracene (DBAhA); CAS No. 53-70-3
51	The following phthalates (or other CAS and EC numbers covering the substance): a) Bis(2-ethylhexyl) phthalate (DEHP); CAS No. 117-81-7, EC No. 204-211-0 b) Dibutyl phthalate (DBP); CAS No. 84-74-2, EC No. 201-557-4 c) Benzyl butyl phthalate (BBP); CAS No. 85-68-7, EC No. 201-622-7
63	Lead; CAS No. 7439-92-1, EC No. 231-100-4 and its compounds

In addition to the compilation of group entries in Annex 2, the Swedish Chemicals Agency, in collaboration with the German Environmental Authority (UBA), has 2017 produced a restriction proposal for perfluorinated carboxylic acids (PFCA) C_9-C_{14} and their precursors. It is estimated that a few hundred substances are covered by the restriction proposal.

The group approach is more commonly used in the restriction process than in classification in accordance with CLP and the authorisation process in REACH. Recently adopted restrictions reveal that this is a feasible route for regulating groups of substances if the restriction proposal shows that use of the group of substances results in an unacceptable risk to human health and/or the environment, and that the proposed measures are motivated from a socio-economic perspective. A restriction covering a group of substances, however, may be associated with considerable additional work for a Member State as compared to a restriction proposal for a single substance.

5 Summary analysis

The existing EU chemicals legislation is largely aimed at assessing substances individually. Processing substances as groups is often considered as an option to increase efficiency and achieve more effective chemicals management. However, as is apparent from the report, grouping is not an unambiguous term. In regard to a group of chemical substances, substances with similar structures are frequently referred to where the structural similarity can result in similar intrinsic properties, but a group of substances can also refer to substances with similar uses. Because grouping can have different meanings in different contexts, the intention in each case must be defined.

Grouping substances based on structural similarity and read-across of data is identified in REACH Annex XI as an alternative method for filling data gaps in substance registrations. In this method, which is also used for classification in accordance with CLP and for SVHC identification, a high scientific level is necessary and good knowledge about the chemical identity of the substances is required. However, grouping is also used in a wider perspective in regulatory risk management and at selection of substances for potential regulatory measures. Whether several substances can and should be processed in groups is decided from case by case and depends on the purpose of the grouping.

Many REACH registrations that use read-across of data are, however, poor with unfounded or insufficiently justified groupings. To achieve general high-quality registrations, ECHA has initiated sector-specific activities in which the registrations for groups of substances are reviewed in dialogue with affected stakeholders.

The Swedish Chemicals Agency works with grouping of substances at several levels. In prioritisation of substances for assessment and analysis of potential measures, groups are identified based on chemical structure, (eco)toxicological properties or areas of use. The in-house developed Prioritisation Table can be used to support this work. The Prioritisation Table can also be used to further supplement ECHA's screening of substances registered in REACH, and thereby identify other (structurally) related substances in a group to achieve broad risk management measures and prevent regrettable substitution.

ECHA's common screening is under continuous development, and grouping of substances based on structural similarity is increasingly used. The various processes in REACH and CLP permit a group approach to varying extents, and grouping is an important factor when considering the best way to implement legislation to reduce risks associated with the use of chemical substances. For the substance evaluation process, grouping is desirable for achieving high efficiency and for ensuring that competent authorities are consistent in their decisions on structurally similar substances. Expanded group evaluations have, however, not been considered to be feasible within the framework of the substance evaluation process. Harmonised classification in accordance with CLP is often the starting point when substances are regulated through REACH. A group approach in a classification can provide the prerequisites for effectively managing substances by group also in REACH processes, and thereby more effectively achieve protection for human health and the environment. Recently adopted classifications in accordance with CLP demonstrate the possibility of having a group approach that includes several substances in the same classification proposal, but that the strategy for managing groups of substances in CLP varies from one case to another.

The Swedish Chemicals Agency has made several classification proposals using a group approach, and the grouping method should be further developed so that group approaches are used whenever possible. Experiences from the agency's work reveal that ECHA can assist in

the analysis of the scope of a classification proposal. The Swedish Chemicals Agency should continue to promote that additional support and practical tools to facilitate grouping in the classification process are developed by ECHA, in consultation with the Member States' competent authorities. It is, however, important to consider the practical consequences of a classification proposal, and to ensure that (group) classifications are understood and can be used by affected stakeholders.

Grouping substances is also used to some extent within the REACH authorisation process. A group-based approach for the prioritisation to Annex XIV can result in increased efficiency when processing subsequent authorisation applications, by setting the same sunset date for several structurally similar substances. In the same line of reasoning, a group-based approach for the identification of SVHC is beneficial (and can prevent regrettable substitution to structurally similar substances with similar hazardous properties)) although each individual substance is processed individually. An alternative scenario with wide group entries on the Candidate List can pose problems in the prioritisation of substances to Annex XIV since the prioritisation is based on the intrinsic properties, use and tonnage of each individual substance.

In REACH, a group approach is commonly used in the restriction process. Recently adopted restrictions reveal that this is a feasible route for regulating groups of substances if the restriction proposal shows that the use of the group of substances results in an unacceptable risk to human health or the environment, and that the proposed measures are motivated from a socio-economic perspective. Another important aspect in this context is to prevent regrettable substitution.

The Swedish Chemicals Agency has previously argued for the need for an organised process or discussion relating to group-based assessments of substances within REACH (Swedish Chemicals Agency, 2014a). During 2016, ECHA presented documentation for additional cooperation between ECHA and Member States' competent authorities which shows that grouping substances is prioritised and occurs increasingly in ECHA. The European Chemicals Agency has further developed support on its website with explanatory examples of grouping and read-across for various (eco)toxicological endpoints. The RAAF (Read-Across Assessment Framework) has also been developed for both human health and the environment as a framework for evaluation of read-across approaches in the REACH and CLP processes.

Additional efforts are needed if more systematic assessment and management of groups of chemical substances are to take place within REACH and CLP. A number of measures for group assessments were identified in the Swedish Chemicals Agency's report "Developing REACH and improving its efficiency – an action plan". Several of the short-term proposed measures are ongoing, such as development of advice and guidance, grouping of substances in the substance evaluation process, and collaboration on grouping between ECHA and Member States' competent authorities. Moving forward, the Swedish Chemicals Agency should continue to work for increased possibilities for grouping within REACH and CLP, and to generate proposals in this area. The agency should also continue to be active in ECHA's common screening to identify groups of substances with the goal of achieving broad risk management measures and prevent regrettable substitution. There is also a need for further discussion on grouping of substances at the political level, in appropriate fora at EU level, in order to enhance the level of protection for human health and the environment.

