Collaborative approach pilot projects

March 2017–March 2018

Final report

Disclaimer

This publication is solely intended for information purposes and does not necessarily represent the official opinion of the European Chemicals Agency. The European Chemicals Agency is not responsible for the use that may be made of the information contained in this document.

Version	Changes	

Collaborative approach pilot projects: March 2017–March 2018

Final report

Reference: ECHA-18-R-10-EN
ISBN: 978-92-9020-509-8
Cat. Number: ED-01-18-426-EN-N
DOI: 10.2823/224234
Publ.date: June 2018
Language: EN

If you have questions or comments in relation to this document please send them (quote the reference and issue date) using the information request form. The information request form can be accessed via the Contact ECHA page at:
http://echa.europa.eu/contact

European Chemicals Agency

Mailing address: P.O. Box 400, FI-00121 Helsinki, Finland
Visiting address: Annankatu 18, Helsinki, Finland

Table of Contents

Table of Figures

Table of Tables

Executive summary

In March 2017, collaborative approach (COLLA) pilot projects were launched for five groups of substances to explore interactions between ECHA, Member State competent authorities (MSCAs) and concerned registrants as an early support process to be applied before the start of regular evaluation processes. The projects aimed at improving the information used to decide on the needs for further regulatory risk management, in particular by inviting industry to proactively improve their dossiers. Based on the review of the pilot projects, and especially evidence of efficiency and effectiveness, it should be decided whether and which form of collaborative approach should be continued from 2018 onwards.

The groups of substances selected for the COLLA pilot projects were relatively large and complex: one group comprised more than 20 substances and four groups had 6 to 8 substances each. Some of these substances were already subject to ongoing regulatory activities, and also, interest was expressed by both MSCAs and registrants. Communications and information exchange were carried out through webinars, teleconferences, physical meetings, emails and phone calls.

The pilot projects were closed between February and March 2018. Reflections on the experiences gained on the collaborative approach and from working with substance groups were collected from all actors through an online survey. The results of the survey were presented and discussed in a workshop on 7 and 8 May 2018 at ECHA's premises as well as during the Risk Management and Evaluation (RiME+) platform meeting on 15 May 2018. The review findings are summarised below.

The collaborative approach is an extension of the regular manual screening, covering groups of substances and allowing for enhanced interaction with industry.

The pilot projects gave all actors the opportunity to gain experience in working with groups of substances. The projects explored how the overall grouping approach can be used to clarify and address the identified concerns, and what type of supporting information is required.

The early interactions allowed conclusions on the required next steps (dossier/substance evaluation, risk management measures) to be made on a more informed basis and with a higher level of confidence.

Regarding the efficiency and effectiveness of the collaborative approach, ECHA notes that it cannot draw firm conclusions. In general, the pilot projects were considered to have provided added value in setting up action plans. However, the efficiency and effectiveness of the plans could even in principle be evaluated only once the industry actions and REACH processes have been completed. Furthermore, the projects were testing two different elements, addressing substances by groups and early interaction with registrants, and it would be difficult to differentiate between their respective impacts on the efficiency or effectiveness. It is noted that the reported resources spent by ECHA and Member States authorities on the projects were significant, and almost equally divided between the screening and the interaction phases. There is no evident point for comparison, as there is yet little experience on addressing groups of substances in manual screening. However, as part of the resources were spent on approach development and capacity building, future early interactions are expected to require less resources.

Based on the above indicated discussions on the review results and project outcomes, ECHA proposed to MSCAs for their CARACAL-27 meeting a way forward with early interaction. Addressing substances in groups, intensifying collaboration between authorities and initiating early interaction with registrants can all be seen as useful elements. However, ECHA does not recommend formalising these aspects under a specific 'collaborative approach' process. Instead, ECHA invited MSCAs to consider the option of an early interaction at the manual screening phase. ECHA proposed certain best practice recommendations on the timing,

practical organisation and documentation of the early interaction. These will aim to ensure the necessary level of consistency and focus in terms of time, resources and scope, as well as that all actors have a common understanding of the process and clear expectations.

1. Introduction

This report describes the results and lessons learnt from five test pilots of a collaborative approach (COLLA) for addressing groups of substances considered for regulatory risk management. ECHA, the Member State competent authorities (MSCAs) and registrants who contributed to the COLLA pilot projects have reviewed the experiences gained during the projects, in particular what went well and what could be improved. The outcomes were reviewed and key learnings and observations were collected mainly through an online survey. As one of the main contributions to the review, ECHA also organised a COLLA Pilot Projects Review Workshop on 7 and 8 May 2018. Authorities discussed the workshop outcome at the Risk Management and Evaluation (RiME+) platform meeting on 15 May 2018.

ECHA has finalised this final project report based on the online survey results, the review workshop discussions and other feedback received. However, as an ECHA report, it does not necessarily present the views of all COLLA pilot project contributors.

The idea of a collaborative approach was first discussed with the directors of MSCAs in November 2016 and with ECHA's Management Board in December 2016. From 28 February to 1 March 2017, ECHA held a workshop called 'Implementation of the ECHA Integrated Regulatory Strategy', which focused on the advantages of addressing substances in groups. A side event on 1 March, open only to authorities, focused on the practical organisation of the collaborative approach and on the possibility to start pilot projects.

It was clarified in the workshop that there is a wide range of activities where ECHA and Member States are already facing the challenge of addressing substances in groups, starting from the current manual screening of substances shortlisted for regulatory actions. In this context, the collaborative approach pilots were intended to test and possibly generate best practices of collaboration between authorities and proactive representatives from industry. It was also stressed that a collaborative approach has a supporting function and does not replace the need for regulatory processes.

The overall idea is that addressing substances in groups based on structural similarity or use, instead of one by one, allows for the development of more effective regulatory strategies and a more consistent and coherent assessment of substances. As indicated in ECHA's annual report for 2017 on the implementation of the SVHC Roadmap[1], the focus of the screening done by Member States and ECHA on substances of potential concern has shifted towards looking at groups of substances with similar hazardous properties. However, the grouping approach also poses new challenges in evaluation, and closer collaboration between ECHA, Member States and registrants can prove very useful in addressing them.

The proposal to test a collaborative approach to address groups of substances under evaluation was endorsed at the CARACAL-23 meeting in March 2017. Several Member States volunteered for the pilot projects by March 2017 (see Chapter 4 below), with the aim of piloting the approach in one year and then reviewing the learnings gained from the projects.

[1] Roadmap for SVHC identification and implementation of REACH risk management measures - Annual Report 2017: https://echa.europa.eu/documents/10162/23668985/svhc_roadmap_annual_report.pdf/66b7cfc1-058f-88a2-bc31-ca190cd763fd.

The report outlines the collaborative approach, the groups of substances addressed in the five pilot projects, the project organisation and approach, the work undertaken, as well as the outcomes of the five pilot projects. In addition, the report presents the results of an online survey on the review of the pilot projects and other feedback, the proceedings of the COLLA Review workshop, the pilot project review conclusions compiled by ECHA, and ECHA's recommendations for the way forward regarding the early interaction approach.

2. Collaborative approach

The following sections describe the purpose, scope, objectives, boundaries and pre-conditions of the collaborative approach as they were presented at the CARACAL-23 meeting and agreed on by the project contributors at the beginning of each of the five pilot projects.

2.1. Purpose, objectives and scope

The collaborative approach refers to **collaboration between ECHA and the MSCAs** on one hand and **collaboration between authorities and the concerned registrants** or relevant industry associations on the other, which goes beyond the regular interaction under the normal evaluation processes. The collaboration aims at identifying shortcomings and **improving the information** on substance identity, hazard and exposure, for the **main purpose of defining whether there is a need for further regulatory risk management**.

Ultimately, the collaborative approach aims to **change a mindset among industry**. Instead of waiting to be addressed by authorities, industry would proactively step forward to improve their dossiers, with support from ECHA and the Member States where relevant.

The **main aims** of the pilot projects on a collaborative approach were to:

- test forms of enhanced collaboration between ECHA, MSCAs and registrants;
- mobilise industry actors to become more proactive;
- understand better the incentives and disincentives for industry to improve information quality; and
- evaluate the efficiency and effectiveness gains of a broad use of collaborative approach projects.

The **specific objectives** of the pilot projects were to:

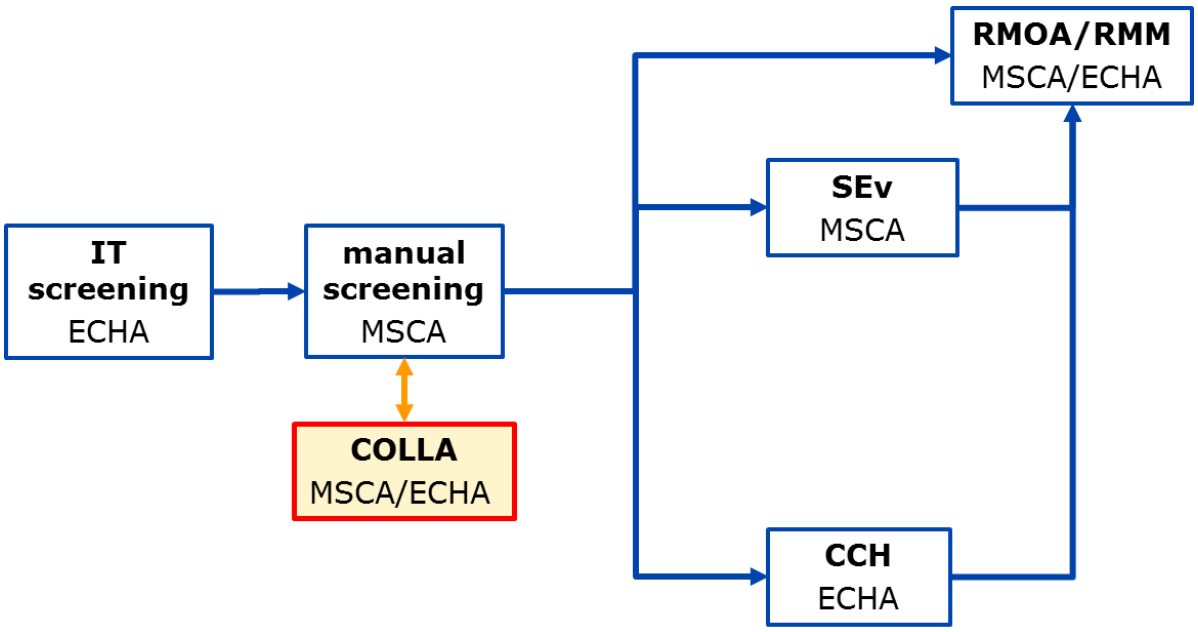
- identify the main shortcomings in the information on key human health and environmental **hazards**, in particular the systemic issues in applying the adaptation possibilities provided in REACH, and to see whether the registrants are ready to address these shortcomings proactively (i.e. before compliance check is launched);
- improve, where relevant, the information on **substance identity**;
- update, where relevant, the information on **uses (including volumes) and exposure**;
- enable authorities, to the extent possible, to define whether there is **a need for further regulatory action** on the group of substances and if so, how to address the group, or whether the group can be considered to be of lower concern.

Therefore, the collaborative approach is an enhancement and continuation of the manual screening, which is instrumental in deciding on the best regulatory route for groups of substances (see Figure 1 below).

The element that registrants can reasonably be expected to improve proactively was considered to be the justification and documentation of adaptations in relation to read-across, categories and weight-of-evidence approaches. Regarding the deficiencies in hazard information, and in particular data gaps on higher-tier human health and environmental endpoints, it was acknowledged that registrants may be reluctant to propose new testing and that requests under compliance check or substance evaluation may be needed.

The **scope** of the collaborative approach includes achieving a better definition of the boundaries of the group of substances, the preliminary assessment of information provided for all the members of the group, the identification of areas of concern, and the identification of the potential regulatory actions. Specific activities performed in the early interaction phase would be defined in a kick-off meeting between MSCAs, ECHA and the relevant actors from industry based on the results of a first screening of the group.

Figure 1: Relationship of collaborative approach early interaction to manual screening and the regulatory processes: evaluation (compliance check, CCH, and substance evaluation, SEv) and risk management (risk management option analysis, RMOA, and risk management, RMM).



In practice, the pilot projects were divided into three phases:

1. Initiation phase – indicative timeline: March to May 2017
    - Selection of the group of substances.
    - Manual screening of the group: defining the grouping boundaries, data gaps, potential regulatory outcomes.

2. Implementation phase – indicative timeline: May 2017 to March 2018
    - Kick-off meeting of concerned MSCAs, ECHA and registrant representatives.
    - Refinement of the preliminary assessment.
    - Possibility of agreements with proactive registrants on deadlines for providing further information already available (e.g. use, exposure) or generating new supporting information (e.g. hydrolysis, toxicokinetics).

- Preparation of a regulatory plan to address the identified concerns, which may require application of compliance check, substance evaluation or risk management option analysis to individual substances or (sub)groups.

3. Review and evaluation phase – April to June 2018, irrespective of the progress of the implementation
    - Review of the outcomes, learnings and observations.

The collaborative approach should facilitate the faster implementation of the Integrated Regulatory Strategy. A regulatory plan should be defined as soon as possible, with consideration of potential benefits coming from additional information provided by the registrants (in the pilots at the latest by March 2018). After that, the timeline follows the normal implementation of related regulatory processes, e.g. in the case of compliance check or substance evaluation, it implies evaluation of the information, the drafting of decisions and formal decision making. However, the idea behind the collaborative approach is that the preliminary work and collaboration with registrants may allow to decrease the amount of time that would be spent on formal decision making and developing more effective testing plans.

2.2. Boundaries and pre-conditions

The following boundaries were defined for the collaborative approach pilots:

- The paradigm change introduced by REACH, i.e. that the responsibility to demonstrate safe use lies with industry, is maintained – the role of ECHA and Member States can only be to provide feedback and advice to industry actors, not to assume their role in complying with the requirements and demonstrating safe use of their substances.

- The collaborative approach is a complementary measure to compliance check and substance evaluation – it is not replacing any of the regulatory measures, but supporting their prioritisation.

- The authorities involved do not commit themselves to any specific action or non-action on the substances addressed.

- Ongoing compliance check or substance evaluation cases are not discontinued.

In addition, the following pre-conditions were required for a collaborative approach:

- Industry actors responsible for all or part of the identified group of substances agree to organise themselves in a manner that enables a structured dialogue with the authorities.

- Volunteering Member States and industry actors commit adequate resources to the work for at least 12 months during the pilot project (an anticipated one full-time equivalent for March 2017-March 2018).

3. Descriptions of pilot project substance groups

Five groups of substances were selected for the COLLA pilot projects. Three of the groups were selected from the groups shortlisted in Round 4 of manual screening[2], while the two other

[2] The shortlist proposed to competent authorities for manual screening in 2017, which included 18 groups of substances of which three were selected for COLLA.

groups were proposed separately, one by a Member State and one by a registrant consortium. The factors considered when selecting the groups were that the groups would be relatively large and complex, some group members would already be subject ongoing regulatory activities, and there was interest expressed from both MSCAs and registrants. Table 1 below shows the groups, initial concerns, and the MSCAs involved in each project. Appendices 1 to 5 give further details on each substance group and how they were formed.

Table 1: The five substance groups under the COLLA pilot projects.

COLLA group	Origin of group	Initial concern	Lead Member State	Partner Member State(s)
EDTA derivatives 22 substances	Manual screening	Reproduction toxicity	United Kingdom	Sweden
Antimony compounds 8 substances	Proposed by registrants	Carcinogenicity	Germany	Lithuania
Polyol acrylates 7 substances	Manual screening	PBT	Germany	Ireland, Luxemburg
Substituted diphenylamines 6 substances	Manual screening	PBT, Mutagenicity	France	Slovenia
Organotin compounds 8 substances	Proposed by MSCA	Reproduction toxicity, STOT	The Netherlands	Sweden, Bulgaria

EDTA derivatives

The initial group comprised 22 aminocarboxylic acid derivatives, 21 identified through IT screening and one manually added at the start of the project. The group was formed around two group seed substances, i.e. the substances that were identified to have a suspected concern through the initial IT screening as part of the common screening approach.

The initial concern for the group seeds was **reproductive toxicity**, as for one seed substance there were indications of adverse effects on fertility in a registration, and for the other substance, registrants reported classification as Repr. 2. The other group members were grouped around the group seeds based both on structural similarity and on read-across arguments made by registrants in REACH registration dossiers as well as categories formed by REACH registrants and by the Organisation for Economic Co-operation and Development (OECD).

During the course of the COLLA project, nine additional aminocarboxylic acid derivatives were identified. Some of these were already part of the registrant category and had been overlooked during the IT screening due to unclear substance identification or because they were not registered under REACH, while others were added to the category during the project. These additional substances were not screened to the same level of detail as the substances in the initial group but have been considered as far as possible in the conclusions.

Antimony compounds

The group of antimony compounds was originally proposed for the collaborative approach by the antimony consortium, as there was already some regulatory activity being carried out on some members of the substance group. Initially, ECHA identified 21 registered compounds in

the REACH database that contained antimony, but the selection was narrowed down to eight compounds, as the other substances only contained antimony in small amounts or were intermediates. The group of eight antimony compounds that were examined was further subdivided into a group containing antimony metal and four trivalent compounds and a group containing three pentavalent antimony compounds.

The initial concern for antimony compounds was **carcinogenicity**, as at least one substance in the group may possess hazardous properties due to (suspected) carcinogenic properties, high RCR, and other exposure/risk-based concerns.

Polyol acrylates

The group of seven polyol acrylates was identified by ECHA during the common screening approach and was built around the group seed based on read-across linkages in the registration dossiers of the substances. The group consists of esters of acrylic acid with polyols.

The initial concern was **PBT**, as one group seed substance was suspected to have persistence and bioaccumulation properties based on experimental data and modelling predictions as identified through IT screening.

Substituted diphenylamines

The group of substituted diphenylamines (SDPAs) was formed around one group seed substance identified by ECHA during the common screening approach. SDPAs are made up of a diphenylamine core and one to four alkyl or phenyl side chains and most are manufactured as UVCB substances. The group originally selected for COLLA consisted of the seven substances registered under REACH that fulfil this structural definition. However, one substance was later dropped due to differences in toxicokinetics and in the toxicological effects in target organs compared to the other six SPDAs.

The initial concern was **PBT**, as one group seed substance was suspected to have persistence and bioaccumulation properties based on experimental data and modelling predictions as identified through IT screening. In addition, a potential **mutagenicity** concern had been identified for some of the group members.

Organotin compounds

The group is a subgroup of organotin compounds and was proposed by the Netherlands. The subgroup consists of REACH-registered disubstituted organotins with a thio bond (S-ligands) and those monosubstituted organotins manufactured with them. In total, eight substances were identified. Authorities are not working on the S-ligands in isolation and organotin substances have been under scrutiny for some time by several Member States.

The initial concern is **reproductive toxicity** and **STOT RE**. Work on these substances started from a broad concern regarding thymus effects, immunotoxicity and neurotoxicity and the harmonised classification for reproduction toxicity for some substances. Recently, industry withdrew their read-across from commonly accepted metabolites, arguing that these do not form in real life. As a consequence, major data gaps may appear for assessing the concern for these eight substances.

4. Project organisation and approach

4.1. Actors and roles

Member States

Each COLLA pilot project was led by one Member State with one or more Member States in a partnership or observer role (see Table 1). Each participating Member State nominated a key contact person, but in addition several experts in toxicology, ecotoxicology and use/exposure participated in the project. Details of roles of MSCAs in each project can be found in Appendices 1 to 5.

ECHA

A key coordinator was assigned for each project from ECHA. ECHA provided general support in coordinating the project as well as expertise in toxicology, environment, substance identification and computational assessment.

Registrants

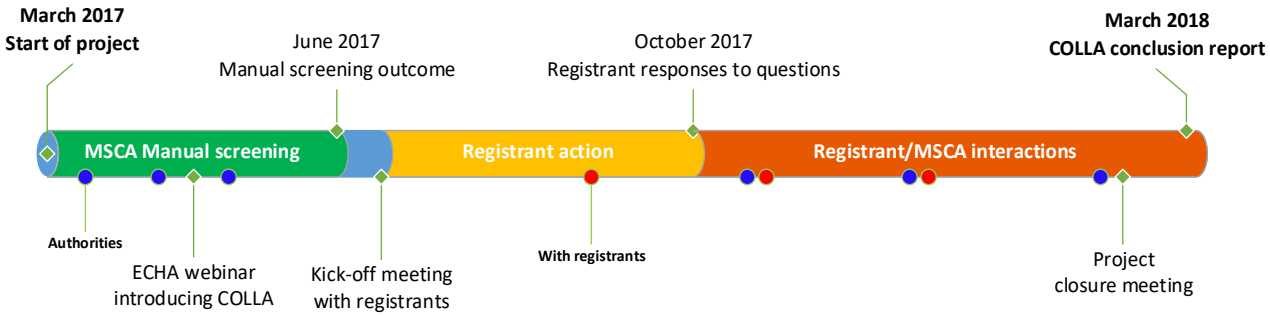
All lead and individual registrants for all substances identified at the start of the pilot projects were invited to participate. One or two decided not to participate in the project to the end, primarily because the substance was not a priority for them or because they chose to cease manufacture, but the majority of the invitees did participate.

The level of organisation of registrants varied between projects. In some projects registrants were represented by an established consortium, while in others there was no consortium or equivalent cooperation. Several experts from registrants contributed through each project.

4.2. Timelines, milestones and interactions

Figure 2 shows the duration of the different stages of the pilot projects and the main deliverables for each step, as well as a general overview of meetings and other interactions during the projects. Further project-specific details can be found in the project closure reports in Appendices 1 to 5.

