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Final Report: Applying a tested procedure for the identification of potential emerging chemical risks in the food chain to the substances registered under REACH – REACH 2

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Abstract

This study applied a procedure for the identification of potential emerging chemical risks in the food chain to substances registered under the REACH Regulation that was previously developed and tested in an EFSA-sponsored pilot study. The selection was limited to substances that (a) were registered with a full registration, (b) met eligibility criteria (e.g. availability of a CAS number and a SMILES notation) and (c) were considered to be inside the applicability domain of the models used in this study (excluding e.g. ionisable compounds and metals). This selection reduced the number of substances from about 15 000 to 2 336 substances that were subsequently assessed in four blocks: environmental releases (based on tonnage and use pattern), biodegradation (using BIOWIN predictions assessed in a battery approach), bioaccumulation in food/feed (using ACC-HUMANsteady modelling) and toxicity (based on classification for carcinogenicity, mutagenicity, reprotoxicity and repeated dose toxicity). A scoring system was applied with a maximum score of 10 in each of the four blocks. The procedure showed a good degree of differentiation in each block. Two weighting scenarios and pivot table selections were applied to the scores in the four blocks. An evaluation of both approaches led to the prioritisation of substances for their potential to represent 'emerging chemical risks' in the food chain. Following additional curation steps, 212 'potential emerging risks' were identified that are considered to (a) be released to the environment and/or poorly biodegraded, (b) bioaccumulate in food/feed and (c) represent a chronic human health hazard. In this study, in-depth evaluations were performed for ten 'potential emerging risks' that so far have not been assessed by an EU regulatory body for their presence in food via the investigated exposure pathway. The selection of these ten substances does not imply that the remaining 202 potential emerging risks are of lower priority.

Key words: Emerging risks, screening, REACH, methodology, environmental release, fate, bioaccumulation, toxicity.

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Summary

The EFSA[1] Working group for the identification of emerging chemical risks in the food and feed chain developed a procedure for the identification of potential emerging chemical risks in the food and feed chain in 2014. This procedure was further elaborated in an EFSA-sponsored pilot study published in 2016 study (Bitsch et al., 2016), that tested its application to substances[2] registered under the REACH Regulation[3] by using 100 data-rich chemicals ('pilot study' hereafter). All these substances were evaluated in relation to the main elements of the procedure:

- Block A: releases to the environment (i.e. exposure potential),
- Block B: biodegradation,
- Block C: bioaccumulation in food/feed and
- Block toxicity (carcinogenicity, mutagenicity, reproductive toxicity and repeated dose toxicity).

Based upon the recommendations of the pilot study, the present study sponsored by EFSA aimed to apply the tested procedure to substances registered under the REACH Regulation. The present final report describes the data used, the methodologies employed and the results for (a) the initial selection of substances, (b) the evaluation of the four elements listed above, (c) the prioritisation of substances as potential emerging chemical risks in the food chain and (d) the in-depth assessment of a subset of prioritised substances.

A stepwise approach was applied for the initial selection of substances. In a first step, substances registered under REACH with a full registration were extracted from ECHA's database. Of the 15 021 substances[4] initially entering the evaluation, this step excluded:

- 4 456 substances registered solely as intermediates handled under strictly controlled conditions: the use of intermediates handled under strictly controlled conditions is assumed to lead only to low releases to the environment, and such substances were therefore excluded from further evaluation.
- 4 511 substances registered only with a NONS registration, i.e. substances notified under previous chemicals legislation that are considered registered under REACH. As for intermediates handled under strictly controlled conditions, tonnage information is not publicly available for these substances. NONS registrations also lack information on the use of the substance, which is another critical input for the assessment of the exposure potential, and many of them lack a CAS number and a SMILES notation. As a consequence, substances with a NONS registration were excluded from further consideration.

6 843 substances[5] remained in the selection process after this first step. In the next step, full registrations lacking a CAS number were excluded, since the CAS number is a required input for the QSAR Toolbox. It should be noted that substances that were excluded for lacking a CAS number are primarily manufactured in low volumes and in many cases are likely outside the applicability domain of the models used in this study. For the remaining 5 380 substances SMILES notations were retrieved in the QSAR Toolbox. Substances for which the QSAR Toolbox did not retrieve a SMILES notation were excluded from further consideration, since the SMILES notation is required to predict input parameters for the biodegradation and bioaccumulation assessments of this study. Further analyses of the

1 A list of abbreviations is provided in the section 'Abbreviations' at the end of this report prior to the Appendices.

2 The terms 'substances' and 'chemicals' are used interchangeably in this report, since a distinction between these terms would make the report very difficult to read. However, it is acknowledged that 'chemicals' in a stricter sense only relate to individual chemicals identified e.g. by a SMILES notation. In contrast, the REACH Regulation in Article 3 defines a substance as 'a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used…' and registrations under this Regulation relate to 'mono-constituent substances', 'multi-constituent substances' and 'UVCB substances'. Thus, while tonnage and use pattern as well as the hazard classification in this study relate to the 'substance', the predicted data for biodegradation and bioaccumulation actually relate to the 'chemical' (i.e. a representative chemical).

3 Regulation (EC) No 1907/2006 of the European Parliament and of the Council

4 Note that the numbers given here are indicative, since a substance with an intermediate registration or a NONS registration may also have a full registration (see section 3.1 for details).

5 Since a substance may be registered with a full and an intermediate registration and substances registered with a NONS registration may also have a full registration (e.g. if the tonnage band has increased), the number of substances remaining in the selection at this stage is higher than the one obtained by simple subtraction (15 021 – 4 456 – 4 511 = 6 054 substances).

substances excluded by this step indicated that the majority are (a) potentially UVCB substances (e.g. petroleum products, fatty acids and other hydrocarbons of variable carbon chain length) or (b) inorganic, organometallic or other substances outside the applicability domain of the models used in this study. After this step, 4 330 chemicals remained in the process of substance selection.

Based on the recommendations of the pilot study, metals and metalloids as well as organometallic, inorganic and ionisable substances were excluded because they are outside the applicability domain of the models used in this study. This step reduced the number of substances to about 2 374 chemicals. As a final step, duplicate datasets (i.e. different chemical structures for a given CAS number) were removed by an informed procedure, and a few more substances were manually excluded because they are outside the applicability domain of the models used resulting in a final selection of 2 336 substances.

These 2 336 chemicals were evaluated for their exposure potential, biodegradation, bioaccumulation and toxicity. While this figure represented only about 16 % of all chemicals registered under the REACH Regulation at the time of evaluation, the approach chosen aimed at ensuring that the chemicals selected (a) have basic information on the tonnage and use publicly available, (b) can be characterised chemically by a CAS number and a SMILES notation and (c) are within the applicability domain of the models used in this study. The methodology for the identification of potential emerging risks proposed in this report is therefore only applicable to a comparatively small fraction of the substances registered under the REACH Regulation, primarily due to data availability and applicability domain considerations[6].

Releases to the environment (block A) were assessed on the basis of (a) the maximum tonnage of the REACH registration and (b) release fractions to the environment as indicated by Environmental Release Categories (ERCs). The approach followed the one developed in the pilot study, resulting in a Tonnage Score and an ERC Score, which are added up to give the Total Score A (maximum of 5 for each component, maximum of 10 for Score A). Since several registrations may exist for any given substance, extraction of tonnage and ERC data from the ECHA CHEM database was performed in a way that ensured that these data actually referred to the same registration. The highest Score A was used for any given substance if several registrations existed. Default worst case scores of 5 were used if tonnage or ERC information was missing. Total Score A has 60 possible values, since five possible Tonnage Scores are combined with 12 possible ERC Scores.

Overall, the distribution of Total Scores A showed a good degree of differentiation. About one-third of the 2 336 substances was assigned a Score A ≥ 6.5, another third a Total Score A of 6 and the last third a Total Score A < 6, with the majority of these assigned a Total Score A < 4. The large fraction of substances assigned a Total Score A of 6 results from the fact that the many substances are assigned an ERC Score 5 and a Tonnage Score of 1.

Both tonnage and use information (ERCs) was available for 93 % of the 2 336 substances, while both types of information were lacking for only 5 substances (0.21 %). Information on ERCs was lacking for 5.1 % of the substances, while information on the tonnage was lacking due to claimed confidentiality for 1.9 % of the substances. Most substances with lacking information on ERCs are registered at low tonnages.

Total Score A is inherently uncertain even if tonnage and ERCs are available. This uncertainty results from the possibility that in any given registration the maximum tonnage is not related to the use resulting in the highest ERC Score. Total Score A therefore represents a conservative value. An evaluation of the tonnage per use, which would limit the uncertainty in the present assessment, is only possible by an assessment of the confidential Chemical Safety Reports (see 'Proposal for possible next steps' in section 5).

The assessment of biodegradation (block B) followed the recommendations in the pilot study and is entirely based on QSAR predictions evaluated in a battery approach. Values for BIOWIN models 3, 5 and 6 were predicted using the QSAR Toolbox for all 2 336 substances and scored according to the methodology developed in the pilot study. This resulted in Score B for all 2 336 substances that were aggregated into three clusters of biodegradable substances (Score B: 1-2), moderately biodegradable substances (Score B: 4-6) and poorly biodegradable substances (Score B: 8-10).

[6] Also see Figure 1 below.

Overall, 42 % of the 2 336 substances were predicted to be biodegradable (Score B: 1-2), while 52 % were predicted to be poorly biodegradable (Score B: 8-10), with the remaining 6% being predicted as moderately biodegradable (Score B: 4-6). These fractions agreed well with those based on predicted data in the pilot study.

As a separate element, a validation of the predicted biodegradation data was performed. For this purpose, 'key values' for biodegradation screening tests in water from REACH registration dossiers were evaluated at ECHA premises in Helsinki (Finland). Such key values were available for 1 567 of the 2 336 selected substances (67 %) and were scored according to the methodology developed in the pilot study. The validation study compared scores based on the predicted data with those based on key values for these 1 567 substances. There was a good level of agreement between predicted and experimental data (based on key values), with 66 % of the substances assigned to an identical persistence class. The combined value for correct predictions and overpredictions[7] was 92 % in this validation study, indicating that the approach employed contains a conservative element that is appropriate for a screening procedure. Extended analyses within this validation study aggregated the results for the 1 567 substances into only two classes ('readily biodegradable' (RB) vs. 'not readily biodegradable' (NRB)) to allow comparisons with literature data. Overall, 67 % of the substances with key values indicating RB were correctly predicted to be RB, while 83 % of the substances with key values indicating NRB were correctly predicted to be NRB based on the battery approach used in this study. The finding of a higher agreement for NRB is fully in agreement with other studies assessing the predictivity of QSARs for biodegradation potential. Overall, the validation study demonstrated a good level of agreement between the predicted data that was used in this procedure and available experimental data.

Bioaccumulation (block C) of the 2 336 substances in food/feed was assessed with the ACC-HUMANsteady model as recommended in the pilot study. All input data required by the model were predicted within the QSAR Toolbox or based on defaults developed in the pilot study. Also in agreement with the pilot study, quartile concentrations (25th, 50th and 75th percentiles) were calculated for every food/feed item. The scoring of the potential for each substance to bioaccumulate into each food/feed item was based on the modelled concentration of each substance relative to the quartiles calculated for all substances. Thus, a concentration of a substance in a food item below the 25th percentile from all substances in this food item resulted in a score of 1, while a concentration at or above the 75th percentile resulted in a score of 10. The maximum score in any food item for a given substance was taken as Score C for this substance. Again, the scoring approach is identical to the one described in the pilot study. However, the quartiles calculated in this study differed from those calculated in the pilot study. Since this study is based on a considerably larger dataset, the new distribution data were used for scoring.

Score C was not evenly distributed across the four groups (scores 1, 3, 6 and 10). Rather, 10 % of the 2 336 substances were assigned a Score C of 1, 40 % were assigned a Score C of 10 with about equal fractions of 25 % each being assigned Scores C of 3 and 6. This distribution results from the fact that Score C is taken as the maximum score obtained in any food item.

The uncertainties in block C relate to uncertainties of the ACC-HUMANsteady software (and models implemented in the software). In particular, applicability of the ACC-HUMANsteady model to less well studied substances, e.g. those accumulating by mechanisms other than lipophilicity, remains a source of uncertainty. This limitation is not specific to ACC-HUMANsteady, but applies to other models as well, which have largely been developed on the basis of data for a very limited number of substances, primarily because measured data (against which such models could be validated) are available for relatively few substances. The applicability to all 2 336 substances selected therefore remains a general source of uncertainty in the assessment.

As recommended in the pilot study, the toxicological profile (block toxicity) of the 2 336 substances was assessed on the basis of classification information. The four endpoints considered in this evaluation are (a) carcinogenicity, (b) mutagenicity, (c) reprotoxicity and (d) repeated dose toxicity. The following classification information was used in the evaluation of the toxicity of the 2 336 substances:

- Harmonised classifications for all four endpoints agreed upon by EU Member States:

[7] Overpredictions are defined here as a lower predicted degree of biodegradation than actual (based on experimental data).

  - Carcinogenicity: Categories Carc. 1A, 1B and 2,
  - Mutagenicity: Categories Muta. 1A, 1B and 2,
  - Reproductive toxicity: Categories Repr. 1A, 1B and 2,
  - Repeated dose toxicity: Categories STOT RE 1 and 2
- Classifications for carcinogenicity by the International Agency for Research on Cancer (IARC): Group 1, 2A and 2B, and
- Self-classifications for all four endpoints (same categories as for harmonised classifications) available in the Classification & Labelling (C&L) Inventory of the European Chemicals Agency (ECHA), an inventory established under the CLP Regulation[8].

While harmonised and IARC classifications could be easily extracted from the ECHA and IARC websites, self-classifications in the C&L Inventory reflect classifications from three different sources:

- Classifications from REACH registration dossiers submitted by the 'lead registrant' jointly for a group of companies ('joint classifications' hereafter),
- Classifications from REACH registration dossiers submitted by individual companies ('individual classifications' hereafter) and
- Classifications not coming from REACH registration dossiers notified to ECHA by other companies ('other classifications' hereafter).

In the case of self-classifications, a (semi-)automated extraction workflow was used to ensure that all classifications are extracted. Joint classifications could be easily identified, since they are flagged in the C&L Inventory as 'joint entries' and this flag was retained during the extraction. However, individual classifications and other classifications are not distinguished in the C&L Inventory. An approach was therefore developed that allowed differentiation of these two types of classifications as well. This differentiation was necessary, since other classifications were judged to be less reliable than individual classifications.

In a hierarchical approach, harmonised classifications were evaluated first, followed by IARC, joint and individual classifications. All substances that were not classified in these sources, but had other classifications for these endpoints were assessed further. While such classifications were considered less reliable, their dismissal was considered too far-reaching. An approach for identifying the potentially more reliable other classifications was developed that considered other classifications for the four endpoints, if this was based on more than two notifications[9]. In these cases, the classification was considered to be based on more than two independent sources, potentially increasing its reliability.

All substances classified for any of the four endpoints in harmonised, IARC, joint, individual or other classifications (in more than two notifications) were initially assigned a Toxicity Score of 10. All other substances were assigned a Toxicity Score of 1.

In the hierarchical evaluation, a Toxicity Score of 10 was initially assigned to

- 281 substances on the basis of a harmonised classification,
- 24 additional substances on the basis of an IARC classification,
- 187 additional substances on the basis of a joint classification (from a REACH registration dossier),
- 22 additional substances on the basis of an individual classification (from a REACH registration dossier) and

[8] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

[9] A notification is defined as a set of classifications for one or more endpoints. Each notification can be supported by one or more notifiers, i.e these notifiers submitted an identical set of classifications. In the C&L Inventory, sets of classifications are presented as different notifications if they are not identical. Even if the differences are minor (e.g. target organ 'lungs' or 'lung damage'), they are treated as different notifications.

- 29 additional substances on the basis of other classifications (selected from a total of 212 substances with classifications for the four endpoints, because these 29 substances fulfilled the criterion of having more than two notifications per endpoint).

Overall, 514 substances were assigned a Toxicity Score of 10 on the basis of harmonised, IARC or classifications from REACH registration dossiers. These were considered to be highly reliable.

For the 29 substances assigned a Toxicity Score of 10 on the basis of other classifications, this score was considered less reliable and toxicity data were therefore checked. Since this involved manual data extraction and evaluation procedures, this task was limited to substances that have scores > 5 (a) in block A or block B and (b) in block C (these are the criteria employed in prioritisation; see below). Application of these criteria resulted in 22 substances for which the toxicity data were checked to confirm or refute the initially assigned Toxicity Score of 10. For 9/22 substances, the Toxicity Score of 10 was confirmed. In most cases, the reliability of the Toxicity Score was rated as low. However, in two cases the reliability was considered high, since a corresponding classification is currently proposed by EU Member States under instruments of the REACH Regulation.

A similar evaluation was also performed for substances assigned an initial Toxicity Score of 1 (out of the total of 212 with other classifications for the four relevant endpoints). For these substances, however, stricter criteria were set (Score A ≥ 5 AND Score B ≥ 8 AND Score C = 10), since the classification for relevant endpoints was only supported by one or two notifications and was therefore considered less valid. Application of these criteria led to 28 substances, for which the toxicity data were manually checked. This evaluation identified three substances, for which the Toxicity Score was increased from 1 to 10, since the data suggest that a classification for one of the four endpoints may be appropriate. The reliability was rated as high, since a corresponding proposal by EU Member States exists, while it was considered low in all other cases.

In total, of the 50 substances with other classifications that were checked for toxicity data, a final Toxicity Score of 10 was assigned to 12 substances.

The impact of impurities on the classification provided in the C&L Inventory was also considered. However, the impact was comparatively small. For the 514 substances with reliable classification information from harmonised, IARC, joint or individual classifications, the classification was impacted by impurities in 17 cases (3.3 %). The reliability of the Toxicity Score for these substances was therefore changed from high to low. However, it must be noted that the impact of impurities in the C&L Inventory is not endpoint-specific. Therefore, such an impact may not relate to the endpoints of interest in this study (but e.g. to skin sensitisation) and the reliability for these endpoints may in fact be high.

In total, 526 substances (23 %) were assigned a final Toxicity Score of 10 and 1 810 substances (77 %) were assigned a Toxicity Score of 1. About 89 % of these 526 substances (N=468) were assigned a Toxicity Score of 10 based on harmonised or joint classifications. Interestingly, 187 substances were classified for at least one of the four endpoints in joint classifications, but did not have a harmonised or IARC classification for these endpoints. This suggests that the data generated under the REACH Regulation indeed lead to the identification of hazards not previously addressed. This finding supports similar observations reported in the literature.

For the prioritisation of substances as potential emerging risks, the following instruments recommended in the pilot study were applied to all the 2 336 selected substances:

- Two weighting scenarios (WS) that calculated total scores from the scores in individual blocks using pre-defined weightings,
- Pivot table selections that allow the user to define cut-off criteria for each block.

The two weighting scenarios recommended in the pilot study calculate total scores with the following algorithms[10]:

WS1: Total Score (WS1) = Score A * Score B + (Score C)² + (Toxicity Score)²

WS2: Total Score (WS2) = ((Score A * Score B + (Score C)²) / 20) * Toxicity Score

A substance was prioritised in WS1 or WS2 if its total score exceeded the 75th percentile of the total scores from all 2 336 substances in the respective weighting scenario.

In the Pivot table selection, the following criteria were applied for the prioritisation of substances[11]:

(Score A > 5 OR Score B > 5) AND Score C > 5 AND Toxicity Score = 10.

These criteria are based on the following considerations:

- A Toxicity Score of 10 is considered a requirement, since only substances classified for any of the four endpoints evaluated (carcinogenicity, mutagenicity, reproductive toxicity or repeated dose toxicity) are likely to induce adverse health effects if present in the food chain.
- A Score C > 5 for bioaccumulation in food (Scores C of 6 and 10) is considered a requirement, since these scores reflect a potential to accumulate in food.
- Scores > 5 either in block A or in block B are considered sufficient to reflect the potential of a substance being present in the environment. This criterion is based on the understanding that a substance may be present in the environment if it (a) enters the environment in significant amounts (high Score A) even if it is readily biodegradable (low Score B) or (b) enters the environment in small amounts (low Score A) but is not or only poorly biodegradable (high Score B).

With respect to weighting scenarios, WS1 prioritised 583 and WS2 prioritised 492 substances. Overall, 707 substances were prioritised in either weighting scenario and 368 substances were prioritised in both weighting scenarios. The distributions of total scores differed substantially between both scenarios. More importantly, both weighting scenarios also prioritised substances that lack high scores in block C and the toxicity block. Furthermore, a substantial number of substances were prioritised in one weighting scenario, but not the other due to weights put on different blocks in WS1 and WS2, respectively.

In contrast to the weighting scenarios, the Pivot table selection allowed defining criteria that have to be met in any case (e.g. a Toxicity Score of 10 and a Score C > 5). Therefore, the Pivot table selection approach was used to prioritise the 2 336 selected substances. Overall, 266 substances were prioritised using the criteria defined above. However, the criterion for blocks A and B (Score A > 5 OR Score B > 5) provided little discrimination since 2 159/2 336 substances (92 %) met this criterion. Disregarding scores for block A and B, 283 substances met the criteria (Score C > 5 AND Toxicity Score = 10). The REACH registration dossiers of the (283 – 266 =) 17 substances that fulfilled the criteria for block C and toxicity but not the criteria for blocks A and B were checked manually in relation to potential environmental releases (all of them are predicted to be readily biodegradable, Score B = 1). This analysis confirmed that substances manufactured at relatively high tonnages (1 000 tonnes per annum or more) are used in applications potentially associated with little environmental releases (e.g. as an intermediate or as a monomer in polymer production). Only one exception was found where the semi-automated evaluation was unable to retrieve relevant information. This substance was added to the list of priority substances (N=267).

Some additional evaluations were performed comparing results from application of the weighting scenarios with those obtained from Pivot table selections. Overall, these evaluations increase the confidence of the prioritisation based on the Pivot table selection. The 267 substances identified therefore served as a starting point and additional information was used to further evaluate these substances.

In a first step, the information on the impact of impurities retrieved in the toxicity assessment (see above) led to the exclusion of 5/267 substances. Exclusion of such substances is meaningful, since the

[10] WS1 corresponds to weighting scenario 4, and WS2 corresponds to weighting scenario 7 in the pilot study; the 'Toxicity Score' in this report is identical to the 'maximum of Score D-F' in the pilot study.
[11] AND/OR refer to logical operators in these criteria.

toxic hazard relates to a different substance (e.g. 1,3-butadiene) than the one assessed in blocks A-C (e.g. n-butane).

Furthermore, detailed manual analyses revealed that some of the 267 substances represented UVCB substances despite the effort made during substance selection to exclude such substances. In these cases, the chemical structure assessed in blocks A-C may not adequately represent the UVCB substance and 50 substances were excluded from further evaluation based on these analyses. In the majority of these cases, the substances are complex petroleum products (N=48).

Overall, 55 substances were excluded and 212 substances were prioritised as potential emerging risks for further evaluation. Within the limitations of the assessment of the individual blocks, the prioritisation is considered reliable for the following reasons:

- All 283 substances with a Toxicity Score of 10 and a Score C > 5 have been assessed in detail, i.e. irrespective of their scores in block A and B. The evaluation is therefore less prone to uncertainties resulting from blocks A and B.
- The 212 priority substances for further evaluation are characterised by a high fraction of substances that are predicted to be persistent due to little or no biodegradation (N=171, 81 %), with the majority predicted not to be biodegradable (N=155, 73 %). Furthermore, only 6/212 substances were assigned a default Tonnage Score (2.8 %) and only 5/212 substances were assigned a default ERC Score (2.4 %). None of the 212 priority substances was assigned a default score for both elements of block A.
- Among the 74 substances, for which the decision of non-prioritisation solely depends on a Score C < 5, only 16 % (N=12)) are predicted to accumulate in air-breathing organisms according to the ECHA Guidance on PBT/vPvB assessment (ECHA, 2017a) and eight of these are petroleum products. Only 6/74 substances (8.1 %) met the screening criteria for bioaccumulation in fish (ECHA, 2017a) and 4 of these are petroleum products. These data suggest that the number of substances disregarded based on potentially wrong ACC-HUMANsteady results is small, if petroleum products are excluded. However, we consider the ACC-HUMANsteady results to be more reliable than the assessment based on simple screening criteria for partitioning coefficients, e.g. due to the inclusion of biotransformation in ACC-HUMANsteady modelling.
- With respect to the Toxicity Score, 203/212 priority substances (96 %) have reliable toxicity data, since the assessment is based on (a) harmonised or IARC classifications (N=88), (b) classifications in REACH registration dossiers (N=112) or (c) other classifications considered reliable due to recent proposals for such a classification within an EU legal framework (N=3). For the remaining 9 substances, the Toxicity Score of 10 is considered more uncertain.
- The decision of non-prioritisation is exclusively dependent on the Toxicity Score of 1 for 517 substances, since these have high score in all other blocks. The majority of these substances (N=470) are not classified in any classification for any of the four endpoints of interest. For the remaining 47 substances, the majority (N=41) was classified for at least one of the four endpoints, but this classification was only supported by two or less notifications. These evaluations show that the confidence in the Toxicity Score of 1 for these 517 compounds is high in most cases. Nonetheless, these substances may become relevant if new toxicity data emerge that would lead to a classification for the endpoints of interest.
- All 212 priority substances have scores > 5 in at least three of the four blocks (conforming to the selection criteria[12]) and 75/212 substances (35 %) have scores > 5 in all four blocks.

Within the limitations of such a screening approach, it must be emphasised that the prioritisation can never be complete in the sense of identifying all potential candidates for further evaluation.

Analyses of these 212 priority substances showed that this study produced valid prioritisation results, since many of the substances ranking high in the two weighting scenarios are also included in several lists from ECHA and/or listed in EFSA's OpenFoodTox database. More specifically, the fraction of substances included in at least three of the eight lists evaluated decreased from 40 % among the 'top

[12] For one substance, Score A was considered to be an underestimate and this substance was selected despite the fact that both Score A and Score B were below 5.

10' priority substances to 28 % among the 'top 25' and further to 14 % among the 'top 50' priority substances (11 % of all 212 substances are included in at least three lists). Furthermore, some of the highest ranking substances in this study (e.g. bisphenol A and tetrabromobisphenol A) were already assessed in-depth by EFSA in relation to their presence in food. However, most of the 212 priority substances were not assessed with respect to human exposure via the food chain. This finding is based on two observations. First, 110 of the 212 priority substances (52 %) were not included in any list at all. Second, illustrative examples of substances included in one or more lists showed that the evaluations do not cover potential risks due to exposure via the food chain.

Overall, the 212 priority substances can generally be considered 'potential emerging chemical risks' (or 'emerging chemical issues' in EFSA's definition) and substance-specific in-depth assessments are required to clarify whether they actually constitute 'emerging chemical risks'[13]. This study successfully identified 'emerging' substances that are potentially relevant for human exposure via the food chain. As noted above, 112 of these 212 priority substances (53 %) were assigned a Toxicity Score of 10 based on classifications in REACH registration dossiers. All of these substances did not have a harmonised or an IARC classification for CMR properties or repeated dose toxicity. This finding illustrates that the present study made full use of information generated under the REACH Regulation and identified substances that were not recognised in approaches based on harmonised and IARC classifications only.

Overall, this study established a link between a chronic health hazard and possible exposure of humans via the food chain. For the majority of the 212 priority substances, such a link has not been previously recognised.

As noted above, all 212 priority substances are considered 'potential emerging chemical risks' in the food chain. Therefore, further in-depth evaluations are required to confirm (or refute) the results of the prioritisation and to judge whether available data are sufficient to conclude that these substances present real 'emerging chemical risks' in the food chain. Within this study, a subset of 10 substances (out of the 212 priority substances) was selected for in-depth evaluations. Selection of substances for this task was based on a combination of (a) high Total Scores in the weighting scenarios and (b) non-consideration in assessments by European authorities. With respect to the latter criterion, several lists from ECHA, but also inclusion in EFSA's OpenFoodTox database were considered. The approach aimed to exclude substances that were already assessed in detail and would therefore not qualify as 'emerging chemical risks'. In another step, substances with a Toxicity Score of low reliability (see above) were excluded from the selection. The maximum REACH registration tonnage was used as a final criterion to limit the selection to slightly more than 10 substances, for which additional information could be manually retrieved and evaluated.

While weighting scenarios were not adequate in the prioritisation of substances for reasons discussed above, they proved to be useful in sub-selecting substances from the pool of prioritised substances.

Among the substances initially selected, some were found to be well-known substances (e.g. four diisocyanates) and were excluded to obtain a list of 10 substances. Among these 10 substances, three other substances were suspected of being degradable by abiotic processes and were therefore replaced. This final replacement did not employ formal criteria, but was based on (a) high tonnage, (b) no relevant previous assessments, (c) no or little hydrolysis and (d) expert judgement considering chemical class and use pattern.

Early during the in-depth evaluation, it turned out that one of the substances selected (melamine cyanurate, CAS No.: 37640-57-6) will release melamine (CAS No.: 108-78-1) in aquatic compartments. These two substances were therefore assessed together.

The 10 substances selected for in-depth evaluation by definition (see prioritisation approach above) all have a Toxicity Score of 10 and a Score C > 5 (in fact, seven have a Score C of 10). All except one (Score B=8) have a Score B of 10, while Score A shows a wider range due to the combination of five possible Tonnage Scores with 12 possible ERC Scores (range of Score A: 2.3-9). All substances have a maximum REACH registration tonnage of 10 000 tpa or more.

For each of the 10 substances, the in-depth evaluation reviewed the input data for block A in REACH registration dossiers to check accuracy of the (semi-)automated extraction procedure and also identify

[13] See section 1 for the meaning of these terms.

any recent updates. This evaluation showed that the ERC Score (and the resulting Score A) was higher than assigned in the original assessment (performed about 18 months earlier) for two substances. With respect to block B, experimental biodegradation data from REACH registration dossiers (and in some cases from existing reviews) were compared with the Score B assigned based on predicted data. For all substances, the score was confirmed.

The toxicity assessment was checked against current classification information to identify errors in the (semi-)automated extraction procedures and also to identify possible updates. Again, the data originally extracted and the resulting Toxicity Score were confirmed for all 10 substances. Furthermore, information in relevant ECHA lists (reflecting e.g. current evaluations under both the REACH and the CLP Regulations) was checked to identify any relevant additional information. This evaluation showed that 3/10 substances are currently assessed for endpoints that were not covered by the classification. For one substance, an update of the current classification as a suspected reproductive toxicant (Repr. Cat. 2) to a stricter classification (Repr. Cat. 1B) is currently under evaluation. The findings illustrate that it is meaningful to check the toxicity information even if the assessment is based on reliable classification information.

In order to assess block C, literature searches were performed to identify publications on the occurrence of these substances in food/feed. Since it was expected that few data are available for these substances, literature searches were also performed to identify publications on the occurrence in the environment (including e.g. discharges from sewage treatment plants). Data from Europe were preferred and data from other countries were only included if no relevant data from Europe could be identified.

Overall, the data identified in literature searches showed that 4/10 substances occur in the environment or in food/feed, either experimentally or in dietary surveys:

- TDCIPP (tris(1,3-dichloro-2-propyl) phosphate, CAS No.: 13674-87-8)
- NBBS (N-butylbenzenesulfonamide, CAS No.: 3622-84-2)
- RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine, hexogen, CAS No.: 121-82-4)
- Sulfolane (tetrahydrothiophene-1,1-dioxide, CAS No.: 126-33-0)

TDCIPP was shown to occur in environmental compartments as well as in food/feed in many studies. With respect to the latter, more extensive monitoring data in food/feed are required to assess the level of exposure via diet in comparison to other pathways (e.g. ingestion of house dust by small children).

NBBS was detected in the environment in several studies. Data from one experimental study does not show a high potential for the uptake in crops, but this requires further confirmation.

Both RDX and sulfolane have been shown to be taken up by crops in several studies. These substances have comparatively specific uses as an explosive (RDX) and an extraction solvent in the petrochemical industry (sulfolane). Most of the available data suggest that the environmental occurrence may be limited to sites of manufacturing and use. However, there is also evidence that environmental contamination may be more widespread. For example, the occurrence of RDX in Swiss lakes may be due to its use in tunnel construction and thus not be limited to military sites.

Overall, monitoring in food/feed is generally recommended for these four substances. For RDX and sulfolane, this may be limited to sites of manufacturing and use, but additional monitoring data on the occurrence in the environment far away from these sources would allow gaining more insight into the extent of contamination.

For 6/10 substances, data on the occurrence in the environment or in food/feed are lacking or are too uncertain:

- 2,2'-methylenebis(6-t-butyl-4-methylphenol) (CAS No: 119-47-1)
- Bis(2-chloroethoxy)methane (CAS No.: 111-91-1)
- 1,3-phenylenediamine (CAS No.: 108-45-2)
- Melamine cyanurate (37640-57-6) and melamine (CAS No.: 108-78-1)

- Diethylmethylbenzenediamine (CAS No.: 68479-98-1)
- Phenol, isopropylated, phosphate (3:1) (CAS No.: 68937-41-7)

Melamine is a special case, since the occurrence of melamine in food and feed is well documented. However, several additional potential sources have been identified. In order to delineate sources, available monitoring data may be analysed in more detail (e.g. a separate analysis of unprocessed and unpackaged food/feed items on which the pesticide cyromazine (which degrades to melamine) was not used). For all other substances, the in-depth evaluation showed that monitoring in environmental media (STP effluents, surface water or other appropriate media) is recommended prior to any monitoring in food/feed to gain more insight into the extent of environmental occurrence.

Overall, the in-depth evaluation confirmed the initial assessment for blocks A and B as well as toxicity. This finding demonstrates that the approach applied in this study produces meaningful results. Such a confirmation was more difficult to obtain for block C, since monitoring data for food/feed were rarely available. If available, there were not considered sufficiently reliable and representative. Monitoring data in environmental media were also found to be very limited for most of the 10 substances evaluated in-depth. Therefore, the in-depth evaluation did not allow a final judgement as to whether these 10 substances actually represent 'emerging chemical risks' as defined by EFSA due to a lack of confirmation for block C. The data retrieved on the occurrence in food were too limited even for the substance with the largest amount of such data (TDCIPP). The 10 substances can therefore only be considered 'potential emerging risks' (or 'emerging chemical issues') in the food chain.

The data generated in this study for all the 2 336 selected substances, including the list of 212 potential emerging risks, the list of 517 substances with scores > 5 in all blocks except the toxicity block and the list of 74 substances with scores > 5 in all blocks except block C are made available as a Microsoft Excel® file to encourage and facilitate other possible applications of these data and of the approach developed in this study by interested stakeholders.

The following two figures provide a graphical abstract of this report. Figure 1 illustrates the substance selection and evaluation steps with a focus on (a) the number of substances remaining and (b) the reason for exclusion of substances in each step. With respect to the latter, a differentiation between those excluded due to lacking data and those excluded for other reasons was chosen for the substance selection part. For the evaluation part, all excluded substances do not meet the criteria of the Pivot table selection approach as described above. Note that this chart summarises the evaluation and prioritisation approach in a very succinct way focussing on the number of substances.

Figure 1: Flow chart of the overall approach: number of substances selected in each step.
* The sum of substances excluded (4 511 + 4 456 = 8 967) is higher than the difference between the total number and those registered with a full registration (15 021 – 6 843 = 8 178) since substances with an intermediate registration or a NONS registration may also have a full registration.

Figure 2 provides a more general summary of the workflow from substance selection through evaluation to prioritisation. For each step, the section in this report that describes the methodological approach in detail is given in square brackets. This figure focusses on the steps until the end of the prioritisation, since the priority substances[14] obtained may be used for several different applications (described in section 5). The in-depth evaluations performed in this report are therefore only one possible application. In fact, section 5 envisages non-target screening approaches as one of the possible next steps to further evaluate the priority substances obtained in this study.

[14] The general term 'priority substances' is used here, since the terms 'portential emerging risk' or 'emering issues' used in this report are related to EFSA's definition of these terms, while a broader meaning is intended here.

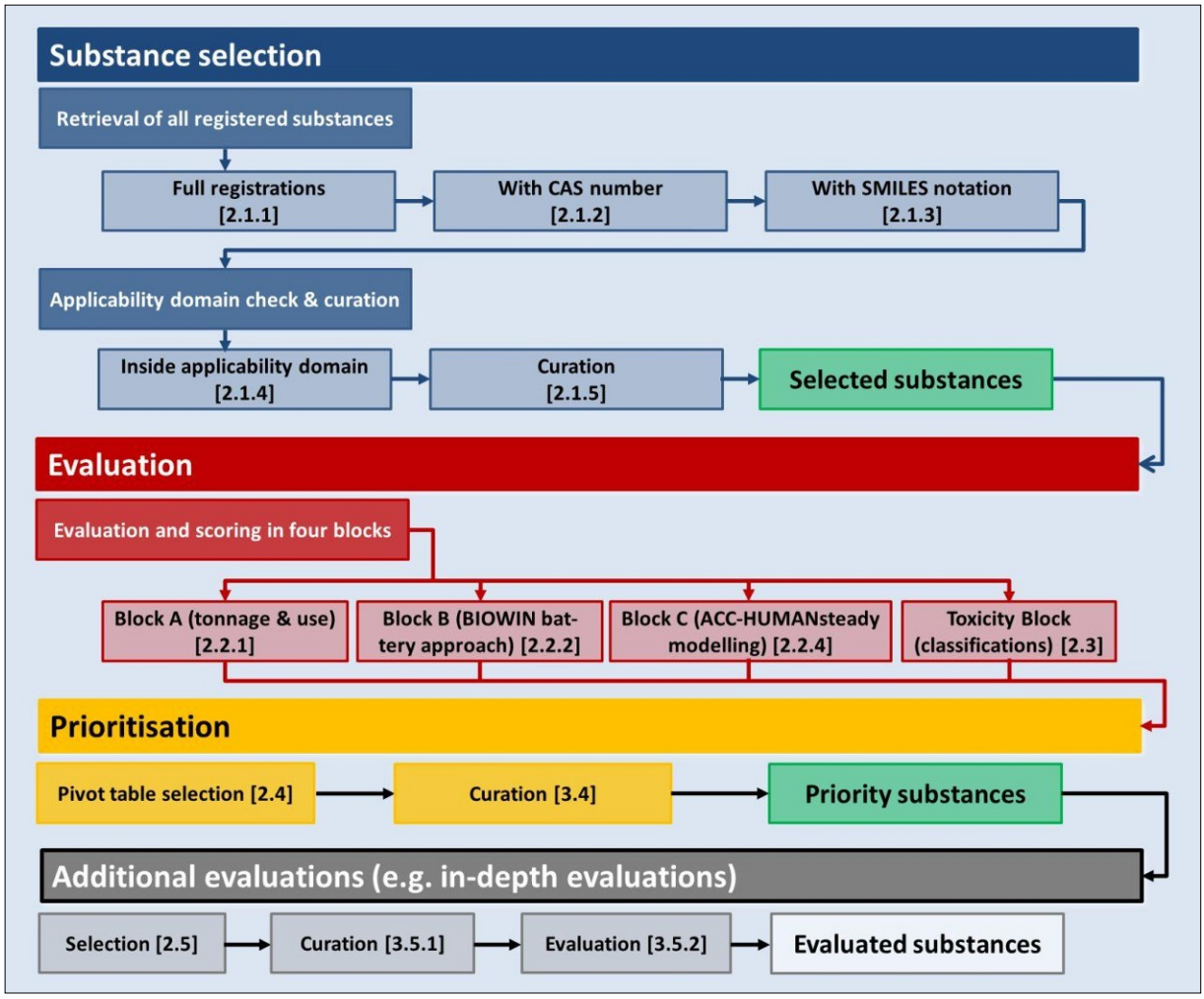

Figure 2: Flow chart of the overall approach.

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1. Introduction

The aim of the present study is to apply a tested procedure for the identification of potential emerging chemical risks in the food chain to the substances registered under REACH. The procedure was tested in a pilot study on behalf of EFSA that was finalised in 2016 (Bitsch et al., 2016). It involves several steps, from substance selection, the identification of data sources and extraction of data from these sources to the curation and evaluation of the data for each relevant endpoint. The final steps consist of the prioritisation of substances based on the scores for each endpoint as well as an in-depth evaluation of a subset of prioritised substances to establish whether the prioritised substances may indeed constitute potential emerging chemical risks in the food chain. The term 'emerging risk' is associated with an inherent limitation in that data are often too limited for an 'emerging substance' to allow a judgement of whether it actually constitutes a risk. As a consequence, EFSA has defined the term 'emerging issue' as described in the following box.

Box: Emerging risks and emerging issues

EFSA has defined an emerging risk '*as a risk resulting from a newly identified hazard to which a significant exposure may occur or from an unexpected new or increased significant exposure and/or susceptibility to a known hazard* (EFSA, 2007). Based on this early definition, it was recognised that risk assessment is a complex process and that many data are needed to judge on whether a risk exists or not. In many cases, such detailed data are lacking, but preliminary data suggest the occurrence of a potential emerging risk. To account for this fact, EFSA has subsequently defined the term 'emerging issues' as issues '*with similar characteristics of an emerging risks (e.g. new hazard, new exposure, new susceptible group), but for which the information collected is preliminary and too limited to be able to assess whether it is (or it could develop) into an emerging risk*' (EFSA, 2012).

This report uses the term 'potential emerging risk' in a general sense, i.e. for all substances identified as 'potentially' constituting an emerging risk, and the term is synonymous with the term 'emerging issue' as described above. In the context of the results presented in sections 3.4 and 3.5, the terms 'emerging chemical issue' and 'emerging chemical risk' are used in the specific meaning described above to differentiate substances with too limited data (i.e. 'potential emerging risks' = 'emerging issues') from those for which the existence of a risk has been confirmed (i.e. 'emerging risks').

This report outlines the data sources and approaches to data collection and evaluation for the relevant endpoints for substances registered under the REACH Regulation. The relevance of a substance in the food chain was evaluated in four specific blocks, with three blocks (A-C) relating to exposure and a fourth block covering the toxicity of the substance:

- Block A: Environmental release
- Block B: Biodegradation
- Block C: Bioaccumulation in food/feed
- Block toxicity: carcinogenicity, mutagenicity, reprotoxicity and repeated dose toxicity

The evaluation of the three exposure blocks A-C is based on the following data:

- For an evaluation of environmental releases, the REACH registration tonnage, that includes production volumes and imports of a substance, is considered an important element in assessing the extent of potential releases into environmental compartments (block A). Other conditions being equal, a substance registered in very high tonnages may be expected to be released to the environment to a higher degree, while a substance produced in relatively low amounts may be expected to be released only to a small degree.

  The use pattern of a substance is considered to be an additional important element in assessing the degree of environmental releases. For example, a substance produced at high tonnages, but produced and used in closed systems only, is likely to be released to the environment only in small quantities. A substance produced at relatively low tonnages, but used in products leading to complete release into environmental compartments (e.g. if it is used in laundry products), may have higher releases than indicated by the tonnage alone. The use of a substance is described in chemical safety assessments performed under the REACH Regulation by a set of use descriptors. One set of descriptors, the Environmental Release Categories

(ERCs), is used in this study, since ERCs they are associated with specific environmental release factors in the ECHA Guidance on environmental exposure estimation (ECHA, 2016b). For example, a default release factor of 6 % (of the tonnage) for releases to wastewater during the manufacture of a substance is assumed in this source.

Information on the tonnage and the use (ERCs) is readily available from REACH registration documents and the information is assessed in block A of the present procedure.

- After release, the behaviour of a substance in the environment will determine whether it will end up in the food chain. As a first step, information on biodegradation is evaluated in block B of the procedure based on predicted biodegradation data evaluated in a battery approach (as recommended in the pilot study). In a second step, the partitioning behaviour as well as bioaccumulation of a chemical in food and feed is assessed in this report in block C, which makes use of a specific model (ACC-HUMANsteady) that allows calculating relative concentrations of a substance in specific food/feed items. The input data required for the model can all be predicted using the QSAR Toolbox or can easily be calculated.

  The developed methodology to identify the bioaccumulative potential of substances in food or feed is unique compared to other regulatory frameworks. For example, in the PBT assessment proposed by ECHA for substances registered under REACH (ECHA, 2017a) or the one proposed by EMA for veterinary medicinal products (EMA, 2015), bioaccumulation is simply assessed based on BCF (bioconcentration factors) in aquatic species or screening criteria for partition coefficients. In contrast, the approach applied in this study assesses bioaccumulation on a more refined level and predicts a bioaccumulation potential for different food matrices, such as vegetables, fruits, dairy products, meat or fish.

The evaluation of the toxicity block is based on the classification of substances under the CLP Regulation for four endpoints reflecting chronic health hazards (carcinogenicity, mutagenicity, reprotoxicity and repeated dose toxicity). Due to the extensive resources needed to extract, curate and evaluate experimental toxicity data for these endpoints, such an approach based on the classification of substances was recommended in the pilot study.

Data from all blocks were evaluated using weighting scenarios and Pivot Table selections to prioritise substances for further evaluation. For a subset of prioritised substances, this report contains such in-depth evaluations.

Finally, this report contains conclusions and recommendations and is accompanied by supplementary material (available from the EFSA website as a Microsoft Excel® file) that contains all relevant data of this study.

1.1. Background and Terms of Reference as provided by the requestor

The objective of this project is to apply a procedure for the identification of potential emerging chemical risks in the food chain to substances registered under REACH. The procedure was tested in a pilot study on behalf of EFSA that was finalised in 2016.

The procedure, which was tested in a pilot study finalised in 2016 on behalf of EFSA, is applied to all chemicals registered under the REACH Regulation that (a) are registered with a full registration (excluding e.g. substances handled exclusively under strictly controlled conditions), (b) meet specific eligibility criteria (availability of a CAS number and a SMILES notation and (c) belong to chemical classes that are within the applicability domain of the models used in this study. Based on the results of this study, the contractor draws conclusions and provides recommendations for future evaluations.

In view of the highly innovative methodology and the many variables to be considered, a close collaboration of the contractor with the EFSA staff, and experts from the former Standing Working Group on Emerging Risks throughout the entire process was enabled to critically check the specific assumptions underlying the approach to be tested.

Contractor: FoBiG and Fraunhofer ITEM

Contract title: Applying a tested procedure for the identification of potential emerging chemical risks in the food chain to the substances registered under REACH – REACH 2

Contract number: OC/EFSA/SCER/2016/01-CT1

2. Data and Methodologies

2.1. Data and methodologies on substance selection

Prior to the evaluation of substances for exposure, environmental fate and toxicity, the dataset has to be prepared. Substances for further evaluation are selected based on the procedure described by Bitsch et al. (2016). For this purpose, all registered substances were extracted from the ECHA CHEM[15] database on 10 January 2017 and saved as a Microsoft Excel® file. This list contains registrations available for all substances. The registrations extracted differ by three important parameters:

- Registration type: a substance may be registered as an intermediate under strictly controlled conditions ('intermediate registration') or with a 'full registration' that covers all other uses;
- Submission type: the registration may have been submitted by a consortium ('joint submission') or by an individual company ('individual submission');
- Tonnage band: the tonnage band may be available as a tonnage range or may have been claimed confidential.

Table 1 shows the information available in the extracted list for the substance type and the tonnage band depending on the registration type. For any given substance, more than one registration may exist that differ by registration type, submission type and the information on the tonnage band available.

Table 1: Available information for submission type and tonnage band information depending on the registration type in ECHA CHEM

Registration type	Submission type	Tonnage band[(a)]
Full	Joint	Tonnage range
		Tonnage Data Confidential
	Individual	Tonnage range
		Tonnage Data Confidential
Intermediate	Joint	Intermediate Use Only[(d)]
	Individual	Intermediate Use Only[(d)]
NONS[(b)]	Joint	Tonnage Data Confidential
	Individual	Tonnage Data Confidential
NA[(c)]	Joint	Intermediate Use Only
	Individual	Intermediate Use Only

(a): Range refers to the tonnage band range (e.g. 1 000 – 10 000 tonnes per annum).
(b): NONS refers to the notification of new substances notified under Directive 67/548/EEC that are considered registered under Article 24 of the REACH Regulation (Regulation (EC) No 1907/2006 of the European Parliament and of the Council).
(c): Not available; this is an exceptional case (about 0.2 % of all registrations).
(d): The assignment is 'tonnage data confidential' for a small number of intermediate registrations (less than 2 %).

While NONS are considered registered under REACH, an upgrade with a full registration is required according to Article 24 of the REACH Regulation if the next tonnage level is reached since the notification under Directive 67/548/EEC. As a consequence, a given substance may also have a NONS and a full registration.

2.1.1. Substances registered with a full registration

The procedure described by Bitsch et al. (2016) limits the evaluation to substances registered with a full registration only. All entries in the extracted list other than 'full registrations' were therefore

[15] Although not officially provided on ECHA's website (http://echa.europa.eu/information-on-chemicals/registered-substances), the name ECHA CHEM is used here for the publicly disseminated information on chemical substances registered under REACH.

removed. Note that for any given substance, more than one registration may exist (e.g. one joint and one individual registration with different tonnage bands).

This step excludes (a) substances registered with an intermediate registration only (i.e. intermediates exclusively handled under strictly controlled conditions) and (b) substances notified under Directive 67/548/EEC ('NONS') as well as (c) a very small fraction of substances for which the registration type is not available ('NA'). As is evident from Table 1, all excluded registrations ('intermediate', 'NONS' and 'NA') do not contain information on the tonnage band, since these data are not publicly available. Further details on this selection step are available in Appendix A.

2.1.2. Substances with a CAS number

In agreement with the recommendations by Bitsch et al. (2016), all entries without a CAS number were removed from the list. This step is necessary since important input parameters for the evaluation are generated using the QSAR Toolbox that requires the input of CAS number when operated in batch mode[16]. In addition, the evaluation of classifications by the International Agency for Research on Cancer (IARC) will be based on CAS numbers (see section 2.3), since the IARC list does not contain EC numbers.

After this step, the list contains substances registered with a full registration that have a CAS number assigned. This list contains more than one entry for some substances defined by a given CAS number. This is the case when several registrations exist for a given substance. For further processing in the QSAR Toolbox, all duplicate CAS numbers were removed, resulting in a list of unique CAS.

Finally, some entries contain more than one CAS number (all listed in the same cell, separated by commas) for a given substance name. These CAS number were manually separated and entered into separate rows and all CAS numbers per name were used in the subsequent steps. Such entries differ by the CAS number but have identical names. Since all subsequent steps are related to the CAS number, these entries are treated as separate substances.

2.1.3. Substances with a SMILES notation

Also in line with the recommendations by Bitsch et al. (2016), substances without a SMILES notation should be excluded from further analysis, since relevant input parameters cannot be predicted for such substances.

In order to retrieve SMILES notation, the list of CAS numbers was loaded into the QSAR Toolbox (version 3.4, 2016). The software then automatically retrieves SMILES notations for these substances from databases included in the software. For a considerable number of substances, the software cannot retrieve a SMILES notation and these substances are removed from the list. This issue is discussed in more detail in Appendix A.

This step results in a list of substances with a full registration, a CAS number and a SMILES notation. The retrieval of SMILES notations for a given CAS number within the QSAR Toolbox returns more than one SMILES notation in a substantial number of cases. This procedure therefore results in duplicate datasets that have identical CAS numbers, but different SMILES notations. For the next step, a list of unique CAS numbers was generated.

2.1.4. Exclusion of substances outside the applicability domain of the models used

The pilot study (Bitsch et al., 2016) did not limit the chemical domain of the substances assessed. However, it turned out that there is considerable uncertainty associated with modelled results, since the underlying models used for blocks B and C were typically developed for neutral organic compounds. Bitsch et al. (2016) therefore recommended to exclude inorganic, organometallic and ionisable substances. Furthermore, metals and metalloids should be excluded for the same reasons.

For this purpose, the list of unique CAS numbers (section 2.1.3) was again loaded into the QSAR Toolbox. This will again lead to the generation of duplicate datasets (retrieval of different SMILES

[16] While SMILES notations can be imported in batch into the QSAR Toolbox, these are not available in the list of substances registered under REACH.

notations for a given substance). However, in contrast to the step described above, this is only the case for substances which are known to have a SMILES notation. Since the QSAR Toolbox profiling described in the next paragraph is a time-consuming process, it was practical to reduce the number of substances first to those that actually have a SMILES notation[17]. The profiling described below was applied to all SMILES notations and may already remove some duplicate datasets (e.g. if one structure for a given CAS number is predicted to be ionised to a large degree, while the other is not).

The QSAR Toolbox contains several profilers that analyse the chemical structure (as defined by its SMILES notation) and assign the substance to a specific class. Among the profilers available, the following ones were considered most appropriate for the exclusion of substances that are outside the applicability domain of the models used in this study (discussed in more detail below):

- Substance type (ST): for exclusion of inorganic, ionised and organometallic substances as well as mixtures
- Groups of elements (GoE): for exclusion of metals, metalloids and organometallic substances
- Chemical elements (CE): for exclusion of substances not containing carbon
- Ionisation at pH 7.4 (ION): for exclusion of ionisable substances; profilers for other pH values (pH 1, 4 and 9) are also available, but pH 7.4 was considered the most appropriate one for an assessment of the behaviour in the environment.

Initial investigations showed that the CE profiler (selecting substances that contain a carbon atom) identifies many substances that are ionised to a large degree, contain metals or are inorganics according to the other profilers. This finding is due to the fact that the CE profiler does not allow selecting substances that contain an 'organic carbon'. Thus, ammonium carbonates are selected by the CE profiler, but they are profiled as inorganics by the ST profiler. Overall, the ST and GoE profilers were therefore used in combination, since they allow a more informed selection procedure than using the CE profiler alone.

The ST and GoE profilers classify substances into specific classes, For example, the ST profiler assigns chemicals to classes such as 'discrete chemical', 'dissociating chemical', 'inorganic' or 'mixture'. The GoE profiler assigns organic substances to the class of 'non-metals', and also identifies 'halogens'. Inorganic substances are assigned to many different classes, such as 'metals', 'metalloids' 'alkali earth', 'rare earth' or 'transition metals'. Table 2 shows the possible classes for these two profilers.

Table 2: QSAR Toolbox profilers and possible profiling results

QSAR Toolbox profiler	Possible profiling classes
Substance Type	Anion, Cation, Discrete chemical, Dissociating chemical, Inorganic, Mixture
Groups of elements	Alkali Earth, Alkaline Earth, Halogens, Metalloids, Metals, Non-Metals, Rare Earth, Transition Metals

Any given substance may be assigned to a single class or multiple classes in each of these two profilers. Thus, a 'discrete chemical' may be 'inorganic' at the same time and the corresponding ST profiling class would be 'Discrete chemical|Inorganic'[18]. A 'discrete chemical' is defined as a substance that can be represented by a unique structure and molecular formula. In contrast, a 'mixture' in the definition of the QSAR Toolbox contains more than one chemical substance. As a consequence, no substance is profiled as being a 'discrete chemical' and a 'mixture' at the same time.

Analyses of the classes and possible combination of classes from these two profilers showed that selection of substances based on a few classes successfully excludes inorganic, organometallic and ionisable substances. Table 3 shows the classes used for selection of substances.

The ionisation profiler is based on pKa and pKb values predicted by models imbedded in the QSAR Toolbox. From these values, the degree of ionisation at pH 7.4 is calculated and converted to bands of

[17] In fact, the predictions of critical input parameters for blocks B and C are even more time-consuming and since they were performed at the same time, reduction of the substances was meaningful.
[18] The QSAR Toolbox uses the vertical bar (|) for separating classes in the exported results.

ionisation, which are then reported in the ION profiler of the QSAR Toolbox[19]. For example, a substance may be classified as 'Acidic [90,100]', which means that 90-100 % of the substance is ionised at pH 7.4. All substances assigned to the class 'Acidic [90,100]' or 'Basic [90,100]' were excluded from the dataset, since these are expected to exist in the environment predominantly (by more than 90 %) in the ionised form. The cut-off value of 90 % is arbitrary and has been chosen for pragmatic reasons. It should be noted that the scoring of the tonnage information uses the upper end of the tonnage range spanning a factor of 10 (see section 2.2.1). A factor of 10 in the ionisation cut-off (inclusion of substances existing in the non-ionised form by 10 % or more) therefore appears reasonable as well. In some cases, the QSAR Toolbox cannot predict pKa or pKb values. In these cases, the substance was considered not to be ionisable and selected for further evaluation.

Table 3 provides a summary of the selection criteria for eligible substances.

Table 3: QSAR Toolbox profilers and profiling results used for selection of eligible substances

QSAR Toolbox profiler	Profiling class for selection
Substance Type	Discrete chemical[(a)]
Groups of elements	Non-metals[(a)] Halogens|Non-Metals[(a)]
Ionisation at pH 7.4	Less than 90 % ionisation

(a): Classification exclusively in this class, i.e. not in combination with another class.

All substances not meeting all three criteria were removed from the list. The final list contains substances

- with a full registration, a CAS number and a SMILES notation and
- that are discrete chemicals characterised as non-metals (with or without halogens) that exist in a non-ionised form at pH 7.4 by at least 10 %.

2.1.5. Removal of duplicates and exclusion of non-eligible substances

For this step, the list of CAS numbers was again loaded into the QSAR Toolbox. This step was required since additional information was retrieved that allows a structured approach to an evaluation of the duplicate datasets in relation to the quality of the SMILES notation.

Step 1: High quality of the SMILES notation

The assessment was based on two different types of information extracted from the QSAR Toolbox: (a) assignment of an EINECS[20] number to the dataset, considered to represent the structure relevant in the evaluation (b) assignment of a high quality rating for the assignment of the 2D structure to the CAS number in the QSAR Toolbox.

The EINECS inventory integrated into the QSAR Toolbox contains 72 561 structures (out of the total 100 204 substances in the EINECS inventory) that were compiled in a uniform way and passed quality assurance steps[21]. The quality assessment for the CAS number/2D structure relationship within the QSAR Toolbox is independent of the EINECS inventory and therefore allows checking the quality of the structure with a second criterion.

For all duplicate datasets, those assigned an EINECS number was retained and those without an EINECS number were removed. In a very specific case, the dataset with an EINECS number was removed, because the molecular formula did not correspond to the molecular formula in the REACH registration dossier, while the one for the duplicate dataset did. In many cases, the datasets with an EINECS number are also assigned a high quality rating, further supporting the use of EINECS number assignment as a criterion.

[19] These predictions and calculations are performed for both acidic and basic ionisation.
[20] European INventory of Existing Commercial chemical Substances
[21] For details on this set, see https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/information-sources/ec_inventory, accessed February 2017.

Since not all datasets have an EINECS number or a quality rating, these remaining duplicate datasets have to be assessed by other means.

Step 2: Consistency of molecular formula/molecular weight and structural formula

In some cases, duplicate datasets differed with respect to molecular formula and, consequently, molecular weight. This occurred e.g. for polymer-like substances, for which sometimes the molecular formula (and SMILES notation) of the monomer structure was given in one dataset, and the formula and SMILES notation for a polymer in the other dataset. Similar cases were observed for UVCB substances[22], for which different representative structures may have been assigned, resulting in duplicate datasets. It must be noted, however, that differing molecular formulas were also observed for some clearly defined substances. All these cases were assessed in the following hierarchical pattern:

- If the molecular formula in the dataset was in agreement with the molecular formula in the REACH registration dossier, the dataset was retained and duplicate datasets with differing formulae were removed. In the case of polymer-like substances and UVCB substances (often characterised by carbon chain length ranges), the molecular formula in the dataset was checked against the range (of carbon chain length and/or molecular weight) given in the REACH registration dossier and duplicate datasets outside this range were removed. Duplicate datasets representing the lower or upper end of the ranges given in the REACH registration dossiers were removed, if a dataset representing the middle of the range was available (see Appendix A for examples). Since no information of the composition of such substances is publicly available, selecting the dataset representing the middle of the range was considered a pragmatic solution.
- In some cases, the molecular formula did not differ, but the SMILES notation and the predicted values (e.g. log Kow, log Koa or biodegradation predictions) differed. In these cases, the structural formula represented by the different SMILES notations in duplicate datasets was checked against the structural formula provided in the REACH registration dossier (if available) or the structural formula contained in other databases. Generally, ChemIDplus of the U.S. National Library of Medicine was used for that purpose.

For these analyses, reference substances assigned in the REACH registration dossiers were also checked in case of doubt[23].

Step 3: Identical predictions

If none of the above steps identified the most appropriate dataset, the predictions of log Kow, log Koa, biotransformation half-live and all three BIOWIN modules were checked for duplicate datasets. If all these predictions were identical between datasets, only one datasets was retained. Since these parameters are decisive for the evaluation of biodegradation and bioaccumulation (see sections 2.2.2 and 2.2.4 below) identical parameters will lead to identical results for these two endpoints.

[22] Substances of unknown or variable composition, complex reaction products or biological materials. Note that the profilers employed are based on the SMILES notation. If 'representative' SMILES notations were assigned to UVCB substances, these may be profiled as 'discrete chemicals' although they are complex mixtures.

[23] In the course of preparing a registration dossier with the obligatory IUCLID software, registrants typically assign a reference substance to the substance registered. Reference substances contain several data elements (e.g. EC and CAS numbers, Molecular formula and SMILES notations, but not all data are always available) that unequivocally identify a substance. Reference substances are made available to IUCLID users in a separate database to ensure consistency.

Step 4: Exclusion of UVCB substances

If all the steps above did not allow identifying a representative structure, duplicate datasets were checked against the REACH registration dossier to identify the most appropriate structure[24]. In almost all cases, the substances turned out to be UVCB substances. Since consultation of the REACH registration dossier did not allow identifying an appropriate structure among these duplicates, all datasets for the substance (identified by the CAS number) were removed. Note that step 2 above also covered UVCB substances. In these cases, however, a representative substance for the structure in the dataset could be identified.

Step 5: Exclusion since properties cannot be predicted

As a last step, datasets were excluded for which at least one of the critical properties (see Step 3 above) could not be predicted. This last step did not specifically address duplicates, but rather excluded substances due to lacking information. During this step, a small number of substances were also excluded since the SMILES notation represented a charged molecule.

Overall, this hierarchical procedure removes duplicate datasets (without exclusion of substances from further evaluation) in steps 1-3. These steps are intended to ensure that the structures evaluated actually correspond to the substances registered under REACH. Steps 4-5 actually exclude substances from further evaluation. In these cases, no appropriate structure could be identified that is within the applicability domain of the models used in the assessments described below.

2.1.6. Summary of approach to substance selection

Figure 3 summarises the approach to substance selection. Handling of the data of REACH registrations is straightforward and easily generates a list of unique CAS numbers meeting the criteria described in sections 2.1.1 and 2.1.2.

The QSAR Toolbox was used in two runs: first, to first select substances for which a SMILES notation is available and second, to generate profiling results and predictions of critical input data for the evaluations in block B and C. Profiling as well as predicting the properties of a substance in the QSAR Toolbox are time-consuming and are entirely based on the SMILES notation. It was therefore important and advantageous to reduce the number of substances first by selecting those with a readily available SMILES notation.

[24] This step also involved checking the EU reference substance assigned in the REACH registration dossier.

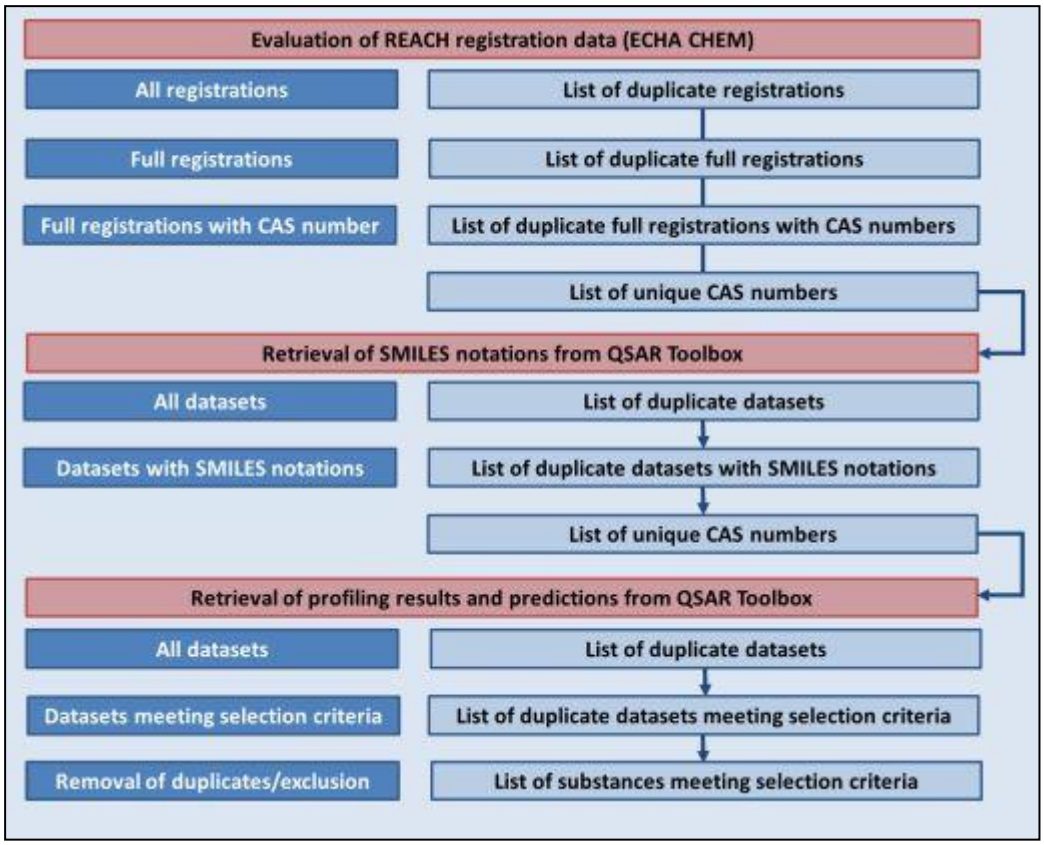


Figure 3: Summary of the approach to substance selection.

2.2. Data and methodologies on exposure and environmental fate

2.2.1. Releases to the environment: tonnage and use information (block A)

Releases to the environment are assessed on the basis of the tonnage manufactured and/or imported in the EU and the uses of a substance with respect to potential releases to the environment. The latter is evaluated on the basis of Environmental Release Categories (ERCs) assigned in REACH registration dossiers to the specific uses of a substance (Bitsch et al., 2016).

The total score for block A ('Total Score A' hereafter) is defined as:

Total Score A = Tonnage Score + ERC Score

The maximum score for both the Tonnage Score and the ERC Score is 5. The maximum Total Score A is therefore 10 (Bitsch et al., 2016).

The following data sources are used:

- Tonnage: The total tonnage band is publicly available from ECHA CHEM and represents the total tonnage manufactured and/or imported per registration. For any given substance, different registrations with different (or even identical) tonnage bands may exist. Tonnage bands are given as a range, with the minimum and maximum spanning a factor of 10 (e.g. 100 – 1 000 tonnes per annum).
- ERCs: Information on ERCs is also publicly available in ECHA CHEM. While for substance-specific assessments information on ERCs must be manually extracted from the REACH registration dossiers, ECHA CHEM allows extracting substances with defined ERCs assigned altogether[25]. For example, a list of substances can be extracted that have been assigned ERC 8C or ERC 8F. The

[25] Note that this feature was not implemented when this evaluation was performed in the pilot study.

resulting list also contains the tonnage band, a feature that is very useful in the evaluation for this study as discussed in the following paragraphs.