In summary, it can be noted that the foundation for group-based assessments and management of substances are present in REACH and CLP. The Swedish Chemicals Agency works with grouping of chemical substances at several levels in the risk management of chemicals.

Grouping methodologies will continuously develop as new proposals are presented, in part within regulatory processes and in part in other work within chemicals management. The options for group-based approaches are, however, decided case by case and depend on the purpose of the grouping. In any future development of the REACH regulation, it will be important that the issue of group-based assessments is addressed through political initiatives from governments, and analyses and studies at authority level.

6 Literature

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Annex 1. Grouping of substances in the work of the Swedish Chemicals Agency, examples

The Swedish Chemicals Agency has worked with groups of substances in several cases in connection with proposals for REACH and CLP processes. In the future, grouping of substances will be used to a greater extent as the methodologies are further developed. So far, grouping has been used for e.g. prioritisation of substances, for finding candidates for harmonised classification, and for read-across of data in proposals for harmonised classification and for SVHC identification. There is a potential to further utilise these methods when preparing new proposals for SVHC identification or restrictions, or selection of substances for substance evaluation. Described below are some examples of how the Swedish Chemicals Agency have used grouping of substances in REACH and CLP processes.

Textile substances – RMOA

Grouping by:

- Use pattern: textile substances
- Technical function: dyes
- Substance group: azo dyes
- Intrinsic properties: skin sensitisers

The Swedish Chemicals Agency has in a government assignment reported on the risks to human health and the environment from chemical substances in textiles (Swedish Chemicals Agency, 2014b). In the assignment, about 3,500 substances were identified as relevant for use in textile production. Of these, the Swedish Chemicals Agency identified 368 functional chemicals with hazardous properties that may occur in high concentrations in textile articles. The substances were subsequently prioritised based on the probability of exposure i.e. the probability of release. The majority of the identified substances were azo dyes (Figure 8). In the appropriation directions for 2015, the Swedish Chemicals Agency was subsequently instructed to draw up recommendations for measures on how to reduce risks associated with hazardous substances in textiles. One of the proposals in the final report is that the Swedish Chemicals Agency shall "[…] investigate the possibilities of introducing additional restrictions on certain azo dyes which are not covered by existing legislation at EU level" (Swedish Chemicals Agency, 2015b).

In a recent risk management option analysis (RMOA) covering textile substances as a group, the Swedish Chemicals Agency investigated various options for risk management measures on skin sensitisers in textiles in the EU[21]. The agency presented various options such as restriction of skin sensitisers in general, or a narrower restriction specifically for disperse dyes (the majority of which include azo dyes).

[21] See PACT (Public Activities Coordination Tool): https://www.ECHA.europa.eu/sv/pact.

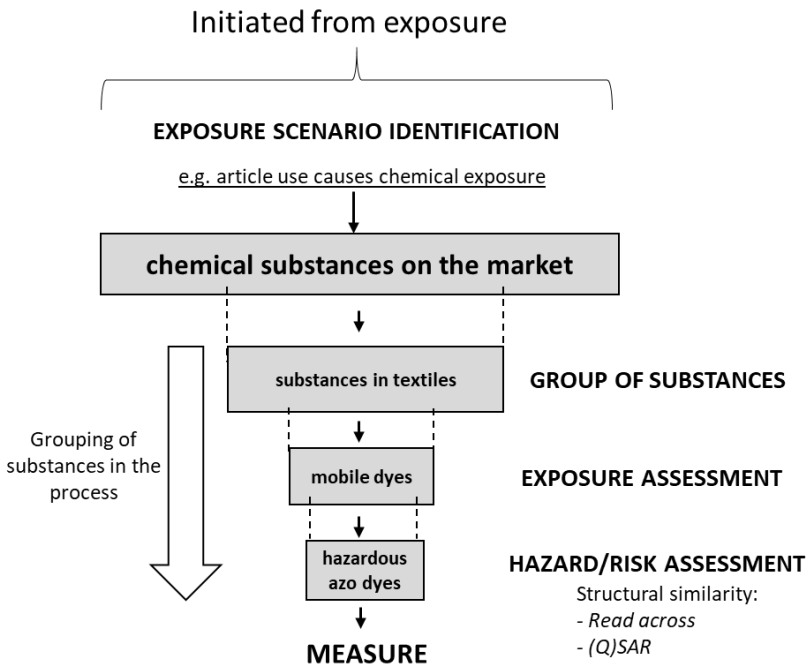

Figure 8. Grouping of textile substances at various levels.

Bisphenols – government assignment within the framework of the Strategy for a non-toxic everyday life

Grouping by:

- Chemical structure
- Regulatory status
- Indicated use
- Intrinsic properties (endocrine disruptor)
- Technical function

The commission from the Swedish Government of implementing the Strategy for a non-toxic everyday life, and achieving the national environmental quality objective A Non-Toxic Environment 2015-2017, included a sub-task on bisphenols. In the sub-task, the Swedish Chemicals Agency developed a new screening methodology that enables identification and prioritisation of substances that may be of concern[22]. The methodology is based on the progressive grouping of substances based on their chemical structure, their possible use in different applications, and their potential endocrine disrupting properties (according to data simulations, (Q)SAR). The methodology is universally applicable and can be applied to other groups of substances (Figure 9).

Bisphenol A (BPA) is a substance that is produced in large volumes and used primarily to manufacture plastics, in particular polycarbonate or epoxy plastics. Bisphenol A may also be present in thermal paper, which is used in receipts for example. The substance is detected in urine and blood samples from almost all humans, which suggests that most of us are continuously exposed to low doses of the substance. Bisphenol A is an endocrine disruptor for

[22] The Swedish Chemicals Agency, 2017. Report no. 5/17, "Bisphenols – a survey and analysis".

humans and can affect our reproductive capability. To reduce exposure to BPA, new rules for bisphenol A have been adopted in Sweden and in the EU over the past two years.

In many instances, BPA can be replaced by other bisphenol substances. However, currently the use of other bisphenols is small in comparison to BPA. On the other hand, information about which bisphenols are used, and knowledge of their toxicological properties is limited. Within the survey, the Swedish Chemicals Agency took a broad approach to the bisphenol group. Bisphenols that may occur in Sweden and the EU were identified, information was compiled for these substances and further analysed for the need for initiatives to manage their current and future risks.