Figure 2: General overview of average timelines, milestones and interactions during the five pilot projects. Major milestones are presented above the timeline, meetings and teleconferences below the timeline.



Most projects started in March 2017 with manual screening by MSCAs. ECHA contacted and invited registrants to participate in the project by sending letters through REACH-IT. ECHA held a webinar in May 2017 for the MSCA and registrant participants. ECHA and MSCAs had several teleconferences (shown in blue) during the manual screening phase and throughout the project. Once the registrants were provided with the manual screening outcome along with

initial questions, a physical kick-off meeting was held with them, hosted by the lead MSCA. For the majority of the projects, no further physical meetings were held and subsequent interactions were carried out through teleconferences (shown in red). All five pilot projects were closed between February and March 2018.

5. Work undertaken

In most of the cases, the MSCAs started performing individual assessments of the different substances in the group before considering the group as a whole. The assessment of the group was done by compiling data matrices with all the observations on the individual substances. The MSCAs were supported by ECHA when needed with expertise in substance identity, human health, environment, chemistry and exposure. During this stage of the projects, MSCAs and ECHA interacted several times to follow up the progress made.

All the concerns and issues for clarification were communicated to the registrants before the kick-off meeting in the form of presentations or draft screening documents. The kick-off meetings for all the projects were physical meetings and organised by the lead MSCAs.

In the kick-off meeting, some issues were clarified to an extent. Furthermore, the registrants committed to address all the remaining questions and concerns from the MSCAs by submitting additional information by agreed deadlines. The information provided by the registrants included new exposure information, proposals to split the group in several subgroups, improved read-across justifications, improved PBT assessments or proposals to address the data gaps in the registration dossiers.

In most projects, this started an iterative process of provision of information and review of this information that required additional interactions between authorities and between authorities and registrants. ECHA supported the MSCAs with expertise in substance identity, human health, environment, chemistry and exposure when needed.

The outcome of the projects were regulatory plans proposed by the MSCAs, also based on proposals and commitments of registrants, and finalised by the project closure meeting.

6. Outcomes

The outcomes of the pilot projects are reported in Table 2.

Table 2: Regulatory plans for the COLLA pilot groups.

COLLA group	Regulatory plan
EDTA derivatives 22 substances	Preliminary conclusion of no action on human health endpoints to be confirmed by the outcome of ongoing compliance checks. Testing proposals triggered for environmental endpoints.
Antimony compounds 8 substances (21 in the initial group)	Tiered approach for substance evaluation: first five substances, then the other three if necessary.
Polyol Acrylates 7 substances	Voluntary testing for human health endpoints, complemented by ongoing compliance checks and testing proposals. Further testing proposals if needed.
Substituted diphenylamines 6 substances	No new regulatory action in addition to the ongoing compliance checks and substance evaluation.

Organotin compounds 8 substances	MSCA will wait for results of ongoing compliance checks.

For the EDTA derivatives group, the main outcome of the pilot project has been the subgrouping of the substances based on structural similarity. There is a preliminary conclusion of no action related to the human health endpoints that will need to be confirmed by the outcome of the ongoing compliance checks for some of the substances in the group. With regard to the environmental endpoints, the registrants have proposed generation of some data to validate and support the read-across approaches. Thus, the registrants agreed to submit testing proposals within six months of the conclusion of the pilot project, after which the testing proposals will be evaluated.

For the antimony compounds group, the outcome has been to follow a tiered approach for substance evaluation which will first include five substances, then the other three if necessary.

For the polyol acrylates group, the initial concern on PBT properties was clarified and not substantiated. With respect to the human health endpoints, the main outcome of the pilot project has been the subgrouping based on structural similarity and the voluntary generation of information to support the read-across approaches in the subgroups. This information will be obtained by the end of 2018 and will serve in deciding whether the read-across approaches are justified or new information needs to be generated. In the latter case, registrants have committed to submit by Q1 2019 the necessary testing proposals to meet the information requirements under REACH.

For the substituted diphenylamines group, it was concluded that there is currently no need to initiate new regulatory action in addition to the ongoing compliance checks and substance evaluation processes. Once the data from those processes are available, it will be decided whether some of the substances still warrant an inclusion into the Community rolling action plan (CoRAP) for PBT properties and if a classification as STOT RE is warranted for some substances.

For the organotin compounds group, most of the substances were under scrutiny in compliance check. The data to be generated needs to be available before concluding on further action. Therefore, the outcome regarding this group of substances was to wait for the results from the different compliance checks before deciding if further action is needed.

With regard to the added value of the early interactions with the registrants to informed decision making on the groups of substances, Table 3 provides an overview of the initial status before any interaction with the registrants, the relevant new information that was provided as a result of the interaction, and the added value. The added value refers to the value that the interactions and the resulting information added to the overall decision making on the groups of substances. Again, it can be seen that the added value is different for the different groups of substances.

The regulatory plans established for all five groups now focus the regulatory actions on the key substances in the groups, the number of which is smaller than in the beginning of the projects. This better regulatory focus is helping to avoid unnecessary animal testing and wrongly timed actions as well as accelerating the addressing of the suspected concerns as fewer regulatory processes are now needed.

Table 3: Relevant information and added value from early interactions.

COLLA group	Initial status	Relevant new information	Added value
EDTA derivatives 22 substances	Developmental toxicity concern identified for some members (CLH). Additional concerns from the assessment related to muta-genicity, fertility toxicity, environ-mental toxicity and exposure potential.	• Improved read-across justifications and sub-grouping. • Information addressing the fertility and mutagenic concerns. • Information on fate and environmental toxicity • Exposure information.	• Subgrouping helped (de)prioritisation for regulatory risk management. • Developmental concern clarified (different for different subgroups). • Mutagenicity concern clarified: not mutagenic. • Exposure potential clarified via improved use descriptions. • Registrants' commitment to provide additional fate information and to submit testing proposals for concerns on environmental toxicity.
Antimony compounds 8 substances	3 substances in CoRAP, concerns: carc., wide dispersive use, exposure of workers, high RCR (below 1 but considered as high by eMSCA), high aggregated tonnage, other exposure.	• New exposure information announced to be submitted. • Proposal for strategy to improve read-across approaches for trivalent and pentavalent compounds.	• Focused strategy on 8 out of 21 substances; more clarity on how to address these under a tiered approach strategy for SEv. • Now only 2 new substances added to CoRAP.
Polyol acrylates 7 substances	PBT concern needs to be clarified. Multiple analogue read-across indicating a *de facto* category read-across.	• Improved PBT assessment. • Ecotoxicity data. • Improved human health -related read-across justifications and subgrouping. • Proposal to address the human health data gaps in the dossiers.	• PBT concern clarified: not PBT. • Subgrouping. • Voluntary generation of data to support and validate read-across. • Clarification of uses of substances (consumer uses advised against) helping to focus risk management.
Substituted diphenylamines 6 substances	PBT concern. Additional concerns from the assessment related to mutagenicity, STOT RE, developmental toxicity and fertility toxicity.	• Improved PBT assessments based on QSAR predictions for the worst-case constituents of the substances. • Improved read-across for human health endpoints.	• PBT concern more focused on the identified fraction leading to the potential concern. Testing strategy based on worst-case constituent approach and starting from Bioaccumulation (B) can be applied at the group level. • Additional concerns remain but can be addressed in a more focused way under the read-across based subgroups.

COLLA group	Initial status	Relevant new information	Added value
Organotin compounds 8 substances	Reproductive toxicity and data gaps for human health endpoints. Exposure unclear. PBT concern.	• Improved read-across justifications. • Proposal to address human health data gaps in dossiers. • New information on exposure and migration rate.	• Exposure potential and migration rate clearer, aiding in prioritisation. • PBT concern partially clear.

7. Review of the pilot projects

All five projects were closed with a review and evaluation phase including a brief discussion of the experiences gained, especially what went well and what could be improved. These initial project-specific reflections can be found at the end of the project closure reports in Appendices 1 to 5.

In parallel, the outcomes of the projects were reviewed and key learnings and observations were collected using an online survey run between 21 February and 12 March 2018. All project contributors – registrants, MSCAs and ECHA – were invited to contribute to the survey. Both individual replies and joint replies (e.g. one reply by consortia or Member States) were received from contributors. At least one registrant, one MSCA and one ECHA contributor replied from each of the five projects. In total, 18 authority representatives (or authorities if a joint reply) and eight registrant or consortia representatives answered the questionnaire.

The structured COLLA project review questionnaire contained both tick-box and open questions. The review questionnaire covered the following aspects of the COLLA projects:

- Key benefits, resources and time spent, stumbling blocks encountered.
- Key learnings and observations on:
  - working with groups of substances;
  - roles of actors;
  - ways of collaboration;
  - project practicalities.

7.1. Feedback from the pilot project review questionnaire

The following subchapters present a summary of the feedback received through the pilot project review questionnaire using both open and tick-box questions in a Webropol survey. Further details, including statistics on registrant and authority experiences and feedback on practicalities and other aspects of the projects, can be found in Appendix 6.

7.1.1. Early interaction

Figure 3 shows the opinions of participating MSCAs and registrants on which type of further information was provided by the registrants during the projects and how useful it was. The information provided was mainly related to read-across justifications, human health and environment-related hazards and uses or exposure. For three of the five pilots, the majority of the contributors found the information provided useful. In one project, contributing MSCAs expressed mixed views on the usefulness of the information provided, while registrants found

it useful. In another project, neither MSCAs nor registrants considered the information useful for developing a better testing strategy.

Figure 3: MSCA and registrant views on information provided or committed by the registrant during the projects: has it closed/is it expected to close relevant data gaps or proved otherwise useful, including the specific areas of the registration dossier. For each project, replies from several contributors from each party, MSCAs and registrants, were collected, thereby ensuring the representation of the majority of their views. If there were equal numbers of yes and no answers, the project result was counted as 0.5 both for yes and no.

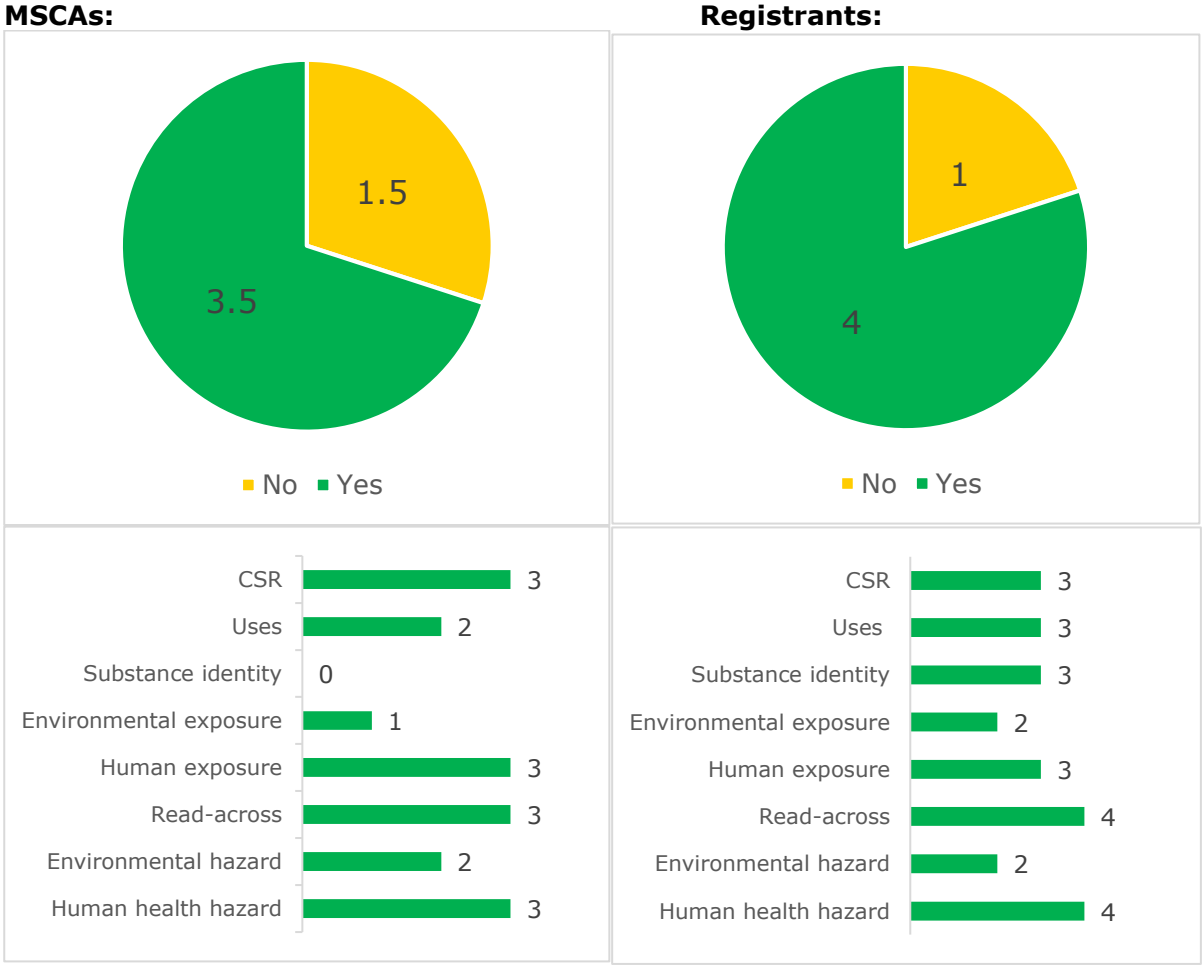
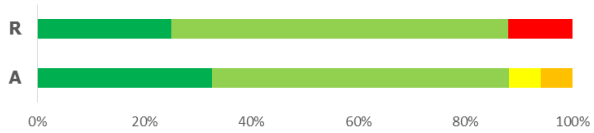
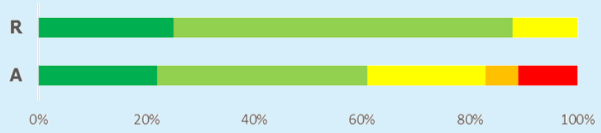
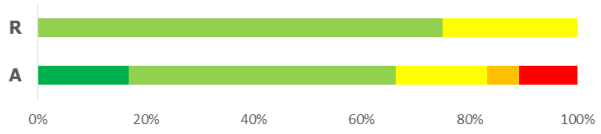
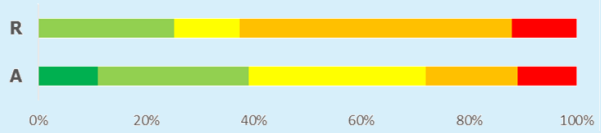
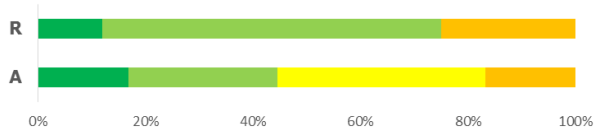
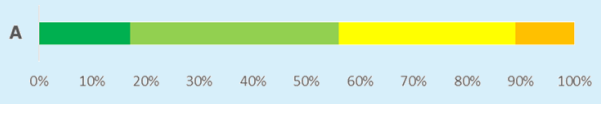
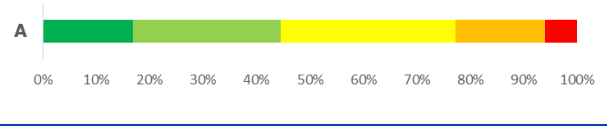


Table 4 shows the views of authorities and registrants on the early interaction between MSCAs and registrants during the projects. The majority of respondents found that this early interaction provided further clarity to all participants and triggered the generation of relevant information for the regulatory processes, hence facilitating the development of better regulatory plans. Most authorities also found that in the medium and long term, the collaborative approach saves time and resources, although based on the open feedback answers, it is clear that some authorities' representatives are not convinced that the process provided efficiency gains. Further summaries of the views on these issues can be found in Appendix 6.

Table 4: Authority and registrant opinions on early interaction between MSCAs and registrants.

	Agree / Somewhat agree / Neutral / Somewhat disagree / Disagree	Total
The early interaction between MSCAs and registrants provides **further clarity** for all participants.		R:8 A:18
The early interaction between MSCAs and registrants triggered the generation of **relevant information** for the regulatory processes.		R:8 A:18
The early interaction between MSCAs and registrants facilitated the development of a **better regulatory plan**.		R:8 A:18
The early interaction between MSCAs and registrants allowed to clarify the scope or accelerate the drawing of conclusions on the need for regulatory action, thus reducing the overall workload.		R:8 A:18
The interaction with the registrants was **more open and useful** than the interaction you would have had with them within the substance evaluation or compliance check processes.		R:8 A:18
In the medium or long run, the COLLA approach **saves time and resources**.		A:18
The COLLA approach helps in formulating a generally accepted regulatory strategy that is **acceptable to both MSCAs and all registrants**.		A:18

However, there were mixed views on whether the early interaction clarified the scope or accelerated the drawing of conclusions on the need for regulatory action, thus reducing the authorities' overall workload. This may be partly because it was not clear from the question which workload was being referred to, only the workload before the start of the official process or that also covering the official processes. In addition, the authorities had mixed views on whether the early interaction helped formulate a regulatory strategy that is acceptable to both MSCAs and all registrants. In fact, in some pilot groups, MSCAs and registrants had different opinions on the regulatory strategy defined for the group.

The feedback given on the early interaction approach, specifically on the interactions during the project, show that confidentiality issues influenced somewhat the practicalities of the collaboration. However, such issues were usually ultimately resolved, except for certain use- and exposure-related information.

According to **feedback from authorities**, most MSCAs considered that registrant representatives were motivated by and committed to the pilot projects and collaboration with

them was smooth, although a few authorities had had a different experience.

Looking further at the authorities' experiences in early interactions, MSCAs seemed to see a difference between COLLA and manual screening based on the following aspects:

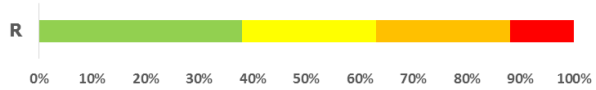
- Interaction with registrants: Many highlighted this as a positive thing about COLLA, as it provided insight into the substances that could not be gained just from the registration dossiers. Nevertheless, it is not needed in all cases (see Figure 4 below).

Level of commitment/resource investment from authorities: The level is higher in COLLA than in manual screening.

Furthermore, MSCAs recommended avoiding having the timeline for COLLA projects coincide with mandatory deadlines, e.g. deadlines for MSCA submission of substance evaluations.

According to **feedback from registrants** contributing to the pilot projects, as indicated in Table 5 below, the registrants had mixed views on whether they had benefitted from the COLLA projects. This seems to be at least partly due to different expectations compared to what was the aim of the pilot projects. Registrants appreciated the opportunity to discuss the issues and concerns raised about their substances with the authorities early on in the process. However, many were disappointed that authorities could not decide during the COLLA project whether their read-across approach was acceptable. There was also disappointment regarding authorities not being able to enhance or modify evaluation decisions issued in the recent past. In addition, registrants recommended not to apply a harmonised time schedule to all COLLA projects, proposing that each group's schedule should be defined separately.

Table 5: Registrants views on benefits of early interactions during the pilot projects.

	Agree	Somewhat agree	Neutral	Somewhat disagree	Disagree	Total
Overall, I feel that as a registrant, I have benefited from COLLA.						R: 8

When asked **whether COLLA should be implemented as a regular informal process**, the majority of both authorities and registrants responded yes, but only under certain conditions and not as a default option. Some of the conditions indicated by authorities were that resources need to be available, registrants need to be committed to active involvement, and for there to be no legal issues to be settled (e.g. on "free riders" within a consortium). Furthermore, authorities indicated that the application of COLLA is useful when it is difficult for MSCAs and ECHA to establish a regulatory plan for the group due to too many open options. Authorities also proposed that COLLA should be more flexible than in the pilot project, with the start and end decided individually for each project.

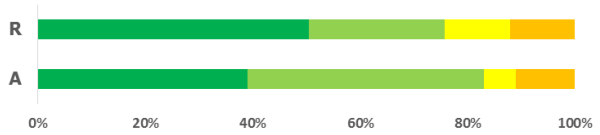
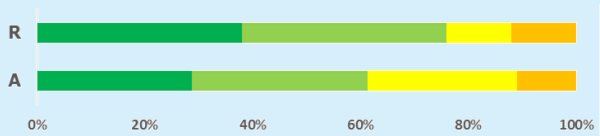
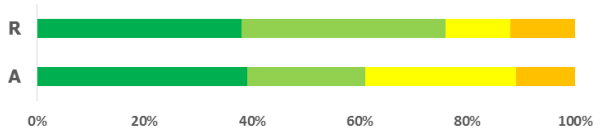
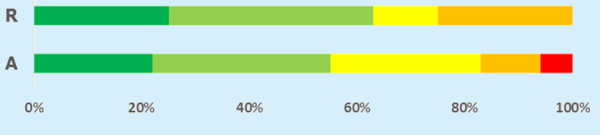
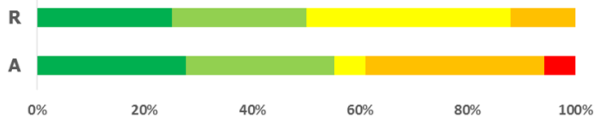
Registrants suggested that COLLA could be useful when substances in the group belong to very different sectors. In addition, some registrants highlighted that registrants should be asked and agree to the approach in advance and have sufficient time and resources allocated. Some also advocated that the collaboration could be made more formal. Some requested clear communication towards external audiences on each COLLA project to avoid stigmatisation or 'blacklisting' of a particular substance or group among the less knowledgeable audience.

More observations by registrants and authorities on early interactions can be found in Appendix 6.