While the tonnage band and the information on ERCs could be extracted separately, such an approach would lead to a problem in the evaluation. Since any given substance may have more than one registration (also see section 2.1), extraction of the tonnage band and the ERCs separately may lead to a situation where the tonnage band comes from one registration, while the ERCs come from a different registration. Since scores for the tonnage and the ERCs are added up, taking this information from different registrations may overestimate the score.

As a consequence, Bitsch et al. (2016) recommended to extract lists of substances with defined ERCs in a hierarchical way starting with the ERCs leading to the highest score down to the one leading to the lowest score (see Table 4). This approach has two major advantages:

- It ensures that the tonnage information and the ERC actually come from the same registration dossier[26].
- In some cases, the total score for block A is so high that further evaluations are not required (see scoring system and Figure 5 below). The number of substances that need to be scored therefore decreases with each extraction.

Table 4 shows the ERC descriptions and the ERC Scores assigned to each individual ERC. The derivation of these scores is explained in Bitsch et al. (2016). The number of 12 different ERC Scores requires 12 different runs, i.e. extractions from ECHA CHEM.

Table 4: Scoring system for use information (ERCs).

ERC no.	ERC description	ERC Score[(a)]	Run[(b)]
4	Industrial use of processing aids	5	
8A	Wide dispersive indoor use of processing aids, open	5	
8D	Wide dispersive outdoor use of processing aids, open	5	1
10B	Wide dispersive outdoor use of long-life articles, high or intended release	5	
11B	Wide dispersive indoor use of long-life articles, high or intended release	5	
5	Industrial inclusion into or onto a matrix	2.5	2
6D	Industrial use of auxiliaries for polymerisation	1.75	3
3	Formulation in materials	1.5	4
12B	Industrial processing of articles with abrasive techniques (high release)	1	5
8C	Wide dispersive indoor use, inclusion into or onto a matrix	0.75	6
8 F	Wide dispersive outdoor use, inclusion in matrix	0.75	
1	Manufacture of chemicals	0.3	7
6A	Industrial use of intermediates	0.25	
6B	Industrial use of reactive processing aids	0.25	
6C	Industrial use of monomers for polymerisation	0.25	8
7	Industrial use of substances in closed systems	0.25	
9A	Wide dispersive indoor use in closed systems	0.25	
9B	Wide dispersive outdoor use in closed systems	0.25	
10A	Wide dispersive outdoor use of long-life articles, low release	0.16	9
2	Formulation of mixtures	0.125	10
12A	Industrial processing of articles with abrasive techniques (low release)	0.125	
8B	Wide dispersive indoor use of reactive substances, open	0.1	11
8E	Wide dispersive outdoor use of reactive substances, open	0.1	
11A	Wide dispersive indoor use of long-life articles, low release	0.0025	12

(a): Maximum normalised score for any of the three compartments (air, water or soil), see Appendix C.
(b): Run of extractions of substance lists from ECHA CHEM.

[26] Note, however, that this approach may still lead to overestimating environmental releases, since the total tonnage may not necessarily be used in a use that is assigned the ERC with the highest score.

Figure 4 illustrates the parameters for the extraction of the list of substances from ECHA CHEM that are assigned any of the five ERCs leading to an ERC Score of 5 (see Table 4).

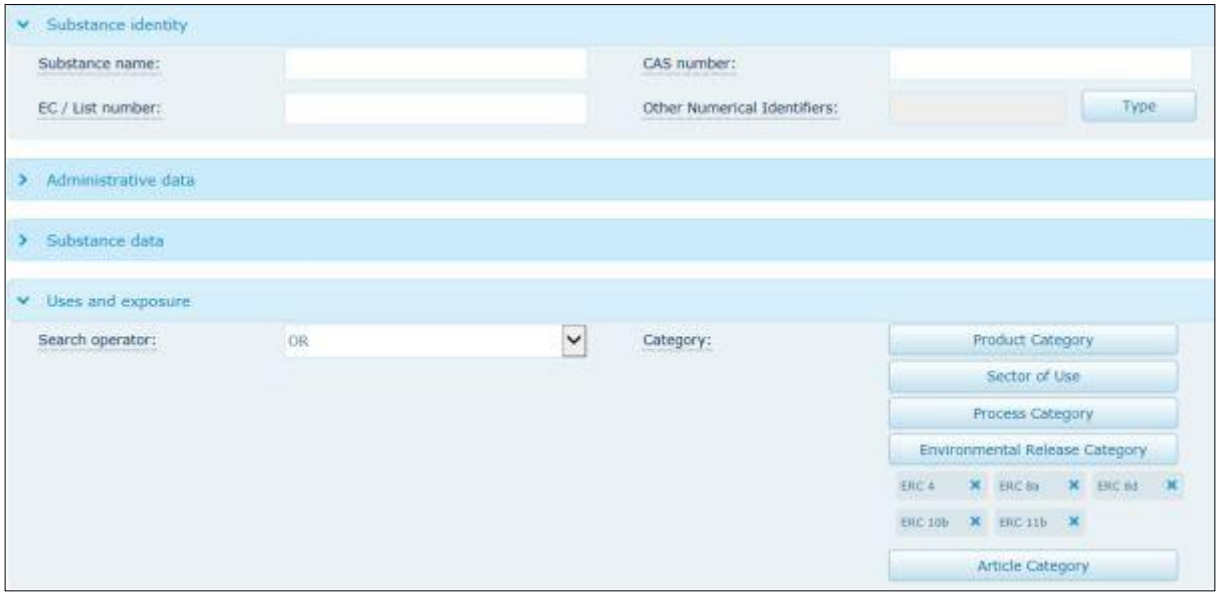


Figure 4: Print screen from ECHA CHEM defining the parameters for extracting the list of substances leading to an ERC Score of 5 (ERC 4, 8A, 8D, 10B or 11B).

As already mentioned above, the Microsoft Excel® file from ECHA CHEM also includes the tonnage band. Therefore, all substances in an extracted list can immediately be scored[27]. For the Tonnage Score, the maximum of the tonnage band is taken and scored according to Table 5 (Bitsch et al., 2016). If the tonnage band was given with the lower end only (e.g. '10+ tonnes per annum'), a 10-times higher values was chosen (100 tonnes per annum in this example) as described in Bitsch et al. (2016).

Table 5: Scoring system for the REACH registration tonnage.

Maximum of REACH registration tonnage band [tpa]	Score
≥10 000 000	5
1 000 000 - <10 000 000	4
100 000 - <1 000 000	3
10 000 - <100 000	2
<10 000	1

In some cases, the first extraction (i.e. substances with an ERC Score of 5) may already lead to a high Total Score A of 8, 9 or 10 that cannot be exceeded by any other combination of ERC and Tonnage Scores (Figure 5). In such cases, the substance does not need to be evaluated further in block A, since the total score for this block is fixed. For the remaining substances, the extraction with the next highest ERC Score is used for evaluation and this procedure is applied until all substances are assessed (see below for substances with missing data).

[27] Technically, the tonnage in the resulting list must first be sorted in descending order, to retrieve the highest tonnage in cases, where more than one registration exists.

		Tonnage Score				
		5	4	3	2	1
ERC Score	5	10	9	8	7	6
	2.5	7.5	6.5	5.5	4.5	3.5
	1.75	6.75	5.75	4.75	3.75	2.75
	1.5	6.5	5.5	4.5	3.5	2.5
	1	6	5	4	3	2
	0.75	5.75	4.75	3.75	2.75	1.75
	0.3	5.3	4.3	3.3	2.3	1.3
	0.25	5.25	4.25	3.25	2.25	1.25
	0.16	5.16	4.16	3.16	2.16	1.16
	0.125	5.125	4.125	3.125	2.125	1.125
	0.1	5.1	4.1	3.1	2.1	1.1
	0.0025	5.0025	4.0025	3.0025	2.0025	1.0025

Figure 5: Matrix for the combined evaluation of Tonnage Scores and ERC Scores.

After all 12 extractions have been completed and scoring performed, the maximum total score for block A was calculated. In principle, different total scores may result from different registrations for the same substance, and a substance may be assigned a higher Total Score A, even if the ERC Score is lower. Table 6 illustrates such a case.

Table 6: Illustrative example for scoring information from two different registrations for the same substance.

Parameter	Registration 1	Registration 2
Maximum of REACH registration tonnage band [tpa]	10 000	10 000 000
Tonnage Score	2	5
ERC Score	5	2.5
Total Score A	7	7.5

The approach employed ensures that the information from different registrations is not lost and that the highest Total Score A is used in the assessment. This also applies to those substances assigned a Total Score A ≥ 8, since a higher Total Score based on subsequent runs is impossible (see Figure 5).

The example in Table 6 also shows that the retrieval of the tonnage during the ERC-based extraction prevents some overestimates. Had the information been retrieved separately, the Total Score A would have been 10 (Tonnage Score 5 from registration 2 and ERC Score 5 from registration 1) instead of 7.5.

Despite the efforts described above, there is an uncertainty inherent in Total Score A. This uncertainty results from the fact that the maximum tonnage used may not be necessarily associated with the use leading to the highest ERC score. For example, a substance may have a maximum tonnage of 100 000 tpa, but only 100 tpa of this maximum may be applied in uses leading to the highest ERC Score. More detailed information, e.g. an allocation of the tonnage to specific uses, is available in chemical safety reports (CSRs). However, this information was not available for evaluation, since CSRs are confidential[28].

[28] It would also impossible to evaluate CSRs for such a large number of substances, since this would involve manual extractions.

The outcome of this evaluation is a list of all 2 336 selected substances with a Tonnage Score, an ERC Score and a Total Score A. However, preliminary evaluations showed that the information required for block A may be missing. Specifically, the following cases were observed:

- The tonnage data is claimed confidential.
- No ERC could be extracted with the approach described above.
- The tonnage data is claimed confidential and no ERC could be retrieved.

Therefore, the following approach for handling missing data was developed. In principle, missing information should be scored conservatively with the maximum score for tonnage and use information, since the tonnage may be high and the use pattern may show a high potential for releases to the environment. This would lead to the assignment of a Total Score A of 10 in cases where information on both the tonnage and the ERC is missing. Such substances may then appear at later stages in the selection of potential emerging chemicals risks, although their releases to the environment may in fact be substantially lower. As a consequence, a slight modification to such a worst case approach to handling missing data was implemented with respect to the type of submission of REACH registration dossiers (individual vs. joint):

- Tonnage data confidential:
  - Joint submission: Tonnage Score 5
  - Individual submission: Tonnage Score 2.5 (one half of the maximum)
- No ERC available: ERC Score 5

The rationale for differentiating joint and individual submissions is based on the fact that several companies are part of a joint submission, while an individual submission represents only a single company. While this does not necessarily mean that the tonnage of an individual submission is lower, it appears reasonable to assume this to be the general case. When the data for all registrations with tonnage data (i.e. not restricted to the selected substances) are compared by submission type (joint or individual), the data support this assumption. Figure 6 show that 90 % of individual submissions relate to registrations at low tonnages (Tonnage Score 1) with only 2 % registered at maximum tonnages that lead to a Tonnage Score of 3. A default Tonnage Score of 2.5 for substances that are lacking tonnage information and were registered by individual submission is therefore considered a conservative assumption. The data also support the use of a default Tonnage Score of 5 for joint submissions to avoid false negatives since almost 10 % of the registrations from joint submissions receive a Tonnage Score of 4 or 5.

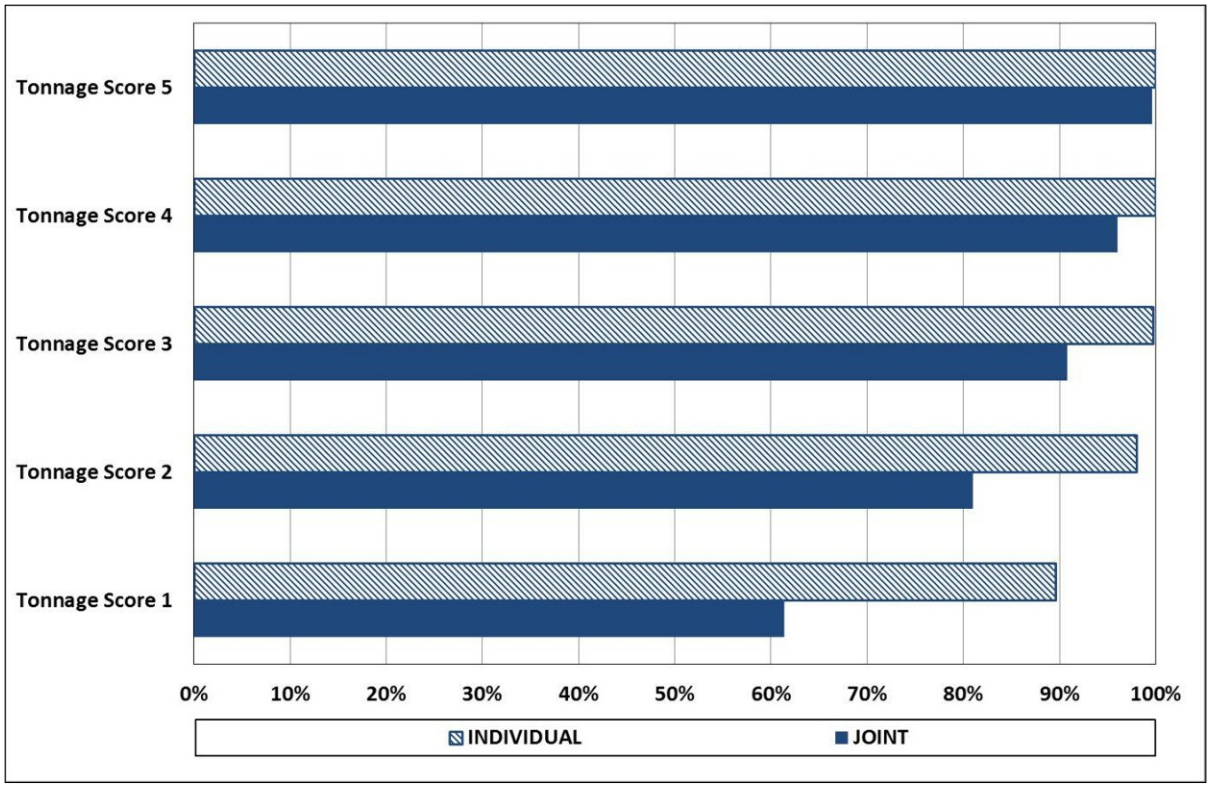


Figure 6: Comparison of Tonnage Score distribution in joint and individual submissions of REACH registrations (cumulative percentage based on 7 475 registrations with tonnage information).

There were a few exceptional cases, in which the first extraction (ERC Score 5) led to a Total Score A of 8 or 9 and no further evaluations were performed for reasons outlined above. In some of these cases, other registrations may exist with no information on both the tonnage band and the use pattern (ERCs). If these are joint submissions, they would theoretically lead to a Total Score A of 10. While this is higher than the one originally assigned, it is also associated with a higher uncertainty. Since the original Total Score A is high and based on available information, the default values were not applied in cases like this.

However, the ERC-based extraction may also result in cases where a substance can be scored after the 12 extraction runs described above and the resulting Total Score A may be low (e.g. 2.5 based on a Tonnage Score of 1 and an ERC Score of 1.5). Another registration for the same substance may exist with a higher tonnage and without any information on the ERC (resulting in assignment of the default ERC Score of 5). This issue was checked, but occurred only in a single case, where 'ERC 0'[29] was assigned, which cannot be extracted from ECHA CHEM. In this specific case, 'ERC 0' reflects very specific uses in an individual submission with low environmental releases[30]. The default ERC Score was not applied and the evaluation based on the registration with information on the tonnage and the ERC retained.

Since the use of these default scores introduces uncertainty to the assessment in block A, the resulting list identifies those substances, for which default scores – either for the tonnage, the use information or both – were assigned.

The final outcome of the evaluation in block A is a list of the 2 336 selected substances with ERC Scores, Tonnage Scores and Total Scores A. In addition, substances for which these scores are based on defaults for missing data can be easily identified.

[29] 'ERC 0' is sometimes assigned in cases, where other descriptors are used, such as specific Environmental Release Categories developed by some industrial and trade associations.
[30] According to the specific Environmental Release Categories assigned in the registration dossier.

2.2.2. Fate: biodegradation (block B)

As recommended by Bitsch et al. (2016), a battery approach of combined QSAR models was applied to assess biodegradation of the selected substances. The developed battery approach combines results of the QSAR models BIOWIN3, BIOWIN5 and BIOWIN6, which are available in the QSAR Toolbox. The battery approach assigns a final score to each of the substances by taking every single output of the BIOWIN models into account (Figure 7). The method is straightforward and easy to apply. BIOWIN models used in the battery approach are shortly introduced below:

- **BIOWIN3**: an expert survey model on ultimate biodegradation,
- **BIOWIN5**: Japanese MITI (Ministry of International Trade and Industry) linear model to predict ready biodegradability,
- **BIOWIN6**: Japanese MITI (Ministry of International Trade and Industry) non-linear model to predict ready biodegradability.

After BIOWIN3/5/6 results were generated within the QSAR Toolbox, they were extracted in order to perform further assessments. BIOWIN3/5/6 results could be generated for the complete substance set (N=2 336), and therefore missing data was not a problem. The battery evaluation of BIOWIN3/5/6 results was performed by simple algorithms that were implemented in Microsoft Excel®.

The scoring followed the recommendations by Bitsch et al. (2016) (Figure 7). In principle, a minimum score of 1 was assigned to substances that were predicted as 'readily biodegradable' in all three models and a maximum score of 10 to substances that were predicted as 'not readily biodegradable' or not 'inherently biodegradable'. The procedure of the battery evaluation is shown in the following figure.

The application of the battery approach results in Score B (biodegradation score) for all 2 336 substances.

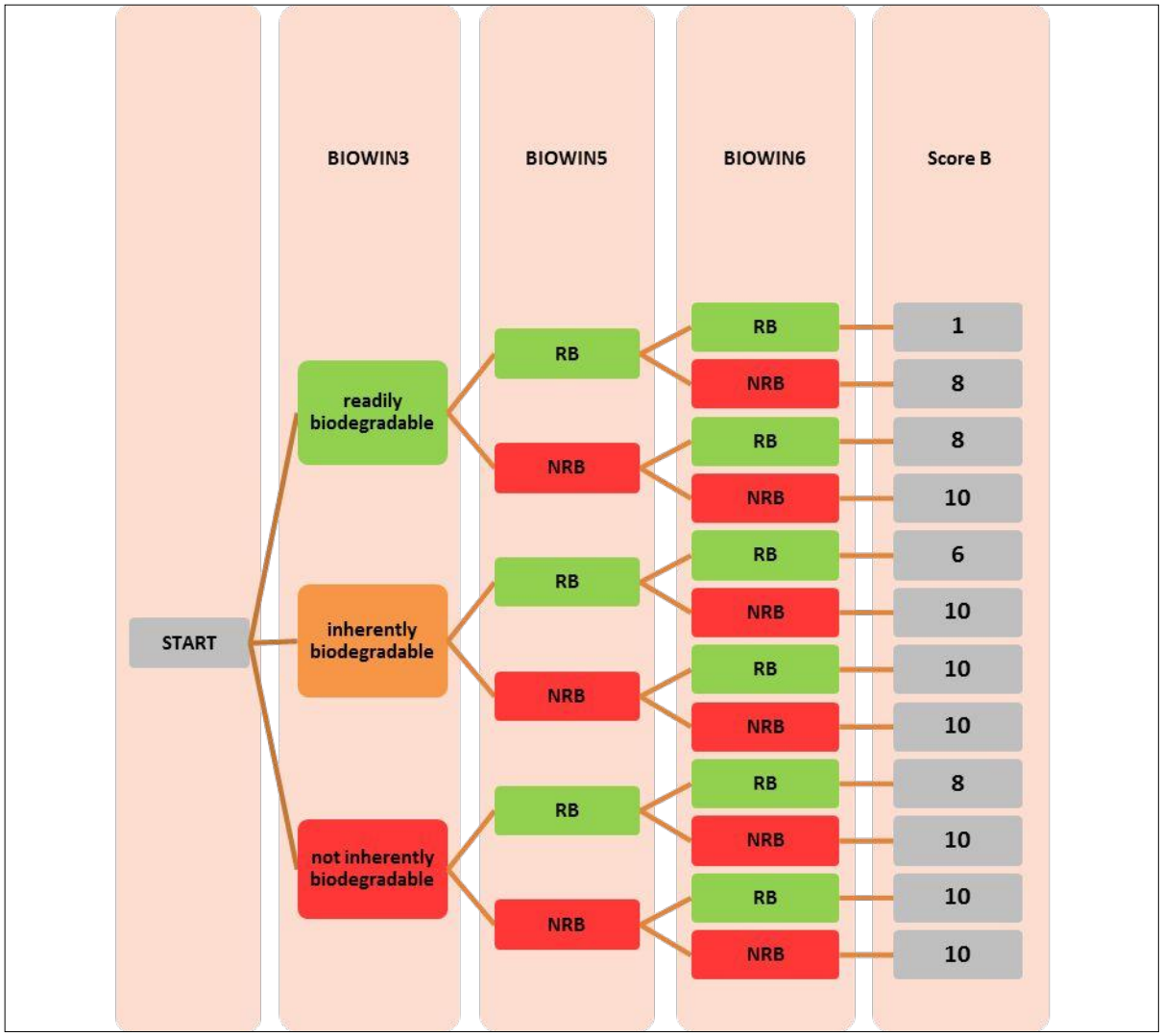


Figure 7: Battery evaluation of BIOWIN3, BIOWIN5 and BIOWIN6 model predictions and scoring according to Bitsch et al. (2016)

Note: RB — readily biodegradable; NRB — not readily biodegradable; score for combination (a) readily biodegradable (BIOWIN3), readily biodegradable (BIOWIN5) and readily biodegradable (BIOWIN6) and (b) not inherently biodegradable (BIOWIN3), readily biodegradable (BIOWIN5) and readily biodegradable (BIOWIN6) was adapted from Bitsch et al. (2016). Note that the combination not inherently biodegradable (BIOWIN3), RB (BIOWIN5) and RB (BIOWIN6) was incorrectly depicted in Bitsch et al. (2016) as leading to a score of 10. The correct score of 8 was used in the evaluations performed by Bitsch et al. (2016) and is shown in this figure.

Block B only assesses biodegradation, i.e. the degradation of a chemical substance by microorganisms. Abiotic degradation processes, such as hydrolysis or phototransformation, are not covered. There are several reasons for this:

- Data on hydrolysis could in principle be predicted by models available in the QSAR Toolbox similar to other properties, such as the BIOWIN predictions, described above. However, the underlying models have a very limited applicability domain and can only predict hydrolysis half-lives for a few classes of chemicals (e.g. esters, carbamates, epoxides and halomethanes). As a consequence, data on hydrolysis would not be available for several of the selected substances and a default approach (conservatively assuming no hydrolysis) would need to be applied for these substances. The assessment would therefore rather reflect the applicability domain of the hydrolysis models than provide meaningful results for a screening assessment.
- While models for phototransformation in air have a wider applicability domain, this degradation pathway is of limited relevance in this study. Thus, a substance should not be excluded from

further consideration solely based on rapid phototransformation in air, since emissions to aquatic compartments may lead to accumulation in food/feed.

- Inclusion of additional sets of predicted data (i.e. for hydrolysis and phototransformation) would increase the overall uncertainty in the evaluation and run the risk of exclusion of false negatives.
- While experimental data could in principle be extracted via eChemPortal, experimental data on phototransformation in air are rarely available and experimental data on hydrolysis require detailed evaluation. ECHA (2017a) stated that a concern for persistent properties '*cannot be removed by significant and substantial loss of the parent substance by hydrolysis alone. Careful consideration of the hydrolysis test is required (for example mass balance is needed to address concerns for losses by volatilisation or absorption to glassware). Rapid hydrolysis also needs to be shown across all environmentally relevant pH. Additional evidence is also needed to examine whether the fate properties of the substance would cause attenuation of the hydrolysis rate in sediment or soil, or whether DOC would similarly affect the rate in aquatic media such as river or sea water. Additional studies, e.g. examining the influence of dissolved organic carbon / adsorption processes on hydrolysis rates, may be necessary for this*.'
- More generally, ECHA (2017a) noted that abiotic processes alone should not be used in an assessment of the persistence of a substance. Furthermore, these authors emphasised that abiotic degradation represents primary degradation and an evaluation of the degradation products is required. Such an evaluation is clearly outside the scope of the screening procedure applied in this study.

Based on these considerations, this study did not cover abiotic degradation. While biodegradation is considered a more important degradation pathway than abiotic processes for the majority of substances covered by this study, abiotic degradation processes should be manually checked prior to any more time-consuming, subsequent evaluation steps. Such a manual evaluation is shown in the selection of substances for in-depth evaluation in this study (see section 2.5 and 3.5).

2.2.3. Fate: validation of predicted biodegradation data (block B)

The use of predicted biodegradation data in a battery evaluation and subsequent scoring as outlined above was already subjected to a limited validation with experimental data in Bitsch et al. (2016). In fact, both the difficulties in evaluating experimental data as well as the good agreement of the scores resulting from predicted data with those resulting from experimental data led to the recommendation to use predicted data for biodegradation (Bitsch et al., 2016).

However, the previous validation was limited to comparatively few substances (N=100) and therefore involves some uncertainty. In order to further validate the approach of using predicted biodegradation data in a battery evaluation for subsequent scoring in a screening procedure, the 2 336 substances selected (see section 3.1) were further analysed.

For this purpose, key values on biodegradation from REACH registration dossiers were used[31]. Such key values are derived by registrants on the basis of experimental data and are then used in the chemical safety assessment (CSA) under REACH. They represent a summary of available data in the form of a single interpretation to be selected from a drop-down list in the IUCLID software[32] (e.g. 'readily biodegradable' or 'under test conditions no biodegradation observed'). The derivation of key values is not a legal requirement. However, key values must be provided in IUCLID to enable their use in the Chemical Safety Assessment and Reporting (CHESAR) tool[33]. As a consequence, it was expected that such key values would be available at least for some of the 2 336 selected substances.

[31] As the most basic information on biodegradation already required at low registration tonnages, biodegradation in water from screening tests was evaluated.

[32] IUCLID (International Uniform ChemicaL Information Database) 'is a software application to record, store, maintain and exchange data on intrinsic and hazard properties of chemical substances.' (https://iuclid6.echa.europa.eu/de/project-iuclid-6, accessed May 2017). Article 111 of the REACH Regulation states explicitly that data shall be submitted to ECHA in IUCLID format.

[33] Use of this tool is highly promoted by ECHA for the chemical safety assessment. The Chemical Safety Report (CSR) can be automatically generated from within the CHESAR tool.

Key values are not disseminated by ECHA via ECHA CHEM, i.e. they are considered confidential and are not publicly available. For this validation study, ECHA extracted key values for the 2 336 substances (if available). Compounds with key values based on experimental data were scored according to the approach described in Bitsch et al. (2016). For each substance, the resulting scores from predictions and key values were assigned to one of the following three persistence classes[34]:

- Scores 8 and 10, reflecting a low degree of biodegradation, i.e. high persistence (HIGH)
- Scores 4 and 6, reflecting a moderate degree of biodegradation (MODERATE) and
- Scores 1 and 2, reflecting a high degree of biodegradation, low persistence (LOW).

These classes are expressed in terms of persistence, since the expression based on the degree of biodegradation (e.g. LOW for scores 8 and 10) was considered counter-intuitive. The term persistence used in this context only addresses biodegradation from screening tests in water and should not be taken as 'overall persistence' or persistence in the meaning of a full PBT assessment.

These three persistence classes follow the ones used in the previous validation described in Bitsch et al. (2016). They are meaningful, since the main aim of the evaluation of biodegradation is the identification of poorly biodegradable substances and the validation can therefore focus on the correct differentiation of poorly biodegradable substances (scores 8 and 10) from biodegradable substances (scores 1 and 2). For example, a substance with a score of 8 from predicted data and a score of 10 based on the key value is assigned to the same class (HIGH). In contrast, a substance with a score of 1 from predicted data and a score of 10 based on the key value is assigned to a different class (LOW and HIGH, respectively). The results of these comparisons were then analysed statistically and all key values for individual substances deleted after completion of the analyses[35].

In order not to lose any information, ECHA extracted key values for biodegradation from all dossiers available for a given substances. As shown in section 3.2.3, this led to more than one key value for a given substance in a few cases. As a consequence, different scores may result for a substance, for which more than one key value was retrieved. In order to address this issue, the statistical analyses were performed in two ways:

- Least conservative key value: the least conservative key value was taken and used for scoring. For example, if the key value 'readily biodegradable' was retrieved, this was used irrespective of the other key value(s) retrieved for this substance. This results in a score of 1 for biodegradation (see scoring described in section 2.2.2 above),
- Most conservative key value: the most conservative key value was taken and used for scoring. For example, if the key value 'under test conditions no biodegradation observed' was retrieved, this was used irrespective of the other key value(s). This results in a score of 10 for biodegradation (see scoring described in section 2.2.2 above).

The two approaches then reflect the extremes of the key values assigned to a given substance. This was considered the most meaningful approach to the issue of differing key values for a given substance, since (a) this issue only occurs for few substances (see section 3.2.3) and (b) a substance-specific discussion of the experimental data and the most meaningful key value was impossible since key values are confidential.

2.2.4. Fate: bioaccumulation in food and feed (block C)

The evaluation of bioaccumulation of chemicals in food and feed was performed according to the recommendations in Bitsch et al. (2016). Bioaccumulation in food and feed of the 2 336 selected substances was predicted with ACC-HUMANsteady. ACC-HUMANsteady is a steady-state mechanistic mass-balance model, which is implemented in Microsoft Excel®. ACC-HUMANsteady consists of a number of modules for chemical bioaccumulation in food and feed. Eleven food items were selected to cover the food categories fish, meat and milk products as well as fruits and vegetables (for specific

[34] These classes are expressed in terms of persistence (simplified here to mean biodegradation from screening tests in water only), since the expression based on the degree of biodegradation (e.g. LOW for scores 8 and 10) was considered counter-intuitive.

[35] This work was performed by the authors of this study at ECHA premises, since the data for individual substances are confidential and were not available for further use outside the statistical evaluation described above.

food items see Table 7). In addition, the module for chemical bioaccumulation in grass was used as a feed item.

Table 7: ACC-HUMANsteady: outline of food/feed items and model input parameters (Bitsch et al. (2016)

Food category	**Fish**		**Meat & milk products**				**Fruits and vegetables**					
							Fruit[a]		Leaf[a]		Root[a]	Tuber[a]
Food/feed item	planktivore[b]	piscivore[c]	beef cattle	dairy cattle[e]	milk	dairy products	apple	grain	lettuce	grass[d]	carrot	potato
Chemical input parameter	*Compound non-specific:* ○ default scenario of ACC-HUMANsteady used for all substances ○ non-lipid organic matter fraction (β) ○ heat of phase transfer (dUow) [J/mol] *Compound specific:* ○ molecular weight [g/mol] ○ log Koa (cut-off values 4 and 12) ○ log Kow (cut-off values -2 and 12) ○ metabolism rate constants ($k_{M\_benthos}$, k_{M_fish}, k_{M_cattle}, k_{M_plants}) [h^{-1}] ○ heats of phase transfer (dUoa, dUaw) [J/mol]											

(a): Plant compartments simulated in ACC-HUMANsteady
(b): Labelled as 'Fish 1' in ACC-HUMANsteady
(c): Labelled as 'Fish 2' in ACC-HUMANsteady
(d): 'Grass' is considered as feed item and undergoes a separate evaluation.
(e): Called 'milk cow' in ACC-HUMANsteady

In order to make parallel processing of many substances possible, a batch version of ACC-HUMANsteady was developed[36] that was applied in this study. Prior to the application to the 2 336 selected substances, ACC-HUMANsteady batch was validated with the same data set of 104 substances that was used for method development in Bitsch et al. (2016). This validation showed that ACC-HUMANsteady batch version predicts identical results as ACC-HUMANsteady applied in Bitsch et al. (2016). The validation ensures that the batch version of ACC-HUMANsteady can be used in the present study.

ACC-HUMANsteady was selected for the evaluation of bioaccumulation in food/feed primarily for the following reasons:

- The software calculates concentration in eleven food items and one feed item, which is a comparatively large number of food items and therefore meaningful to EFSA.
- The software, unlike most other software tools, can be run in batch which is required for a screening procedure as the one used in this project.
- All compound-specific input data can be predicted by the QSAR Toolbox, which is useful in the context of this screening procedure.
- The software implements more up-to-date models than e.g. the EUSES software used for assessing human exposure via the environment under the REACH Regulation (Undeman and McLachlan, 2011).

Limitations of the software are discussed in section 3.2.4.

[36] The batch version was kindly programmed by the developers of the software (Emma Undeman, Matthew MacLeod, Stockholm University, Sweden).

Details on ACC-HUMANsteady model application are described in Bitsch et al. (2016). In short, the 'default scenario' of ACC-HUMANsteady for the environment was used for model simulations and therefore no further model adaptations are necessary. This default environmental scenario of ACC-HUMANsteady is set in accordance with the regional default scenario of EUSES (RIVM, 2004) in relation to the physical (abiotic) environment. For example, an area of 40 400 km^2 and a height of the air compartment of 1 000 m is considered for this region (Czub and McLachlan, 2004). The 'default scenario' further assumes a total amount of 1 tonne of a chemical present in this region (identical for each substance), which is distributed into the different compartments and – ultimately – food/feed items until a steady-state is reached. These distribution and partitioning processes depend on the physico-chemical properties of the substance and the concentrations predicted are also impacted by the biotransformation half-lives. As a consequence of assuming a default tonnage being present in a default regional environment (rather than substance-specific emissions[37]), absolute concentrations predicted by ACC-HUMANsteady in this study have no meaning and the evaluation is entirely based on relative considerations as explained below.

ACC-HUMANsteady requires several substance-specific parameters. Model input parameters were collected in a separate Microsoft Excel® data sheet and converted or calculated where necessary. All required input parameters are outlined in Table 7 and specifications are provided in Table 8. Compound-independent parameters were non-lipid organic matter fraction (β) and heat of phase transfer octanol-water (dUow). Compound-specific parameters were molecular weight, log Koa, log Kow, metabolism rate constants and heats of phase transfer octanol-air and air-water (dUoa, dUaw). All compound-specific parameters could be either directly generated by the QSAR Toolbox (i.e. molecular weight log Koa, log Kow) or calculated with values derived from the QSAR Toolbox (i.e. heats of phase transfer (dUoa, dUaw), metabolism rate constants). No input data were missing.

There are three kinds of log Kow values integrated in the QSAR Toolbox, i.e. experimental log Kow values (Exp Log P), predicted log Kow values by KOWWIN (V1.68) (log Kow) and values predicted by the Multicase programme (logP Multicase). These were used in a tiered approach as described and justified in Bitsch et al. (2016). First, existing experimental log Kow values were selected. If these were not available, values could be retrieved with KOWWIN (V1.68) for all remaining substances. Therefore, the use of logP Multicase was not necessary. With respect to log Koa, the complete data set was generated with KOAWIN (V1.10) based on the air-water partition coefficient model. Cut-off values were set for log Koa and log Kow, because lower or higher values do not produce meaningful results in ACC-HUMANsteady. Lower and upper bound cut-off values for log Koa were 4 and 12, respectively. Lower and upper bound cut-off values for log Kow were -2 and 12, respectively (see Bitsch et al. (2016) for details). The biotransformation half-lives ($t_{1/2}$, days) for fish were extracted from the QSAR Toolbox and converted in metabolism rate constants (k_{M_fish}, h^{-1}). The following formula was applied:

$$k_{M\_fish} = {\ln(2)}/{t1_{/2}} \qquad [d^{-1}] = {\ln(2)}/{t1_{/2}} * {1}/{24} \qquad [h^{-1}].$$

[37] Such emissions tot he regional environment are estimated in environmental exposure assessments under the REACH Regulation, but are not publicly available.

Table 8: Details on compound-specific input parameters: non-lipid organic matter fraction, heats of phase transfer (J/mol) and metabolism rate constants (h-1) (Bitsch et al., 2016)

Non-lipid organic matter fraction [-]	Heats of phase transfer [J/mol]	Metabolism rate constants [h^{-1}]
β = 0.035 (a)	ΔUow = -20 000 (b)	**Benthos**(d) $k_{M\_benthos} = k_{M\_fish} * 1$ ICF = 1
	ΔUoa = (-8.796 * log Koa – 13.57) * 1 000 (c)	**Fish** $k_{M\_fish} = k_{M\_fish} * 1$ ICF = 1
	ΔUaw = ΔUow – ΔUoa (b)	**Cattle** $k_{M\_cattle} = k_{M\_fish} * 4$ (e) ICF = 4
		Plants $k_{M\_plants} = k_{M\_fish} * 1$ ICF = 1

Note: Advice on parameter input: personal communication with Emma Undeman and Matthew MacLeod, ITM Stockholm, Sweden. ICF – interspecific correction factor.
(a): Taken from literature (Arnot and Gobas, 2004)
(b): Taken from literature (Armitage and Wania, 2013)
(c): Taken from literature (MacLeod et al., 2007)
(d): Organisms living in or on the seabed, such as worms, crabs and lobsters.
(e): Taken from literature (Takaki et al., 2015)

The scoring was performed as recommended by Bitsch et al. (2016). The scoring system was based on the modelled concentrations for the complete data set of 2 336 substances. The scoring of the substances consisted of two steps. In step 1, quartiles were calculated for each food/feed item from the concentrations modelled for the complete data set of 2 336 substances. In step 2, each of the 2 336 substances was scored according to the concentration modelled for this substance in the specific food/feed item. Scores assigned to concentration ranges (established in step 1) were:

- A score of 1 was assigned if the concentration of the substance was < 25th percentile of all concentrations in the respective food/feed item;
- A score of 3 was assigned if the concentration of the substance was < 50th percentile of all concentrations in the respective food/feed item;
- A score of 6 was assigned if the concentration of the substance was < 75th percentile of all concentrations in the respective food/feed item;
- A score of 10 was assigned if the concentration of the substance was ≥ 75th percentile of all concentrations in the respective food/feed item.

The information on a single substance in each food/feed item was stored. The maximum score retrieved in any of the food/feed items was selected as Score C (final bioaccumulation score).

2.3. Data and methodologies on toxicity

Information on toxicity is assessed on the basis of classification and labelling from different sources. Classification and labelling under the CLP Regulation[38] for the four endpoints evaluated (carcinogenicity - Category Carc. 1A, 1B and 2), mutagenicity (Category – Muta. 1A, 1B and 2), reproductive toxicity (Category – Repr. 1A, 1B and 2) and repeated dose toxicity (Category - STOT RE[39] 1 and 2) will be used. In addition, classification for carcinogenicity by the International Agency for Research on Cancer (IARC) will be used for the endpoint carcinogenicity (Group 1, 2A and 2B).

The following data sources are evaluated in a hierarchical approach as recommended in Bitsch et al. (2016):

- Harmonised classifications (i.e. classification agreed upon by EU Member States) for the four endpoints were extracted from the Classification & Labelling Inventory database (C&L Inventory hereafter). This information is available via the ECHA website under https://echa.europa.eu/de/information-on-chemicals/cl-inventory-database for download as a Microsoft Excel® file. Note that the information in this file was last updated in September 2016. Figure 8 illustrate such an entry (harmonised classification for formaldehyde).
- IARC: The carcinogenicity classifications Group 1, 2A and 2B from IARC was retrieved from the internet page of the International Agency for Research on Cancer (IARC). The classifications were available in a Microsoft Excel® file and the information was extracted. Note that the information in this file was last updated in May 2017.
- C&L Inventory: for information on classifications for the four endpoints from registrations under REACH (joint or individual submissions) or notifications without a REACH registration dossier[40]. The information from these self-classifications was extracted from the C&L Inventory, where the classification and labelling for every substance is available in a single page (see Figure 9 for an example). The page for every substance was opened semi-automatically using a KNIME[41] workflow. For the 2 336 selected substances, the information on classification and labelling from the source text was transferred to a Microsoft Excel® sheet. In the file, for every substance every classification for one endpoint present on the website is listed as one single row. After some curation steps (e.g. for substances with more than one CAS number), the information was converted to an access database for selection of information coming from joint or single registrations. Note that the data was extracted in May 2017, with some revisions in July 2017 for a small number of substances due to extraction errors.

  A notification is defined as a set of classifications for one or more endpoints. Each notification can be supported by one or more notifiers, i.e. these notifiers submitted an identical set of classifications. In the C&L Inventory, sets of classifications are presented as different notifications if they are not identical. Even if the differences are minor (e.g. target organ 'lungs' or 'lung damage'), they are treated as different notifications. The (semi-)automated KNIME workflow described above allowed the extraction of the entire classification information in all notifications. Classifications belonging to the same notification are identified by the same ID in the extracted data (see the last column in Figure 10 below).

From these three sources and taking into account information from ECHA on substances with registration dossier having classifications for the four endpoints, the following groups of classified substances can be distinguished:

- Harmonised classifications
- IARC classification
- Self classifications

[38] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

[39] Specific target organ toxicity – repeated exposure

[40] Both classifications from REACH registrations and those from other notifications are collectively called self-classifications as opposed to harmonised classifications agreed upon by EU Member States.

[41] KNIME ('Konstanz Information Miner') is a free software tool for data mining, machine learnng and interactive data analysis.

- Joint classifications (from REACH registration dossiers; submitted by the 'lead registrant' for a group of companies)
- Individual classifications (from REACH registration dossiers; submitted by an individual company)
- Other classifications (not from REACH registration dossiers)

2.3.1. Harmonised classifications

For the 2 336 selected substances, information on harmonised classification was downloaded as a Microsoft Excel® file from the ECHA website.

According to the CLP Regulation the classification for the different endpoint is defined as follows[42]:

Carcinogenicity

Category 1: Known or presumed human carcinogens

- Category 1A: Known to have carcinogenic potential for humans, classification is largely based on human evidence
- Category 1B: Presumed to have carcinogenic potential for humans, classification is largely based on animal evidence

Category 2: Suspected human carcinogens

Mutagenicity

Category 1: Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans.

- Category 1A: The classification in Category 1A is based on positive evidence from human epidemiological studies.
- Category 1B: The classification in Category 1B is based on: – positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or – positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells.

Category 2: Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. The classification in Category 2 is based on: – Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from: – Somatic cell mutagenicity tests in vivo, in mammals; or – Other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays.

Reprotoxicity

Category 1: Known or presumed human reproductive toxicant

- Category 1A: Known human reproductive toxicant. The classification of a substance in this category is largely based on evidence from humans.
- Category 1B: Presumed human reproductive toxicant. The classification of a substance in this category is largely based on data from animal studies.

Category 2: Suspected human reproductive toxicant

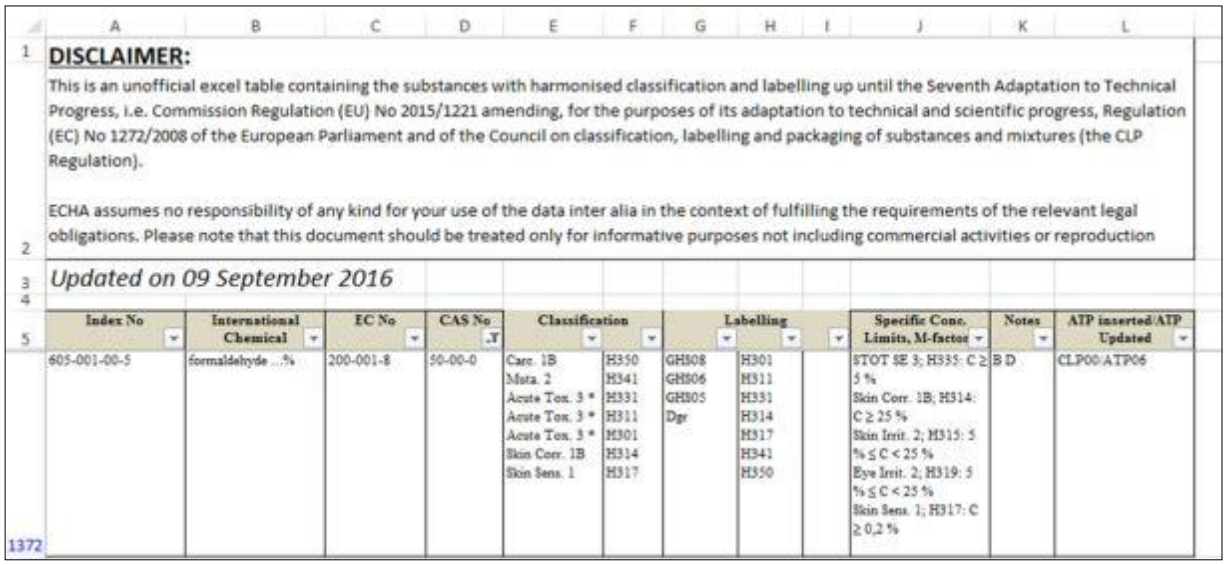
Specific target organ toxicity – repeated exposure

STOT RE 1: Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure.

[42] Regulation (EC) No 1272/2008; also see: Guidance on the Application of the CLP Criteria Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 5.0 July 2017

STOT RE 2: Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure.

The following figure shows the information available for formaldehyde in the harmonised classification file as an illustrative example.



DISCLAIMER:

This is an unofficial excel table containing the substances with harmonised classification and labelling up until the Seventh Adaptation to Technical Progress, i.e. Commission Regulation (EU) No 2015/1221 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

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Updated on 09 September 2016

Index No	International Chemical	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factor	Notes	ATP inserted/ATP Updated
605-001-00-5	formaldehyde ...%	200-001-8	50-00-0	Carc. 1B Muta. 2 Acute Tox. 3 * Acute Tox. 3 * Acute Tox. 3 * Skin Corr. 1B Skin Sens. 1	H350 H341 H331 H311 H301 H314 H317	GHS08 GHS06 GHS05 Dgr	H301 H311 H331 H314 H317 H341 H350		STOT SE 3; H335: C ≥ 5 % Skin Corr. 1B; H314: C ≥ 25 % Skin Irrit. 2; H315: 5 % ≤ C < 25 % Eye Irrit. 2; H319: 5 % ≤ C < 25 % Skin Sens. 1; H317: C ≥ 0,2 %	B D	CLP00/ATP06

1372

Figure 8: Screenshot for harmonised classification and labelling of formaldehyde (source: Microsoft Excel® file downloaded from C&L Inventory)

The information for each substance was extracted from the file and converted to a Microsoft Access® database to evaluate the information.

2.3.2. IARC classifications

The IARC classifications on carcinogenicity are also available as a Microsoft Excel® file. The information for each substance was extracted from this file and converted to a Microsoft Access® database to evaluate the information.

IARC[43] defines the classification for the endpoint carcinogenicity as follows:

IARC Group 1: The agent is carcinogenic to humans.

IARC Group 2A: The agent is probably carcinogenic to humans.

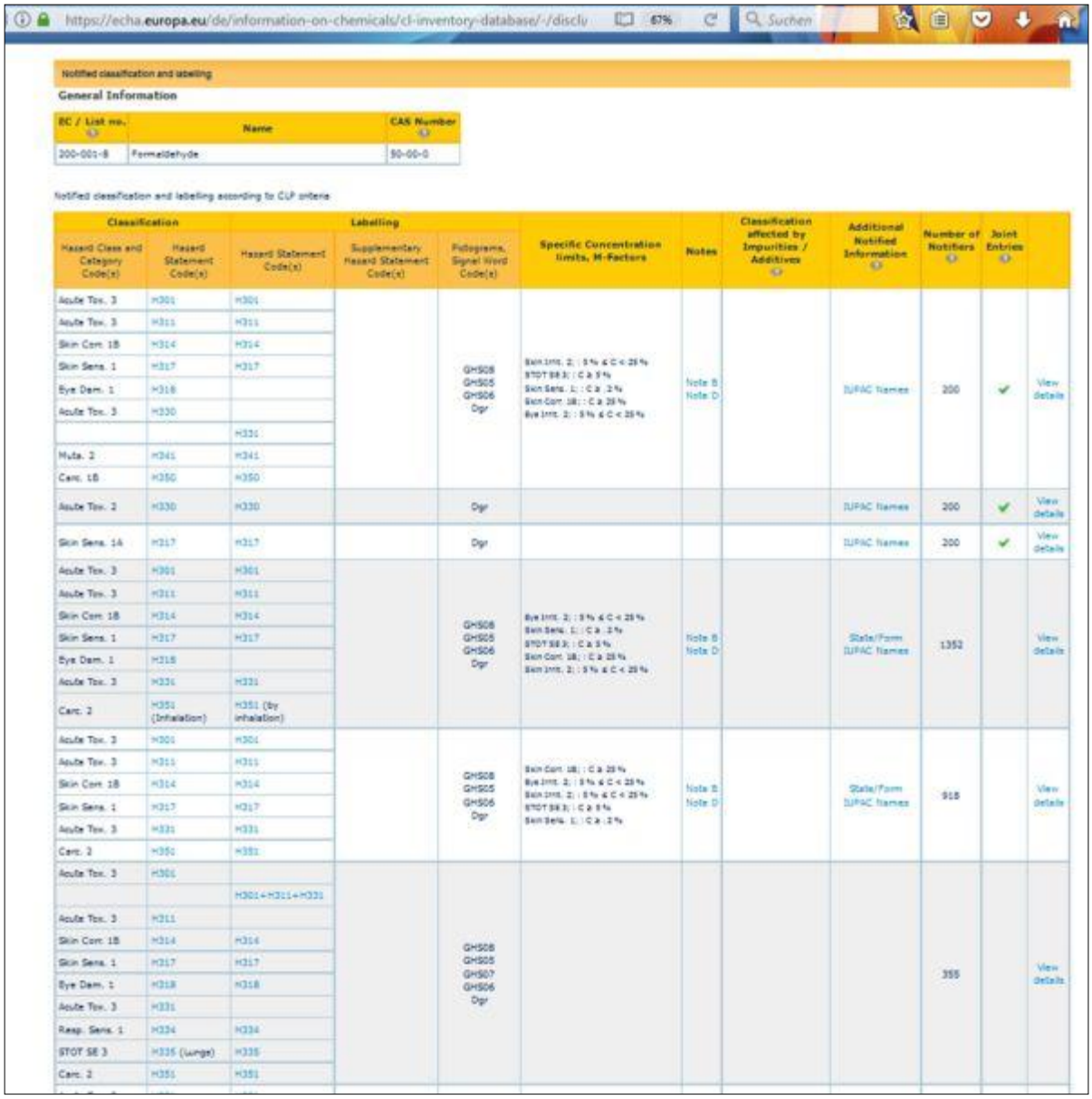
IARC Group 2B: The agent is possibly carcinogenic to humans.

2.3.3. Self-classifications from joint submissions under REACH

The information from self-classifications was derived from the C&L Inventory, where information from joint registrations is highlighted with a check mark symbol in the field joint entries. Substances having a registration dossier from a joint submission under REACH ('joint classifications' hereafter) are considered notified under the CLP Regulation.

The information for formaldehyde in the C&L Inventory is shown in the figure below.

[43] Preamble to the IARC Monographs B. SCIENTIFIC REVIEW AND EVALUATION 6. Evaluation and rationale. online available at http://monographs.iarc.fr/ENG/Preamble/currentb6evalrationale0706.php



Notified classification and labeling

General Information

EC / List no.	Name	CAS Number
200-001-8	Formaldehyde	50-00-0

Notified classification and labelling according to CLP criteria

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Classification affected by Impurities / Additives	Additional Notified Information	Number of Notifiers	Joint Entries	
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)							
Acute Tox. 3	H301	H301		GHS08 GHS05 GHS06 Dgr	Skin Irrit. 2; : 5 % ≤ C < 25 % STOT SE 3; : C ≥ 5 % Skin Sens. 1; : C ≥ 1 % Skin Corr. 1B; : C ≥ 25 % Eye Irrit. 2; : 5 % ≤ C < 25 %	Note B Note D		IUPAC Names	200	✔	View details
Acute Tox. 3	H311	H311									
Skin Corr. 1B	H314	H314									
Skin Sens. 1	H317	H317									
Eye Dam. 1	H318										
Acute Tox. 3	H330										
		H330									
Muta. 2	H341	H341									
Carc. 1B	H350	H350									
Acute Tox. 2	H330	H330		Dgr				IUPAC Names	200	✔	View details
Skin Sens. 1A	H317	H317		Dgr				IUPAC Names	200	✔	View details
Acute Tox. 3	H301	H301		GHS08 GHS05 GHS06 Dgr	Eye Irrit. 2; : 5 % ≤ C < 25 % Skin Sens. 1; : C ≥ 1 % STOT SE 3; : C ≥ 5 % Skin Corr. 1B; : C ≥ 25 % Skin Irrit. 2; : 5 % ≤ C < 25 %	Note B Note D		State/Form IUPAC Names	1352		View details
Acute Tox. 3	H311	H311									
Skin Corr. 1B	H314	H314									
Skin Sens. 1	H317	H317									
Eye Dam. 1	H318										
Acute Tox. 3	H331	H331									
Carc. 2	H351 (Inhalation)	H351 (by inhalation)									
Acute Tox. 3	H301	H301		GHS08 GHS05 GHS06 Dgr	Skin Corr. 1B; : C ≥ 25 % Eye Irrit. 2; : 5 % ≤ C < 25 % Skin Irrit. 2; : 5 % ≤ C < 25 % STOT SE 3; : C ≥ 5 % Skin Sens. 1; : C ≥ 1 %	Note B Note D		State/Form IUPAC Names	918		View details
Acute Tox. 3	H311	H311									
Skin Corr. 1B	H314	H314									
Skin Sens. 1	H317	H317									
Acute Tox. 3	H331	H331									
Carc. 2	H351	H351									
Acute Tox. 3	H301			GHS08 GHS05 GHS07 GHS06 Dgr					355		View details
		H301+H311+H331									
Acute Tox. 3	H311										
Skin Corr. 1B	H314	H314									
Skin Sens. 1	H317	H317									
Eye Dam. 1	H318	H318									
Acute Tox. 3	H331										
Resp. Sens. 1	H334	H334									
STOT SE 3	H335 (Lunge)	H335									
Carc. 2	H351	H351									

Figure 9: Screenshot for classification and labelling information of formaldehyde (source: C&L Inventory web page, accessed August 2017)

The information was derived from the C&L Inventory, transferred to the Microsoft Excel® file for further processing. Figure 10 shows the structure of the information. Only the information for the endpoints carcinogenicity and mutagenicity is shown for the sake of clarity. Differences in numbers of notifiers between Figure 9 and Figure 10 are due to different dates of extraction (May 2017 for extraction to Microsoft Excel® file and August 2017 for screenshot). The information from the C&L Inventory used for evaluation therefore represents the state at the time of extraction in May 2017 and may have been updated since then. Note that several notifications do not reflect the current harmonised classification (Carc. Cat. 1B), but report the old harmonised classification (Carc. Cat. 2). The joint classification correctly adapts the harmonised classification as Carc. Cat. 1B. This example illustrates that some of the notifications are out-dated and contravene the harmonised classification.

Number	new url	Status	EC	Name	CAS Number	Classificatio	No of Notifie	Joint Entries	ID
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Muta. 2	195	Yes	59435
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 1B	195	Yes	59435
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	1352		59438
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	918		59439
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	355		59440
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	102		59441
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Muta. 2	79		59442
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 1B	79		59442
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Muta. 2	77		59443
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 1B	77		59443
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Muta. 2	66		59444
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 1B	66		59444
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Muta. 2	46		59445
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 1B	46		59445
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	45		59446
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	37		59447
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Muta. 2	35		59448
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 1B	35		59448
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	33		59449
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	29		59450
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	27		59451
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Muta. 2	27		59452
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 1B	27		59452
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	26		59453
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	19		59455
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	18		59456
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Muta. 2	15		59457
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	15		59457
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	12		59458
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	11		59459
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	7		59460
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	6		59461
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 2	6		59462
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Muta. 2	6		59463
55163	https://echa	200	200-001-8	Formaldehyd	50-00-0	Carc. 1B	6		59463

Figure 10: Screenshot from classification information for carcinogenicity and mutagenicity of formaldehyde as available in the Microsoft Excel® file (data source: C&L Inventory web page, state May 2017)

The information for each substance was extracted from the file and converted to a Microsoft Access® database to evaluate the information.

2.3.4. Self-classifications from individual submissions under REACH

As for self-classifications from joint registrations the information from other self-classifications was also retrieved in the same way as described above. The information on classification and labelling from individual submissions under REACH ('individual classifications' hereafter), however, is not highlighted with a check mark symbol in the field joint entries (see Figure 9 above). As a consequence, classification information from individual submissions under REACH cannot be distinguished from other self-classifications (not coming from REACH registration dossiers) in the C&L Inventory, which are described in section 2.3.5.

Information provided by ECHA on substances with registration dossiers having classifications for the four endpoints was therefore used to further discriminate substances having no joint classification but an individual classification. ECHA generated a list of substances among the 2 336 selected substances that are classified for any of the four endpoints evaluated for the purpose of this study (483 substances in total). If any given substance did not have a joint classification, but was included in the ECHA list, this substance was considered to have an individual classification from a REACH registration

dossier for at least one of the four endpoints. Substances with an individual classification are also considered notified under the CLP Regulation. There are substances that have one or more joint as well as one or more individual classification. This is the case when two or more dossiers have been submitted under the REACH Regulation (also see section 2.1 for different registration and submission types). Due to the hierarchical approach, such substances are evaluated on the basis of the joint classification first (see above). Only if this does not include a classification for the four endpoints, an individual classification for these endpoints is considered. As a consequence, data for all individual classifications cannot be generated by the (semi-)automated procedure of data extraction and the number of substances with individual classifications for the four endpoints (i.e. the sum of those confirming a joint classification and those diverging from the joint classification), cannot be generated.

The information for each substance was extracted from the file and converted to a Microsoft Access® database to evaluate the information.

2.3.5. Self-classifications from notifications without a REACH registration

For this subgroup, classification information from notifications was also retrieved in the same way as described above. The information on classification from such notifications is not highlighted with a check mark symbol in the field joint entries (see Figure 9 above).

If a given substance did not have a harmonised classification, a joint classification and was not included in the list of 483 substances extracted by ECHA (see 2.3.4 above), the classification retrieved from the C&L Inventory was considered not to be coming from a REACH registration dossier. In this case, the classification results from notifications under the CLP Regulation from companies that did not have to register the substance under the REACH Regulation ('other classifications' hereafter). These classifications are regarded of lower reliability than all the other classifications mentioned above for the following reasons:

- The classifications cannot be checked against any experimental data supporting such a classification, since such data are not submitted with notifications in the C&L Inventory.
- Under Article 4 of the CLP Regulation, manufacturers, importers and downstream users are required to classify substances and mixtures before placing them on the market. Manufacturers and importers of substances are also required to register a substance under the REACH Regulation and their classification will generally be reflected in the joint or individual classifications described above. In these cases, the classification can be checked against the data reported in the REACH registration dossier. Classifications by downstream users, in contrast, are independent of the data generated under REACH and their basis cannot be checked.
- There are several examples of single notifications by a single notifier in the C&L Inventory that diverge not only from joint or individual classifications, but also from legally binding harmonised classifications.
- The classifications in the C&L Inventory are not checked or curated by ECHA.

For these reasons, one possible approach would be to disregard such other classifications completely. It should be noted that all 2 336 substances have been registered and therefore assessed with respect to classification for all endpoints. If none of these evaluations resulted in a classification, this has to be taken as evidence for non-classification for the respective endpoints. Selecting all these substances would increase the risk of identifying false positives that would later turn out to possess no toxicological hazard at all.

However, there may be cases in which the classification in the registration dossier may be too favourable or not be representing the complete data basis. Therefore, inclusion of potentially more reliable other classifications in the evaluation were considered on the following basis:

- Classifications for the four endpoints by a single notifier in a single notification are not considered reliable.
- In principle, the classification supported by the highest number of notifiers could be taken. However, in some cases, the highest number of notifiers supports the joint classification. More

importantly, the number of notifiers alone is not considered to be an indication of increased reliability, since the underlying information may come from a single source.

- The number of notifications, in contrast, is more likely to reflect assessments by independent sources. If several notifications support the classification for a given endpoint, such a classification is more likely to have a real data basis. As stated above, a single notification (which is often supported by only one notifier) is clearly not sufficient to assume a higher reliability for other classifications. On the other hand, the number of notifications also depends on the importance of the substance on the market and a cut-off set too high may exclude substances with only a low number of total notifications.
- The total number of notifications for the four endpoints is not considered as relevant for defining other classifications as being more reliable. In some cases, there are e.g. 4 notifications for the relevant endpoints, but these are equally divided among all endpoints (i.e. one notification per endpoint). Rather the number of notifications per endpoint was considered as a relevant criterion.

In a pragmatic approach, all other classifications with more than two notifications per endpoint were considered more reliable (assigned an initial Toxicity Score of 10) than those with one of two notifications per endpoint only (assigned an initial Toxicity Score of 1). The cut-off of two notifications is arbitrary, but aims to strike the right balance between avoiding too many false positives and potentially overlooking substances that may possess a relevant hazard.

Again, the information for each substance was extracted from the file and converted to a Microsoft Access® database to evaluate the information.

Checking 'other classifications' for toxicity data

As noted above, more than two notifications for any of the four endpoints suggest a higher reliability than classifications suggested in only one or two notifications and therefore assigned a higher initial Toxicity Score of 10. Nonetheless, all Toxicity Scores based on these 'other classifications' are still considered less reliable than those based on harmonised classifications, IARC classifications or classifications coming from REACH registration dossiers for reasons discussed above. It was therefore decided to manually check, whether toxicity data support the 'other classifications' assigned. Since a substantial number of substances with 'other classifications' was identified, these evaluations were restricted to those substances with high scores in the other blocks A-C. For these substances, overlooking a toxicological hazard would be most critical.

The criteria for 'high scores' in blocks A, B and C were identical to the ones applied in the prioritisation using Pivot table selections (see section 2.4 below) for substances with 'other classifications' supported by more than two notifications:

- Score A > 5 OR Score B > 5 AND
- Score C > 5

For substances with 'other classifications' supported by only one or two notifications, stricter criteria were applied to limit the search for toxicity data to an acceptable number of substances.

- Score A ≥ 5 AND
- Score B ≥ 8 AND
- Score C = 10

Data sources

The following data sources were evaluated for toxicity data on the substances selected:

- First, it was checked whether the classification information in Classification & Labelling Inventory database[44] is impacted by impurities and result noted for further consideration in the final evaluation.

[44] https://echa.europa.eu/de/information-on-chemicals/cl-inventory-database/, accessed February-March 2018.

- The substances were then searched in ECHA CHEM[45] and all potentially relevant information retrieved. This search was not limited to the REACH registration dossiers, but retrieved all information hosted by ECHA. For example, this search also identified substances for which a harmonised classification under the CLP Regulation is proposed or substances which were subject to substance evaluation under the REACH Regulation. The sources retrieved were screened for relevant information and these were documented. If this step already identified unequivocal data supporting a Toxicity Score of 10 (e.g. a proposed harmonised classification for carcinogenicity), no further evaluation of other sources was performed. If no such information was retrieved, the following steps were performed.
- The REACH registration dossiers publicly available via ECHA CHEM were consulted and the data for the endpoints found in the 'other classification' screened. If several different studies existed, the focus was placed on those identified as 'key studies' and other studies representing experimental results (rather than e.g. QSAR predictions) rated with a reliability score of 1 or 2. This focus was required, since some registration dossiers include all data for a given endpoint (including e.g. QSAR predictions and read-across data from similar substances), even if there are one or two studies reliable experimental studies for the substance itself. Relevant information was extracted and documented in all cases.
- Finally, information from sources included in OECD's eChemPortal[46] was screened in order to consider data potentially not included in REACH registration dossiers. In addition, these sources may also provide different interpretations of data included in REACH registration dossiers than those given by registrants. Not all databases included in eChemPortal contain information relevant for this evaluation. The following sources are the ones that most often had such kind of information:
  - EFSA OpenFoodTox: Chemical Hazards Database of the European Food Safety Authority, which contains links to all EFSA publications on risk assessments of chemicals in food and feed.
  - INCHEM: A consolidated collection of chemical safety information from intergovernmental organizations, which provides links to other sources, such as IARC evaluations and OECD Screening Information Datasets (SIDS).
  - NICNAS IMAP: Data from the Australian Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework that feed into the National Industrial Chemicals Notification and Assessment Scheme's (NICNAS).
  - OECD HPV: Data generated under OECD's HPV Chemicals Programme is recorded in the OECD Existing Chemicals Database.
  - US HPVIS: Information generated under US EPA's High Production Volume (HPV) Challenge Programme and included in the US High Production Volume Information System (HPVIS).

Details on all sources are available from the eChemPortal website[47].

Relevant information from these sources was extracted and documented (see Appendix K).

Data evaluation and its limitations

Extracted and documented data were evaluated. Such an evaluation based on the summary data retrieved is subject to interpretation in most cases. For example, many different genotoxicity studies may exist for a given substance, with some positive and some negative results. An interpretation whether a substance should be classified for this endpoint will require a substance-specific assessment that also considers the reliability of the studies. While reliability ratings were available for studies included in the REACH registration dossiers, this is typically not the case for studies reported in other sources. Since full study reports are not publicly available for any of the studies, it was impossible to perform such an in-depth assessment in the context of this evaluation. Similarly, comparatively low NOAEL values may emerge from studies on repeated dose toxicity. While these would suggest a

[45] http://echa.europa.eu/information-on-chemicals, accessed February-March 2018.
[46] https://www.echemportal.org/echemportal/page.action?pageID=9, 'substance search', accessed February-March 2018.
[47] https://www.echemportal.org/echemportal/substancesearch/page.action?pageID=2, accessed March 2018.

hazard with respect to this endpoint, classification for repeated dose toxicity under the CLP Regulation may not be justified in some cases. For example, small changes in body weight gain without significant toxicity, small changes in clinical biochemistry or similar parameters as well as changes in organ weights without evidence of organ dysfunction often do not justify a classification according to the CLP Regulation. Again, analysis of the severity of the effects and their relevance for classification typically requires an in-depth assessment that often will rely on full study reports.

As a consequence of these considerations, a registrant with knowledge of full study reports may have interpreted the findings of a study quite differently than it was done in this evaluation, which had to be based on whether there is an indication of a hazard suggesting possible classification for the endpoint in question. The evaluation, however, could not be performed at the level of detail required for a valid classification proposal. As will be detailed in section 3.3.5, however, this limitation is not only relevant for the present evaluation. There are also examples, where the interpretation of basically the same data differs between registrants and e.g. authorities of EU Member States.

The results of the evaluation were analysed statistically as to whether the initial Toxicity Scores of 10 or 1 could be confirmed or whether data exist that would result in a different Toxicity Score. The ultimate conclusion whether a score is confirmed or not differs on a case-by-case basis. If the score was not confirmed, a brief explanation of the main reason is provided in Appendix K. For example, if there are some positive *in vitro* studies on genotoxicity, but all *in vivo* studies for this endpoint are negative, an initial Toxicity Score of 10 for genotoxicity was not confirmed with the reasoning '*in vivo* negative'. As another example, a substance may show some mild effects in repeated dose toxicity studies at comparatively high doses. These findings are unlikely to meet the criteria for classification and an initial Toxicity Score of 10 for repeated dose toxicity was not confirmed. The overall assessment of whether a toxicity score is confirmed or not thus involves some expert judgement. It may be questioned in more in-depth analyses of the original studies for reasons discussed above.