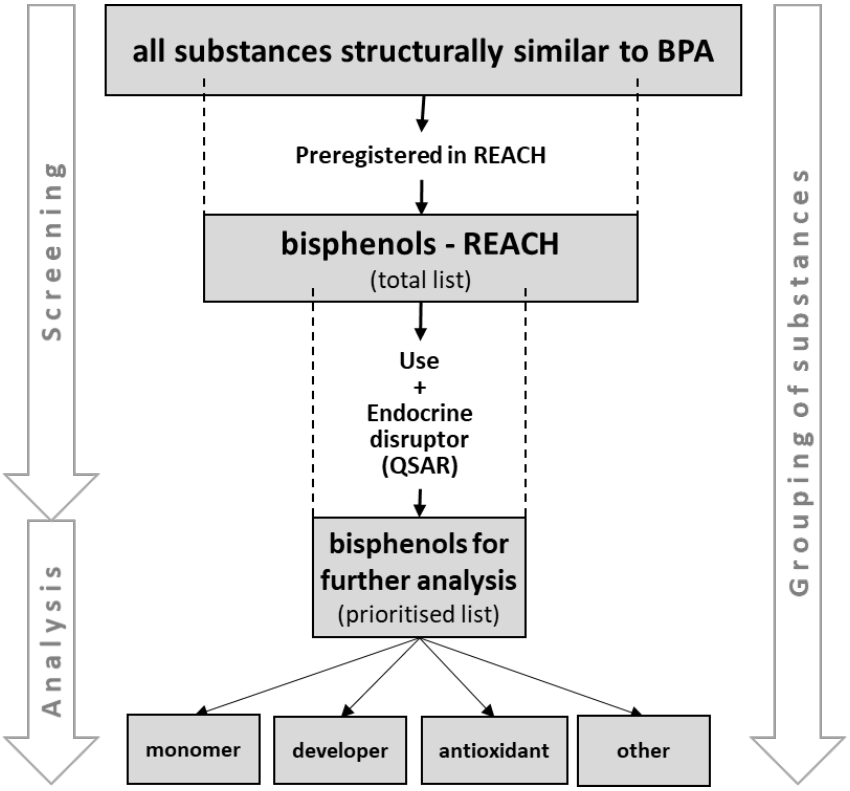

Figure 9. Method for identifying and prioritising bisphenols. 39 bisphenols were subject to a more detailed review.

The Swedish Chemicals Agency identified more than 200 substances with a chemical structure similar to BPA, and which can be found on the European market. A group of 39 substances was prioritised based on indicated uses and potential endocrine disrupting properties, and the substances were therefore included in a more detailed review of available information. In a recent RMOA developed under 2018, the Swedish Chemicals Agency investigated various options for risk management measures on one of these prioritized bisphenols.[21]

Silanes – substance evaluation and classification

Grouping by:

- Substance group: trimethoxysilanes
- Chemical structure

Two structurally related silanes, trimethoxymethylsilane (EC No. 214-685-0) and trimethoxyvinylsilane (EC No. 220-449-8), were evaluated in the substance evaluation process leading to increased efficiency in the overall work on these substances. The registrant did not provide sufficiently well-documented justification for grouping and read-across of data between these two substances (or other structurally related substances). As a result, further information was requested on mutagenicity. Available information for skin sensitisation was adequate for classification of both substances and the classification proposals were finalised by the Swedish Chemicals Agency in 2017.

Phthalates – classification and SVHC identification

Grouping by:

- Use pattern: softeners
- Substance group: phthalates
- Structural similarity – read-across

Phthalates, i.e. diesters of phthalic acid, form a large group of substances with varying toxicity where phthalates with 4-6 hydrocarbon side chains show reproductive toxicity. Several Member States, including Sweden, have worked for many years on regulating phthalates (C_4-C_6) and currently there are 14 phthalates (entries) on the Candidate List (Table 5). These are both single substances such as DEHP, and entries containing several different phthalates such as 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear. In one case, the SVHC identification is linked to the presence of a constituent/impurity (dihexyl phthalate) that exceeds the classification threshold, i.e. 0.3%.

Another phthalate, dicyclohexyl phthalate (DCHP), has been proposed as a SVHC. The Swedish Chemicals Agency proposed that DCHP should be identified both in accordance with Article 57c (Repr. 1B) and as an endocrine disruptor (in accordance with Article 57f), but MSC could not agree (five Member States voted against) and the proposal has now been sent to the EU Commission for further processing[23].

[23] Voting in the REACH Committee December 2017.

Table 5. Phthalates on the Candidate List.

Substance name	EC No.	Reason for inclusion (Art. 57)	Date
1,2-Benzenedicarboxylic acid, di-C6-C10-alkyl esters or mixed decyl and hexyl and octyl diesters, with ≥0.3% dihexyl phthalate (EC No. 201-559-5)	271-094-0 272-013-1	c	15/6/2015
1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear	271-093-5	c	16/6/2014
Dihexyl phthalate	201-559-5	c	16/12/2013
Dipentyl phthalate (DPP)	205-017-9	c	20/6/2013
1,2-Benzenedicarboxylic acid, dipentyl ester, branched and linear	284-032-2	c	19/12/2012
Diisopentyl phthalate	210-088-4	c	19/12/2012
n-Pentyl-isopentylphthalate	-	c	19/12/2012
Bis(2-methoxyethyl) phthalate	204-212-6	c	19/12/2011
1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich	276-158-1	c	20/6/2011
1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters	271-084-6	c	20/6/2011
Diisobutyl phthalate	201-553-3	c,f	13/1/2010
Benzyl butyl phthalate (BBP)	201-622-7	c,f	28/10/2008
Bis(2-ethylhexyl)phthalate (DEHP)	204-211-0	c,f	28/10/2008
Dibutyl phthalate (DBP)	201-557-0	c,f	28/10/2008

If a CMR substance is to be included on the Candidate List it must have a harmonised classification as CMR category 1A/1B. All phthalates that are classified as Repr. 1B are now on the Candidate List with the exception of DCHP (see above). Probably there are more phthalates that have this intrinsic property, but for these to be identified as SVHC, they must first be classified. Currently, work is ongoing on the classification of two phthalates, diisooctyl phthalate (CAS No. 27554-26-3; FR) and diisohexyl phthalate (CAS No. 71850-09-4; SE)[24]. Grouping and read-across of data have generally been part of the strategy for the classifications of the phthalates.