7.1.2. Addressing groups of substances

Table 6 shows views of authorities and registrants contributing to the projects on addressing groups of substances in the pilot projects. A clear majority of those who replied found that working with a group of substances allowed for a more efficient identification of data gaps, leading to the definition of more efficient regulatory plans. Overall, the grouping of substances was seen as supporting effective and efficient regulatory actions.

Table 6: Authority and registrant opinions on addressing groups of substances in the pilot projects.

	Agree / Somewhat agree / Neutral / Somewhat disagree / Disagree	Total
Addressing groups instead of individual substances allowed **a more efficient identification of data gaps** regarding hazards, exposure and risk.		R:8 A:18
Addressing groups instead of individual substances allowed defining **more efficient regulatory plans** regarding exposure and risk.		R:8 A:18
Addressing groups instead of individual substances allowed defining **more effective regulatory plans**, e.g. by **reducing testing requirements and vertebrate testing**.		R:8 A:18
Addressing groups instead of individual substances allowed **creating synergies between new and ongoing regulatory actions**.		R:8 A:18
Assessing substances as a group is a more functional approach than assessing them individually.		R:8 A:17

However, authorities and registrants had mixed views on whether the grouping approach saved time or resources compared to reaching the same screening/testing plan conclusions by performing the assessment on individual substances. Considering the majority of the views, authorities acknowledged time savings for three groups, but not for the other two groups. Registrants found that time savings were obtained for half of the groups, but not for the other half, as there were mixed views on one group.

Authorities' concerns regarding time and resources when working with groups were mostly related to the group's size and complexity, as the larger or more complex the group, the more time it could be expected to require. However, as pointed out by some authorities and registrants, larger categories created by registrants have to be addressed as a whole to ensure fairness and consistency. Authorities also pointed out that the number of registrants and organisations (e.g. whether there is a functioning consortium) also impacts resources and time spent. The feedback indicated that the development of regulatory strategies taking into

account ongoing and already planned regulatory actions on similar substances is complex, but there are benefits. For example, it was indicated that for the pilot groups we now have a clearer picture of how actions on individual substances can be magnified to cover the whole group, including future registrations, and how to ensure better consistency in how the group members are addressed. However, the project experience also showed that building testing strategies for groups is sometimes very challenging and complicated due to alternative directions in the plan depending on the outcome of the ongoing action.

Furthermore, the project experiences showed that also the addressing of substances in groups even without fruitful early interaction enables more efficient identification of data gaps regarding hazards, exposure and risk, and thereby the development of more efficient regulatory plans. This is because addressing substances by group allows regulatory plans to be more focused and reduce the need for vertebrate testing. Furthermore, addressing groups allows synergies between new and ongoing regulatory actions to be considered.

Both authorities and registrants indicated several aspects that would make a substance group more suitable for the collaborative approach. These were, for example, reasonable group size, clarity on substance identity, and read-across to the same source substance. There were also suggestions for COLLA to be used to clarify substance identity for UVCB substances, for example, and to clarify read-across aspects.
More observations by registrants and authorities on working with groups of substances can be found in Appendix 6.

7.1.3. Experiences and feedback on project practicalities

Both the authorities and registrants who contributed to the pilot projects gave mostly positive feedback on the communications during the projects. Some contributors saw a need to enhance the communication package provided in the initiation phase, as well as for earlier communication of the timelines planned for the different interaction milestones.

Based on the opinions of most respondents, the practical aspects of the pilot projects worked mostly well, but there is room for improvement. The survey feedback contained many concrete proposals on how to improve the practicalities of the projects, related to the reporting templates used, data matrices and organisation of meetings as well as the different phases of interaction.

7.2. Resources used by authorities

ECHA and MSCAs tracked in at least an approximate way the resources they used during the pilot projects. A summary of the results and some project-specific observations are provided below. However, there is no data available on time spent by the observer MSCAs on the pilot projects. Overall, the estimates reflect the order of magnitude and allow some general reflections.

The five COLLA pilot projects covered about 50 substances in total, with one group containing more than 20 substances and four groups containing 6 to 8 substances each. The reported time has been averaged per group, representing a virtual group of 10 substances.

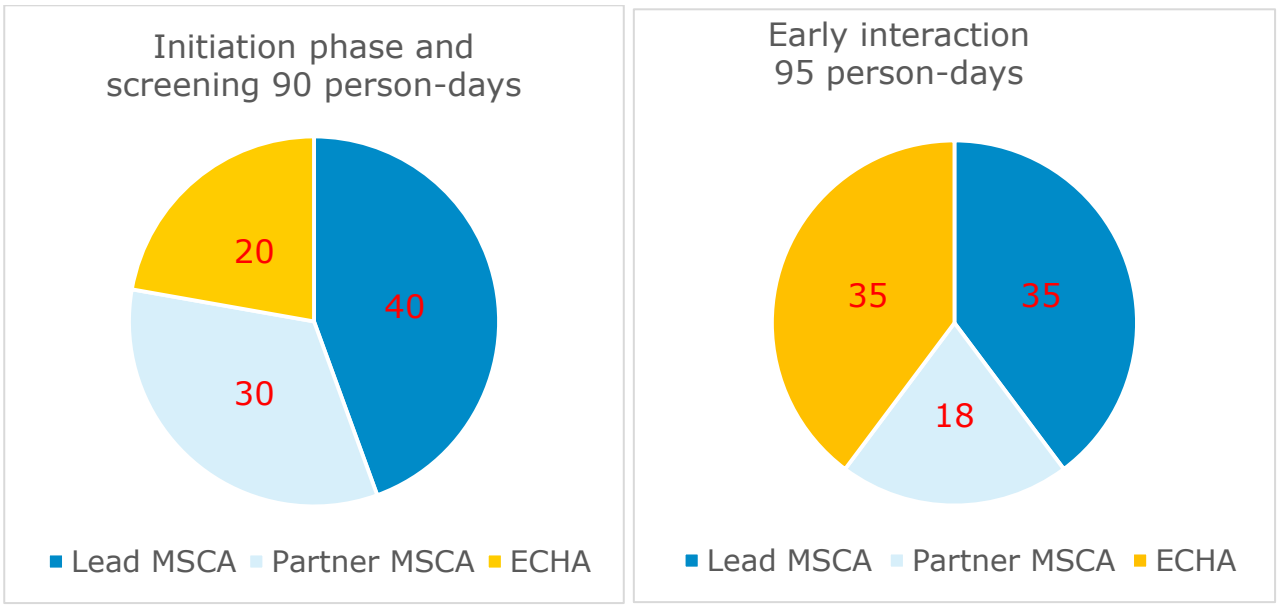
ECHA spent on average about 53 person-days on each of the COLLA projects, which is a full-time equivalent (FTE) of about 0.24 per group and 1.2 in total. ECHA spent the most time during the interaction phase, as ECHA organised the teleconferences between the authorities and contributed expert support for the review of the further information provided.

MSCAs spent on average about 123 person-days on each of the COLLA projects, which is about 0.54 FTE per group. The most time was spent in the screening phase – about 40 person-days

by the lead MSCA and about 30 person-days by the partner MSCA, in total about 70 days or 0.3 FTE for each group. In the interaction phase, MSCAs spent about 53 person-days (0.24 FTE) per group. On average, the lead MSCA spent about twice as much time on the interactions as the partner MSCA.

Figure 4 shows the total ECHA and MSCA resources spent on average per group in the initiation phase and screening and in the early interaction phase. The latter phase is the true COLLA 'add-on', as the MSCAs screen such groups anyway. Therefore, in total, authorities spent about 185 person-days (about 0.84 FTE) per group.

Figure 4: Summary of total MSCA and ECHA resources spent on average per group in the initiation phase and screening and in the early interaction phase (excluding outliers).



The time reports by MSCAs showed that both the screening and interaction phases require substantial work. For some projects, such as that on antimony compounds, MSCA spent much more time than the average for reasons to be further clarified.

Screening took more time for large groups than for middle-sized groups, as could be expected, even though screening needed to be kept less in-depth. However, the time reports also showed that during the early interaction phase, the size of the group did not strongly affect the amount of resources spent by authorities. In fact, under a collaborative approach, less resources were spent per substance in a larger group than in a smaller group.

The screening under COLLA can be compared with the normal manual screening. In the normal manual screening, MSCAs are recommended to spend about two days per substance (although in reality this can be more). This is a shorter period of time than the average of about 7 days spent per substance under COLLA. Moreover, based on the feedback given by MSCAs, the screening for COLLA groups was more in-depth than a normal group screening.

In analysing the time spent in COLLA, the piloting effects should be taken into account. This is the first time such an early interaction exercise has been performed, and it is expected that future cases will require less resources.

ECHA notes that having a partner MSCA bears a high cost in terms of resources, especially when the partner MSCA performs a shadow assessment and it does not entail a division of the work.

7.3. Outcome of COLLA review workshop and RiME+ feedback

7.3.1. COLLA review workshop

ECHA organised a workshop on the review of the five COLLA pilot projects from 7 to 8 March 2018. The workshop was an important part of the review of the pilot projects and aimed to support ECHA in making a proposal on whether and how to continue with the collaborative approach in future.

The workshop had the following main objectives:

- To review the COLLA pilot projects and consider how to implement forms of a collaborative approach in addressing groups of substances in the future.
- To review in particular detail:
  - the outcomes of the COLLA projects;
  - how the expected benefits of a collaborative approach were fulfilling expectations;
  - the collaboration between ECHA and MSCAs and between the authorities and the registrants/industry representatives, and to make recommendations for improvements;
  - how the COLLA approach supported addressing groups of substances.
- To collect other key learnings and observations from the COLLA projects.

The workshop comprised three plenary sessions and one dedicated session for competent authorities at the end of the workshop to discuss certain aspects of COLLA and next steps. In addition, two breakout groups were organised to discuss topics around the main topics of the workshop. These breakout groups:

- Reviewed the five pilot projects, covering aspects such as:
  - Does COLLA provides added value to authorities and registrants?
  - Efficiency and effectiveness gains;
  - Roles of actors and communication;
  - COLLA practicalities
- Discussed opportunities for COLLA in the future
  - What are the substance groups that can benefit the most from COLLA?
- Made suggestions for improving COLLA
  - How can we enhance the efficiency and efficacy of COLLA?

The outcomes of the breakout group discussions were reported and discussed during the third session on the second day of the workshop. For more details on the workshop agenda, see 0.

Representation of contributing MSCAs and registrants in the workshop was good. In addition, there was a good number of other MSCAs participating to the workshop. A total of 14 Member States/EEA countries were present and two followed the proceedings via WebEx. From among ECHA's accredited stakeholders, Cefic, Eurometaux and Concawe participated; none of the public interest NGOs participated. Representatives of the European Commission also participated in the workshop. In total, the workshop had 29 external participants on-site as well as eight such attendees via WebEx.

The workshop was successful in addressing all the main topics. The discussions were lively and constructive and no major controversial issues were raised, although there were differing views on the details of the future approach. The workshop concluded that most of the five pilot projects provided added value for authorities and registrants. However, while there is evidence from multiple sources of improved effectiveness, it is not clear to which extent the collaborative approach improved efficiency. In fact, the pilots demanded significant resources from MSCAs and it is not clear to which extent this would reduce workload in the following

steps of the processes. On the other hand, it was recognised that future collaborative approaches would likely lead to a major reduction of workload based on the learnings from the pilot projects, in particular those related to the clarification and limitation of the scope, a better definition on the roles and practical arrangements. In this regard, many of the suggestions tabled by the pilot project contributors to improve future COLLA projects were supported by the workshop.

The workshop recommended the application of an early interaction approach with registrants in the future for certain substance groups, listing criteria for the groups that can benefit the most from such early interaction. For instance, when at least one of the group members should be a substance of potential concern, when part of or the whole group should already be defined by the registrants or by other (inter)national organisations, and when there is a weak read-across justification but the hypothesis seems to be plausible. It was also noted that although a larger group may be more difficult to handle, such a group may benefit more from an early interaction with the registrants. At the same time, groups involving several ongoing regulatory processes may not benefit from an early interaction. The early interaction was proposed to be applied after MSCA manual screening, before the official evaluation processes are launched. Overall, ECHA's proposal on the future early interaction approach was supported by the workshop. For example, a 'lag time' may be required before the start of the default six-month interaction period, to allow industry actors to organise themselves.

It was clarified that COLLA is an extension of the manual screening, where an early interaction with registrants is considered convenient to conclude on the actions to take. To emphasise that the expected outcome of COLLA is a decision on the actions to be taken, and this decision is to be taken by the authorities (normally an MSCA), ECHA had initially referred to the outcome as a 'regulatory plan'. In fact, the terms 'conclusion document of manual screening' and 'justification document' as used in the pilot projects were not clear to registrants. However, the term 'regulatory plan' was considered possibly misleading, for example potentially excluding non-regulatory actions. It was acknowledged that the expected outcome document from early interaction is an updated version of the conclusion document of the manual screening which includes the proposal of priority actions to take. A term like 'plan for next actions' could be suitable.

As a more general conclusion, it was seen that in the future it may be better to simply refer to 'early interaction', rather than a 'collaborative approach', as the extra optional step after manual screening.

In the closed session for competent authorities, the authorities' roles, resources, and other matters in relation to COLLA-type of interaction were discussed. It was recommended that the screening justification document for the substance group should be updated when conclusions from early interaction are available. On the other hand, there should be flexibility in what the authorities can share with the registrants, for example, summary documents or presentations. It was suggested for the State of Play-bulletin of the RiME+ meeting to be used to let other authorities know about ongoing early interactions.

Regarding roles of authorities, it was concluded that MSCAs can work alone or in pairs, depending on resources. When working in pairs, the recommendation is to split work between environment and human health (and exposure) and not to split the group into two. ECHA is prepared to continue providing support in the initiation of early interaction with materials such as templates and data matrices, as well as through scientific expertise upon request. It was recommended that ECHA join each early interaction at least as an observer to facilitate overall coordination and consistency. ECHA could run such early interactions also alone. Only a few MSCAs currently have the resources to launch new early interaction cases. Some MSCAs were considering proposing groups for an early interaction based on the 2018 manual screening. It was agreed that ECHA will clarify who should do what in the follow-up of early interaction, for example check that promised testing proposals been submitted.

7.3.2. RiME+ feedback

The COLLA pilot projects, the conclusions from the COLLA review workshop and ECHA's proposal on a future early interaction approach were also discussed during the Risk Management and Evaluation (RiME+) meeting on 15 May 2018.
As in the COLLA review workshop, it was highlighted that it is not clear whether COLLA has improved efficiency in regulatory action. It was also noted that collaboration with registrants should not be seen as equal to working with groups of substances and thereby just add new layers to the whole process.

Members States also highlighted some benefits that may be brought by early interaction with registrants. For instance, the interaction may help scope the work in the formal steps of the process, lead to deprioritisation of the whole case and thus save resources, and help the evaluating Member State process more quickly draft decisions and formal comments from registrants in substance evaluation. There was clear support for informal interactions with registrants before the formal REACH processes. It was stressed that authorities need to define upfront the purpose of the interaction is, as well as define the scope, timelines and practicalities of the interaction case-by-case. Early development and sharing of the risk management option analysis (RMOA) was proposed as a way to make regulatory outcomes clear to industry and to put (at least some) pressure on registrants to update the dossiers and on downstream users to provide information. It was also concluded that there should be better early interaction with registrants, and a holistic approach to determine what authorities' purpose is under the Integrated Regulatory Strategy. An early interaction approach should be flexible in a case-by-case manner and the benefits should be weighed against the resources spent.

8. Pilot project review conclusions

8.1. General conclusions

This section presents the general conclusions drawn by ECHA on the COLLA pilot projects, based on the analysis of the review survey results (Chapter 7), the project outcomes (Chapter 6) and the discussions at the COLLA Pilot Projects Review Workshop.

The following main overall gains from the COLLA pilot projects were identified:

- For each of the five substance groups, there is now a better-informed plan for next actions. There is more clarity on the priority regulatory actions to take, and which substances to apply them to.
- The concerns that merit further actions were identified earlier in time.
- In many cases, additional concerns were identified while some of the initial concerns were clarified and closed.

For more details, see Table 3 in Chapter 6.

In general, the pilot projects helped to clarify whether and how a grouping approach can be used to clarify and address identified concerns, and what type of supporting information is required to clarify the concern and to justify the grouping. The pilots also verified the concerns that merit further action and allowed conclusions on the required next steps (if any) to be made on a more informed basis and with a higher level of confidence (e.g. dossier/substance evaluation, risk management measures). Conclusions on concerns need to wait for the results of the planned testing and other relevant actions, which may not be conclusive. However, such plans also show potential (still to be confirmed) to clarify concerns through the more focused

application of compliance check and substance evaluation as well as of actions by the registrants.

Overall, most of the five pilot projects brought added value for authorities and registrants. However, while there was evidence of improved effectiveness, it is not clear to what extent COLLA improved efficiency. In fact, the pilots demanded significant resources from MSCAs, and it is not clear to what extent this would reduce workload in the following steps of the processes. Therefore, with respect to one of the general objectives – to test the efficiency and effectiveness of the collaborative approach to see if it is worthwhile to continue or intensify the approach from 2018 onwards – ECHA notes that it cannot draw firm conclusions. The pilot projects were generally considered to have provided added value in addressing the groups and defining action plans. However, in practice, the efficiency and effectiveness of the plans could even in principle be evaluated only once the industry actions and REACH processes have been completed. Furthermore, the pilots were testing two different elements, addressing substances by groups and early interaction with registrants, and it would be difficult to differentiate between their respective impacts on efficiency or effectiveness.

The spent resources reported by ECHA and Member State authorities were significant, in total an average of 53 and 123 person-days per group (5.3 and 12.3 person-days per substance), respectively. This overall workload was almost equally divided between the screening and interaction phases, ECHA spending more resources in the latter phase. However, as part of these resources were consumed by the approach development and capacity building, future early interactions can be expected to require less resources. Furthermore, there is no evident point for comparison, as there is yet little experience on addressing groups of substances in manual screening or on interacting with industry on groups at this early stage. However, ECHA's recommendation for a maximum of two person-days to be used per substance in the manual screening puts the spent resources into perspective. To allow for another comparison, the current maximum for transfer of funds for substance evaluation is 65 person-days of work per substance. The pilot projects also provided insight into when such early interaction could or could not achieve the expected benefits, as well as considerations on the resources and time required.

ECHA acknowledges that early interaction may lead to spontaneous generation of information. However, this may lead to issues related to data and cost sharing. With the current REACH provisions on data sharing, it seems difficult for authorities to facilitate such data sharing.

8.2. Conclusions on specific aspects of COLLA

Based on the project outcomes and feedback, the following conclusions could be made on **early interaction**.

In general, early interaction was appreciated due to its clear benefits, including:

- the opportunity to obtain clarifications, especially on group boundaries and read-across justification;
- the support it provides to the selection of better regulatory action; and
- the possibility to accelerate of the launch of further testing and improved effectiveness through the avoidance of unnecessary or wrongly timed actions.

However, early interaction requires a substantial amount of work to be carried out early in the process of addressing substances of potential concern, and there was a mixed perception among the project contributors on whether the interaction improved efficiency or not. The question that remains is the extent to which the work performed upfront pays back by allowing more focused, and therefore less demanding, regulatory plans. Furthermore, the early

interaction may not be additional work if it simply requires performing an assessment that would be in any case required later in the following regulatory processes. The pilot project experiences have provided us with a better understanding of how the time spent in COLLA could be reduced, for example, by a clearer understanding of the aims at the beginning of the early interaction and by improving the practicalities (e.g. reporting templates, data matrices and meeting preparations). Therefore, future early interaction projects may achieve a higher level of efficiency.

Based on the five pilot projects it is difficult to distinguish between the benefits obtained from addressing substances by groups and those obtained related to the early interaction. However, focusing on the value added by the information obtained during the early interaction (see Table 6 in Chapter 6) there is some evidence of increased efficiency and effectiveness in terms of reduced workload and faster identification of substances needing regulatory action. However, as explained above, these indications need to be verified after completion of the action plans and need to be related to the workload associated to the early interaction, and therefore are not sufficient at present to draw firm conclusions on the effectiveness and efficiency of the collaborative approach.

INDICATIONS OF EFFICIENCY AND EFFECTIVENESS OF COLLA IN THE FIVE PILOTS, AS COMPLIED BY ECHA

EDTA derivatives

- COLLA allowed defining subgroups among the substances and accelerated consideration for priority for regulatory risk management. In addition, the developmental concern was clarified to be different for different subgroups.
- Authorities concluded that there was sufficient information to clarify the concerns, pending the outcome of ongoing testing. Awaiting the results of ongoing testing and the confirmation of read-across appears to be the most efficient way forwards.

Antimony compounds

- Open questions could be clarified, and an update of registration dossiers and additional information were announced to be delivered.

Polyol acrylates

- The early interaction allowed clarifying and concluding on the initial concern without the need to open a formal process.
- The subgrouping proposed by registrants during the early interaction has also served to focus the assessment of the data gaps for the human health endpoints.
- The voluntary generation of data will likely support and validate the read-across approaches and thus save resources, in terms of the compliance checks that would have otherwise been triggered and the tests that would have been requested through these formal processes.

Substituted diphenylamines

- No new compliance checks or testing proposals are currently needed to address missing information related to the current concerns. This will speed up the resolution of the suspected PBT and human health-related concerns for the substances in the group, as the related further information needed will be generated faster than if new processes would have to be launched to generate it.

Organotin compounds

- No new compliance checks or testing proposals are needed at present to address missing information related to the current concerns. This will speed up the resolution of the suspected concerns for the substances in the group, as the related further information needed will be generated faster than if new processes would have to be launched to generate it.