2.3.6. Scoring

The substances were selected for scoring in a hierarchical way (see Figure 11) as recommended in the pilot study (Bitsch et al., 2016). First, all substances having a harmonised classification for any of the four endpoints (carcinogenicity, mutagenicity, reprotoxicity and repeated dose toxicity) were assigned a Toxicity Score of 10. Of the remaining substances, those having an IARC classification were assigned a Toxicity Score of 10. Afterwards, joint and individual classifications were assigned a Toxicity Score of 10. Finally, substances with 'other classifications' were scored. As outlined above, the Toxicity Score for these substances depends on the manual evaluation of additional toxicity data and was only ascertained for substances with high scores in blocks A-C. As a consequence, there were 7 substances that were initially assigned a Toxicity score of 10 based on 'other classifications', but this was not verified using additional toxicity, since the scores for blocks A-C were low (as defined in the criteria in section 2.3.5. In these cases, the final Toxicity Score was set to 1, since there was no positive evidence that a Toxicity Score of 10 was justified.

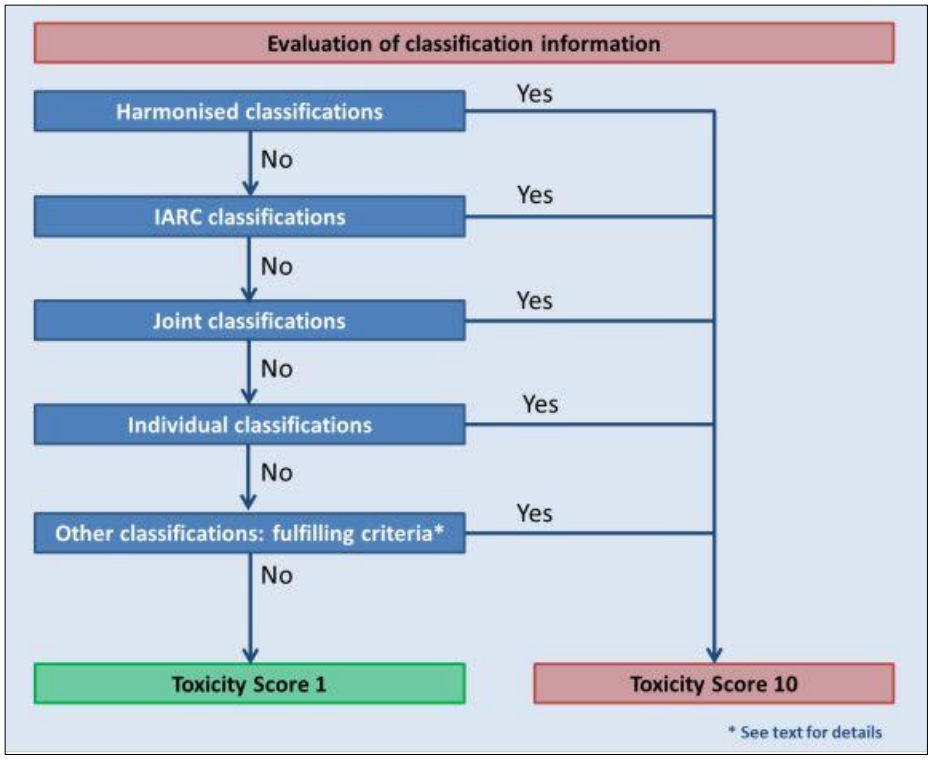


Figure 11: Overview of hierarchical evaluation of substances for scoring

Toxicity Scores were flagged with the following reliability ratings:

- High: all harmonized, IARC and REACH registration classifications; 'other classifications' supported by proposed classifications under EU legislation.
- Low: all remaining 'other classifications'.

2.4. Data and methodologies for the selection of priority substances

Potential priority substances were selected after all scores for every block had been assigned to each substance of the dataset. Scores were available for block A (environmental release), block B (biodegradation) and block C (bioaccumulation in food/feed). For toxicity, the score is based on classification information for any of the four endpoints of interest (see section 2.3).

In order to evaluate the substances according to the different scores assigned in each block, three approaches were applied:

- Weighting scenarios,
- Pivot table selections and
- A combination of weighting scenarios and Pivot table selections.

As a first approach, weighting scenarios (WS) were used in order to create a ranking of the substances based on a calculated total score. This was done by simple algorithms, i.e. two different formulas that put weight on different blocks to calculate the total score (see formulas below). The total score was then used to prioritise the 2 336 substances. In-depth evaluation of the different weighting scenarios was performed in the pilot study (Bitsch et al., 2016). Following the recommendations of the pilot study, two weighting scenarios were applied[48]:

- WS1: Total Score (WS1) = Score A * Score B + (Score C)² + (Toxicity Score)²
- WS2: Total Score (WS2) = ((Score A * Score B + (Score C)²) / 20) * Toxicity Score

Substances can then be ranked according to their total score in each weighting scenario.

[48] WS1 corresponds to weighting scenario 4 and WS2 corresponds to weighting scenario 7 in the pilot study.

The second approach consisted of the use of a Pivot table. A criterion for each block had to be fulfilled in order to be selected as a priority chemical. The Pivot selection does not result in a ranking, but rather a well-chosen compilation of substances that are selected as priority substances. The following criteria were applied:

- Toxicity Score = 10 AND,
- Score C > 5 AND,
- Score B > 5 OR Score A > 5

These criteria are based on the following considerations:

- A Toxicity Score of 10 is considered a requirement, since only substances classified for any of the four endpoints evaluated (carcinogenicity, mutagenicity, reproductive toxicity or repeated dose toxicity; see section 2.3) are regarded as potential emerging risks in the food chain.
- A Score C > 5 for bioaccumulation in food (Scores C of 6 and 10, see section 2.2.4) is considered a requirement, since these scores reflect a potential to accumulate in food.
- Scores > 5 either in block A or in block B are considered sufficient to reflect the potential of a substance being present in the environment. This criterion is based on the understanding that a substance may be present in the environment if it (a) enters the environment in significant amounts (high Score A) even if it is readily biodegradable (low Score B) or (b) enters the environment in small amounts (low Score A) but is not or only poorly biodegradable (high Score B). Since Score A is subdivided into a Tonnage Score and an ERC Score (reflecting the use pattern), the criterion of Score A > 5 covers substances that are (a) manufactured in very large volumes irrespective of their use pattern (a Tonnage Score of 5 is assigned to substances manufactured at 10 000 000 tonnes per annum or more; see Table 5) as well as (b) substances manufactured at smaller volumes, but potentially released to the environment from their applications (see sections 2.2.1).

The ranking of substances according to their total score by means of the weighting scenarios and the selection of potential emerging risk substances by means of the Pivot table approach were used to generate a list of priority substances for further evaluation in the screening procedure.

2.5. Data and methodologies for the in-depth evaluation

The previous steps have identified priority substances that should be evaluated in-depth in order to verify whether they actually represent emerging chemical risks in the food chain. Such an evaluation may in principle be carried out for all priority substances. However, in-depth evaluation is time-consuming and involves manual data retrieval and several evaluation steps. As a consequence, in-depth evaluation has been limited to 10 substances in the context of this study due to the resources available. This restriction does not imply that substances not evaluated in-depth in this study are of a lower priority.

2.5.1. Selection of substances for the in-depth evaluation

In order to select 10 substances for the in-depth evaluation, it was considered meaningful to identify those substances that have already been assessed in the past. Such substances are less likely to qualify as emerging chemical risks, since they have already received some attention and may have also been regulated for their presence in food or feed. However, experience from the pilot study (Bitsch et al., 2016) has shown that past assessments may have been limited to other pathways than the ones addressed in this study (e.g. exposure from food contact materials) or that past assessments may have been unable to consider more recent scientific findings and/or improvements in modelling tools. Therefore, coverage of a substance by some previous assessment schemes does not necessarily indicate that the substance does not qualify as an emerging chemical risk in the food chain.

The following sources were checked to identify substances that are likely to have already been assessed[49]:

[49] Data were retrieved in May 2018.

- EFSA OpenFoodTox[50]: Substances included in EFSA's OpenFoodTox database; inclusion of a substance in the database does not necessarily imply that the substance has been assessed in detail. For example, only toxicological data for one or two endpoints are given for some substances in the database. However, inclusion in the database indicates that a substance has already been looked at by EFSA. EFSA's OpenFoodTox database contains data for more than 4 400 substances assessed since EFSA's inception in 2002 (Dorne et al., 2017). Previous assessments, e.g. by the Standing Committee on the Food Chain and Animal Health (SCOFCAH) may not be included in the database. As will be shown in section 3.5, even if an assessment by EFSA exists for a given substance, this may not be related to exposure via the environment, but other pathways of exposure (e.g. through food contact materials).
- Candidate List[51]: Substances included in the 'Candidate List of substances of very high concern (SVHC) for Authorisation' under the REACH Regulation; inclusion of substances in this list suggests that they may be ultimately included in the Authorisation List (see below). The Candidate List contained 191 entries at the time of evaluation.
- Authorisation List: Substances included in Annex XIV of the REACH Regulation ('Authorisation List') cannot be used after a fixed 'sunset date' unless an authorisation has been granted to a specific company for a specific use. The ultimate aim of both inclusion in the Candidate List and the Authorisation List is the substitution of such a chemical. The Authorisation List contained 43 entries at the time of evaluation.
- Restriction List[52]: Substances included in Annex XVII of the REACH Regulation ('Restriction List') are restricted in their use. This list also includes restrictions adopted under previous legislation (i.e. Directive 76/769/EEC). Restrictions are often limited to certain user groups (e.g. consumers) or uses. For example, the entry related to bisphenol A restricts the placing on the market of thermal paper containing ≥ 0.02 % bisphenol A. The Restriction List contained 68 entries at the time of evaluation.
- CoRAP[53]: Substances identified in the Community Rolling Action Plan (CoRAP) for substance evaluation under the REACH Regulation; listing in the CoRAP indicates that EU Member States evaluate the substance in more depth, following the initial grounds for concern (given in the listing) or additional concerns identified during the evaluation. The evaluation is based on the REACH registration dossier, but also integrates additional available data. Generally, substance evaluation is limited in scope and often does not include an assessment of human exposure via the environment. The CoRAP contained about 350 entries at the time of evaluation.
- PACT List[54]: The Public Activities Coordination Tool (PACT) list specifies substances for which (a) a risk management option analysis (RMOA) or (b) an informal hazard assessment for PBT/vPvB or endocrine disrupting properties has been completed or is underway. The PACT procedure primarily serves the purpose to identify the most appropriate follow-up risk management options, such as inclusion in the Candidate List or substance evaluation. The outcome may also identify no need for further regulatory risk management actions. The informal hazard assessment will conclude on PBT/vPvB or endocrine disrupting properties, e.g. whether these properties are confirmed or not. These evaluations will generally not assess human exposure via the environment. The PACT list contained about 420 entries at the time of evaluation.
- Biocides[55]: Substances assessed under EU legislation as biocidal active substances. The list contains approved biocidal active substances as well as those not approved and active substances under review. The assessment is usually focussed on direct human exposure and – depending on the product type – on indirect human exposure through the consumption of food and drinking water that have come into contact with the biocidal active substance. While indirect exposure of humans via the environment, i.e. exposure due to emissions to air and

50 https://www.efsa.europa.eu/en/data/chemical-hazards-data, accessed May 2018.
51 https://echa.europa.eu/candidate-list-table, accessed May2018.
52 https://echa.europa.eu/substances-restricted-under-reach, accessed May 2018.
53 https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table, accessed May 2018.
54 https://echa.europa.eu/de/pact, accessed May 2018.
55 https://echa.europa.eu/information-on-chemicals/biocidal-active-substances, accessed May 2018.

water, in principle needs to be covered as well according to the most recent ECHA Guidance (ECHA, 2017c), this is appears to be rarely documented in the published assessment reports of the evaluating competent authorities. The list of biocidal active substances contained about 740 entries at the time of evaluation.

- EU RAR[56]: Substances assessed in EU Risk Assessment Reports (RAR) under past EU legislation. A RAR typically also addresses human exposure via the environment. However, the information in a RAR represent the pre-REACH state and may be outdated in a substantial number of cases (also see Bitsch et al., 2016). RARs were prepared for 142 substances.

These sources focus on European chemical legislation and do not cover assessments carried out in other countries, which will be considered during the actual in-depth evaluation. This approach was chosen for practical reasons, since the sources mentioned can be analysed in a (semi-)automated manner, while assessments performed internationally are not easily accessible to a (semi-)automated retrieval and evaluation procedure.

Approach 1: High-ranking substances not listed

Since substances already assessed should not be selected for in-depth evaluation, this approach starts from the substances not listed in any of the sources assessed. Intuitively, the highest ranking substances among the substances not listed in any source are candidates for further in-depth evaluation. The ranking resulting from application of the weighting scenarios (see section 3.4.1) can be applied to select such high ranking substances. Substances with identical total scores in a weighting scenario are assigned identical ranks (i.e. several substances may be assigned rank 1, rank 2 etc.). In order to illustrate the selection and resulting number of substances, an approach based on a Pivot table will be used.

The substances retrieved are compiled in a preliminary list of selected substances.

Approach 2: Substances listed in defined sources only

As mentioned above, listing of a substance in some of the sources evaluated does not necessarily indicate that the substance has been assessed in relation to its accumulation in the food chain and human exposure via the environment. For example, inclusion of a substance in the CoRAP list for substance evaluation may be related to specific issues, such as clarification of individual endpoints (e.g. reprotoxicity) and associated classification. In addition, even exhaustive assessments, such as the ones performed in EU Risk Assessment Reports, may not adequately cover bioaccumulation in food/feed (Bitsch et al., 2016). For this reason, the limitation of substance selection to those not listed in any source (as in approach 1) may exclude relevant substances.

In contrast, a substance listed on the Candidate List can be expected to be eventually included in the Authorisation List with substitution of this substance being the ultimate aim. Therefore, substances included in the Candidate List should not be selected for in-depth evaluation. Similarly, a substance included in the EFSA database has been identified by EFSA as being relevant in some sense in relation to food and feed safety. While inclusion in the database does not by itself imply that an in-depth assessment has been performed for human exposure via the environment, all substances included in the EFSA database and at least one additional source are not selected. Again, this reflects a pragmatic approach to reduce the number of substances.

The second approach therefore starts from those substances that are listed only in defined sources, i.e.:

- listing in a single source only (except the Candidate List) or
- listing in more than one source (but not in the Candidate List or the EFSA database).

In order to further limit the number of substances, ranking according to the weighting scenarios is applied as in approach 1.

The substances retrieved by approach 2 are combined with the ones selected by approach 1 in a preliminary list of candidates for in-depth evaluation.

[56] https://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation, accessed May 2018.

Final selection for in-depth evaluation

The cut-off for high-ranking substances was set differently in both approaches to result in a similar number of substances from both approach 1 and approach 2 (about 20 each). As is shown in section 3.5, the substances selected are characterised by high scores in all blocks except block A, for which a wide range is observed (especially in approach 2). Therefore, the final step in substance selection is based on the tonnage, selecting substances with a maximum REACH registration tonnage of 10 000 tpa or more. This value was chosen in a pragmatic, iterative procedure to identify a sufficiently low number of substances, from which the 10 substances for in-depth evaluation can be manually selected.

For the final selection as a substance for in-depth evaluation, abiotic degradation processes should be manually checked and substances showing substantial degradation should not be selected for in-depth evaluation (see section 2.2.2). Based on the results shown in section 3.5, this was the case for three of the ten substances initially selected. These three substances were manually replaced by three other substances. This replacement did not follow the formal approach described above, but considered the following elements:

- Substances not listed in any of the sources evaluated
- Focus on high tonnages
- Focus on substances that are not easily hydrolysable
- Expert judgement, including consideration of chemical class and use pattern

While this replacement procedure involves subjective elements, it was considered meaningful to avoid selection of similar substances. For example, application of the formal approach would have selected another substance used primarily as an explosive. With one explosive already selected, this was not considered meaningful. Manual replacement was also considered unproblematic, since the ten substances selected for in-depth evaluation are not claimed to be representative for the 212 priority substances. In fact, selection of other substances for in-depth evaluation is greatly encouraged (see section 5).

The approach described above does not explicitly exclude substances already regulated for their presence in food/feed in the EU. However, it is highly unlikely that a substance not included in EFSA's OpenFoodTox database is already regulated in this field (e.g. because it was already assessed before EFSA was established). As the results in section 3.5 illustrate, all substances proposed for in-depth evaluation are not listed in the EFSA database (except melamine, which was added for reasons discussed in section 3.5.1). In addition, we are not aware of any EU regulations on the presence of any of the ten selected substances in food.

2.5.2. In-depth evaluation

General approach

The in-depth evaluation performed for 10 substances involves a review of available information for each substance in relation to the four blocks (environmental release (block A), biodegradation (block B), bioaccumulation in food/feed (block C) and toxicity (toxicity block, i.e. the endpoint responsible for assignment of a Toxicity Score of 10)). Depending on the information already used in the assessment, the level of detail in the in-depth evaluation will vary. For example, a substance classified for mutagenicity in a harmonised classification will require no additional evaluation steps, while assessments based on modelling (biodegradation (block B) and bioaccumulation (block C)) will require more extended data searches and evaluations.

In addition, data on environmental releases (block A) will rarely be available, while monitoring data in some environmental compartments (e.g. surface water and soil) may exist for some substances. It is therefore meaningful to search for data in relation to environmental occurrence, which in fact reflects a combination of releases (block A) and biodegradation (block B).

Table 9 summarises the information that will be evaluated as well as relevant sources for the in-depth evaluation. There are in principle three levels of the in-depth evaluation:

- Level 1 (L1) consists of a check of information used in the assessments to ensure that this information is still correct. For example, the maximum tonnage of registrations under REACH and the ERCs assigned will be checked again for block A.
- Level 2 (L2) compares information used in the assessment with other available data. Since biodegradation (block B) was assessed on the basis of predicted data, experimental data on biodegradation in the REACH registration dossiers will be compared with the scoring based on predicted data. In some cases, additional data from reviews may be helpful, e.g. if such a comparison leads to equivocal results.
- Level 3 (L3) evaluates additional data that were not used as such in the assessment, but may provide additional insight and/or corroborate modelling results. For example, information from the life cycle tree in REACH registration dossier provides additional insight, whether a substance is only used in industrial settings or whether it is also used by professionals and consumers or whether release from articles during the service life may be important.

Table 9: Information to be evaluated and relevant sources for the in-depth evaluation

Parameter*	Information checked [a]	Sources[b]
ENVIRONMENTAL RELEASE (block A)	Maximum tonnage and critical ERC Score (L1) Life-cycle tree information from dossier (L3)	Dossier Dossier
BIODEGRADATION (block B)	Biodegradation based on predicted data compared with experimental data (L2)	Dossier/ Reviews
ENVIRONMENTAL OCCURRENCE (block A-B)	Monitoring data in environmental compartments (L3) Human biomonitoring data (L3) provide additional information on human exposure	Reviews/ Literature
	Substance listed in database portal (used as an indication that monitoring data are available; individual sources will be checked for values) (L3)	IPCHEM
OCCURRENCE/ACCUMU-LATION IN FOOD/FEED (block C)	Monitoring data in food/feed as well as experimental studies on accumulation in food/feed (L3)	Reviews/ Literature
Toxicity (relevant endpoint(s)	Toxicity classification (L1)	Dossier/C&LI/ IARC
	DNELs (oral, long-term, systemic effects, general population) compared with other reference values (L3)	Dossier/ Reviews

(a): The level of evaluation outlined above (L1-L3) is given in brackets.
(b): Dossier refers to REACH registration dossier; see text for details on literature and reviews evaluated; C&LI: Classification & Labelling Inventory database.

Obviously, monitoring data in food/feed are the most important information in the context of this study, since the presence of a substance in food/feed suggests that the assessment based on modelling was correct. However, there are some issues to consider in this context:

- A substance may be monitored in food/feed as a result of exposure pathways not covered by this assessment, e.g. through food contact materials, due to the use as a plant protection product, due the use as a biocide in the production of food/feed or due to the use in food processing. This possibility should be accounted for when interpreting available data to the extent possible.
- Monitoring data in food/feed will often not be available. As a consequence, monitoring data in environmental compartments (e.g. surface water and soil) are searched and evaluated as surrogate information.
- While human biomonitoring data are considered a valuable piece of information, the pathway of exposure cannot be ascertained and positive results in humans may e.g. be the result of inhalation exposure or intake due to the use of a substance in food contact materials.

In relation to toxicity information, the assessment based on the classification of substances is considered reliable and does not require additional checking (see section 3.3). However, the source of

the information is checked again to verify the classification. In addition, reference values for oral exposure of the general population (including DNELs from REACH registration dossiers) are retrieved as additional information.

Data searches

Data were searched by three different means:

- Reviews were searched via OECD's eChemPortal, which provides access to a wide variety of sources[57] and portals. For example, eChemPortal provides a link to INCHEM of the International Programme on Chemical Safety (IPCS)[58], which in turn provides access e.g. to WHO's Environmental Health Criteria (EHC) monographs, JECFA's monographs and evaluations and several other sources. Apart from eChemPortal, TOXNET of the U.S. National Library of Medicine (NLM)[59] was searched for additional information. This portal provides access to multiple databases, such as HSDB and ITER, the latter providing access to reference values derived by several organisations.
- Literature on occurrence in environmental media as well as in food/feed was searched via:
  - Web of Science (Clarivate Analytics)
  - Scopus (Elsevier)
  - PubMed of the U.S. National Library of Medicine (NLM)[60]
  - Google Scholar[61]

  Search strategies depended on the number of hits initially retrieved, but were generally limited to the occurrence in the environment and in food/feed using appropriate search terms.
- Specifically for monitoring data, the IPCHEM portal[62] was used as an additional starting point to identify monitoring programmes under which a substance was covered. Data from these programmes were retrieved, if access to the corresponding databases is public. For restricted databases, a request to the data owners was filed by EFSA and data made available evaluated.

In addition, the sources identified in the selection of substances for in-depth evaluation (e.g. a CoRAP listing; see sections 2.5.1 and 3.5.1) were consulted and any relevant additional information on the toxicity identified.

Reporting

For each substance, an 'in-depth evaluation sheet' was prepared that summarises the information retrieved for the different elements shown in Table 9. This sheet also includes an overall assessment, conclusions, monitoring methods in food/feed and other media and the scores in critical food/feed categories (see section 2.2.4).

In general, concentrations in food/ feed or in environmental compartments, such as surface water, soil and groundwater, were reported using meaningful descriptors (e.g. mean values and ranges). Values given in the sources were reported, i.e. no mean values were generally calculated from reported data. In a few cases, a large amount of data was available, preventing reporting of every single observation. In these cases, data were summarised in a meaningful way. On the other hand, several studies were retrieved that only indicated whether a substance was detected or not. Thus, if the in-depth evaluation sheets contain phrases such as 'detected in groundwater' without additional data this implies that no concentrations were reported.

Data from Europe were preferred, but data from other regions were reported if no or only few data from Europe were available for a substance.

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57 https://www.echemportal.org/echemportal/page.action?pageID=9, accessed July 2018; list of participating databases: https://www.echemportal.org/echemportal/substancesearch/page.action?pageID=2.
58 http://www.inchem.org/pages/search.html, accessed July 2018. Note that the eChemportal also includes links to INCHEM. However, experience shows that sometimes hits are lost and INCHEM is therefore searched separately.
59 https://toxnet.nlm.nih.gov/, accessed July 2018.
60 https://www.ncbi.nlm.nih.gov/pubmed/, accessed July 2018.
61 https://scholar.google.com/, accessed July 2018.
62 https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html, accessed July 2018; note that access to some of the databases is restricted.

3. Results and Discussion

3.1. Substance selection

This section describes the results of the substance selection process defined in section 2.1. The approach is largely based on (semi-)automated processes that lead to the generation of duplicate entries at two different levels of the process: (a) duplicate registrations since a given substance may be registered with several registrations (differing e.g. in the type of registration and the tonnage registered) and (b) duplicate datasets that result from the fact that different SMILES notations may be assigned to a substance identified by a CAS number. This latter case applies for example to substances containing constituents of different chain lengths (e.g. 'alcohols, c9-11-iso-, c10-rich'), for which different representative members may be assigned in different databases.

Since both kind of duplicates may differ in parameters important in the evaluations of this study (tonnage and physico-chemical properties), it is desirable to keep duplicates rather than to delete them too early in the substance selection process. In fact, the example above shows that retaining duplicates with different SMILES notations may be useful to ultimately select the most appropriate structure for further evaluation (see section 2.1.5 and 3.1.4).

The following terminology is used in the paragraphs below to differentiate entries for substances identified by a unique CAS number:

- The term 'duplicate registrations' is used in the evaluation presented in section 3.1.1 for datasets with identical CAS numbers differing e.g. in the tonnage band of the registration.
- The term 'duplicate datasets' is used in sections 3.1.2-3.1.4 for datasets with identical CAS numbers differing e.g. in SMILES notations, molecular formulae or predicted values.

The number of unique chemicals corresponding to the number of datasets is reported for the following evaluations, where meaningful.

3.1.1. Substances with a full registration and a CAS number

The extraction of information on registered substances from ECHA CHEM described in sections 2.1.1 and 2.1.2 resulted in the number of registrations shown in Table 10. The table also shows the number of percentage of registrations, for which CAS numbers are available. Note that a given substance may be registered both as an intermediate and with a full registration. Similarly, NONS that received a tonnage upgrade have a NONS registration, but also an additional full registration (see section 2.1).

Table 10: Available registrations by type of registration and differentiation by CAS number availability

Registration type	Number of registrations[(a)]	CAS No. available	CAS No. not available
Full	7 422	5 795 (78 %)	1 627 (22 %)
Intermediate	5 040	4 203 (83 %)	837 (17 %)
NONS	4 533	1 116 (25 %)	3 417 (75 %)
Total	**16 995**	**11 114 (65 %)**	**5 881 (35 %)**

(a): Number of registrations as evaluated from the extracted information. Registrations of members of a joint submission for any given substance are not counted separately. Intermediate registrations include 5 000 intermediate registrations and 40 registrations for which registration type is 'NA'.

Substances with a full registration and a CAS number are selected for the evaluation. The 5 795 full registrations represent 5 380 substances identified by a unique CAS number.

Exclusion of substances with a full registration, but without a CAS number leads to an exclusion of 1 627 registrations (1 499 unique substances). Of these, 1 461 registrations (90 %) have an EC no. assigned (corresponding to 1 337 unique substances). These substances are excluded for a technical reason, i.e. since EC numbers cannot be loaded into the QSAR Toolbox. This step therefore excludes a substantial number of substances due to a technical limitation. However, many of these substances

are produced at low tonnages and those produced at high tonnages are generally complex mixtures or substances outside the applicability domain of the models used in blocks B and C. The exclusion of substances with a full registration, but without a CAS number is analysed in more detail in Appendix A.

Intermediates handled exclusively under strictly controlled conditions (i.e. substances with an intermediate registration only) are not considered further, since they are not expected to be released to the environment in large quantities (5 040 registrations, corresponding to 4 456 unique substances).

Substances registered as NONS are a special case. These substances were notified under Directive 67/548/EEC and are considered registered under REACH according to Article 24 of the REACH Regulation. The 4 533 NONS registrations represent 4 511 substances identified by unique EC numbers. While these substances are included in the ECHA CHEM database, no tonnage information is disseminated and the corresponding dossiers contain no use information (in particular no ERCs relevant for block A) and very little other information. This lack of information is due to the fact that the dossiers were generated automatically from older databases. An upgrade of these dossiers is only required when the tonnage band increases. Such substances are then included as full registrations in the ECHA CHEM database and are included in further substance selection steps.

As discussed in more detail in Appendix A, NONS registrations most likely relate to substances manufactured in low tonnages. Since this interpretation was based on a small subset of NONS, additional analyses using the QSAR Toolbox were performed for the 1 116 NONS registrations associated with a CAS number. For 57 % of these NONS registrations, the QSAR Toolbox could not retrieve a SMILES notation, while this figure is only 16 % for the full registrations (see Table 11 below). In addition, even a name was missing for the majority of these NONS registrations. Among the remaining substances, 274 meet the criteria defined in section 2.1.4 and 56 (20 %) also have a full registration (tonnage and use information is therefore available) and are therefore selected for further evaluation. The remaining 218 substances lack tonnage and use information. Selection of these substances for further evaluation would result in high default scores for block A and therefore increase the risk of selecting false positives, especially in the light of suggestive evidence that their tonnage may actually be low.

In contrast to NONS registrations, tonnage and use information is usually available for full registrations. While the tonnage may be claimed confidential for full registrations as well, this is rarely the case (96/5 795 full registrations; 1.7 %).

Overall, this first selection step identified 5 380 substances with a full registration that are identified by a unique CAS number. These substances are analysed in the next step. Registration duplicates are removed by selecting only unique CAS numbers for upload in the QSAR Toolbox in the next step[63].

3.1.2. Substances with a SMILES notation

Upon loading the list of 5 380 CAS numbers, the QSAR Toolbox automatically assigns SMILES notations to these substances (see section 2.1.3). Since the SMILES notations are retrieved from different databases included in the QSAR Toolbox, more than one SMILES notation may be assigned to a given CAS number. This leads to a total of 6 693 datasets, corresponding to 5 372 unique substances. Compared with the 5 380 substances loaded into the QSAR Toolbox, 8 substances are lost, since some chemical data are claimed confidential and cannot be exported from QSAR Toolbox. These 8 substances are produced at low tonnages with maximum REACH registration tonnages of 10 000 tpa (n=1), 1 000 tpa (n=1), 100 tpa (n=4) or 10 tpa (n=2). The loss of these substances is therefore considered acceptable.

These 6 693 datasets include duplicates, i.e. two or more datasets for a given CAS number. In turn, SMILES notation cannot be assigned to some substances, reducing the number of datasets for further evaluation. Overall, the retrieval of SMILES notations in the QSAR Toolbox returned the number of datasets shown in Table 11.

[63] While the registration duplicates include information on the tonnage, this exclusion of registration duplicates is not a problem, since specific tonnage-ERC combinations are extracted and evaluated in block A (see sections 2.2.1and 3.2.1).

Table 11: Number of datasets (including duplicates) retrieved from the QSAR Toolbox

Total no. of datasets	Datasets with a SMILES notation	Datasets without a SMILES notation
6 693	5 631 (84 %)	1 062 (16 %)

No SMILES notation could be retrieved for a substantial fraction of the datasets. However, even a name is unavailable for 114 of these 1 062 datasets (11 %) in the QSAR Toolbox. For the remaining 945 datasets, additional analyses presented in Appendix A indicate that these relate primarily to substances that (a) are potentially UVCB substances (e.g. petroleum products, fatty acids and other hydrocarbons of variable carbon chain length) or (b) are inorganic, organometallic or other substances outside the applicability domain of the models used in this study. This is particularly true for substances produced in high tonnages, which are often petroleum products (e.g. 'fuel oil, no.2') metals or residues from metal processing (e.g. 'flue dust, lead-refining'), inorganics (e.g. 'chromium iron oxide') or derived from biological materials ('orange, sweet, extract'). Further analyses as well as additional illustrative examples are included in Appendix A.

The 5 631 datasets with SMILES notations correspond to 4 330 substances identified by a unique CAS number. These datasets contain duplicate datasets (different SMILES notations for a given CAS no.; see section 2.1.3). Nonetheless, all these datasets are further processed in the next step for reasons described below.

3.1.3. Exclusion of substances outside the applicability domain of the models used

The pilot study (Bitsch et al., 2016) did not limit the chemical domain of the substances assessed. However, it turned out that there is considerable uncertainty associated with modelled results, since the underlying models used in blocks B and C were typically developed for neutral organic compounds. Bitsch et al. (2016) therefore recommended to exclude inorganic, organometallic and ionisable substances.

For this purpose, the criteria defined in section 2.1.4 were applied to the profiling results of the QSAR Toolbox (version 3.4, 2016) for all 5 631 datasets. Overall, 2 660 datasets meet the criteria defined in Table 3. More than half of the datasets are excluded by this step (Table 12).

Table 12: Number of datasets meeting the selection criteria (selected) and not meeting the selection criteria (excluded)

Total no. of datasets	Selected datasets	Excluded datasets
5 631	2 660 (47 %)	2 971 (53 %)

Further analyses summarised in Figure 12 show that about two thirds of the datasets (66 %) of the 2 971 datasets are excluded because the substances are predicted to be ionised by more than 90 % at pH 7.4 (either as the sole criterion or in combination with the other criteria; see Appendix A for details).

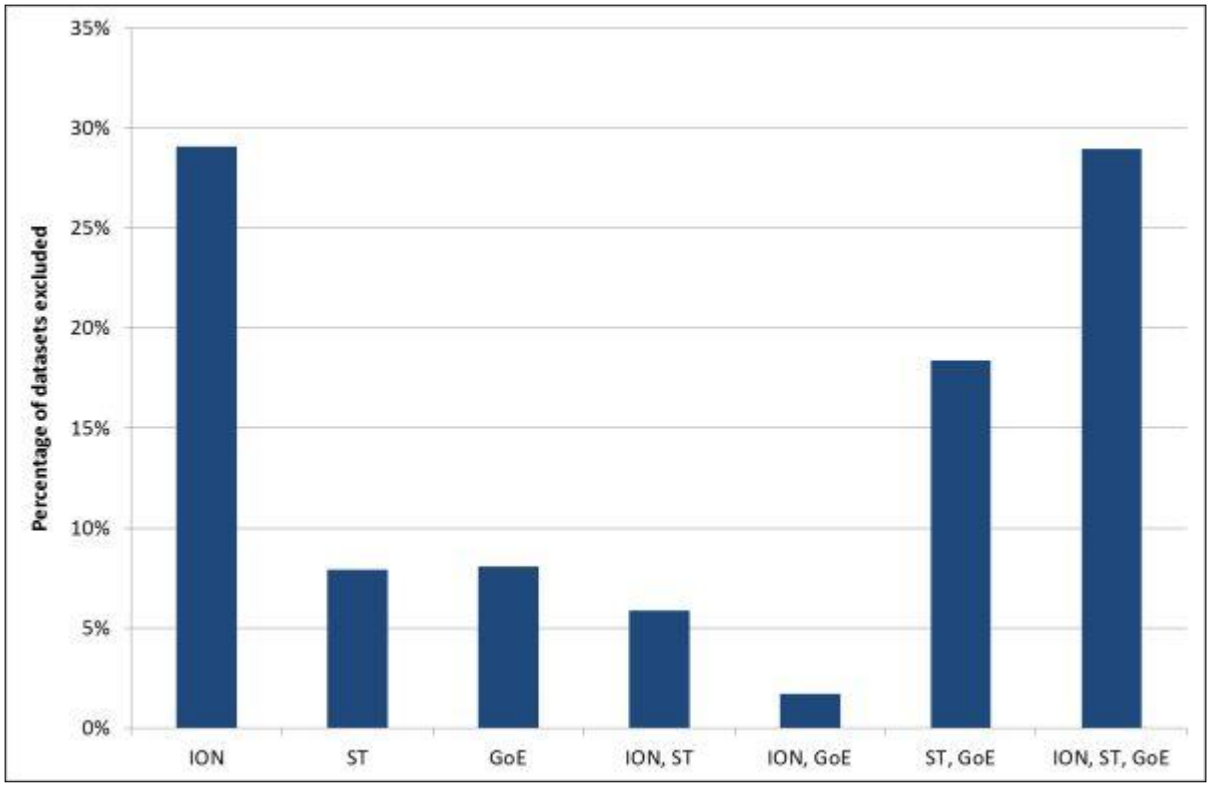


Figure 12: Summary of the exclusion based on QSAR Toolbox profilers.
QSAR Toolbox profilers: ST – substance type; GoE – groups of elements; ION: ionisation at pH 7.4.

Additional analyses using a fourth, independent profiler support the exclusion process and suggest that the profilers used correctly identify substances that should not be evaluated further, since they are outside the applicability domain of the models used in blocks B-C. Table 13 shows illustrative examples of excluded substances that are further discussed in Appendix A.

Table 13: Examples of excluded substances

CAS no.	Name	Reason for exclusion[(a)]
2458-08-4	3α,7α-dihydroxy-12-oxo-5β-cholan-24-oic acid	Ionisation
7446-11-9	sulphur trioxide	Inorganic
91770-03-5	fatty acids, tall-oil, reaction products with boric acid and diethanolamine	Metalloid
2272-11-9	ethanolamine oleate	Ionisation; mixture
2489-05-6	silver docosanoate	Ionisation; transition metal
5188-07-8	sodium methyl mercaptan	Dissociating chemical; alkali earth
2457-01-4	hexanoic acid, 2-ethyl-, barium salt	Ionisation; dissociating chemical; alkaline earth

(a): Exclusion based on one profiler only (first three substances), two profilers combined and based on three profilers combined (last substance); see Table 17 for details.

The final list contains substances

- with a full registration, a CAS number and a SMILES notation;
- that are discrete chemicals characterised as non-metals (with or without halogens) that exist in a non-ionised form at pH 7.4 by at least 10 %.

The 2 660 datasets selected represent 2 374 unique substances (i.e. 2 374 different CAS numbers). Again, duplicate datasets are retained and will only be removed in the next step.

3.1.4. Removal of duplicates and exclusion of non-eligible substances

The next run in the QSAR Toolbox described in section 2.1.5 resulted in the export of 2 657 datasets. The figure is marginally lower than the one that resulted from the previous evaluation. This is due to the fact that export from the QSAR Toolbox is prevented for datasets that are claimed confidential. No substance is lost, since the three datasets lost relate to three substances for which duplicate datasets exist. In fact, high quality datasets according to the criteria described in section 2.1.5 remain in the evaluation.

Table 14 summarises the results of the hierarchical removal of duplicates explained in detail in section 2.1.5.

Table 14: Summary of the removal of duplicates and exclusion of non-eligible substances

Step[(a)]	Number of datasets	Number of substances
Total entering evaluation	2 657	2 374
Removed duplicates (steps 1-3)	255	0
Total remaining after steps 1-3	2 402	2 374
Excluded substances (steps 4-5)	66	38
Total remaining	**2 336**	**2 336**

(a): The steps are described in section 2.1.5.

The data show that the main effect, as intended, is the removal of duplicate entries, which does not lead to the exclusion of substances from further evaluation. Rather, steps 1-3 are intended to ensure that the structure evaluated actually represents the substance registered under REACH. This was ensured by choosing structures assigned an EINECS number, but also manual evaluations for more than 150 datasets.

Overall, 196 of the 255 duplicate datasets[64] removed in steps 1-3 were removed in step 1 due to a lacking EINECS number (see detailed statistics in Appendix A). While it was impossible to check all duplicates removed in step 1, individual examples show that the approach chosen is appropriate. For example, two datasets were retrieved from the QSAR Toolbox for hydroxycitronellal (7-hydroxy-3,7-dimethyloctan-1-al; CAS No.: 107-75-5). The first dataset was selected and the second dataset was removed, since no EINECS number was assigned to this dataset. Table 15 shows that the two datasets also differ in the SMILES notation and the molecular formula.

Table 15: Information in two datasets for hydroxycitronellal (CAS No.: 107-75-5)

Dataset	CAS no.	SMILES	Molecular formula	EINECS
1	107-75-5	CC(CCCC(C)(C)O)CC=O	C10H20O2	203-518-7
2	107-75-5	CC(C)(O)CCCC(C)(C)CC=O	C11H22O2	NA[(a)]

(a): Not available

From the chemical name 7-hydroxy-3,7-dimethyloctan-1-al of the substance, it is clear that it is a C10 compound rather than a C11 compound. This example illustrates that the selection of the duplicate dataset with an EINECS number assigned identifies the correct structure. It also shows that incorrect SMILES notations may be present in data extracted from the QSAR Toolbox.

For this specific example, the correct structure would have been identified even in the absence of an EINECS number for both duplicate datasets. As described in section 2.1.5, the next step in the hierarchical evaluation of duplicate datasets involves checking the molecular formula against the one reported in the REACH registration dossier. In this example, the correct molecular formula is also given in the REACH registration dossier and dataset 1 in Table 15 would have been selected.

Such manual cross-checks were performed for several duplicate datasets that had no EINECS number assigned in step 2. This step evaluated the consistency of molecular formula/molecular weight and

[64] As explained in section 2.1.5, duplicate in this context always refers to datasets with identical CAS numbers as extracted from the QSAR Toolbox.

structural formula. As an example, two datasets were retrieved for the substance 'alcohols, C9-11-iso-, C10-rich' already briefly discussed in section 3.1. Table 16 shows that the SMILES notation in the second dataset in fact refers to a C10 structure (8-methylnonan-1-ol; isodecanol), while the SMILES notation in the first dataset refers to a C9 structure containing two alcohol groups (nonane-1,8-diol). Both structures have different physico-chemical properties, such as log Kow values also shown in the table.

Table 16: Information in two datasets for 'Alcohols, C9-11-iso-, C10-rich' (CAS No.: 68526-85-2)

Dataset	CAS no.	SMILES	Molecular formula	Log Kow
1	68526-85-2	CC(O)CCCCCCCO	C9H20O2	2.16
2	68526-85-2	CC(C)CCCCCCO	C10H22O	3.71

In this example, dataset 2 was selected since the name of the substance indicates that it is C10-rich. The REACH registration dossier also mentions 8-methylnonan-1-ol (dataset 2) as a representative structure, further supporting the selection made. Furthermore, the reference substance[65] assigned to the REACH registration substance provides 8-methylnonan-1-ol as the representative structure for this UVCB substance.

It is important to note that the structure of dataset 1 is not incorrect. It describes one constituent of the substance 'alcohols, C9-11-iso-, C10-rich'. However, the evaluation showed that this is not the most representative structure for this substance. This example illustrates that an informed decision on including a UVCB substance in the evaluation is possible in some cases. More details on these steps of removing duplicate datasets (but no substances) are included in Appendix A.

The data in Table 14 show that 66 datasets representing 38 substances had to be excluded based on the criteria defined in section 2.1.5 (steps 4-5). Most of these substances (n=34, 89 %) were excluded because no representative structure could be identified for UVBC substances (n=23) or because at least one critical input parameter could not be predicted (n=11). Only 5 of the 38 substances excluded are registered with maximum tonnages that would result in a high tonnage score in block A. Among these are UVCB substances, such as liquefied petroleum gas (LPG) and polypropylene glycol, for which a representative structure was not available and polymers that are outside the applicability domain of the models used (see Appendix A for details).

Overall, the removal of duplicates allowed the selection of the most appropriate structure for each substance. The examples presented above as well as in Appendix A demonstrate that retaining duplicate datasets throughout much of the data extraction process is meaningful, since this allows a well-founded selection towards the end of the process. However, in some cases no appropriate structure could be identified or critical parameters could not be predicted, leading to the exclusion of substances. However, the fraction of substances excluded (38/2 374, 1.6 %) is small.

3.1.5. Summary and conclusions on substance selection

Substance selection was based on REACH registration data in the ECHA CHEM database and data generated with the QSAR Toolbox. Figure 13 provides a simplified summary of the number of registrations/datasets and substances selected at each stage.

[65] See footnote 23 for details on the use of reference substances.

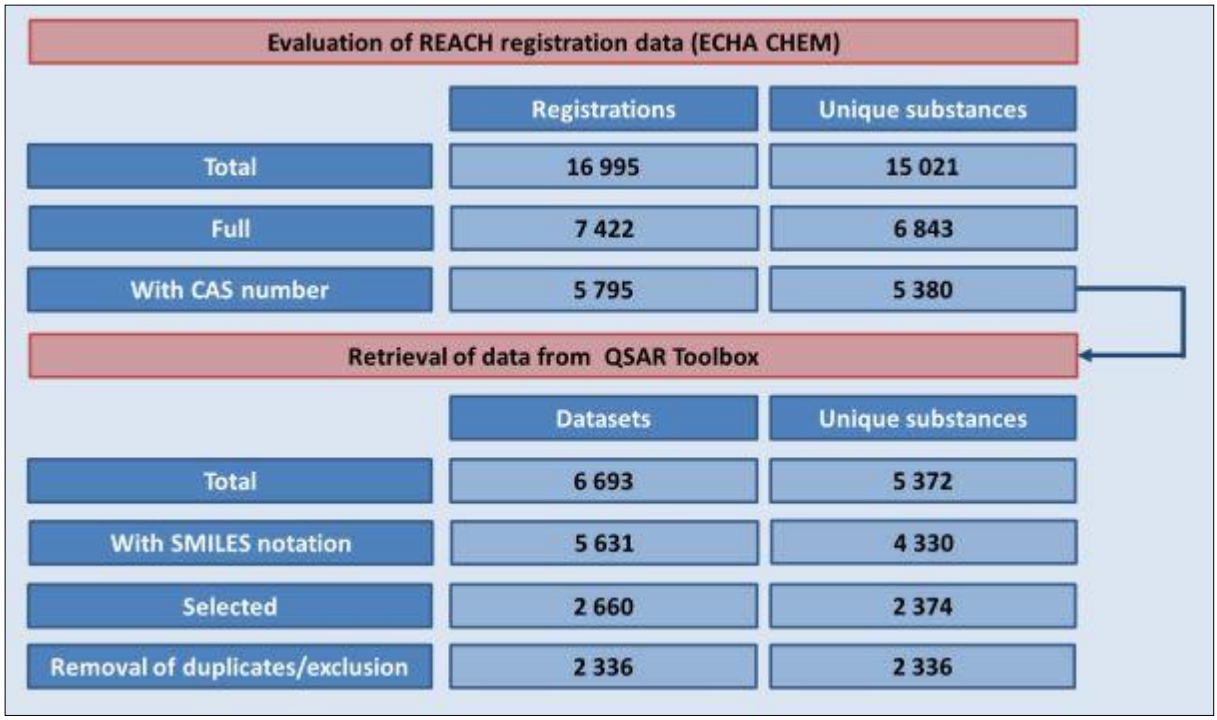


Figure 13: Summary of registrations, datasets and substances in the selection process

The number of substances is reduced from a total of 15 021[66] substances registered under REACH to 5 380 substances (36 %) registered with a full registration and assigned a CAS number. The loss of a substantial number of substances is caused by:

- a justified exclusion of intermediates handled under strictly controlled conditions (4 456 unique substances; 'intermediate registrations'); these are expected to lead to low releases to the environment;
- a limitation of the QSAR Toolbox that requires a CAS number as an input, when a batch of substances is loaded into the QSAR Toolbox (leading to the exclusion of 1 463 substances) and
- an exclusion of NONS (4 511 substances) because no tonnage and use information is publicly available (and a CAS number is lacking for most of these substances)[67].

With respect to the two latter points, detailed analyses presented in Appendix A suggest that these substances primarily represent (a) chemicals produced at low tonnages that would receive only a low tonnage score in block A and/or (b) chemicals outside of the applicability domain of the models used. Furthermore, the fact that SMILES notations could not be retrieved for the majority of NONS with a CAS number means that critical parameters required for modelling could not be predicted, even if these substances were included.

The second large reduction in the number of substances is caused by lacking SMILES notations. SMILES notations are a requirement for the prediction of critical parameters in the evaluation approach. Again, detailed analyses showed that many of the substances excluded due to a lacking SMILES notation are outside of the applicability domain of the models used.

These first exclusion steps primarily eliminate substances from further evaluation that are unlikely to fall within the applicability domain of the models used, are produced only at low tonnages or used only as intermediates under strictly controlled conditions, lack important information (e.g. a SMILES

[66] The total number of substances as well as the number of substances with a full registration are approximate. There are a few cases, in which no CAS number, no EC number and no name is available, making it impossible to decide whether these are duplicates or not.

[67] Note that the sum of the substances excluded (4 456 + 1 463 + 4 511 = 10 430) is higher than the difference between the total number of registered substances and those registered with a full registration (15 021 – 5 380 = 9 641) because a substance with an intermediate registration or a NONS registration may also have a full registration.

notation) or a combination of these factors. Due to the (semi-)automated processes applied exclusion of substances that might qualify as potential emerging chemical risks in the food chain can, however, not be excluded. This limitation points to the fact that the approach employed in this study is intended to identify such potential emerging chemical risks, but can of course not identify all potential emerging chemical risks in the food chain.

The ultimate selection of substances, which reduces the number of substances from 4 330 to 2 336 unique chemicals, is justified by the applicability domain of the models used (exclusion e.g. of inorganic substances and metals, organometallic and ionisable compounds).

Overall, the selection of 2 336 substances (16 % of those registered) may appear to be too restricted. It would have been possible to increase this number, e.g. by retrieving SMILES notations for substances lacking a CAS number, but no tool that allows batch assignment of SMILES notations to EC numbers could be located. Furthermore, the detailed analyses in Appendix A indicate that SMILES notations are sometimes inappropriate for chemicals such as UVCB substances, which form a large bulk of the substances lacking a CAS number. In the context of this study, which uses predictions e.g. of biodegradation potential and bioaccumulation in food based on properties predicted from the SMILES notation, an attempt was made to include the most appropriate structures for the chemicals evaluated rather than to include as many chemicals as possible. In this context, the evaluations in Appendix A have shown that retaining duplicate datasets retrieved from the QSAR Toolbox was important in making an informed judgement on the selection and exclusion of chemical structures.

Finally the approach to substance selection reduces the risk of identifying a large number of 'false positives'. Since tonnage and use information for NONS is not publicly available, a default worst case score of 10 would result in block A. The evaluations on the basis of publicly available data indicate that this most likely is an overestimate for the vast majority of these substances[68].

Overall, 2 336 substances are selected that are further assessed in blocks A, B, C as well as in relation to their toxicity.

3.2. Exposure and environmental fate

3.2.1. Releases to the environment: tonnage and use information (block A)

The tonnage and use information was extracted in 12 different runs progressing from those uses that lead to a high ERC Score to uses that lead to a low ERC Score (see section 2.2.1 for the justification of this approach and a detailed description).

ERC Scores

Almost two-thirds of the 2 336 selected substances received the maximum ERC Score of 5 based on available use information (N=1 480, 63 %, based on ERC 4, 8A, 8D, 10B or 11B; Figure 14). This finding is not unexpected, since many chemicals have full registrations that cover the use as a processing aid (ERC 4, 8A and 8D). Another 119 substances (5.1 %) are assigned an ERC Score of 5 due to missing use information (no ERC retrieved).

[68] Note that NONS registered with a full registration due to a tonnage upgrade are included in the evaluation (see Appendix A).

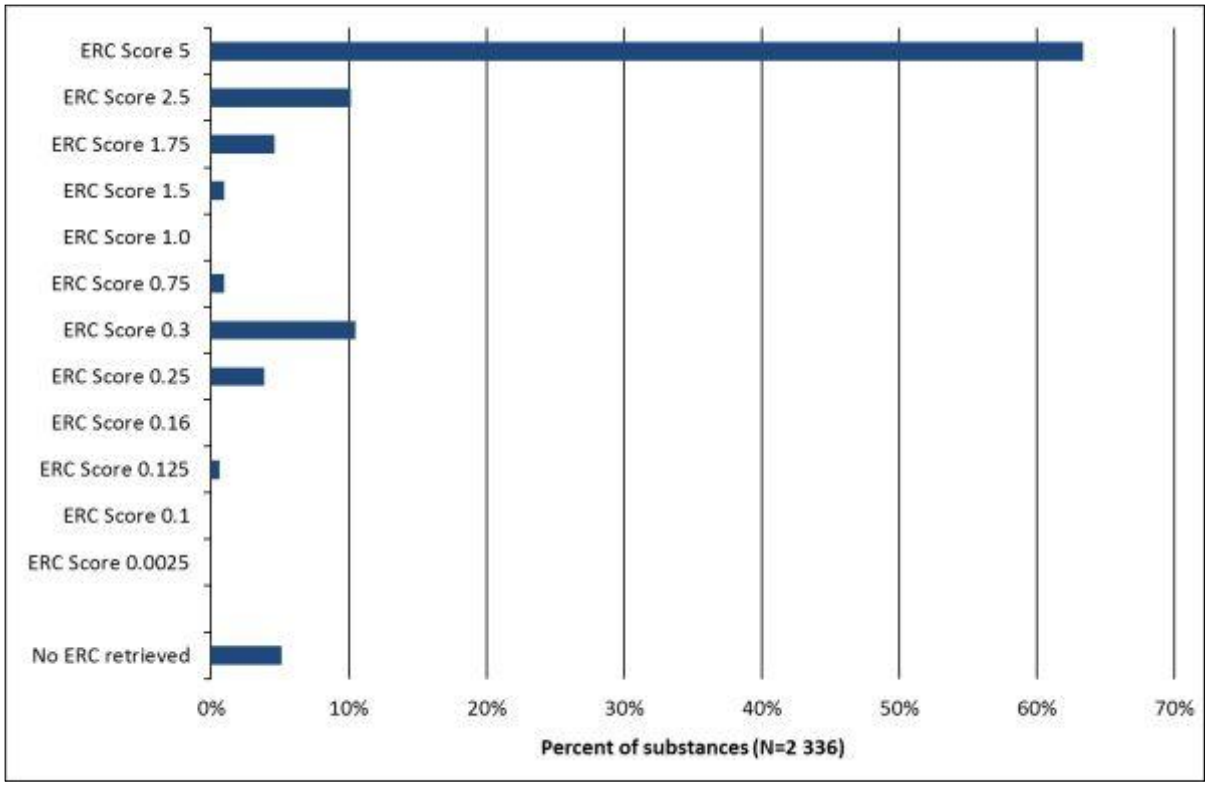


Figure 14: Distribution of ERC Scores assigned to the 2 336 selected substances in the hierarchical evaluation
Count of ERC Score 5 is based on substances with available data; substances for which no ERC could be retrieved are assigned an ERC Score of 5, but are displayed here separately.

As explained in section 2.2.1, tonnage information was retrieved together with the extraction of the ERCs and could be scored in parallel with the scoring of the use information. When the ERC Score of 5 and the Tonnage Score resulted in a Total Score A of 8 or higher, no further evaluation was required, since any other combination of the ERC Score and the Tonnage Score will be lower than 8 (also see Figure 5). This was the case for 428 substances (i.e. 28 % of the 1 480 substances that were assigned an ERC Score of 5). The remaining 1 057 substances with an ERC Score of 5 were further assessed as described in section 2.2.1. These substances are manufactured at comparatively low tonnages and a different registration dossier with a lower ERC Score, but a high Tonnage Score may exist (see illustrative example in Table 6).

The data also indicate that about 10 % of the substances are assigned ERC Scores of 2.5 (ERC 5, representing industrial uses where the substances is included into or onto a matrix, such as dyes that are included in a fibre matrix in the textile industry) and 0.3 (ERC 1, representing manufacture of a substance). Note that due to the hierarchical nature of the evaluation described in section 2.2.1, Figure 14 only depicts the number of substances for which this was the maximum ERC Score assigned. For example, most of the substances have ERC 1 assigned, since most of them are manufactured in the EU[69]. However, in many cases this did not lead to a maximum ERC Score, since they have other uses that resulted in a higher ERC Score.

As indicated above, an ERC could not be retrieved for 119 substances, since this information was lacking in the data available in ECHA CHEM (the impact of this lack of information is addressed in more detail in the context of the Total Score A below). Lacking ERCs in REACH registration dossiers may have several reasons. Use information (e.g. ERCs) is only required for the exposure assessment performed in the context of a chemical safety assessment, which in turn is generally only required (a) if the REACH registration tonnage per registrant is 10 tpa or higher and (b) if the substance is

[69] The only exeption are substances that are not manufactured in the EU, but completely imported (these are required to be registered under the REACH Regulation, but have no ERC 1 assigned).

classified. If the maximum tonnage of a registration is 10 tpa[70], a chemical safety assessment (CSA) may therefore not be required. In this case, the registrant is unlikely to have identified the uses of the substances and therefore did not report information on ERCs. This may even be the case for a maximum tonnage of 100 tpa in joint submissions, if the tonnage per individual registrant is below 10 tpa[71]. Further analyses indeed show that the fraction of substances with a maximum registration tonnage of 10 or 100 tpa among the 119 substances without an ERC is considerably higher than among the 2 217 substances, for which an ERC could be retrieved (Figure 15). Overall, 72 % of the substances without an ERC have a maximum tonnage of 10 or 100 tpa, while this fraction is only 32 % for the substances with an ERC retrieved.

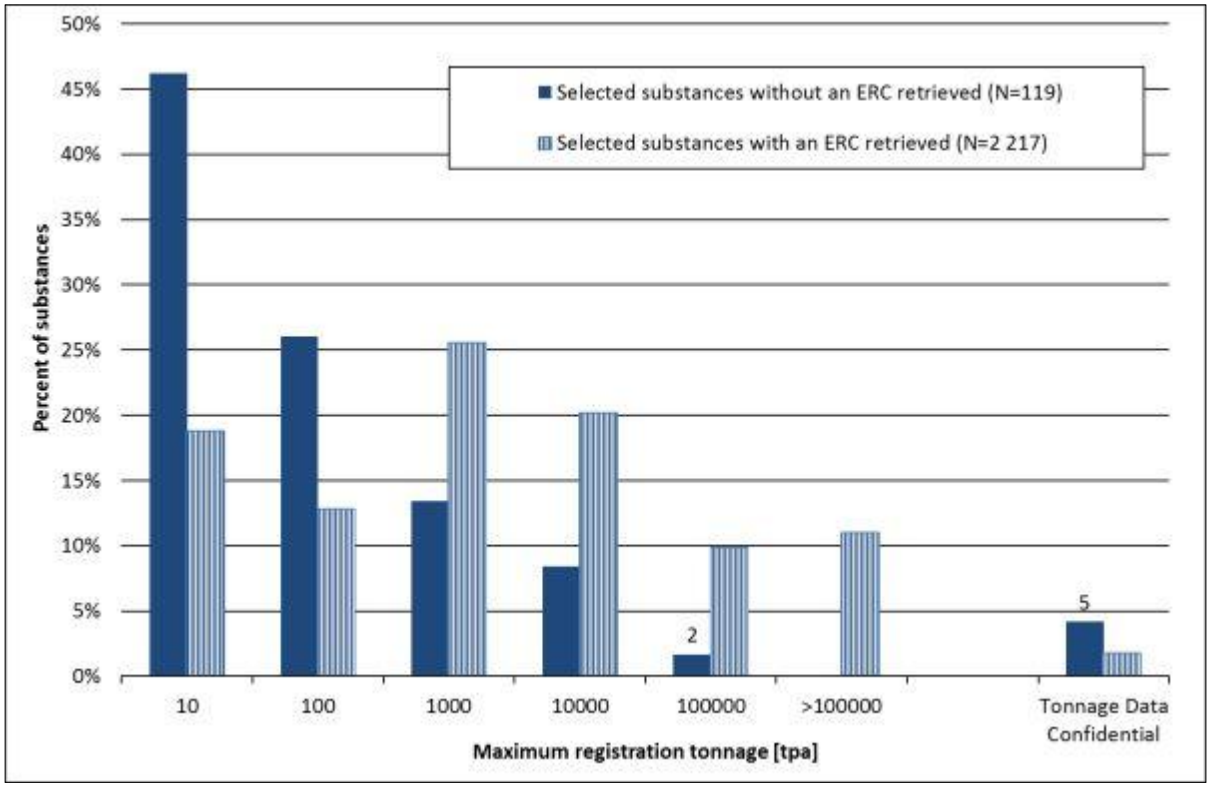


Figure 15: Comparison of maximum registration tonnages for substances with and without an ERC retrieved.

It must be noted that even if the tonnage per registrant is above 10 tpa, the identification of uses may not be necessary, since a CSA involving an exposure assessment and risk characterisation is not required. This is the case, if the substance is not classified and may explain the remaining cases for which no ERC could be retrieved. The latter issue was checked for the 2 substances with a maximum tonnage of 100 000 tpa (CAS No.: 5435-64-3 and 64741-98-6) and the 5 substances with confidential tonnage data (CAS No.: 144-15-0, 27955-94-8, 521284-22-0, 691-37-2 and 75-02-5) among the 119 substances without an ERC (see Figure 15). In-depth evaluations were performed since these substances receive a high Tonnage Score, and together with a high ERC Score may receive very high Total Scores A.

[70] Tonnage band: 1-10 tpa; if this relates to a joint submission, the tonnage per registrant is even lower.
[71] For example, if 5 registrants with 8 tpa each submit jointly, the total tonnage band of this registration will be 10-100 tpa, while each registrant has a tonnage below 10 tpa.

Table 17: Substances without an ERC that would receive a high Tonnage Score

CAS number	Name	Maximum tonnage [tpa]	Dossier information[(a)]
144-15-0	tris(2-ethylhexyl) 2-(acetyloxy)propane-1,2,3-tricarboxylate	Tonnage Data Confidential	Not classified, individual submission, no use information at all; CSA confidential
27955-94-8	tris(hydroxyphenyl)-ethane	Tonnage Data Confidential	Classified, individual submission(b), use 'industrial manufacture'; no ERC; CSA yes
521284-22-0	(1r)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol hydrochloride	Tonnage Data Confidential	Classified, joint submission, no use information at all; CSA yes
5435-64-3	hexanal, 3,5,5-trimethyl-	100 000	Classified, joint submission, industrial use as an intermediate only; no ERC; CSA no
64741-98-6	extracts (petroleum), heavy naphtha solvent	100 000	Classified, joint submission, several industrial, professional and consumer uses identified (e.g. use as a fuel); no ERCs; CSA yes
691-37-2	1-pentene, 4-methyl-	Tonnage Data Confidential	Classified, joint submission, no use information at all; CSA yes
75-02-5	vinyl fluoride	Tonnage Data Confidential	Classified, joint submission, no use information at all; CSA yes

(a): The classification refers to any classification, since this is decisive for the need to identify uses.
(b): There is also a joint submission for this substance with a maximum tonnage of 10 tpa, which provides no use information at all. This would lead to a lower Total Score A of 6.

These data illustrate that all except one substance are classified. The substances with confidential tonnage data may in fact be registered at tonnages below 10 tpa and therefore may not require a CSA with identification of the uses for reasons discussed above. However, the information manually extracted from the REACH registration dossiers (Table 17) show that CSAs were performed for all substances that are classified as required under the REACH Regulation. The only exception is 'hexanal, 3,3,5-trimethyl' (CAS No.: 5435-64-3). It is unclear why a CSA has not been performed for this substance, since both the tonnage and the classification information require such a CSA. In all other cases, it is unclear whether the CSA involves an environmental exposure assessment or not.

Note that there is no legal obligation to assign ERCs and a full CSA can be carried out without these descriptors.

The seven substances shown in Table 17 are assigned a high Total Score A (between 7.5 and 10) due to the lack of information (see section 2.2.1 for the different default Tonnage Scores for joint and individual submissions).

Overall, this analysis suggests that lacking ERCs can be explained by (a) a lacking requirement to identify the uses due to low tonnages of the registrations or (b) because the substance is not classified, or (c) because registrants have chosen not to assign ERCs. Most of the substances with lacking ERCs are registered at low tonnages (see Figure 15), an issue that will be further discussed in the context of the Total Score A below.

Tonnage Scores

The maximum of the REACH registration tonnage was scored according to the approach described in section 2.2.1. Figure 16 shows the distribution of the Tonnage Scores resulting from the evaluation. The figure also presents the distribution of Tonnage Scores for three different datasets for comparison:

- All full registrations with a CAS number (see Table 51 in Appendix A; including duplicate registrations),

- All full registrations without a CAS number (see Table 51 in Appendix A, including duplicate registrations),
- Tonnage band data provided by ECHA registration statistics[72], excluding intermediate and NONS registrations. Note that these summary statistics do not have to respect confidentiality claims in relation to the tonnage.

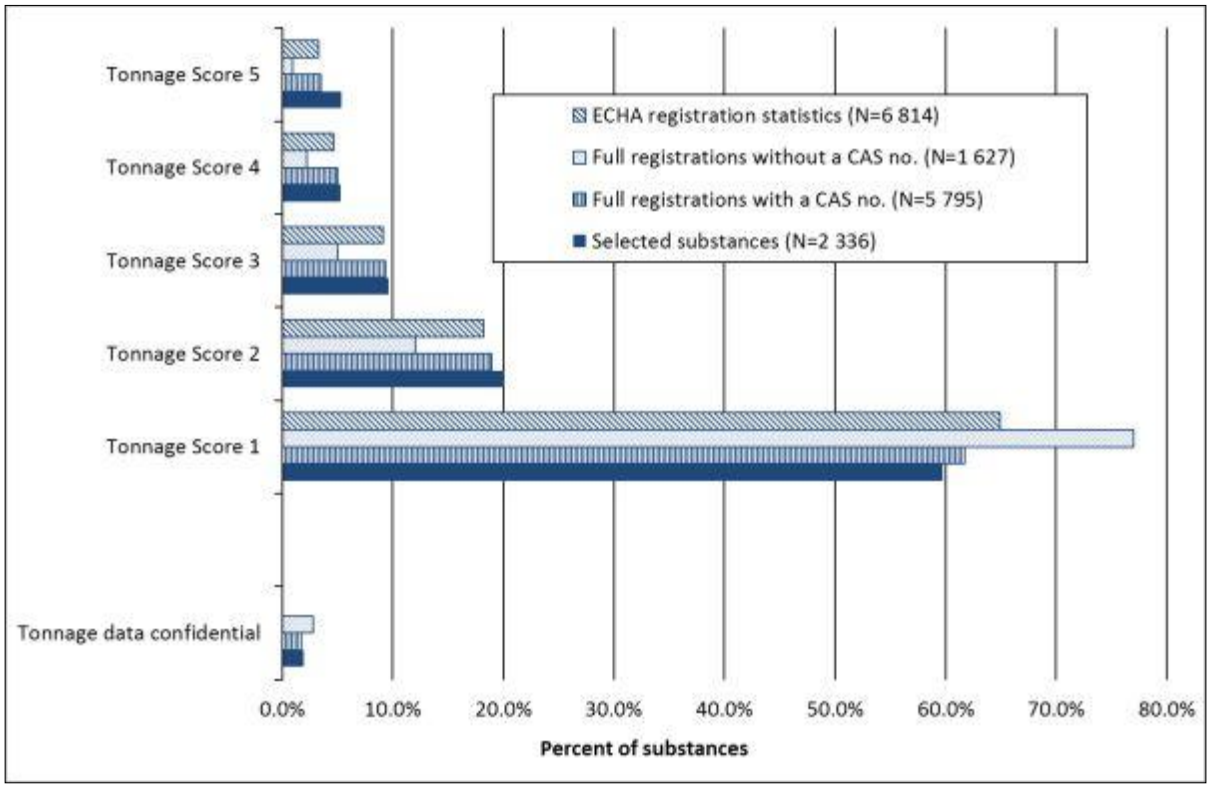


Figure 16: Distribution of Tonnage Scores assigned to the 2 336 selected substances in the hierarchical evaluation and Tonnage Scores in comparative datasets.

The data illustrate that the majority of the selected substances is registered at low tonnages leading to a Tonnage Score of 1 (N=1369, 59 %). However, the fraction of selected substances with a Tonnage Score of 1 is lower than in the datasets chosen for comparison. In particular, this fraction is considerably lower when compared with the full registrations lacking a CAS number (also see detailed discussion in Appendix A). As a consequence, the fraction with Tonnage Scores > 1 in the 2 336 selected substances is higher than in the other datasets, most notably for Tonnage Score 5.