Cadmium compounds – classification and SVHC identification

Grouping by:

- Use pattern: partly overlapping
- Substance group: cadmium compounds
- Structural similarity – read-across

Cadmium and cadmium compounds are toxic due to the formation of cadmium ions (Cd^{2+}) when dissolved in the environment or directly in an organism. The potency of different cadmium compounds is therefore dependent on their solubility in water. Uses of metallic cadmium and cadmium compounds overlap but are not identical (Figure 10). Nonetheless, it is possible in many uses that one cadmium compound can be replaced by a structurally

[24] RAC opinion June 2017.

similar substance, i.e. another cadmium compound. It is therefore important to have a group-based approach in relation to risk managing measures for cadmium and its compounds.

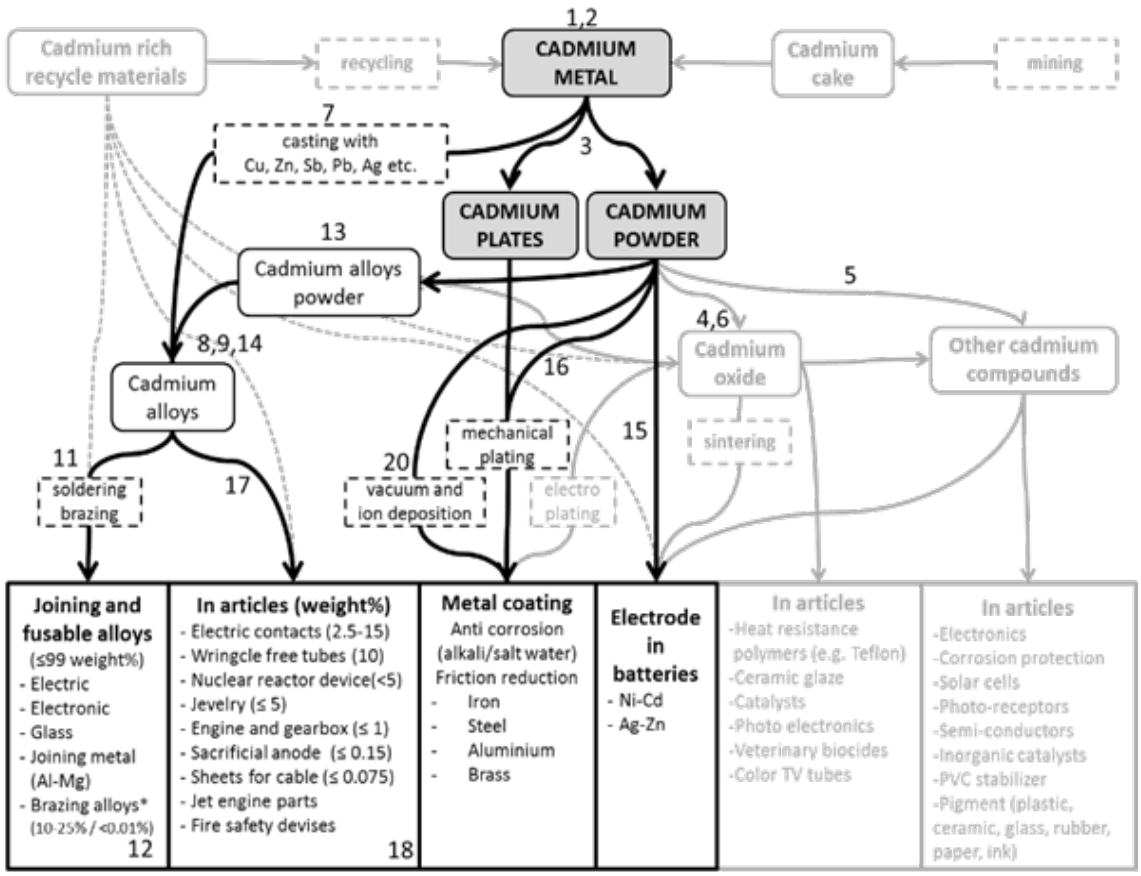

Figure 10. Areas of use for cadmium.

When the Swedish Chemicals Agency started their work to propose cadmium compounds for the Candidate List in 2012, six substances had a harmonised classification as Carc. 1B and therefore meet the criteria for SVHC in accordance with REACH Article 57(a) (Table 6). Common for these six substances was also their STOT RE1 classification due to kidney and bone toxicity. Historically, health risk assessments of cadmium have been based on kidney toxicity; in recent years this has been supplemented and, to a certain extent, replaced by bone toxicity. The carcinogenicity has normally not been the critical effect in the risk assessment of cadmium. Because authorisations in REACH only need to take into consideration the effects on which inclusion of the substance on the Candidate List is based, the SVHC proposals included the effects on bone and kidneys (i.e. in accordance with Article 57 (f), equivalent level of concern). The sequential SVHC identification for several structurally related cadmium compounds made the work efficient.

Table 6. Cadmium compounds on the Candidate List by the end of 2014.

Substance	EC No.	REACH registration	Reason for inclusion (Art. 57)	Date
Cadmium	231-152-8	full	a,f	20/6/2013
Cadmium oxide	215-146-2	full	a,f	20/6/2013
Cadmium sulphide	215-147-8	full	a,f	16/12/2013
Cadmium chloride	233-296-7	full	a,b,c,f	16/6/2014
Cadmium fluoride	232-222-0	none	a,b,c,f	17/12/2014
Cadmium sulphate	233-331-6	intermediate	a,b,c,f	17/12/2014

The Swedish Chemicals Agency identified three additional cadmium compounds self-classified as Carc. 1B (Table 7). A harmonised classification is required if these compounds are to be identified as SVHC. In the classification proposals compiled by the Swedish Chemicals Agency in 2015, grouping and read-across of data was used. The substances were subsequently included on the Candidate List in January 2018.

Table 7. Recently classified cadmium compounds. Since 2018 included on the Candidate List.

Substance	EC No.	REACH registration	Classification of significance for SVHC	Reason for inclusion (Art. 57)	Date
Cadmium hydroxide	244-168-5	full	Carc. 1B, Muta 1B, STOT RE1	a,b,f	15/1/2018
Cadmium carbonate	208-168-9	full	Carc. 1B, Muta 1B, STOT RE1	a,b,f	15/1/2018
Cadmium nitrate	233-710-6	full	Carc. 1B, Muta 1B, STOT RE1	a,b,f	15/1/2018

Nonylphenol ethoxylates – restriction

Grouping by:

- Substance group: nonylphenol ethoxylates
- Structural similarity – read-across

The EU restriction of nonylphenol ethoxylates (NPE) in textiles is defined neither by the EC number nor the CAS number. The molecular formula used to identify the substance is the general $(C_2H_4O)_nC_{15}H_{24}O$ and the IUPAC name is ”Nonylphenol, branched and linear, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues)”. This wide (group) description cover all occurring forms and variants of NPE and thus provides a broad risk management measure. The Swedish Chemicals Agency prepared the restriction proposal that was adopted during 2015.