On the experience of new forms of interactions among ECHA, MSCAs and registrants, the following was observed.

Generally, participants felt that there was a good level of commitment from all parties involved. In some pilot groups, MSCAs indicated that they felt registrants were not willing to cooperate constructively or that they were interested in postponing actions.

In the various pilot projects, there was a different balance in leadership between ECHA and the MSCAs, depending on project specificities. Furthermore, the partnership between MSCAs can

be challenging due to different approaches, but was generally considered very useful. There was good cooperation between ECHA and MSCAs, and in particular with MSCAs' evaluation experts that are not points of contact in normal dossier or substance evaluation cases. On scientific and evaluation issues, there was easy alignment between ECHA and MSCA experts at this point of the process, as it was early and informal.

When looking at incentives and disincentives for industry to improve information, through the early interaction ECHA gained a better understanding of registrant and SIEF issues and dynamics, on matters such as triggers for dossier update and data sharing. However, in some projects there was resistance to voluntary actions within some consortia.

About the opportunity for applying forms of collaborative approach in the future, based on the feedback received, most authorities and registrants support application of early interaction to groups of substances, although not as a default for all cases. The COLLA review workshop compiled key criteria for the selection of candidate groups for early interaction.

It seems that the major difficulties encountered during the pilot project interactions were associated with the following issues:

- Effective handing of large groups of substances.
- Dealing with substance groups with one or more group member being subject to ongoing REACH and CLP processes.
- Limited resources for early interaction available from MSCAs, also taking into account that this work is not paid.
- Confidentiality issues – however, these were mainly overcome in the projects, except for exposure/use information.
- How to align informal and later formal assessment with involvement of other MSCAs during substance or dossier evaluation decision-making.

In all five pilot projects, the registrants were mostly willing to collaborate. However, it seems that some of their expectations of authorities accepting read-across or deprioritisation of their substances were not met. The early interactions triggered cooperation among the registrants of similar substances who did not collaborate previously, and some of the consortia were revitalised.

Most of the practicalities for the five pilot projects went well but there is room for improvement. In the received feedback (see Chapter 7.1 above), there are many concrete and good proposals to improve the practicalities of early interaction, for example, with regard to reporting templates and data matrices used and meeting practicalities. There is a need to make early interaction more flexible and tailorable for each group while still working with clear boundaries and pre-conditions.

The feedback also indicated that there may be a need to clarify what a plan for next actions (i.e. the expected outcome of early interaction) is, and to clarify where and when authorities accept read-across and where there is no need for authorities to verify read-across.

The project outcomes and feedback show that the grouping of substances is widely supported for effective and efficient regulatory actions. There are the following clear benefits from working with groups of substances:

- a more efficient identification of data gaps;
- the taking into account ongoing processes; and

- the definition of more efficient/effective regulatory plans.

However, there are also challenges, including:

- complex assessments;
- the need for a new approach and organisation to be able to address groups of substances – as learnt from the initial trials with MSCAS, the process is not just the summary of individual assessments, which are in some cases made by different experts;
- complex plan for next actions taking into account fixed ongoing processes; and
- no apparent time savings in the short term.

9. ECHA's recommendations for the way forward

ECHA made a proposal for a future **early interaction approach** to the MSCAs for their CARACAL-27 meeting on 27 June 2018. The proposal is not repeated here, to avoid inconsistencies when the approach is finalised later on based on the MSCA consultation.

Addressing substances in groups, intensifying collaboration between authorities and initiating early interaction with registrants can all be seen as useful elements. However, based on the review conclusions, ECHA does not recommend formalising these aspects under a specific 'collaborative approach' process. Instead, ECHA invites the MSCAs to consider the option of an early interaction at the manual screening stage.

The scope and objectives of the early interaction should be defined taking into account that it is an option to seek a better conclusion of the manual screening. This option should be considered case by case, based on expected benefits and on a consideration of required resources and time.

ECHA will propose certain best practice recommendations on the timelines, practical organisation, the division of work between authorities and reporting. These will aim to ensure the necessary level of consistency and focus in terms of time, resources and scope, as well as that all actors have a common understanding of the process and clear expectations.

10. List of abbreviations and acronyms

CCH	Compliance check
CLH	Harmonised classification and labelling
CLP	Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures
COLLA	Collaborative approach
CoRAP	Community rolling action plan
CSA	Chemical safety assessment
CSR	Chemical safety report
DNEL	Derived no-effect level
ECHA	European Chemicals Agency

ED	Endocrine disruptor
EDTA	Ethylenediaminetetraacetic acid
EOGRTS	Extended one-generation reproductive toxicity study
IUCLID	International Uniform Chemical Information Database
MSCA	Member State competent authority
NONS	Notification of new substances (under pre-REACH EU legislation)
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, bioaccumulative and toxic
PEC	Predicted environmental concentration
PNEC	Predicted no-effect concentration
QSAR	Quantitative structure-activity relationship
RAAF	Read-Across Assessment Framework
RAR	EU Existing Chemicals Regulation Risk assessment report
RCR	Risk characterisation ratio
REACH	Regulation (EC) No 1907/2006 concerning the registration, evaluation, authorisation and restriction of chemicals
REACH-IT	A central IT application that supports industry, Member State competent authorities and ECHA to securely submit, process and manage data and dossiers
RiME+	Risk Management and Evaluation expert platform
SEV	Substance evaluation
RMM	Risk management
RMOA	Risk management option analysis
SID	Substance identity
SIEF	Substance information exchange forum
SDPA	Substituted diphenylamine
SVHC	Substance of very high concern
TPE	Testing proposal examination
UVCB	A substance of unknown or variable composition, complex reaction product or biological material
vPvB	Very persistent and very bioaccumulative

Appendix 1: COLLA project closure report for EDTA derivatives

1. Introduction

The project closure report summarises the information on the group of EDTA derivatives addressed in the collaborative approach (COLLA) pilot project, their suspected concerns and potential information gaps, as well as previous regulatory activities on them.

The report also outlines how the project was run and what its outcome was in terms of a regulatory plan for the group of substances.

2. Group description

2.1. Group formation

The initial group comprised 22 aminocarboxylic acid derivatives, 21 identified through IT screening and one manually added at the start of the project.

Table 1: Substances in the initial COLLA group.

Short name	EC number	CAS number	Highest tonnage band	Active registrations
EDTA-H4	200-449-4	60-00-4	1 000–10 000	13
EDTA-Na4	200-573-9	64-02-8	10 000-100 000	13
EDTA-Na2H2	205-358-3	139-33-3	1 000-10 000	11
EDTA-CaNa2	200-529-9	62-33-9	1 000-10 000	5
EDTA-CuNa2	237-864-5	14025-15-1	1 000-10 000	5
EDTA-Cu(NH4)2	268-018-3	67989-88-2	100-1 000	1
EDTA-FeNa	239-802-2	15708-41-5	1 000-10 000	7
EDTA-Fe(NH4)(NH4)OH	270-232-7	68413-60-5	1 000-10 000	1
EDTA-MgNa2	238-372-3	14402-88-1	100-1 000	4
EDTA-MnNa2	239-407-5	15375-84-5	1 000-10 000	6
EDTA-MnK2	268-144-9	68015-77-0	100-1 000	2
EDTA-ZnNa2	237-865-0	14025-21-9	10 000-100 000	8
EDTA-Zn(NH4)2	267-400-7	67859-51-2	100-1 000	1
DTPA-H5	200-652-8	67-43-6	100-1 000	5
DTPA-Na5	205-391-3	140-01-2	10 000-100 000	8
DTPA-K5	404-290-3	7216-95-7	10-100	1 (+ 1 NONS)
DTPA-FeHNa	235-627-0	12389-75-2	100-1 000	1
DTPA-FeNa2	243-136-8	19529-38-5	1 000-10 000	6
DTPA-Fe(NH4)2	289-064-0	85959-68-8	100-1 000	3
PDTA-H4	400-400-9	1939-36-2	NONS	(3 NONS)

PDTA-FeNH4	400-660-3	111687-36-6	0-10	No active registrations
HEDTA-Fe(III)Na	257-036-7	51181-50-1	100-1 000	2

During the course of the project, nine additional aminocarboxylic acid derivatives were identified. Some of these were already part of the registrant category and had been overlooked during the IT screening due to unclear substance identification or because they were not registered under REACH, while others were added to the category during the course of the project. These additional substances were not screened to the same level of detail as the substances in the initial group but have been considered as far as possible in the conclusions.

Table 2: Substances identified during the COLLA project.

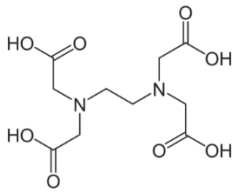
Short name	EC number	CAS number	Highest tonnage band	Active registrations
EDTA-(NH4)3H	240-073-8	15934-01-7	0-10	2
EDTA-(NH4)2H2	244-063-4	20824-56-0	10-100	3
EDTA-Na3H	205-758-8	150-38-9	Pre-registered	
EDTA-CuK2	277-749-7	74181-84-3	0-10	1
EDTA-FeK	259-411-0	54959-35-2	100-1 000	2
EDTA-Mn(NH4)2	304-037-6	94233-07-5	0-10	1
EDTA-ZnK2	238-729-3	14689-29-3	10-100	1
HEDTA-H3	205-759-3	150-39-0	0-10	1
HEDTA-Na3	205-381-9	139-89-9	1 000–10 000	7

Structural formulas

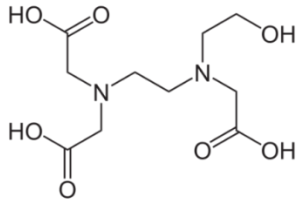
The substances belong to a group of aminocarboxylic acid-based chelants. They have similar molecular structures containing common functional groups. All members have a molecular structure with an ethylenediamine (EDTA), propanediamine (PDTA) or diethylenetriamine (DTPA) backbone with 3 to 5 acetic acid groups attached to the nitrogens. Some of the substances are based on hydroxyethylethylenediamine (HEDTA) backbone where an acetic acid group of EDTA is replaced by a 2-hydroxyethyl group.

The structures of the four free acids are shown below.

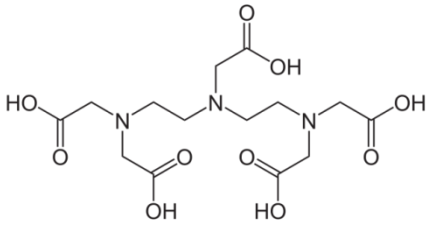
EDTA-H4, $(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$



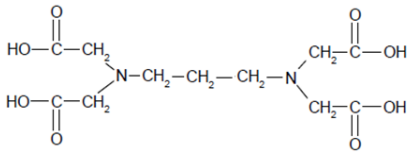
HEDTA-H4, $(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)(CH_2CH_2OH)$



DTPA-H5, $(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)CH_2CH_2N(CH_2COOH)_2$



PDTA-H4, $(HOOCCH_2)_2NCH_2CH_2CH_2N(CH_2COOH)_2$



The carboxylate group may be in the form of the free acid or the carboxylate anion where one or more of the hydrogens have been neutralised to an ammonium or metal salt (NH_4^+, Na^+, K^+). These are called 'empty' chelates. They may also be complexed with metal ions (Ca^{2+}, Mg^{2+}, Zn^{2+}, Cu^{2+}, Fe^{2+}, Fe^{3+}).

2.2. Initial concerns

The group was formed around two group seed substances that were identified through IT screening as part of the common screening approach. The two group seeds are listed below, along with the reason why they were identified through IT screening. The initial concern for the group seeds was **reproductive toxicity**.

Table 3: Group seeds for the initial group.

Short name	EC number	CAS number	Reason for shortlisting
DTPA-FeHNa	235-627-0	12389-75-2	Substance shows high toxicity (low NOAEL/LOAEL) and adverse effects on fertility as indicated in a registration.
PDTA–H4	400-400-9	1939-36-2	Substance is classified as a reproductive toxicant (category 2) by at least one REACH registrant and does not have a harmonised classification for that hazard class.

The other group members were grouped around the two group seeds based both on structural similarity and on read-across arguments made by registrants in REACH registration dossiers as well as categories formed by REACH registrants and by the OECD.

2.3. Previous regulatory activities

Some of the substances in the group have been under previous regulatory action, as listed in the table below.

Table 4: Ongoing or past regulatory action for the group under COLLA. See main chapter 10 for abbreviations.

	RMOA	REACH process			Authorisation		Restriction	CLH	Previous legislation	
EC entries		CCH	TPE	SEv	Candidate List	Annex XIV	Annex XVII	Annex VI (CLP)	NONS	RAR
EDTA-H4 200-449-4			✓					✓		✓
EDTA-Na4 200-573-9			✓					✓		✓
EDTA-Na2H2 205-358-3			✓							
EDTA-MnNa2 239-407-5		✓								
DTPA-H5 200-652-8	✓							✓*		
DTPA-Na5 205-391-3	✓							✓*		
DTPA-K5 404-290-3								✓*	✓	
PDTA-H4 400-400-9								✓	✓	
PDTA-Fe(NH4) 400-660-3									✓	

*The three DTPA substances listed above have been recently concluded as warranting classification as Repr. 1B by the Committee for Risk Assessment (RAC) but have not yet been included in Annex VI to CLP.

None of the substances are regulated under the Biocidal Products, Plant Protection Products or Persistent Organic Pollutants regulations.

3. Project organisation and approach

3.1. Actors and roles

Member States

Member State	Role
United Kingdom	Lead
Sweden	Partner/observer

The UK was in the lead, with Sweden serving as a partner during manual screening and as an observer later on. In addition to key contact persons, experts in toxicology and ecotoxicology contributed extensively to the project from both MSCAs, as well as on use and exposure from the lead MSCA.

ECHA

ECHA provided general support in coordinating the project as well as expertise in toxicology and substance identification.

Registrants

Three lead registrants and one individual registrant were identified for 20 of the 22 substances

identified at the start of the project and invited to participate. Key contact points for each registrant were nominated, but in addition, several experts also participated from each registrant, including some from joint registration members (particularly thSA DABEER company).

For the other two substances of the initial group, one had no active registrations and two NONS registrants for the other were notified but did not respond.

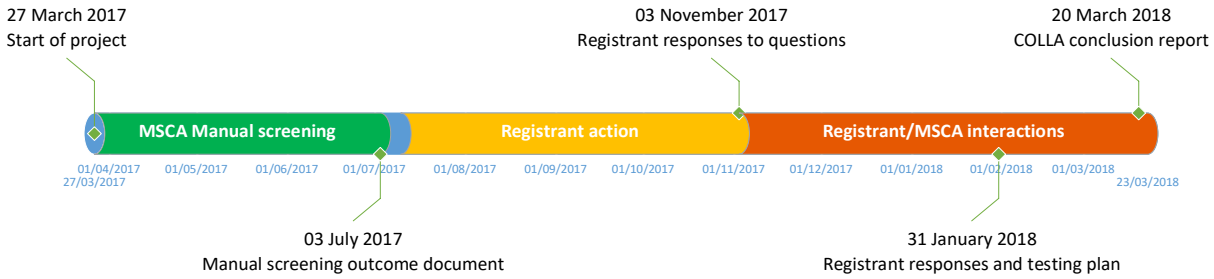
Table 5: Lead and individual registrants participating in the COLLA project.

Registrant	Role	Number of substances
Akzo Nobel Functional Chemicals BV	Lead	16
BASF SE	Lead	3
Dow Chemical Company Ltd	Lead	1
ADOB Sp. z o.o. Sp. k.	Individual	4

The registrants established coordinated expert teams in toxicology, ecotoxicology, substance identification and read-across. These teams were composed of individuals from both lead and member registrants.

Of the 10 substances identified during the project, nine had one of the companies above as lead registrant. The remaining substance had a different lead registrant, but some of the registrants above are members of that joint submission. That lead registrant was not invited to take part in the project due to time constraints as the substance was identified so late in the project. However, the participating registrants were requested to inform other registrants as needed during the project.

3.2. Timelines and milestones



The timeline above shows the duration of the different stages of the project and the main deliverables for each step. The initial group was identified in early 2017 and MSCAs started their manual screening in late March. Registrants were provided the initial conclusions from the manual screening in early July 2017 and given until the end of October to respond. The time to respond to the initial questions was rather long as RAC concluded on CLH proposals for three of the substances in late June and the opinions were published in August. Registrants requested for time to be given to analyse these opinions and take their arguments into account.

3.3. Interactions during the project

The timeline above shows the meetings during the projects. There were two face-to-face meetings involving all participants. The first was the kick-off meeting on 10 July 2017, hosted by the competent authority of the United Kingdom, and the second was the follow-up meeting on 1 December, hosted by Akzo Nobel. All other meetings were held as teleconferences.

MSCAs and ECHA conferred several times during the initiation and manual screening phase. This was necessary to clarify roles and tasks and align views. Registrants were contacted by ECHA in early May.

The general view held by all participants was that the second face-to-face meeting in December was the most productive and useful of all the interactions.

4. Work undertaken

Before the start of the project, the principal concern regarding the aminocarboxylic acid-based derivatives was reproductive toxicity. Three of the substances were in the process of harmonised classification and labelling with the proposed classification of Repr. 2, and there were some indications of developmental toxicity in studies with other substances. Prior to the kick-off meeting, RAC reached an opinion that classification as Repr. 1B was warranted. During the manual screening, other concerns regarding mutagenicity were raised. In addition, concerns were raised over the environment and exposure potential. Some of the questions raised by registrants and the answers given are summarised below.

4.1. Human health

The principal toxicological consideration for this group of substances is the potential for chelating zinc, creating zinc deficiency, which can result in adverse consequences for both adults and offspring. The potential for reproductive toxicity, particularly developmental toxicity, to arise through this mode of action has been a particular focus of attention. Some of these substances contain metal ions that can, in themselves, pose significant toxicity, e.g. Mn ions.

Some questions raised with registrants at the kick-off meeting:

- How does the category hold up in light of the RAC opinion and their consideration of other EDTA and DTPA substances? Should the category be subdivided?

- There are a number of other similar chelates that are registered that were not included in the category – why? Are there any relevant data on those substances that can be used? Are there any relevant data being generated?

- The two PDTA substances in the screening group were not included in the registrants category (although the OECD category included PDTA-Na4). Given that there is a relevant study, why was this not used? Is there any explanation for their higher toxicity?

- Is there an explanation as to why EDTA-MnNa2 seems to be much more potent than the other EDTA substances (effects seen in the developmental study)?
- Are there any mutagenicity concerns at doses that would be anticipated to cause zinc depletion?
- Do the adverse effects in the one-generation study conducted with PDTA-H4 raise any concerns regarding a potential fertility hazard for this category?

During the collaboration, the registrants updated their category justification document and provided answers to the initial questions raised in the kick-off meeting and the subsequent follow-up. They provided a further subgrouping of the substances and introduced several new substances in the category, also providing justifications for why they do not include PDTA derivatives in the category. They also provided more information on potential for mutagenicity.

4.1.1. Category members and subgrouping

The new subgroupings are based on the 'empty' chelates (subdivided depending on the type of backbone – EDTA, DTPA or HEDTA) and the metal chelates (where a metal complex has been formed; including a subgroup of metal chelates having certain toxicological properties).

Subcategory 1: 'Empty' chelates

1a: DTPA-based empty chelates

CAS number	EC number	Short name
67-43-6	200-652-8	DTPA-H5
140-01-2	205-391-3	DTPA-Na5
7216-95-7	404-290-3	DTPA-K5

1b: EDTA-based empty chelates

CAS number	EC number	Short name
60-00-4	200-449-4	EDTA-H4
64-02-8	200-573-9	EDTA-Na4
139-33-3	205-358-3	EDTA-Na2H2
15934-01-7	240-073-8	EDTA-(NH4)3H
20824-56-0	244-063-4	EDTA-(NH4)2H2
150-38-9	205-758-8	EDTA-Na3H

1c: HEDTA-based empty chelates

CAS number	EC number	Short name
139-89-9	205-381-9	HEDTA-Na3
150-39-0	205-759-3	HEDTA-H3

Subcategory 2: Metal chelates – DTPA-, EDTA- and HEDTA-based

CAS number	EC number	Short name
12389-75-2	235-627-0	DTPA-FeHNa
19529-38-5	243-136-8	DTPA-FeNa2
85959-68-8	289-064-0	DTPA-Fe(NH4)2
62-33-9	200-529-9	EDTA-CaNa2
15708-41-5	239-802-2	EDTA-FeNa
68413-60-5	270-232-7	EDTA-Fe(NH4)2OH
54959-35-2	259-411-0	EDTA-FeK
14402-88-1	238-372-3	EDTA-MgNa2
14025-21-9	237-865-0	EDTA-ZnNa2
14689-29-3	238-729-3	EDTA-ZnK2
67859-51-2	267-400-7	EDTA-Zn(NH4)2
51181-50-1	257-036-7	HEDTA-Fe(III)Na

Subcategory 3: Metal chelates with metal ions that may cause toxicity in addition to Zn depletion

CAS number	EC number	Short name
14025-15-1	237-864-5	EDTA-CuNa2
74181-84-3	277-749-7	EDTA-CuK2
67989-88-2	268-018-3	EDTA-Cu(NH4)2
15375-84-5	239-407-5	EDTA-MnNa2
68015-77-0	268-144-9	EDTA-MnK2
94233-07-5	304-037-6	EDTA-Mn(NH4)2

PDTA chelants

Not part of registrant category, and according to the registrants, these substances are no longer used.