In general, the distribution of the Tonnage Score for the 2 336 selected substances is most similar to the distribution for the full registrations with a CAS number. This finding is not surprising, since these full registrations formed the basis for substance selection (see section 2.1). This observation, however, demonstrates that the additional steps in substance selection (e.g. exclusion of substances lacking a SMILES notation or exclusion of metals, ionisable and other substances; see section 2.1) did not result in a shift in the tonnage distribution.

While the comparison with full registrations with and without a CAS number suffers from the fact that these include duplicate entries, this is not true for ECHA registration statistics, which are based on substances rather than registrations. The distribution of Tonnage Scores based on ECHA registration statistics lies between the full registrations with a CAS number and the full registrations without a CAS number. This can be explained by the fact that the ECHA registration statistics do not differentiate between entries with and without a CAS number.

[72] ECHA registration statistics: https://echa.europa.eu/regulations/reach/registration/registration-statistics/registered-substances-tonnage-band, accessed May 2017.

Overall, only 44 substances (1.9 %) of the selected substances have no public tonnage information. This fraction is lower than the fraction of substances without use information (no ERC retrieved; 5.1 %; see above). Of these 44 substances, the majority (N=39, 87 %) is assigned a default Tonnage Score of 5, since they are registered with a joint submission. The remaining substances are registered only by individual companies and are therefore assigned a lower default Tonnage Score of 2.5 (see section 2.2.1). The impact of assigning these default values is discussed in the context of the Total Score A in the following section.

Total Scores A

Total Score A is calculated by adding up the ERC Score and the Tonnage Score (see section 2.2.1). Figure 17 shows the distribution of Total Scores A in absolute numbers in the set of 2 336 selected substances. The figure also illustrate the number of substances (a) for which the tonnage information is claimed confidential, (b) for which no ERC could be retrieved and (c) for which both types of information was not available (the absolute numbers for the latter are presented above the bars).

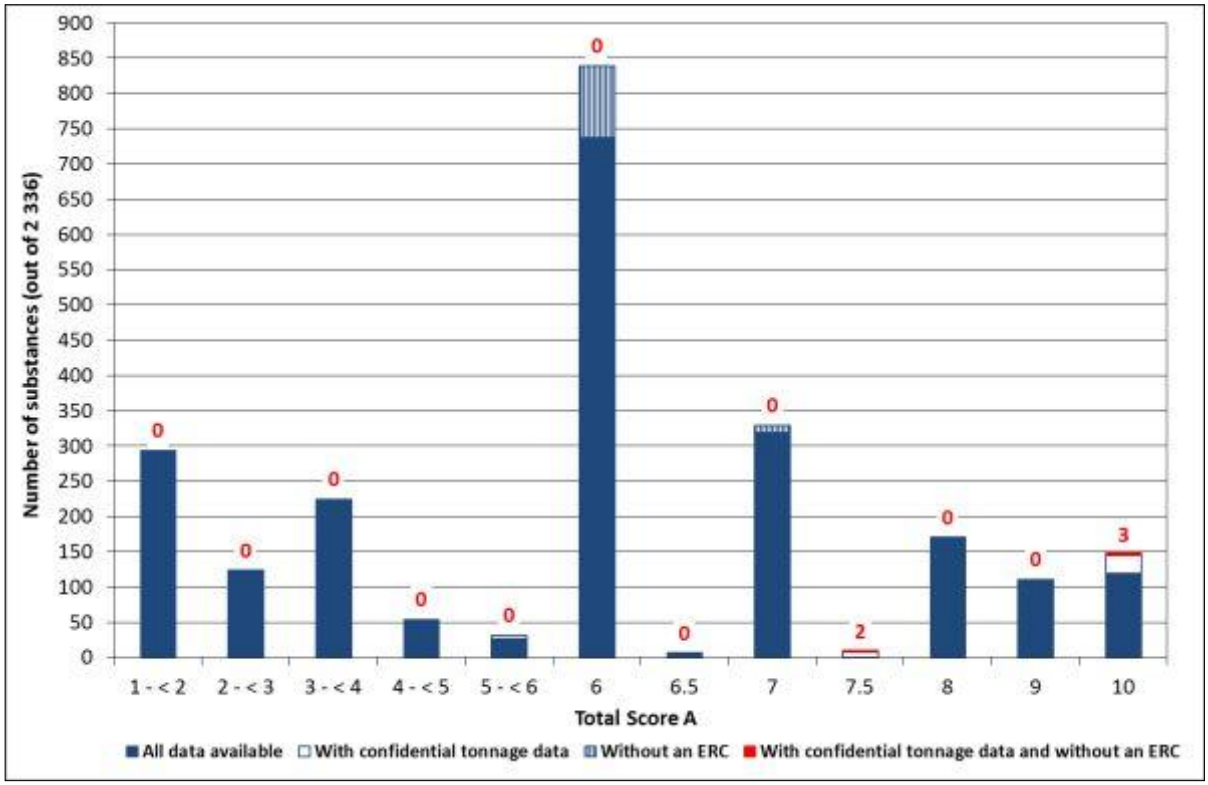


Figure 17: Distribution of Total Scores A assigned to the 2 336 selected substances and identification of substances with default scores.
Numbers above bars represent the numbers of substances with neither tonnage nor use information.

Overall, both tonnage and use information (ERCs) is available for the vast majority of substances (2 178/2 336, 93 %). Both types of information are lacking for only 5 substances, of which 3 are registered by joint submissions, leading to a Total Score A of 10 based on the default worst case scores for lacking tonnage and use information. The other 2 substances are registered by individual submissions resulting in a Total Score A of 7.5 (see section 2.2.1).

The 2 336 selected substances show the following general distribution:

- One-third (N=773, 33 %) is assigned a Total Score A ≥ 6.5;
- Another third of substances (N=839, 36 %) is assigned a Total Score A of 6;
- The last third of substances (N=724, 31 %) is assigned a Total Score A < 6, with the majority assigned a Total Score A < 4.

The large fraction of substances assigned a Total Score A of 6 results from the fact that the majority of the selected substances is assigned an ERC Score 5 (63 % with ERC Score 5 based on available data and 5.1 % with default ERC Score 5 due to missing data; see Figure 14) and a Tonnage Score of 1 (59 %; see Figure 16). Most of the substances with a Total Score A of 6 have data on the tonnage and the use. However, Figure 17 illustrates that the fraction of substances in this group for which no ERC could be retrieved is substantial (12 %). In fact, the majority of the 119 substances for which no ERC could be retrieved (ERC Score 5) are registered at low tonnages leading to a Tonnage Score of 1 (N=102, 86 %; see Figure 15 and discussion above).

Lacking tonnage information contributes primarily to Total Scores A of 10, i.e. 20 % of the substances assigned a Total Score A of 10 have a default worst case Tonnage Score of 5 due to lacking tonnage information. Also, the Total Score A of 7.5 is assigned to two substances lacking tonnage information and use information as well as two substances having both types of information (hardly discernible in Figure 17 due to the low numbers). Finally, there are 5 substances among the 31 substances with Total Scores A of 5-<6 that have confidential tonnage information (16 %).

Apart from these groups, the fraction of substances assigned default values for tonnage information, use information or both types of information is small.

Overall, the distribution of Total Scores A shows a good degree of differentiation. The fraction of substances with lacking data is small and only 5 of the 2 336 substances lack both types of information, resulting in very uncertain Total Scores A (see Table 17).

This small number results from the exclusion of NONS in substance selection, for which tonnage and use information is always lacking. Had these been included, a much larger number of substances would have been assigned Total Scores A of 7.5 and 10 (ERC Score 5 and Tonnage Score of 2.5 or 10; see section 2.2.1). These substances would have dominated the higher Total Scores A, but their basis would have been highly uncertain.

Since lacking tonnage and/or use information increases the uncertainty in the Total Score A, this information will be retained and will be helpful e.g. when selecting substances for in-depth evaluation. It must also be noted that Total Score A involves an inherent uncertainty even if tonnage and use information is available. This uncertainty results from the fact that in any given registration the maximum tonnage is not necessarily related to the use resulting in the highest ERC Score (see section 2.2.1). . This issue could be resolved by an assessment of the confidential Chemical Safety Reports (see 'Proposal for possible next steps' in section 5).

3.2.2. Fate: biodegradation (block B)

The scores for the 2 336 substances were distributed as follows: 42 % (983/2 336) of the substances had a score of 1, 5.6 % (131/2 336) a score of 6, 4.8 % (113/2 336) as score of 8 and 47 % (1 109/2 336) a score of 10 (Table 18). Therefore, the majority of substances is assigned the lowest score 1 or the highest score 10. A total of 1 353 substances are assigned Scores B of 6, 8 or 10, indicating little or no biodegradation of these substances. According to Bitsch et al. (2016), the scores can be translated into qualitative results. The qualitative results represent phrases that are based on interpretation of experimental results of various test guidelines for ready or inherent biodegradability (e.g. OECD TG 301 or 302, respectively). Translated, 42 % of the substances are 'readily biodegradable' and 47 % are 'not inherently biodegradable' or recalcitrant ('under test condition no biodegradation observed'); 5 % are 'not readily biodegradable' and 6 % are 'inherently biodegradable *not fulfilling specific criteria'* (for explanation on experimental results please see footnote of Table 18).

Table 18 shows that the differentiation into score 2 ('readily biodegradable, but failing 10-d window') and 4 ('inherently biodegradable *[fulfilling specific criteria]*') is impossible by the BIOWIN battery approach, because of the limited sensitivity of the model outputs. Therefore, the percentage of score 2 and 4 are 0 % for predicted results. This is not the case for experimental results (see Bitsch et al. (2016) and section 3.2.3).

Table 18: Results on biodegradation for 2 336 substances registered under REACH

Score	Number of substances	Percentage of 2 336 substances	Translated to interpretation on results[(a)]
1	983	42 %	Readily biodegradable
2 [(b)]	0	–	Readily biodegradable, but failing 10-d window
4 [(b)]	0	–	Inherently biodegradable [*fulfilling specific criteria*]
6	131	5.6 %	Inherently biodegradable, *not fulfilling specific criteria*
8	113	4.8 %	Not readily biodegradable
10	1109	47 %	Not inherently biodegradable / Under test condition no biodegradation observed

(a): Definition of biodegradation results according to ECHA Guidance R.7b (2016a) and more detailed in the EU TGD (EC, 2003) and the EUSES background report (RIVM, 2004)
Readily biodegradable: pass level of >= 70 % DOC removal or >= 60 % ThOD or >= 60 % ThCO2 production within 28 days and reached within a 10-d window (10-d window starts at a pass level of 10 % DOC removal or ThOD or ThCO2 production)
Readily biodegradable, but failing 10-d window: pass level of >= 70 % DOC removal or >= 60 % ThOD or >= 60 % ThCO2 production must be reached within 28 days, not limited to a 10-d window
Inherently biodegradable: results of a ready biodegradability test slightly <70 % DOC removal or slightly <60 %ThOD or slightly <60 % ThCO2 production or pass level reached, but exceeding 10-d window; or results of an inherent biodegradability test: >70 % theoretical BOD or >70 % DOC removal or >70 % COD within 28 days
Inherently biodegradable, fulfilling specific criteria: pass level of >70 % theoretical BOD or >70 % DOC removal or >70 % COD must be reached within 7-d window (OECD 302C: within 14-d window), log-phase should not be >3 days, percentage removal before accounting for biodegradation should be <15 %
Inherently biodegradable, not fulfilling specific criteria: pass level of >70 % theoretical BOD or >70 % DOC removal or >70 % COD must be reached within <= 28 days

(b): The differentiation into score 2 ('readily biodegradable, but failing 10-d window') and 4 ('inherently biodegradable [*fulfilling specific criteria*]') is impossible by the BIOWIN battery approach, because of limited sensitivity of model outputs.

The score distribution of 2 336 substances into predominantly minimum and maximum score, and a small number into medium scores is satisfactory. The results are in very good agreement with previous results of the same method for a smaller data set of 100 substances (Bitsch et al. (2016); excluding four positive controls).

Figure 18 compares the distribution of scores from predicted biodegradation data in this study with those predicted in the pilot study (Bitsch et al., 2016) in clustered scores of 1-2, 4-6 and 8-10 (also referred to as persistence classes LOW, MODERATE and HIGH in the validation study). The figure shows the distribution of scores for the full data set of 2 336 substances and the data set of the pilot study (100 substances, excluding four positive controls). The pattern of an almost equal distribution between scores 1-2 and 8-10 is consistent, i.e. 42-47 % and 49-52 %, respectively. Furthermore, percentages of chemicals receiving scores 6 or 8 are consistently low, i.e. 4.0-5.6 %. In-depth evaluation of corresponding experimental results for the full data set of the 2 336 substances is discussed in section 3.2.3.

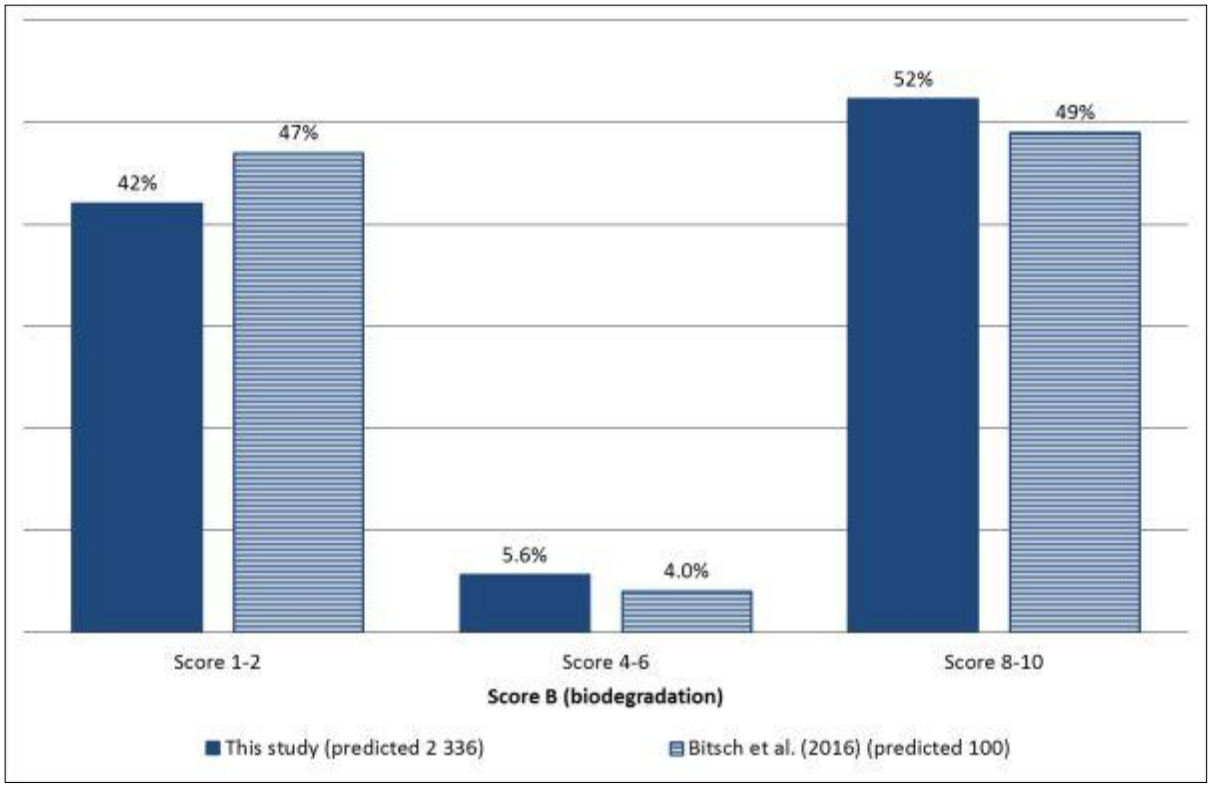


Figure 18: Comparison of the distribution of biodegradation scores for 2 336 substances registered under REACH and the pilot study (Bitsch et al., 2016) in clustered scores

In summary, the application of the BIOWIN3/5/6 battery approach is straightforward and easy to execute. Generated results are in very good agreement with results of the pilot study, i.e. the distribution of scores for biodegradation of 2 336 substances are similar to the distribution of 100 substances of the pilot study (Bitsch et al., 2016).

The majority of 2 336 selected substances receive the minimum or maximum score, i.e. 42 % (983/2 336) or 47 % (1 109/2 336), respectively. The level of differentiating biodegradable from poorly biodegradable substances is therefore considered good. The biodegradation score for each substance is further processed in the identification of potential emerging risks in the food chain. Biodegradation results based on the BIOWIN battery approach as well as results for the single BIOWIN models are compared in Appendix C.

3.2.3. Fate: validation of predicted biodegradation (block B)

Overview

The recommendation to use predicted data in a battery approach was based on the finding that predicted biodegradation data agree well with experimental data when used in the scoring applied in this study (Bitsch et al., 2016). However, this observation was based on a relatively small set of 100 substances. To further investigate the relationship between predicted and experimental biodegradation data, key values were compared with predicted data for the 2 336 substances selected. Such key values represent a summary by registrants of the experimental data available (see section 2.2.3 for details).

Overall, key values were available for 1 567 of the 2 336 selected substances (67 %). This high fraction of substances in our set was unexpected, since there is no legal requirement to fill in the key value in the REACH dossier and derivation of key values (i.e. the IUCLID dataset) only became more meaningful with the implementation of the CHESAR tool (not available e.g. at the 2010 REACH registration deadline). One possible explanation for this high fraction is the fact that only substances with a full registration are selected (see section 2.1.1), for which a chemical safety assessment is

required, if they are classified[73]. Such a chemical safety assessment is easily performed with the IUCLID-compatible CHESAR tool, which requires key values to be entered in IUCLID.

The data in Table 19 show that a single key value was retrieved for the vast majority of the 1 567 substances for which a key value was available (1 495/1 567 substances, 95 %). Differing key values were only retrieved for 72 substances, with the majority having two different key values.

Table 19: Availability of key values for biodegradation in registration dossiers of the 2 336 selected substances

Key value	Number of substances
One consistent key value from all dossiers(a)	1 495
Two different key values from all dossiers	67
Three different key values from all dossiers	5
Total number of substances with at least one key value	1 567

(a): Includes cases where only one dossier was available and cases, where the key value in different dossiers was identical.

As discussed in more detail in Appendix B, different key values sometimes do not lead to different scores. More importantly, different scores do not necessarily lead to different classes in the approach used in the validation study, since each class represents two scores (see section 2.2.3). As a consequence, 53 substances are assigned to different classes based on the different key values, while 19 are not (see section 2.2.3 for the class differentiation).

Comparison of predicted biodegradation data with those derived from key values in REACH registration dossiers

The two assessments (one using the least conservative and one using the most conservative key value for these 53 substances with different classes due to different key values) lead to negligible differences in the context of this validation study. This finding results from the fact that the fraction of substances, for which the classes differ, is very small (53/1 567, 3.4 %). Appendix B provides more details on these two assessments.

Since differences between the two assessments in class assignment exist only for 53 substances, and the differences in the results are negligible, mean values of the two assessments are shown below.

As outlined in section 2.2.3, the comparison is performed by assigning the scores for each substance (a) based on the predicted data and (b) based on the key values to three different classes: HIGH (scores 8 and 10), MODERATE (scores 4 and 6) and LOW (scores 1 and 2) persistence[74]. The resulting class assignment based on predicted data can then be compared with the class assignment based on the key values for any given substance. These comparisons are grouped as follows:

- Matching: a substance is assigned to the same class (e.g. LOW) based on predicted data and based on the key value;
- Overprediction: a substance is assigned to a higher persistence class (e.g. HIGH) based on the predicted data than based on the key value (e.g. MODERATE);
- Underprediction: a substance is assigned to a lower persistence class (e.g. LOW) based on the predicted data than based on the key value (e.g. HIGH).

The results of these comparisons for 1 567 substances are shown in Figure 19. Compared to the pilot study (Bitsch et al., 2016) that was based on a much smaller set of substances, the fraction of matching assessments is somewhat lower in the more comprehensive validation presented here (66 % vs. 76 %; also see detailed data in Table 20 below). Overall, there is a good level of agreement between the biodegradation potential derived from predicted data and the one based on key values.

[73] Such a chemical safety assessment is generally not required for substances registered as intermediates under strictly controlled conditions or for substances that are not classified.

[74] As stated in section 2.2.3 classes are expressed in persistence rather than biodegradation potential, since class HIGH e.g. is then associated with the highest scores.

The more detailed data in Table 20 below show that about one fourth of the 2 336 substances are consistently assessed as poorly biodegradable in both evaluations.

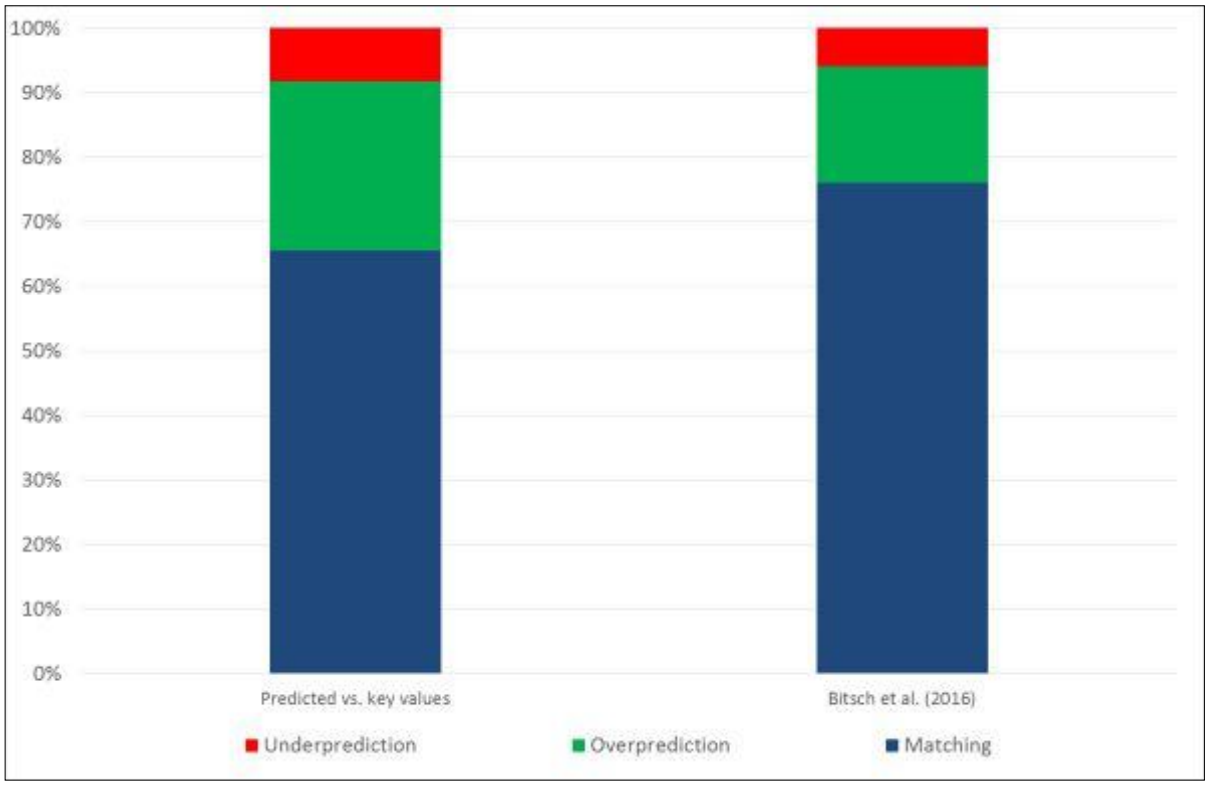


Figure 19: Summary of the validation study based on 1 567 substances and comparison with the results of validation in Bitsch et al. (2016) based on 104 substances

Overpredictions of persistence, i.e. a lower predicted degree of biodegradation than actual (based on experimental data), in the present validation are higher than in the previous validation reported by Bitsch et al. (2016). This finding may be related to differences in the evaluation of experimental data. Bitsch et al. (2016) evaluated reliable experimental data on biodegradation, which often led to several different results for a given substance. These authors selected the most frequent result reported. For example, if two studies reported no biodegradation and one study resulted in the conclusion of the substance being readily biodegradable, this substance was assessed as not being biodegradable (score 10; HIGH persistence class). In contrast, registrants may have chosen 'readily biodegradable' (score 1; LOW persistence class) as the key value for this substance, which is in agreement with the REACH guidance document (ECHA, 2016a)[75].

Substances that are overpredicted can be considered false positives in the context of the evaluation of biodegradation used in this study. Thus, a substance is predicted to be poorly biodegradable (highly persistent), while in fact it may be readily biodegradable (15 % of the cases; see Table 20 below). While this represents a conservative element typical for screening procedures, false positives may represent a problem in the ultimate identification of emerging chemical risks. In the assessment of 2 336 substances, false positives will be identified in later stages of the study, when substances are selected for further evaluation. Two issues should be kept in mind in the context of this discussion:

- The selection of key values by registrants may tend towards the most favourable value, which may not entirely reflect the overall data basis on biodegradation for a given substance. Further evaluations at later stages of this study may identify such cases.

[75] According to this guidance document, ready biodegradability observed in a reliable test generally outweighs negative results in other tests due to the stringent conditions of the underlaying tests.

- For models BIOWIN 5 and BIOWIN 6, MITI (I) test data (OECD TG 301 C) by the Japanese Ministry of International Trade and Industry (MITI) form the experimental data basis used. The special inoculum applied in OECD TG 301 C (continuous culture of inoculum from mixed sources with synthetic sewage) is known to lead to lower biodegradation potency compared to other ready biodegradability tests using the inoculum directly (Kayashima et al., 2014; Gartiser et al., 2017). Therefore, BIOWIN 5/6 may indicate non-ready biodegradability while in fact ready biodegradability might be demonstrated by other tests.
- Biodegradation is an important element in the approach to the identification of potential emerging chemical risks in the food chain. However, even a readily biodegradable substance may be present in the environment, if released to the environment in large amounts (Bitsch et al., 2016). While such a substance may have been a false positive based on predicted biodegradation data, further evaluations during later stages may demonstrate that such a substance occurs in the environment and is therefore relevant for further consideration.

When the sum of matching comparisons and overpredictions are considered, the fraction of substances is similar in this validation study (92 %) and the pilot study (94 %; see Table 20). This is also evident in the corresponding level of underpredictions that are in the same range for this and the previous validation, i.e. 8.3 % and 6.0 %, respectively (Figure 19). Table 20 demonstrates that about one half of the underpredicted substances are predicted to be readily biodegradable (LOW persistence class), while the key values suggest that they are only poorly biodegradable (HIGH persistence class). These false negatives are less likely to be selected for further evaluation in later stages of this study. While the loss of such substances is not desirable, it cannot be avoided in a screening procedure.

Table 20 shows more detailed data of the results of the validation study and data from the previous validation by Bitsch et al. (2016). Since the differences between the two assessments of key values (see section 2.2.3 for details on these assessments) are negligible in the context of this validation study, mean values of these two assessments are shown.

Table 20: Details of the validation study results based on overall data set

Comparisons[(a)]	**Persistence class assignments (predicted-key values)[(b)]**			**Sum**
MATCHING				
	LOW-LOW	MODERATE-MODERATE	HIGH-HIGH	
Predicted vs. key values	38 %	0.83 %	26 %	66 %
Bitsch et al. (2016)				76 %
OVERPREDICTION				
	MODERATE-LOW	HIGH-LOW	HIGH-MODERATE	
Predicted vs. key values	3.5 %	15 %	7.2 %	26 %
Bitsch et al. (2016)				18 %
UNDERPREDICTION				
	LOW-HIGH	MODERATE-HIGH	LOW- MODERATE	
Predicted vs. key values	4.2 %	1.1 %	3.0 %	8.3 %
Bitsch et al. (2016)				6.0 %

All values rounded to two significant figures.

(a): For predicted vs. key value comparisons, the mean of the two assessments based on the least and the most conservative key value are shown, since the difference between the two assessments is negligible in the context of this validation study (see Appendix B for details).

(b): The first class indicates the one derived from predicted data, while the second class indicates the one based on key values. For example, 3.5 % of the substances are assigned to the MODERATE persistence class based on predicted data, but to the LOW persistence class based on the key values.

The percentages in Table 20 relate to all 1 567 substances in the validation study. The same data can also be analysed separately for each of the three persistence classes of the key values (Table 21). For examples, 599 of the 896 substances (67 %) with key values indicating class LOW also are assigned to this class based on the predicted data in the battery evaluation. These 599 substances correspond to the 38 % (599/1 567) shown in Table 20 for the LOW-LOW comparison. Table 21 also shows the percentage of correctly predicted substances per persistence class of the key value and the overall

evaluation of correctly predicted substances as well as over- and underpredicted substances. These latter figures correspond to the ones given in Table 20 (the marginal difference in the figure for underpredictions is due to rounding of the means from the least conservative and most conservative assessment of the key values).

Table 21: Details of the validation study results based on persistence class of key value

Key value	Total	Predicted						
		LOW		MODERATE		HIGH		Correct predicted
LOW	896	**599**	**67 %**	*55*	*6.1 %*	*242*	*27 %*	67 %
MODERATE	173	47	27 %	**13**	**7.5 %**	*113*	*65 %*	7.5 %
HIGH	499	66	13 %	18	3.5 %	**415**	**83 %**	83 %
Correct total	1 567	599		13		415		66 %
Overpredictions	1 567			55		355		26 %
Underpredictions	1 567	113		18				8.4 %

All values rounded to two significant figures. Correct predictions are set in bold and overpredictions (predicted to be less biodegradable than indicated by the key value) are set in italics.

In order to compare these data with literature values, predicted data and key values were aggregated into two groups:

- Substances that are readily biodegradable (persistence class LOW, scores 1-2, as defined in section 2.2.3)
- Substances that are not readily biodegradable (persistence classes MODERATE and HIGH, scores 4-10, as defined in section 2.2.3); this involves adding up the figures for the classes MODERATE and HIGH

Table 22 shows the resulting figures for these aggregated groups.

Table 22: Aggregation of the results of the validation study

	Total	Predicted RB		Predicted NRB		Correct predicted
Key value RB	896	**599**	**67 %**	*297*	*33 %*	67 %
Key value NRB	672	113	17 %	**559**	**83 %**	83 %
Correct total	1 567	599		559		74 %
Overpredictions	1 567			297		19 %
Underpredictions	1 567	113				7.2 %

All values rounded to two significant figures. Correct predictions are set in bold and overpredictions (predicted to be less biodegradable than indicated by the key value) are set in italics.

The data in Table 21 and Table 22 clearly show that ready biodegradability (RB, persistence class LOW) can be less accurately predicted than non-ready biodegradability (NRB, persistence classes MODERATE and HIGH). This finding is fully in agreement with past research (see e.g. Tunkel et al., 2000; Boethling et al., 2004; Posthumus et al., 2005; Tunkel et al., 2005).

The data shown in Table 22 are compared with literature values obtained in other studies in Table 23. The studies used for comparison are not necessarily exhaustive, since a full literature search was beyond the scope of this study. Note also that not all studies report all values presented in the table.

Table 23: Comparison of results from this study with literature values

BIOWIN model	Source	N[(a)]	Correct predictions[(b)]		
			RB	NRB	Total
3/5/6	This study	1 567 (57 %)	67 %	83 %	74 % (93 %)
3/5	Boethling et al. (2004)	374 (26 %)			88 % (95 %)
	Boethling (2014)	218 (49 %)	72 %		
	Posthumus et al. (2005)	110 (30 %)	48 %	90 %	77 % (93 %)
3/6	Posthumus et al. (2005)	110 (30 %)	52 %	92 %	80 % (95 %)
3	Boethling et al. (2004)	374 (26 %)	69 %	95 %	86 %
	Boethling (2014)	218 (NA)	73 %		
	Posthumus et al. (2005)	110 (30 %)	79 %	81 %	80 % (86 %)
5	BIOWIN5 validation set[(d)]	295 (44 %)	80 %	82 %	81 %
	Boethling et al. (2004)	374 (26 %)	60 %	92 %	81 %
	Boethling (2014)	201 (49 %)	69 %		
	Pizzo et al. (2013)	722 (NA)			82 %
	Posthumus et al. (2005)	110 (30 %)	52 %	82 %	73 % (87 %)
	Tunkel et al. (2005)	370 (25 %)	81 %	82 %	82 %
6	BIOWIN6 validation set[(d)]	295 (44 %)	79 %	82 %	81 %
	Boethling et al. (2004)	374 (26 %)	64 %	89 %	82 %
	Boethling (2014)	201 (49 %)	70 %		
	Pizzo et al. (2013)	722 (NA)			83 %
	Posthumus et al. (2005)	110 (30 %)	55 %	87 %	77 % (91 %)
	Tunkel et al. (2005)	370 (25 %)	70 %	87 %	83 %

All values rounded to two significant figures.

(a): Fraction of readily biodegradable substances given in parentheses; NA: not available.

(b): Correct predictions of RB, NRB and total; because of their relevance for a conservative screening assessment, total correct predictions including overpredictions (RB compounds predicted as NRB) are given in parentheses.

(c): EPISuite™, On-Line BIOWIN™ User's Guide (v4.10).

(d): Reported by Tunkel et al. (2000).

The data illustrate quite a broad range of correct predictions:

- 48-81 % for correct predictions of ready biodegradability in literature values (AM: 67 %, median: 70 % (N=16))

  This study: 67 %

- 81-95 % for correct predictions of non-ready biodegradability in literature values (AM: 87 %, median: 87 % (N=12))

  This study: 83 %

- 73-88 % for total correct predictions in literature values (AM: 81 %, median: 81 % (N=15))

  This study: 74 %

This study therefore resulted in slightly lower correct predictions of both ready and non-ready biodegradability compared to the arithmetic mean and median from literature values. For total correct predictions, this study identified a value that is at the lower end of the range from all other studies. However, several issues have to be considered when interpreting these findings:

- This study by far included the highest number of substances (N=1 567 compared to a maximum of 722 in other studies), representing broad ranges of chemical classes. This may have an effect on the degree of correct predictions.
- The battery approach employed is conservative, which is appropriate for a screening procedure. This approach leads to a substantial number of overpredictions (26 %; see Table 21 and Table 22). While the percentage of total correct predictions is lower than in most other studies,

the sum of total correct predictions and overpredictions in this study (93 %) is in the range of values in other studies (86-95 %; see Table 23). Importantly, it is similar to the values found with other battery approaches (93-95 %), but somewhat higher than the values observed with individual BIOWIN models (86-91 %; see Table 23).

- The percentage of readily biodegradable substances (based on experimental data) in the dataset of this study (57 %; see Table 23) is higher than in all other studies. Since ready biodegradability is less well predicted than non-ready biodegradability, the percentage of total correct predictions is lower the higher the fraction of readily biodegradable substances in the dataset. When the literature data are normalised to the percentage of readily biodegradable substances of 57 %, the difference between this study and the 12 literature values, for which such a normalisation can be performed, is much less pronounced. The value of 74 % for total correct predictions observed in this study is within the range of values from literature and only marginally lower than AM and median from the other studies (Table 24).

Table 24: Comparison of results from this study with literature values normalised to the same fraction of RB substances

Source	Correct predictions	
	Total[(a)]	Total normalised to 57 % RB in dataset[(b)]
This study	74 %	74 %
Literature values:		
MIN	73 %	65 %
AM	81 %	75 %
MEDIAN	81 %	76 %
MAX	88 %	81 %

All values rounded to two significant figures.
(a): N=15
(b): N=12; calculated with the following formula: (Percentage correct RB * 0.57) + (Percentage correct NRB * 0.43)

Based on these considerations, the battery approach employed in this study shows an average performance for correct predictions when compared with literature values. However, it results in better performance when correct predictions and overpredictions are considered. This is not surprising, since the approach employed includes a comparatively high degree of conservatism. For example, a substance is only classified as readily biodegradable in the battery approach of this study, if it is readily biodegradable in all three BIOWIN models. Since the batteries in the other studies included only two BIOWIN models, the requirements for a prediction of ready biodegradability are lower.

Despite this conservatism, however, 113 substances of the 672 substances with experimental data indicating non-ready biodegradability are predicted to be readily biodegradable (17 %; see Table 22). This figure is in the range of literature values for the three individual BIOWIN models 3, 5 and 6: 13-19 % (Posthumus et al., 2005); 14-18 % (Boethling et al., 2004), but is higher than the values found by these authors for BIOWIN batteries (BIOWIN3/5 and BIOWIN3/6: 6.8-10 %). This finding may be related to issues such as the chemical domain of compounds assessed in the various studies. However, this issue cannot be addressed further, since the identity of the 113 substances was not available for further analyses (see section 2.2.3).

It must also be noted that 47 of the 113 substances with experimental data indicating non-ready biodegradability are inherently biodegradable (see Table 21), while 66 have experimental data indicating no biodegradation or no inherent biodegradation.

Discussion of the validation study

The validation study shows a good level of agreement between the biodegradation potential derived from predicted data and the one based on key values extracted from REACH registration dossiers, which largely reflect experimental data on biodegradation. This validation for 1 567 of the 2 336 selected substances corroborates the findings of an earlier validation with only 104 substances.

There is a large body of literature on the reliability of predicting biodegradation with BIOWIN models. A detailed discussion of this subject is beyond the scope of this study. However, the following issues emerge from the evaluations performed in this study:

- When BIOWIN predictions are taken to differentiate readily biodegradable substances from those that are not readily biodegradable (i.e. a more simple class assignment than the one used in the scoring system of this study), a reasonable level of agreement for screening purposes is sometimes observed even with individual BIOWIN models. However, it is generally acknowledged that battery approaches result in better predictions (see e.g. Boethling et al., 2004; Posthumus et al., 2005; Bitsch et al., 2016; ECHA, 2016a).
- The comparison of the results of this study with literature values in relation to ready/non-ready biodegradability shows a reasonable performance, when the fraction of readily biodegradable substances is accounted for. In fact, the evaluations show that a normalisation of the datasets to the fraction of readily biodegradable substances may change the results considerably.
- The present approach includes a conservative element and leads to a level of correctly and overpredicted substances (93 %) that is fully in agreement with other battery approaches.
- The fraction of substances with experimental data indicating non-ready biodegradability, but predictions suggesting ready biodegradability is comparatively high. Further analyses of these substances are impossible due to confidentiality of key values, but the difference to other studies may be related to issues of chemical domain. Furthermore, there may be cases, where only a single valid test was performed and the result of non-biodegradability was used as the key value. Further testing would possibly have identified ready biodegradability and therefore resulted in a correct prediction. This suggestion is also based on the fact that different ready biodegradability tests deviate considerably with regard to relevant experimental conditions, which ultimately affects their comparability, i.e. probability of biodegradation for a given compound (Gartiser et al., 2017). Again, because further substance-specific analyses are impossible, this issue cannot be addressed in more detail.

It must also be stressed that the nature and quality of the experimental data may be different in different studies. Some of the literature values are based on experimental data obtained from a single test, while the key values used in this study may have been derived from several screening test results.

The differentiation into ready and non-ready biodegradability was only performed to allow comparisons with literature values. The differentiation into three persistence classes in this study leads to a similar picture. While predictions on biodegradation unavoidably lead to some over- and underpredictions, the high fraction of matching assessments (66 %) and the low fraction of underpredictions (8.3 %) show that the approach of using predicted biodegradation data for screening procedures is acceptable.

3.2.4. Fate: bioaccumulation in food and feed (block C)

As described in section 2.2.4, the scoring of predicted bioaccumulation concentrations involved two steps. First, the quartiles for each food item and grass (feed) were calculated in Microsoft Excel®. Calculated quartile concentrations (25th, 50th (median) and 75th percentile) are depicted for each food item and grass in Table 25. The predicted concentrations for food and feed items are interpreted as an indication of potential chemical partitioning and bioaccumulation in food and feed. They are used as relative figures that are depending on the input data set (in this case: 2 336 substances). Absolute concentrations were simulated using the same ACC-HUMANsteady environmental default scenario for all substances that assumes a default tonnage being present in a default regional environment (identical for all 2 336 substances; see section 2.2.4). As a consequence, the absolute concentrations presented in the table have no meaning, since they are based on the 'default scenario' of ACC-HUMANsteady and are not related to any real emissions to the environment. For this reason, the scoring is based on relative considerations, the concentration of a substance in a food item relative to the quartile concentrations of the modelled concentration range for all substances in that food item.

Table 25: Quartiles of concentrations in the eleven food items and grass (N=2 336)

Percentile	Concentration in food item [ng/g wet weight]						
	Fish 1	Fish 2	Apple - Fruit	Grain - Fruit	Potato - Tuber	Lettuce - Leaf	Carrot - Root
25th	5.63E-07	2.53E-07	4.93E-09	5.29E-08	1.29E-09	1.93E-08	6.18E-11
50th	1.86E-04	7.03E-05	5.49E-07	9.18E-06	3.49E-08	2.86E-06	1.51E-09
75th	2.89E-01	3.37E-02	4.49E-05	7.29E-04	8.17E-06	1.69E-04	3.93E-07
	Beef Cattle	Dairy cattle	Milk	Dairy Products		Grass - Leaf	
25th	4.82E-08	6.00E-08	2.08E-08	8.31E-08		3.38E-08	
50th	1.58E-06	3.54E-06	1.07E-06	4.90E-06		4.13E-06	
75th	1.54E-04	1.82E-04	6.17E-05	2.73E-04		2.59E-04	

As the data set for 2 336 substances is substantially larger than the data set of the pilot study (N=100, Bitsch et al. (2016)), it was interesting to explore whether shifts occurred in the distribution of predicted concentrations between the two data sets. Figure 20 illustrates observed upward or downward shifts of quartile concentrations for 2 336 substances compared to the pilot study. Note that the middle line of the graph (marked in red) shows an equal prediction of quartile concentrations between this study and the pilot study (Bitsch et al., 2016). If the dark bars (indicating the predicted concentrations of this study) are above the middle line, this indicates that a predicted quartile concentration is higher in this study compared to the pilot study. In contrast, a shift below the middle line indicates a lower predicted quartile concentration in this study compared to the pilot study. Overall, the distribution of predicted concentrations is somewhat different for the larger data set of this study compared to the smaller data set of pilot study. Median concentrations shift upwards for the food/feed items fish 1, fish 2, apple, grain, lettuce, dairy cattle, dairy products and grass. The 75th percentile concentration is higher for potato and carrot, and every calculated quartile concentration (25th, 50th and 75th percentile) decreases for beef cattle and milk (Figure 20).

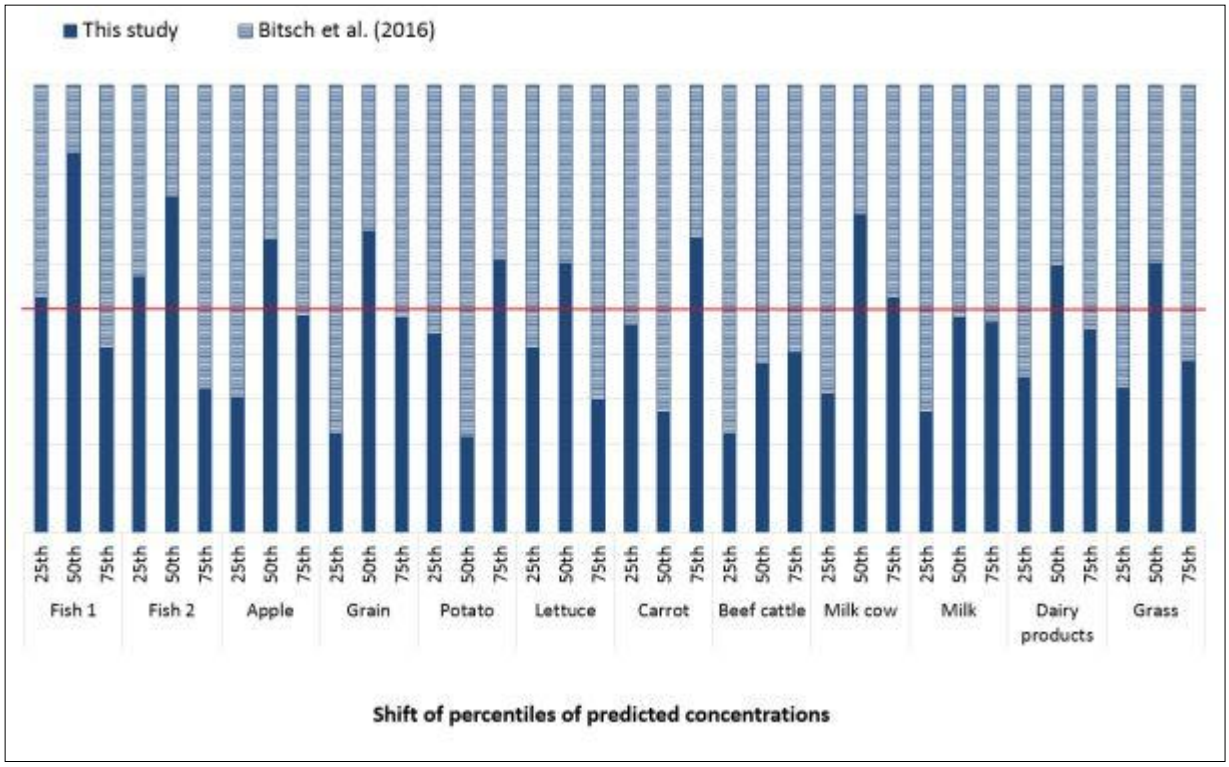


Figure 20: Shift of predicted 25th, 50th and 75th percentile concentrations in every food/feed item (N=2 336 substances) with respect to predictions from the pilot study (Bitsch et al. (2016) (N=103; of the 104 substances 1 had missing data)

Note: The middle line of the graph (marked in red) depicts an equal prediction of quartile concentrations between this study and the pilot study (Bitsch et al. (2016). If the dark bars (indicating the predicted concentrations of this study) are above the middle line, this indicates that a predicted quartile concentration is higher in this study compared to the pilot study. In contrast, a shift below the middle line indicates a lower predicted quartile concentration in this study compared to the pilot study.

The distribution of the predicted concentrations lays in the nature of input data (see Appendix D). As the data set of 2 336 substances is statistically more powerful than the smaller data set of the pilot study, newly calculated quartile concentrations are considered more robust and reliable. Therefore, they were adopted and used for the scoring of bioaccumulation potential of the 2 336 substances.

After scoring each substance, the highest score retrieved in any of the food items was further processed as Score C (bioaccumulation) in the screening procedure (grass was not integrated in this score, because it was considered feed). Figure 21 illustrates the distribution of Score C: e.g. 40 % of the substances are assigned a Score C of 10 and therefore have at least a Score C of 10 in one of the food items (see also discussion below). Feed item grass has an equal Score C distribution of 25 % for score 1, 3, 6 and 10 (not graphically illustrated).

Such an equal score distribution of 25 % (584/2 336) in score 1, 3, 6 and 10 was not retrieved for all food items. For some food items (i.e. fish 1, fish 2, beef cattle, dairy cattle, dairy products and apple), some substances shifted to a higher score range. For fish 1, beef cattle and apple, this only involved the shift of individual substances (e.g. score 1 for 583 substances and score 3 for 585 substances). For the other three food items, more substances moved from score 6 to score 10 than expected by the statistical distribution. In these cases, several substances were predicted to yield exactly the concentration of the calculated 75th percentile and were therefore assigned a score of 10. These shifts therefore result from the definition of scores, e.g. for score 10 to include all substances with concentrations at the 75th percentile or higher. The observed shift into a high score range included 16 substances for a food item at maximum (0.68 %).

The distribution of Score C is very similar in this study compared to the distribution in the pilot study (Figure 21). The very similar distribution of bioaccumulation scores between the two data sets makes sense, because the scoring is entirely based on quartile concentrations (25th, 50th and 75th percentiles), which generate similar fractions of scores for each food/feed item in either data set.

Moreover, it illustrates that the chemical characteristics of both data sets are very similar, i.e. the distribution of input parameters resemble each other. The substance selection applied in this study (e.g. the exclusion of ionisable and organometallic substances; see section 3.1) did not lead to a shift of Score C distribution, and therefore the approach of choosing the highest score in any of the food items as Score C (bioaccumulation) seems a robust approach for the screening procedure.

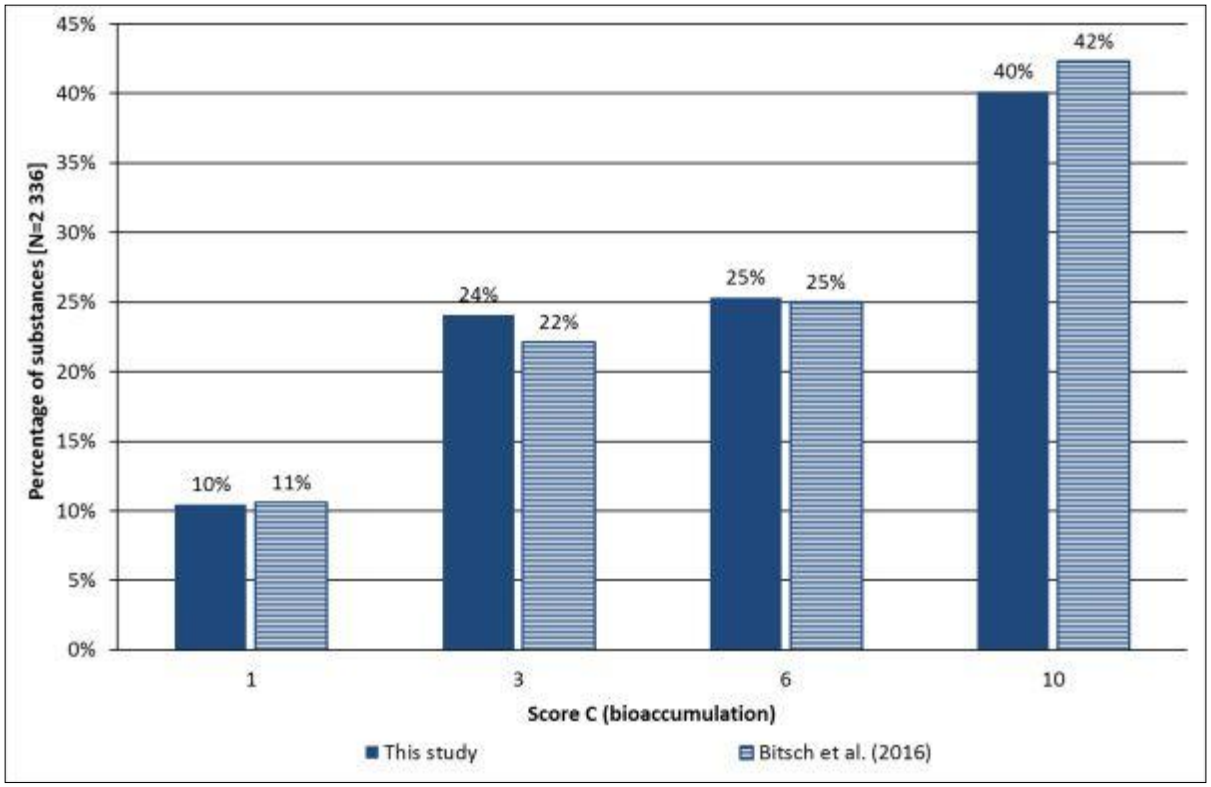


Figure 21: Comparison of the distribution of Score C (bioaccumulation) for 2 336 substances registered under REACH and the pilot study (Bitsch et al., 2016)

Figure 22 shows the distribution of the maximum Score C of 10 for the food categories 'Fish' (fish 1 and 2), 'Fruits and vegetables' (apple, grain, lettuce, carrots, potato), 'Meat and milk products' (beef cattle, dairy cattle, milk, dairy products) as well as across all food categories (see also Table 7). In total, 40 % of the 2 336 selected substances received a maximum Score C of 10 (Figure 21 or Figure 22 illustrated in 'all food categories') and 9.2 % (216/2 336) have this maximum score in only one of the three food categories (Figure 22). Food categories 'Fish' and 'Meat and milk products' have similar patterns: while 27 % (630/2 336 or 633/2 336, respectively) have a Score C of 10, only 0.60 (14/2 336) or 0.47 % (11/2 336), respectively, have a unique Score C of 10 in the respective category only. The food category 'Fruits and vegetables' has a slightly different pattern. The ratio of maximum Score C of 10 is higher as well as the ratio of a unique Score C of 10 in only this food category: 37 % (873/2 336) of the substances have a Score C of 10 and 8.1 % (191/2 336) have this maximum score in only 'Fruits and vegetables'. This food category therefore contributes most of the substances with a maximum Score C of 10 in one category only of the entire dataset (191/216 substances).

For food category 'Fruits and vegetables', Score C of 10 is generally based on (a) a score of 10 in above-ground crops (apple, grain and lettuce) or (b) a score of 10 in below-ground crops (potato and carrot; details not shown). This reflects the modelling approaches in ACC-HUMANsteady and is also illustrated by the poor correlation between scores in above-ground and below-ground crops (see Appendix D).

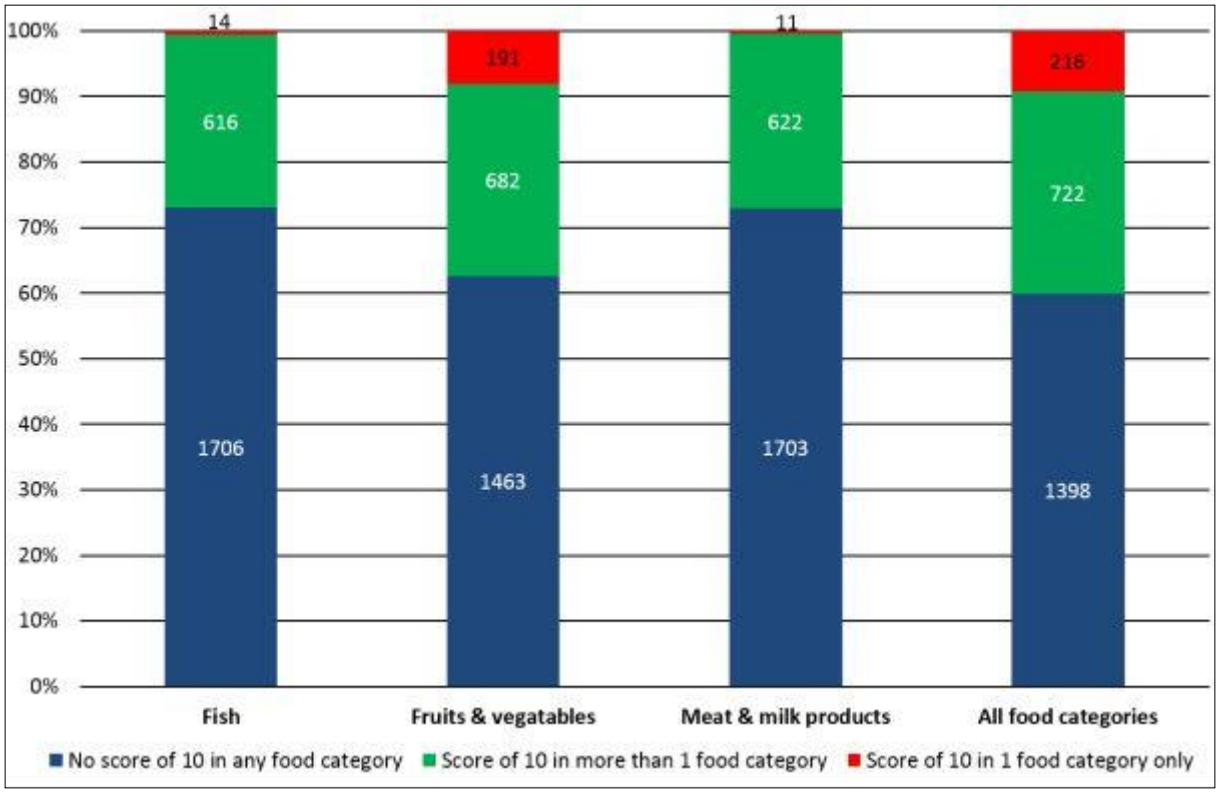


Figure 22: Patterns of Score C of 10 in the different food categories: no score of 10, score of 10 and score of 10 in only one food category (N=2 336)

In summary, the distribution of Scores C is as follows: 244 substances receive a score of 1 (10 %), 563 substances a score of 3 (24 %), 591 substances a score of 6 (25 %) and 938 substances a score of 10 (40 %). The total number of substances predicted to be bioaccumulating in food (Score C > 5) is 1 529 (65 %). These scores are further processed in the screening procedure. Of the 2 336 substances, 9.2 % of the substances have a unique Score C of 10 in only one food category, primarily in 'Fruits and vegetables'. Despite the conservative approach of choosing the highest score assigned in any of the food items, the applied screening procedure results in a good distribution of Score C with 34 % of substances receiving a score of 1 or 3.

Uncertainties of the approach chosen relate to the uncertainties of ACC-HUMANsteady (and models implemented in the software). A major issue in this context is the applicability domain of these models. To address this issue, substance classes outside the applicability domain of models used for assessing bioaccumulation in food (e.g. inorganics and ionisable compounds) were excluded from the assessment (see section 2.1.4). Nonetheless, the models implemented in ACC-HUMANsteady are generally derived on the basis of data for a very limited number of substances or substance groups. The applicability to all 2 336 substances selected therefore remains a general source of uncertainty in the assessment. ACC-HUMAN software – like other similar models – is validated only to a very limited extent, primarily because measured data against which such a validation could be performed are available for only a few well-know and extensively studied substances, such as PCBs. For example, a good agreement of data predicted by ACC-HUMAN (non-steady-state version) with measured data was observed for PCBs (Czub and McLachlan, 2004).

The pilot study (Bitsch et al., 2016) gave some useful insights that should be considered in the context of the more general uncertainties described above:

- Three of the four positive controls (DDT, PCBs and BDE-99) were predicted to bioaccumulate in food, which is in agreement with available data.
- Another polybrominated diphenyl ether (BDE-209) was predicted to accumulate in food by ACC-HUMANsteady and this substance was evaluated as leading to one of the highest dietary exposures among the BDEs evaluated (EFSA, 2011c).

- Tris(1-chloro-2-propyl) phosphate received the maximum score for bioaccumulation in fruit and vegetables (but not in fish or meat). Experimental data show that this substances indeed appears to bioaccumulate in these kind of foods (Trapp and Eggen, 2013; Hyland et al., 2015a; Hyland et al., 2015b).
- The fourth positive control (PFOS) was predicted not to bioaccumulate in food. This substance represents a case in which bioaccumulation in food is most likely governed by mechanisms other than lipophilicity. While PFOS accumulates in food, it does not accumulate in fatty tissues (EFSA, 2008). This observation suggests that ACC-HUMANsteady – like similar other models – is unable to predict bioaccumulation by such mechanisms.

In a more general sense, ACC-HUMANsteady – while predicting concentrations in many food items – does not address bioaccumulation in all food items. For example, bioaccumulation in other livestock products (e.g. pork and chicken meat) as well as in many different fruits and vegetables is not assessed. This is most likely the result of lacking models available for assessing these pathways. Taking bioaccumulation in chicken as an example, development of such models is complicated by the fact that chicken take in higher amounts of soil (relatively to their body weight) than all other livestock. As a consequence, the concentrations of PCDD/Fs and dl-PCBs are consistently higher in free-range eggs than in eggs from animals kept indoors and in fact reflect contamination of the soil (CVUA Freiburg, 2006; Schwarz et al., 2014). This example illustrates that different models for bioaccumulation in chicken would probably be needed.

Little research has been done in relation to a comparison of bioaccumulation of organic substances in different food items (e.g. different livestock species or different vegetables). For example, the distributions of concentrations of six out of seven indicators PCBs were similar in beef, pork and chicken fat in a study in South Korea (Kim et al., 2004). In contrast, congener profiles of PCDD/Fs and dl-PCBs in the liver differed between cows and ewes in an Italian study (Benedetto et al., 2016), but these authors cautioned to overemphasise these differences due to lacking information e.g. on the location of the farms, the diet of the animals and agricultural practices that may affect contaminant levels. Overall, data are insufficient to draw any conclusions in a more general sense. As a consequence, it is impossible to state whether 'beef cattle' and 'dairy cattle' are representative for other livestock products or whether the fruits and vegetables covered in this assessment are representative for other crops.

However, it must be stressed that the main aim of the assessment in block C is differentiating substances with a potential for bioaccumulation in food with those with little potential for such a bioaccumulation in a screening assessment. It addresses accumulation in a comparatively large number of different food items, but is unable to address potential accumulation in an extensive number of food items. Overall, these uncertainties and limitations preclude a more detailed assessment in this screening procedure (apart from the comparison discussed in the next section). In fact, a broad categorisation with four scores based on quartiles of the distribution of concentrations was chosen instead of more sophisticated approaches (e.g. ten scores based on deciles of the distribution or continuous scores based on concentrations relative to the maximum concentration) since the latter would suggest a level of detail or accuracy that cannot be achieved in this assessment.

Comparison of results for bioaccumulation in food with screening criteria

The most recent version of the ECHA Guidance on PBT/vPvB assessment (ECHA, 2017a) defines new screening criteria for bioaccumulation in 'air-breathing organisms'. These screening criteria are intended to account for bioaccumulation in organisms other than aquatic organisms, but 'air-breathing organisms' are not clearly defined in the Guidance. Only in one sentence, the term 'air-breathing (terrestrial) organisms' is used, therefore excluding air-breathing aquatic organisms (air-breathing fish and all cetaceans). These screening criteria are defined as:

log Kow > 2 AND log Koa > 5

These criteria only apply to substances that are (a) efficiently absorbed from the diet, (b) are not subject to biotransformation within the organism and (c) show negligible active transport into or out of the organism.

These new criteria were used for a comparison with Score C results obtained for the entire dataset of this study.

Figure 23 shows the fraction of substances with a Score C of 1, 3, 6 or 10 that fulfils the screening criteria. For example, only 3 of the 244 substances with a Score C of 1 (1.2 %) fulfil the screening criteria. In contrast, 703 of the 938 substances with a Score C of 10 (75 %) fulfil these criteria. The fraction of substances with a Score C > 5 (i.e. Score C = 6 or 10) used in the assessment as indicating bioaccumulation potential is also shown (1 096/1 529, 72 %).

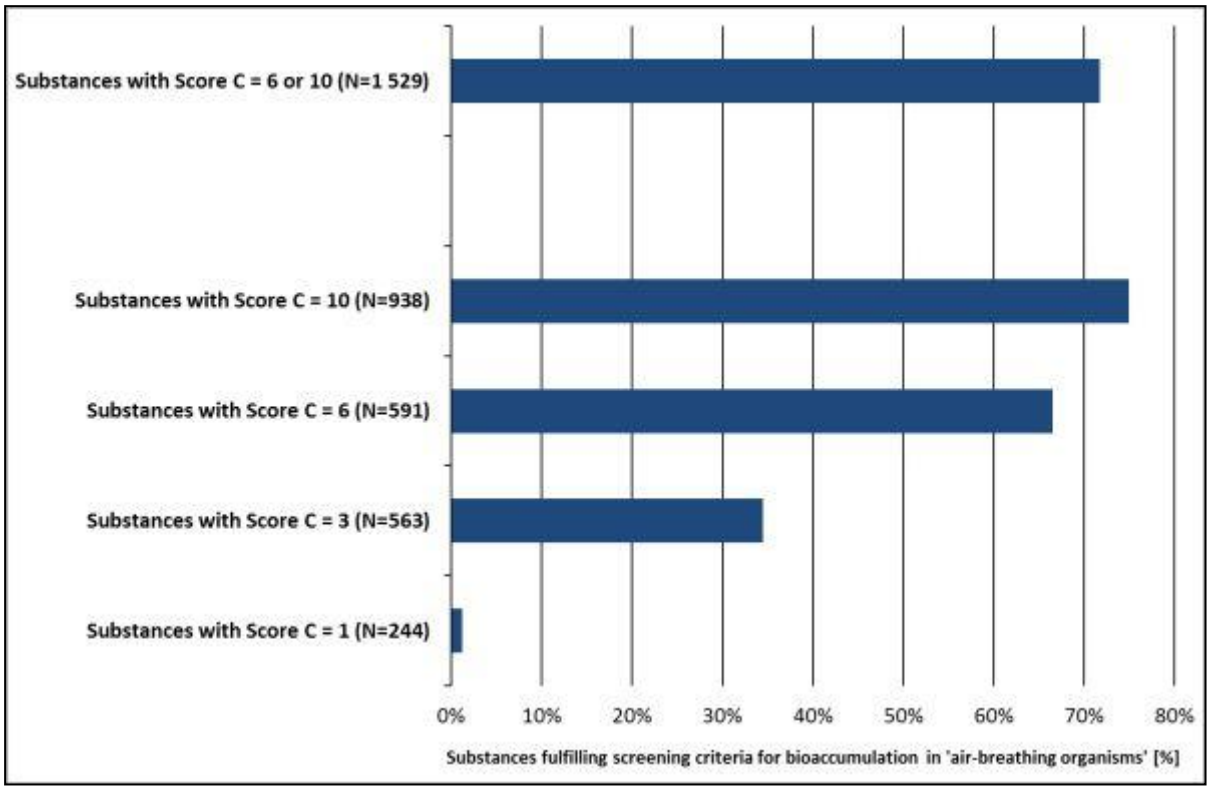


Figure 23: Comparison of the assessment of bioaccumulation in food (block C) with the screening criteria for 'air-breathing organisms' of the ECHA Guidance on PBT/vPvB assessment (ECHA, 2017a).

This analysis shows a good general agreement between the assessment of bioaccumulation in this study and the screening criteria for bioaccumulation in 'air-breathing organisms'. This finding is somewhat surprising given that the approaches differ substantially. While the ECHA Guidance only uses two cut-offs (log Kow, log Koa), the ACC-HUMANsteady model considers more properties (e.g. the metabolism half-life of a substance) and models accumulation in different food items.

An evaluation of substances not showing agreement between the screening criteria and Score C also provides valuable insight. This is performed for the 'extreme' ends of Score C, i.e. substances assigned a Score C of 1 and substances assigned a Score C of 10, for which no agreement is observed:

- 3 of the 244 substances that are assigned a Score C of 1 (and are therefore predicted not to accumulate in food in this study), fulfil the screening criteria for bioaccumulation in air-breathing (terrestrial) organisms.

  All 3 substances have a log Kow above the screening criterion of log Kow > 2 (3.32-3.74), but the log Koa is only marginally above the screening criterion of log Koa > 5 (5.01-5.08). The ECHA Guidance discusses cut-off values of 5.25 and 5.5 for log Koa, but then uses a value of 5 (most likely a rounded value, also ensuring conservatism for a screening approach). In fact, one of the main sources cited in the ECHA Guidance to establish this cut-off (Armitage and Gobas, 2007) states that chemicals with a log Koa value < 5.25 do not accumulate even if the log Kow is high. Based on this criterion of log Koa < 5.25, the 3 substances are correctly predicted not to accumulate in food by the scoring approach of this study based on ACC-HUMANsteady modelling.

- 235 of the 938 substances that are assigned a Score C of 10 (and are therefore predicted to accumulate in food in this study) do not fulfil the screening criteria.

  All of these substances have log Koa values > 5 (and therefore fulfil this screening criterion), but do not fulfil the log Kow criterion (range of log Kow: -7.42-1.99). In other words, none of these 235 substances fails both criteria. According to the ECHA Guidance substances with log Kow < 2 are expected not to accumulate due to rapid elimination by urinary excretion (ECHA, 2017a). This argument is relevant for air-breathing organisms and indicates that the screening criteria to not cover any potential accumulation in plants.