NPE occurs in textiles because of its use as a detergent and emulsification agent during textile manufacture. The problem of NPE in textiles is primarily that it is washed out and ends up in the environment. Here it can be degraded to nonylphenol which, in addition to being highly toxic for aquatic organisms, also has endocrine disruptor properties. NPE in itself is also toxic for aquatic organisms. The purpose of the restriction is to lower the levels of nonylphenol and NPE in the environment, thus reducing the environmental risks from nonylphenol and NPE, and to reduce the endocrine disruptor effects of nonylphenol.

Organotin compounds – classification

Grouping by:
- Substance group: dialkyl organotin compounds - Structural similarity – read-across

By grouping dialkyl organotin compounds containing two labile anionic ligands, dimethyltin, dibutyltin and dioctyltin compounds have been assessed within the framework of the OECD Cooperative Chemicals Assessment Programme. The respective categories of dialkyl organotin compounds were assumed to form common hydrolysis products after oral ingestion, and read-across of data within the categories are therefore valid. Based on the available toxicokinetic data and indirect analysis of formed hydrolysis products, the conclusion was that dialkyl organotin dichlorides (such as dibutyltin dichloride, DBTC) are formed as common hydrolysis products at low pH (Figure 11).

OECD considered primarily the following aspects when justifying read-across:

- structure (dialkyltin)
- physico-chemical properties (hydrolysis)
- toxicokinetics (in vitro studies show hydrolysis at low pH)

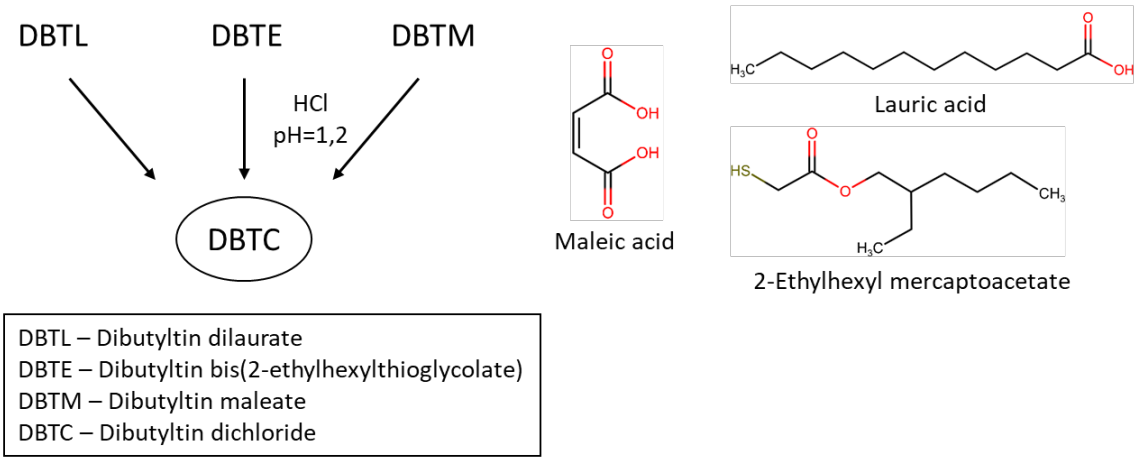

Figure 11. OECD has previously grouped dibutyltin compounds on the assumption that a common hydrolysis product, DBTC, is formed after oral ingestion. Only three of the six dibutyltin compounds in the category are presented [25].

Doubt has recently been raised about the common hydrolysis product DBTC. Within REACH, new studies have been performed that enabled direct analysis (NMR) of the hydrolysis product for DBTE under specific experimental conditions. Instead of loss of both ligands from the central tin ion, the studies indicate that one thioglycolate ligand remains attached to the tin ion. The assumption that a common hydrolysis product is formed is

[25] OECD, 2006. SIDS initial assessment profile. "Dibutyltin dichloride and selected thioglycolate esters". Available on: http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=3c211d5f-afb4-4b0e-a9a0-ecbd9b2253ec.

therefore questioned, and read-across within the category, from the source substance DBTC to the target substance DBTE, is no longer valid.[26]

The Swedish Chemicals Agency has recently prepared a classification proposal for dibutylbis(pentane-2,4-dionato-O,O')tin ($DBT(acac)_2$, where acac is the anion of acetylacetone). Based on the assumption that acac is loosely bound to the tin ion (based on relevant toxicokinetic data) and with new hydrolysis data (Figure 12) it was concluded that read-across of data for reproductive toxicity and STOT RE within a category is, in this case, valid. Both the source substance (one of several) and the target substance form the same hydrolysis product ($ClBu_2SnOSnBu_2Cl$) at low pH, a dimer of the original source substance. The identified hydrolysis product has a different chemical structure to the original assumed structure in the OECD category (DBTC) and demonstrates the complexity in chemistry that can occur.[27] In summary, it is important to consider both the chemical properties (reactivity, chemical equilibria) and the toxicity when creating a category of structurally similar substances. Identification of common degradation products/intermediates may depend on the conditions and the experimental techniques used for detection.

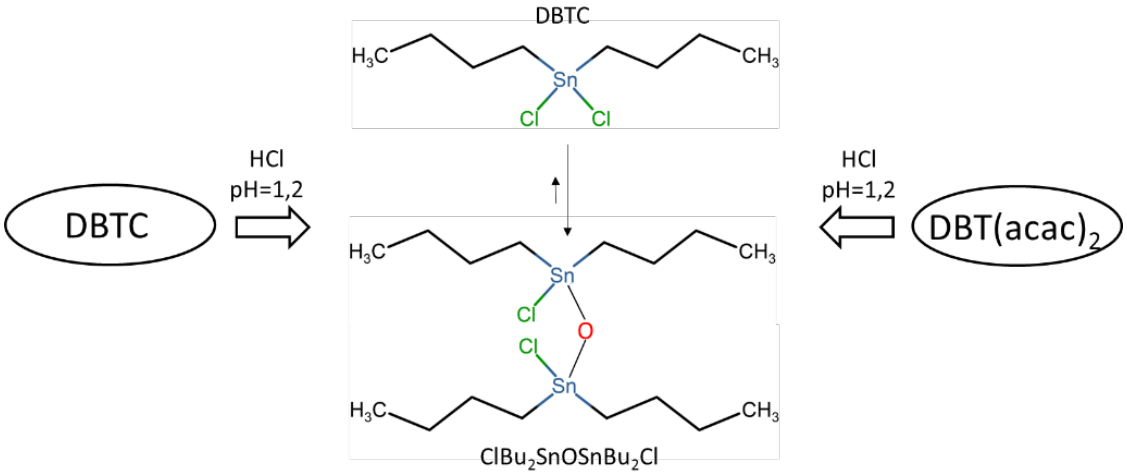

Figure 12. New hydrolysis studies within the framework of REACH with direct analysis of the hydrolysis products formed from source substances and target substances under specific conditions.