CAS number	EC number	Short name
1939-36-2	400-400-9	PDTA-H4
111687-36-6	400-660-3	PDTA-FeNH4

4.1.2. Toxicological concerns

Mutagenicity

Based on the information provided during the project, MSCAs considered that there was sufficient information to conclude there are no concerns for mutagenicity for DTPA and EDTA chelates. There is a compliance check decision requesting three *in vitro* genotoxicity tests on HEDTA-Na3 (205-381-9) and ECHA should consider any new data, as it will inform on the validity of the group and inclusion of the HEDTA chelates. As it is assumed by industry that *in vitro* aneuploidy induction is secondary to zinc depletion, including experiments to support this assumption should be considered if the registrants are generating additional *in vitro* data.

Sexual function and fertility

The MSCAs note that there are no standard studies to cover the fertility endpoint. There is evidence that some members of the group can cause adverse effects in the testes of rats. The most plausible mode of action is via zinc depletion. In most cases, it seems that the limited potency of the chelant is such that the testicular effect only arises at very high dose levels which are of little toxicological significance. A screening study for reproductive/developmental toxicity (OECD test guidelines 421 or 422) has been requested for HEDTA-Na3 through dossier evaluation. Alongside the anticipated results on HEDTA, the registrants should provide a well-reasoned weight-of-evidence assessment which addresses mode of action for the induction of testicular toxicity. As the mode of action is presumed to be common to all category members, further explorations using one representative substance (an empty chelate with high Zn-binding affinity) is recommended. Such testing could aid in addressing the information gaps for the substances under any future compliance checks.

Developmental toxicity

Overall there is sufficient information from which to gather an understanding of developmental toxicity for the EDTA and DTPA chelates in the category. There are no data for this endpoint for any of the three HEDTA substances, but two studies have been requested in a compliance check. ECHA will consider this new data during the follow-up to the compliance check.

4.2. Environment

During the manual screening of the group, MSCAs did not identify any specific PBT/vPvB or environmental endocrine disruption concerns. However, MSCAs raised several questions relating to biodegradablility, ecotoxicity and read-across for environmental endpoints between complexes.

This included queries about the assumption that some complexes were 'inherently biodegradable' or 'ultimately biodegradable'. MSCAs also questioned why there was no consideration of the toxicity of the metal ion when the metal-containing chelates were released to the environment and justification for ecotoxicity read-across between different ligands.

Further queries related to environmental risk assessment PEC and PNEC assumptions. Registrants provided additional information to explain the grouping based on intrinsic properties and stability constants and how this information impacts biodegradability. The registrants have agreed to update the read-across justification providing further information on the intrinsic properties of the substances and proposed enhanced ready biodegradation testing on substances with a range of stability constants.

The registrants have proposed additional testing to support the ecotoxicity read-across and their hypothesis that complexes with high stability constants have limited availability of the metal ion and therefore low ecotoxicity.

The individual test designs will be agreed through a testing proposal evaluation. The registrants should submit the testing proposal within six months of the conclusion of the COLLA project.

The MSCAs agree with the proposed additional work and are satisfied with the grouping approach in principle. They include a range of recommendations and points that need to be addressed both during and following the proposed testing by registrants and when updating the read-across justification document, the chemical safety report and the environmental risk assessment.

4.3. Use and exposure

Aminocarboxylate chelants are used as chelating/complexing agents and micronutrients with applications in agriculture, building and construction, cleaners and detergents, the oil and gas sector, metal plating and electronics, personal care products, pulp bleaching, dietary supplementation, pharmaceuticals and food preservation[3]. They are used to control the behaviour of metal ions in water (e.g. to prevent or limit the rate at which lime scale builds up), to provide controlled dosing of metal ions to plants in fertilisers and to address iron deficiency in humans and animals. Across the group, some derivatives are used exclusively as fertilisers, whereas others have a wider range of applications.

Two PDTA-based chelates have also been included in this category (PDTA-H4 and PDTA-Fe(NH4)). Historically, these had uses in photographic processing. This use has declined with the move to digital cameras, and the registrants state that they no longer produce PDTA-based chelates.

This is a large group of substances with a complex use pattern. MSCAs were not able to fully analyse any substance with regard to exposure and use within the timeframe of the COLLA project, but registrants were given feedback on the exposure assessments and the safe use recommendations for the three DTPA salts that RAC proposes should be classified as Repr 1B. Some initial questions were raised at the kick-off meeting, such as why certain substances have a wide range of uses while others much more limited, whether the substances are generally used alone or in combination with others of the same group and what the role of the substance is in intermediate uses.

Registrants provided some initial responses to the questions raised and MSCAs were able to get a better picture of the potential for exposure to humans and the environment, helping the lead MSCA to provide tailored feedback to registrants of these three DTPA salts participating in the COLLA project. In this feedback, the lead MSCA provided recommendations to registrants on ways to improve the reporting of uses in their dossiers and aspects of registrants' guidance on safe use that needed further work. The lead MSCA also identified several general questions for discussion with the wider exposure community such as downstream users.

5. Project outcomes

5.1. Screening outcome and regulatory/testing plan

There are some actions still pending on some substances, such as Compliance Checks, and registrants have committed to conducting testing on several substance as well as providing more information on various aspects such as read-across justifications. Therefore, currently no further regulatory actions are considered by the MSCAs.

ECHA and MSCAs will review the group after one year with a view to determine whether follow up actions (e.g. CCH) are needed.

Human health

The following specific conclusions on human health aspects were made for the different subgroups:

1. 'Empty' chelates

[3] See the chelates product guide by Akzo Nobel Functional Chemicals B.V. (May 2017) for examples: https://chelates.akzonobel.com/siteassets/20170714-download-product-dissolvineproductguide2017web.pdf (accessed 2 February 2018).

   a. DTPA-based empty chelates: *Currently no action; MSCAs to consider the need for an RMOA once the classification Repr. 1B has entered into force*.
   b. EDTA-based empty chelates: *Currently no action; industry to consider the need for further information on fertility, considering also the outcome of compliance check of HEDTA subcategory.*
   c. HEDTA-based empty chelates: *Currently no action pending the outcome of the compliance check follow-up by ECHA.*
2. Metal chelates – DTPA-, EDTA- and HEDTA-based: *Currently no action.*
3. Metal chelates with metal ions that may cause toxicity in addition to Zn depletion: *Currently no action.*
4. PDTA chelants: *Currently no action, as substances not produced anymore.*

Environment

Currently no action, pending the submission of testing proposals.

5.2. Initial reflections on lessons learnt and best practices recommended for the future

The following reflections and recommendations are from ECHA's coordinator of the COLLA pilot project.

All participants found the second face-to-face meeting to be the most fruitful meeting, while the kick-off meeting was found not to be that useful. This is most likely because all participants were better prepared for the second meeting than for the first, further highlighting that the most fruitful kind of interaction is face-to-face meetings to which all parties come well prepared. Registrants noted that this type of interaction would have been even more fruitful had it occurred earlier in the project, which further backs the conclusion that a well-prepared kick-off meeting is crucial.

The large size of a substance group adds to the complexity of the project and workload of all parties, but this is particularly true for exposure and use assessment. For hazard assessment, the size of the group is important, but structural similarities and clear mode of action can make the assessment easier for larger groups than for smaller groups where the similarities are less clear. This is often not the case when assessing exposure and uses.

Appendix 2: COLLA project closure report for antimony compounds

1. Introduction

The project closure report summarises the information on the group of antimony compounds addressed in the collaborative approach (COLLA) pilot project, their suspected concerns and potential information gaps, as well as previous regulatory activities on them.

The report also outlines how the project was run and what its outcome was in terms of a regulatory plan for the group of substances.

2. Group description

2.1 Group formation

Diantimony trioxide, antimony sulphide and antimony were already included in the Community rolling action plan (CoRAP) for evaluation by Germany in 2018.

For identifying antimony compounds in ECHA's IUCLID database of registered substances, a text mining method was used to find antimony-relevant entries in the IUPAC name, CAS name, molecular formula, SMILES structure string, and other substance-identifying fields in the registration dossiers.

The outcome was a list of antinomy substances, for which registration information and other data that is available in the substance screening databases was added. The purpose was to provide relevant data in a meaningful reporting format, for the manual screening work in the Member States to have as powerful tools as possible.

Based on these IT algorithms, the following additional antimony compounds were identified in ECHA's IUCLID database.

EC number	CAS number	Substance name
215-175-0	1309-64-4	Diantimony trioxide
215-237-7	1314-60-9	Diantimony pentoxide
215-713-4	1345-04-6	Antimony sulphide
231-146-5	7440-36-0	Antimony
233-047-2	10025-91-9	Antimony trichloride
239-444-7	15432-85-6	Sodium antimonate
249-820-2	29736-75-2	2,5,7,10,11,14-hexaoxa-1,6-distibabicyclo[4.4.4]tetradecane
251-735-0	33908-66-6	Sodium hexahydroxoantimonate
232-353-3	8007-18-9	Antimony nickel titanium oxide yellow
269-052-1	68186-90-3	Chrome antimony titanium buff rutile
232-382-1	8012-00-8	Pyrochlore, antimony Lead yellow
270-185-2	68412-38-4	Manganese antimony titanium buff rutile
273-791-5	69029-45-4	Lead, dross, antimony-rich
273-795-7	69029-51-2	Lead, antimonial, dross
310-061-8	102110-60-1	Slimes and Sludges, battery scrap, antimony- and Lead-rich

403-500-0	159120-95-3	A mixture of: bis[4-diphenylsulfoniumphenyl]sulfide-bishexafluoroantimonate; thiophenoxyphenylsulfonium hexafluoroantimonate
404-420-9	71786-70-4	bis(4-dodecylphenyl)iodonium tetrafluoroantimonate
407-840-0	100011-37-8	(η-cumene)-(η-cyclopentadienyl)iron(II) hexafluoroantimonate
931-161-3	-	(diphenylsulfaniumyl)phenyl]sulfanyl}phenyl)diphenylsulfanium; tris(hexafluorostibanuide); {2-[(4-chlorophenyl)sulfanyl]phenyl}diphenylsulfanium
931-210-9	-	Aluminium silicate and titanium oxide matrix doted with vanadium, nickel, and antimony
939-456-9	-	Fluorchlorapatite doped with antimony and manganese

Of these substances, all the following ones were not included in the antimony compound group for the COLLA project.

EC Number	CAS Number	Substance Name		Tonnages tpa
232-353-3	8007-18-9	antimony nickel titanium oxide yellow		1000-10000
269-052-1	68186-90-3	chrome antimony titanium buff rutile	Pigments composed of several metals	10000-100000
232-382-1	8012-00-8	pyrochlore, antimony lead yellow		10-100
270-185-2	68412-38-4	manganese antimony titanium buff rutile		100-1000
273-791-5	69029-45-4	Lead, dross, antimony-rich	Dross	1000-10000
273-795-7	69029-51-2	Lead, antimonial, dross		1000-10000
310-061-8	102110-60-1	Slimes and sludges, battery scrap, antimony and lead rich	Transported isolated intermediate	
403-500-0	159120-95-3	A mixture of bis[4-diphenylsulfoniumphenyl]sulfide-bishexafluoroantimonate, thiophenoxyphenyl sulfonium hexafluoroantimonate		0-10; 10-100, confidential
404-420-9	71786-70-4	bis(4-dodecylphenyl)iodonium tetrafluoroantimonate	Low tonnage	confidential
407-840-0	100011-37-8	(η-cumene)-(η-cyclopentadienyl)iron(II) hexafluoroantimonate		confidential
931-161-3		(diphenylsulfaniumyl)phenyl]sulfanyl}phenyl)diphenylsulfanium; tris(hexafluorostibanuide); {2-[(4-chlorophenyl)sulfanyl]phenyl}diphenylsulfanium		10-100
931-210-9		Aluminium silicate and titanium oxide matrix doted with vanadium, nickel and antimony		10000-100000
939-456-9		Fluoroapatite doted with antimony and manganese		100-1000

The omitted substances were not included for the following reasons:

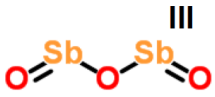
- Antimony is only present as a fraction in the listed pigments and effects observed cannot be clearly linked to antimony alone.
- Manufacture of three pigments seems to involve antimony trioxide, which is included in the COLLA pilot project.
- Dross, isolated intermediates or low tonnages are currently considered of lower concern to human health in a first attempt of implementing COLLA.
- Use as doting agent – antimony is present in a very small percentage in the doting agent.
- Because of resource and time limitations, only a limited number of substances could be included in the project.

The following remaining substances were selected as a group suitable for the COLLA pilot project.

EC Number	CAS Number	Substance Name	Tonnages tpa
215-175-0	1309-64-4	diantimony trioxide	10000+
215-237-7	1314-60-9	diantimony pentoxide	100 – 1000
215-713-4	1345-04-6	antimony trisulphide	100 – 1000
231-146-5	7440-36-0	antimony	10000 – 100000
233-047-2	10025-91-9	antimony trichloride	1 – 10
239-444-7	15432-85-6	sodium antimonate	10 – 100
249-820-2	29736-75-2	2,5,7,10,14-hexa oxa-1,6-distibabicyco[4,4,4]tetradecane	100 – 1000
251-735-0	33908-66-6	sodium hexahydroxoantimonate	1000 - 10000

This group was further divided into three groups: elemental antimony, trivalent antimony compounds, and pentavalent antimony compounds.

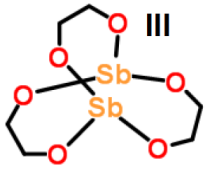
trivalent antimony compounds with Sb_2O_3 as reference:



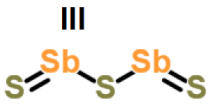
diantimony trioxide, Sb_2O_3,
CAS#: 1309-64-4, EC#: 215-175-0

oxidised to

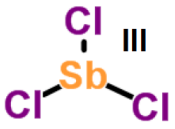
antimony metal, Sb
CAS#: 7440-36-0, EC#: 231-146-5



diantimony tris(ethylene glycolate),
$C_6H_{12}O_6Sb_2$, CAS#: 29736-75-2
EC#: 249-820-2

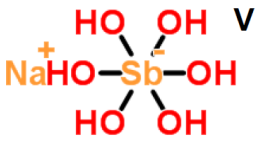


antimony trisulphide,
Sb_2S_3, CAS#: 1345-04-6,
EC#: 215-713-4

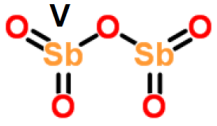


antimony trichloride, $SbCl_3$,
CAS#: 10025-91-9,
EC#: 233-47-2

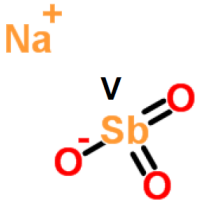
pentavalent antimony compounds with $NaSb(OH)_6$ as reference:



sodium hexahydroxoantimonate,
$NaSb(OH)_6$, CAS#: 33908-66-6,
EC#: 251-735-0



diantimony pentoxide,
Sb_2O_5, CAS#: 1314-60-9,
EC#: 215-237-7



sodium antimonate,NaO_3Sb,
CAS#: 15432-85-6,
EC#: 239-444-7

3. Initial concerns

At least one substance in the group of antimony compounds may possess hazardous properties due to (suspected) carcinogenic properties, high RCR, and other exposure/risk based concerns.

Furthermore, based on the use profile from all the related registrations, significant exposure of humans or the environment to at least some of the substances in the identified group cannot be ruled out.

3.1 Previous regulatory activities

Substance name	EC number	Previous regulatory activities
Antimony	231-146-5	Harmonised C&L (group entry, index number: 051-003-00-9), CCH, RL 2009/48/EC (Substances restricted in Toys), CoRAP 2018
Diantimony trioxide	215-175-	Harmonised C&L (index number: 051-005-00-X), 10/2011/EC (Food Contact Regulation), Existing substances Regulation No. 793/93, CoRAP 2018
Antimony trisulphide	215-713-4	CoRAP 2018
Antimony triglycolate	249-820-2	Harmonised C&L (group entry, index number: 051-003-00-9), CoRAP 2018
Sodium hexahydroxoanti-monate	251-735-0	Harmonised C&L (group entry, index number: 051-003-00-9), CCH, TPE.
Sodium antimonate	239-444-7	Harmonised C&L (group entry, index number: 051-003-00-9).
Antimony trichloride	233-047-2	Harmonised C&L (index number: 051-001-00-8), CoRAP 2018.

4. Project organisation and approach

4.1 Actors and roles

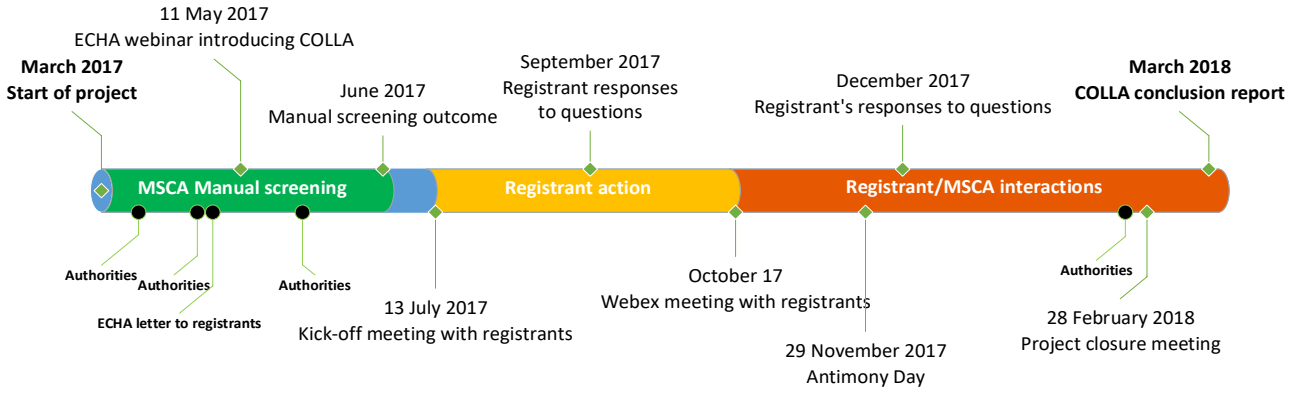
Member States: German competent authority took the lead for the assessment; Lithuanian competent authority acted as an observer.

Registrants: The International Antimony Association (i2a) took the lead and represented the registrants of the antimony compounds addressed within the COLLA project. The lead registrants were also directly involved in the project.

ECHA: Provided support in coordinating the project as well as expertise in toxicology.

4.2 Timelines and milestones

The timeline below shows the duration of the different stages of the COLLA project and the main deliverables for each step.



The manual screening lasted until the end of June 2017 and marked the conclusion of the initiation phase of the COLLA project. The implementation phase started with the kick-off meeting with the lead registrants, where the assessing MSCA communicated all the identified issues in this group of substances. Registrants provided an initial response to questions raised by the MSCA on 1 September 2017, and complementary and more extensive on 11 December 2017, following the exchange with the German competent authority on 12 October.

Finally, clarifications, further actions for the registrants and a testing strategy were recorded in the project closure meeting on 1 March 2018.

4.3 Interactions

All meetings were held as WebEx teleconferences, except for the kick-off meeting with the lead registrants, which was a physical meeting hosted by the German competent authority on 13 July 2017 at its premises in Dortmund, Germany. In addition, the authorities were invited to take part in the 'Antimony Day' hosted by i2a in Brussels on 29 November 2017.

Intense communication between authorities and registrants after the kick-off meeting served to clarify questions raised by authorities and to provide feedback to registrants whenever information was provided.

5. Work undertaken

The manual screening was performed by the German competent authority. It covered human health issues and exposure. A data matrix with all the observations was compiled.

Before the kick-off meeting, the German competent authority submitted questions to industry. In the kick-off meeting, the German competent authority presented an overview on the data for the antimony compounds group. The available data on short-term toxicity as well as on repeated dose toxicity, developmental toxicity, fertility, genotoxicity and carcinogenicity were summarised and toxicological data gaps as well as the insufficiently documented read-across justifications were indicated.

Formal data gaps were identified for the endpoint reproductive toxicity. For other endpoints for several substances within the group, the read-across justification and its accordance with the Read-Across Assessment Framework (RAAF) needed further assessment.

Due to lung toxic effects of one compound, based on data for acute toxicity and repeated dose toxicity, the possibility for STOT-SE/RE classification was discussed.

i2a compiled data for the kick-off meeting where the German competent authority submitted a catalogue of questions mainly related to:

- the bioavailability of the individual antimony compounds (relevant for read-across assessment);
- adequacy of read-across between the pentavalent and trivalent antimony compounds with regard to carcinogenic potential and repeated dose toxicity in view of probable differences in toxicokinetics; and
- mode of action of lung carcinogenicity (related to particles and/or soluble metal ions).

In addition to that, the German competent authority presented a list of topics concerning worker exposure and use related issues which were briefly discussed. It was highlighted that the exposure scenarios are very generic, covering a broad array of activities and tasks. In addition, it was pointed out that information on the particle size distribution in the workplace air with respect to the respiratory fraction – preferably measured data – is desirable. Industry was also asked if other or more recent measurement data are available that were not considered in the chemical safety report.

The open questions on exposure of specific substances could not be discussed in detail at the kick-off meeting due to the confidentiality of exposure information. Instead, chemical safety report-specific questions were sent to the different registrants in writing after the kick-off meeting. As the answers to these questions were submitted later, the clarification of exposure and toxicological issues was not synchronous.

The questions raised prior to and at the kick-off meeting were answered by i2a on 1 September 2017. At the end of August, the German competent authority submitted further substance-specific questions to i2a with regard to worker and consumer exposure; further questions were submitted prior to and during the WebEx in October 2017. I2a answered these questions in December 2017. The final feedback provided by the German competent authority to i2a on 22 February 2018 was discussed on 1 March in the final WebEx meeting.

On 29 November 2017, ECHA and the German competent authority also took part in the 'Antimony Day' hosted by i2a, where the representatives of the authorities and the supply chain discussed antimony-related issues.