  Interestingly, all 235 substances are assigned a Score C of 10 based on accumulation in fruits & vegetables. This suggests that the approach applied in this study predicts a bioaccumulation potential that is not covered by the screening criteria defined in the ECHA Guidance. In this sense, ACC-HUMANsteady modelling and subsequent scoring appears to provide more data for an assessment of bioaccumulation as well as additional insight into potential pathways.

  However, many of these 235 substances are not only assigned a Score C of 10 for fruits & vegetables, but also for meat & milk products (N=96) or meat & milk products and fish (N=105; i.e. Score C =10 in all three groups). Overall, 34 substances are assigned a Score C of 10 in fruits & vegetables alone (i.e. lower scores in the other two groups). Since all 235 substances have relatively short predicted biotransformation half-lives in fish (< 0.55 d; biotransformation considered for all food groups; see section 2.2.4), a lack of biotransformation is unlikely to be the reason for the predicted accumulation. The reason why 201 substances are predicted to accumulate in meat & milk (and 105 substances also in fish) cannot be discerned by a simple analysis of the input values. These differences are likely to result from more complex modelling approaches implemented in the ACC-HUMANsteady model.

Analysing the data starting from those fulfilling the screening criteria of the ECHA Guidance, a total of 1 293 of the 2 336 substances included in this study (55 %) fulfil these criteria[76]. The majority of these substances (1 096/1 293, 85 %[77]) are predicted to accumulate in the approach used in this study (Score C > 5), while 15 % are predicted not to accumulate (almost exclusively assigned a Score C of 3; Score C = 1 assigned only to 3 substances as shown above). Figure 24 shows details of these evaluations.

As shown above, the cut-off for log Koa in the ECHA Guidance appears to have been rounded to yield a conservative cut-off, which is lower than log Koa values reported in the studies serving as a basis. Additional analyses were therefore performed using different cut-offs for log Koa, while retaining the other screening criterion (log Kow > 2). Figure 24 illustrates the effects of using these different cut-offs for log Koa. If the cut-off for log Koa is changed from > 5 to > 5.5, the fraction of substances predicted to accumulate in this study increases from 85 % to 90 % (58 % assigned a Score C of 10 and 32 % assigned a Score C of 6) with a corresponding decline in the fraction of substances predicted not to accumulate. At a criterion of log Koa > 7.5, almost all substances fulfilling the criteria are predicted to accumulate in this study.

[76] This assessment presents the data only in a different way. The number of 1 293 substances is also evident in Figure 21 Score C = 10: 938 substances x 74.9 % = 703 substances; Score C = 6: 591 substances x 66.5 % = 393 substances; Score C = 3: 563 substances x 34.5 % = 194 substances; Score C = 1: 244 substances x 1.2 % = 3 substances; Total: 1 293 substances

[77] The percentages in Figure 22 only add up to 84 % due to rounding.

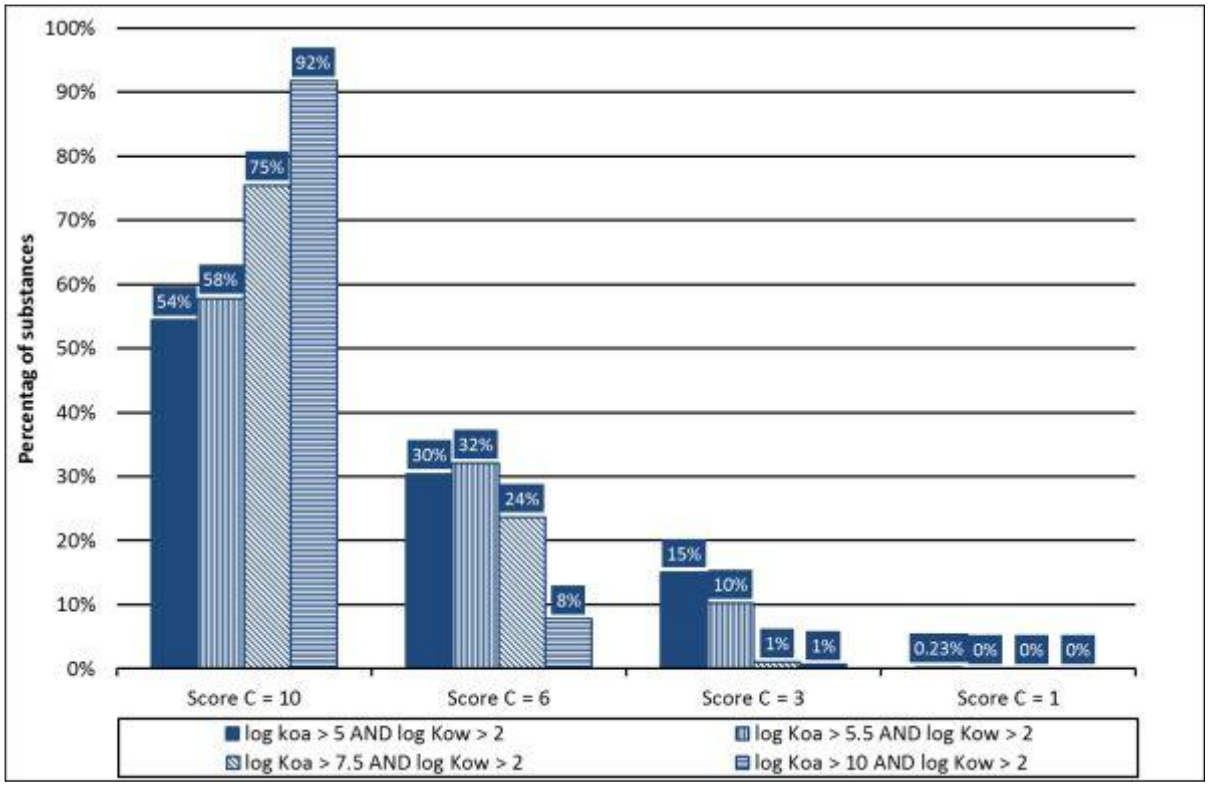


Figure 24: Comparison of the assessment of bioaccumulation in food (block C) with the screening criteria for 'air-breathing organisms' and changing cut-offs for log Koa.
Full bars represent the screening criteria in the ECHA Guidance (ECHA, 2017a)

Overall, these comparisons of results obtained in this study with the screening criteria defined in the new ECHA Guidance on PBT/vPvB assessment (ECHA, 2017a) show a good level of agreement. Differences observed may be due to the more complex modelling approach implemented in ACC-HUMANsteady when compared with simple cut-off values. This is also illustrated by the finding that the only 3 substances fulfilling the screening criteria, but assigned a Score C of 1 in this study have a log Koa just slightly above the cut-off. The more complex model is not dependent on strict cut-offs as implemented in the screening criteria. In addition, the cut-off values in the ECHA Guidance do not address bioaccumulation in plants, while this is evaluated in ACC-HUMANsteady with five different, plant-derived food items (apple, carrot, grain, lettuce and potato).

It must be stressed that the screening criteria of the ECHA Guidance are primarily based on modelling approaches established for only a few food webs and largely reflect knowledge on neutral hydrophobic chemicals. For example, the cut-off value for log Koa of 5.25 was developed for such chemicals in the soil-earthworm-shrew food web model (Armitage and Gobas, 2007). Knowledge – and models based thereupon – for very polar non-volatile compounds (log Kow < 2, log Koa > 5) appear to be much more limited. The accumulation in food predicted for such chemicals in this study may be the subject of further research.

3.2.5. Aggregation of results for blocks A-C

The scores from individual blocks will be aggregated in later stages of this study, when all evaluations (i.e. including the toxicity assessment) are complete. Nonetheless, an initial aggregation of the scores from blocks A (releases to the environment), B (biodegradation) and C (bioaccumulation in food/feed) is considered useful. Such an evaluation elucidates the distribution of aggregated data and also helps analysing the impact of missing data in block A.

For this purpose, scores from the three individual blocks were simply added up:

Score A-C = Total Score A + Score B + Score C

Total Score A is composed of the Tonnage Score and the ERC Score and is the only element that includes default values for missing data (see sections 2.2.1 and 3.2.1).

Since each block contributes a maximum score of 10, the maximum Score A-C is 30. Overall, there is a good differentiation in Scores A-C with a range of 3.30-30. In order to analyse the distribution of data, quartiles for Score A-C were calculated and resulted in the following values (Appendix D provides additional details on the distribution of Score A-C in the set of 2 336 substances):

Score A-C, 25th percentile: 13
Score A-C, 50th percentile: 18
Score A-C, 75th percentile: 23

The results for Score A-C were then analysed by differentiation of four different groups:

- Score A-C < 25th percentile (Score A-C < 13)
- Score A-C 25th percentile - < 50th percentile (Score A-C 13 - < 18)
- Score A-C 50th percentile - < 75th percentile (Score A-C 18 - < 23)
- Score A-C ≥ 75th percentile (Score A-C ≥ 23)

Figure 25 shows the distribution of the 2 336 substances in these four groups. There is some deviation from the purely statistical distribution (25 % or 584 substances in each group), especially in the group representing the lowest Scores A-C. Similar to the observations made for Score C (see section 3.2.4) these shifts result from the fact that many substances yield exactly the score of a given quartile and the number of substances in any group therefore depends on whether this quartile value is included. For example, if the group with the lowest Scores A-C is defined as '≤ 13' (instead of '< 13'), the number of substances in this group increases from 524 to 642, while the number in the next group decreases from 611 to 564. The figures for such an alternative approach are also included in Figure 25. The comparison demonstrates that the approach applied in this study ensures that substances with Scores A-C exactly matching the quartile value are assigned to the higher group.

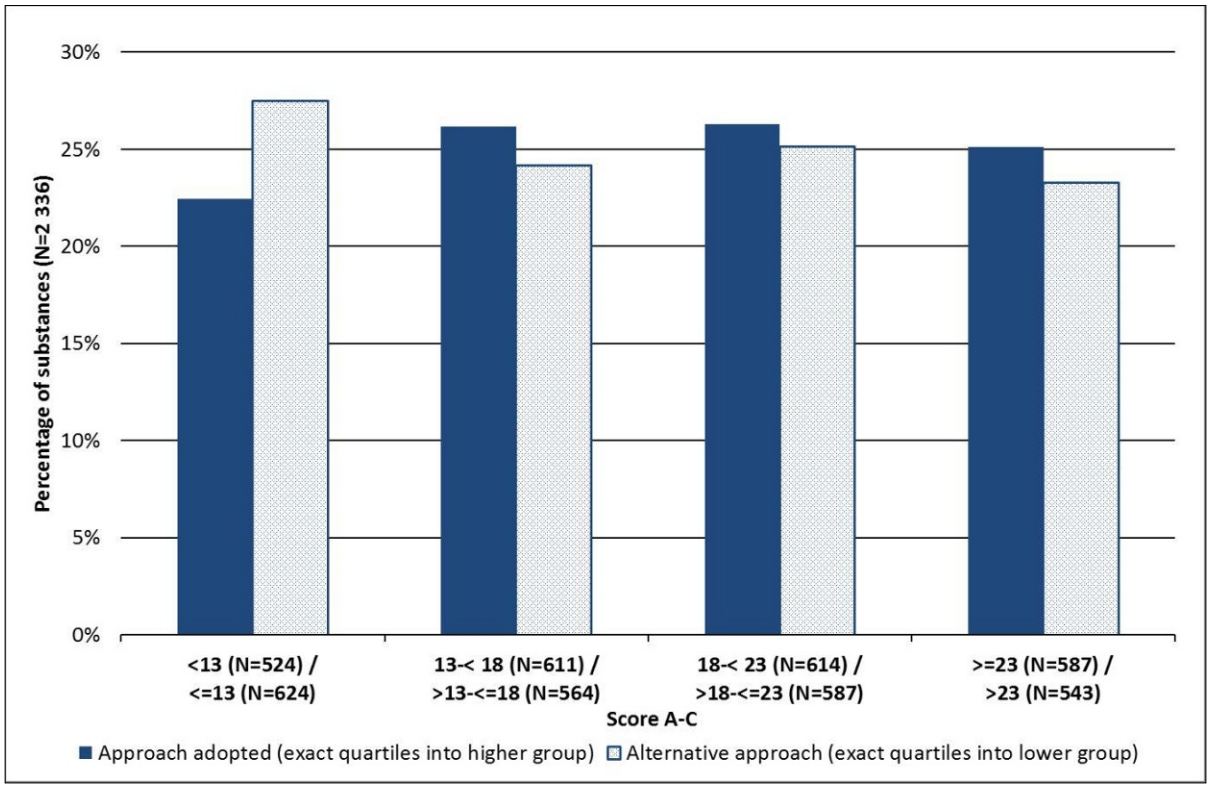


Figure 25: Distribution of the 2 336 selected substances among four groups for Score A-C.
Group definitions and number of substances on the x-axis are for the approach adopted / the alternative approach.

Additional analyses evaluate the impact of missing data for releases to the environment (block A). Figure 26 shows that tonnage and use information was available for 95 % of the substances in all groups except the one with the highest Scores A-C (Score A-C ≥ 23; tonnage and use information available for 88 % of the substances). In this latter group, 69 substances lack tonnage information (N=12; 2.0 %), use information (N=55; 9.4 %) or both (N=2; 0.34 %). This finding was expected since missing information is assigned default scores for block A (often worst case in character), making a high Score A-C more likely. However, the data also show that missing information on either the tonnage or the use does not necessarily lead to a high Score A-C. The 5 substances that lack both tonnage and use information (see section 3.2.1) are distributed among the group with Scores A-C ≥ 23 (N=2), the group with Scores A-C of 18 - < 23 (N=2) and the group with Scores A-C of 13 - < 18 (N=1). The fraction of these substances in each group is shown above the bars in Figure 26.

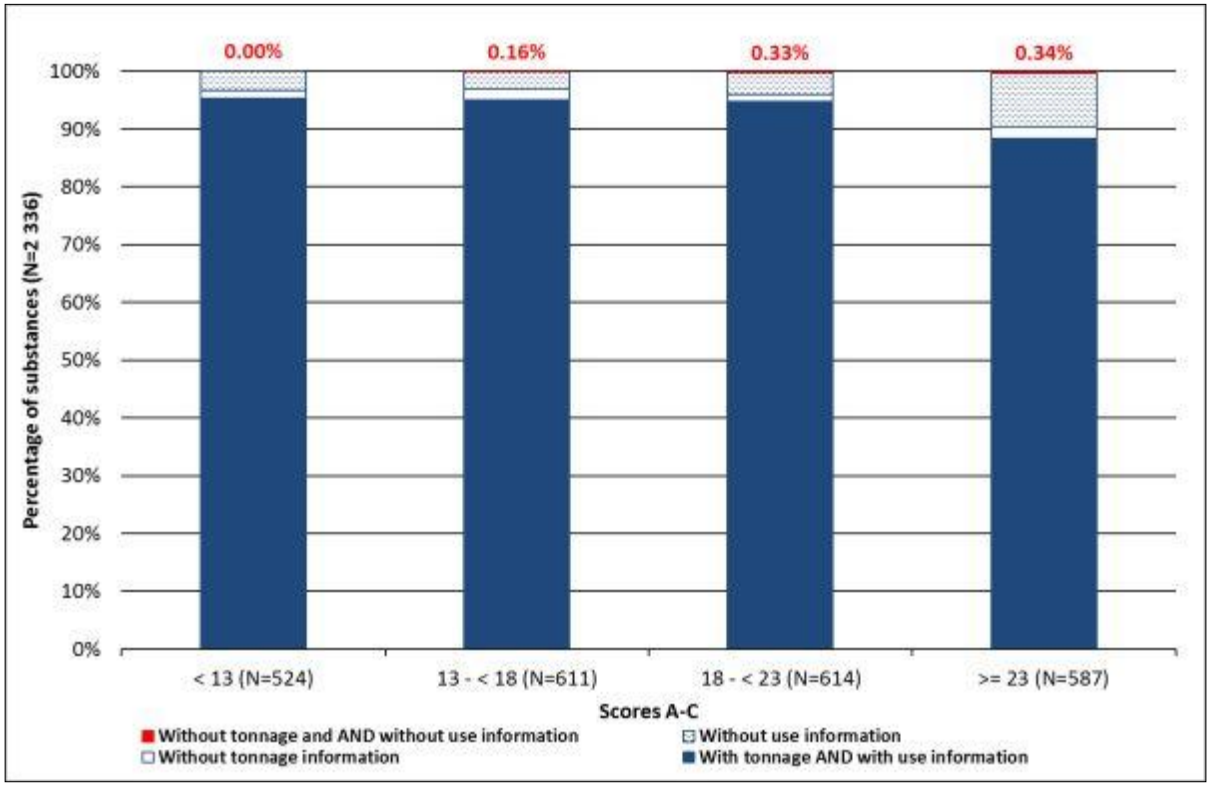


Figure 26: Distribution of the 2 336 selected substances among four groups for Score A-C and relative impact of missing data.
Numbers above the bars represent the fraction of substances in each group with neither tonnage nor use information.

The impact of missing information was analysed in more detail for the 587 substances with Scores A-C ≥ 23. For this purpose, the data were grouped by the maximum REACH registration tonnage used for the assessment. Figure 27 shows the results of this evaluation (the Tonnage Scores corresponding to the maximum tonnage are included as well).

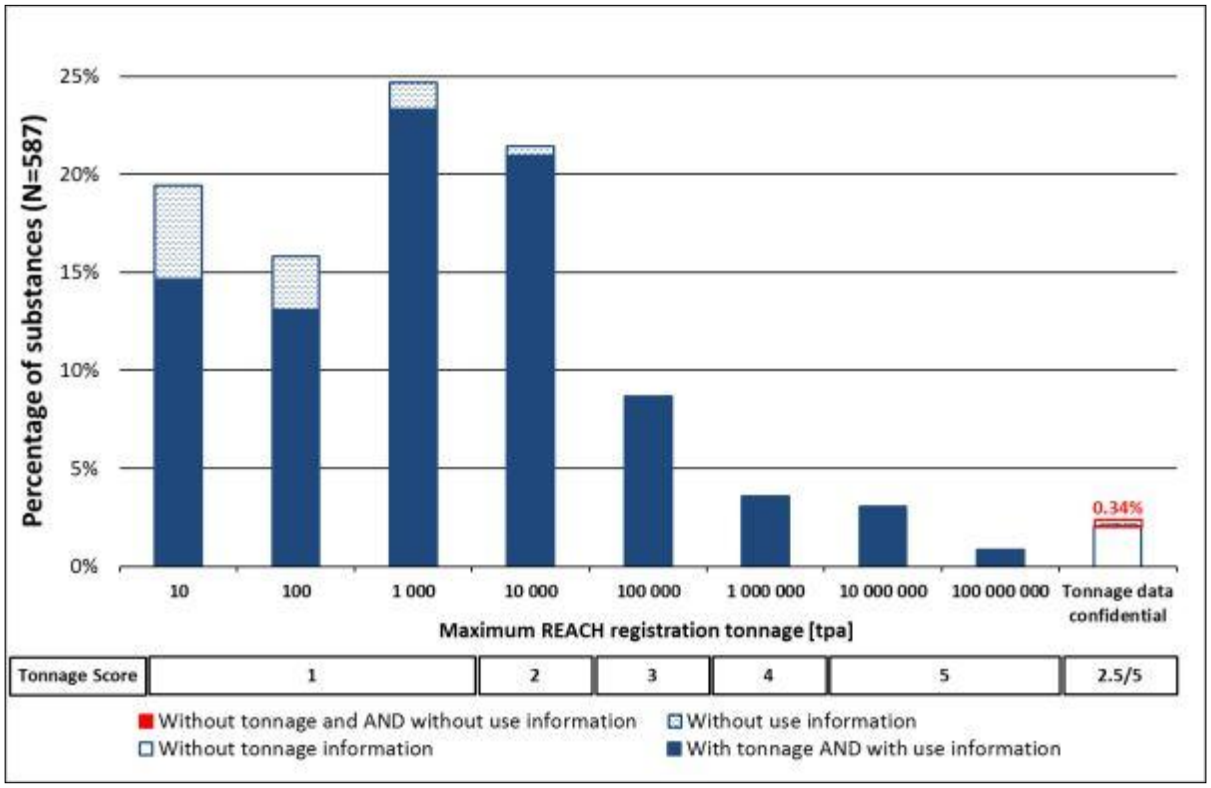


Figure 27: Distribution of the 587 substances with Scores A-C ≥ 23 by maximum tonnage.

The data indicate that even in this group with Scores A-C ≥ 23 many of the substances with lacking use information (ERC Score 5) are registered at low tonnages, mostly resulting in Tonnage Scores of 1 (with few assigned a Tonnage Score of 2). This finding is similar to the one obtained for the total set of 2 336 substances (see section 3.2.1). These substances are assigned a Total Score A of 6 (ERC Score 5 for missing data and Tonnage Score 1). For this group of chemicals with a Total Score A of 6, Score B and Score C together must at least be 17 to result in Score A-C ≥ 23. With the scoring employed for these blocks (see sections 2.2.2 and 2.2.4), such a value is only assigned, if Score C is 10 and Score B is 8 or 10, i.e. these substances are predicted to accumulate in food/feed and are predicted to be poorly or not biodegradable.

In fact, 257 substances of the 587 substances (44 %) with a Score A-C ≥ 23 have a Score A-C of 26 (11 % of the total set) and these clearly stand out in the relative frequency distribution (see Appendix E). The vast majority of these are assigned a Total Score A of 6 and maximum scores of 10 in blocks B and C each (N=245; 42 % of those with Scores A-C ≥ 23). However, only for 51 of these substances the ERC Score of 5 is based on missing data, while the remaining substances are assigned an ERC Score of 5, because they are registered for uses that lead to this maximum ERC Score. This is in agreement with the observation that use information is available for the majority of these substances (see Figure 27).

As mentioned above, tonnage information is missing for few substances in this group (N=14/587; 2.4 %; see also Figure 27). These substances are assigned a Tonnage Score of 2.5 or 5 (see section 2.2.1) and the Total Score A will depend on the ERC Score. Interestingly, all these substances are assigned ERC Scores of 2.5 or 5 and the Total Score A ranges between 7.5 and 10. The sum of Score B and Score C must therefore at least be 16 and 13, respectively, which is achieved by several combinations:

- Lowest possible Score B is 6 (Score C is 10): 2/14 substances;
- Lowest possible Score C is 3 (Score B is 10): 2/14 substances;
- Score B is 8 and Score C is 6 or 10: 2/14 substances;

- Score B is 10 and Score C is 6: 3/14 substances;
- Maximum scores of 10 in both blocks: 5/14 substances.

The aggregated Scores A-C were also analysed in relation to contributions of Score B and Score C. For this purpose, substances are assessed as poorly biodegradable at a Score B or 8 or 10 and assessed as bioaccumulative in food at a Score C of 6 or 10 for easier comparisons. Figure 28 illustrates that the fraction of poorly biodegradable and bioaccumulative substances increases with increasing Score A-C (as expected).

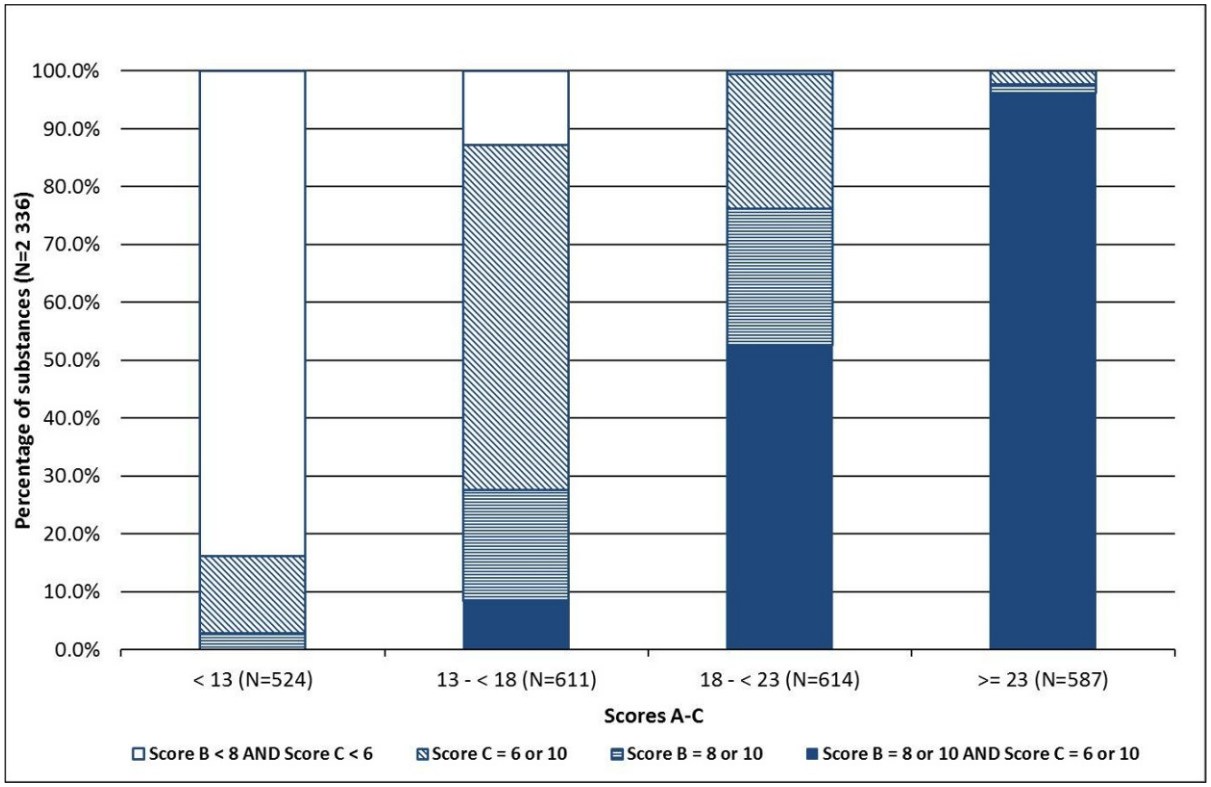


Figure 28: Distribution of the 2 336 selected substances among four groups for Score A-C by Score B and Score C.

Among the 587 substances with Scores A-C ≥ 23, 564 (95 %) are predicted to be poorly biodegradable and bioaccumulative. Note also that this group does not include any substance that is predicted to be both biodegradable (Score B < 8) and not bioaccumulative (Score C < 6). The fraction of such substances in the group with Scores A-C of 18 - < 23 is very small (N=4; 0.65 %).

Overall, the impact of missing data in block A is small. Substances with Scores A-C ≥ 23 include about 12 % of substances with lacking tonnage and/or use information. However, the vast majority of these substances are predicted to be poorly biodegradable and bioaccumulative in food. It must also be noted that Total Score A has an inherent uncertainty, even if both tonnage and use information is available. This uncertainty is related to the fact that the maximum tonnage is not necessarily applied in the use leading to the highest ERC Score (see sections 2.2.1 and 3.2.1). This would imply that the emphasis placed on a low Total Score A should be somewhat less than the one placed on low scores in the other blocks.

This interpretation as well as additional consequences of the evaluations will be further discussed in the interim evaluation of this study, when all evaluations have been performed. Since the evaluations presented above are based on simply adding up the scores from blocks A, B and C, the results may be different in the interim evaluation, when weighting scenarios will be applied.

3.3. Toxicity

For the assessment and scoring of toxicity, information from classification was considered in a first step. The results on classifications for four endpoints from the different classification types are reported in the following chapters. More detailed analysis on the classified substances with comparison for specific endpoints is provided in Appendix F.

3.3.1. Harmonised Classifications

Of the 2 336 selected substances, 281 substances have a harmonised classification and labelling for the specific endpoints (12 %). The table below gives an overview on the classification of these substances. The endpoint carcinogenicity has the highest number of classifications, only 108 substances are classified for mutagenicity. Classification for reprotoxicity and repeated dose is present for a similar number of substances (48 and 45).

Table 26: Classification for the four endpoints of the 281 substances with harmonised classifications

Classification endpoint	No. of substances
Carcinogenicity	212
Mutagenicity	108
Reprotoxicity	48
STOT RE	45

Overall, 100 substances have both classifications for carcinogenicity and mutagenicity, while only 6 have also a classification for reprotoxicity. Only one substance among the 2 336 selected substances is classified for all four endpoints. This substance is acrylamide (CAS No.: 79-06-1).

Butane (CAS No.: 106-97-8) is a specific case. While the pure substance has no harmonised classification for the four endpoints, the substance containing ≥ 0.1 % butadiene (CAS No.: 106-99-0; EC no. 203-450-8) has a harmonised classification as Carc. Cat. 1B and Muta. Cat. 1A. This is an example where impurities are triggering the classification as shown in Figure 29 to Figure 31. In these cases, the stricter classification was used for the assessment.

Figure 29: Screenshot of the two entries in the C&L Inventory for butane

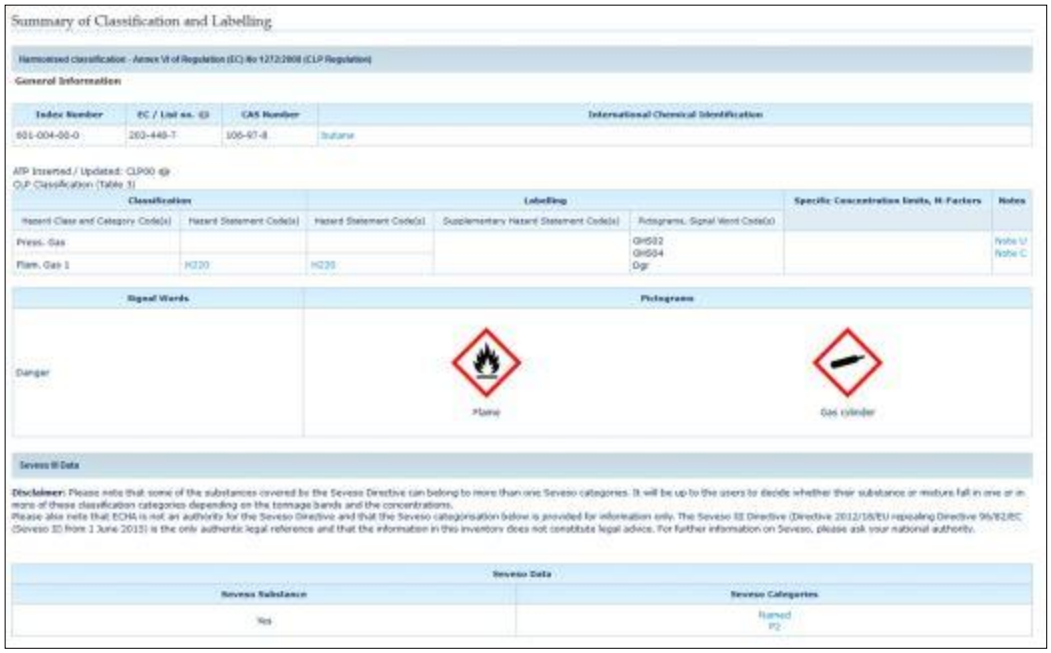


Figure 30: Screenshot with harmonised classification entry in the C&L Inventory for "pure" butane

Figure 31: Screenshot with harmonised classification entry in the C&L Inventory for butane containing ≥ 0.1 % butadiene (EC no. 203-450-8)

In order to examine the impact of classifications reflecting impurities rather than the substance as such, all harmonised classifications (i.e. not only those related to the 2 336 substances evaluated in this study) reported in Annex VI of the CLP Regulation were considered. A total of 4 249 entries were retrieved. Of these, 1 644 (39 %) contain a classification for any of the four endpoints. If the classification is affected by impurities, this is indicated in the name of the harmonised classification entry by a specific concentration of the impurity given in % or ppm (see Figure 29). Of the 1 644 entries with a classification for any of the four endpoints, only 57 (3.5 %) contain such a concentration criterion in the name. Further inspection of these 57 entries revealed that in most cases, the concentration does not relate to an impurity. For example, two entries exist for hydroxylamine that reflect differences in the concentration of the substance as such in an aqueous

solution and are not related to an impurity: (1) 'hydroxylamine ....% [> 55 % in aqueous solution]' and (2) 'hydroxylamine ....% [≤ 55 % in aqueous solution]'. Both entries are classified for carcinogenicity and repeated dose toxicity and the difference relates to the fact that higher hydroxylamine concentrations in aqueous solutions have to be classified as an unstable explosive.

Overall, there are only 7 entries (0.42 %) where an impurity is likely to be responsible for the harmonised classification for any of the four endpoints. Apart from the example of butane discussed above, this relates for example to methyl acrylamidomethoxyacetate and methyl acrylamidoglycolate (both to be classified as carcinogens if they contain ≥ 0.1 % acrylamide). Among the 281 substances with a harmonised classification for any of the four endpoints, an impurity is likely to be responsible for this classification in the case of the following 3 substances (1.1 %):

- Crystal violet (basic violet 3) (CAS No.: 548-62-9) containing ≥ 0.1 % of Michler's ketone: harmonised classification for carcinogenicity; no classification is available for the substance with < 0.1 % of Michler's ketone. The REACH registration dossier defines the substance as containing ≥ 0.1 % of Michler's ketone and no separate registration exists for the substances containing lower concentrations of Michler's ketone. As a consequence, the 'joint classification' for this substance (containing ≥ 0.1 % of Michler's ketone) does not indicate that this classification is due to an impurity.

  The carcinogenicity data reported in the registration dossier show carcinogenic effects in experimental animals for the substance as such without any reference to Michler's ketone (CAS No.: 90-94-8). In addition, profiling both the substance itself (using the SMILES notation also applied for estimating environmental fate properties) and Michler's ketone in the QSAR Toolbox revealed identical alerts in carcinogenicity-related profilers (e.g. 'nitrenium ion formation - tertiary aromatic amine' in OECD's DNA binding profiler or 'aromatic amine type compounds' in the oncologic primary classification profiler). These data suggest that the substance itself may possess carcinogenic properties and that the corresponding classification is relevant and not entirely due to the presence of an impurity.
- Isobutane (CAS No.: 75-28-5) containing ≥ 0.1 % butadiene: harmonised classification for carcinogenicity and mutagenicity; substance containing < 0.1 % butadiene not classified for any of the four endpoints. These data clearly indicate that the classification for carcinogenicity and mutagenicity is triggered by the impurity, while the substance itself is not of concern in the context of this study.
- Butane (CAS No.: 106-97-8) containing ≥ 0.1 % butadiene harmonised classification for carcinogenicity and mutagenicity; substance containing < 0.1 % butadiene not classified for any of the four endpoints. The same conclusion as for isobutane applies to butane.

These data indicate that the fraction of substances for which an impurity determines the harmonised classification is very small (2/281, 0.71 %).

Overall, the 281 substances having a harmonised classification for any of the four endpoints are assigned a Toxicity Score of 10.

3.3.2. IARC Classifications

Regarding classification by IARC, 74 of the 2 336 substances have classifications in any of the three IARC groups 1 (n = 10), 2A (n = 20) or 2B (n = 44), i.e. categories reflecting known or suspected human carcinogens (Table 27).

Table 27: IARC classification of the selected substances

IARC group	No. of substances
1	10
2A	20
2B	44

It should be noted that IARC also included specific uses of the substances in their classification system. For example, ethanol (CAS No.: 64-17-5) is classified as carcinogenic in IARC Group 1 when

searched by the CAS no., but the agent is specified as 'Ethanol in alcoholic beverages'. The harmonised classification under the CLP Regulation does not contain such a classification. Nonetheless, ethanol was assessed as a carcinogen in the present evaluation, i.e. the classification by IARC was maintained for scoring.

Methyl methanesulphonate (CAS 66-27-3) is classified in IARC Group 2A and is therefore assigned a Toxicity Score of 10. Note that this substance has no harmonised classification under the CLP Regulation or joint classification for this endpoint (although a joint submission exists and the substance is classified for other endpoints). However, four notifications include a classification as Carc. Cat. 1A or Carc. Cat. 1B (Figure 32).


Notified classification and labelling

General Information

EC / List no.	Name	CAS Number
200-625-9	Methyl methanesulphonate	66-27-3

Notified classification and labelling according to CLP criteria

Classification			Labelling							
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)	Specific Concentration limits, M-Factors	Notes	Classification affected by Impurities / Additives	Additional Notified Information	Number of Notifiers	Joint Entries	
Acute Tox. 3	H331	H331		GHS07 GHS06 Dgr				State/Form IUPAC Name	1	✔	View details
Skin Irrit. 2	H315	H315									
Eye Irrit. 2	H319	H319									
STOT SE 3	H335 (inhalation)	H335									
Acute Tox. 3	H301	H301		GHS08 GHS06 Dgr				IUPAC Name	23		View details
Skin Irrit. 2	H315	H315									
Eye Irrit. 2	H319	H319									
STOT SE 3	H335	H335									
Carc. 1B	H350	H350									
Acute Tox. 3	H301	H301		GHS06 Dgr					3		View details
Acute Tox. 3	H301	H301		GHS08 GHS06 Dgr				State/Form IUPAC Name	2		View details
Skin Irrit. 2	H315	H315									
Eye Irrit. 2	H319	H319									
STOT SE 3	H335 (respiratory tr...) (inhalation)	H335									
Carc. 1B	H350	H350									
Acute Tox. 3	H301	H301		GHS08 GHS06 Dgr				State/Form IUPAC Name	1		View details
Muta. 1B	H340										
Carc. 1B	H350	H350									
Repr. 2	H361	H361									
Acute Tox. 4	H302	H302		GHS08 GHS07 Dgr					1		View details
Skin Irrit. 2	H315	H315									
Eye Irrit. 2	H319	H319									
STOT SE 3	H335 (Respiratory syst...)	H335									
Muta. 2	H341	H341									
Carc. 1A	H350	H350									

Figure 32: Screenshot with classification entry in the C&L Inventory for methyl methanesulphonate (CAS 66-27-3).

In contrast to this example, most of the substances with IARC classifications have also a harmonised classification and are included in the 281 substances mentioned above. Therefore, only 24 additional substances are retrieved from IARC classifications and these are assigned a Toxicity Score of 10 on the basis of the IACR classification.

3.3.3. Joint classifications

In total, 453 substances of the 2 336 substances have a joint classification for the four endpoints evaluated. Table 28 gives an overview on the classification of these substances. The endpoints carcinogenicity and STOT RE have the highest number of classifications, only 141 substances are classified for mutagenicity. Classification for reprotoxicity is present for 236 substances.

Table 28: Classification for the four endpoints of the 453 substances with joint classification

Classification endpoint	No. of substances
Carcinogenicity	250
Mutagenicity	141
Reprotoxicity	237
STOT RE	250

Overall, 119 substances have both classifications for carcinogenicity and mutagenicity, while 91 have also a classification for reprotoxicity. Forty-one substances are classified for all four endpoints.

As some of these are already considered as classified based on harmonised or IARC classifications, 187 additional substances are assigned a Toxicity Score of 10 based on joint classifications only (i.e. they do not have a harmonised classification and have not been classified by IARC for carcinogenicity).

Similar to harmonised classifications, joint classifications may also be impacted by impurities. This issue was analysed in more detail by evaluating the entries in the C&L Inventory. Of the 187 substances assigned a Toxicity Score of 10 on the basis of joint classifications, 158 substances (84 %) have no indication that this classification may be affected by an impurity[78]. Of the remaining 29 substances, 17 substances (9.1 %) have a clear indication that the classification is affected by an impurity. However, even in these cases the impurity may only affect the classification for one endpoint (e.g. carcinogenicity), but not another endpoint (e.g. repeated dose toxicity). Such cases cannot always be clearly differentiated in the C&L Inventory. The remaining 12 substances (6.4 %) could not be evaluated on the basis of the C&L Inventory, largely because the entry identified by the CAS number is no longer available[79]. As a consequence of these problems, all 29 substances were manually checked for classification information in the joint submission of the REACH registration dossier. This approach also allowed identifying more detailed information on the impact of impurities. The following cases can be differentiated on the basis of these evaluations:

- True positives (N=16): the toxic hazard is confirmed

  The toxic hazard (i.e. a classification for any of the four endpoints in the REACH registration dossier) is not related to an impurity. This also includes substances for which the classification is indicated to be affected by an impurity in the C&L Inventory. The following examples illustrate typical cases:

  – 2-(4-tert-butylbenzyl)propionaldehyde (CAS No.: 80-54-6) has a joint classification as Repr. Cat. 1B for a product called 'technical'. The REACH registration dossier states that this product is only handled as an intermediate under strictly controlled conditions and that the classification for reproductive toxicity is triggered by the impurity 3-(1,1-dimethylethyl)-.alpha.-methyl-Benzenepropanal (CAS No.: 62518-65-4). The dossier (i.e. the joint classification) also includes a classification as Repr. Cat. 2 for a product called 'extra' that is obviously the one that is put on the market. No reference to the impurity is made for this classification and the composition[80] of this substance (unlike the one for the 'technical' product) does not include the impurity mentioned.

  – Prop-2-yn-1-ol (CAS No.: 107-19-7) has a classification for carcinogenicity that is impacted by an impurity (formaldehyde, CAS No.: 50-00-0). However, this substance is also classified for repeated dose toxicity and this classification is not impacted by the impurity. Interestingly, this substance also has a harmonised classification, which, however, does not cover any of the four endpoints. This is another example, where the classification from a REACH registration dossier is stricter than the harmonised classification (see section 3.3.6).

  – As a last example in this group, 2,4,6-trimethylphenol (CAS No.: 527-60-6) is classified for repeated dose toxicity irrespective of the composition (e.g. also for a 'high purity grade' product). The classification impacted by an impurity relates only to other endpoints (e.g. skin sensitization).

[78] Technically, this was analysed by checking whether a flag was set in the column ‚Classification affected by Impurities / Additives' in the C&L Inventory.

[79] There are recurrent problems in the C&L Inventory database associated with CAS number searches.

[80] Although not required in the past, the classification of a substance is now often linked to a specific composition in the REACH registration dossiers.

- False positives (N=13[81]): the toxic hazard is not confirmed

  The toxic hazard (i.e. a classification for any of the four endpoints in the REACH registration dossier) is clearly related to an impurity. Again, some examples illustrate typical cases:

  – Diethyl ether (CAS No.: 60-29-7) is classified for carcinogenicity (Carc. Cat. 2) in a joint classification. However, the REACH registration dossier states that this classification only relates to a 'crude' product by a single member of the joint submission, which contains acetaldehyde (CAS No.: 75-07-0) as an impurity. Acetaldehyde has a harmonised classification as Carc. Cat. 2. Diethyl ether without this impurity is not classified for any of the four endpoints in the joint classification.

  – The acetaldehyde impurity is also responsible for the classification of acetaldehyde oxime (CAS No.: 107-29-9) in the joint classification. The REACH registration dossiers explicitly states that the 'classification as a carcinogen Cat. 2 is related to the acetaldehyde impurity'. The substance not containing acetaldehyde is not classified for any of the four endpoints.

  – As a last example, tert-pentyl hydroperoxide (CAS No.: 3425-61-4) is classified as a suspected mutagen (Muta. Cat. 2). Again, the REACH registration dossier states that this refers to products containing an impurity (≥ 1 % di-tert amyl peroxide). The product containing < 1 % di-tert amyl peroxide is not classified for any of the four endpoints.

These examples illustrate that false positives may result from the (semi-)automated evaluation of the C&L Inventory. However, the observation that the classification is impacted by an impurity is in itself not sufficient to disregard such a classification. Further inspection of the REACH registration dossiers is required to check, whether the classification due to an impurity relates to any of the four endpoints evaluated in this study.

Overall, 13/187 (7.0 %) of the joint classifications are considered false positives in the context of this study, while 174/187 (93 %) are considered true positives. The fraction of false positives is higher than for harmonised classifications (0.71 %; see section 3.3.1). This finding is not surprising since joint classifications may define different compositions with different classifications, e.g. substances with different impurity profiles manufactured by different members of the joint submission.

3.3.4. Individual classification

Individual classifications could only be identified indirectly by selecting those substances that are included in the ECHA list of substances classified for the four endpoints, but not classified for the four endpoints in a joint classification (or when no joint classification is available; see section 2.3.4 for details). Some substances may have both joint and individual classifications for the four endpoints, but these are not identified separately. Overall, individual classifications for the four endpoints are considered only for substances that do not have harmonised, IARC or joint classifications for the four endpoints. The evaluation resulted in 22 additional substances that are classified for the four endpoints in individual classifications. No general overview of classified endpoints is provided for individual classifications due to the low number of substances.

When some of these substances were checked manually, it turned out that a few substances actually do have a joint classification, but this is not flagged in the C&L Inventory. An example is 1-chloro-2-nitrobenzene (CAS No.: 88-73-3), which is classified for carcinogenicity, reprotoxicity and repeated dose toxicity in the joint REACH registration. It is unclear, why the corresponding entry in the C&L Inventory is not flagged accordingly. Nonetheless, this substance is identified correctly using hierarchical evaluation approach.

These 22 substances having an individual classification for any of the four endpoints are assigned a Toxicity Score of 10.

For two of these 22 substances (9.1 %), the classification is impacted by an impurity and the substance not containing this impurity is not classified for any of the four endpoints.

[81] This includes one substance that is no longer classified for any of the four endpoints. It is likely that such a classification in the past was removed from the registration dossier and this may have involved the classification for a specific composition due to an impurity.

3.3.5. Other classifications

Overall, 212 substances have other classifications for the four endpoints evaluated, but are not classified for the four endpoints in harmonised, IARC, joint or individual classifications. Table 29 gives an overview on the classification of these substances. Compared to joint classifications the distribution for other classifications is different. The endpoints carcinogenicity, mutagenicity and reprotoxicity are classified with nearly equal numbers (57-70), while a higher number of substances has a classification for repeated dose toxicity (STOT RE: 104).

Table 29: Classification for the four endpoints of the 212 substances with other classification

Classification endpoint	No. of substances
Carcinogenicity	57
Mutagenicity	67
Reprotoxicity	70
STOT RE	104

Thirty-one substances have both classifications for carcinogenicity and mutagenicity, while 9 have also a classification for reprotoxicity. Five substances are classified for all four endpoints (Table 30) and these are discussed below in some more detail to assess the quality of these classifications.

Table 30: Identity of the five substances that have other classifications for all four endpoints

Substance	CAS no.
Propane	74-98-6
Chlorobenzene	108-90-7
2,6-di-tert-butyl-p-cresol	128-37-0
Heptane	142-82-5
1-butoxypropan-2-ol	5131-66-8

Propane has a harmonised classification and a joint classification, both of which cover none of the four endpoints evaluated. The classification as Muta. Cat. 1B and Carc. Cat. 1A is affected by impurities and supported by 1 notification from 1 notifier. Another notification from 1 notifier classified the substance as Repr. Cat. 2 and STOT RE 2. Since no supporting data are available in the C&L Inventory for these entries, the rationale of these other classifications cannot be evaluated.

For chlorobenzene, heptane and 1-butoxypropan-2-ol[82], the classification for all four endpoints comes from a single notification by a few notifiers (between 1 and 7). These substances have harmonised and joint classifications, but none of these covers any of the four endpoints. In addition, the classifications by the highest number of notifiers (>350 for each substance) do not cover these endpoints.

The classification for the four endpoints for 2,6-di-tert-butyl-p-cresol comes from different numbers of notifications by different numbers of notifiers. There are three notifications each for carcinogenicity and reprotoxicity, 4 for mutagenicity and 20 for repeated dose toxicity. However, the joint classification does not cover any of the four endpoints. In addition, the six notifications with the highest number of notifiers (supported by several hundred notifiers each) do not include a classification for any of the four endpoints.

These examples illustrate that other classifications may identify additional substances as representing critical hazards for the four endpoints evaluated. However, the limited analyses presented on the six substances above indicate that such other classifications are often not matched by (a) harmonised classifications, (b) classifications from REACH registration dossiers and (c) other classifications by in other notifications or by the highest number of notifiers. Rather, these classifications appeared to often result from one notification by very few notifiers that are not matched by most other

[82] For this substance, the classification by the single notifier includes almost all endpoints for which a substance can be classified, which obviously makes no sense at all. For example, the substance is classified both as a flammable solid and as a flammable liquid.

classifications. In this context, it must be stressed that information in the C&L Inventory is not examined by ECHA in relation to consistency and reliability and represents the state as submitted by companies. The only exception is 2,6-di-tert-butyl-p-cresol, for which several notifications provide classifications for the four endpoints (also see discussion below).

The selection of all 212 substances with other classification would lead to a high risk of false positive substances given the limitations discussed above. However, to make best use of the substances a more in depth evaluation of the data was made in relation to number of notifications. As shown in Table 31 the majority of substances has only one notification for a single endpoint. For the other substances the pattern is diverse with regard to the number of notifications and the number of endpoints. Substances with more than 2 notifications per endpoint will be assigned an initial Toxicity Score of 10, while the remaining substances are assigned an initial Toxicity Score of 1 (see section 2.3.5 for the rationale).

Table 31: Overview of number of notifications for the 212 substances with other classification

No. of total notifications	Distribution	N	%	Initial Toxicity Score = 10
1	One notification for a single endpoint	119	56 %	
2	Two notifications for a single endpoint	12	6 %	
2	One notification each for two different endpoints	30	14 %	
3	**Three notifications for a single endpoint**	**6**	**3 %**	**yes**
3	Two notifications for one endpoints and 1 notification for another endpoint	4	2 %	
3	Three notifications for three different endpoints	7	3 %	
4	**Four notifications for a single endpoint**	**3**	**1 %**	**yes**
4	**Three notifications for one endpoint and one notification for another endpoint**	**4**	**2 %**	**yes**
4	Two notifications for one endpoint and two notifications for another endpoint	4	2 %	
4	One notification each for four different endpoint	4	2 %	
4	Two notifications for one endpoint and one notification each for two other endpoints	3	1 %	
>4	**More than 4 notifications with at least 3 per one endpoint**	**16**	**8 %**	**yes**
Total		212		
Total with initial Toxicity Score of 10		**29**		

In total, 29 of the 212 substances (almost 14 %) have a classification in more than two notifications for any of the four endpoints.

Table 32 shows the evaluation by the number of notifications for the 212 substances with regard to the four specific endpoints. For the endpoint carcinogenicity, 45 of 57 substances are classified by one notification only and seven substances by two notifications. Only five substances are classified by three notifications. A similar pattern is observed for mutagenicity, although the number of notifications is higher (4 and 9). For reprotoxicity the number of substances having classification by more than two notifications is 10 and covers a range from 3 to 9 notifications. Most substances have classification for repeated dose (STOT RE), with 75 of 104 with 1 notifications and also show a higher proportion of substances with more than two notifications (N=18). Also, the range of the number of notifications is larger (3-33).

Table 32: Endpoint specific number of notifications for the 212 substances with other classifications

Endpoint	Total	By 1 notification	By 2 notifications	By >2 notifications (range)
Cancer	57	45	7	5 (3)
Muta	67	56	9	2 (4 and 9)
Repro	70	54	6	10 (3-9)
STOT RE	104	75	11	18 (3-33)

With respect to the 29 substances classified in more than two notifications, most classifications relate to repeated dose toxicity (STOT RE), either alone (N=8) or in combination with one of the other three endpoints (N=10; 18 substances in total; 62 %). Five of the 29 substances (17 %) are classified for carcinogenicity in more than two notifications, either alone (N=1) or in combination with one of the other three endpoints (N=4).

Example for 'other classification' assigned a Toxicity Score of 10 and reasons for differences with 'joint classification'

1,2,3,5,6,7-hexahydro-1,1,2,3,3-pentamethyl-4H-inden-4-one (CAS No.: 33704-61-9) has 16 notifications in the C&L Inventory, of which one is the joint classification that does not cover the four endpoints (supported by 822 notifiers). Eight of the remaining 15 notifications classify for STOT RE 2, while seven do not. The two notifications with the next highest numbers of notifiers (29 and 28 notifiers) classify the substance as STOT RE 2 and one of these notifications specifies kidney as target organ. The REACH registration dossier for the substance does not include a classification for STOT RE (which is in agreement with the (semi-)automated procedure applied here). The registration dossier includes one endpoint study record for repeated dose toxicity (study according to OECD 408, rat, 90 day oral exposure). A NOAEL of 10 mg/kg is reported based on changes in urine pH and kidney weight. No histopathological changes in the kidney were observed. Without having a more detailed look to the study report, it is not clear if this endpoint fulfils the criteria for classification as STOT RE, but the registrants concluded that this is not the case.

A substantial number of eight notifications, however, concluded that this substance has to be classified for STOT RE. Since the data basis of these notifications is unclear, it cannot be assessed, whether the classification is based on the same 90-day oral toxicity study in rats or on some other study. Therefore, the argumentation of the notifiers cannot be evaluated. As the guidance on classification for the endpoint STOT RE (ECHA, 2017b) includes aspects of expert judgement and subjective elements, different evaluations could be made by different experts judging effects in the sense of the classification criteria or not. In the example above, the differences in the assessment of the effects on kidney as adverse or severe leads to the classification as STOT RE by eight notifiers, but not by the registrants and seven other notifiers. This example illustrates that the approach of scoring other classifications supported by more than two notifications may also cover some of these differences in evaluating available toxicological data.

Overall, 29/212 substances with 'other classifications' are assigned an initial Toxicity Score of 10 and 183/212 substances are assigned an initial Toxicity Score of 1. This screening step based on the number of notifications limits the risk of selecting a large numbers of false positives while taking into account information on classification supported by several notifications that may have come to the same conclusion independently.

The impact of impurities on the classification was not checked for all of these 212 substances. Rather, this analysis was restricted to the substances identified in the next step, since it involves a manual evaluation of data in the C&L Inventory.

Checking toxicity data

As outlined in section 2.3.5, 'other classifications' are still considered less reliable than classifications from harmonised, IARC or REACH registration classifications. Therefore, the toxicity data for these substances were checked manually to identify whether the initial Toxicity Score can be confirmed. This evaluation was limited to those substances with high scores in blocks A-C as described in section 2.3.5, to check the Toxicity Score for those substances that may qualify as priority substances.

Among the 29 substances with an initial Toxicity Score of 10, 22 substances also met the criteria for high scores in blocks A-C. The remaining 7 substances were all predicted not to accumulate in food (Score C of 1 or 3) and 6 of these were predicted to be readily biodegradable. Toxicity data for these substances were not checked, since they are unlikely to qualify as priority substances.

In addition, 28/183 substances with an initial Toxicity Score of 1 also met the criteria for high scores in blocks A-C. Note that for this group, the criteria for 'high scores' in blocks A-C were stricter, since the Toxicity Score is considered even less reliable (see section 2.3.5). The selection and additional justification for this approach is described in Appendix J.

Overall, toxicity data were checked for 71 endpoints for a total of 50 substances:

- 22 substances (36 endpoints) assigned an initial Toxicity Score of 10
- 28 substances (35 endpoints) assigned an initial Toxicity Score of 1

For none of the 50 substances, the classification considered in the assignment of the initial Toxicity Score was impacted by impurities according to the information in the C&L Inventory. This finding is not unexpected, since a more detailed assessment of substance identity and the impact of impurities on classification may not be performed in the notifications that form the basis of the classifications for these 50 substances. Quite in contrast, classifications from REACH registration dossiers, which include a more in-depth assessment of substance compositions and impurities, are sometimes impacted by impurities (3.5 % of the cases; see section 3.3.6). This finding should not be interpreted as an absence of an impact of impurities, since the data basis of the classifications for these 50 substances cannot be assessed.

Table 33 shows the result of the evaluation of the initial Toxicity Scores for the 50 substances. The data retrieved and their evaluation for all 50 substances is included in Appendix K.

Table 33: Results of checking the Toxicity Score based on 'other classifications'.

Toxicity Score[a]	Per endpoint[b]		Per substance[b]	
10 -> 10	**11**	**(31 %)**	**9**	**(41 %)**
10 -> 1	25	(69 %)	13	(59 %)
Total	36		22	
1 -> 1	**32**	**(91 %)**	**25**	**(89 %)**
1 -> 10	3	(9 %)	3	(11 %)
Total	35		28	
Score confirmed	**43**	**(61 %)**	**34**	**(68 %)**

(a): Toxicity Score in the initial evaluation -> Toxicity Score after checking toxicity data
(b): Numbers of substances and percentages with the score confirmed are in bold.

The data demonstrate that:

- 41 % of the substances assigned an initial Toxicity Score of 10 because the 'other classification' was based on more than two notifications were also assigned a Toxicity Score of 10 after checking toxicity data; this figure is substantial, given the fact that these substances do not have a harmonised classification or a classification in REACH registration dossiers (although they are all registered) for any of the four endpoints considered;
- 89 % of the substances assigned an initial Toxicity Score of 1 because the 'other classification' was based on only one or two notifications were also assigned a Toxicity Score of 1 after checking toxicity data (see below for the three substances (11 %) that were assigned a Toxicity Score of 10);

- the initial Toxicity Score of either 1 or 10 was confirmed for 68 % of the substances. This represents a high percentage considering that the differentiation between the two scores uses an arbitrary cut-off value of two notifications, which has no scientific basis. Rather, the cut-off was chosen in a pragmatic approach of avoiding too many false positives and potentially overlooking substances that may possess a relevant hazard;
- the results are slightly different when evaluated per endpoint. This observation is due to the fact that a substance may be classified for more than one of the four endpoints. The initial score may then be confirmed for one endpoint, but not for other endpoints. Different patterns per substance were noted for substances classified for several endpoints (e.g. scores confirmed for all endpoints, not confirmed for all endpoints, confirmed for one, but not other endpoints etc.).

Overall, the evaluation shows that the applied approach is meaningful. However, due to the limitations discussed above, the assignment of a Toxicity Score of 10 in this evaluation only suggests a potential hazard of the substance for the corresponding endpoint. It should not be confused with a proposal for classification for this endpoint. Such a proposal would need to be based on an in-depth assessment and would also need to discuss the differences in interpretation of the data between registrants (who did not classify the substance for the endpoint in question) and any new classification proposed.

The issue of different interpretations is also illustrated in the following examples that represent typical cases noted during the evaluation:

- Toxicity Score of 10 confirmed (N=9, only some examples below):
  - 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone (CAS No.: 119313-12-1)

    Initial Toxicity Score of 10 for reprotoxicity confirmed, since there is a proposal for harmonised classification (Repr. Cat 2) for this substance; ECHA's Risk Assessment Committee (RAC) proposed a more stringent classification (Repr. Cat. 1B);
  - Paracetamol (CAS No.: 103-90-2)

    Initial Toxicity Score of 10 for mutagenicity confirmed, since there are many more studies than those reported in the REACH registration dossier; some of these indicate a genotoxic potential not only in vitro, but also in vivo according to the review by IARC.
  - 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (CAS No.: 2386-87-0)

    Initial Toxicity Score of 10 for mutagenicity confirmed, since the substance evaluation under REACH proposed classification as mutagen (Muta. Cat. 2) and REACH registration dossier also noted genotoxic potential (but data considered insufficient for classification).

    Initial Toxicity Score of 10 for repeated dose toxicity confirmed, since the substance evaluation under REACH proposed classification for repeated dose toxicity (STOT RE 2) and additional data suggest effects at comparatively low doses.
- Toxicity Score of 10 not confirmed (N=13, only some examples below):
  - Paracetamol (CAS No.: 103-90-2)

    Initial Toxicity Score of 10 for carcinogenicity not confirmed, since there is no study in REACH registration dossiers and an IARC classification in Group 3; the majority of studies (including the more recent, well conducted ones) do not indicate a carcinogenic hazard.

    Initial Toxicity Score of 10 for repeated dose toxicity not confirmed, since toxicity data suggest toxic effects only at comparatively high doses.
  - 2-nitro-p-phenylenediamine (CAS No.: 5307-14-2)

    Initial Toxicity Score of 10 for mutagenicity not confirmed, since – while there are some positive *in vitro* studies – *in vivo* studies were consistently negative according to both the REACH registration dossier and other sources.

Initial Toxicity Score of 10 for carcinogenicity not confirmed, since studies reported in the REACH registration dossier were considered negative and IARC classified this substance in Group 3.

- benzenamine, reaction products with aniline hydrochloride and nitrobenzene (CAS No.: 101357-15-7)

  Initial Toxicity Score of 10 for mutagenicity not confirmed, since all studies reported in the REACH registration dossier were considered negative and no information from other sources was available.

  Initial Toxicity Score of 10 for repeated dose toxicity not confirmed, since the study reported in the REACH registration dossier reported a relatively high NOAEL and no information from other sources was available.

- 2-(2-ethoxyethoxy)ethanol (CAS No.: 111-90-0)

  Initial Toxicity Score of 10 for reprotoxicity not confirmed, since effects on sperm motility in a 2-generation study in rats was not considered relevant for classification in the REACH registration dossier and since another source discussed these effects to be potentially related to impurities (although did not rule out effects of the substance itself completely). Overall, this was considered insufficient to support a Toxicity Score of 10.

  Initial Toxicity Score of 10 for repeated dose toxicity not confirmed, since studies in the REACH registration dossier as well as more extensive studies discussed in other sources identified high NOAEL values.

- Toxicity Score of 1 confirmed (N=25; only some examples below):

  - Paraffin waxes and Hydrocarbon waxes, chloro (CAS No.: 63449-39-8)

    Initial Toxicity Score of 1 for repeated dose toxicity confirmed, since studies in the REACH registration dossier and in other sources identified high NOAEL values. However, the Toxicity Score of 1 for carcinogenicity was not confirmed and a score of 10 assigned (see below).

  - Pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) (CAS No.: 6683-19-8)

    Initial Toxicity Score of 1 for carcinogenicity confirmed, since a carcinogenicity study reported in the REACH registration dossier was negative and other sources did not identify a carcinogenic hazard.

  - p-phenylenediamine (CAS No.: 106-50-3)

    Initial Toxicity Score of 1 for repeated dose toxicity confirmed, since studies in the REACH registration dossier and other studies identified low NOAEL values, but these appeared to be related to effects of low severity (body/organ weight changes). This example illustrates the importance of data interpretation. For example, small changes in body weight or organ weight in the absence of altered organ function and histopathological effects may not trigger classification, even if NOAEL values are low. However, it cannot be ruled out that other authors would interpret the same data as resulting in a classification for this endpoint, if full study reports could be assessed.

  - Bis(pentabromophenyl) ether (CAS No.: 1163-19-5)

    Substance identified as SVHC, but not based on human health endpoints

    Initial Toxicity Score of 1 for reprotoxicity confirmed, since no effects observed in 1-generation study; some effects in other sources, but relevance for classification unclear; no classification proposed in former EU Risk Assessment Report.

    Initial Toxicity Score of 1 for mutagenicity confirmed, since all studies reported in the REACH registration dossier were considered negative and no information from other sources was available; no classification proposed in former EU Risk Assessment Report.

Initial Toxicity Score of 1 for repeated dose toxicity confirmed, since studies in the REACH registration dossier as well as studies discussed in other sources identified high NOAEL values and did not note an indication of specific target organ toxicity. However, one source emphasised neurodevelopmental effects as the critical endpoint with low LOEL values (non-guideline study with single exposure). This is an example, where the adverse nature of these effects would need to be assessed in detail in order to decide on a possible classification for this endpoint.

- 3-hydroxy-N-(o-tolyl)-4-[(2,4,5-trichlorophenyl)azo]naphthalene-2-carboxamide (CAS No.: 6535-46-2)

  Initial Toxicity Score of 1 for mutagenicity confirmed, since all studies reported in the REACH registration dossier were considered negative and no information from other sources was available.

- benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene (CAS No.: 68411-46-1)

  Initial Toxicity Score of 1 for repeated dose toxicity confirmed, since studies in the REACH registration dossier identified comparatively low NOAEL values, but the effects were considered as not severe and registrants concluded that no classification is required; no other sources provided relevant information on this endpoint.

- 2-(2H-benzotriazol-2-yl)-p-cresol (CAS No.: 2440-22-4)

  Initial Toxicity Score of 1 for repeated dose toxicity confirmed, since studies in the REACH registration dossier identified moderate NOAEL values, but the effects were considered as not severe and registrants obviously concluded that no classification is required; other sources discussed no additional data.

- N-(5-chloro-2-methoxyphenyl)-3-hydroxy-4-[[2-methoxy-5-[(phenylamino)carbonyl]-phenyl]azo]naphthalene-2-carboxamide (CAS No.: 67990-05-0)

  Initial Toxicity Score of 1 for mutagenicity confirmed, since all studies reported in the REACH registration dossier were considered negative and no information from other sources was available.

- Toxicity Score of 1 not confirmed (N=3, all cases below):

  - 2-(2-butoxyethoxy)ethyl 6-propylpiperonyl ether (piperonyl butoxide; CAS No.: 51-03-6)

    Initial Toxicity Score of 1 for reprotoxicity confirmed, but additional data identified a proposed classification for carcinogenicity Cat. 2 (not previously identified) under the Biocidal Products Regulation (BPR)

  - Paraffin waxes and Hydrocarbon waxes, chloro (CAS No.: 63449-39-8)

    Initial Toxicity Score of 1 for carcinogenicity not confirmed, since the interpretation of the registrant (not expected to be carcinogenic) is not as evident in other sources; IARC classification in Group 2B (possibly carcinogenic) of chlorinated paraffins; however, this relates to different chain lengths and degree of chlorination; this is a typical example of interpreting the same data somewhat differently and where a final conclusion is impossible without in-depth substance-specific assessment, but a Toxicity Score of 10 was assigned based on existing data.

  - 9,10-anthracenedione, 1,4-bis(butylamino)- (CAS No.: 17354-14-2)

    Initial Toxicity Score of 1 for mutagenicity not confirmed due to positive results in one strain in the Ames test reported in the REACH registration dossier (in two independent studies). Such individual positive results may not be sufficient for classification, but may suggest a hazard nonetheless. In addition, other sources did not rule out a genotoxic mode of action and a Toxicity Score of 10 was assigned.

The evaluation of the toxicity data show that in some cases the confirmation or non-confirmation of the score is clear-cut. For example, if ECHA's Risk Assessment Committee (RAC) or EU Member States in the context of a substance evaluation under REACH came to the conclusion that classification for

one of the four endpoints is warranted, the Toxicity Score of 10 appears to be well justified. Similarly, there were some cases (in particular for those substances initially assigned a Toxicity Score of 1), where no additional data were available and the data in the REACH registration dossier were unequivocal and supported the initial score. In these cases, it remains unclear why one or two notifications classified the substance for the endpoint in question. However, the lack of any additional supporting toxicity data is consistent with the conclusion in the REACH registration document that the substance does not require classification for the endpoint in question.

However, in many other cases the situation is more equivocal. For example, positive and negative results may be available in genotoxicity and while a general rule was applied (negative *in vivo* studies outweighing positive *in vitro* studies), this may not be valid in all cases based on more in-depth analyses. In addition, data on repeated dose toxicity must be interpreted with respect to the severity of effects in order to judge on a possible classification. In these cases, the possible basis for the notifications indicating a classification could be identified. However, the registrants still came to a different conclusion. Sometimes, this conclusion is in agreement with the one in other sources, sometimes it is not. In all these cases, it is impossible to conclude whether a classification would be justified or not in the context of this evaluation. Again, such a judgement would require a substance-specific in-depth assessment with access to full study reports, which are not publicly available.