The Swedish Chemicals Agency is also participating in the Collaborative Approach (see section 4.3) where a group of organotin compounds containing thioester ligands is included. One purpose of the initiative is to improve the REACH registrations without using the normal regulatory processes. The group of organotin compounds included is of particular interest to evaluate considering that the read-across strategy used by the registrants is questioned.

[26] Of the different dialkyl diorganotin compounds, it is the thioglycolate-based compounds in particular that seem to have distinct hydrolysis behaviour.
[27] The exact structure for $ClBu_2SnOSnBu_2Cl$ is assigned to a dimer, $(ClBu_2SnOSnBu_2Cl)_2$, see Davies A. G. (2004). Difunctional distannoxanes, $XR_2SnOSnR_2X$. *J. Chem. Res.* 309-314.

estimated 200 substances, providing an effective risk management measure for a large group of highly fluorinated substances.

The use of PFAS in fire fighting foams leads to direct emissions to the environment. Sweden has many examples of contaminated soil and drinking water, the most likely source of which is fire fighting foam. This has resulted in a recent proposal by the Swedish Chemicals Agency for a national restriction on the use of the group PFAS in fire fighting foams[30]. All PFAS have been included because of their persistence.

[30] The Swedish Chemicals Agency, 2016. Report no. 1/16, "Förslag till nationella regler för högfluorerade ämnen i brandsläckningsskum".

Annex 2. Grouping of substances in REACH restrictions (Annex XVII)

Table 8. Restrictions that cover groups of substances in REACH Annex XVII.

No.	Designation of the substance, of the group of substances or of the mixture (from REACH, Annex XVII)
1	Polychlorinated terphenyls (PCTs)
3	Liquid substances or mixtures fulfilling the criteria for any of the following hazard classes or categories set out in Annex I to Regulation (EC) No 1272/2008: a) Hazard classes 2.1 to 2.4, 2.6 and 2.7, 2.8 types A and B, 2.9, 2.10, 2.12, 2.13 categories 1 and 2, 2.14 categories 1 and 2, 2.15 types A to F b) Hazard classes 3.1 to 3.6, 3.7 adverse effects on sexual function and fertility or on development, 3.8 effects other than narcotic effects, 3.9 and 3.10 c) Hazard class 4.1 d) Hazard class 5.1
6	Asbestos fibers a) Crocidolite; CAS No. 12001-28-4 b) Amosite; CAS No. 12172-73-5 c) Anthophyllite; CAS No. 77536-67-5 d) Actinolite; CAS No. 77536-66-4 e) Tremolite; CAS No. 77536-68-6 f) Chrysotile; CAS No. 12001-29-5, CAS No. 132207-32-0
9	a) Soap bark powder (Quillaja saponaria) and its derivatives containing saponines; CAS No. 68990-67-0, EC No. 273-620-4 b) Powder of the roots of Helleborus viridis and Helleborus niger c) Powder of the roots of Veratrum album and Veratrum nigrum d) Benzidine and/or its derivatives; CAS No. 92-87-5, EC No. 202-199-1 e) o-Nitrobenzaldehyde; CAS No. 552-89-6, EC No. 209-025-3 f) Wood powder
10	a) Ammonium sulphide; CAS No. 12135-76-1, EC No. 235-223-4 b) Ammonium hydrogen sulphide; CAS No. 12124-99-1, EC No. 235-184-3 c) Ammonium polysulphide; CAS No. 9080-17-5, EC No. 232-989-1
11	Volatile esters of bromoacetic acids: a) Methyl bromoacetate; CAS No. 96-32-2, EC No. 202-499-2 b) Ethyl bromoacetate; CAS No. 105-36-2, EC No. 203-290-9 c) Propyl bromoacetate; CAS No. 35223-80-4 d) Butyl bromoacetate; CAS No. 18991-98-5, EC No. 242-729-9
12	2-Naphthylamine; CAS No. 91-59-8, EC No. 202-080-4 and its salts
13	Benzidine; CAS No. 92-87-5, EC No. 202-199-1 and its salts
15	4-Aminobiphenyl, xenylamine; CAS No. 92-67-1, EC No. 202-177-1 and its salts
16	Lead carbonates: a) Neutral anhydrous carbonate ($PbCO_3$); CAS No. 598-63-0, EC No. 209-943-4 b) Trilead-bis(carbonate)-dihydroxide 2Pb CO_3-$Pb(OH)_2$; CAS No. 1319-46-6, EC No. 215-290-6
17	Lead sulphates: a) $PbSO_4$; CAS No. 7446-14-2, EC No. 231-198-9 b) Pb_xSO_4; CAS No. 15739-80-7, EC No. 239-831-0
18	Mercury compounds
19	Arsenic compounds
20	Organostannic compounds