6. Project outcomes

6.1 Screening outcome and regulatory/testing plan

Registration dossiers for the three Community rolling action plan (CoRAP) entries for antimony metal, antimony trioxide and antimony trisulphide will be updated as soon as possible after 31 March 2018. For the human health part, different key studies were identified and being amended at IUCLID level, resulting in new DNELs and taking into account a new read-across approach. The read across justification for the human health endpoints will include justifications following ECHA's current Read-Across Assessment Framework (RAAF) guidance document. For the two remaining trivalent substances, antimony trichloride and antimony triglycolate, added to CoRAP in late 2017, i2a informed that the dossiers will be updated as soon as possible.

A new questionnaire for data on worker exposure was sent out by i2a to producing and using companies. Originally, the incorporation of human biomonitoring and air monitoring had been considered for the starting phase, however, due to different levels of awareness among participants and to the complexities of human biomonitoring, i2a decided to initially focus solely on air monitoring. This is in agreement with the priorities of the German competent authority for the upcoming substance evaluation.

There was agreement that antimony compounds are outside the applicability domain of QSAR to inform on read-across. As regards genotoxicity, enough in vitro and in vivo data seem to be available to compare Sb substances in this regard. The goal of i2a's current programme is the validation of a method for Sb quantification and speciation in workplace, testing, and biological samples, following a tiered approach.

BfR expressed interest in the Epithelix model proposed by i2a to compare the lung toxicity potential of antimony substances, but clarified that it could currently only serve as supporting information and not as an alternative to animal tests because this would require an official validation of the assay. To validate this assay, in vivo data for multiple substances would be necessary to eventually extrapolate from Epithelix results to avoid further animal testing. During the substance evaluation, further reflection on the suitability of assay testing compared to in vivo testing would be made by the authorities to decide on further information requests.

The justification for read-across with regard to reproductive toxicity in the updated dossiers will be based on the current RAAF document by ECHA. i2a indicated that they still planned to follow a weight-of-evidence approach for this endpoint. This will be documented in the updated dossiers and subsequently be subject to scrutiny under substance evaluation.

i2a indicated that the updated chemical safety reports for the three existing CoRAP entries will contain more specific exposure scenarios which will serve as the basis for substance evaluation and further refinement.

Regarding the monitoring programme on worker exposure, i2a considers the generation of first data as from the beginning of 2019 feasible, depending on the generation of data by the monitoring partners. While the monitoring is initially focused on the inhalative exposure route, the risk assessment under substance evaluation will cover both dermal and inhalative exposure.

Regarding consumer exposure, it was not possible to gather additional measured data from the registrants or the downstream user associations contacted by i2a and no monitoring was initiated.

i2a would appreciate if Germany could submit formal letters to raise awareness and willingness for participation among downstream users involved in the respective sectors. The German competent authority considered it possible for these supporting letters to be sent during the evaluation year. Regarding antimony compounds in consumer articles, i2a is currently organising the contribution to ECHA's plastics additive project. The information will be used for the creation of an inventory of additives, scheduled by ECHA for April 2018, for which information collection is still ongoing. The finalised inventory will be used for a ranking based on the release potential from plastics matrices according to a computational model currently under development. It should however be noted that the ranking shall not be directly used for exposure assessment.

The publication of the CoRAP for 2018-2020 on 20 March 2018 marked the official start of evaluation for the five trivalent antimony compounds included in the CoRAP – three existing entries (antimony metal, antimony trichloride and antimony triglycolate) as well as two new entries, antimony trichloride and antimony triglycolate.

6.2 Initial reflections on lessons learnt and best practices recommended for the future

Necessary toxicological information can only be requested on the basis of a formal REACH process. Concerning workplace exposure and uses, updates of the registration dossiers are announced. It is not yet clear if the quality of data will be improved and if missing information

will be de delivered by the updates. In any case, industry is aware of the topics that are of specific concern. Mutual understanding was increased by the project. An exchange within the supply chain was also initiated.

In addition, a workplace monitoring programme is planned. Industry offered to keep German authorities informed about the progress of the programme. This is highly appreciated by the authorities.

The group justification document was not considered adequate for the purposes of this project.

Substance evaluation is still necessary. Two additional trivalent antimony substances were added to the CoRAP.

From the authorities' perspective, the interaction with ia2, one main representative from industry for the group, was considered very beneficial. Nevertheless, the workload resulting from the assessment of a group of substances in a limited timeframe was considerable. Regarding potentially confidential information on uses and exposure, namely chemical safety reports, an interaction with the respective registrants was also required. A collaborative or group-based approach may not be the best way forward in every case and is highly dependent on the cooperation of the parties involved.

Specifically, it was concluded by German competent authority that at this stage it is uncertain whether COLLA can help to increase efficiency of regulatory actions. Formal REACH processes are still necessary to request new data. It is necessary to carefully consider on a case-by-case basis whether a group-specific screening according to COLLA is beneficial. Additionally, group boundaries should be clarified, and read-across and grouping justifications should be assessed and ideally also confirmed by ECHA beforehand.

One disadvantage of the collaborative approach is that also substances of lower concern may need to be assessed, and in cases where the outcome is that no further regulatory action is recommended, there is no benefit from investing more resources at the beginning. Thus, a benefit of regulatory outcome would have to be expected from the approach.

i2a elaborated that the activities, while conceived regardless of COLLA, were certainly boosted by the project and allowed for an acceleration of the necessary steps. One registrant agreed that participating in the COLLA project improved the development and considerations of the ongoing activities. However, i2a pointed out that the activities are not harmonised beyond the EU and actors from industry have to deal with requirements on a global scale, which contributes to their workload. Nevertheless, i2a considered the underlying group approach of COLLA beneficial and even necessary.

Appendix 3: COLLA project closure report for polyol acrylates

1. Introduction

The project closure report summarises the information on the group of polyol acrylates addressed in the collaborative approach (COLLA) pilot project, their suspected concerns and potential information gaps, as well as previous regulatory activities on them.

The reports also outlines how the project was run and what its outcome was in terms of a regulatory plan for the group of substances.

2. Group description

2.1 Group formation

The group was proposed by ECHA based on read-across linkages in the registration dossiers of the substances. The group consists of esters of acrylic acid with polyols and, in total, seven substances were identified (see table below)

Shortlist number	EC number	Substance name	Abbreviation
138	302-434-9	2-[[2,2-bis[[(1-oxoallyl)oxy]methyl]butoxy]methyl]-2-ethyl-1,3-propanediyl diacrylate	Di-TMPTTA
139	239-701-3	2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate	TMPTA
140	235-921-9	Hexamethylene diacrylate	HDDA
141	256-032-2	(1-methyl-1,2-ethanediyl)bis[oxy(methyl-2,1-ethanediyl)] diacrylate	TPGDA
142	500-066-5	Propylidynetrimethanol, ethoxylated, esters with acrylic acid	TMPeoTA
143	500-114-5	Glycerol, propoxylated, esters with acrylic acid	GPOTA
144	601-566-7	2-[2-[2-[2-(1-methyl-2-prop-2-enoyloxy-ethoxy)ethoxymethyl]-2-[2-(2-prop-2-enoyloxypropoxy)ethoxymethyl]butoxy]ethoxy]propyl prop-2-enoate	Laromer PO 33F

2.2 Initial concerns

The initial concern for this group of substances was potential vPvB properties considering that substance with shortlist number 138 was suspected to have persistence and bioaccumulation properties based on experimental data and modelling predictions. Furthermore, based on the use profile from all the related registrations, significant exposure for humans and/or the environment could not be ruled out.

2.3 Previous regulatory activities

The majority of the substances in this group have been under some scrutiny already. Substance with shortlist number 138, the group seed substance, is the only one that had not.

Substance 139 was subject of a substance evaluation performed by the French competent authority and substances 141 and 144 were subject to compliance checks according to ECHA's current regulatory strategy.

The scrutiny of the substances with shortlist numbers 140, 142 and 143 was targeted and mostly related to substance identity issues.

3. Project organisation and approach

3.1 Actors and roles

Member States

Member State	Role
Germany	Lead
Ireland	Partner
Luxembourg	Partner

The work was distributed as follows:

- The German competent authority, supported by the Luxembourgish competent authority, assessed the environmental part of the registration dossiers.
- The Irish competent authority assessed the human health part of the registration dossiers.

Each Member State competent authority nominated a key contact person and coordinator, but additional experts participated in the project and meetings.

ECHA

ECHA provided support in coordinating the project as well as expertise in (eco)toxicology and substance identification.

Registrants

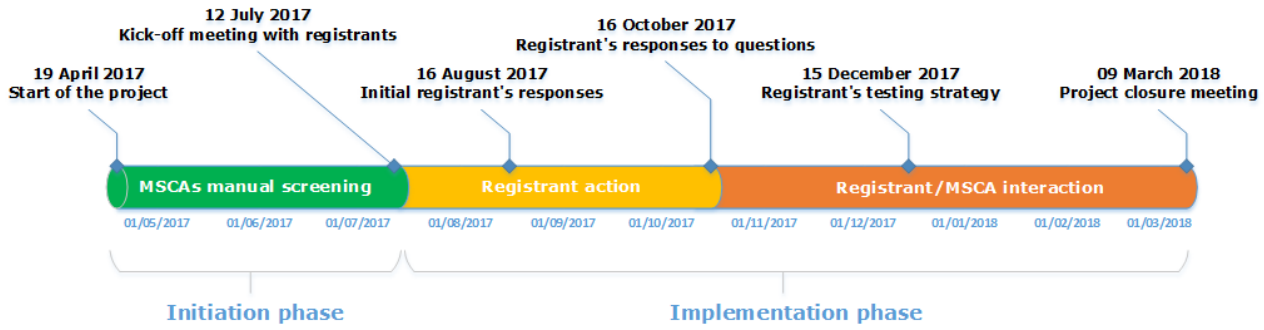
EC number	Abbreviation	Lead registrant	Tonnage band
302-434-9	Di-TMPTTA	Allnex Belgium NV/SA	100-1000
239-701-3	TMPTA	KIST Europe Forschungsgesellschaft mbH	>1000
235-921-9	HDDA	BASF SE	>1000
256-032-2	TPGDA	BASF SE	>1000
500-066-5	TMPeoTA	KIST Europe Forschungsgesellschaft mbH	>1000
500-114-5	GPOTA	BASF Health and Care Products France S.A.S.	>1000
601-566-7	Laromer PO 33F	BASF SE	100-1000

The lead registrants for all seven substances (see table above) were invited to participate in the COLLA project. Representatives of the seven substances participated throughout the duration of the project.

Participating registrants were organised in a consortium (PARAD Consortium) with one principal contact, but several experts participated in the meetings and contributed to the project.

3.2 Timelines and milestones

The timeline below shows the duration of the different stages of the COLLA project and the main deliverables for each step.

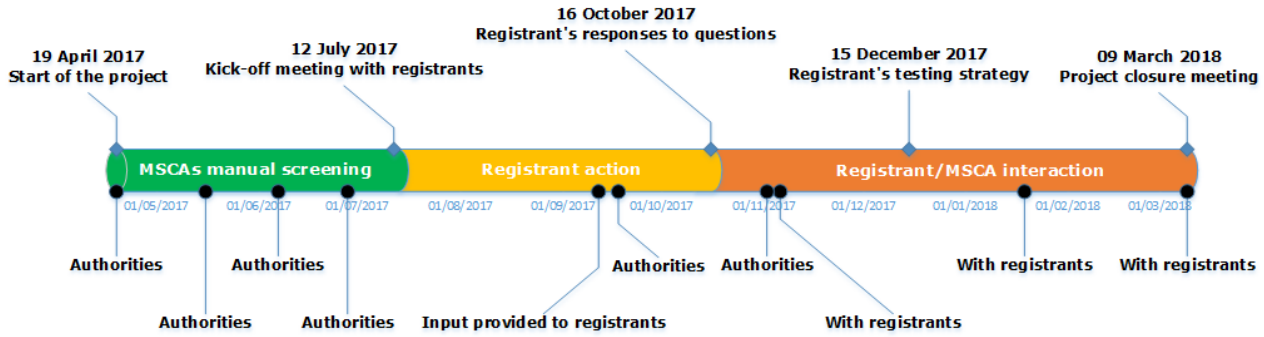


The manual screening lasted until the end of June 2017 and marked the conclusion of the initiation phase of the COLLA project. The implementation phase started with the kick-off meeting with the registrants, where the MSCAs communicated all the identified issues for this group of substances. Registrants provided an initial response to questions raised by the MSCAs on 16 August 2017, but the final responses to the questions were provided on 16 October 2017, considering the input received by MSCAs on 12 September 2017.

After further interactions and clarifications, a testing strategy was agreed in the project closure meeting on 9 March 2018.

3.3 Interactions during the project

The timeline below shows the meetings during the project. All the meeting were held as WebEx teleconferences except for the kick-off meeting with the registrants, which was a physical meeting hosted by the German competent authority on 12 July 2017 at its premises in Dortmund, Germany.



MSCAs and ECHA met several times during the initiation phase. This was necessary to clarify roles and tasks and align views.

Several meetings between authorities and registrants after the kick-off meeting served to clarify questions raised by authorities and provide feedback to registrants whenever information was provided.

4. Work undertaken

As previously mentioned, the manual screening work was divided between Member States – while the competent authorities of Germany and Luxembourg assessed the environmental part, the competent authority of Ireland assessed the human health part.

Different assessors in the competent authorities of Germany and Luxembourg performed individual assessments of the substances, after which these were considered together to account for the group of substances. This was done by compiling a data matrix containing all the observations.

The Irish competent authority followed a similar approach, and individual assessments were done for the substances before considering the group as a whole. A data matrix was subsequently compiled, highlighting data gaps and the use of read-across.

The initial concern on PBT properties was not confirmed by the assessment. Some information was requested to clarify the concerns in this regard.

The initial observations for the human health endpoints highlighted that although the registrants did not explicitly pursue a category approach, the links made with analogue read-across approaches indicated that the registrants proposed a category read-across *de facto*. However, the lack of data and a robust read-across justification did not allow for the verification of the plausibility of the read-across approaches.

The registrants provided an initial response to the observations on the human health endpoints on 16 August 2018. The registrants proposed subgrouping of the substances with the inclusion of additional substances and an example of a read-across justification to use to justify the different subgroups. Considering the feedback provided by the authorities to this initial response, the registrants then provided their responses to the issues highlighted by the authorities by the agreed deadline on 16 October 2018. In this response, the registrants reorganised the substances and proposed a new subgrouping removing all the previously proposed additional substances with the exception of one. To further support the read-across, the registrants also proposed to generate bridging data in the form of screening studies according to OECD test guideline 422 for those substances that did not yet have such data – substances with shortlist numbers 141, 142 and 143.

By the project closure meeting on 9 March 2018, the initial concern on PBT properties was already clarified and not substantiated. In addition, the registrants provided a testing plan including proof of having already commissioned the OECD test guideline 422 studies.

5. Project outcomes

5.1 Screening outcome and regulatory/testing plan

As a result of this project, the initial concern on PBT properties was clarified and not substantiated. With regard to the human health endpoints, the registrants suggested the following substances (indicated using the COLLA shortlist number) to be considered under the four subgroups based on structural similarity:

- Group 1: Substances 140 and 141
- Group 2: Substances 142, 143 and 144
- Group 3: Substance 138
- Group 4: Substance 139

It is worth noting that the additional substance included in the subgrouping proposed on 16

October 2018 was not included in the final subgrouping proposed by the registrants. In addition, the registrants voluntarily committed to generate bridging data through screening studies according to OECD test guideline 422 to further support and validate the read-across approaches. The registrants provided proof of having already commissioned these studies. The bridging data will be available by the end of 2018.

For groups 1 and 2, it was agreed that the registration dossiers will be updated by Q1 2019, with the results of the bridging data and either a read-across justification or, in the case that the read-across no longer holds, the appropriate testing proposals.

For substance 138, it was agreed that the registration dossier will be updated by Q3 2018 with testing proposals to address the data gaps in human health endpoints.

For substance 139, no further action was foreseen in addition to the ongoing substance evaluation.

5.2 Initial reflections on lessons learnt and best practices recommended for the future

A physical kick-off meeting was seen as a positive aspect of the collaborative approach. However, the initial reflections seem to show that registrants' expectations were not met. For example, it was expected that the authorities could already decide during the project if the read-across was acceptable or not.

Outcomes of the collaborative approach identified by the authorities were that the PBT concern was clarified and the read-across approaches for the human health endpoints are now stronger than they were before.

Appendix 4: COLLA project closure report for substituted diphenylamines

1. Introduction

The project closure report summarises the information on the group of substituted diphenylamines (SDPAs) addressed in the collaborative approach (COLLA) pilot project, their suspected concerns and potential information gaps, as well as previous regulatory activities on them.

The report also outlines how the project was run and what its outcome was in terms of a regulatory plan for the group of substances.

2. Group description

2.1. Group formation

The COLLA project on SDPAs covered the substances presented below.

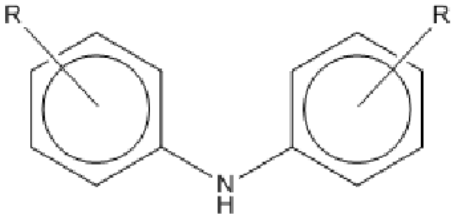
EC number	CAS number	Substance name
239-816-9	15721-78-5	Bis(4-(1,1,3,3-tetramethylbutyl)phenyl)amine
253-249-4	36878-20-3	Bis(nonylphenyl)amine
270-128-1	68411-46-1	Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene
204-539-4	122-39-4	Diphenylamine
233-215-5	10081-67-1	4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]aniline
272-940-1	68921-45-9	Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene
270-485-3	68442-68-2	Benzenamine, N-phenyl-, styrenated

SDPAs are widely used lipophilic antioxidants mostly used in lubricants. As stated in the 2016 OECD report[4] based on a previous work carried out by Canada[5], they are made up of a diphenylamine core and one to four alkyl or phenyl side chains. The common synthetic pathway for the production of SDPAs is through an electrophilic aromatic substitution reaction

[4] OECD (2016). Case study on the use of integrated approaches for testing and assessment for repeat dose toxicity of substituted diphenylamines (SDPA). OECD Series on Testing & Assessment, No. 252. ENV/JM/MONO(2016)50. https://one.oecd.org/document/ENV/JM/MONO(2016)50/en/pdf
[5] Screening Assessment for Substituted Diphenylamines. Environment and Climate Change Canada. Health Canada. December 2017. https://www.canada.ca/content/dam/eccc/documents/pdf/pded/sdpas/English%20Screening%20Assessment%20for%20Substituted%20Diphenylamines1.pdf .

between an olefin and diphenylamine (DPA) through reductive alkylation. The starting material, DPA, is reacted with an olefin in the presence of hydrogen. The resulting reaction product is typically purified by distillation[6].

The general structure of SDPAs is presented in the figure below. The amine group acts as an electron donating group and therefore the electrophilic aromatic substitution by alkenes of DPA will occur at the para-position (preferred) and/or ortho-position to the amine. SDPAs in the subgroups further described below have 1 to 4 substituents on the diphenylamine core. The chemical structures of SDPAs vary according to the olefin used for synthesis, the manufacture process, and the number and position of substituents on the aromatic ring. Therefore most SDPAs are UVCB-type substances. However, in the grouping there are substances where the position and branching pattern of the side chain is specified in the chemical name (e.g. benzenamine, 4-(1,1,3,3-tetramethylbutyl)-N-[4-(1,1,3,3-tetramethylbutyl)phenyl]-).”



R - branched alkyl or phenyl groups

In the 2016 report by OECD it is proposed for the human health assessment (specifically for oral repeat-dose toxicity) to create subcategories to allow read-across between the members of a subcategory. OECD has defined four different subgroups into which the different substances evaluated in this COLLA project are distributed:

- **Subgroup 1 - Monoalkylated SDPAs**: None of the substances of the group addressed in this project belongs to this subgroup.
- **Subgroup 2 - SDPAs with variable number of alkyl substitutions**: EC number 270-128-1 (UVCB, CoRAP/DE) and EC number 253-249-4 (UVCB, CoRAP/FR).
- **Subgroup 3 – Dialkylated SDPAs**: EC number 239-816-9 (mono-constituent; group seed).
- **Subgroup 4 - SDPAs with variable number of phenyl substitutions**: EC number 270-485-3 and EC number 233-215-5 (both mono-constituents, group members).
- **SDPA mixture with variable number of alkyl and phenyl substitutions** not considered part of a broader subgroup: EC number 272-940-1 (UVCB, group member).