Overall, the toxicity score assigned in this evaluation must therefore still be considered less reliable than the toxicity scores assigned on the basis of harmonised classifications, classifications from REACH registrations or the ones based on IARC classifications. The only exceptions are the toxicity scores for 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone (CAS No.: 119313-12-1), 7-oxabicyclo[4.1.0]-hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (CAS No.: 2386-87-0) and 2-(2-butoxyethoxy)ethyl 6-propylpiperonyl ether (piperonyl butoxide; CAS No.: 51-03-6) that are based on proposed classifications within the EU legal framework (CLP, REACH or Biocidal Products Regulations).

3.3.6. Summary and discussion

Figure 33 shows that about 22 % (514 substances) are assigned a Toxicity Score of 10 based on classification from the first four types (harmonised, IARC, joint and individual classifications), while 12 additional substances (0.51 %) are assigned a Toxicity Score of 10 based on 'other classifications' when assessed as described in sections 2.3.5 and 3.3.5. With respect to the latter, it must be noted that the selection of these substances for checking additional toxicity data (and therefore the Toxicity Score assigned) already involves some incorporation of results from blocks A-C. This was necessary to limit the manual check of toxicity data to a manageable number of substances (see section 3.3.5 for details). The total number of substances assigned a Toxicity Score of 10 is 526 (23 % of the entire dataset).

In total, 200 of the 212 substances with 'other classifications' are assigned a Toxicity Score of 1 based procedure described above. While the evaluation of the substances with 'other classifications' has some limitations and had to be limited to those most likely to qualify as priority substances based on their scores in blocks A-C, it must be noted that 1 610 out of the 1 810 substances with a Toxicity Score of 1 (89 %) are not classified for any of the four endpoints in any source. The Toxicity Score of 1 is therefore well justified.

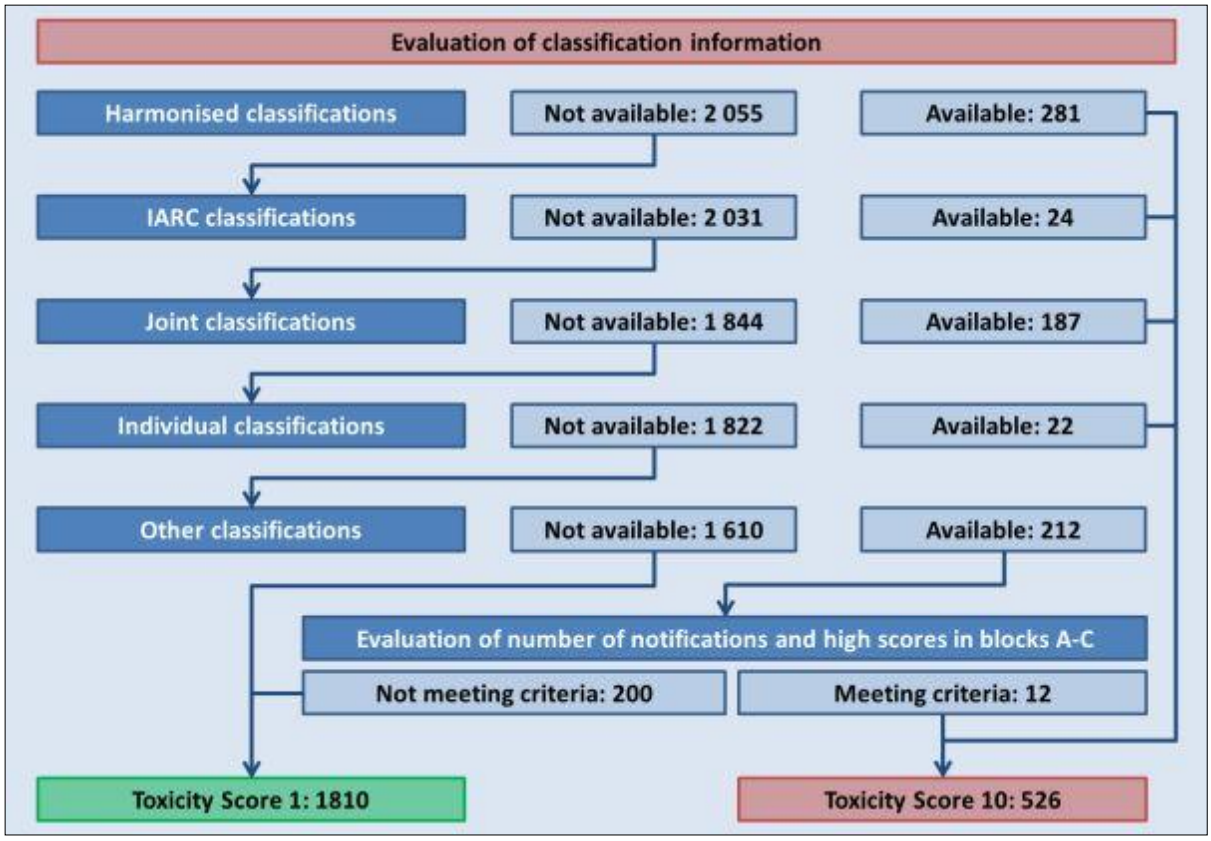


Figure 33: Availability of classification information for the 2 336 selected substances among the five types of classifications and without any classification for the four endpoints.

As shown in the figure, most of the 526 substances are assigned a Toxicity Score of 10 on the basis of harmonised and joint classifications (N=468, 89 %). The other types of classification only contribute to a minor extent.

Interestingly, of the 187 additional substances classified on the basis of joint classifications, 157 did not have a harmonised classification at all. However, 30 of these 187 substances had a harmonised classification, but this did not cover any of the four endpoints assessed. One example is ethylene glycol (CAS No.: 107-21-1), which is classified in the joint classification for acute and repeated dose toxicity, while the harmonised classification only covers acute toxicity. Another example is prop-2-yn-1-ol (CAS No.: 107-19-7), which is classified for repeated dose toxicity in the joint classification, but not in the harmonised classification (see section 3.3.3). These observations suggest that the data generated under REACH lead to the classification of substances for endpoints that have not been previously covered. This finding supports earlier observations on a different dataset (Oltmanns et al., 2014). These authors analysed 142 chemicals produced at very high tonnages in the EU and found that 29 substances with harmonised classifications for human health endpoints were classified in REACH registration dossiers for at least one additional endpoint (i.e. an endpoint not covered by the harmonised classification). Based on the underlying data, the Toxicity Score of 10 for the 514 substances with harmonised, IARC, joint and individual classifications is generally considered reliable. However, additional evaluations show that the classification is impacted by impurities in the case of 17/514 substances (3.3 %). The Toxicity Score of 10 for the 12 substances with 'other classifications' is considered less reliable in 9 cases and is considered reliable in 3 cases, because classification proposals based the EU legal framework (CLP, REACH or Biocidal Products Regulations) exist.

Overall, the Toxicity Score of 10 is considered less reliable for 26 substances (either due to the impact of impurities (N=17) or since the confirmation of the score based on 'other classifications' is still considered uncertain (N=9)). Not all of these substances, however, are prioritised for further evaluation (see section 3.4).

3.4. Selection of priority substances

As described in section 2.4, the prioritisation based on the scores assigned in each block has been tested according to three different approaches:

- Weighting scenarios (see section 3.4.1),
- Pivot table selections (see section 3.4.2) and
- A combination of weighting scenarios and Pivot table selections (see section 3.4.3).

These approaches and the results obtained are described in the following sections.

3.4.1. Weighting scenarios

Weighting scenarios 1 (WS1) and 2 (WS2) were used to calculate the respective total score for 2 336 substances. The 75th percentile of the total score was used as cut-off for prioritisation in each weighting scenario. All substances that have a total score above the 75th percentile were identified as priority substances. The maximum total score for WS1 and WS2 is 300 and 100, respectively. The calculated 75th percentile for WS1 and WS2 is 156 and 8.00, respectively (Table 34). While the 75th percentile value is about 50 % of the maximum in WS1, it is only 8 % of the maximum in WS2. This finding results from the fact that WS2 weights the toxicity score to a higher degree than WS1. Most of the 1 810 substances with a Toxicity Score of 1 are assigned a Total Score (WS2) of 8.00 or lower (N=1 727, 95 %), which determines the 75th percentile. In fact, the algorithm for WS2 leads to a maximum Total Score (WS2) of only 10 if the Toxicity Score is 1 (and maximum scores in all other blocks), a fact that is also responsible for the differences in the distribution of total scores between WS1 and WS2, see Figure 34).

The data in Table 34 also show that several substances have a score exactly matching the 75th percentile value in WS2 (N=218), while this is only the case for 7 substances in WS1. These substances are not prioritised since priority substances are defined as those substances with a total score exceeding the 75th percentile. Most of the 218 substances with a total score of 8.00 in WS2 have a Toxicity Score of 1 (N=209, 96 %).

Overall, Table 34 shows that the fraction of substances exceeding the 75th percentile is 25 % (583/2 336) for WS1 and 21 % (492/2 336) for WS2. These substances are prioritised in the weighting scenario approach. The figure deviates from the theoretical value (2 336 substances * 25 % = 584 substances) in WS2 due to the large number of substances having total scores identical to the 75th percentile.

The data in Table 34 also show the number of substances for the following combinations:

- WS1 AND WS2: Substances must be prioritised in both weighting scenarios (i.e. the overlap between the two weighting scenarios)
- WS1 OR WS2: Substances must be prioritised in any of the two weighting scenarios (or both)

Table 34: Calculated 75th percentiles of total scores for weighting scenarios 1 and 2 (WS1, WS2) and number of substances with total scores above the 75th percentiles in WS1, WS2, WS1 AND WS2 as well as WS1 OR WS2

Parameter	WS1	WS2	WS1 AND WS2	WS1 OR WS2
75th percentile	156	8.00	Not applicable	Not applicable
N>75th percentile	583	492	368	707
Percentage of 2 336 substances	25 %	21 %	16 %	30 %
N=75th percentile	7	218	Not applicable	Not applicable

Overall, 339 substances are prioritised only in one of the two weighting scenarios, resulting in a total of 707 substances that are prioritised in either of the two weighting scenarios (or both), while 368 substances are prioritised in both weighting scenarios (Table 34). The 339 substances prioritised in one weighting scenario but not the other can be characterised as follows:

- Substances prioritised in WS1 (but not in WS2) represent compounds that have scores > 5 in blocks A, B and C, but a Toxicity Score of 1 (N=215, i.e. the difference between the 583 substances prioritised in WS1 and the 368 prioritised in both weighting scenarios). These substances are predicted to be released into the environment, to persist in the environment due to little or no biodegradation and to accumulate in food. Almost all of these substances (N=207) have a maximum score of 10 in block B and a maximum score of 10 in block C. However, they are not prioritised in WS2, since they are not classified for any of the four relevant toxicity endpoints. In most of these 215 cases (N=198, 92 %), the Toxicity Score of 1 is considered reliable, since the substances are not classified in any source. Of the remaining 17 substances, all except one were classified in 'other classifications' in only one or two notifications (see section 3.3.5).
- Substances prioritised in WS2 (but not in WS1) represent compounds that have a Toxicity Score of 10, but scores < 5 in block C (N=54), block B (N=81) or block A (N=51). Since several substances have scores < 5 in more than one of these blocks (e.g. in block B and block A), the total number in this group is 124 (i.e. the difference between the 492 substances prioritised in WS2 and the 368 prioritised in both weighting scenarios). Some of these substances may be prioritised in the future, e.g. if the tonnage or use pattern changes and Score A increases or if they are detected in the environment. For example, 70 of these 124 substances are predicted to be accumulating in food (Score C = 6), but are not prioritised in WS2 because they are predicted to be released to the environment in small amounts (Score A < 5), are predicted to be readily biodegradable (Score B = 1) or both. Note that 60 of these 70 substances are prioritised in the Pivot table selection discussed below, which requires a score > 5 only in one of blocks A and B. All except one of these 124 substances are classified for at least one of the four endpoints in harmonised classifications, IARC classifications or classifications in REACH registration dossiers. The Toxicity Score of 10 for these substances is therefore considered reliable.

This discussion shows that the differences between the two weighting scenarios reflect the different weights assigned to different blocks. Due to these differences, 339 of substances is prioritised in one but not the other weighting scenario.

Depending on the weights attributed to different blocks and the distribution of values, each weighting scenario also prioritises substances that lack high scores in block C or the toxicity block. As discussed above, blocks A and B may be interrelated and a high score in one of these blocks may be sufficient to assume that this substance may be present in the environment. In contrast, a Toxicity Score of 10 and a Score C > 5 can be considered critical properties for the identification of potential emerging risks in the food chain.

Table 35 shows that WS1 prioritises 298 substances with a Toxicity Score of 1 (51 %) and WS2 prioritises 128 substances with a Score C (bioaccumulation) of 1 or 3 (26 %). However, the data also show that both weighting scenarios prioritise substances that lack a critical criteria, even if the corresponding block is assigned a high weight in the weighting scenario: WS1 prioritises 72 substances (12 %) that are predicted not to accumulate in food (Score C < 5) and WS2 prioritises 83 substances with a Toxicity Score of 1 (17 %). It must be noted, however, that none of the weighting scenarios prioritises substances that lack both properties.

Table 35: Prioritised substances in WS1, WS2 or WS1 AND WS2 and further differentiation of those lacking critical properties

Parameter	WS1	WS2	WS1 AND WS2
Number of substances prioritised	583	492	368
Substances with Toxicity Score = 1	298 (51 %)	83 (17 %)	83 (22 %)
Substances with Score C < 5	72 (12 %)	126 (26 %)	72 (20 %)
Fraction with Toxicity Score = 1 OR Score C < 5	63 %	43 %	42 %
Substances with Toxicity Score = 1 AND Score C < 5	0	0	0

Based on these data, the combination of both weighting scenarios may be an option. The data in ☐show that the fraction of substances with a Toxicity Score of 1 decreases significantly (22 % instead

of 51 % in WS 1 alone) and the fraction of substances with a low Score C is also reduced (20 % instead of 26 % in WS2). This selection of 368 substances, however, still contains substances that are not classified for any of the four toxicity endpoints or have a low potential for accumulation in food. Although no substances possess both of these properties, 42 % of the 368 substances possess either of these two properties.

The distribution of total scores for 2 336 substances is depicted in Figure 34 for WS1 and WS2. The 583 substances prioritised in WS1 and the 492 substances prioritised in WS2 are highlighted in the plot. The distribution for WS1 shows a more steady decrease of total scores across all substances, while such a decrease is only apparent for about 400 substances in WS2. As discussed above, this difference in the distributions is due to the high weight attributed to the toxicity score in WS2.

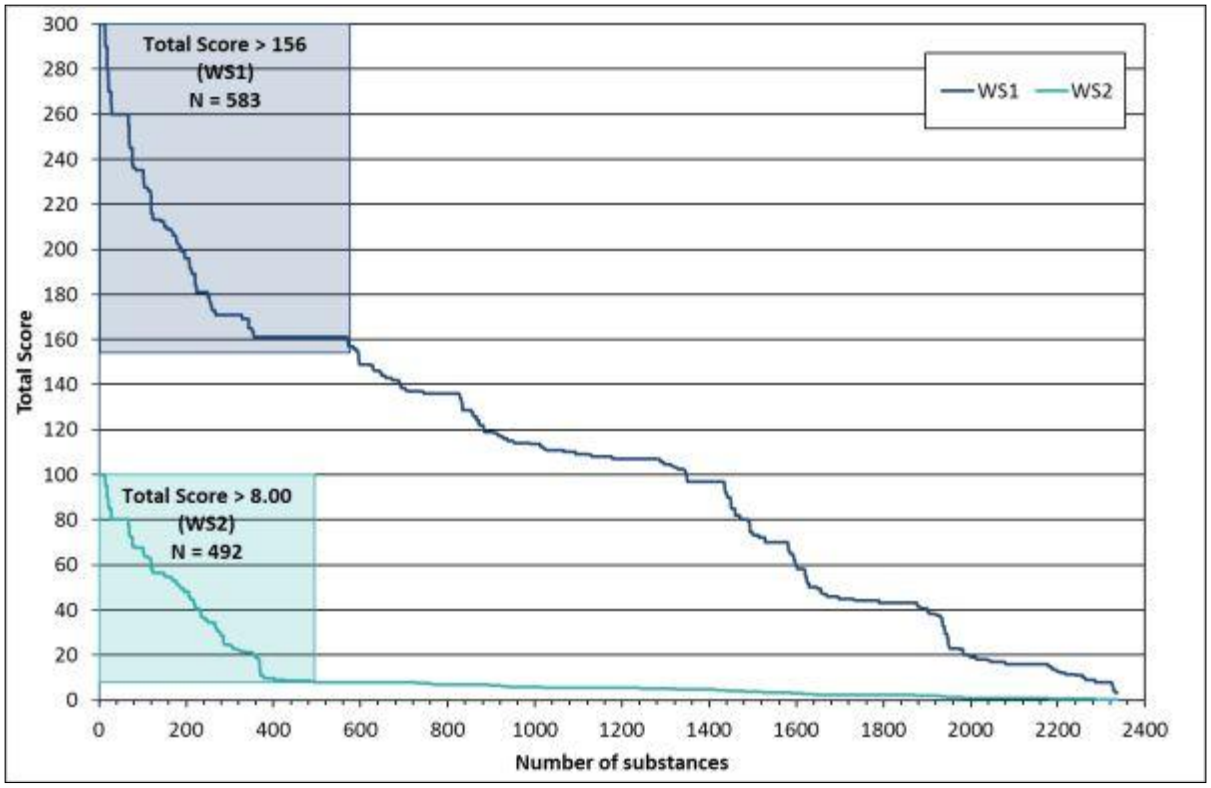


Figure 34: Distributions of total scores for 2 336 substances applying weighting scenario 1 (WS1) and weighting scenario 2 (WS2) (75th percentile WS1 = 156; 75th percentile WS2 = 8.00).

Based (a) on the finding that WS1 and WS2 still identify a comparatively large fraction of substances that either lack toxicity or are predicted not to accumulate in food and (b) on the distribution of total scores shown in Figure 34, an alternative definition of priority substances was tested. In order to target the upper part of total scores, 90th percentiles of total scores were calculated. Since the 90th percentile represents a rather strict cut-off, all substances with total scores at or above the 90th percentile were prioritised. Table 36 shows the results of this prioritisation.

Table 36: Prioritised substances in WS1, WS2 or both WS1 and WS2 if the 90th percentile is applied (and further differentiation of those lacking critical properties)

Parameter	WS1	WS2	WS1 AND WS2
Total Score ≥ 90th percentile	249	233	229
Substances with Toxicity Score = 1	20 (8.0 %)	0	0
Substances with Score C < 5	34 (14 %)	38 (16 %)	34 (15 %)
Substances with Toxicity Score = 1 AND Score C < 5	0	0	0

These data show that all substances with a Toxicity Score of 1 are eliminated in WS2 and significantly reduced in WS1. In addition, the fraction of substances with a Score C < 5 is reduced in WS2 (but not in WS1). However, even with the application of this stricter cut-off, about 15 % of the substances prioritised in the weighting scenarios are predicted not to accumulate in food. Twenty substances are prioritised in WS1, but not in WS2. All of these substances have very high scores in block A and maximum scores both in block B and block C, but a Toxicity Score of 1. Four substances prioritised in WS2 are not prioritised in WS1, since the Total Score in WS2 is slightly above the 90th percentile, while it is slightly below the 90th percentile in WS1.

Figure 35 summarises the results from the weighting scenario evaluations using both the 75th and the 90th percentile cut-offs.

Substances prioritised in WS1, WS2						
	WS1		WS2		WS AND WS2	
	>P75	≥P90	>P75	≥P90	>P75	≥P90
Number of substances	583	249	492	233	368	229
Toxicity Score = 1	51 %	8.0 %	17 %	0	22 %	0
Score C < 5	12 %	14 %	26 %	16 %	10 %	15 %
Toxicity Score = 1 AND Score C < 5	0	0	0	0	0	0

Figure 35: Comparison of results in WS1 and WS2 with priority substance definition of total score > 75th percentile (>P75) and ≥ 90th percentile (≥P90), respectively.

Overall, applying this stricter criterion reduces the fraction of substances lacking critical properties, but still includes a substantial fraction of those lacking a bioaccumulation potential.

3.4.2. Pivot table selection

The Pivot table functionality of Microsoft Excel® was used as a different tool for selecting priority substances next to the weighting scenarios. In contrast to weighting scenarios, such a selection offers the possibility to define specified criteria (i.e. scores in each block) that have to be met in order to qualify as a priority substance.

The Pivot table selection prioritises 11 % (266/2 336) of the substances (Table 37). These 266 priority substances fulfil all requirements of having the Toxicity Score of 10, a bioaccumulation score (block C) > 5 and either an environmental release score (block A) or biodegradation score (block B) > 5. As discussed above, scores > 5 in either of these two blocks were considered sufficient for prioritisation. However, 111 of the 266 priority substances (42 %) have scores > 5 in both block A and block B. Fifty-four of these 266 substances (20 %) are predicted to be readily biodegradable (Score B = 1) and these substances are prioritised because they have a Score A > 5 and are therefore expected to be released to the environment in significant amounts. In fact, most of these 54 substances (N=37) have a Score A of 7 or higher. Furthermore, one half of these 54 substances have a maximum REACH registration tonnage of 100 000 tpa or more. The selection of either Score A > 5 or Score B > 5 only removed 17 substances from the set of 283 substances that have a Toxicity Score of 10 and a Score C > 5, resulting in the 266 priority substances.

Table 37: Number of priority substances selected by the Pivot table approach and further Pivot table selections defining other Pivot table queries.

Para-meter	Toxicity Score = 10 AND Score C > 5 AND			
	Any Score A and any Score B	**Score A > 5 OR Score B > 5**	*Score A > 5 AND Score B > 5*	*Score A>5 AND Score B=1*
N	*283*	**266**	111	54

In contrast to weighting scenarios (which only apply a cut-off to the total score), the Pivot table selection applies cut-offs to each block. While the scores are largely categorical for block B (biodegradable or not), block C (bioaccumulative or not) and the toxicity block (toxic or not), the situation is different for block A, in which scores are almost continuous (60 possible scores resulting from a combination of 5 possible Tonnage Scores and 12 possible ERC Scores, see Figure 5). As a consequence, substances with Scores A just below the cut-off, but fulfilling all other criteria are not prioritised. However, this applies only to very few substances. For example, only 6 additional substances are prioritised if the criterion is changed from Score A > 5 to Score A > 3 (N=272 instead of N=266). This is superior to the weighting scenarios, in which – especially in WS2 – a large fraction of substances is assigned a total score at or only slightly below the cut-off (see e.g. Figure 34).

The following Venn chart illustrates the number of substances fulfilling every single criterion as well as the combinations (Figure 36). The data show that 1 423/2 336 substances (61 %) meet both the criteria of Score C > 5 and Score A > 5 OR Score B > 5. Slightly more than one half of the substances that are assigned a Toxicity Score of 10 also meet all other criteria applied in the Pivot table selection (266/526, 51 %).

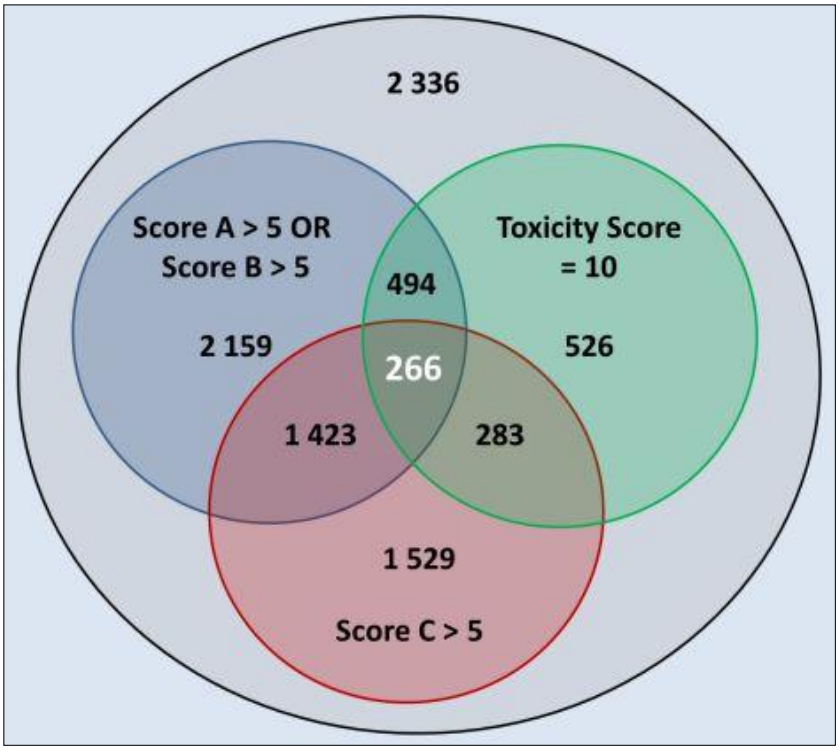


Figure 36: Number of substances meeting the criteria of the Pivot table selection for the 2 336 substances in the dataset.

It is evident from these data, that the criteria for block A and block B have little impact on the number of substances prioritised in the Pivot table selection. Overall, 283 substances meet the criteria for toxicity and bioaccumulation (block C). This number is only slightly reduced by 17 substances due to the application of the criteria for block A and B (N=266). It is also obvious that this observation is due to the large number of substances fulfilling the latter criteria (N=2 159).

3.4.3. Integration of the results from weighting scenarios and Pivot table selections

Overall, the evaluations presented above can be summarised as follows:

- Weighting scenarios
  - 583 substances are prioritised by WS1,
  - 492 substances are prioritised by WS2,
  - 368 substances are prioritised in both WS1 AND WS2,
  - 707 substances are prioritised in either WS1 OR WS2.

  Substances with a Toxicity Score of 1 or a Score C < 5 are selected in all scenarios. Their fraction can be reduced by application of the 90th percentile as a cut-off.
- Pivot table selection:
  - 283 substances are prioritised if only the toxicity and bioaccumulation criteria are set (Toxicity Score = 10 and Score C > 5).
  - 266 substances are prioritised in the Pivot table selection with the original criteria (i.e. 283 substances - 17 substances due to application of the criterion for block A and block B).

To further analyse the different approaches of selecting priority substances, weighting scenarios and Pivot table selections were combined. In Figure 37, the substances prioritised by the Pivot table selection were plotted into the ranking distribution of weighting scenarios 1 and 2. All substances prioritised by the Pivot table approach are also prioritised in WS2. In contrast, the priority substances of WS1 differed from the Pivot table selection: 60 substances prioritised in the Pivot table selection did not exceed the 75th percentile priority cut-off of the total score in WS1. As a consequence, only 206 substances prioritised in the Pivot table selection are also prioritised in WS1.

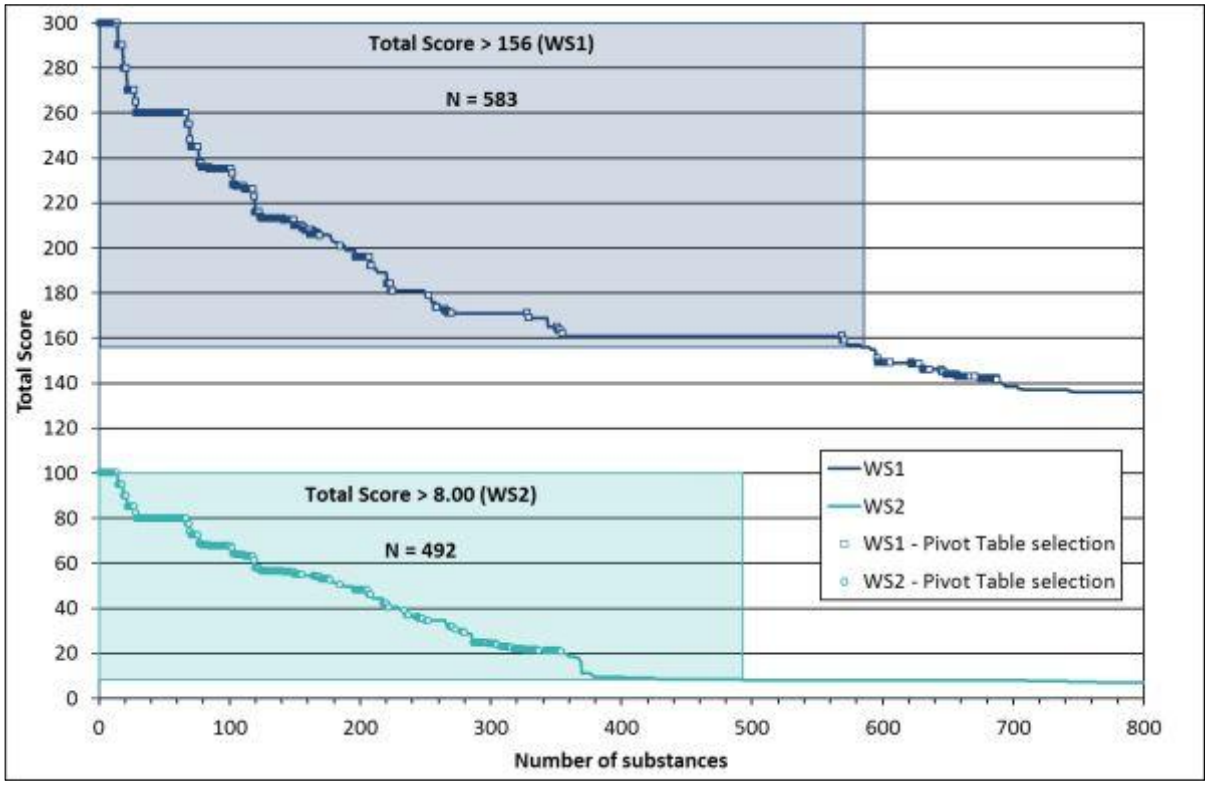


Figure 37: Distribution of total scores for 2 336 substances of weighting scenario 1 (WS1) and weighting scenario 2 (WS2) in combination with substances prioritised by the Pivot table selection (N=266). Only the first 800 substances are shown.

The 60 substances prioritised in the Pivot table selection, but not in WS1 can be further characterised as follows:

- All 60 substances are prioritised in WS2.
- All 60 substances have a Toxicity Score of 10 and a Score C of 6.
- 19 substances are not readily biodegradable (Score B > 5), but have a very low Score A < 1.5; most of these (N=15) have a maximum REACH registration tonnage of 100 tonnes per annum or less.
- 41 substances are biodegradable (Score B = 1), but have a Score A > 5; most of these substances have a Score A of 7 or above (N=27) and almost half of the 41 substances have a maximum REACH registration tonnage of 100 000 tpa or more (N=17) or confidential tonnage data (N=2).
- The total score in WS1 of these 60 substances ranges between 141.3 and 149.0 and is only slightly below the 75th percentile of 156 (also see Figure 17).

These 60 substances are prioritised in the Pivot table selection because either Score A or Score B is above 5. However, they are not prioritised in WS1 because blocks A and B are assigned a relatively high weight in this weighting scenario. In contrast, WS2 prioritises these substances because it places a higher weight on the toxicity score and less weight on blocks A and B. In the light of these considerations, and given the fact that these substances have total scores only slightly below the 75th percentile in WS1, these 60 substances should be prioritised as well.

Technically, the selection of priority substances in a combination of the weighting scenarios and the Pivot table selection can be described as:

- Prioritised in any weighting scenario (WS1 OR WS2) AND prioritised in the Pivot table selection: N=266

However, these 266 substances are identical to the 266 substances prioritised in the Pivot table selection alone. The Pivot table selection is therefore superior to the prioritisation with weighting scenarios, since

- it allows defining criteria that have to be met in any case. It therefore excludes substances that (a) have a Toxicity Score of 1 and/or (b) are predicted not to accumulate in food (Score C < 5). As shown above, the fraction of such substances in both weighting scenarios is substantial. Even with the application of a stricter cut-off (> 90th percentile of total scores), such substances are not completely excluded in the weighting scenarios.
- the cut-offs used in the Pivot table selection differentiate substances by (more or less) categorical parameters: biodegradable or not, bioaccumulating or not, toxic or not. Only Score A is of a more continuous nature. In contrast, the weighting scenarios apply strict cut-offs to the total score and a substantial fraction of substances with total scores at or only slightly below the cut-off are excluded.
- the cut-offs in weighting scenarios are impacted by the distribution of scores for individual blocks and the resulting total score. As shown above, the distributions of the two weighting scenarios differ and are the consequence of the weight put on individual blocks.

While the Pivot table selection correctly prioritises substances with critical properties, there may be substances that are excluded in the Pivot table selection because both Score A and Score B are below 5. Since both parameters involve some uncertainty (see sections 3.2.1 and 3.2.2), additional analyses were performed.

For this purpose, the 707 substances prioritised in either WS1 or WS2 (or both) were evaluated. As demonstrated in section 3.4.1 above, the fraction of substances with a Toxicity Score of 1 or a Score C < 5 is substantial. Overall, 266 of these 707 substances are also prioritised in the Pivot table selection, while 441 substances are prioritised in either WS1 or WS2 (or both), but not in the Pivot table selection. These 441 substances can be characterised as follows:

- 298 have a Toxicity Score of 1 and do not need to be considered further.

- Of the 143 substances with a Toxicity Score of 10, 126 have a Score C < 5 and do not need to be considered further.
- The remaining 17 substances have a Toxicity Score of 10 and a Score C > 5. All of them are readily biodegradable (Score B = 1) and are assigned a Score A between 1.125 and 4.5. Since Score A and Score B are both < 5, these substances are not prioritised in the Pivot table selection. These 17 substances are identical to the 17 substances that represent the difference between those with a Toxicity Score of 10 and a Score C > 5 in the entire dataset (N=283, out of the total of 2 336) and those prioritised in the Pivot table selection (N=266) as shown in Figure 36.

These 17 substances are possible candidates for the final selection of priority substances, if Score A can be shown to underestimate potential releases to the environment. Table 38 shows relevant information related to block A (Tonnage and ERC Scores as well as the maximum REACH registration tonnage for these substances). Ten of these substances have relatively high maximum REACH registration tonnages (1 000 tpa or above) and the low Score A results from a comparatively low ERC Score. For hydroquinone, the REACH registration data on the uses indicate that an 'ERC 0' was assigned for several uses, since the assessment was based on other descriptors, such as spERCs. Such use descriptors cannot be assessed by the semi-automated screening procedure applied in this study (see section 2.2.1) and the ERC Score is therefore only based on uses to which a specific ERC was assigned. This may result in an underestimate of the ERC Score. For the other nine substances with maximum REACH registration tonnages of 1 000 tpa or above, the low ERC Score was confirmed (use as an intermediate, as a monomer in polymer production or in similar applications likely to be associated with comparatively low environmental releases). This also applies to acrylamide monomer, which has the highest tonnage of any of these 17 substances.

Table 38: Relevant data for 17 possible priority substance candidates

CAS	NAME	Maximum tonnage [tpa]	Tonnage Score	ERC Score
924-42-5	N-methylolacrylamide	10 000	2	1.75
123-31-9	Hydroquinone	100 000	3	0.30
5117-12-4	2-propen-1-one, 1-(4-morpholinyl)	10	1	1.75
142-16-5	2-butenedioic acid (z)-, bis(2-ethylhexyl) ester	10 000	2	0.30
420-04-2	Cyanamide	10 000	2	0.30
923-02-4	N-methylolmethacrylamide	10 000	2	0.30
1416808-92-8	(3e)-2-chloro-3-(hydroxymethylene)-cyclohexene-1-carbaldehyde	10	1	0.30
79-39-0	2-methylprop-2-enamide	10 000	2	2.5
79-06-1	Acrylamide monomer	1 000 000	4	0.30
131-17-9	Diallylphthalate	1 000	1	2.5
605-50-5	Isoamyl phthalate	100	1	2.5
105-76-0	Dibutyl maleate	10 000	2	0.30
62-56-6	Thiourea	1 000	1	0.30
79-07-2	2-chloroacetamide	100	1	0.30
556-52-5	Glycidol	100	1	0.25
60-35-5	Acetamide	100	1	0.25
82428-30-6	7-oxabicyclo[4.1.0]hept-3-ylmethyl 2-methylprop-2-enoate	10	1	0.125

These evaluations show that hydroquinone may be included as an additional priority substance due to the high tonnage and the questionable completeness of ERC information despite its rating as readily biodegradable (Score B = 1). Nonetheless, the evaluations also demonstrate that the approach applied is generally valid and leads to the exclusion of substances if they are produced at low tonnages and/or used as intermediates/monomers. These substances are unlikely to be released to

the environment in large quantities, which – together with their ready biodegradability – justifies their exclusion from further evaluation.

3.4.4. Prioritisation for further evaluation

Substances were prioritised in sections 3.4.1-0 above using different approaches. These evaluations have shown that the Pivot table selection provides the most meaningful results for prioritisation. Nonetheless, the Pivot table selection applies strict criteria and additional substances may be included based on other considerations. In addition, a first inspection of the priority substances identified some cases, which may need to be excluded from further evaluation (see discussion below). Overall, the prioritisation for further evaluation is therefore based on the following steps that are discussed in the sections below:

- Step 1: Prioritisation from Pivot table selections
- Step 2: Inclusion of additional substances based on substance-specific evaluations for block A
- Step 3: Exclusion of substances from the priority list

Steps 1 and 2 are based on the evaluations presented in sections 3.4.1-0 In contrast, step 3 involves a refinement of the list of priority substances for further evaluation.

Step 1: Prioritisation from Pivot table selections

From the evaluations presented in sections 3.4.1-0, 266 substances are prioritised based on the Pivot table selection. All of these substances are also prioritised in WS 2 and 206 of them are prioritised in WS1. As demonstrated in section 3.4.3, the remaining 60 substances all receive a total score in WS1, which is only slightly below the 75th percentile. These are prioritised as well for further evaluation.

It is important to note that all 283 substances with a Toxicity Score of 10 and a potential for bioaccumulation (Score C > 5) in the total set of 2 336 substances have been addressed:

- 266 substances have been prioritised and
- 17 substances, although not conforming to the criteria of the Pivot table selection, have been assessed further, since they meet both the toxicity and the bioaccumulation criteria (see section Table 38 above and step 2 below).

Step 2: Inclusion of additional substances based on substance-specific evaluations for block A

As discussed in section 3.4.3, hydroquinone (CAS No.: 123-31-9) is included as a priority substance. Hydroquinone belongs to the group of 17 substances that are not prioritised in the Pivot table selection because both Score A and Score B are below 5 (Toxicity Score = 10 and Score C > 5). In contrast to the remaining 16 substances, however, the ERC Score for hydroquinone is potentially an underestimate. In addition, this substance is registered at a high tonnage. Non-prioritisation is confirmed for the remaining 16 substances.

After step 2, 267 priority substances were identified. Since Scores A and B are combined by an OR operator in the Pivot table selection, additional analyses were performed in relation to block A and B for these 267 substances. The evaluations show that these 267 substances are characterised by a high fraction of substances that are predicted to be persistent due to little or no biodegradation (Score B > 5; N=212, 80 %), with the remainder being selected due to Scores A above 5 (N=55, 20 %). More details are provided in Appendix G.

Step 3: Exclusion of priority substances

Exclusion of substances for which the toxicity classification is impacted by impurities

Steps 1 and 2 above have identified a total of 267 priority substances. As shown in section 3.3, some of the classifications for the four toxicity endpoints are impacted by impurities. Since the biodegradation and partitioning behaviour of the impurity may substantially differ from the one of the substance assessed, a toxicity score that is related to an impurity should not be combined with the fate of the substance. These substances for which the Toxicity Score of 10 is impacted by an impurity were therefore excluded from further evaluation at this stage.

Overall, this was the case for 5/267 substances (1.9 %), all of which represented mono-constituent substances. It should be noted that – within the scope of this project – the impact of impurities on the classification could only be assessed based on the record in the C&L Inventory. In the records, the impact of impurities is not related to a specific endpoint (e.g. impurities having an impact on the classification for skin sensitisation), while this is usually the case. Therefore, such an impact may in fact not relate to the four endpoints covered in this assessment, but rather to other endpoints. For example, the impurity may be responsible for classification as a skin sensitiser (not relevant in this project), while it does not affect the classification as a carcinogen (relevant in this project). This could only be ascertained in a more in-depth substance-specific assessment. As a consequence, there may be some cases among these 5 substances, which could qualify as priority substances in an in-depth assessment.

Exclusion of these 5 substances due to the impact of impurities on the toxicity classification results in 262 substances to be assessed further.

Exclusion of substances for which the chemical structure may not adequately represent the substance

Despite the effort made (a) to evaluate only discrete organic chemicals and (b) to eliminate duplicates (see sections 2.1 and 3.1 for details), inspection of the names of the 262 prioritised chemicals showed that some of these substances can be considered UVCB substances representing petroleum products. Overall, 48 substances were identified as petroleum products, of which

- 46 substances have the term 'petroleum' in their name. Typical substance groups are 'distillates (petroleum)', 'gas oils (petroleum)', 'residues (petroleum)' or 'extracts (petroleum)', each of which with several substances defined by the refining process. In many cases, these substances are described by identical SMILES notations. In fact, there are only 20 different SMILES notations for these 46 substances and 19 substances are described by the SMILES notation representing benzo(a)pyrene.
- 2 substances were also considered petroleum products: 'lubricating oils' and 'petrolatum'. In addition, the SMILES notation was not representative of the substance in both cases. Aromatic hydrocarbons are included in the REACH registration dossier for 'lubricating oils' as constituents, while the SMILES notation represents a branched alkane. Similarly, the REACH registration dossier for 'petrolatum' describes the substances as being primarily composed of hydrocarbons with more than 25 carbon atoms, while the SMILES notation represents a structure with 24 carbon atoms.

All these 48 entries are excluded from further evaluation for the following reasons:

- The SMILES notation assigned (which determines all modelled environmental fate properties) may not be representative for the UVCB substance.
- While benzo(a)pyrene represents the toxic hazard identified (i.e. carcinogenicity), an evaluation of PAHs contamination from petroleum products is not considered meaningful for this study, since this issue is well-known for decades and does not represent an emerging risk.

Exclusion of these 48 substances results in 214 prioritised substances.

Since the example of petroleum products described above indicated that the substance selection may have also identified other UVCB substances as discrete chemicals, all 214 substances have been evaluated manually with respect to their REACH registration data. Full details of this evaluation are provided in Appendix I. Overall, this analysis showed that the majority of substances (N=196, 92 %) was registered as mono-constituent substances. Nine substances were registered as multi-constituent substances, but the evaluation presented in Appendix I showed that these substances are described by an adequate SMILES notation. All substances registered as UVCB (9/214) were identified as 'organic' in the registration dossier (i.e. not considered 'petroleum products'). In two of these nine cases the SMILES notation did not adequately represent the substance and these substances were therefore excluded. However, the evaluation showed that in the remaining seven cases, the structure adequately represented a constituent of the UVCB substance.

Overall, another 2 substances were excluded resulting in 55 substances excluded altogether. The original list of 267 priority substances therefore decreases to 212 priority substances. It must be noted

that the exclusion steps applied involve manual evaluation steps and were therefore not applied at earlier stages, when many more substances were in the selection.

Remaining duplicate SMILES notations

As shown above, duplicate SMILES notations were identified for many of the petroleum products excluded. Among these 212 priority substances remaining, there are only three pairs of substances (i.e. 6 substances) with identical SMILES notations. Table 39 shows the relevant data for these substances.

Table 39: Duplicate SMILES notations for priority substances identified by different CAS numbers among the 212 substances selected.

No.	CAS No.	Name	Score A	Score B	Score C	Toxicity Score
1A	108-78-1	2,4,6-triamino-1,3,5-triazine	9	10	10	10
1B	37640-57-6	1,3,5-triazine-2,4,6(1h,3h,5h)-trione, compd. with 1,3,5-triazine-2,4,6-triamine (1:1)	5.5	10	10	10
2A	95-70-5	2-methyl-p-phenylenediamine	6	10	10	10
2B	615-50-9	2-methyl-p-phenylenediamine sulfate	6	10	10	10
3A	584-84-9	4-methyl-m-phenylene diisocyanate	6.5	10	6	10
3B	26471-62-5	m-tolylidene diisocyanate (reaction mass of 4-methyl-m-phenylene diisocyanate and 2-methyl-m-phenylene diisocyanate)	9	10	6	10

These entries are retained for further evaluation, since the SMILES notation in these cases represents the 'parent' compound (suffix 'A' in the first column of Table 39). For example, the SMILES notation representing 2-methyl-p-phenylenediamine has been assigned to both 2-methyl-p-phenylenediamine and its sulfate. The substances identified by suffix 'B' in the first column of Table 39 may in fact release the 'parent' compound or exist under environmental conditions as the 'parent' compound. In fact, concentrations in the environment may be higher than expected on the basis of the 'parent' compound alone, since two substances may actually contribute to environmental releases. In this context, retaining duplicate SMILES notation in all evaluation steps for block A, block B, block C and the toxicity evaluation was very meaningful.

Overall, 55 substances were excluded in step 3 with most of them (N=48, 87 %) being excluded because they are UVCB substances representing petroleum products. A total of 212 substances were identified as priority substances.

3.4.5. Assessment of prioritisation

In order to check the validity of the approach for prioritisation, these 212 priority substances were analysed in more detail. The listings applied in the selection of substances for the in-depth evaluation (see sections 2.5 and 3.5)[83] were used to provide insight into whether the 212 priority substances have already been identified in instruments related to EU chemicals legislation (e.g. inclusion in the Candidate List under the REACH Regulation) or assessed in some form by EFSA (as evidenced by their inclusion in EFSA's OpenFoodTox database; see section 2.5 for details). A priority substance included in any of these lists may indicate the correct identification of an 'emerging chemical risk', while a priority substance not listed in any of these sources may identify an 'emerging chemical issue' (see section 1 for a definition of these terms). However, as indicated in section 2.5, listing in any of these sources only suggests that some aspects were addressed (e.g. the hazard with respect to a particular endpoint), but does not necessarily indicate that a risk assessment in relation to accumulation in the food chain was performed.

[83] While these listings were primarily evaluated for the selection of substances for in-depth evaluation, using these data in the analyses presented here is also meaningful. Section 2.5 describes the background and meaning of the various lists and section 3.5.1 provides additional results.

In a first step, the 10 substances with the highest Total Scores in both weighting scenarios ('top 10' priority substances; see section 3.4.1 for details on weighting scenarios) were compared with the remaining 202 priority substances. Subsequently, priority substances not included in any of the lists are compared with those that are included in at least one of these lists to identify possible differences.

'Top 10' priority substances

Figure 38 shows the results of the comparison of the 'top 10' priority substances with the remaining 202 priority substances. For each group, percentages of listings exceed 100 %, since any given substance may be included in more than one list. It is evident that only two of the ten high ranking substances are not listed in any of the sources evaluated (20 %), while the other eight high ranking substances are listed in at least one source. Six of these eight substances are subject to substance evaluation under REACH (CoRAP listing). Furthermore, a considerable fraction of these substances (a) is included in the Candidate List, the Authorisation List and/or the Restriction List, (b) is included in EFSA's OpenFoodTox database and/or (c) was assessed in EU Risk Assessment Reports (RAR) under past EU chemicals legislation. Table 40 provides additional information on the listings for these ten high-ranking substances.

In contrast to the 'top 10' priority substances, more than half (N=108, 53 %) of the remaining 202 priority substances are not listed in any of the sources evaluated. As a consequence, the percentage of substances listed in the sources shown in Figure 38 is consistently lower than for the 'top 10' priority substances.

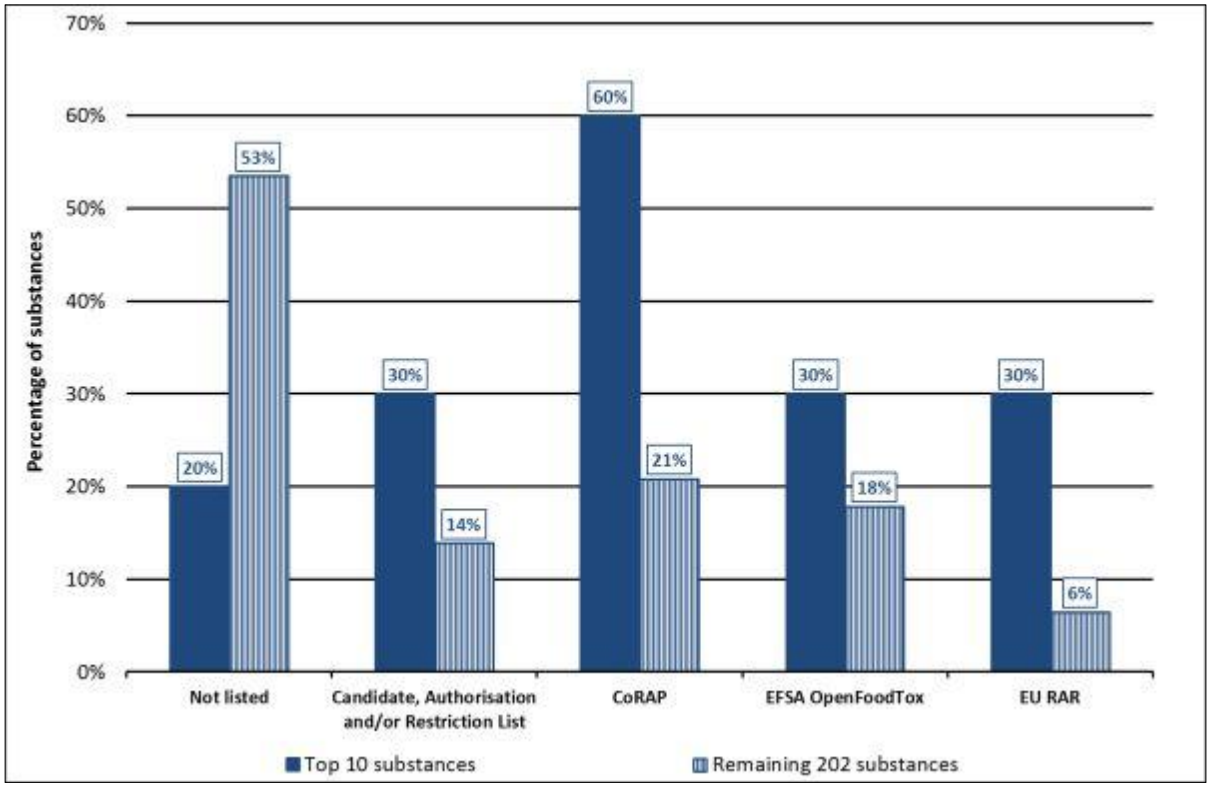


Figure 38: Coverage of 'top 10' substances and the remaining 202 priority substances by instruments of EU chemicals legislation and EFSA assessments

Note: The graph focusses on the most important listings and does not present data for some of the lists evaluated (e.g. the PACT list) for the sake of simplicity. However, the category 'not listed' only includes substances not listed in any of the sources evaluated. For the Candidate, Authorisation and Restriction Lists, the combined data are shown (i.e. the percentage of substances listed in any of these lists). All substances in the Authorisation List are also included in the Candidate List.

Table 40: Listings of top 10 substances.

CAS No.	Name	Listings
80-05-7	Bisphenol A	EFSA OpenFoodTox, Candidate List, Restriction List, PACT List, CORAP, EU RAR
25637-99-4	Hexabromocyclododecane	EFSA[(a)], Candidate List, Authorisation List, EU RAR
101-68-8	4,4'-Methylenediphenyl diisocyanate	Restriction List, PACT List, CORAP
79-94-7	Tetrabromobisphenol A	EFSA OpenFoodTox, PACT List, CORAP, EU RAR
108-78-1	Melamine	EFSA OpenFoodTox
51-03-6	Piperonyl butoxide	CORAP, Biocides
101-02-0	Triphenyl phosphite	CORAP, PACT List
119-47-1	2,2'-methylenebis(6-t-butyl-4-methylphenol)	CORAP
63449-39-8	Chlorinated paraffins (C23, 43% chlorine)	Not listed[(b)]
68937-41-7	Phenol, isopropylated, phosphate (3:1)	Not listed

(a): This substance was also assessed by EFSA (EFSA, 2011a), but a listing was not retrieved since the CAS number and the name is not included in the OpenFoodTox database.
(b): Note that this substance represents long-chain chlorinated paraffins. Chlorinated paraffins are currently under assessment by EFSA[84] and the related short-chain chlorinated paraffins are now covered by the Stockholm Convention[85].

These data illustrate that

- the procedure applied in this study identified as 'top 10' priority substances several substances that have also been identified in other sources as being of a high priority:
  - The top six substances in Table 40 have been assessed in detail by EFSA with respect to their presence in food/feed (bisphenol A, hexabromocyclododecane, tetrabromobisphenol A and melamine) and/or are subject to various regulatory instruments[86].
  - The other four substances did not (yet) receive as much attention and all of them entered the selection for in-depth evaluation; as discussed in more detail in section 3.5. Two of these substances were finally included in the in-depth evaluation.
- the procedure selected as priority substances (other than the `top 10´) listed in some of the sources evaluated. As shown in Table 41 below, this is the case for 102 of all 212 priority substances. However, it is questionable whether a full-scale risk assessment with respect to food chain accumulation was actually performed for these substances. As explained in section 2.5, many of these sources primarily indicate that specific issues are being evaluated (e.g. classification for a particular toxicity endpoint), but the level of detail of the respective evaluations can only be assessed in substance-specific assessments that are beyond the scope of this study (see, however, the results of the in-depth evaluation for 10 substances presented in section 3.5.2).
- the procedure also identified among the priority substances a large percentage of substances not listed in any source:
  - N=2 among the 'top 10' (20 %)[87] and
  - N=108 among the remaining 202 priority substances (53 %).

  While the evaluation based on the 'top 10' priority substances is limited by the small number of substances, additional analyses suggest that priority substances with a high rank are less likely

[84] See http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2016-00801, accessed January 2019.
[85] See http://chm.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2509/Default.aspx#LiveContent[SCCP], accessed January 2019.
[86] Inclusion in the Candidate List, Authorisation List, Restriction List under the REACH Regulation or coverage by the Biocidal Products Regulation as shown in Table 40.
[87] Note, however, that the Toxicity Score of the chlorinated paraffin was considered to be of low reliability (see section 3.5.1).

not to have been included in any list. For example, eight of the 'top 25' priority substances are not listed in any source (32 %), while this is the case for 102 of the remaining 187 priority substances (55 %).

The evaluations presented above are primarily based on whether a substance is listed in at least one source or not. The same data were also analysed in a more quantitative way by checking in how many lists a substance is actually included (out of a total of eight lists; see section 2.5). Figure 39 illustrates that substances with a high rank in this study are more likely to be included in more than one list compared to those with lower ranks (as assessed by the mean number of listings per substance). For example, the 'top 10' priority substances are included on average in 2.2 lists, while all 212 priority substances are included in 0.92 lists (substances not listed in any list counted as "0"). Furthermore, the fraction of substances included in at least three lists is considerably higher among the highest ranking substances. Thus, 40 % of the 'top 10' and 28 % of the 'top 25' priority substances are included in 3 or more lists, while this is only the case for 11 % of all 212 priority substances (Figure 39).

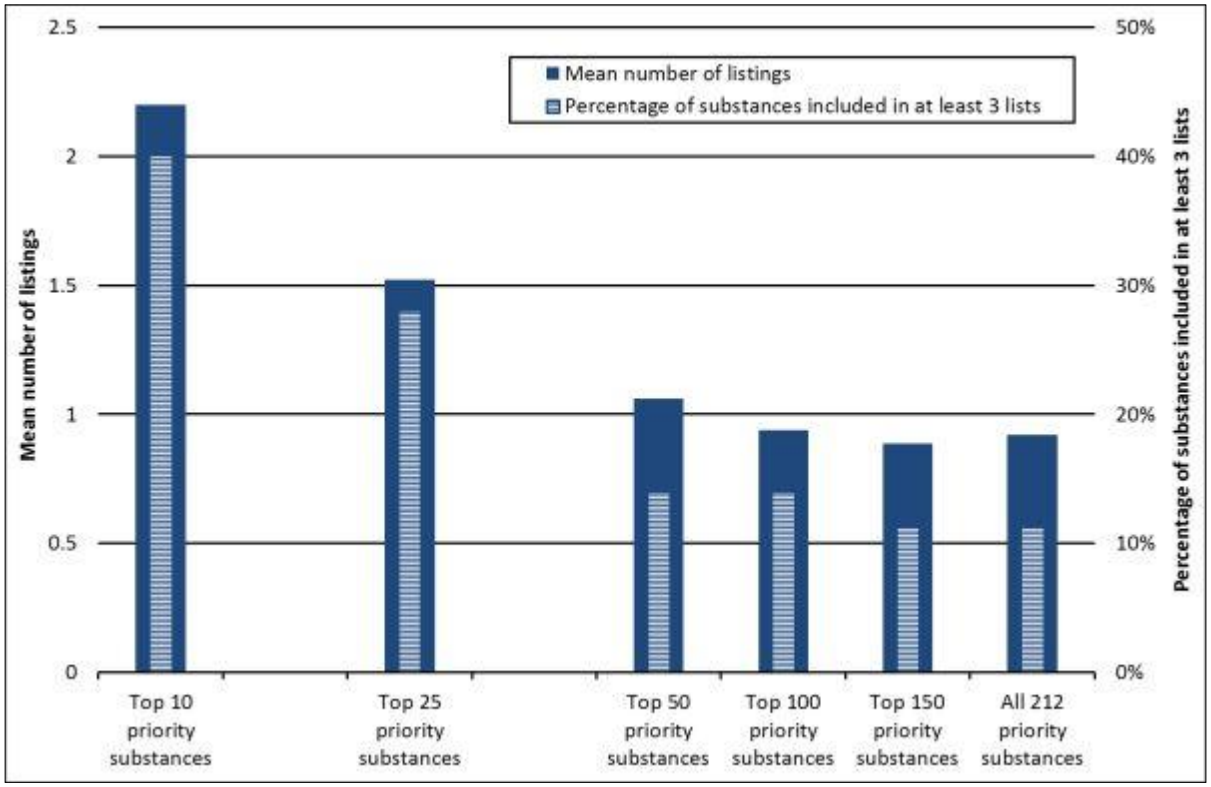


Figure 39: Mean number of listings per substance and percentage of substances included in at least three lists: dependence on ranks in weighting scenarios.

Substances not listed were assigned a value of "0", all other substances were assigned the number of lists in which they were included. For example, a substance found only in EFSA's OpenFoodTox database (but no other list) was assigned a value of "1".

Overall, the procedure identifies almost identical fractions of substances that have already been included in at least one of the lists and of substances not included in any list (Table 41). The prioritisation of 102 substances that are also listed in other sources is not surprising, since some of the prioritisation schemes of the respective lists use information that is similar to the one used in this study. For example, a high total tonnage, wide dispersive uses and CMR properties are among the criteria for the selection for substances for substance evaluation (CoRAP listing)[88]. However, it must be reiterated that substances listed in one of the sources have not necessarily undergone a detailed

[88] The tonnage is reflected in the Tonnage Score and the use pattern is reflected in the ERC Score (both added up to result in the Total Score A) of this study. With respect to toxicity, this study considers repeated dose toxicity in addition to CMR properties.

risk assessment with respect to the food chain (or 'human exposure via the environment' as this pathway of exposure is called under REACH). For example, the substance evaluation (CoRAP listing) for bisphenol A (CAS No.: 80-05-7), which is among the 'top 10 priority substances in this study (see Table 40), included a risk assessment for consumers and the environment and led to the conclusion of a need for follow-up regulatory action at EU level and the identification as a SVHC with subsequent listing in the Candidate List. However, human exposure via the environment (as assessed in this study), was not addressed during substance evaluation. The substance evaluation for another 'top 10' priority substance (tetrabromobisphenol A (CAS No.: 79-94-7) did not (yet) consider any exposure- or risk-related issue but only led to the request of additional studies. While both substances were evaluated for their presence in food by EFSA (EFSA, 2011b, 2015), these examples illustrate the instruments such as substances evaluation may be limited to certain aspects that do not include human exposure via the food chain (even for such substances where substantial data are available). For the remaining four 'top 10' priority substances in Table 40 that are listed in CoRAP (but were not assessed by EFSA), substance evaluation did not address human exposure via the environment (N=3) or has not yet started (N=1).

These evaluations and examples illustrate that this study identified priority substances that (a) were also prioritised for evaluation under EU regulatory frameworks for chemicals and food safety, but (b) appear to have rarely been assessed with respect to human exposure via the food chain. With respect to the latter, possible exceptions are substances included in EFSA's OpenFoodTox database as indicated by the examples above. However, inclusion in this database does not necessarily indicate that an assessment of human exposure via the food chain has been performed. For example, of the nine 'top 25' priority substances that are listed in EFSA's OpenFoodTox database four substances were assessed in detail (the ones shown in Table 40), while five substances have only been assessed for their use as (or impurity in) food/feed additives, their use in food contact materials or as a pesticide (diuron, CAS No.: 330-54-1). Exposure of humans as a result of releases to the environment and subsequent accumulation in the food chain has not been the subject of these assessments (except for the releases due to the use as a pesticide in the case of diuron).

Comparison of priority substances by listings and endpoints

The finding that 110 priority substances are not listed in any of the sources evaluated demonstrates that this study identified substances that have not yet received attention either under the EU regulatory framework for chemicals (i.e. lists related to the REACH or the Biocidal Products Regulations) or for food safety (i.e. listing in EFSA's OpenFoodTox database). Several factors may be responsible for this finding:

- The listings may be more focussed on substances possessing CMR properties than those classified for repeated dose toxicity (STOT RE) only.
- The listings may largely be based on harmonised classifications only, since these have been agreed by EU Member States. As outlined in section 2.3, this study was not limited to harmonised classifications, but also considered IARC classifications for carcinogenicity as well as classifications from REACH registration dossiers and other classifications under the CLP Regulation for all relevant endpoints.

Based on these considerations, the origin of the classification was evaluated in more detail for all 212 priority substances differentiated by (a) classification for CMR endpoints and repeated dose toxicity only as well as (b) inclusion in one of the lists or not. Table 41 provides an overview based on this differentiation.

Table 41: Overview of 212 priority substances differentiated by endpoints and listings

Endpoint for classification	Total	Listed	Not listed
CMR properties	145	84 (58 %)	61 (42 %)
Repeated dose toxicity only	67	18 (27 %))	49 (73 %)
Total	212	102 (48 %)	110 (52 %)

These data illustrate that a classification for CMR properties indeed increases the likelihood that a substance is included in at least one of the lists. Thus, 58 % of the 145 priority substances classified

for CMR properties are listed, while this is the case for only 27 % of those classified for repeated dose toxicity.

Figure 40 shows the results after differentiation by the origin of the classification. The data clearly illustrate that a harmonised classification more likely results in inclusion in at least one of the lists than any other classification. This is most evident for CMR properties. There are 61 priority substances with a harmonised classification for CMR endpoints and 51 of these (84 %) are included in at least one of the lists. In contrast, only 10 priority substances with a harmonised classification for CMR properties (16 %) are not listed. Classifications for CMR properties by IARC and in REACH registration dossiers (joint and individual classifications) may also result in a listing, but the fractions are considerably lower when compared with harmonised classifications. Interestingly, the other classifications show a comparatively large fraction of CMR substances being listed (N=5, 50 %). However, two of these five substances are now proposed for a harmonised classification for CMR properties and the Toxicity Score has a low reliability in the remaining three cases. Furthermore, it must be stressed that the total number of substances with IARC, individual or other classifications (N=10-11 in each group) is small and differences in percentages should therefore not be overemphasised for these groups.

For repeated dose toxicity, the differences are much less pronounced. In fact, the percentages of substances listed in at least one source and those not listed are almost identical for the two groups representing the highest number of substances (harmonised and joint classifications). The most prominent finding with respect to repeated dose toxicity is the fact that this endpoint is clearly less likely to result in a listing in one of the sources evaluated when compared with CMR properties (also see Table 41).

Box: The impact of REACH

The data in Figure 40 illustrate that the majority of the 212 substances is prioritised based on joint (N=97, 46 %) or individual (N=15, 7.1 %) classifications in REACH registration dossiers (N=112, 53 %, in total). These substances did not have a harmonised classification for CMR properties or repeated dose toxicity and were also not classified for carcinogenic effects by IARC at the time of evaluation. These figures demonstrate that the use of classification information from REACH registration dossiers greatly increases the number of prioritised substances. This finding may be related to two issues. First, it may take a long time before substances receive a harmonised or IARC classifications, while the classification in REACH registration dossiers is a faster process. Second, registrants may base their classifications on studies only that are not in the public domain (i.e. company-owned study reports). Both issues may be interrelated. For example, a substance classified for CMR properties (Cat. 1A or 1B) in the REACH registration dossier on the basis of unpublished studies is expected to be eventually prioritised by ECHA for a harmonised classification. However, this is a comparatively slow process, since it also depends on EU Member States supporting such a classification.

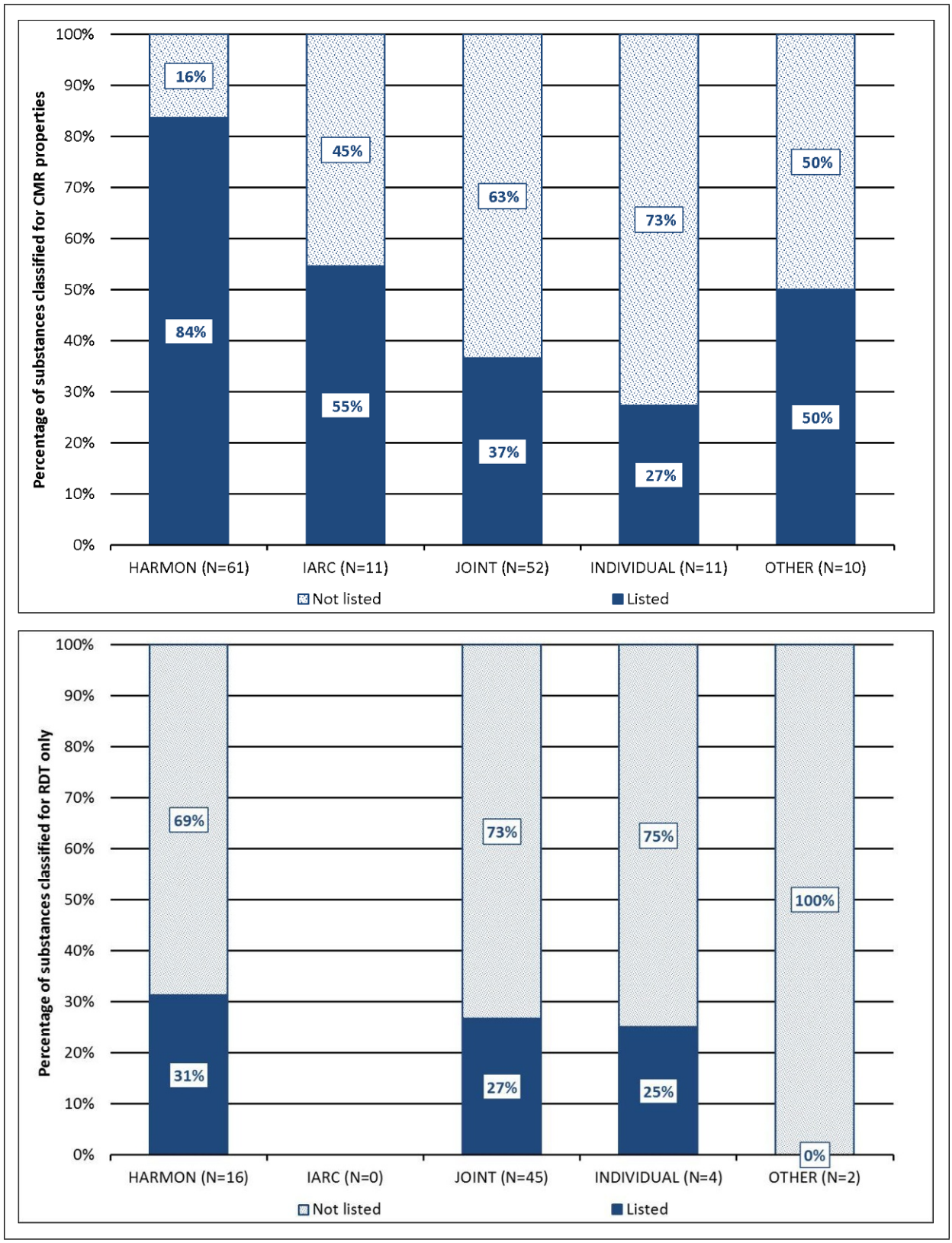


Figure 40: Percentage of substances classified for CMR properties (top; N=145) and repeated dose toxicity (RDT) only (bottom, N=67): relationship with listings.