22	Pentachlorophenol; CAS No. 87-86-5, EC No. 201-778-6 and its salts and esters
23	Cadmium; CAS No. 7440-43-9, EC No. 231-152-8 and its compounds
27	Nickel; CAS No. 7440-02-0, EC No. 231-111-4 and its compounds
28-30	Substances which appear in Part 3 of Annex VI to Regulation (EC) No 1272/2008 classified as CMR category 1A or 1B
31	a) Creosote, wash oil; CAS No. 8001-58-9, EC No. 232-287-5 b) Creosote oil, wash oil; CAS No. 61789-28-4, EC No. 263-047-8 c) Distillates (coal tar), naphthalene oils, naphthalene oil; CAS No. 84650-04-4, EC No. 283-484-8 d) Creosote oil, acenaphthene fraction, wash oil; CAS No. 90640-84-9, EC No. 292-605-3 e) Distillates (coal tar), upper; heavy anthracene oil; CAS No. 65996-91-0, EC No. 266-026-1 f) Anthracene oil; CAS No. 90640-80-5, EC No. 292-602-7 g) Tar acids, coal, crude; crude phenols; CAS No. 65996-85-2, EC No. 266-019-3 h) Creosote, wood; CAS No. 8021-39-4, EC No. 232-419-1 i) Low temperature tar oil, alkaline; extract residues (coal), low temperature coal tar, alkaline; CAS No. 122384-78-5, EC No. 310-191-5
40	Substances classified as flammable gases category 1 or 2, flammable liquids category 1, 2 or 3, flammable solids category 1 or 2, substances and mixtures which, in contact with water, emit flammable gases, category 1, 2 or 3, pyrophoric liquids category 1 or pyrophoric solids category 1, regardless of whether they appear in Part 3 of Annex VI to Regulation (EC) No. 1272/2008 or not.
43	Azocolourants and azodyes
46	Nonylphenol ethoxylates (C2H4O)nC15H24O
47	Chromium (VI) compounds
50	Polycyclic aromatic hydrocarbons a) Benzo[a]pyrene (BaP), CAS No. 50-32-8 b) Benzo[e]pyrene (BeP); CAS No. 192-97-2 c) Benzo[a]anthracene (BaA); CAS No. 56-55-3 d) Chrysen (CHR), CAS No. 218-01-9 e) Benzo[b]fluoranthene (BbFA), CAS No. 205-99-2 f) Benzo[j]fluoranthene (BjFA); CAS No. 205-82-3 g) Benzo[k]fluoranthene (BkFA), CAS No. 207-08-9 h) Dibenzo[a,h]anthracene (DBAhA); CAS No. 53-70-3
51	The following phthalates (or other CAS and EC numbers covering the substance): a) Bis(2-ethylhexyl) phthalate (DEHP); CAS No. 117-81-7, EC No. 204-211-0 b) Dibutyl phthalate (DBP); CAS No. 84-74-2, EC No. 201-557-4 c) Benzyl butyl phthalate (BBP); CAS No. 85-68-7, EC No. 201-622-7
52	The following phthalates (or other CAS and EC numbers covering the substance): a) Diisononyl phthalate (DINP); CAS No. 28553-12-0 and 68515-48-0, EC No. 249-079-5 and 271-090-9 b) Diisodecyl phthalate (DIDP); CAS No. 26761-40-0 and 68515-49-1, EC No. 247-977-1 and 271-091-4 c) Di-n-octyl phthalate (DNOP); CAS No. 117-84-0, EC No. 204-214-7
56	Methylenediphenyl diisocyanate (MDI); CAS No. 26447-40-5, EC No. 247-714-0 including the following specific isomers: a) 4,4´-Methylenediphenyl diisocyanate; CAS No. 101-68-8, EC No. 202-966-0 b) 2,4´-Methylenediphenyl diisocyanate; CAS No. 5873-54-1, EC No. 227-534-9 c) 2,2´-Methylenediphenyl diisocyanate; CAS No. 2536-05-2, EC No. 219-799-4
62	a) Phenylmercury acetate; EC No. 200-532-5, CAS No. 62-38-4 b) Phenylmercury propionate; EC No. 203-094-3, CAS No. 103-27-5 c) Phenylmercury 2-ethylhexanoate; EC No. 236-326-7, CAS No. 13302-00-6 d) Phenylmercury octanoate; EC No. -, CAS No. 13864-38-5 e) Phenylmercury neodecanoate; EC No. 247-783-7, CAS No. 26545-49-3

Annex 3. Grouping of substances in REACH substance evaluation

Table 9. Structurally similar substances in the CoRAP update 2016–2018.

Year	Member State	EC No.	CAS No.	Substance name	Initial grounds for concern*	Source
2016	Germany	218-407-9 (G1)	2144-53-8	3,3,4,4,5,5,6,6,7,7,8,8, 8-Tridecafluorooctyl methacrylate	Potential endocrine disruptor, suspected PBT/vPvB, other hazard, wide dispersive use, exposure of environment	Already in CoRAP
		241-527-8 (G1)	17527-29-6	3,3,4,4,5,5,6,6,7,7,8,8, 8-Tridecafluorooctyl acrylate		
2016	Italy	211-063-0 (G2)	628-96-6	Ethylene dinitrate	Suspected R, suspected sensitiser, potential endocrine disruptor, suspected PBT/vPvB, wide dispersive use, high (aggregated) tonnage	New
		211-745-8 (G2)	693-21-0	Oxydiethylene dinitrate	Suspected C, suspected R, potential endocrine disruptor, suspected PBT/vPvB, high RCR	
2016	UK	275-702-5 (G3)	71617-10-2	Isopentyl p-methoxycinnamate	Potential endocrine disruptor, wide dispersive use, consumer use	Already in CoRAP
		629-661-9 (G3)	83834-59-7	2-Ethylhexyl trans-4-methoxycinnamate	Suspected PBT, potential endocrine disruptor, possible risk, wide dispersive use, consumer use, environmental exposure, high (aggregated) tonnage	
2017	Germany	215-535-7 (**)(G4)	1330-20-7	Xylene	Suspected CMR, suspected sensitiser, wide dispersive use, consumer use, cumulative exposure, high RCR, high (aggregated) tonnage	Already in CoRAP
		905-562-9 (G4)	n.a.	Reaction mass of ethylbenzene and m-xylene and p-xylene	Suspected R, suspected sensitiser, other: neurotoxicant, wide dispersive use, consumer use, exposure of sensitive populations, high RCR, high (aggregated) tonnage	
		905-588-0 (G4)	n.a.	Reaction mass of ethylbenzene and xylene		
2017	UK	217-496-1 (G5)	1873-88-7	1,1,1,3,5,5,5-Heptamethyltrisiloxane	Suspected PBT/vPvB	New
		241-867-7 (G5)	17928-28-8	1,1,1,3,5,5,5-Heptamethyl-3-[(trimethylsilyl)oxy] trisiloxane	Suspected PBT/vPvB, wide dispersive use	
2018	Bulgaria	202-773-1 (G6)	99-62-7	1,3-Diisopropylbenzene	Suspected R, suspected PBT/vPvB, exposure of workers	New
		202-826-9 (G6)	100-18-5	1,4-Diisopropylbenzene		