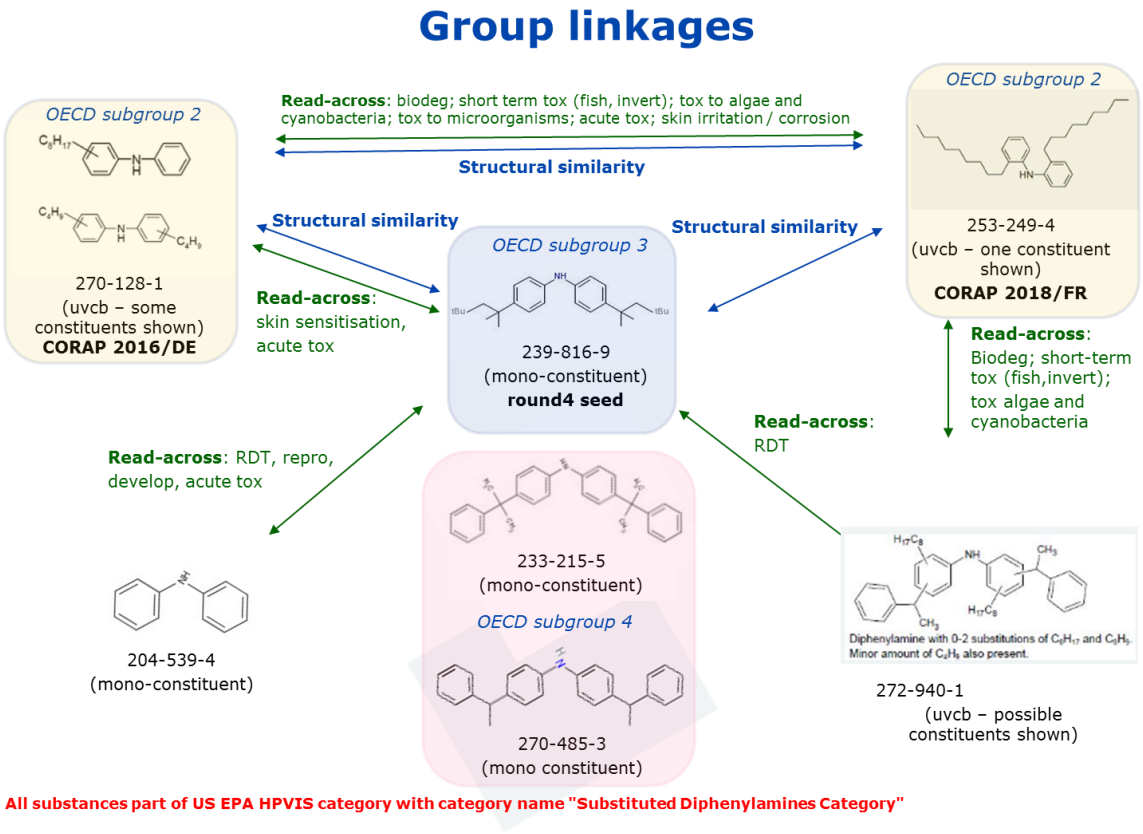
The hypothesis is that although all substances share a common diphenylamine substructure, there are structural differences related to the degree of substitution and nature of the side chains. These differences correlate to observed differences in the physicochemical properties and predicted toxicokinetics parameters. As a result, the SDPAs have been sub-grouped based on structural considerations of the side chains, namely the number of substitutions on DPA and type (alkyl vs. phenyl) as well as composition for UVCBs. The members within each subgroup are considered structurally close. The OECD also considered the structurally related changes to properties including molecular weight, logKow, and predicted oral bioavailability as the basis for forming subgroups.

[6] Substituted Diphenylamines Category Justification and Testing Rationale – Rubber and Plastic Additives Panel, American Chemistry Council, 2003. Submission to the US EPA under the HPV Chemical Challenge Program, Merrifield VA.

This approach is relevant for assessment of the group members and may be an interesting starting point for defining relevant subgroups among the different substances addressed in this COLLA group. The subgroups may be different for human health and environment, since they may not be based on the same properties/effects.

Substances within the present group under screening are the registered substances that fulfil this structural definition. Diphenylamine (DPA), although not substituted, contains the same functional groups that can be relevant in a mode-of-action analysis for the remaining members of the group under assessment. However, due to the toxicokinetic differences (different metabolism) between DPA and the SPDAs and some different target organs in the available studies, it is considered at this stage that DPA did not need to be further assessed within this project.

The linkages between the group members can be seen in the diagram below.



2.2. Initial concerns

Screening of these substances started based on the suspected PBT and mutagenicity concerns identified for some of the group members.

2.3. Previous regulatory activities

Many of the SDPA group substances have been under some scrutiny already and subject to dossier and substance evaluations. These are summarised in the table below. See main chapter 10 for abbreviations.

	RMOA	REACH process			Authorisation		Restriction	CLH	Process under other EU legislation		Previous legislation		Other processes under EU legislation
EC number		CCH	TPE	SEv	Candidate List	Annex XIV	Annex XVII	Annex VI (CLP)	PPP	BPR	NONS	RAR	
239-816-9	No	No	Yes	No	No	No	No	No	No	No	No	No	No
253-249-4	No	yes	yes	yes	No	No	No	No					
270-128-1	No	yes	yes	yes	No	No	No	No					Yes
204-539-4	No	No	No	No	No	No	No	Yes	No	No	Yes	yes	Yes
233-215-5	No	Yes	Yes	Not yet	No	No	No	No	No	No	No	No	No
272-940-1	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No
270-485-3	No	No	No	No	No	No	No	No					Yes

3. Project organisation and approach

3.1. Actors and roles

Member States

Member State	Role
France	Lead
Slovenia	Partner

The lead Member State was France, supported by the partner Member State Slovenia. The Member State competent authorities nominated a key contact person and coordinator, but additional experts also participated in the project and meetings.

As the lead Member State, France coordinated the project, but expertise was provided by both Member States, specifically regarding human health, environment and exposure.

ECHA

ECHA provided general support in coordinating the project as well as expertise in toxicology, environment, substance identification and computational assessment.

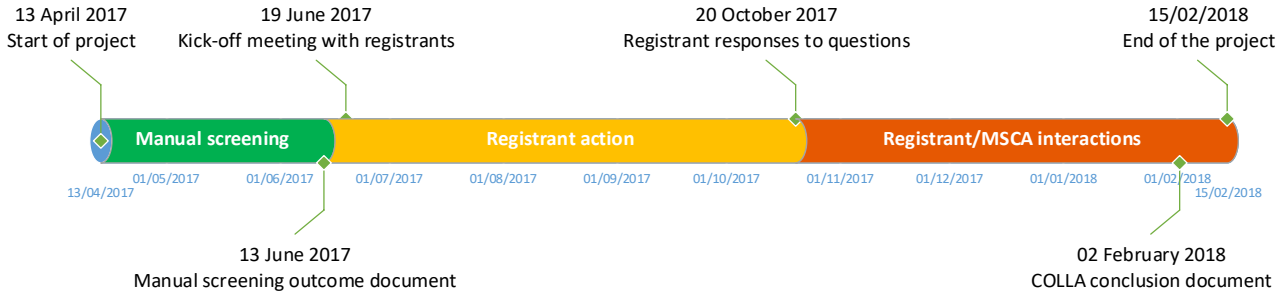
Registrants

No.	Substance name	EC number	Lead registrants
1	Bis(4-(1,1,3,3-tetramethylbutyl)phenyl)amine	239-816-9	Sustainability Support Services (Europe) AB The Acta Group EU, LTD (1)
2	Bis(nonylphenyl)amine	253-249-4	BASF SE
3	Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene	270-128-1	BASF SE
4	Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene	272-940-1	Chemtura Manufacturing UK Ltd (CA02)
5	4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]aniline	233-215-5	Addivant UK Ltd (USAA)
6	Benzenamine, N-phenyl-, styrenated	270-485-3	Sustainability Support Services (Europe) AB

The registrants for substances indicated in the table above were invited to participate in the COLLA project. Representatives of five substances participated throughout the project, but the manufacture of EC 272-940-1 was ceased after the kick-off meeting.

There was no consortium or equivalent cooperation among the participating registrants.

3.2. Timelines and milestones



The timeline above shows the duration of the different stages of the project and the main deliverables for each step. The manual screening phase lasted until mid-June, with the draft manual screening outcome document provided to registrants on 13 June 2017. Lead registrants for three substances provided responses to questions raised in the manual screening outcome document through the submission of a registration dossier update by 20 October 2017 (with one update received with a slight delay). MSCAs then provided the final COLLA group screening report in early February 2018.

3.3. Interactions during the project

The timeline above shows the meetings and other interactions during the project. All meetings were held as teleconferences except the kick-off meeting with registrants, which was a physical meeting hosted by the French competent authority ANSES in Paris on 19 June 2017.

At the beginning of the project, registrants were contacted by ECHA in early May 2017, and they participated in the webinar organised by ECHA on 11 May 2017 introducing the collaborative approach and pilot projects. MSCAs and ECHA met several times during the project, especially during the manual screening phase.

4. Work undertaken

The Slovenian competent authority screened more deeply two of the substances (EC 272-940-1 and EC 204-539-4), while the French competent authority screened the rest of the substances but held several exchanges regarding the entire group. The screening entailed compiling data matrices with the data relevant for the suspected concerns. ECHA supported

the MSCAs with expert reviews of the draft screening outcomes and with QSAR predictions for PBT at the constituent level.

During the kick-off meeting on 19 June 2017, the French and Slovenian competent authorities presented an overview of the screening performed and the main questions raised on some or all the SPDAs in order to clarify the different concerns on the substance group. Following discussion on these issues, the concerned registrants were asked to provide better information in their respective dossiers to address the issues raised in the draft screening report. The authorities sought improvement from registrants (as dossier updates by 20 October 2017) on the following information:

- Substance identity and UVCB compositions, since this is important for the PBT assessment and for the identification (by means of QSAR predictions) of the worst-case constituent(s) representative for their registered substances.

- For environment issues, the next step will then be to identify the worst constituent(s) for PBT characterisation and which degradation simulation studies are still needed for the SDPA group and which experimental BCF values need to be generated.

- Regarding the concerns on human health hazards, authorities asked the registrants to explore the possibility of applying the OECD subgrouping approach used for the RDT endpoint also to the other endpoints of concern. Registrants can then propose which substances need to be further tested within each subgroup to cover the data gaps indicated. Registrants were also invited to consider the liver/thyroid effects observed in the different RDT studies and whether classification is needed.

- For exposure-related issues, registrants were invited to consult the R14 guidance for the best approach to follow and to update the exposure assessments accordingly.

Dossier updates with responses to the questions raised by MSCAs were submitted only for EC 253-249-4, EC 271-128-1 and EC 239-816-9. The French competent authority consequently screened the new information provided by December 2017 and updated the group screening report accordingly in January 2018, including also a proposal for a regulatory/testing plan for the SDPA group (see Chapter 5).

The updated final screening report was shared with the contributing registrant in early February and was discussed at the project closure teleconference meeting on 15 February 2018.

5. Project outcomes

5.1. Screening outcome and regulatory/testing plan

The overall hazard and exposure findings of the substances belonging to the group, based on the MSCA screening and the further information provided by some of the registrants, are presented below.

Substance identity

No new information was received and there is no remaining concern.

Environment

A further QSAR analysis was done on the bioaccumulation potential of the constituents. Since several evaluation processes are ongoing, at the moment it is not possible to conclude on the

PBT concern for the different substances. However, the additional data provided during the ongoing evaluation processes (compliance check, substance evaluation), especially for UVCB substances, will allow to identify the constituents of highest concern.

Human health

Only a few dossier updates were received during the project providing further information related to human health. Based on the new information received for bis(4-(1,1,3,3-tetramethylbutyl)phenyl)amine (group seed, EC 239-816-9), it was concluded that the information requirements may be not fulfilled by some registrants depending on acceptance of read-across approach. This is related to that read-across within OECD subgroup 3 is supported by recent data but it is more uncertain with other SDPAs. A low bioavailability is expected, meaning that this substance may not be a worst-case/priority within the SPDA category. There is a remaining concern on toxicity to reproduction for this substance.

For EC 253-249-4 and EC 270-128-1, the conclusions for the human health part are that suspected concerns may be partially addressed once the studies requested in the ongoing compliance checks becomes available.

The following overall conclusions were made on the human health-related aspects of the assessment:

- Read-across is possible only among substances which belong to the same OECD subgroup.
- Some new information was received for the group seed, but information on EC 270-485-3 is missing.
- Original concerns remain for some subcategories:
    - Effects on liver: Classification as STOT RE seems warranted for some subgroups, especially subgroup 2.
    - Effects on thyroid: Needs to be clarified for substances from subgroup 2.
    - Concern for development: Remains for substances belonging to subgroups 2 and 3.
    - Concern for mutagenicity: Remains for substances belonging to subgroup 3.

Exposure

No new information was received on exposure, therefore the previous conclusions remain: ECETOC TRA model based exposure estimation is not suitable for sprayed non-volatile substances nor for a UVCB. High RCR for some scenarios and, if measurements exist, it can be added to the registration dossiers.

Since there are several already ongoing evaluation processes for group members, there is a need to wait for the new data to draw firm conclusions. No new compliance checks or testing proposals are needed to address missing information related to the current concerns. At the moment, the initial concerns for PBT/vPvB and mutagenicity remain and new concerns for thyroid effects and possible developmental effects were identified. Regarding the possible regulatory strategy, some substances may need to be included in the CoRAP when PBT data is available, and the classification of some substances as STOT RE may be warranted and is to be considered during the processes that are ongoing and that will follow.

5.2. Initial reflections on lessons learnt and best practices recommended for the future

There is no consortium for the SDPAs and therefore collaboration was not very easy for the registrants.

Some registrants felt that the different COLLA meetings were held too early, since a significant amount of data is still missing. The work will be easier when more information will be available and it will be possible (or not) to make references between substances and to draw sound conclusions. However, it is still beneficial to have an overview on the already ongoing processes for the group members.

For the next COLLA round, the substances should perhaps be more carefully chosen.

The collaborative approach was initiated to enhance also the collaboration between ECHA and MSCAs. This goal was achieved.

Appendix 5: COLLA project closure report for S-ligand organotin compounds

1. Introduction

The project closure report summarises the information on the group of S-ligand organotin compounds addressed in the collaborative approach (COLLA) pilot project, their suspected concerns and potential information gaps, as well as previous regulatory activities on them.

The reports also outlines how the project was run and what its outcome was in terms of a regulatory plan for the group of substances.

2. Group description

2.1. Group formation

The group chosen is a subgroup of organotin compounds and was proposed by the Netherlands. The subgroup consists of REACH-registered disubstituted organotins with a thio bond (S-ligands) and those monosubstituted organotins manufactured with them. In total, eight substances were identified (see table below).

In addition to the eight substances covered here, there are 26 other organotin substances registered under REACH and many more notified to the C&L Inventory. Authorities are not working on the S-ligands in isolation, but other organotin substances have for some time been under scrutiny by several Member States.

EC number	CAS number	Substance name	Abbreviation
Monosubstituted organotin compounds			
248-227-6	27107-89-7	Octyltin tris(2-ethylhexylthioglycolate)	MOT(EHMA)3/MOTE
260-828-5	57583-34-3	Tris(2-ethylhexylthioglycolate)methyltin	MMT(EHMA)3/MMTE
Disubstituted organotin compounds			
214-688-7	1185-81-5	dibutylbis(dodecylthio)stannane	DBTSL
234-186-1	10584-98-2	2-ethylhexyl 4,4-dibutyl-10-ethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	DBT(EHMA)2/DBTE
239-581-2	15535-79-2	Dioctyltin thioglycolate	DOTTG
239-622-4	15571-58-1	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	DOT(EHMA)2/DOTE
260-829-0	57583-35-4	Bis(2-ethylhexylthioglycolate)dimethyltin	DMT(EHMA)2/DMTE
284-461-5	84896-44-6	diisotridecyl 3,3'-[(dibutylstannylene)bis(thio)]dipropionate	DBT

2.2. Initial concerns

Work on these substances started from a broad concern regarding thymus effects, immune toxicity and neurotoxicity and the harmonised classification for reproduction toxicity for some substances. Recently, industry withdrew their read-across from commonly accepted metabolites, arguing that these do not form in real life. As a consequence, major data gaps may appear for assessing the concern for these eight substances.

2.3. Previous regulatory activities

The subgroup of organotins has been under some scrutiny already and subject to screenings, evaluations and regulatory action. These are summarised in the table below. See main chapter 10 for abbreviations.

EC number	Abbreviation	Manual screening	RMOA	SEv	Authorisation		Restriction	CLH	Other processes under EU legislation
					Candidate List	Annex XIV	Annex XVII	Annex VI (CLP)	
248-227-6	MOTE	x		X					PBT EG, ED EG
260-828-5	MMTE	x		X				X	
214-688-7	DBTSL	x					Entry 20		
234-186-1	DBTE	x					Entry 20		
239-581-2	DOTTG	x					Entry 20		
239-622-4	DOTE		x		X		Entry 20	X	Food contact materials[7], PBT EG
260-829-0	DMTE	x	x					X	
284-461-5	DBT	x					Entry 20		

All substances have been subject to manual screening or risk management option analysis. The conclusion from manual screening for most substances was either dossier or substance evaluation. MOTE and MMTE are included in the Community rolling action plan (CoRAP) but evaluation has not yet started. Several of the disubstituted tin compounds are covered by the restriction entry 20 in Annex XVII to REACH[8]. In addition, DOTE is under consideration for restriction in tattoo inks.

Several substances have a harmonised classification in Annex VI to CLP. DOTE is currently under CLH with a proposal to downgrade the classification from Repr. 1B to Repr. 2.

3. Project organisation and approach

3.1. Actors and roles

Member States

Member State	Role
The Netherlands	Lead
Sweden	Partner
Bulgaria	Partner/observer

[7] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. DOTE is listed in the Union list. The specific migration limit (SML) is 0.006 mg/kg expressed as tin.

[8] Annex XVII, Entry 20 on organotin-compounds reads: …No 6; they shall not be used after 1 January 2012 in the following articles for supply to, or use by, the general public, where the concentration in the article, or part thereof, is greater that the equivalent of 0.1 % by weight of tin: textile articles intended to come into contact with the skin, gloves, footwear or part of footwear intended to come into contact with the skin, wall and floor coverings, childcare articles, female hygiene products, nappies, two-component room temperature vulcanisation moulding kits (RTV-2 moulding kits)

The lead Member State was the Netherlands, supported by partner Member States Sweden and Bulgaria. Each Member State competent authority nominated a key contact person and coordinator, but additional experts participated in the project and meetings. Both the Netherlands and Sweden were active during the entire duration of the project, but Bulgaria was mostly active during the initiation phase, with an observer role towards the end.

As the lead Member State, the Netherlands took on a lot of the work related to coordinating the project, but expertise was provided by all Member States, on human health, environment, chemistry and exposure.

ECHA

ECHA provided general support in coordinating the project as well as expertise in toxicology, substance identification and computational assessment.

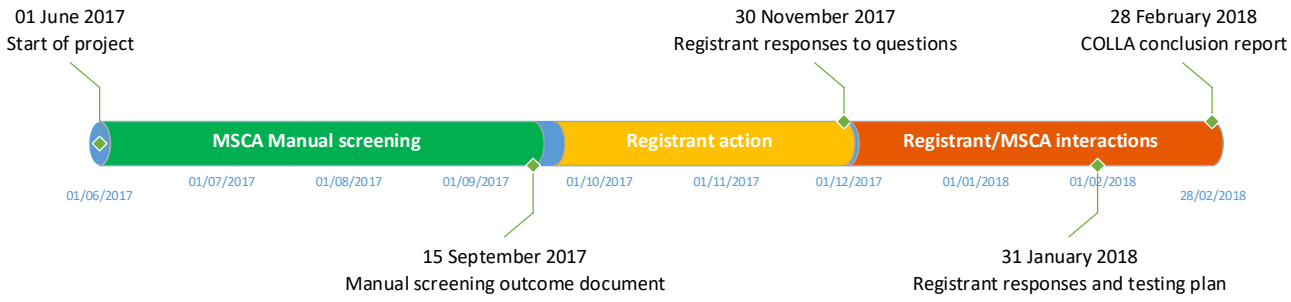
Registrants

EC number	Abbreviation	Lead registrant	Tonnage band
248-227-6	MOTE	Galata Chemicals GmbH	> 1000
260-828-5	MMTE	PMC Vlissingen B.V.	100-1000
214-688-7	DBTSL	Evonik Nutrition & Care GmbH	1-10
234-186-1	DBTE	Galata Chemicals GmbH	10-100
239-581-2	DOTTG	Galata Chemicals GmbH	100-1000
239-622-4	DOTE	Galata Chemicals GmbH	> 1000
260-829-0	DMTE	PMC Vlissingen B.V.	> 1000
284-461-5	DBT	Galata Chemicals GmbH	1-10

The lead registrants for all eight substances (see table above) were invited to participate in the COLLA project. The registrants for seven substances participated throughout the project. The registrants for DBTSL only participated in the kick-off meeting and did not participate further in the project; the substance is registered at a low tonnage band with no information requirements for repeated dose toxicity or reproductive toxicity. As the structure is somewhat different from that of the other substances (it does not have a thiol-glycolate ligand type), it was not considered in the read-across strategy proposed by the registrants.

Participating registrants were organised in a consortium, with one principal contact point, but several experts participated in the meetings and contributed to the project.

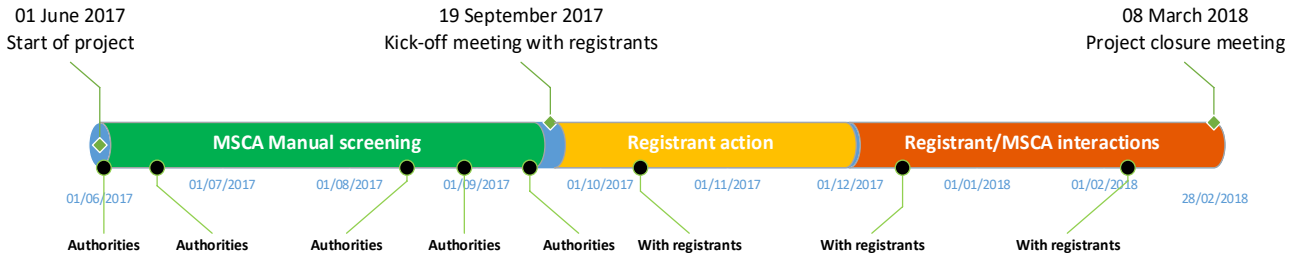
3.2. Timelines and milestones



The timeline above shows the duration of the different stages of the project and the main deliverables for each step. The project started later than other COLLA pilot projects. The Netherlands proposed the group in late May 2017 and the project started in June. The manual

screening phase lasted until mid-September, with the manual screening outcome document provided to registrants on 15 September. Registrants provided initial responses to questions raised in the manual screening outcome document by the end of November 2017. After further interactions and clarifications, registrants provided their final responses to questions and the testing plan by the end of Jan 2018. Member State competent authorities then provided their final conclusion report by the end of February 2018.