Note: IARC only classifies for carcinogenic properties. This group was nonetheless included in the plot for repeated dose toxicity to allow easier comparison of groups between the upper and the lower plot.

The findings presented above may partly be explained by the fact that this study used a classification for CMR properties and repeated dose toxicity irrespective of the corresponding hazard class (as defined in the CLP Regulation). Thus, suspected CMR substances (Cat. 2) were assigned the same Toxicity Score of 10 as those for which the evidence is more convincing (Cat. 1A and 1B). The same applies to repeated dose toxicity for which STOT RE1 and STOT RE2 were both assigned a Toxicity Score of 10 (see section 2.3). In contrast, listing in the sources evaluated may be more focussed on substances classified as CMR Cat. 1A/1B or STOT RE1. In order to analyse the impact of the hazard class, the 110 substances not listed in any source were evaluated in more detail. Since the extraction of the classifications for the four endpoints (see section 2.3) did not differentiate between the hazard classes, this information had to be extracted manually. This evaluation was performed for substances with a high reliability of the Toxicity Score (N=102)[89] only.

Table 42 shows the result of this evaluation. Substances classified only for repeated dose toxicity (RDT) are almost exclusively classified in the less stringent hazard class STOT RE 2. Notably, the only two substances classified in STOT RE 1 have a joint classification for this endpoint. The findings are more diverse for substances classified for CMR properties. The data illustrate that most of the substances with a harmonised classification for CMR properties are considered only suspected CMR substances (Cat. 2, 70 %). In contrast, the fraction of suspected (Cat. 2) and 'confirmed' CMR substances (Cat. 1A/1B, IARC Group 1/2A) is almost identical in all other classifications. This observation may reflect the fact that a substance with a harmonised classification in Cat. 1A/1B is more likely to have already been listed in one of the sources evaluated, thus reducing the fraction among those not listed (see Figure 40, top).

Table 42: Hazard classes of 102 priority substances not listed in any source

Origin of classification[(a)]	CMR			RDT (STOT RE)[(d)]		
	Total	Cat. 1A/1B[(b)]	Cat. 2[(c)]	Total	Cat. 1	Cat. 2
HARMON	10	3	7	11		11
IARC	5	3	2			
JOINT	31	15	16	33	2	31
INDIVIDUAL	8	4	4	3		3
OTH-YES	1		1			
All non-harmonised	*45*	*22*	*23*	*36*	*2*	*34*
Total	55	25	30	47	2	45

(a): See section 2.3 for details on these types of classification.
(b): Includes IARC Group 1 and 2A.
(c): Includes IARC Group 2B.
(d): Classified for repeated dose toxicity (RDT) only. Many CMR substances are also classified for RDT, but they have only been included in the CMR group in this evaluation for the sake of simplicity.

The finding that almost half of the CMR substances identified from other than harmonised classifications are classified in Cat. 1A/1B (N=22, 49 %) demonstrates that the approach applied in this study does not lead to an identification of suspected CMR substances only. The data in Table 42 show that most of the 22 substances with Cat. 1A/1B CMR properties from classifications other than harmonised classifications are assigned to this group due to joint or individual classifications from REACH registration dossiers (N=19, 86 %). The same is true for Cat. 2 CMR substances for which 20/23 non-harmonised classifications come from REACH registration dossiers (87 %).

This evaluation shows that the procedure applied in this study makes full use of data generated under the REACH Regulation (i.e. the classifications for relevant hazardous properties) that have not yet recognised by other bodies in the context of chemical and food safety. While the data basis of these classifications could not be checked in the context of this study except for the issues discussed in section 2.3 (e.g. the impact of impurities), there is little reason to believe that registrants will classify a substance for a particular hazard if the underlying data are not convincing. In this context, it is

[89] Of the 110 substances not listed in any source, six substances were not evaluated because the reliability of the Toxicity Score was low (see section 3.3). REACH registration dossiers for two more substances could not be accessed since these substances are no longer characterised by the CAS number of the original evaluation. Hazard classes were extracted in December 2018.

worth noting that 2 of the 15 substances with a joint classification for Cat. 1A/1B CMR properties recently received an identical harmonised classification[90]. This illustrates that classification information from REACH registration dossiers may ultimately result in harmonised classifications although there is no automated procedure in place that this will happen. This observation also supports using classifications from REACH registration dossiers as done in this study.

Overall, the evaluations presented above allow drawing the following conclusions:

- This study identified among the highest ranking substances several chemicals that have already been assessed under EU chemicals and/or food safety legislation illustrating that the procedure applied is capable of identifying relevant substances.
- It identifies 102 priority substances that are included in at least one of the lists evaluated. Without substance-specific evaluations, it is impossible to judge whether these substances have been fully assessed with respect to their entry into the food chain and subsequent human exposure. However, due to the nature of the lists evaluated and based on illustrative examples it is likely that this is not the case for the majority of these 102 substances. Even if a substance has been assessed by EFSA, this assessment may only relate to specific pathways of exposure (e.g. from food contact materials), but may not cover human exposure via the food chain as assessed in this study.
- Finally, this study identifies 110 substances that are not listed in any of the sources and were therefore not yet assessed for their risk in the food chain. Most likely, listings (i.e. prioritisation for risk assessments or other evaluations) are largely based on harmonised classifications and therefore tend to overlook hazardous properties identified in other classifications. In this context, classifications in REACH registration dossiers provide important additional information.
- Overall, the 212 priority substances can generally be considered 'emerging chemical issues' (see section 1 for definitions). They are classified for relevant toxic hazards and are predicted to result in exposure of humans via the food chain. However, the data basis for exposure is too limited to conclude whether they actually present 'emerging chemical risks' in the food chain. Substance-specific evaluations of the 102 priority substances included in at least one of the lists may show that (a) they do actually represent an 'emerging chemical risk', (b) there is no risk at current exposure levels or (c) that the listing does not allow concluding on the risk from exposure via the food chain. The 110 substances not included in any of the list clearly represent an 'emerging chemical issue' and there are no other assessments that would allow a conclusion on whether they constitute an 'emerging chemical risk'.
- Ultimately, this study establishes a link between a chronic health hazard and possible exposure of humans via the food chain. For the majority of the 212 priority substances, such a link has not been previously recognised.

The in-depth evaluation in section 3.5 will further illustrate these issues for a limited number of substances.

3.4.6. Summary and discussion

Figure 41 summarises the approach to prioritisation leading to the final selection of 212 priority substances. Out of the total of 2 336 substances, 212 substances (9.1 %) are prioritised for further evaluation.

[90] Implemented by Commission Regulation (EU) 2017/776 of 4 May 2017 (the 10th Adaptation to Technical Progress (ATP) of the CLP Regulation) that entered into force on 1 December 2018. Since this harmonised classification was not in force at the time of extraction of the classification information, these substances were assessed by the joined classification.

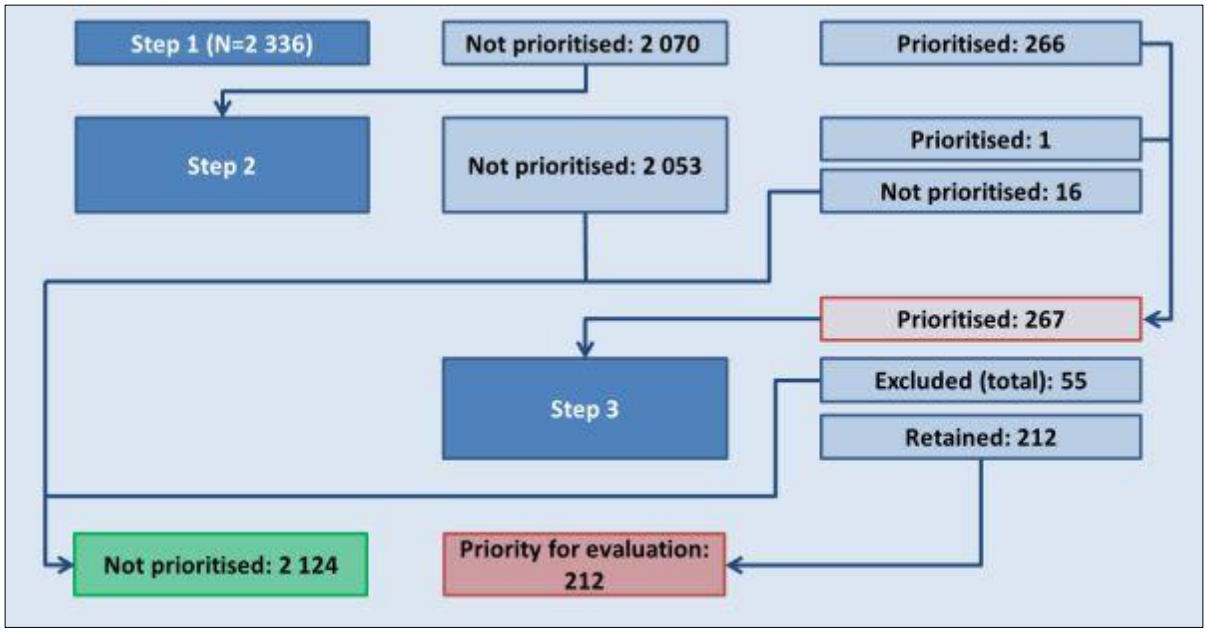


Figure 41: Prioritisation workflow with number of prioritised substances.
See section 3.4.4 for details on steps 1-3.

The following sections discuss the assessment in the different blocks and the overall result, focussing on the reliability of the data.

Discussion of Scores A (environmental release) and B (biodegradation)

Apart from the general limitations discussed in sections 3.2.1 and 3.2.2, the impact of both of these blocks is limited in the approach applied, since the Pivot table selection prioritises substances that have high scores in either block. In addition, the following approaches ensure that only few substances (if any) are excluded because of their scores in these two blocks:

- All 283 substances with a Toxicity Score of 10 and a Score C > 5 have been assessed in detail, i.e. irrespective of their scores in block A and B. Additional manual evaluations of the 17 substances with Score A < 5 and Score B < 5 have identified only a single substance for further evaluation, since Score A may be an underestimate. While Score B was not checked against experimental data, the remaining substances produced at higher tonnages are all exclusively used as intermediates, monomers in polymer production or similar applications that are potentially associated only with low releases to the environment.
- Lowering the cut-off for Score A in the Pivot table selection from Score A > 5 to Score A > 3 would only lead to the inclusion of six more substances (see section 3.4.2).

The exclusion of 48 substances representing petroleum products in step 3 lowers the fraction of substances registered at high tonnages (and therefore of substances with high Scores A). However, the 212 priority substances for further evaluation are characterised by a high fraction of substances that are predicted to be persistent due to little or no biodegradation (Score B > 5; N=171, 81 %), with the majority predicted not to be biodegradable (Score B = 10; N=155, 73 %; see Appendix G for details).

Only 6/212 substances were assigned a default Tonnage Score (2.8 %) and only 5 substances were assigned a default ERC Score (2.4 %)[91]. None of the 212 priority substances was assigned a default Score for both elements of block A.

[91] A default Tonnage Score was assigned if the tonnage data were confidential and a default ERC Score was assigned, when no information on ERCs could be extracted (see section 2.2.1).

Discussion of Score C (bioaccumulation)

The general limitations of the assessment for block C are discussed in section 3.2.4. Due to these limitations, all 2 124 substances not prioritised after step 3 were further analysed. Of these,

- 1 810 substances (85 %) are not classified for any of the four toxicity endpoints; most of these (N=1 610) are not classified in any classification, while the remaining 200 substances were classified in other classifications that were considered not reliable or could not be assessed in detail (according to the approach described in section 2.3);
- 314 substances (15 %) are classified for relevant toxicity endpoints; among these,
  - 176 substances are predicted to be readily biodegradable (Score B = 1) and
  - 138 substances are predicted not to be readily biodegradable (Score B > 5), of which
    - 28 substances have a Score A < 5 and
    - 110 substances have a Score A > 5.

Among these 110 substances, 36 substances were excluded from prioritisation in step 3, because they represent petroleum products (N=34) or because the toxicity classification was impacted by an impurity (N=2).

For the remaining 74 substances (also see below Table 44), the decision of non-prioritisation is exclusively due to a Score C < 5 (Score C = 1: N=23, Score C = 3, N=51). Due to the uncertainty of the bioaccumulation assessment, these 74 substances were further evaluated using the screening criteria for bioaccumulation in 'air-breathing organisms' (log Kow > 2 AND log Koa > 5) of the ECHA Guidance on PBT/vPvB assessment (ECHA, 2017a). The basis of these criteria is described in more detail in section 3.2.4, where the comparison for the complete dataset is reported.

Among these 74 substances, 12 substances (16 %) fulfil these criteria and 8 of these are petroleum products assigned an identical SMILES notation[92] (also see discussion in section 3.4.4). The remaining 4 substances are all prioritised in WS1 and WS2, because they have high scores in all blocks except block C. With respect to bioaccumulation in fish, the screening criterion is defined as log Kow > 4.5 irrespective of log Koa (ECHA, 2017a). Only 6/74 substances (8.1 %) fulfil this criterion and 4 of these substances are petroleum products.

These data suggest that the number of substances disregarded based on the ACC-HUMAN steady result is small, if petroleum products are excluded based on the justification presented in section 3.4.4. However, we consider the ACC-HUMANsteady results to be more reliable than the assessment based on simple screening criteria for partitioning coefficients, e.g. due to the inclusion of biotransformation in ACC-HUMANsteady modelling.

The six substances that (a) do not represent petroleum products and (b) meet the screening criteria for bioaccumulation either in air-breathing organisms or aquatic organisms according to the ECHA Guidance on PBT/vPvB assessment (ECHA, 2017a) are shown in Table 43 together with information from REACH registration dossiers on bioaccumulation (bioconcentration factors (BCF) in fish, where available).

[92] The SMILES notation for these substances represents naphthalene (CAS No.: 91-20-3).

Table 43: Information on bioaccumulation from the REACH registration dossiers for substances fulfilling ECHA's screening criteria (except petroleum products).

CAS No.	Name	BCF_{exp}[(a)]	BCF_{est}[(a)]
Substances meeting the screening criteria for bioaccumulation in air-breathing organisms			
68391-11-7	Pyridine, alkyl derivs.	No data: log Kow (experimental) 2.1 and 2.39	
91-20-3	Naphthalene	23-168	
91-66-7	N,N-diethylaniline	(1) 44-168; (2) 30-95	71
99-97-8	N,N-dimethyl-p-toluidine	No data	33
Substances meeting the screening criteria for bioaccumulation in aquatic organisms			
68526-56-7	Alkenes, c9-11, c10-rich	No data	10 – 174[(b)]
4904-61-4	1,5,9-Cyclododecatriene	1 920-14 800	No data

(a): Experimental (BCF_{exp}) from reliable studies and estimated (BCF_{est}) bioconcentration factors (BCF) are shown.
(b): A higher value of 18 000 for a C15 compound is also reported; the range reported refers to all other compounds.

With the exception of 1,5,9-cyclododecatriene, there is little indication that these substances may be bioaccumulating in fish. Bioaccumulation in air-breathing organisms is not reported in the REACH registration dossiers, since this criterion was only recently introduced in the ECHA Guidance. However, the four substances meeting the screening criteria for air-breathing organisms were all predicted in this study not to accumulate in food. Interestingly, the log Koa values for these four compounds are only slightly above the cut-off of 5.0 (log Koa 5.04-5.72). As discussed in section 3.2.4, the criterion of log Koa > 5 may be very conservative.

These evaluations suggest that – if at all – only a small fraction of relevant substances (i.e. excluding petroleum products) may have been excluded on the basis of the bioaccumulation assessment alone.

Discussion of Toxicity Score

Overall, 203 of the 212 prioritised substances (96 %) have reliable toxicity data, since the assessment is based on harmonised classifications (N=77, 36 %), IARC classifications (N=11, 5.2 %), joint classifications in REACH registration dossiers (N=97, 46 %), individual classifications in REACH registration dossiers (N=15, 7.1 %) or other classifications considered reliable, because a corresponding classification is also proposed within a EU legal framework (N=3, 1.4 %)[93]. For the remaining 9 substances (4.2 %), the Toxicity Score of 10 is considered more uncertain since the classification is based on other classifications supported by a limited evaluation of toxicity data (see sections 2.3.5 and 3.3.5).

As shown in section 3.4.4, substances for which the toxicity classification is impacted by impurities were excluded from prioritisation. This increases the overall confidence in the prioritisation approach. However, it must be noted that the decision of non-prioritisation is exclusively dependent on the Toxicity Score of 1 for 517 substances, since these have high score in all other blocks (also see below Table 44). The majority of these substances (N=470, 91 %) are not classified in any classification for any of the four endpoints of interest. For these substances, it can be concluded that there are currently no indications that they represent a hazard in relation to the four endpoints covered in this assessment. In relation to the remaining 47 substances,

- the majority (N=41) was classified for at least one of the four endpoints, but this classification was only supported by two or less notifications and these substances were therefore assigned an initial Toxicity Score of 1; the toxicity data were checked for 25 of these 41 substances, since they had very high scores in blocks A-C according to the criteria defined in section 2.3.5 and the initial Toxicity Score of 1 was confirmed in all cases;

[93] See section 2.3 for definitions of the different classifications; see section 3.3.5 for the three other classifications considered reliable.

- the remaining 6 substances were initially assigned a Toxicity Score of 10, but this was not confirmed after checking the toxicity data (see sections 2.3.5 and 3.3.5).

These evaluations show that the confidence in the Toxicity Score of 1 for these 517 compounds is high in most cases. It should be emphasised that the toxicity assessment reflects current knowledge and these substances may be seen as a repository, which could be checked in the future for new information (e.g. classification for the four endpoints). This may be warranted, since these substances meet all other criteria of the Pivot table selection (i.e. scores > 5 in blocks A, B and C). To facilitate such future evaluations, data on these 517 substances are made available (see section 5).

The data presented above also show that 112 of the 212 priority substances (53 %) are assigned a Toxicity Score of 10 due to classifications submitted by registrants in the REACH registration dossiers (i.e. 97 joint and 15 individual classifications). It must be reiterated that harmonised and IARC classifications were checked first in a hierarchical approach (see section 2.3) and classifications from REACH registration dossiers were only used for substances that did not have harmonised or IARC classifications for any of the four endpoints. This observation demonstrates that this study made full use of the classifications generated under REACH by registrants. These substances would not have been prioritised in an approach that would have limited itself to the use of harmonised and IARC classifications only.

Overall prioritisation results

While the prioritisation approach presented above already addressed the substances excluded from prioritisation at the various stages, it is meaningful to characterise the entire set of substances with respect to prioritisation. Table 44 shows a matrix reflecting the number of substances for each combination of scores in the four blocks. These data show that the combinations can be broadly divided into the following three groups:

- 1 479 of the 2 336 substances (63 %) have a score < 5 in two or more blocks. These figures are shown in italics in Table 44 note that they include one substance (hydroquinone) that was prioritised because detailed analyses indicate that Score A may be an underestimate (see section 3.4.3;
- 591 substances (25 %) have a score < 5 in only one block:
  - 74 substances in block C only; these substances were already discussed above;
  - 517 substances in the toxicity block only; also discussed above.
- 266 substances (11 %) are initially prioritised; these figures are shown in bold in Table 44.

Table 44: Summary of the distribution of all 2 336 substances (upper part) and the 212 priority substances (lower part)

All 2 336 substances									
Score A		<5				**>5**			
Score B		<5		**>5**		<5		**>5**	
Score C		<5	**>5**	<5	**>5**	<5	**>5**	<5	**>5**
Toxicity Score	1	*56*	*89*	*91*	*301*	*282*	*339*	*135*	517
	10	*15*	*17*[(a)]	*23*	**101**	*131*	**54**	74	**111**
212 prioritised substances									
Toxicity Score	**10**		**1**[(a)]		**96**		**40**		**75**

Numbers in italics indicate that these substances have scores < 5 in two or more blocks; bold numbers indicate that these substances have been initially prioritised (N=267, see Figure 18) in the upper part and simply reflect the 212 priority substances in the lower part.
[(a)]: One substance in this group (hydroquinone) was prioritised in step 2 above, since Score A is likely to be an underestimate (see section 3.4.3).

The lower part of Table 44 shows the 212 final priority substances in their corresponding group. It is evident that – compared to the 266 substances initially prioritised – most substances are excluded in the group with Scores A > 5. This reflects the fact that many petroleum products were excluded, which have very high tonnages and therefore very high Scores A (see Appendix G for details).

Overall, this evaluation prioritises 212 substances for further evaluation. The discussion above demonstrates that meaningful results are obtained to the extent possible within such a screening procedure. The fact that all prioritised substances have scores > 5 in at least three of the four blocks[94] and 75/212 substances (35 %) have scores > 5 in all four blocks increases the confidence in the prioritisation.

Within the limitations of such a screening approach, it must be emphasised that the prioritisation can never be complete in the sense of identifying all potential candidates for further evaluation.

Correlation of scores

In order to test whether the scores in all blocks assessed are independent of one another, correlation coefficients between scores were calculated (see Appendix H for full details). The evaluation shows that there is low correlation between scores in individual blocks. A maximum correlation coefficient (R) of 0.353 was calculated for the correlation between Score B and Score C (for all other correlations $R \leq 0.15$). This finding is not unexpected, since substances showing little tendency to be biodegraded by microorganisms in the environment may also be more resistant to metabolism by plants and livestock.

Further analyses of the correlation between Score B and Score C showed that 76 % of the substances predicted to be poorly biodegradable (Score B > 5), were also predicted to bioaccumulate in food, while 24 % were predicted not to bioaccumulate. In contrast, half of the substances predicted to be readily biodegradable in the environment were predicted to bioaccumulate in food, while the other half was predicted not to bioaccumulate. These data suggest that poor biodegradation is a slightly better predictor of the bioaccumulation potential in food than ready biodegradation.

Overall, this evaluation shows that there is generally low correlation between most of the scores. While there may be some correlation between scores B and C, the overall correlation is poor. In addition, even for the substances predicted not to be biodegradable at all (Score B = 10), 21 % are predicted not to bioaccumulate in food. Full details of these evaluations are presented in Appendix H.

These findings increase the confidence in the applied approach and indicate that the results obtained are meaningful.

3.5. In-depth evaluation

3.5.1. Selection of substances for the in-depth evaluation

The different lists of sources screened (see section 2.5.1) include a total of 5 823 substances, of which 5 781 are identified by CAS numbers. More than half of the 212 substances prioritised in section 3.4 are not listed in any of these sources (N=110). Most of the remaining substances are listed in two or more sources as shown in Table 45.

[94] There is only a single exception. In this case, Score A < 5 is considered to be an underestimate as explained in section 3.4.3.

Table 45: Overview of substances already assessed among the 212 priority substances.

	No. of substances	Percentage
Not mentioned in any source	110	52 %
EFSA OpenFoodTox only	14	6.6 %
Authorisation List only	0	0 %
Restriction List only	1	0.47 %
CoRAP only	15	7.1 %
PACT List only	6	2.8 %
Candidate List only	11	5.2 %
EU RAR	2	0.94 %
Biocides	1	0.47 %
Mentioned in two sources	42	20%
Mentioned in more than two sources	10	4.7 %
Total	212	100 %

Approach 1: High-ranking substances not listed

As shown in Table 45, 110 of the 212 priority substances are not listed in any of the sources evaluated. From these 110 substances, those substances are selected that rank high in the weighting scenarios. Note that substances with identical total scores in a weighting scenario are assigned identical ranks (i.e. there are several substances assigned rank 1, rank 2 etc.; see section 2.5). In order to illustrate the selection and resulting number of substances, a Pivot table is used.

Figure 42 shows the selection of substances up to rank 48, a cut-off chosen in a pragmatic approach to select the highest ranking substances. Note that ranking is identical in WS1 and WS2 in these higher ranks. While this selects 51 substances in total (details not shown) since some ranks are assigned to multiple substances, 24 substances are not listed in any of the sources evaluated (see top left box in the figure; also see the explanation below the figure for 'reading' this Pivot table selection). The finding that more than half of the substances (N=27) are listed in at least one of the sources evaluated is not surprising, since some of the prioritisation criteria applied in this study are also used in other schemes (e.g. high tonnage, persistence and toxicity). The data also show that the toxicity score is considered to be of low reliability for 4 of these 24 substances (17 %), a fraction that is considerably higher than for all priority substances (9/212, 4.2 %; see section 3.4.5).

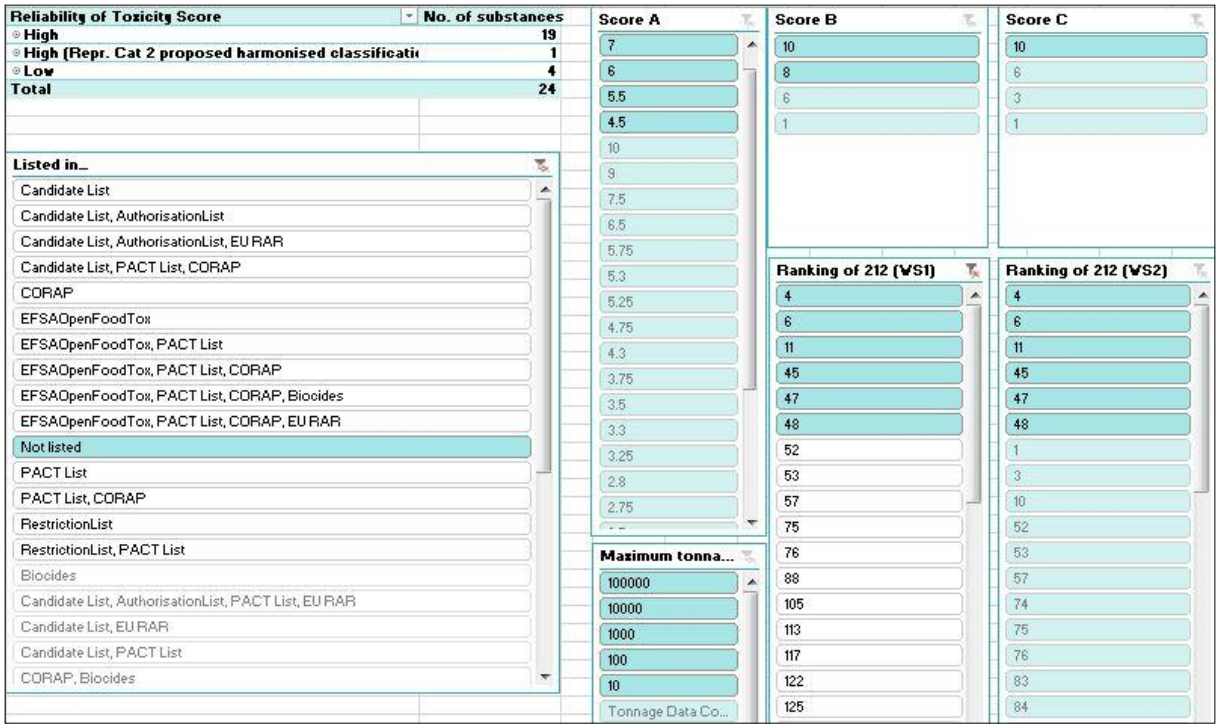


Figure 42: Selection of high-ranking substances not listed in any source among the 212 priority substances.
The upper left list identifies the number of substances selected, differentiated by the reliability of the toxicity score. The criteria set can be identified by a red 'x' in the top right corner of each parameter. The values observed for these substances are highlighted in each parameter box. In this selection, substances up to rank 48 are selected (set for WS1, but identical in WS2) as well as those that are not listed in any of the sources evaluated.

The results demonstrate that these 24 substances are characterised by maximum scores in block C and very high scores of 8 or 10 in block B with moderate scores in block A (note that all 212 substances have a Toxicity Score of 10, since this was a requirement for selection as priority substance). In addition, at least some of these substances are registered at high tonnages (maximum of 100 000 tpa).

After exclusion of the four substances with a low reliability of the toxicity score, 20 substances remain in the selection. These substances are not listed in any of the sources evaluated, but are ranking high in the weighting scenarios.

Approach 2: Substances listed in defined sources only

The second approach started from substances listed in defined sources only. As described in section 2.5, listing in some sources may not indicate that the substance has been assessed in-depth. In other cases, the assessment covered by the listing may be outdated. The selection shown in Figure 43 identifies 56 substances with a wide range of Score A (1.25-9) and all possible Scores B. By definition, all substances have a Score C of 6 or 10 and a Toxicity Score of 10 (see section 3.4). The maximum tonnage is in the low (10 tpa) to high range (1 000 000 tpa) and the ranks in WS1 and WS2 also show a wide range (not all shown in Figure 43). Two substances have a toxicity score assigned a low reliability.

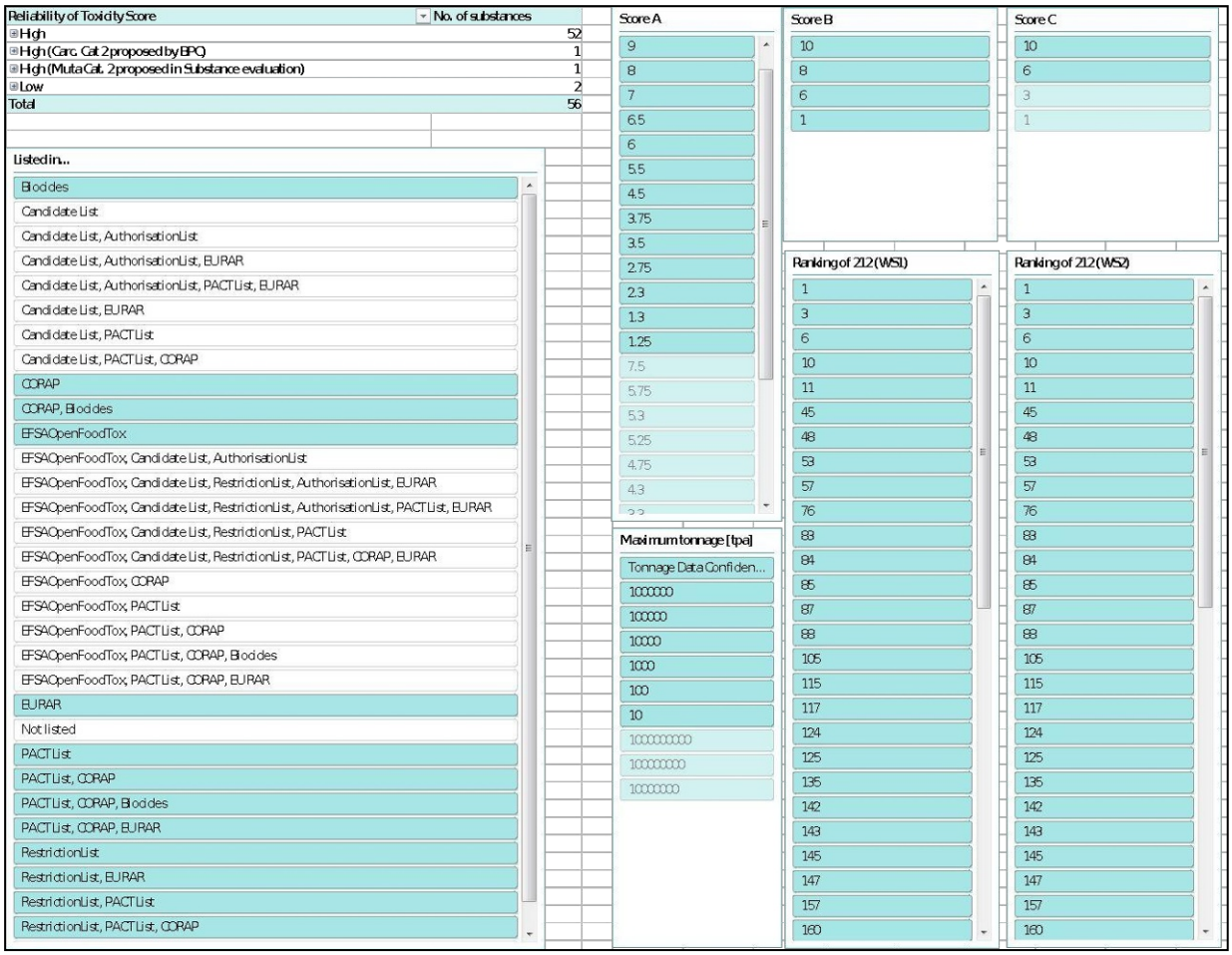


Figure 43: Selection of substances in approach 2 – step 1.

In order to further limit the number of substances, several options can be envisaged, such as focussing on substances with very high scores in blocks A-C or on those with very high tonnages. This can be achieved by again applying the ranking in the weighting scenarios. Figure 44 shows the results, when the selection is limited to substances up to rank 84. This rank was chosen to obtain a similar number of substances as in approach 1. Again, ranking is identical in WS1 and WS2 in these higher ranks. This cut-off selects 23 substances, of which only one has a low reliability assigned to the toxicity score. The data show that Scores B and C are high for selected substances and very low Scores A of 1.25 and 1.3 are eliminated from the selection. Substances with a maximum tonnage of 1 000 000 tpa are retained.

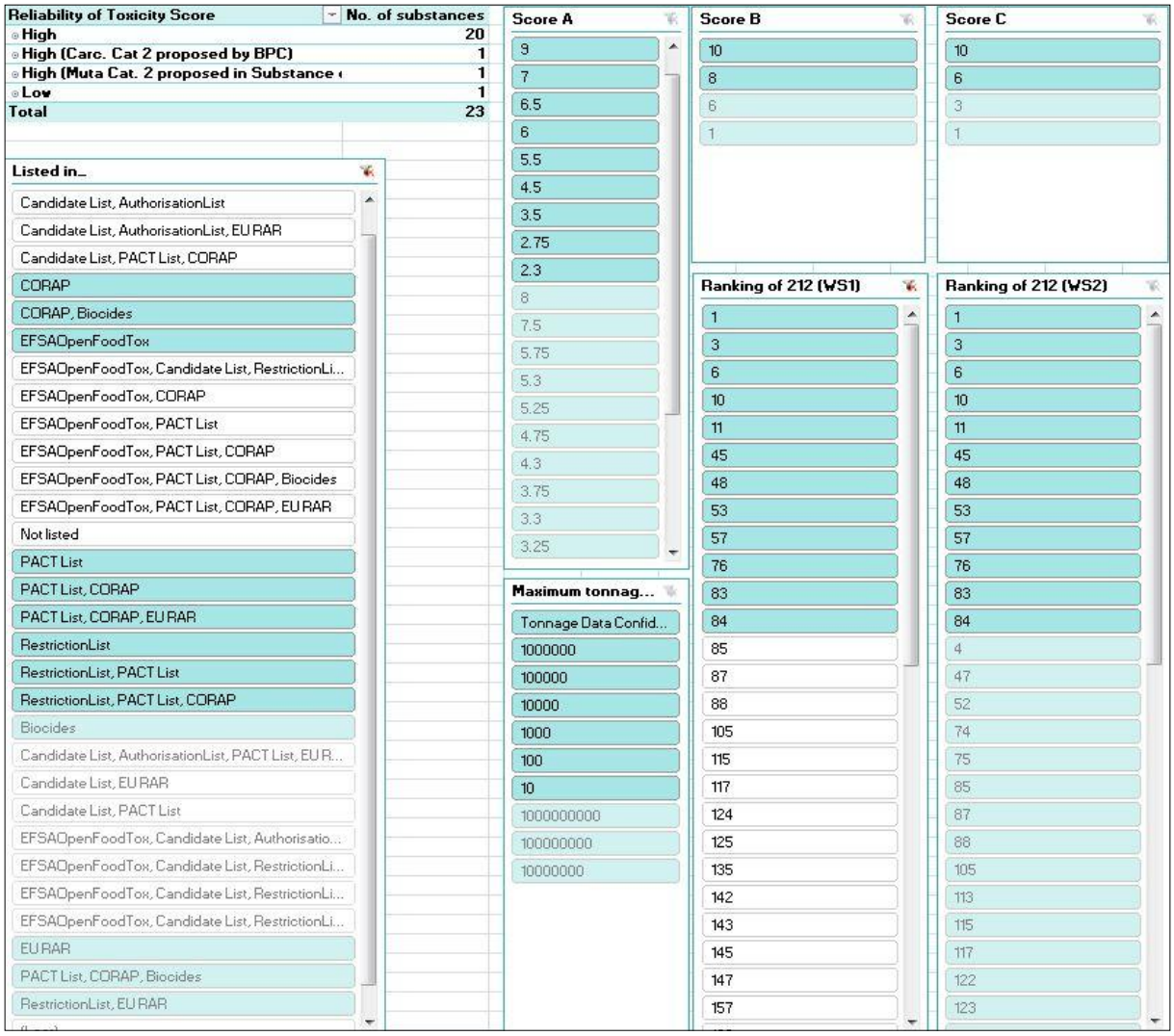


Figure 44: Selection of substances in approach 2 – step 2.

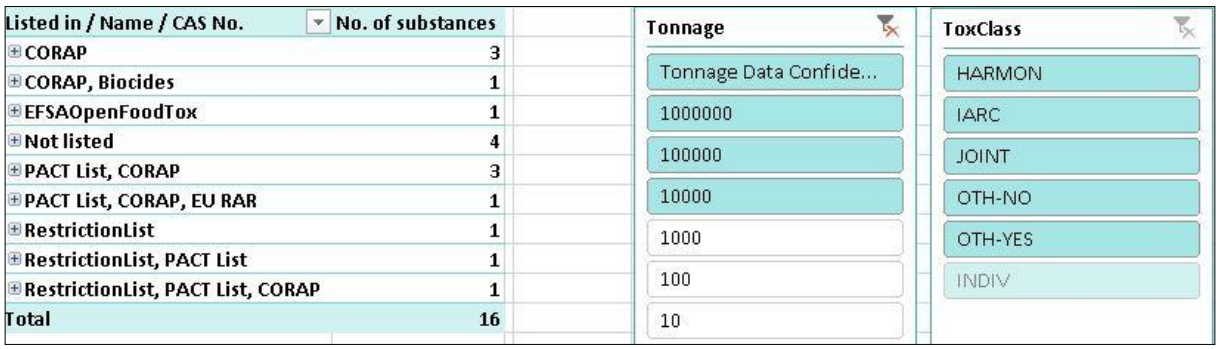
After exclusion of the substance with a low reliability of the toxicity score, 22 substances remain in the selection. These substances are listed only in defined sources (potentially not reflecting an in-depth assessment of their presence in food/feed) and are ranking high in the weighting scenarios.

Final selection for in-depth evaluation

Overall, the two approaches described above identified 42 substances for in-depth evaluation. About half of these are not listed in any of the sources evaluated, while the other half is listed only in defined sources. The toxicity score is considered reliable for all substances, since substances with toxicity scores considered to be of low reliability were excluded in both approaches above. All of these 42 substances rank high in the two weighting scenarios and can therefore be considered to be particularly relevant.

In order to further reduce this list to 10 substances for in-depth evaluation it is tempting to select those with maximum scores in blocks B and C and very high scores in block A. However, given the limitations discussed in sections 3.2 and 3.4, the scores in individual blocks should not be overemphasised. The maximum tonnage was therefore taken as an additional criterion, since a high tonnage may lead to environmental exposure, even if a substance is not used in wide-dispersive uses, such as down-the-drain products. Note again that all 42 substances have high scores in blocks B-C and the toxicity block and only Score A shows a wide range; see Figure 42 and Figure 44). In a first step, all substances with a maximum REACH registration tonnage of 10 000 tpa or more (or without tonnage information ('tonnage data confidential'); this relates to a single substance) are selected.

A new Pivot table was constructed to provide additional information on selected substances. Figure 45 shows that this limitation to a maximum tonnage of 10 000 tpa or more reduces the number of substances from 42 to 16, of which four are not listed in any source, while the remaining substances are listed in a single source (N=5) or several sources (N=7). The data also show that (a) substances with a toxicity classification in an individual REACH registration ('INDIV' in the parameter 'ToxClass') and (b) substances listed solely in the PACT list are no longer selected when including high tonnages only. Finally, the toxicity classification of these 16 substances is derived from different sources.



Listed in / Name / CAS No.	No. of substances
CORAP	3
CORAP, Biocides	1
EFSAOpenFoodTox	1
Not listed	4
PACT List, CORAP	3
PACT List, CORAP, EU RAR	1
RestrictionList	1
RestrictionList, PACT List	1
RestrictionList, PACT List, CORAP	1
Total	16

Figure 45: Final selection of substances for in-depth evaluation – step 1.

These substances could be further reduced by application of a higher tonnage threshold. However, exclusion of substances registered with a maximum tonnage of 10 000 tpa would result in only 6 substances remaining. In addition, manual inspection of the 16 substances initially selected is feasible so that no further reduction by Pivot table selections is required. Additional information for these substances is shown in Table 46. The data illustrate that four diisocyanates are among the 16 substances and all of these are registered at high tonnages. These substances are subject to a variety of measures under the REACH Regulation. While these measures do not necessarily reduce emissions to the environment from industrial sources (e.g. since the restriction is only related to consumer uses), it does not appear to be meaningful to identify these substances as potential emerging risks. This conclusion is also indicated by the fact that these compounds are reactive chemicals that are expected to undergo rapid transformation once released to the environment. Melamine is another substance registered at high tonnages, but the substance has already been assessed in detail by EFSA[95]. However, EFSA did not specifically address human exposure to melamine via the environment, since the Authority did not consider the substance to be persistent and bioaccumulative (based on the low log Kow). In contrast, the present study rated melamine as bioaccumulative on the basis of ACC-HUMANsteady modelling. In addition, data in the REACH registration dossier considered the substance not to be readily biodegradable and potentially as not being inherently biodegradable, confirming the Score B of 10 assigned in this study based on predicted biodegradation data. Since a related compound (melamine cyanurate) is included in the 10 substances selected for in-depth evaluation (see below), melamine will be assessed together with melamine cyanurate. This approach is also meaningful, since (a) both substances were evaluated in block B and block C based on the same SMILES notation (i.e. the one for melamine) and (b) melamine cyanurate is expected to release melamine under environmental conditions (see the following box).

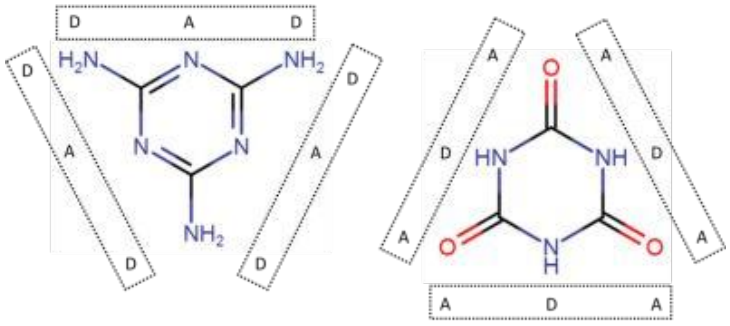
[95] See https://www.efsa.europa.eu/de/efsajournal/pub/1573, accessed May 2018.

Box: chemistry of melamine cyanurate

According to WHO (2009), melamine cyanurate is not simply a salt between an amine base (melamine) and a weak acid (cyanuric acid) but rather a strong complex formed by hydrogen donor-acceptor pairs and aromatic ring stacking interactions. Based on spectroscopic studies the enamine form of melamine and the keto form of cyanuric acid are the resonance structures favoured in acidic to neutral solutions.

Each melamine monomer provides three unshared pairs of electrons (hydrogen bond acceptors (A)) by the sp^2 hybridized nitrogen atoms of its triazine ring and six hydrogen bond donors (D) by its amine residues. This results in the geometry of a triangle, with each side constituted by the sequence D-A-D. Cyanuric acid in its keto configuration provides three hydrogen bond donors (sp^3 hybridized nitrogen atoms of the ring) as well as six hydrogen acceptors sites (two electron pairs per carbonyl oxygen) in the geometry of a triangle, with each side constituted by the sequence A-D-A. Importantly, the sequence is in complementary orientation to the one of melamine.

In consequence, each triangular D-A-D side of melamine can interact with each triangular A-D-A side of cyanuric acid (see structures below, modified from WHO (2009)). This explains the extraordinary strong interaction between melamine and cyanurate leading to self-assembly into a stable crystal lattice. In addition, triazine aromatic ring stacking interactions further facilitate such an assembly.



Melamine Cyanuric acid

As a result, the water solubility of melamine cyanurate (2.7 mg/L at 20°C, pH 6-7.5) is about three orders of magnitude lower than the one of melamine (3480 mg/L at 20 °C, pH 7.7) and cyanuric acid (2000 mg/L at 25°C, pH 7.0; all values taken from the REACH registration dossiers).

Upon dissolution of melamine cyanurate - which is expected finally to occur under environmentally relevant conditions (dilute solutions) - melamine and cyanuric acid are set free and will have their individual environmental fate based on their molecular properties as given in published REACH registration dossiers: cyanuric acid is expected to degrade at the bottom of surface waters, in sediment and soils, while melamine is expected to persist. Adsorption to solid matter is expected to be low for both compounds.

Piperonyl butoxide (CAS No.: 51-03-6) has been evaluated in the context of its use in biocidal products and has been approved for the use in product type 18 (insecticides, acaricides and products to control other arthropods)[96]. This evaluation also led to the proposal as a suspected carcinogen (Carc. Cat. 2) by ECHA's Biocidal Product Committee in its opinion published in June 2016[97], a fact that led to the assignment of a Toxicity Score of 10, while the initial Toxicity Score was 1 (see section 3.3.5). This opinion also noted with respect to the authorisation of biocidal products containing piperonyl butoxide as an active substance: '*An assessment of the risk in food and feed areas may be required at product authorisation where use of the product may lead to contamination of food and feeding stuffs*' [98]. No biocidal product containing piperonyl butoxide has yet been authorised[99]. The

[96] https://echa.europa.eu/information-on-chemicals/biocidal-active-substances?p_p_id=echarevbiocides_WAR_echarevbiocidesportlet&p_p_lifecycle=0&p_p_col_id=column-1&p_p_col_pos=1&p_p_col_count=2&_echarevbiocides_WAR_echarevbiocidesportlet_rml_id=100.000.070, accessed June 2018.
[97] https://echa.europa.eu/documents/10162/610a1218-bb3d-4ec7-935b-2ee581bf97c7, accessed June 2018.
[98] https://echa.europa.eu/documents/10162/610a1218-bb3d-4ec7-935b-2ee581bf97c7, accessed June 2018.

more detailed assessment report on the approval of piperonyl butoxide as an active substance in product type 18 biocidal products noted that the substance should be considered as a potential carcinogen with a threshold mode of action (NOAEL for carcinogenic effect in mice of 30 mg/kg bw/day (LOAEL 100 mg/kg bw/day)[100].

Piperonyl butoxide was also evaluated by JMPR, with the last toxicological evaluation performed in 1995 and the last evaluation of residue and analytical aspects performed in 2002. NOAELs for rodents from several studies were found to be 30 mg/kg bw/day (from the carcinogenicity study mentioned above) or higher, while a lower NOAEL of 16 mg/kg bw/day was observed in a 1-year toxicity study in dogs. This formed the basis of setting the ADI of 0.2 mg/kg bw/day (safety factor 100)[101]. JMPR also derived MRLs for several food/feed items in 2002, which related to the use of piperonyl butoxide in insecticides used in the production or processing of food/feed[102].

While it is noted that these assessments do not necessarily consider human exposure via the environment (e.g. from formulation of insecticide products), piperonyl butoxide is not selected for in-depth evaluation, since this substance has been assessed and provisions are in place or foreseen to consider possible human intake from food. Note that this was the only substance, for which the tonnage information was confidential.

Table 46: Additional information for 16 substances initially selected.

CAS No.	Name [Synonyms]	Listed in	ToxClass	Tonnage
Initially proposed for in-depth evaluation				
68937-41-7	Phenol, isopropylated, phosphate (3:1)	Not listed	JOINT	10 000
108-78-1	Melamine	EFSA OpenFoodTox	IARC	1 000 000
37640-57-6	1,3,5-triazine-2,4,6(1h,3h,5h)-trione, compd. with 1,3,5-triazine-2,4,6-triamine (1:1) [Melamine cyanurate]	Not listed	JOINT	100 000
121-82-4	Hexahydro-1,3,5-trinitro-1,3,5-triazine [RDX; Hexogen]	Not listed	JOINT	10 000
80-51-3	Benzenesulfonic acid, 4,4'-oxybis-, 1,1'-dihydrazide	Not listed	JOINT	10 000
108-45-2	1,3-phenylenediamine	CORAP	HARMON	10 000
119-47-1	2,2'-methylenebis(6-t-butyl-4-methylphenol)	CORAP	JOINT	10 000
2386-87-0	7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate	CORAP	OTH-YES	10 000
101-02-0	Triphenyl phosphite	PACT List, CORAP	JOINT	10 000
13674-87-8	Tris(1,3-dichloro-2-propyl) phosphate	PACT List, CORAP, EU RAR	HARMON	10 000
68479-98-1	Diethylmethylbenzenediamine	PACT List, CORAP	HARMON	10 000
Not proposed for in-depth evaluation				
101-68-8	4,4'-methylenediphenyl diisocyanate	Restriction List, PACT List, CORAP	HARMON	1 000 000
5873-54-1	2,4'-methylenediphenyl diisocyanate	Restriction List, PACT List	HARMON	100 000
2536-05-2	2,2'-methylenediphenyl diisocyanate	Restriction List	JOINT	10 000
26471-62-5	Toluene diisocyanate	PACT List, CORAP	HARMON	1 000 000
51-03-6	2-(2-butoxyethoxy)ethyl 6-propyl-piperonyl ether [Piperonyl butoxide]	CORAP, Biocides	OTH-NO	TDC[(a)]

[(a)]: Tonnage Data Confidential

[99] https://echa.europa.eu/information-on-chemicals/biocidal-products, searched on 22 June 2018.
[100] http://dissemination.echa.europa.eu/Biocides/ActiveSubstances/1344-18/1344-18_Assessment_Report.pdf, accessed June 2018.
[101] http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/Report1995.pdf, accessed June 2018.
[102] http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/Report_2002.pdf, accessed June 2018.

Among the substances initially proposed, 'phenol, isopropylated, phosphate (3:1)' ('ip-TPP' hereafter) is a special case, since it is registered as a UVCB substance, but has been retained in the selection, since the structure assessed in this study was considered representative for this compound (see Table 85 in Appendix I). The following box provides additional information on this substance and its constituents.

Box: ip-TPP

The substance assessed in this study (CAS No.: 68937-41-7) is registered as an UVCB consisting of up to 19 constituents. According to the REACH registration data, this UVCB substance contains constituents that have phenyl moieties both with and without an isopropyl group attached. In addition, constituents vary by the number of isopropyl groups attached to a single phenyl moiety and the position of the isopropyl group(s). While triphenyl phosphate (i.e. no isopropyl group attached to any of the three phenyl moieties; CAS No.: 115-86-6) is also one of the constituents, this assessment considers constituents with at least one isopropyl attached to a phenyl moiety. Triphenyl phosphate is registered under REACH and the substance is not classified for any human health hazard.

It appears that tris(isopropylphenyl) phosphate, i.e. an isopropyl group at every phenyl moiety, has been assigned the CAS No.: 68937-41-7 in some cases and the CAS No.: 26967-76-0 in other cases. The substance name tris(isopropylphenyl) phosphate does not specify the position of the isopropyl groups, but in some cases the CAS No.: 68937-41-7 was used for tris(4-isopropylphenyl) phosphate and the CAS No.: 26967-76-0 was used for tris(2-isopropylphenyl) phosphate (Fisk et al., 2003; Brooke, 2009; Sjögren et al., 2010).

For the modelling approaches in this study, a specific chemical structure (identified by the SMILES notation) was required. The structure used represents tris(4-isopropylphenyl) phosphate, i.e. a substance with one (and only one) isopropyl group attached at para position to all three phenyl moieties. This specific structure has been occasionally assigned the CAS No.: 68937-41-7 in the past (according to (Sjögren et al., 2010)), but is now usually assigned the CAS No.: 2502-15-0 (according to Bergman et al. (2012)). The SMILES notation provided for the reference substance in the REACH registration for ip-TPP (CAS No.: 68937-41-7) corresponds to exactly the same structure. A substance with the CAS No.: 2502-15-0 is not registered under REACH and is also not contained in ECHA's Classification & Labelling Inventory.

As discussed in more detail in the in-depth evaluation sheet for ip-TPP below, the following mono-substituted isopropyl triphenyl phosphates (i.e. isopropylphenyl diphenyl phosphates) may be particularly relevant:
2-Isopropylphenyl diphenyl phosphate (CAS No.: 64532-94-1)
3-Isopropylphenyl diphenyl phosphate (CAS No.: 69515-46-4)
4-Isopropylphenyl diphenyl phosphate (CAS No.: 55864-04-5)
All of these three substances are constituents of the UVCB substance ip-TPP according to REACH registration data, but none of these substances (as identified by their CAS numbers) is contained in any ECHA database as an individual substance.

In a final step, abiotic degradation of the 10 substances initially proposed for in-depth evaluation (see Table 46) was evaluated on the basis of data reported in the REACH registration dossiers. Based on experimental studies on hydrolysis, the following three substances were deselected based on a hydrolysis half-life of less than 2 days:

- Benzenesulfonic acid, 4,4'-oxybis-, 1,1'-dihydrazide (CAS No.: 80-51-3): Hydrolysis half-life at 25 °C: 5.8 h (pH 9) – 9.2 h (pH 4) in a study according to OECD Test Guideline 111.
- – 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (CAS No.: 2386-87-0): Hydrolysis half-life at room temperature: 21 h (pH 4) – 42 h (pH 9) estimated from analytical method development and water solubility studies.
- Triphenyl phosphite (CAS No.: 101-02-0): Hydrolysis half-life at 20 °C: 0.43 h (pH 8.99) – 21.9 h (pH 4.09) in a study according to OECD Test Guideline 111 (14.7 h (pH 7.03) at 12 °C).

Note that this evaluation of hydrolysis data did not apply the detailed criteria discussed in section 2.2.2 (e.g. an evaluation of the hydrolysis products), since this is beyond the scope of this study. The criterion of a hydrolysis half-life of less than 2 days was chosen to reflect rapid hydrolysis in a

pragmatic approach due to the lack of regulatory criteria for this endpoint. These three substances were manually replaced by three substances not listed in any of the sources evaluated as described in section 2.5.1.

Overall, 10 substances are finally selected for in-depth evaluation, with melamine and melamine cyanurate being considered together (i.e. 11 substances altogether). Table 47 summarises the data for these substances. With respect to listings in the EU in the sources evaluated the 11 substances (if melamine and melamine cyanurate are treated separately):

- are not listed in any of the sources evaluated (N=6), of which
  - four substances are classified for repeated dose toxicity only
  - two substances are classified for reprotoxicity (ip-TPP: Repr. Cat. 2; sulfolane: Repr. Cat. 1B)
- are listed in CoRAP only (N=2) or EFSA OpenFoodTox only (N=1),
- are listed in more than one source (N=2).

Table 47: Toxicity endpoint and scores for 10 substances selected for in-depth evaluation

CAS No.	Name [Abbreviation/Synonym]	Listing[a]	Toxicity [b]		Tonnage[c]	Score		
			Endpoint	Basis		A	B	C
121-82-4	Hexahydro-1,3,5-trinitro-1,3,5-triazine [RDX; Hexogen]	Not listed (A1)	STOT RE	JOINT	10 000	4.5	10	10
68937-41-7	Phenol, isopropylated, phosphate (3:1) [ip-TPP]	Not listed (A1)	REPR-STOT RE	JOINT	10 000	7	10	10
37640-57-6	Melamine cyanurate	Not listed (A1)	STOT RE	JOINT	100 000	5.5	10	10
108-78-1	Melamine	EFSA OpenFoodTox (A2)	CARC	IARC	1 000 000	9	10	10
108-45-2	1,3-phenylenediamine	CoRAP (A2)	MUTA	HARMON	10 000	2.3	10	10
119-47-1	2,2'-methylenebis(6-t-butyl-4-methylphenol)	CoRAP (A2)	REPR	JOINT	10 000	7	10	10
13674-87-8	Tris(1,3-dichloro-2-propyl) phosphate [TDCIPP]	PACT, CORAP, EU RAR (A2)	CARC	HARMON	10 000	3.5	10	10
68479-98-1	Diethylmethylbenzenediamine	PACT, CORAP (A2)	STOT RE	HARMON	10 000	2.75	10	10
111-91-1	Bis(2-chloroethoxy)methane	Not listed (MR)	STOT RE	JOINT	100 000	3.3	10	6
126-33-0	Tetrahydrothiophene-1,1-dioxide [Sulfolane]	Not listed (MR)	REPR	JOINT	10 000	7	8	6
3622-84-2	N-butylbenzenesulfonamide [NBBS]	Not listed (MR)	STOT RE	JOINT	10 000	4.5	10	6

[a]: A1: Approach 1; A2: Approach2; MR: Manual replacement (see text for details).
[b]: Endpoint and basis of the classification that led to the assignment of a Toxicity Score of 10 (see section 2.3).
[c]: Maximum of the REACH registration tonnage band (see section 2.2.1).

The data summarised in Table 47 also show that except for melamine (see discussion above) none of these substances is listed in EFSA's OpenFoodTox database. As already indicated, inclusion of a substance in one of the lists evaluated does not necessarily suggest that this substance has been assessed in relation to bioaccumulation in the food chain. For example, 1,3-phenylenediamine (CAS No.: 108-45-2) is listed on the CoRAP for substance evaluation under REACH, but the exposure/risk-related reasons given in the justification document only relate to 'exposure of workers' and 'high (aggregated) tonnage'. Clarification of exposure-related issues may be sought during substances evaluation (not yet finalised), but it is unclear, whether this will involve a more detailed assessment of human exposure via the environment (including exposure from food). As another example, 2,2'-methylenebis(6-t-butyl-4-methylphenol) (CAS No.: 119-47-1) was selected for substance evaluation to clarify concerns about reprotoxicity and endocrine disruption. The substance evaluation performed in 2016 was entirely hazard-based and identified the need for a harmonised classification as a reproductive toxicant (Cat. 1B). A corresponding proposal for a harmonised classification as Repr. Cat. 1B has been submitted for public consultation in October 2018[103], but has not yet been agreed upon at the time of finalisation of this report. The joint classification as a reproductive toxicant (Cat. 2) in the REACH registration document has led to a Toxicity Score of 10 in this study. This example illustrates that a CoRAP listing alone does not necessarily mean that the substance has been assessed in relation to its accumulation in the food chain (also see in-depth evaluation sheet for this substance in section 3.5.2 below).

The data also indicate a mix of those with a harmonised classification (N=3), a joint classification (N=7) and melamine being considered as toxic on the basis of an IARC classification (see sections 2.3.5 and 3.3.5). The Toxicity Score of 10 for these substances is based on several different endpoints or their combinations: carcinogenicity (N=2), mutagenicity (N=1), reprotoxicity (N=3) and repeated dose toxicity (N=6). Six substances are CMR substances and five substances were assigned a Toxicity Score of 10 solely due to repeated dose toxicity (N=11, since melamine and melamine cyanurate are treated separately for the purpose of these analyses).

Table 47 also provides an overview of the scores for blocks A-C for all substances selected for in-depth evaluation (by definition, all these substances have a Toxicity Score of 10). The data show that

- all substances have a Score C of 10 except the 3 substances selected manually as replacements for those being subject to rapid hydrolysis; this observation is not surprising, since these substances are assigned relatively low ranks in the weighting scenarios and were therefore not selected in approach 1 above;
- all except one have a Score B of 10;
- Scores A show a wider range of 2.3-9; the in-depth evaluation will offer the opportunity to analyse whether substances with a low Score A actually occur in the environment (if such data are available);
- all substances with a Score C of 10 except 1,3-phenylenediamine are assigned this maximum score in all three food groups (fish, fruits & vegetables, meat & milk products), while the three substances with a Score C of 6 are assigned this score only in below ground (root/tuber) crops and have Scores C < 5 in all other food/feed items (details not shown; also see section 3.2.4).

The maximum tonnage of these substances is primarily moderate (10 000 tpa), the only exceptions being melamine/melamine cyanurate (1 000 000 and 100 000 tpa, respectively) and bis(2-chloroethoxy)methane (100 000 tpa). This is not surprising, since substances with higher tonnages are more likely to have been prioritised (and assessed) under some other scheme.

Values for log Kow for these 10 substances[104] show a wide range of -1.4 to 9.1, but log Koa values are very high (9.6-11) for the eight substances selected in approach 1 and approach 2 that have a Score C of 10. Substances with a Score C of 6 have lower log Koa values (4.0-6.4), while log Kow values are in a range also observed for those substances with a Score C of 10 (although the maximum log Kow is lower). Table 48 shows the log Kow and log Koa values for the substances selected for in-depth evaluation (Score C is again shown for easier reference).

[103] See https://echa.europa.eu/harmonised-classification-and-labelling-consultation/-/substance-rev/20805/term, accessed October 2018.
[104] Melamine and melamine cyanurate have identical values since the same SMILES notation was assigned to both substances.

Table 48: Log Kow and log Koa values for 10 substances selected for in-depth evaluation

CAS No.	Name/Synonym	log Kow[(a)]	log Koa[(a)]	Score C
121-82-4	Hexahydro-1,3,5-trinitro-1,3,5-triazine [RDX; Hexogen]	0.870	**9.96**	10
68937-41-7	Phenol, isopropylated, phosphate (3:1) [ip-TPP]	**9.07**	**12.0**	10
37640-57-6 108-78-1	Melamine cyanurate Melamine	-1.37	**10.8**	10
108-45-2	1,3-phenylenediamine	-0.330	**6.96**	10
119-47-1	2,2'-methylenebis(6-t-butyl-4-methylphenol)	**6.25**	**12.0**	10
13674-87-8	Tris(1,3-dichloro-2-propyl) phosphate [TDCIPP]	**3.65**	**10.6**	10
68479-98-1	Diethylmethylbenzenediamine	**2.60**	**9.63**	10
111-91-1	Bis(2-chloroethoxy)methane	1.30	**5.10**	6
126-33-0	Tetrahydrothiophene-1,1-dioxide [Sulfolane]	-0.77	4.00	6
3622-84-2	N-butylbenzenesulfonamide [NBBS]	**2.31**	**6.36**	6

[(a)]: All values rounded to two significant figures (also see section 2.2.4); log Kow and log Koa values meeting the criteria in ECHA (2017a) are highlighted in bold.

When compared with the screening criteria for bioaccumulation in air-breathing organisms in the ECHA Guidance on PBT/vPvB assessment (ECHA, 2017a) of log Kow > 2 AND log Koa > 5, five of the substances meet these criteria (four with a Score C of 10, one with a Score C of 6), while the remaining five substances[105] do not meet the criteria. While four of them meet the criterion for log Koa, none of them meets the criterion for log Kow. The finding that substances with low log Kow values are predicted to bioaccumulate was already addressed in section 3.2.4, noting that high log Koa values are found for these substances. As indicated in section 3.2.4, such hydrophilic substances may be taken up in plants. The in-depth evaluation of the 10 substances in section 3.5.2 will further examine this issue in a substance-specific manner.

Discussion

In order to further analyse the selection procedure, high tonnage substances were evaluated in some more detail. Among the 212 priority substances, there are 29 substances with high maximum REACH registration tonnages (100 000 tpa or higher; also see Appendix G), of which

- 8 are included in the Candidate List (and were therefore not selected); 7 of them are also listed in at least one other source (among them 3 substances included in the Authorisation List),
- 7 are included in EFSA's OpenFoodTox database and at least one other list except the Candidate list (and were therefore not selected)
- 14 were not excluded based on these listing criteria; of these
  - 9 substances were initially not selected because the reliability of the toxicity score is low (N=1) or because they do not rank very high in the weighting scenarios (N=8); one of the latter eight substances was subsequently selected manually as a replacement (bis(2-chloroethoxy)methane);
  - 5 substances were initially selected in Approach 1 (N=1) or Approach 2 (N=4) described above. Of these 5 substances, 3 diisocyanates were not proposed for in-depth evaluation (see Table 46), while the remaining 2 substances are selected (melamine as well as melamine cyanurate (evaluated together).

These data demonstrate that most of the 29 high tonnage substances among the 212 priority substances were already assessed or did not rank high in the evaluation. Four of the 29 substances are included in the in-depth evaluation.

Inclusion in the Candidate List with the ultimate aim of inclusion in the Authorisation List and subsequent substitution clearly justifies non-selection for in-depth evaluation, since the corresponding hazard has already been addressed and action taken. This will ultimately also reduce any exposure via the food chain. However, inclusion in EFSA's OpenFoodTox database (as with several of the other

[105] Melamine and melamine cyanurate considered together, since they were assessed based on the same SMILES notation.

sources) does not necessarily imply that a substance has been assessed in-depth for its presence in food. Even if a substance is listed in at least one additional source, this fact does not in itself suggest that such an assessment is available. As shown in section 2.5, this listing criterion was chosen in a pragmatic approach. Therefore, the seven substances not selected due to inclusion in EFSA's OpenFoodTox database and at least one other list were further evaluated. All of these substances do not rank high, since they have a Score B of 1 (N=1), a Score C of 6 (N=1) or both a Score B of 1 and a Score C of 6 (N=5). There is a single substance with a Score C of 10 and a Score B of 10 (4-t-butyl-phenol, CAS No.: 98-54-4). This substance is assigned rank 85 and therefore just misses selection in approach 2. It was already assessed by EFSA (name in OpenFoodTox database: 4-(1,1-dimethylethyl)-phenol) and is included in the list of flavouring substances in Commission Implementing Regulation (EU) No 872/2012. Therefore, selection for in-depth evaluation does not appear meaningful.

The six other substances (phenol, formaldehyde, hydroquinone, ethylene glycol, 1,3,5-trioxane and furfuryl alcohol) are assigned ranks of 120 or higher. Most of these substances and their corresponding risks are well known and have been addressed by EFSA in a variety of evaluations. While these do not necessarily relate to human exposure via the environment (but e.g. exposure through food contact materials), it does not appear meaningful to select these substances for in-depth evaluation.

The approach applied to substance selection excludes four of the five substances that are ranking highest in both weighting scenarios. Apart from piperonyl butoxide (see discussion above), bisphenol A (CAS No.: 80-05-7) and hexabromocyclododecance (CAS No.: 25637-99-4) are excluded, since both substances are included in the Candidate List. A chlorinated paraffin (CAS No.: 63449-39-8) is not selected, since the reliability of the Toxicity Score was rated as low (see section 3.3.5). Melamine is also among these high ranking substances and is selected for in-depth evaluation as discussed above.