2018	Germany	215-175-0 (G7)	1309-64-4	Diantimony trioxide	C, wide dispersive use, exposure of workers, high RCR, high (aggregated) tonnage, other exposure	New
		215-713-4 (G7)	1345-04-6	Antimony sulphide	Suspected C, wide dispersive use, exposure of workers, high RCR, other exposure	
		231-146-5 (G7)	7440-36-0	Antimony	Suspected C, wide dispersive use, exposure of workers, high RCR, high (aggregated) tonnage other exposure	
2018	Germany	258-904-8 (G8)	53988-10-6	1,3-Dihydro-4(or 5)-methyl-2Hbenzimidazole-2-thione	Potential endocrine disruptor, exposure of environment	New
		262-872-0 (G8)	61617-00-3	1,3-Dihydro-4(or 5)-methyl-2Hbenzimidazole-2-thione, zinc salt		
2018	Latvia	204-407-6 (G9)	120-55-8	Oxydiethylene dibenzoate	Suspected R, wide dispersive use, consumer use, exposure of environment exposure of workers, high (aggregated) tonnage	Already in CoRAP
		248-258-5 (G9)	27138-31-4	Oxydipropyl dibenzoate	Suspected R, wide dispersive use, consumer use, exposure of environment, exposure of workers, high RCR, high (aggregated) tonnage	
2018	UK	202-423-8 (G10)	95-48-7	o-Cresol	Suspected M	New
		203-577-9 (G10)	108-39-4	m-Cresol	Suspected C	

** Further concerns may be identified during substance evaluation process.*

***The substance identifiers may change as a consequence of the clarification of the registered substance identity by ECHA. This may lead to changes in the name or/and identifiers of the substance.*

Table 10. Structurally similar substances in the CoRAP update 2017–2019.

Year	Member State	EC No.	CAS No.	Substance name	Initial grounds for concern*	Source
2017	Germany	244-617-5 (G1)	21850-44-2	1,1'-(Isopropylidene) bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]	Potential endocrine disruptor, suspected PBT/vPvB, high (aggregated) tonnage	Already in CoRAP
		306-832-3 (G1)	97416-84-7	1,1'-(Isopropylidene) bis[3,5-dibromo-4-(2,3-dibromo-2-methylpropoxy) benzene]	Potential endocrine disruptor, suspected PBT/vPvB, exposure of environment	New
2018	Germany	215-175-0 (G2)	1309-64-4	Diantimony trioxide	C, wide dispersive use, exposure of workers, high RCR, high (aggregated) tonnage, other exposure	Already in CoRAP
		215-713-4 (G2)	1345-04-6	Antimony sulphide	Suspected C, wide dispersive use, exposure of workers, high RCR, other exposure	
		231-146-5 (G2)	7440-36-0	Antimony	Suspected C, wide dispersive use, exposure of workers, high RCR, high (aggregated) tonnage, other exposure	
2018	Germany	215-535-7** (G3)	1330-20-7	Xylene	Suspected CMR, suspected sensitiser, wide dispersive use, consumer use, cumulative exposure, high RCR, high (aggregated) tonnage	Already in CoRAP
		905-562-9 (G3)	n.a.	Reaction mass of ethylbenzene and m-xylene and p-xylene	Suspected R, suspected sensitiser, other: neurotoxicant, wide dispersive use, consumer use, exposure of sensitive populations, high RCR, high (aggregated) tonnage high (aggregated) tonnage	
		905-588-8 (G3)	n.a.	Reaction mass of ethylbenzene and xylene	Suspected R, suspected sensitisers, other: neurotoxicant, wide dispersive use, consumer use, exposure of sensitive populations, high RCR, high (aggregated) tonnage	
2018	Germany	258-904-8 (G4)	53988-10-6	1,3-Dihydro-4(or 5)-methyl-2Hbenzimidazole-2-thione	Potential endocrine disruptor, exposure of environment	Already in CoRAP
		262-872-0 (G4)	61617-00-3	1,3-Dihydro-4(or 5)-methyl-2Hbenzimidazole-2-thione, zinc salt		

2018	Latvia	204-407-6 (G5)	120-55-8	Oxydiethylene dibenzoate	Suspected R, wide dispersive use, consumer use, exposure of environment exposure of workers, high (aggregated) tonnage	Already in CoRAP
		248-258-5 (G5)	27138-31-4	Oxydipropyl dibenzoate	Suspected R, wide dispersive use, consumer use, exposure of environment, exposure of workers, high RCR, high (aggregated) tonnage	
2018	UK	217-496-1 (G6)	1873-88-7	1,1,1,3,5,5,5-Heptamethyltrisiloxane	Suspected PBT/vPvB	Already in CoRAP
		241-867-7 (G6)	17928-28-8	1,1,1,3,5,5,5-Heptamethyl-3-[(trimethylsilyl)oxy] trisiloxane	Suspected PBT/vPvB, wide dispersive use	
2019	Bulgaria	202-773-1 (G7)	99-62-7	1,3-Diisopropylbenzene	Suspected R, suspected PBT/vPvB, exposure of workers	Already in CoRAP
		202-826-9 (G7)	100-18-5	1,4-Diisopropylbenzene		

* *Further concerns may be identified during substance evaluation process.*

***The substance identifiers may change as a consequence of the clarification of the registered substance identity by ECHA. This may lead to changes in the name or/and identifiers of the substance.*

Annex 4. Documentation and guidance

Guidance on grouping of chemical substances based on toxicity, etc. is available at EU, OECD and international level. This report has focused on a selection.

Table 11. Summary of the documentation and guidance on grouping of chemical substances.

Title	Description	Source
Grouping of substances and read-across	ECHA website Contains introductory text, explanatory examples, general guidance on (Q)SAR and grouping of substances as well as the more specific Read-Across Assessment Framework (RAAF).	https://ECHA.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
Grouping of Chemicals: Chemical Categories and Read-Across	OECD website Contains introductory text, explanatory examples and general guidance on grouping of chemicals.	http://www.oecd.org/chemicalsafety/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm
The OECD (Q)SAR Toolbox	OECD website Contains introductory text, instructions and examples for the use of the (Q)SAR Toolbox software, and a link to download the program.	http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm
OECD Existing Chemicals Database	OECD website Contains a number of chemical categories that have been assessed within OECD.	http://webnet.oecd.org/hpv/ui/ChemGroup.aspx
Substance Groupings Initiative	Government of Canada website. Contains overarching chemical categories (9), the purpose of which is to rationalise various risk management initiatives.	http://www.chemicalsubstanceschimiques.gc.ca/group/index-eng.php
Chemical Categories Used to Review New Chemicals under TSCA	US EPA website. Contains overarching chemical categories (56), primarily intended to divide substances into groups based on similar hazard profiles.	http://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/chemical-categories-used-review-new

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