3.3. Interactions during the project



The timeline above shows the meetings during the projects. All meetings were held as teleconferences except the kick-off meeting with registrants, which was a physical meeting hosted by the Dutch competent authority at a conference centre in Amsterdam on 19 September 2017.

MSCAs and ECHA met several times during the initiation and manual screening phase. This was necessary to clarify roles and tasks and align views. Registrants were contacted early on (early June) by ECHA and consortium representatives quickly contacted the Dutch competent authority. Informal telephone calls between the Dutch MSCA and the consortium before the kick-off meeting helped to clarify the roles and expectations beforehand.

Several meetings between authorities and registrants after the kick-off meeting served to clarify questions raised by authorities and provide feedback to registrants on answers already provided. In addition, the Dutch MSCA attended a meeting of the consortium in Oct 2017.

It was the general view held by all participants that the physical kick-off meeting was most crucial and productive of all interactions.

4. Work undertaken

As majority of the substances had already been under scrutiny by Member States before, the manual screening phase was relatively resource-light. Bulgaria manually screened DBTSL, but for the other substances, conclusions from previous assessments were collected and consolidated. Member States presented a very detailed toxicological overview of the organotin substances and raised several questions in the manual screening conclusion document, some of which are presented below. The principal concern raised with these substances is the lack of hazard data, particularly for the endpoints of reproductive and repeated dose toxicity, due to the withdrawal of read-across arguments by registrants. In addition, authorities raised some concerns over PBT aspects and exposure concerns, as well as physico-chemical properties.

4.1. Human health

Questions proposed by MSCAs to registrants

How do you propose to generate the information that is currently missing in the registration dossiers (either by an alternative read-across hypothesis, testing or a combination thereof)?

1. *What are the consequences of the withdrawn read-across approaches for the group of thiobased organotins?*
    a. *How are the registrants planning to fulfil the information requirements for health endpoints?*
    b. *Are new read-across strategies plausible? What categories, subcategories?*

Human health issues discussed

In terms of structural similarity and based on similarities observed in hydrolysis studies, read-across between MMTE, MBTE and MOTE, and DMTE, DBTE and DOTE may be possible if indeed further bridging studies would support a similar toxicological characteristic or toxicological trend.

It was signalled by both ECHA and the evaluating Member States that at present (except for DOTE), there is insufficient information on each of the individual substances with regard to toxicity, with no information on the mechanism of toxicity or on the compounds that dominate toxicity (being the parent compound or any of its metabolites). There are no *in vivo* metabolism studies available to be able to conclude on common intermediates or metabolites among the organotins. The hydrolysis studies provide insufficient insight into the degradation or metabolism that will take place in an intact organism to be sufficient on its own to build a read-across on.

For DOTTG and DBT, the organotin consortium considers that read-across of toxicity endpoints is possible from DOTE and DBTE, respectively.

Compliance checks are ongoing for the majority of substances, for example, MMTE, MOTE, DBTE and DOTTG, and the consortium agreed not to propose a read-across adaptation for the information requested. The registrants suggested for two additional studies to be added to the already ongoing testing to strengthen the possible read-across. However, the registrants indicated that they cannot get the necessary support among registrants to conduct them through a 'voluntary initiative', and suggested that this information be requested either by ECHA through a compliance check or by one of the Member States in the context of a substance evaluation.

The evaluating Member States concluded that the read-across adaptation as prepared by the organotin consortium may be plausible. In terms of structural similarity and based on similarities observed in hydrolysis studies, read-across between MMTE, MBTE and MOTE, and DMTE, DBTE and DOTE may be possible if indeed further bridging studies would support a similar toxicological characteristic or toxicological trend.

It is however unclear from the supplied documentation on the read-across adaptation how this is motivated. The adaptation lacks a proper assessment of the available toxicity studies to support the read-across hypothesis and the conditions under which the to-be-generated information under compliance check may strengthen or refute the hypothesis. This is especially so for DOTTG (having a cyclic structure) and DBT (not being a thiol), which are structurally much more different from the other substances in the project group.

The evaluating Member States concluded that except for DOTE (for which all information seems available), it is most appropriate for this set of substances to await assessing the possible need for further regulatory measures until the information requested by compliance check is generated. For DOTE, there is currently no testing ongoing and the information that will be generated on the other substances is not expected to impact its hazard assessment.

4.2. Environment

Member States have flagged PBT issues for some thiol-ligand organotins. For several environmental endpoints, the information requirements were fulfilled using read-across from other dibutyltins based on hydrolysis studies. However, there were uncertainties on the hydrolysis rate, raising questions on whether or not the read-across is valid. Furthermore, with the data gaps on toxicity for some thiol-ligand organotins, it was not possible to evaluate the Toxicity-criterion in the PBT assessment.

The organotin consortium provided a summary of the available information in the registration dossiers. For most substances, they argued that from data on the substances themselves or read-across within the group of substances, there is enough information to conclude these substances are not PBT/vPvB. Nevertheless, they suggested that a bioaccumulation study for DMTE and hydrolysis data on DBT may help strengthen the read-across within the group.

Overall for DOTE, DMTE, DBTE and DBT, the evaluating Member States tended to conclude that the argumentation used to substantiate the statement as being 'not PBT nor vPvB' is insufficient to be conclusive or at least comprehensive. They would like to invite the organotin consortium to further strengthen their read-across adaptation by a more detailed elaboration on the information available and further testing where needed. Re-evaluation of the available data is suggested once the information requested through compliance for the various substances will become available.

4.3. Use and exposure

With respect to a possible concern for exposure, in the registration dossiers it is indicated that exposure to the thiol-ligand organotin might occur during formulation, use at industrial sites, consumer uses and article service life. Wide dispersive use has been indicated in the dossiers. As the organotins in this group are included in a polymer or matrix, it is expected that exposure to the thiol-ligand organotins might be limited when using the final article. Consumer exposure to tin compounds from PVC articles may be low, but as these compounds can be found in products with material based on plastic (e.g. food packaging and storage, toys, mobile phones), there are still uncertainties regarding the actual (combined) exposure.

The MSCAs asked questions on the functionality of the organotin compounds in the PVC, whether they are chemically bound in the matrix, and whether there were data on release rates from the products. They also wanted to know whether there were data on worker exposure, what the impact of recycling was, and whether the substances were interchangeable in function.

From the information provided by the organotin consortium, the evaluating Member States tentatively concluded that the consumer exposure to tin compounds from PVC articles is low, and the migration of these compounds from food packaging and storage, containers for pharmaceuticals and toys is regulated. However, there may be uncertainties regarding the actual (combined) exposure.

Overall, questions related to exposure level of workers and the combined exposure of consumers after the regulatory actions are insufficiently addressed. The organotin consortium stated that information on exposure and uses is difficult to obtain from their downstream users further down the supply chain, as there is no direct contact with these users. Often the information on exposure and uses is highly confidential and therefore not shared in the supply chain. The organotin consortium indicated that downstream users are not always familiar with their REACH obligations and that their influence on the uses by downstream users further down the supply chain is limited.

The evaluating Member States invited the organotin consortium to provide more detailed information on exposure to the best of their abilities and to update their registration dossiers accordingly so that this information can be taken into account in any follow-up regulatory risk management evaluations.

5. Project outcomes

5.1. Screening outcome and regulatory/testing plan

Overall, the evaluating Member States concluded the following:

- Together with the organotin consortium, that serious testing is needed to fill the information gaps in the registration dossiers of the seven organotin substances included in the study.
- Compliance check is already ongoing for most substances (with the exception of DBT) to address these information gaps.
- The outcome of the compliance checks should be followed up by evaluating any further need for regulatory risk management measures once results arrive.
- The read-across adaptation for human heath for MMTE, MBTE, MOTE, DMTE, DBTE and DOTE seems plausible but needs further elaboration on the justification provided.
- No read-across adaptations were proposed by the organotin consortium to fill the compliance check information requirements.
- The read-across adaptation for human health is less convincing for DBT. The organotin consortium should further elaborate on the availability of proper bridging studies to motivate the adaptation proposed.
- For environmental health, the organotin consortium should further substantiate their motivation on why these substances are not PBT or vPvB and further testing may be needed to show that the substances are indeed not bioaccumulative.
- Exposure information is still too limited to conclude on risk assessment and invite industry to update their dossiers before further regulatory measures on this group of substances are considered.

5.2. Initial reflections on lessons learnt and best practices recommended for the future

The following reflections and recommendations are from the ECHA coordinator of the organotin COLLA pilot project.

- The organotin project had a shorter timeline than other COLLA pilot project due to a later start. Nevertheless, a lot was achieved in the time available. This can largely be attributed to the 'running start' of the project, where most of the Member States were very familiar with the substances and had been working on organotins for some time. Registrant and Member State representative knew each other beforehand to some extent and communication was easier.
- The kick-off meeting was seen as very fruitful by all participants. This was again due to the familiarity with all with the substances and the ground work done by MSCA representatives beforehand in clarifying issues and presenting concrete concerns. This allowed registrants to be better prepared for the meeting.
- A well-functioning consortium was another key aspect of the success of the project. Communication lines within the consortium appeared to be very clear.

- Registrants stated that they found the COLLA exercise to be a good forum for discussion and worth the effort.
- Member States agreed that the exercise was worth the effort and valuable information and understanding was gained. However, they stressed that this should be seen in the wider context and although the project has run its course, the work on organotin substances is ongoing.

Appendix 6: Detailed feedback from the pilot project review questionnaire

The following sections present further details on the experiences and feedback provided by authorities and registrants for the pilot project review questionnaire through the **open questions** in the Webropol survey.

1. Early interaction

Overall, both registrants and authorities appreciated the opportunity for early interactions and saw the benefits these can bring. It gives an opportunity for registrants to become more involved as partners in the process and can serve to clarify issues upfront, resulting in less need for animal testing. However, many highlighted the considerable resources it took to engage in these interactions, both by registrants and authorities. Considerable doubt was expressed by a number of respondents as to whether there was an efficiency gain in the overall process, but this will remain to be seen as the substances progress through the regulatory processes.

2. Addressing groups of substances

Participants generally agreed that working on groups of substances was beneficial and made sense. However, this comes with its own set of complications and problems. According to the feedback given, one of these is the added workload at the beginning of the process, and authorities had several suggestions as to how ECHA could better help in the assessment (e.g. by creating data matrices). Likewise, it was indicated that incorrect grouping can lead to difficulties and wrong assumptions, so care should be taken when grouping is performed. Grouping also does not automatically mean that the same concern applies to all substances in the group.

The **authorities** which contributed to the pilot projects indicated that substances or groups of substances with the following features would be most suitable for work under the collaborative approach:

- Groups containing a **reasonable number of substances**.
- UVCBs and multiconstituent substances were proposed as possibly benefitting more from COLLA clarifications. However, contradicting this, it was also proposed that there should be a well defined **substance identity** for all substances.
    - COLLA could be applied, for example, where registrants identify such a group and only few if any of the group members are already under different regulatory processes. However, if it is already apparent that regulatory risk management is coming for some group members, registrants may be less willing to improve read-across, among other things.
- Substances with endpoints populated by **read-across to the same source substance**. Also, **where clarification on the read-across or category approaches would help with future regulatory processes**, such as dossier or substance evaluation. In addition, groups or categories which have been proposed by industry, meaning that they have already worked together to produce the read-across/category justification.

- **Cases where there is a need to clarify use and exposure information**, as these requests are more difficult to address under formal REACH data generation processes (compliance check or substance evaluation). Up to now, grouping has been based on chemical similarity and read-across; grouping can in principle be based on, for example, uses, exposure and fate, but then the project approach may be quite different.

- **Groups of substances where it may be possible to substitute hazardous group members** with less hazardous group members to help authorities better understand the risks and the technical limitations influencing the potential uses of each group member.
    - For example, for groups with members in the CoRAP or in the Candidate List, this might be good for identifying a better substance evaluation process or substitutes in the authorisation processes.

- Groups with the **registrants engaged and in a consortium or willing to collaborate openly with their competitors**.

- For the upcoming screening of substances <100 tpa, the classic screening scheme may be applied. However, the data basis is smaller and alternative methods for data acquisition might be necessary, and this could be supported by targeted grouping. Grouping may give the opportunity to effectively handle UVCBs or constituents of UVCBs – however, practical issues are yet to be clarified, and MSCAs have to invest considerable effort to fill data gaps. Possible consequences are a focus on groups which are of interest for other reasons (e.g. perfluorinated substances, petroleum compounds).

The **registrants** which contributed to the pilot projects indicated that the following types of substances or groups of substances would be most suitable for the early interaction approach:

- Substances that are the most **structurally similar, where there is a potential to apply read-across** to more efficiently fill data gaps. Also, substances where there is similarity in impurity profile, solubility/bio-availability profile, toxicological profile, mode of action.
    - For example, where there are small changes in a sub-structure part of a molecule; whether the substance is UVCB or not does not matter so much.

- **So-called data-rich substances** where basic information is available on more than one substance in each group, so an adverse outcome pathway with a weight-of-evidence approach can be applied to describe the mode of action involved in the endpoint of concern.

3. Experiences and feedback on project practicalities

3.1. Communications

The **registrants** who contributed to the pilot projects gave mostly positive feedback on the communications during the projects. They highlighted that it is very important that the aims and potential consequences of the COLLA project are made clear to registrants at the start and that registrants are allowed to prepare before the initial meeting. Teleconferences were found to be useful for discussing specific issues, but a well-prepared face-to-face meeting early on in the project was found to be essential. Registrants also reminded that competition law and confidential business information presents additional challenges when collaborating with other registrants of similar/same substances.

The lead registrants who participated in the projects ensured communication within their SIEF in many ways, including email, conference calls and consortium meetings. Some registrants tailored communication to SIEF members based on whether they were part of the consortium or not, as non-consortium members are generally less involved and too much information might lead to confusion.

3.2. Feedback on phases of the COLLA projects

The following section presents the key elements of the detailed feedback received on the different phases of the COLLA projects.

3.2.1. Project initiation phase and kick-off meeting

The contributing **registrants** indicated that the expectations and objectives of the COLLA project should be clear upfront and that the practicalities (calendar, deliverables, etc.) are set out from the start. Authorities should acknowledge that registrants need time to organise themselves, especially if they do not know each other beforehand, and it should be made clear to registrants that significant time investment may be needed. Some indicated that registrants should be involved at an earlier stage of the grouping and that is should be made clear that grouping does not automatically mean that all substances are considered hazardous.

The participating **authorities** agreed that that it is important to make the project objectives and expectations clear to registrants beforehand. Many considered that the introductory webinar and guidelines provided by ECHA were very good in setting the scene and providing information on objectives, scope and other aspects of the projects. Some proposed that better guidance is needed on what can be addressed under COLLA and what should be tracked under substance evaluation and compliance check. A clear division of work between lead and partner MSCAs, preferably along lines of human health and environment would be better than dividing work by substances. MSCAs must be given sufficient time at the start of the project to conduct the screening, identify issues and discuss with partner MSCAs.

All parties highly appreciated the face-to-face kick-off meeting and provided several suggestions on how to improve the meeting. These ranged from very practical things such as ensuring WebEx connections worked for remote participants and that meetings were not organised during holiday season, to more reflective comments such as not expecting too much from the first interactions and only using them as a tool to inform industry.

3.2.2. Submission and review of further information

Registrants highlighted that clear deadlines and reasonable timeframes should be set for the further information to be provided. Some appreciated the flexibility that COLLA offered in providing the information in different formats to IUCLID. **Authorities** also stressed that clear and reasonable timelines were needed, but also emphasised that authorities need to be clear when making their requests to registrants. Sometimes it is better to discuss more frequently and to spread the work over the duration of the project. Authorities should not be rushed at the end to conclude on the material provided.

3.2.3. Definition of an optimal regulatory plan

There were suggestions from **authorities** that ECHA should create an example testing strategy decision tree and that ECHA and MSCAs should agree in general terms what type of information registrants could provide under such a collaborative approach. The roles and responsibilities of all parties should be clear and it should be made clear to registrants that regulatory actions will not be dropped. Nevertheless, it is important to reach an agreement with registrants during the process. Both **registrants** and **authorities** agreed that groups with substances with several ongoing regulatory activities were not good candidates for the

collaborative approach, as there was not much flexibility allowed for actions.

3.2.4. Project closure

While some **authorities** felt that there was sufficient time given to reach a conclusion and determine a way forward, others felt that the end was rushed. Several commented that how the outcome of the project should be documented needs to be clear, and that the timelines for follow-up actions need to be agreed on by all parties. The outcome also needs to be available should there be any subsequent scrutiny of the substances by other MSCAs in the future.

3.3. COLLA schedule

Several **registrants** highlighted in their feedback that they felt that the timelines were too restrictive and did not allow for extensive read-across validation and additional testing. They indicated that the timelines should be made more flexible and that the initiation time should be extended. The timing of the pilot project close to the last REACH registration deadline was also seen as inconvenient.

Appendix 7

Workshop on the review of the collaborative approach (COLLA) pilot projects

7-8 May 2018
Guido Sacconi conference room, ECHA
Annankatu 18, Helsinki, Finland

AGENDA

Monday 7 May 2018		
13.30	Registration	
14:00 - 15:00	**Session I** **Introduction and setting the scene**	Chair: Leena YLÄ-MONONEN ECHA
14:00	1. a) Welcome. Background and objectives of the workshop	Leena YLÄ-MONONEN ECHA
14:10	1. b) COLLA approach and the five projects	Claudio CARLON ECHA
14:20	1. c) Results of the five COLLA pilot projects	Jesus VAZQUEZ RODRIGUEZ ECHA
14:35	1. d) Main results from the survey on the review of the COLLA pilot projects	Hannu BRAUNSCHWEILER ECHA
14:50	Questions and clarifications	All
15:00 - 16:30	**Session II** **Review of COLLA projects: past and future**	Chair: Leena YLÄ-MONONEN ECHA
15:00	2. a) German competent authorities' experiences in working with COLLA groups of substances	Helene FINDENEGG BAuA, Germany
15:15	2. b) COLLA experiences of registrants	Yannick DZIECHCIAREK AkzoNobel Chemicals
15:30	2. c) Commentary and starter for discussion on COLLA experiences	Fleur VAN BROEKHUIZEN, RIVM, Netherlands and Martin BAEHR, Organotin consortium
15:40	Discussion	All

16:00	2. d) ECHA proposal for the way forward with COLLA	Palmi ATLASON ECHA
16:10	Questions and clarifications	All
16:20	2. e) Key topics for the breakout groups and practical arrangements	Norbert BORNATOWICZ, ECHA
16:30 - 17:00	Coffee break	
17:00 - 18:30	**Breakout groups**	
	Breakout group 1 Meeting room K323	Breakout group chair: Hannu BRAUNSCHWEILER Rapporteur: Norbert BORNATOWICZ
	Breakout group 2 Meeting room K324	Breakout group chair: Fleur VAN BROEKHUIZEN Rapporteur: Louise CONWAY
18:30	End of Day 1	

Tuesday 8 May 2018		
09:00 - 12:00	**Session III Conclusions and recommendations**	Chair: Leena YLÄ-MONONEN ECHA
09:00	3. a) Reports from the breakout groups	Rapporteurs
	Discussion	All
10:30 - 11:00	Coffee break	
	3. b) Future of COLLA?	All
	3. c) Other recommendations for the future	All
	3. d) Conclusions of the workshop	Chair
12:00	End of the workshop	
12:00 - 13:00	Lunch	

Tuesday 8 May 2018		
13:00 - 15:00	**Closed session for competent authorities: COLLA in the Integrated Regulatory Strategy**	Chair: Leena YLÄ-MONONEN ECHA
13:00	1. a) Introduction	Claudio CARLON ECHA
13:10	1. b) Roles of authorities in COLLA	All
	Discussion	All
13:40	1. c) Resources of authorities and intention to propose new groups for COLLA	All
	Discussion	All
14:10	1. d) Other COLLA issues from the authorities	All
	Discussion and conclusions from the closed session	All
15:00	End of competent authorities session	

Topics for the two breakout groups

Common topics for the two breakout groups

1. Does COLLA bring added value to authorities and registrants when working with certain groups of substances?
2. What are the substance groups that can benefit the most from COLLA?
3. When and how to decide to start a COLLA?
4. Expected outcome from COLLA:
    - What is a regulatory plan?
    - Acceptance of read-across, what can be done under COLLA?

Specific topics for breakout group 1

5. Roles of actors and communications:
    - How can we facilitate the provision of use/exposure information under COLLA considering confidentiality and competition law?

- How to ensure cost-sharing/data-sharing of proposed testing with all members of the SIEF?
- How can we avoid a kind of observatory attitude from some registrants/ consortia? How can we facilitate the consortium internal dynamics?

Specific topics for breakout group 2

6. How can we enhance efficiency and efficacy of COLLA?
    - Do we agree on time bound approach? Can it be reduced to six months?
    - What degree of flexibility could we have in COLLA? E.g. improved practicalities (timeline, reporting…)
    - How can we promote pro-active and constructive approach?
    - How can we make it more attractive for Member States?
    - Should we make it more public?

EUROPEAN CHEMICALS AGENCY
ANNANKATU 18, P.O. BOX 400,
FI-00121 HELSINKI, FINLAND
ECHA.EUROPA.EU