3.5.2. In-depth evaluation

General overview

Ten substances were evaluated in-depth and the results are presented per substance in the 'in-depth evaluation sheets' below. Table 49 summarises the results of the in-depth evaluation for the 10 substances. Blocks A and B as well as the classification information were checked against data in the REACH registration dossier (and in the C&L Inventory, where necessary) in order to check whether data are still correct (block A and toxicity) or whether experimental data support the predictions (block B). Data on the occurrence in the environment as well as in food/feed were retrieved from the literature and other sources identified during the data searches (see section 2.5.2). Occurrence of a substance in the environment (e.g. surface water) generally confirms the evaluation in blocks A and B, while occurrence of a substance in food/feed generally confirms the evaluation in block C (see discussion below for exceptions).

The following assignments are used in this summary for each evaluated block (block A, block B, toxicity block as well as for occurrence in the environment and in food/feed):

- YES: Data support the evaluation
  - Blocks A-B and toxicity block: data in the REACH registration dossiers support the scores assigned.
  - Occurrence in the environment: data support the evaluation in relation to presence in environmental media (e.g. surface water) in various locations.
  - Occurrence in food/feed: data demonstrate the occurrence in food/feed in field studies, experimental studies or other studies such as market survey and total diet studies.
- (YES): Data show the occurrence
  - Blocks A-B and toxicity block: data support the scores assigned, but uncertainties remain.
  - Occurrence in the environment: data generally support the evaluation in relation to presence in environmental media (e.g. surface water), but the data reflect specific situations or local conditions. This also includes cases in which the substance has been detected in some studies, but has not been detected in other studies.

  - Occurrence in food/feed: data generally demonstrate the occurrence in food/feed in field studies, experimental studies or other studies such as market survey and total diet studies, but the data are limited, e.g. since they reflect specific situations or do not allow unequivocal assignment of food/feed contamination to pathways via the environment as a source (e.g. if contamination from food contact materials is also possible). This also includes cases in which the substance has been detected in some studies, but has not been detected in other studies.

- NO
  - Blocks A-B and toxicity block: data in the REACH registration dossiers do not support the scores assigned
  - Occurrence in the environment and in food/feed: the substance has been included in measurements, but has not been detected. If this only relates to few measurements, the next category ('???') is assigned.
- ???
  - Blocks A-B and toxicity block: not applicable, since substances in the in-depth evaluation have data for these blocks and unclear situations are not expected.
  - Occurrence in the environment and in food/feed: data are lacking completely, relate to only a few samples or are considered uncertain for other reasons.

Table 49: Summary of in-depth evaluation for 10 substances

CAS No.	Name/Synonym	Score confirmed A	Score confirmed B	Occurrence environment	Occurrence food/feed	Toxicology confirmed
121-82-4	Hexahydro-1,3,5-trinitro-1,3,5-triazine [RDX; Hexogen]	YES	YES	(YES)	YES	YES, STOT RE2 (joint classification) US EPA Carc. Group C (1988)
68937-41-7	Phenol, isopropylated, phosphate (3:1) [ip-TPP]	YES	YES	???	???	YES, Repr. Cat. 2 and STOT RE2 (joint classification)
37640-57-6 108-78-1	Melamine cyanurate Melamine	YES[(a)]	YES	(YES)	???	YES, STOT RE2 (joint classification) YES, IARC Group 2B
108-45-2	1,3-phenylenediamine	YES[b)]	YES	(YES)	???	YES, Muta. Cat. 2 (harmonised classification) CoRAP: possibly additional endpoint
119-47-1	2,2'-methylenebis(6-t-butyl-4-methylphenol)	YES	YES	(YES)	???	YES, Repr. Cat. 2 (joint classification) CoRAP/harmonised classification proposal: Repr. Cat. 1B
13674-87-8	Tris(1,3-dichloro-2-propyl) phosphate [TDCIPP]	YES	YES	YES	YES	YES, Carc. Cat. 2 (harmonised classification) CoRAP/PACT: possibly additional endpoints
68479-98-1	Diethylmethylbenzenediamine	YES	YES	???	???	YES, STOT RE2 (harmonised classification) CoRAP/PACT: possibly additional endpoints
111-91-1	Bis(2-chloroethoxy)methane	YES	YES	(YES)	???	YES, STOT RE2 (joint classification)
126-33-0	Tetrahydrothiophene-1,1-dioxide [Sulfolane]	YES	YES	(YES)	YES	YES, Repr. Cat. 1B (joint classification)
3622-84-2	N-butylbenzenesulfonamide [NBBS]	YES	YES	YES	???	YES, STOT RE2 (joint classification)

(a): Score A increases from 5.5 to 8 for melamine cyanurate based on more recent REACH registration data; in addition, an undisclosed amount is used as an intermediate under strictly controlled conditions for melamine.

(b): Score A increases from 2.3 to 3.75 based on more recent REACH registration data (increase in ERC Score); in addition, an undisclosed amount is used as an intermediate under strictly controlled conditions.

The in-depth evaluation involves different elements. As a first element, information in the REACH registration dossiers is evaluated to check whether the data for block A (tonnage and ERC) used in the initial assessment are accurate and up-to-date. For block B, experimental data from the REACH registration dossiers on biodegradation are checked to confirm the assessment based on predicted biodegradation data. For both blocks (A and B), the in-depth evaluation supports the initial assessment for all 10 substances (melamine cyanurate and melamine assessed as one substance). With respect to block A, the in-depth evaluation in fact shows that more recent data point to a higher Score A than the initial assessment due to increases in ERC Scores for two substances.

In relation to the toxicity, the initial classification used in the assessment was checked again to identify any recent changes and to check correctness of the semi-automated extraction of classification information. The in-depth evaluation confirmed the initial classification and the Toxicity Score assigned. In addition, substances were searched on the ECHA website and any relevant additional information was retrieved. The data in Table 49 show that the in-depth evaluation identified potential additional endpoints than the ones suggested by the initial classification for some substances. These additional endpoints are currently evaluated under the REACH Regulation (mostly substance evaluation (CoRAP)). In the case of 2,2'-methylenebis(6-t-butyl-4-methylphenol) an on-going assessment under substance evaluation (CoRAP) does not involve an additional endpoint, but rather a stricter classification for reprotoxicity (possible re-classification from Cat. 2 to Cat 1B).

Overall, the in-depth evaluation generally supports the initial assessment for blocks A and B as well as the toxicity block. The data on environmental occurrence and the occurrence in food/feed are more heterogeneous. Data availability on the occurrence both in environmental media and in food/feed also differs substantially between the 10 substances. Nonetheless, different patterns can be identified as characterised by the following two groups:

- Group 1: The substance was detected in environmental compartments and/or in food/feed ('YES' assigned in Table 49 at least for 'occurrence environment' or 'occurrence food/feed').
- Group 2: Data on the occurrence both in the environment and in food/feed are uncertain or lacking ('(YES)' or '???' in Table 49).

Table 50 shows the assignment of the 10 substances to these two groups on the basis of the results in Table 49. Melamine is a special case, since this substance has been shown to occur in food/feed (EFSA, 2010). However, it is unclear whether these data reflect occurrence in food/feed due to environmental releases. In fact, in many cases they are more likely to reflect adulteration of food/feed or be the result of other pathways, such as the use of the pesticide cyromazine or from food contact materials (see in-depth evaluation sheet below in this section). As a consequence, the occurrence in food/feed as a result of environmental releases has been rated as uncertain ('???') in Table 49 and Table 50.

Box: Melamine in fruits and vegetables

In an attempt to exclude most other pathways of melamine contamination of food, melamine concentrations in unprocessed fruits and vegetables were obtained from the Competent Authority of an EU Member State. Data for 2015 (N=96), 2016 (N=149) and 2017 (N=215) could be evaluated. Overall, melamine concentrations were above the limit of detection (10 µg/kg) in 1.0 % (2015), 4.0 % (2016) and 4.7 % (2017) of the samples. For the 10 samples above the limit of detection in 2017, melamine concentrations ranged between 12 and 31 µg/kg. The maximum value was found in carrots from the Netherlands followed by spring onions from Morocco (30 µg/kg; both from non-organic production). Three of the 10 detects were from organic production, but two of these were from a non-EU country (a third one from Spain: 15 µg/kg in aubergines). Within the entire dataset, a maximum value of 890 µg/kg was observed (Lamb's lettuce from Germany sampled in 2016, non-organic production).

These data suggest that the frequency of detection is comparatively low, but appears to increase with the number of samples. Melamine occurrence in fruits and vegetables may result from cyromazine use, but the detection in samples from organic production may suggest contamination via the environment.

Table 50: Summary of in-depth evaluation groups

CAS No.	Name/Synonym	Occurrence environment	Occurrence food/feed
Group 1			
13674-87-8	Tris(1,3-dichloro-2-propyl) phosphate [TDCIPP]	YES	YES
121-82-4	Hexahydro-1,3,5-trinitro-1,3,5-triazine [RDX; Hexogen]	(YES)	YES
126-33-0	Tetrahydrothiophene-1,1-dioxide [Sulfolane]	(YES)	YES
3622-84-2	N-butylbenzenesulfonamide [NBBS]	YES	???
Group 2			
119-47-1	2,2'-methylenebis(6-t-butyl-4-methylphenol)	(YES)	???
111-91-1	Bis(2-chloroethoxy)methane	(YES)	???
108-45-2	1,3-phenylenediamine	(YES)	???
37640-57-6 108-78-1	Melamine cyanurate Melamine	(YES)	???[(a)]
68479-98-1	Diethylmethylbenzenediamine	???	???
68937-41-7	Phenol, isopropylated, phosphate (3:1) [ip-TPP]	???	???

[(a)]: Assessment relates to the occurrence in food/feed resulting from environmental releases.

Overall, the data suggest an occurrence in the environment or in food/feed (or both) for four substances (Group 1). For these substances, monitoring in food/feed is generally recommended. For the six remaining substances, monitoring in environmental compartments rather than food/feed is recommended to gain more insight into the extent of environmental occurrence. More specifically, the in-depth evaluation indicates that the following approach may be useful:

- Group 1: Monitoring in food/feed is recommended
  - TDCIPP: all food/feed items

    TDCIPP was already analysed in food in Sweden and Belgium and the intake of the substance from food calculated from the measured data. Dietary TDCIPP intake was found to be about three orders of magnitude lower than the reference value (Poma et al., 2017; Poma et al., 2018). In addition, intake of organophosphorus flame retardants via house dust is generally believed to be higher than intake from food (see e.g. Sundkvist et al., 2010; Cequier et al., 2015). However, these observations are limited by the fact that (a) the studies in Belgium and Sweden are based on very small sample sizes per food category, (b) the comparison with a toxicological reference value does not consider possible carcinogenicity of the substance (harmonised classification as Carc. Cat. 2), and (c) any estimation on intake via house dust critically depends on several assumptions, such as the dust intake per day. A more detailed database on the occurrence in food/feed is therefore helpful to more fully evaluate the contribution of diet as a pathway of exposure to TDCIPP.
  - RDX: all food/feed items
  - Sulfolane: potato and carrot (and other below ground root and tuber crops)

    Both substances were shown to be taken up by crops. The main uses for RDX (explosive) and sulfolane (extraction solvent in the petrochemical industry) and most of the available data on the occurrence in the environment suggest that the environmental occurrence may be limited to sites of use. Monitoring of food/feed items may therefore be most meaningful close to sites of use (e.g. close to (former) army training grounds or other sites of use in the case of RDX and close to petrochemical installations in the case of sulfolane). Such monitoring activities may be accompanied by monitoring in groundwater (RDX) and surface water or STP effluents (sulfolane) in the same areas. However, the data retrieved in the in-depth evaluation illustrate cases where the substances were also detected far away from the site of actual use. RDX was detected in Swiss lakes and sulfolane was emitted in large amounts into river water from a waste treatment facility. The fact that the latter was only detected by non-target screening analyses (since emissions were not required to be monitored for sulfolane) suggests that emissions to

the environment may go unnoticed in other cases. Therefore, monitoring far away from sources would be helpful in identifying the extent of environmental contamination by these compounds and a more general monitoring in food/feed may be meaningful if these substances are shown to occur in areas far away from potential sources.

  - NBBS: potato and carrot (and other below ground root and tuber crops), grapes

    For NBBS, one experimental study indicates no or only comparatively low uptake in crops. However, the data are too limited to reach a final conclusion and more extensive monitoring in food/feed is recommended. Further experimental studies using different crops may also be helpful in confirming (or refuting) the data currently available. NBBS has also been shown to occur naturally in a few non-European plant species.

- Group 2: Initial monitoring in STP effluents, river water or other appropriate compartments to gain more insight into the extent of environmental occurrence is recommended, since data on environmental occurrence in Europe are uncertain or lacking. Monitoring in food/feed items is currently not recommended for these substances, but may be performed once a substance has been shown to occur in the environment.
  - 2,2'-methylenebis(6-t-butyl-4-methylphenol): the substance was detected in groundwater in Slovenia in one study (no concentrations given), but no other data on environmental occurrence in Europe and no data on occurrence in food/feed exist. The high log Kow (6.25 in this assessment, identical experimental value in REACH registration dossier) suggests a high adsorption potential; monitoring in sewage sludge, sediment and soil may therefore be more meaningful than monitoring in STP effluents and river water.
  - Bis(2-chloroethoxy)methane: the substance was detected in the Elbe river in Germany in the 1990ies (probably related to a single source), but no other data on environmental occurrence in Europe and no data on occurrence in food/feed exist.
  - 1,3-phenylenediamine: the compound was detected in leachate from a former landfill site in Germany, but no other data on environmental occurrence in Europe and no data on occurrence in food/feed exist.
  - Melamine cyanurate / melamine: the occurrence of melamine in food and feed is well documented, but several potential sources exist. In order to delineate sources, available monitoring data may be analysed in more detail (e.g. a separate analysis of unprocessed and unpackaged food/feed items on which the pesticide cyromazine (which degrades to melamine) was not used). Alternatively, monitoring activities could be directed towards maize and some other crops (see in-depth evaluation sheet for details);
  - Diethylmethylbenzenediamine: no data on environmental occurrence or the occurrence in food/feed exist for this substance.
  - ip-TPP: no data on environmental occurrence in Europe or the occurrence in food/feed exist, but relevant metabolites of ip-TPP were detected in the urine of children and their mothers in several studies in the USA. The high log Kow (9.07 in this assessment, 4.92-5.17 based on experimental data in in REACH registration dossier) suggests a high adsorption potential; monitoring in sewage sludge, sediment and soil may therefore be more meaningful than monitoring in STP effluents and river water.

This in-depth evaluation shows that differentiated results are obtained by analysing data on the occurrence in the environment and in food/feed.

In-depth evaluation sheets

This section includes the in-depth evaluation sheets for all 10 substances (in the same order as they appear in Table 50).

Name/synonyms: Tris(1,3-dichloro-2-propyl) phosphate [TDCIPP] **CAS No.: 13674-87-8**		**In-depth evaluation sheet**
Parameter*	**Result**	**Source****
ENVIRONMENTAL RELEASE (BLOCK A)	Tonnage Score confirmed (10 000 t/a maximum) ERC Score confirmed (ERC3)	Dossier
	Use pattern***: MAN, FORM, IND, ASL	Dossier
	Primarily used as a flame retardant in polyurethane foam (both rigid and flexible), most of which is used by the automotive industry; some minor other uses	Reviews (ECB, 2008; OECD, 2009)
BIODEGRADATION (BLOCK B)	Score confirmed: 'under test conditions no biodegradation observed' (OECD TG 301 B, GLP; OECD TG 301 C – no data on GLP); no anaerobic biodegradation observed in a non-guideline study; not inherently biodegradable (MITI-II test) Soil: <6% biodegradation within 17 weeks (OECD TG 307, GLP) Considered persistent in PBT assessment	Dossier
	Biodegradation in river and sea water was low to none (0 to 22% within 14 days, lower degradation with lower initial concentration) Hydrolysis half-life estimated to be > 120 days at pH 9 and longer at other pH values (20 °C).	Reviews (ECB, 2008; OECD, 2009)
ENVIRONMENTAL OCCURRENCE (BLOCK A-B)	Range of concentrations in wastewater (STPs): Influent of STPs: 15 ng/L (Spain) – 820 ng/L (Norway) Effluent of STPs: 20 ng/L (Germany) – 740 ng/L (Norway) Sediment: <0.09 ng/g (Norway) – 8 800 ng/g (Norway, car demolishing site) In addition, detected in sludge (3.3-260 ng/g dw.) of 11 Swedish STPs	Reviews (Reemtsma et al., 2008; Van der Veen and de Boer, 2012) and literature (Marklund et al., 2005a; Rodil et al., 2012)
	Detected in 12/12 STP influent samples (median: 80 ng/L, maximum: 1350 ng/L) and in 12/12 effluent samples (median: 110 ng/L, maximum: 310 ng/L) in an STP in Düsseldorf, Germany; detected in 12/12 STP influent samples (median: 86 ng/L, maximum: 180 ng/L) and in 12/12 effluent samples (median: 120 ng/L, maximum: 180 ng/L) in an STP in Cologne, Germany	Literature (LANUV, 2003)
	River water samples > LoD (LoD not given): 66/89 (74 %) in 7 EU Member States (2013-2014); range: 0.0039-0.028 µg/L	Database (EMPODAT, 2018)
	Concentrations in European rivers: Aire: 62-149 ng/L Danube: N=56/57 > LoD, AM: 11.4 ng/L, range: 6-22 ng/L Danube tributaries: N=14/14 > LoD, AM: 10.8 ng/L, range: 3-28 ng/L Elbe: 6.4-31 ng/L; Ems: 8-35 ng/L; Meuse: 37 ng/L; Scheldt: 19-67 ng/L; Rhine: 13-36 ng/L; Ruhr: 50 ng/L; Tiber: <0.7 ng/L; Weser: 5.3-27 ng/L; Spanish rivers: <2-70 ng/L	Review (ICPDR, 2015), partly based on Bollmann et al. (2012)
	Example for some higher concentrations: Four rivers in the state of Hessen (Germany)): N=154/175 > LoD, AM: 117 ng/L, range: <LoD-1 284 ng/L, calculated loads at the mouth of these rivers: 1.1-15.5 kg/a Elbe (Germany, sampling 2013): AM: 155 ng/L; higher than previous values possibly due to increased use (substitute of other flame retardants)	Literature (Quednow and Püttmann, 2008; Wolschke et al., 2015)
	Detected inside (3.44 and 3.69 ng/L) and outside (1.38 ng/L) the Danube delta, in seawater from the Georgian coast (0.78-	Literature (Mariani et al.,

	1.43 ng/L, N=3), in seawater from the Ukrainian coast (0.69-2.57 ng/L, N=3) and in open seawater (0.32-0.84 ng/L, N=12) in 2017 (EU Joint Black Sea Survey 2017 (EMBLAS II))	2018)
	Detected in 16/16 samples in a Swedish river in four monitoring campaigns (2014-2015; maximum 62 ng/L); mass fluxes per capita calculated at five locations in the river up to 1.2 mg/week	Literature (Blum et al., 2018a; Blum et al., 2018b)
	A US study identified very high concentrations in household laundry wastewater (median: 13.5 µg/L, maximum: 65.6 µg/L; median in household dust from the same homes: 1 620 µg/kg); estimates suggested that residential laundry waste-water may be primarily responsible for concentrations measured in the STP influent	Literature (Schreder and La Guardia, 2014)
	Detected in 53 rainwater samples from 5 locations (median: 2-24 ng/L, maximum: 2-53 ng/L) and 43 snow samples from 4 locations (median: 5-40 ng/L, maximum: 23-113 ng/L) in Germany; detected in snow samples in Sweden (4-230 ng/kg, no clear correlation with road traffic); detected in 3/6 tap water samples in Central Spain (3.8, 8.8 and 37.1 ng/L	Literature (Marklund et al., 2005b; Regnery and Püttmann, 2009; Esteban et al., 2014)
	Concentrations in sediments: Sediment: <0.09 ng/g (Norway) – 8 800 ng/g (Norway, car demolishing site) Sediment of a landfill site: 1 500–4 100 ng/g Sediment from river Danube (in Austria): not detected (<0.64 ng/g)	Review (Van der Veen and de Boer, 2012)
	Concentrations in indoor environments: Indoor air: <0.11 ng/m^3 (Sweden) – 150 ng/m^3 (Sweden, hospital ward); overall, not detected in 7/9 studies Settled indoor dust: <0.05-67 µg/g (Sweden)	Reviews (Reemtsma et al., 2008; Van der Veen and de Boer, 2012)
	Metabolite in urine detected, evaluation per year (Sweden): 2000: N=146 men; N>LoD: 82 %, AM: 0.39 µg/L, range: <LoD-8.8 µg/L 2004: N=197 men; N>LoD: 81 %, AM: 0.45 µg/L, range: <LoD-20 µg/L 2009: N=254 men; N>LoD: 91 %, AM: 0.42 µg/L, range: <LoD-4.4 µg/L 2013: N=204 men & women; N>LoD: 87 %, AM: 0.44 µg/L, range: <LoD-8.3 µg/L	Literature (Norén et al., 2017)
	Metabolite in urine detected (Norway, 2012): - 52 % of 48 mothers (AM: 0.25 µg/L, median: 0.08 µg/L, maximum: 2.1 µg/L, N=244) - 61 % of 54 paired children (AM: 0.33 µg/L, median: 0.23 µg/L, maximum: 3.3 µg/L, N=112)	Literature (Cequier et al., 2015)
	Metabolite in urine detected in 25 % of 59 adults (Belgium): maximum: 3.5 µg/L	Review (Saillenfait et al., 2018)
	TDCIPP detected > LoD in 2/93 urine samples (maximum: 2.5 µg/L) of mother-child-pairs in Austria; in contrast to other studies, this investigation obviously analysed the substance itself rather than its metabolite	Literature (UBA, 2011)
	Assigned to category B (some existing human biomonitoring data for Europe data, but insufficient to provide a clear pic-ture) in prioritisation background for European human biomo-nitoring programme (HBM4EU); among the 20 flame retar-dants (out of 62 screened) that should receive some attention	Review (Melymuk, 2017)
	Detected in artic environments, including biota, and considered among the chemicals of emerging arctic concern by the inter-	Review (AMAP, 2017)

	governmental Arctic Monitoring and Assessment Programme (AMAP)	
	Found in database portal (EMPODAT database, Austria Biomonitoring and EMBLAS: see above)	IPCHEM
OCCURRENCE/ ACCUMULA-TION IN FOOD/FEED (BLOCK C)	TDCIPP was analysed in a market basket survey in Sweden (53 composite food samples from 12 food categories); high mean concentrations (> 0.25 µg/kg; all concentrations on wet weight basis) were found in: - Fats/oils: AM: 1 µg/kg, range: <2 µg/kg (N=4) - Beverages: AM: 0.86 µg/kg, range: 0.64-1.07 µg/kg (N=2) - Sugar/sweets: AM: 0.74 µg/kg, range: <0.5-1.23 µg/kg (N=2) - Cereals: AM: 0.38 µg/kg, range: <0.5-0.89 µg/kg (N=5) - Vegetables: AM: 0.37 µg/kg, range: <0.05-1.06 µg/kg (N=5) - Fish: AM: 0.29 µg/kg, range: <0.20-1.05 µg/kg (N=5) - Fruits: AM: 0.29 µg/kg, range: <0.15-0.57 µg/kg (N=5) - Potato: AM: 0.29 µg/kg, range: 0.18-0.49 µg/kg (N=5) The authors calculate a mean daily intake for the adult population of 11.9 ng/(kg x d)	Literature (Poma et al., 2017)
	TDCIPP was one of seven (out of 14 targeted) flame retardants detected above the LoD in foodstuff sampled in Belgium (N=165 food samples in 14 food categories); high mean concentrations (> 1 µg/kg; all concentrations on wet weight basis) were found in: - Fats and oils (due to inclusion of fish oil supplements in this category): AM: 20.18 µg/kg, range: 16.09-57.04 µg/kg (N=10) - Cheese: AM: 3.09 µg/kg, range: 1-13.08 µg/kg (N=17) - Baby food: AM: 1.71 µg/kg, range: 1.08-6.58 µg/kg (N=17) - Potato: AM: 1.01 µg/kg, range: 0.18-2 µg/kg (N=4) In addition, high maximum values were observed for fish (maximum: 3.28 µg/kg, AM: 0.5 µg/kg, N=45) and 'stock and other food' (maximum: 2.53 µg/kg, AM: 0.89 µg/kg, N=4) The authors calculate a mean daily intake for the adult Belgium population of 9.6 ng/(kg x d)	Literature (Poma et al., 2018)
	Analysed in duplicate diets of a Norwegian cohort (N=61) collected over a 24 h period; all samples were below the LoD	Literature (Xu et al., 2017)
	In a total diet study in the UK, 120 total diet samples were apparently also analysed for TDCIPP, but the results are not differentiated by substance	Literature (Gilbert et al., 1986)
	The EU Risk Assessment Report in 2008 estimated total intakes of 699 ng/(kg x d) (local scenario with the highest exposure) and 15.2 ng/(kg x d) (regional scenario), with the largest fraction (> 80 % in both scenarios) resulting from the intake of crops (of which root crops had the highest contribution)	Review (ECB, 2008)
	Detected in 170 pooled samples of wild European eel (*Anguilla anguilla*) from 26 locations in Flanders (Belgium; sampling 2000-2009); concentrations reported as sum of six organo-phosphorus flame retardants (AM: 11 ng/g ww. (44 ng/g lipid), range: 3.4-44 ng/g ww. (7.1-329 ng/g lipid)); substance-specific data only provided for calculated human intakes, for TDCIPP: general population: 0.012 ng/(kg x d) (AM, range: 0.0041-0.051 ng/(kg x d)), high intake group: 0.29 ng/(kg x d) (AM, range: 0.1-1.3 ng/(kg x d)), contamination dominated by other organophosphorus flame retardants than TDCIPP	Literature (Malarvannan et al., 2015)

	In Sweden, concentrations consistently < LoD in marine herring (pooled samples from 4 locations), marine perch (individual/pooled samples from 2 locations) and other marine species (mussels, eelpout and salmon form 4 locations); consistently < LoD in freshwater perch (individual/pooled samples from 7 locations); detected in freshwater close to sources (e.g. STPs): perch from 3 locations: 55 ng/g lipid (median, range: 49-140 ng/g lipid), carp from 1 location: 36 ng/g lipid (all samples referred to above taken in 2007 (except carp taken in 2003); detected in human milk samples (pooled samples from 5 locations/years (N=37-90 per location and year) and 1 individual sample; sampling years: 1997-2006): 4.3 ng/g lipid (median, range: 1.6-3.5 ng/g lipid), contamination dominated by other organophosphorus flame retardants than TDCIPP	Literature (Sundkvist et al., 2010)
	Uptake in plants (strawberry, lettuce) experimentally shown	Literature (Hyland et al., 2015a; Hyland et al., 2015b)
	Not detected in blubber and liver of 20 harbour porpoises (*Phocoena phoceona*) in the UK in 2012	Literature (Papachlimitzou et al., 2015)
	No accumulation observed in benthic and pelagic food webs of the Western Scheldt estuary (The Netherlands)	Literature (Brandsma et al., 2015)
	BCF (fish, *Oryzias latipes*; published, non-guideline): 45 L/kg (31-59)	Dossier
TOXICITY (RELEVANT ENDPOINT(S))	Score confirmed: Carc. Cat. 2 (harmonised classification); also classified in joint submission	Dossier
	DNEL (oral, long-term, systemic effects, general population): 17 µg/(kg x d), based on repeated dose toxicity: 2 a, rat, hyperplasia in kidney)	Dossier
	CORAP identification as potential endocrine disruptor (justification document for the selection of a CoRAP substance, Germany, 2017); results of substance evaluation not yet available	ECHA website[106]
	PACT list: Listing for possible CMR; assessment currently under development, feeds into substance evaluation	ECHA website[107]
ASSESSMENT	With respect to environmental releases and biodegradation, a large body of data supports the assessment of this study, since TDCIPP has been consistently detected in many environmental compartments. In addition, the substance has been detected in a variety of foodstuffs in Belgium and Sweden as well as in fish collected close to emission sources (i.e. STPs). The fact that TDCIPP was below the limit of detection in a duplicate diet study in Norway in all 61 samples is somewhat surprising given the other findings, but may be related to the methodology (one sample consists of all food and drink consumed over the past 24 h, thus potentially diluting higher concentrations in some foods). Finally, available human biomonitoring data demonstrate the exposure of humans. While the pathway of exposure cannot be identified in biomonitoring studies, exposure by other pathways (e.g. inhalation and ingestion of house dust) is generally believed to be higher for organophosphorus flame retardants than intake from food (see e.g. Sundkvist et al., 2010; Cequier et al., 2015). It must be noted, however, that the sample sizes of available studies on the occurrence in food are generally very small, the data are quite variable (see	

106 https://echa.europa.eu/de/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1812cfe58, accessed September 2018.

107 https://echa.europa.eu/de/pact/-/substance-rev/14203/term?_viewsubstances_WAR_echarevsubstanceportlet_SEARCH_CRITERIA_EC_NUMBER=237-159-2&_viewsubstances_WAR_echarevsubstanceportlet_DISS=true, accessed September 2018.

	e.g. higher values in Belgium than in Sweden) and that most of the comparative estimates (food vs. dust) depend on several assumptions (e.g. on the amount of dust ingested). The EU RAR of 2008 generally identified 'no risk need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already' in relation to human exposure via the environment. However, this conclusion is entirely based on EUSES modelling. The toxicity assessment is confirmed (harmonised classification as a suspected carcinogen). In addition, an assessment of TDCIPP as a potential endocrine disruptor is currently underway in the context of substance evaluation under the REACH Regulation in the EU.
CONCLUSION	More detailed monitoring in food/feed is recommended to allow a more reliable estimate of the intake via this pathway for different population groups. Dietary supplements based on fish oil should be included.
MONITORING METHODS	Monitoring methods for food items are described in the literature (Xu et al., 2017; Poma et al., 2018); a method for lipid-rich matrices has also been published (Chu and Letcher, 2015).
CRITICAL FOOD/FEED§	Fish, meat & milk products, fruits and vegetables, grass (Score C = 10 in all items)

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed

** Dossier: REACH registration dossier

*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life

§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

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Name/synonyms: Hexahydro-1,3,5-trinitro-1,3,5-triazine [RDX; Hexogen] CAS No.: 121-82-4		In-depth evaluation sheet
Parameter*	**Result**	**Source****
ENVIRONMENTAL RELEASE (BLOCK A)	Tonnage Score confirmed (10 000 t/a maximum) ERC Score confirmed (ERC5)	Dossier
	Use pattern***: MAN, FOR, IND, PROF; ASL	Dossier
	Almost exclusive use as an explosive; potentially used in mining and quarrying (Norway, Finland and Sweden) and in the Manufacture of fabricated metal products, except machinery and equipment (Finland only)	Dossier and reviews (ATSDR, 2012; NLM, 2018a); SPIN database
BIODEGRADATION (BLOCK B)	Score confirmed: 'under test conditions no biodegradation observed' (OECD Guideline 301 B, RL2, GLP) Soil: not easily biodegraded under aerobic condition in soil (EPA OPPTS 835.3300, RL1, non-GLP)	Dossier
	No biodegradation in water and soil under aerobic conditions, but under anaerobic conditions	Reviews (ATSDR, 2012; NLM, 2018a)
ENVIRONMENTAL OCCURRENCE (BLOCK A-B)	Detected in surface water, groundwater and soil at or near military sites	Reviews (ATSDR, 2012; NLM, 2018a)
	Concentrations measured: untreated wastewater from RDX-manufacturing plant (presumably USA): 3.28 mg/L (N=1); groundwater at former ammunition sites in Lower Saxony (Germany): 21 µg/L and in Saxony (Germany): 2.4 mg/L (N=1 for each) RDX detection frequency and concentration range at 34 US Department of Defence sites: groundwater (12/34; <LoD-36 mg/L), surface water (3/34; >0.004-109 mg/L), soil (22/34; <Lod-13 900 mg/kg), sediment (6/34; 2-120 000 mg/kg)	Literature (Godejohann et al., 1998; Gadagbui et al., 2012; Shi et al., 2015)
	Concentrations in Swiss lakes: AM: 0.2, MAX: 0.81 ng/L (Lake Thun and Lake Brienz); AM: 7.24, MAX: 15 ng/L (Lake Lucerne); all samples in sediment <LoD; occurrence related to external sources (e.g. sites manufacturing explosives, former military sites, tunnel construction/mining) rather than to munitions dumped in the three lakes (containing about 78 kg RDX)	Literature (VBS, 2012)
	RDX released slowly, but continuously from a commercial polymer-bonded explosive under simulated UK weather conditions	Literature (Kumar et al., 2017)
	Not found in database portal	IPCHEM
OCCURRENCE/ ACCUMULATION IN FOOD/FEED (BLOCK C)	Crops irrigated with RDX-contaminated water contain RDX; several studies showed uptake of RDX from soil in plants and accumulation appeared to depend on plant species; higher plants recommended for phytoremediation of contaminated sites.	Reviews (ATSDR, 2012; NLM, 2018a)
	Most likely route of general population exposure in the vicinity of military sites is ingestion of contaminated drinking water or crops irrigated with contaminated water.	Reviews (ATSDR, 2012; NLM, 2018a)
	High hazard indices found at/around former gunnery range, almost exclusively due to modelled intake from fruits, vegetables and grains (RDX concentration in soil measured), but not from fish or meat intake.	Literature (Ryu et al., 2007)
	Bioaccumulation potential with little or only slow transformation of RDX in plants; higher plants recommended for phytoremediation of contaminated sites.	Review (Cataldo et al., 1993)
	Evaluation of available studies on plant accumulation: Soil-to-plant bioconcentration ratio (BCR): N=23, range: 0.06-79 (but see below), AM: 5.81, median: 2.39, GM: 1.60; high values e.g. in alfalfa, spinach shoots and lettuce leaves, lower values e.g. in tomato fruit, bush bean fruit and bean roots	Reviews (McKone and Maddalena, 2007; Gadagbui et al., 2009)

	Mean BCF (shoot) in rye grass (*Lolium perenne*) 71.8 (range (N=3): 19.2-108.3; BCF values appeared to be inversely related with RDX concentrations in soil (range: 10-154 mg/kg dw.); similar results in additional tests with the same species (BCF (shoot): AM: 17, range 2-58), and with alfalfa (*Medicago sativa*; BCF (shoot): AM: 37, range 3-134) ; in both species, highest BCF at lowest concentration in soil (14 mg/kg dw.); third study with rye grass identified confirmed these findings (BCF (shoot): range: 0.17-14.6), again with highest BCF at lowest RDX concentration in soil (11.1 mg/kg dw.)	Literature (Best et al., 2006; Best et al., 2008; Rocheleau et al., 2008)
	Experimental studies with crop plants (maize (*Zea mays*), sorghum (*Sorghum sudanese*), wheat (*Triticum aestivum*), soybean (*Glycine max*), rice (*Oriza sativa*)) and bush bean (*Phaseolus vulgaris*) demonstrated uptake/accumulation of RDX with higher levels in aerial parts (leaves) than in roots; significant accumulation in edible parts of tomato, lettuce and radish from soil demonstrated, but no uptake from irrigation water containing 73 µg/L RDX; higher concentrations in shoot than in root also shown for spinach and carrot and wheat (with particularly high concentrations in carrot shoot)	Literature (Harvey et al., 1991; Cataldo et al., 1993; Fellows et al., 1995; Price et al., 2002; Vila et al., 2007a; Vila et al., 2007b; Chen et al., 2011)
	No bioaccumulation in fish (*Ictalurus punctatus*; EPA OPP 72-6; GLP not stated), BCF ca. 2 L/kg.	Dossier
	Low bioaccumulation potential in fish; experimental bioconcentration factors in edible tissue of three fish species 1.2–6.4; uptake predominantly from water and not from diet (e.g. when fed oligochaete worms (*Lumbricus variegatus*); also no significant bioaccumulation in coastal marine biota (seven species)	Reviews (ATSDR, 2012; Lotufo, 2017; NLM, 2018a); literature (Belden et al., 2005; Houston and Lotufo, 2005; Lotufo et al., 2010; Lotufo, 2011; Ballentine et al., 2015)
	Little bioaccumulation in earthworms (*Eisenia fetida, Eisenia andrei*; BCF: 1.86-33); indications of higher BCF at lower RDX concentrations in soil in one study, but not in another study; little biotransformation and some potential for accumulation noted in literature	Literature (Best et al., 2006; Sarrazin et al., 2009; Zhang et al., 2009; Savard et al., 2010) and review (Lotufo, 2017)
	Some retention (4 % of the label applied) of RDX in prairie voles (*Microtus ochrogaster*) fed a diet of plant materials grown in RDX-amended soils (15 mg/kg)	Literature (Fellows et al., 2006)
TOXICITY (RELEVANT ENDPOINT(S))	Score confirmed: Classification STOT RE2 (central nervous system effects) in joint submission	Dossier
	DNEL (oral, long-term, systemic effects (neurotoxicity), general population): 100 µg/(kg x d)	Dossier
	Reference Dose US EPA (1988) (oral, chronic, systemic: prostate inflammation): 3 µg/(kg x d) Minimum Risk Level ATSDR (2012) (oral, chronic, systemic: CNS effects population): 100 µg/(kg x d)	ITER database (NLM, 2018b); IRIS database (US EPA, 2018)
	Classification for carcinogenicity US EPA (1988): Group C (possible human carcinogen), Oral Slope Factor: 0.11 per mg/(kg x day) [Risk of 1 x 10^{-6} corresponds to 9 ng/(kg x d)][$]	IRIS database (US EPA, 2018)
ASSESSMENT	The main uncertainty relates to environmental releases, since the occurrence in environmental media is only clearly established at or around (former) military sites. However, data in Swiss lakes suggest that more widespread contamination is possible. In addition, former military sites remediated for other uses (gardening/ farming) may	

	need to be considered. Uptake and accumulation in crops (as predicted by ACC-HUMANsteady) as well as the significance of this pathway is well established, while accumulation in fish (also predicted in this study) is unlikely based on available data. Data in meat (from animals fed contaminated diet) is lacking. The toxicity is well established, but reference values differ by a factor of about 30. An old assessment by US EPA classifies RDX for possible carcinogenicity.
CONCLU-SION	Monitoring in food (crops) and feed (grass, alfalfa) recommended, if the substance is known to be present in the area (monitoring in groundwater recommended, since RDX may be present in groundwater at contaminated sites, even if it is not detectable in soil).
MONITO-RING METHODS	The literature on the uptake of RDX in plants cited above generally provides some information on sampling and analytical methods. The most detailed information is found in Price et al. (1997). These authors describe the analysis of RDX in plant tissues by modifying US EPA SW-846 Method 8330 (HPLC analysis in water, soil and sediment)[108] and provide information on sample preparation and clean-up procedures specifically required for plant tissues. Fellows et al. (1995) also provide a good overview. A method for the analysis in animal liver is described in the literature (Pan et al., 2005); analyses in water are covered by ISO 22478:2006.
CRITICAL FOOD/FEED§	Fish, meat & milk products, fruits and vegetables, grass (Score C = 10 in all items)

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed

** Dossier: REACH registration dossier

*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life

$ Calculation not in source

§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

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Name/synonyms: Tetrahydrothiophene 1,1-dioxide [Sulfolane] CAS No.: 126-33-0		In-depth evaluation sheet
Parameter*	**Result**	**Source****
ENVIRONMENTAL RELEASE (BLOCK A)	Tonnage Score confirmed (10 000 t/a maximum) ERC Score confirmed (ERC8d)	Dossier
	Use pattern***: MAN, FOR, IND, PROF, ASL	Dossier
	Primarily used as a solvent for extraction of aromatic hydrocarbons from oil refinery streams and acid gas purification; minor uses include e.g. the use as a cleaning agent, use in the fractionation of wood tars and fatty acids, uses in textile manufacturing and finishing and as a solvent in pharmaceutical manufacturing; use in rubber products.	Dossier and review (OECD, 2004)
BIODEGRADATION (BLOCK B)	Score confirmed: 'not readily biodegradable' (OECD Guideline 301 C, non-GLP, RL2); inherently biodegradable, not fulfilling specific criteria (WoE, rapid quantitative aerobic mineralisation in bioreactors using adapted mixed microbial populations) Soil: non-standard studies indicate biodegradation with a half-life <120 days at environmentally relevant temperatures between 8-10 °C under aerobic conditions. Considered not persistent (aerobic conditions) in PBT assessment. Considered persistent (low nutrient levels / anaerobic conditions) in PBT assessment.	Dossier
	Biodegradation of sulfolane confirmed for a variety of aerobic microcosms derived from sulfolane contaminated environmental samples if nutrient enriched and aerobic (typical for most surface waters): complete removal within 5 to 11 weeks. Under very low nutrient conditions typical for ground water, sulfolane may persist.	Reviews (CCME, 2006b, a)
ENVIRONMENTAL OCCURRENCE (BLOCK A-B)	Non-target screening by authorities identified maximum concentrations of 70 µg/L in the river Ruhr (Germany) in February 2009; concentrations remained above the LoD for about 2 weeks; further investigations identified the effluent of a STP as the source (520-42 000 µg/L), which received input from a facility treating hazardous waste (2 000-28 000 µg/L); resulting concentrations in raw water abstracted from Ruhr river for drinking water preparation: 6.7-13.4 µg/L; total amount emitted estimated to be 3-4 tonnes	Literature (LANUV, 2010)
	Detected in the Canadian environment in the vicinity of facilities where it has been used (maximum values at contaminated sites: 701 mg/kg soil, 800 mg/L groundwater and 185 mg/L surface water; expected not to be present away from such facilities	Reviews (CCME, 2006b, a)
	Not found in database portal	IPCHEM
OCCURRENCE/ ACCUMULATION IN FOOD/FEED (BLOCK C)	In an area affected by contaminated groundwater in North Pole (Alaska, USA), sulfolane concentrations were above the LoD in 21/56 samples (representing 27 plant species). Highest concentrations were observed in green beet leaf (2/2 detects: 28.4-198 µg/kg), leaf lettuce (3/3 detects: 25-92.8 µg/kg), red leaf lettuce (2/2 detects: 41.4-64.8 µg/kg), current (1/1 detects: 41.1 µg/kg), tomato (2/4 detects: <LoD-28.1 µg/kg) and zucchini fruit (1/4 detects: <LoD-24.7 µg/kg); sulfolane was also detected at lower concentrations (5-20 µg/kg) in other crops, such as broccoli, cabbage, cauliflower as well as carrot and potato; irrigation water from wells contained 31.5-247 µg/L	Literature (Alaska DHSS, 2012)
	Rapidly taken up and translocated to shoots in soybean (*Glycine max*) and tomato (*Lycopersicon lycopersicum*); average TSCF of 0.86	Literature (Dettenmaier et al., 2009)

	Exposure of a single apple tree to an irrigation solution containing 55 mg/L sulfolane, resulted in concentrations of 3 730 mg/kg fresh weight (leaves; with signs of toxicity) and 16 mg/kg fresh weight (fruit, no signs of toxicity) after 30 days; BCF (fruit): 2.8 kg of fresh fruit/kg of wet soil	Literature (Chard et al., 2006)
	Shown to be taken up by cattail (*Typha latifolia*) with higher concentrations in leaves than roots (average leaf to root ratio of 53)	Literature (Doucette et al., 2005)
	Detected in wetland vegetation (6 species) from a contaminated site and its surroundings (range: <LoD-73 mg/kg ww.), but not in control samples from background site; higher concentrations in plant heads/leaves than in roots	Literature (Headley et al., 1999)
	BCF (fish, *Cyprinus carpio*; non-standard guideline; non-GLP): <1.3 - <13 L/kg (<LOD at 2 exposure concentrations)	Dossier
TOXICITY (RELEVANT ENDPOINT(S))	Score confirmed: Repr. Cat. 1B (joint classification)	Dossier
	DNEL (oral, long-term, systemic effects, general population): 15 µg/(kg x d), based on repeated dose toxicity: 90 d, rat, reduced immunological parameters in females	Dossier
	Range of eight different derivations of reference doses (2006-2014): 1–13 µg/(kg x d); lowest and highest value (as well as DNEL) based on same study using different approaches in reference value derivation.	Review[109]
ASSESSMENT	Environmental occurrence may be limited to areas in the vicinity of sites using the substances. However, an individual case illustrates that the substance was detected by non-target screening and may therefore occur in the environment unnoticed in other cases. Available experimental data on uptake in plants suggest that sulfolane concentrations may be higher in above ground parts (e.g. leaves) than below ground parts of plants (e.g. roots). This is in contrast to the modelling results of this study, which predicted accumulation in below ground parts of crops (carrot roots and potato tubers). A field study in Alaska indicates that below ground crops may contain sulfolane when irrigated with contaminated water, although levels are lower than in leafy crops. In agreement with this assessment, OECD (2004) identified the substance as a candidate for further work and concluded that '*there is a potential for indirect human exposure via drinking water and food crops in areas surrounding processing plants*'. These authors also recommended '*member countries perform an exposure assessment for […] indirect human exposure*'. The Toxicity Score is confirmed (joint classification as a reproductive toxicant). Reference values differ by more than one order of magnitude solely due to different methodologies.	
CONCLUSION	Monitoring in below ground crops recommended, if the substance is known to be present in the area (monitoring in water recommended).	
MONITORING METHODS	An overview of available methods for different media (air, water, vegetation) is available (Headley et al., 2002).	
CRITICAL FOOD/FEED§	Fruits and vegetables: below ground crops only (potato and carrot, Score C = 6)	

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed
** Dossier: REACH registration dossier
*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life
§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

[109] https://www.tera.org/Peer/sulfolane/Sulfolane_peer_review_final_report.pdf, accessed September 2018.

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Name/synonyms: Benzenesulfonamide, n-butyl- [NBBS] CAS No.: 3622-84-2		In-depth evaluation sheet
Parameter*	**Result**	**Source****
ENVIRONMENTAL RELEASE (BLOCK A)	Tonnage Score confirmed (10 000 t/a maximum) ERC Score confirmed (ERC5)	Dossier
	Use pattern***: MAN, FORM, IND, ASL	Dossier
	Manufacture of rubber and plastic (polyamide) products; use as a plasticiser	Dossier and data-bases (SPIN, 2018; GSBL, 2018)
BIODEGRADA-TION (BLOCK B)	Score confirmed: not readily biodegradable (18% within 28 days; OECD Guideline 301 B, GLP); Surface water simulation test (OECD 309): negligible biodegradation (half-life 858 d); no soil simulation test data available	Dossier
	Not readily biodegradable (0% within 28 days)	Database (J-Check, 2018)
ENVIRONMENTAL OCCURRENCE (BLOCK A-B)	Own evaluation of 8 120 surface water samples from 836 monitoring stations analysed in France (2016-2017): Samples > LoD (0.1/0.5 µg/L): 478/8 120 (5.9 %) Monitoring stations with samples > LoD: 276/836 (33 %) Only samples > LOD: AM 1.20 µg/L, median: 0.886 µg/L, range 0.102-25.7 µg/L)	Database (NAÏADES, 2018)
	River water samples > LoD (LoD not given): 3/1 598 (0.19 %) in 7 EU Member States (2002-2014); no data from France; three positive samples from the Netherlands (0.5-2.09 µg/L)	Database (EMPODAT, 2018)
	Detected in 3/5 German rivers (2001-2009; N=8-20 per river for detects, N=1 per river for non-detects) and 1/6 European rivers (2006-2008; no. of samples not given); interpreted as indicating more widespread occurrence	Literature (Schwarzbauer and Ricking, 2010)
	Detected at five locations in Dutch rivers (range: 90-300 ng/L; N=1 per river)	Literature (van Stee et al., 2002)
	Removed from the list of compounds relevant for drinking water production from the Dutch river Meuse due to low detection frequency	Literature (van der Hoek et al., 2015)
	Identified in suspect screening in Nordic countries, i.e. NBBS was among the most frequently detected compounds in STP effluents	Literature (Schlabach et al., 2017)
	Detected in 15/16 samples in a Swedish river (but not in discharging STP effluents) in four monitoring campaigns (2014-2015; maximum 130 ng/L); non-detection in STP effluents could be results of higher LoD in this matrix compared to river water; spatial and temporal analyses along the river suggest high persistence and mobility in the aqueous compartment; mass fluxes per capita calculated at five locations in the river up to 1.2 mg/week	Literature (Blum et al., 2018a; Blum et al., 2018b)
	In spatial analyses, consistently detected in all 19 samples in Lippe river (Germany) except at the river source (range: 10-140 ng/L) in four monitoring campaigns (1999-2001) as well as in a tributary and an STP effluent; concentrations and loads generally increasing towards the river mouth (before discharge into the Rhine river); maximum load close to river mouth: 362 g/d	Literature (Dsikowitzky et al., 2004a; Dsikowitzky et al., 2004b)
	Detected in influents (0.26-2.4 µg/L) and effluent (0.24-2.0 µg/L) of six municipal STPs (24 h composite samples; presumably Germany); detected in STP effluent after tertiary treatment (0.4-0.8 µg/L, N=8, membrane filtration) and a lake	Literature (Huppert et al., 1998; Hartig et al., 2001)

	(0.1-0.26 µg/L, N=5) in Berlin (Germany)	
	Detected in 21/21 treated and 18/20 untreated wastewater samples from a municipal solid-waste-treatment plant in Castellón (Spain)	Literature (Pitarch et al., 2010)
	Detected at 3/3 sampling stations (high salt/brine) in the Ebro estuary (Spain).	Literature (Serrano et al., 2012)
	Detected in seawater in the coastal area of Portofino (Italy): time-weighted concentrations estimated from long-term (22-72 days) passive sampling at three sites: 79, 216 and 547 ng/L; detected near Kavala city (Greece) in 1/4 seawater samples (20 ng/L) and 3/8 inland water samples (63, 210 and 550 ng/L) potentially with direct industrial input	Literature (Grigoriadou et al., 2008; Di Carro et al., 2018)
	Detected in some groundwater samples in Maribor (Slovenia) in two seasonal monitoring campaigns (detected in 1/15 boreholes in summer and in 3/15 in winter); detected in 2/300 English and 2/45 French chalk groundwater samples (maximum: 1.28 µg/L)	Literature (Lapworth et al., 2015; Mali et al., 2017)
	Detected in leachate of 2/3 landfill sites (presumably in Norway; household and general industrial waste), in seepage water and leachate of a landfill in Germany (420, 590 and 710 µg/L at three locations)	Literature (Schwarzbauer et al., 2002; Slack et al., 2005; Eggen et al., 2010)
	Found in database portal (NAÏADES database: see above; EMPODAT database: see above)	IPCHEM
OCCURRENCE/ ACCUMULATION IN FOOD/ FEED (BLOCK C)	Detected in wine (31 samples of 14 different wines) with mean concentrations up to 2.2 µg/L; no difference between wines in plastic casks and bottled wine	Literature (Duffield et al., 1994)
	No or comparatively low uptake in barley, wheat, oilseed rape, meadow fescue and four cultivars of carrot; simulations suggest that this may be due to degradation (based on a predicted half-life in soil of 30 days)	Literature (Eggen et al., 2013; Trapp and Eggen, 2013)
	Detected in 3/149 polypropylene baby bottles (AM: 64 µg/kg, range: 38-108 µg/kg)	Literature (Simoneau et al., 2012)
	Natural occurrence in the roots of a herbaceous plant (*Angelica sinensis*) from northwest China and a tree (*Pygeum africanum*) distributed across the entire continent of Africa.	Literature (Deng et al., 2006; Schleich et al., 2006)
	BCF (fish) ≤ 3.6 L/kg (OECD 305 C, GLP)	Database (J-Check, 2018)
	BCF (fish, Cyprinus carpio; OECD 305 C): 3.5 – 3.6 L/kg	Dossier
TOXICITY (RELEVANT ENDPOINT(S))	Score confirmed: STOT RE 2 (joint submission)	Dossier
	DNEL (oral, long-term, systemic effects, general population): 83 µg/(kg x d), based on repeated dose toxicity: 28 d, rat, liver enlargement and hepatocyte hypertrophy, thymic atrophy and lymphocytolysis	Dossier
ASSESSMENT	The main uncertainty relates to the occurrence in food/feed, as the occurrence in environmental media is clearly shown in several European countries (the low detection frequency in some studies might be related to comparatively high LoDs). One experimental study identified no accumulation in crops, but the data appear too limited to allow a final judgement. Occurrence in wine may suggest contamination of grapes, but may also be the result of migration from food contact materials (e.g. tubing used in processing). Natural occurrence in a few non-European plant species has been demonstrated. The Toxicity Score is confirmed (joint classification for repeated dose toxicity). The DNEL is based only on a subacute study.	
CONCLUSION	Monitoring in food (potato, carrot, grapes) is recommended based on the available data.	

MONITORING METHODS	A method for analysis in crops is described in the literature (Eggen et al., 2013; Trapp and Eggen, 2013).
CRITICAL FOOD/FEED§	Fruits and vegetables: below ground crops only (potato and carrot, Score C = 6)

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed
** Dossier: REACH registration dossier
*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life
§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

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Name/synonyms: 2,2'-Methylenebis(6-t-butyl-4-methylphenol) CAS No.: 119-47-1		In-depth evaluation sheet
Parameter*	**Result**	**Source****
ENVIRONMENTAL RELEASE (BLOCK A)	Tonnage Score confirmed (10 000 t/a maximum) ERC Score confirmed (ERC8A)	Dossier
	Use pattern***: MAN, FORM, IND, PROF, CONS, ASL	Dossier
	Used as an antioxidant and stabilizer in rubber and a variety of (co)polymers	Reviews (OECD, 2003; EC-HC, 2009)
BIODEGRADA-TION (BLOCK B)	Score confirmed: 'under test conditions no biodegradation observed' (OECD Guideline 301 C, GLP) Soil/surface water: no simulation tests available Considered persistent based on screening criteria	Dossier
	Screening criteria for P met (not readily biodegradable); biodegradation in water expected to be slow	Reviews (TC NES, undated; OECD, 2003; EC-HC, 2009)
ENVIRONMENTAL OCCURRENCE (BLOCK A-B)	Detected in groundwater in Slovenia in two monitoring campaigns; detected in effluent from STP (0.4-0.9 ng/L, N=4), its sludge (1.2-2.1 ng/g, N=4), but not in the receiving river (<0.2 ng/L, N=4) in China	Literature (Liu et al., 2015; Mali et al., 2017)
	Identified as potentially high risk for environment in model-based prioritisation for the EU WFD (i.e. relatively high predicted concentration in water)	Literature (Daginnus et al., 2011)
	Could be extracted from childcare articles (teat, soother), from 1/8 stretch films for packaging fresh meat, from 3/10 rubber nettings for meat packaging; detected in 1/26 food packaging (6 µg/g) in Spain and tentatively detected in another food packaging	Literature (Bouma et al., 2003; Bouma and Schothorst, 2003; Petersen et al., 2004; Dopico-García et al., 2007; Lago and Ackerman, 2016)
	Listed by stakeholders as high priority for potential monitoring of new chemical threats to predatory birds in the UK, but not further considered	Shore et al. (2007)
	Not found in database portal	IPCHEM
OCCURRENCE/ ACCUMULATION IN FOOD/FEED (BLOCK C)	No data on the occurrence in food/feed	
	Exposures through food and breast milk could occur based on high log Kow, but considered low due to low concentrations in water and soil in Canada (predicted values only)	Review (EC-HC, 2009)
	BCF (Fish, Cyprinus carpio; OECD 305, 1996;GLP): 360-810 L/kg (tot. lipid content, i.e. 4.93%)	Dossier
	BCF (experimental): 23-125, 400-840; does not meet criteria for bioaccumulation in aquatic organisms; probably due to limited uptake through gills	Reviews (TC NES, undated; OECD, 2003; EC-HC, 2009)
	Log BCF (observed): 1.97, but substance may be too bulky to cross cell membranes	Literature (Dimitrov et al., 2003; Dimitrov et al., 2005)
TOXICITY (RELEVANT ENDPOINT(S))	Score confirmed: Repr. Cat. 2 (joint classification)	Dossier
	DNEL (oral, long-term, systemic effects, general population): 318 µg/(kg x d), based on repeated dose toxicity: 18 m, rat, slight increase in relative liver weights	Dossier
	CORAP identification as potential endocrine disruptor and suspected reproductive toxicant; substance evaluation concluded	ECHA website[110]

[110] https://echa.europa.eu/de/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e180b880ff, accessed September 2018.

	that potential endocrine disruptive properties are of low concern, but proposed a classification as Repr. Cat. 1B (Denmark, 2017); proposal for a harmonised classification as Repr. Cat. 1B submitted by Denmark in October 2018 (on-going)
ASSESSMENT	Uncertainty relates to environmental releases, since the substance was rarely monitored, and to presence in food, since no data are available. However, some other sources identify a potential for environmental exposure and OECD (2003) recommended local/regional exposure assessments because of the low NOAEL for this chemical for critical effects on testes. There may be an additional exposure pathway via food contact materials. The Toxicity Score is confirmed (classification as a suspected reproductive toxicant, Repr. Cat. 2); a recent assessment under substance evaluation suggests even clearer evidence for this endpoint (proposed classification in Repr. Cat. 1B). The current DNEL may not cover this endpoint, since it is based on repeated dose toxicity.
CONCLUSION	Initial monitoring in environmental compartments recommended to gain more insight into contamination pattern in Europe; due to the high log Kow value, monitoring in sewage sludge and/or soil appears more meaningful than monitoring in water; studies on the occurrence in food/feed are currently not recommended.
MONITORING METHODS	No information found for food/feed; methods for environmental analyses are reported in the literature (Liu et al., 2015; Mali et al., 2017).
CRITICAL FOOD/FEED§	Fish, meat & milk products, fruits and vegetables (Score C = 10 in all items except above ground fruits and vegetables (Score C = 6))

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed

** Dossier: REACH registration dossier

*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life

§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

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Name/synonyms: Bis(2-chloroethoxy)methane CAS No.: 111-91-1		In-depth evaluation sheet
Parameter*	**Result**	**Source****
ENVIRONMENTAL RELEASE (BLOCK A)	Tonnage Score confirmed (100 000 t/a maximum) ERC Score confirmed (ERC1)	Dossier
	Use pattern***: MAN, IND, ASL	Dossier
	Used mainly as a chemical intermediate for polysulfide rubber	Reviews (NLM, 2018)
BIODEGRADATION (BLOCK B)	Score confirmed: 'under test conditions no biodegradation observed' (4% DOC removal within 28 days; OECD Guideline 301 E, non-GLP) Soil: no simulation test data available Considered persistent / very persistent (not readily biodegradable; hydrolytically stable)	Dossier
	Not expected to readily biodegrade in the environment: 0% biodegradation using a settled domestic wastewater inoculum – 0% biodegradation through three subcultures	Reviews (NLM, 2018)
ENVIRONMENTAL OCCURRENCE (BLOCK A-B)	Detected in the river Elbe (Germany) and one of its tributaries in 1995-1997 (maximum concentration: 3.58 µg/L), but at lower concentrations between 1998-2000 (maximum 0.11 µg/L); probably related to a single point source	Review (ARGE Elbe, 2002) and literature (Wennrich et al., 1997)
	Detected in rubber plant effluents (maximum: 140 mg/L); Detected in 0.1 % of 834 surface water samples (median < 10 µg/L); not detected in 86 rainwater samples; identified in 4/21 samples along the Ohio River (concentrations ≤ 0.1 µg/L), not found in other stations along the river; detected in 0.8 % of 521 (all referring to old data from the USA)	Reviews (NLM, 2018)
	Detected in 4/521 streambed sediments in the USA (maximum: 58 µg/kg dw.) and in 1/102 samples from municipal STPs in Oregon (33 ng/L)	Literature (Lopes and Furlong, 2001; Hope et al., 2012)
	Found in database portal, but database not publicly available. The data most likely represent the ones also evaluated in a prioritisation approach for the Water Framework Directive. The only information available indicates that the substance was monitored in two Member States (156 analyses in total), but no information on concentrations or the fraction of detects is provided.	IPCHEM and literature (IOW/INERIS, 2009)
	Did not meet technical screening criteria for second list of priority substances in Canada (reason not discernible)	Literature (Koniecki et al., 1997)
OCCURRENCE/ACCUMULATION IN FOOD/FEED (BLOCK C)	No data on the occurrence in food/feed	
	BCF: No data available	Dossier
TOXICITY (RELEVANT ENDPOINT(S))	Score confirmed: STOT RE 2 (joint classification)	Dossier
	No DNEL derived by the registrants, as no hazards were identified	Dossier
	Chronic oral Reference Dose US EPA (2006): 3 µg/(kg x d)	Website[111]
ASSESSMENT	Uncertainty relates to environmental releases, since the substance was rarely monitored, and to presence in food, since no data are available. Environmental occurrence may be related to single (industrial) point sources, but data are insufficient to reach a final conclusion on the extent of contamination in Europe.	

[111] https://cfpub.epa.gov/ncea/pprtv/documents/Bis2chloroethoxymethane.pdf, accessed September 2018.

	The Toxicity Score is confirmed (joint classification for repeated dose toxicity). No DNEL for the general population was derived by registrants with the justification that no hazard was identified. This is an unusual approach given the classification for repeated dose toxicity. The low provisional reference dose derived by the US EPA points to a comparatively high toxic potential.
CONCLUSION	Initial monitoring in STP effluents and/or surface water is recommended to gain more insight into contamination pattern in Europe; studies on the occurrence in food/feed are currently not recommended.
MONITORING METHODS	No information found for food/feed; Wennrich et al. (1997) describe an analytical method for river water. US EPA Method 8270D[112] describes a method for the determination of semi-volatile organic compounds (including bis(2-chloroethoxy)methane) in several matrices (waste, soil, water).
CRITICAL FOOD/FEED§	Fruits and vegetables: below ground crops only (potato and carrot, Score C = 6)

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed

** Dossier: REACH registration dossier

*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life

§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

References for bis(2-chloroethoxy)methane

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[112] Online at: https://www.epa.gov/sites/production/files/2015-07/documents/epa-8270d.pdf, accessed August 2018.

Name/synonyms: 1,3-Phenylenediamine CAS No.: 108-45-2		In-depth evaluation sheet
Parameter*	**Result**	**Source****
ENVIRONMENTAL RELEASE (BLOCK A)	Tonnage Score confirmed (10 000 t/a maximum); two additional intermediate registrations (tonnage undisclosed) ERC Score *not* confirmed (ERC6D, corresponding to ERC Score 1.75 (old: 0.3); Score A increases from 2.3 to 3.75)	Dossier
	Use pattern***: MAN, IND, PROF	Dossier
	Used in the manufacture of dyes and rubber/polymers and possibly some other applications	Dossier and review (NLM, 2018)
BIODEGRADATION (BLOCK B)	Score confirmed: the analogue substance p-phenylenediamine proved to be neither ready nor inherently biodegradable: 30% biological oxygen demand in an OECD 301D test (GLP) within 28 d; no additional degradation observed upon extension of the test to 84 d Soil: no reliable data available Considered persistent, not very persistent due to photodegradation and abiotic decomposition in aerobic environment	Dossier
	May be susceptible to biodegradation by acclimated activated sludge; indirect photolysis in water considered main removal process (half-live approx. 19-30 sunlight hours)	Review (NLM, 2018)
ENVIRONMENTAL OCCURRENCE (BLOCK A-B)	Detected in water samples from a former landfill site in Germany and in wastewater from resorcinol production in China (77 mg/L)	Literature (Schmidt et al., 1999; Cheng et al., 2017)
	Phenylenediamine (including 1,3-phenylenediamine) listed in the US Toxic Release Inventory and included in the proposal for a harmonized list of pollutants in a global Pollutant Release and Transfer Registry	Review (OECD, 2014)
	Detected in drinking water from an unspecified location	Review (NLM, 2018)
	Not found in database portal	IPCHEM
OCCURRENCE/ ACCUMULATION IN FOOD/FEED (BLOCK C)	No data on the occurrence in food/feed	
	Detected in a multilayer film (out of 18 tested) intended for food packaging (Europe)	Literature (Pezo et al., 2012)
	Analysed, but obviously not migrated from cooking utensils (Spain)	Literature (Sendon et al., 2010)
	Log BCF (observed): 0.38	Literature (Dimitrov et al., 2005)
	BCF (fish, *Cyprinus carpio*; OECD 305C, 1981): 1.3 – 24 L/kg	Dossier
TOXICITY (RELEVANT ENDPOINT(S))	Score confirmed: Muta. Cat. 2 (harmonised classification), also classified in joint submission. However, registrants evaluate available data as indicating no need for classification for mutagenicity.	Dossier
	CORAP identification as suspected reproductive toxicant (justification document for the selection of a CoRAP substance, Latvia, 2016); results of substance evaluation not yet available	ECHA website[113]
	DNEL (oral, long-term, systemic effects, general population): 60 µg/(kg x d) based on repeated dose toxicity: 90 d, rat, effects on liver and kidney)	Dossier
	Reference Dose US EPA (1986) (oral, chronic, systemic: hepatotoxicity): 6 µg/(kg x d); based on same NOAEL as DNEL	IRIS database (US EPA, 2018)

[113] https://echa.europa.eu/de/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e180b927b2, accessed September 2018.

	derivation
ASSESSMENT	Uncertainty relates to environmental releases, since the substance was rarely monitored, and to presence in food, since no data are available. There may be an additional exposure pathway via food contact materials. The Toxicity Score is confirmed (harmonised classification as a suspected mutagen), but registrants evaluated the data as indicating no need for classification for this endpoint. An on-going assessment under substance evaluation will evaluate concerns related to possible reproductive toxicity.
CONCLUSION	Initial monitoring in STP effluents, landfill leachate and/or surface water is recommended to gain more insight into contamination pattern in Europe; studies on the occurrence in food/feed (crops) are currently not recommended.
MONITORING METHODS	No information found for food/feed; methods for determination in water (Less et al., 1998; Schmidt et al., 1998; Schmidt et al., 1999) and sediment (Kadokami et al., 2012) are reported.
CRITICAL FOOD/FEED§	Fish, meat & milk products, fruits and vegetables, grass (Score C = 10 in below ground fruits and vegetables; Score C = 6 in all other items)

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed

** Dossier: REACH registration dossier

*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life

§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

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Name/synonyms: Melamine (MEL) and Melamine cyanurate (MCY) **CAS No.: 108-78-1 (MEL); 37640-57-6 (MCY)**		**In-depth evaluation sheet**
Parameter*	**Result**	**Source****
ENVIRON-MENTAL RELEASE (BLOCK A)	MCY: Tonnage Score of 3 confirmed (100 000 tpa), ERC Score of 2.5 too low (more recent evaluation leads to ERC Score of 5 (ERC4)) MEL: Tonnage Score of 4 confirmed (1 000 000 tpa), ERC Score confirmed (ERC10b)	Dossiers
	Use pattern*** (MEL & MCY): MAN, FOR, IND, PROF, ASL	Dossiers
	MCY: Production of rubber and plastic products, use in coatings (including textile coatings) and several other products and as a flame retardant MEL: Mainly used in the production of melamine resins (>97 % in Europe)	Dossiers and database (SPIN, 2018) Review (OECD, 2002)
BIODEGRA-DATION (BLOCK B)	Score confirmed (MCY): 'under test conditions no biodegradation observed' (OECD 301B, non-GLP); not inherently biodegradable due to MEL constituent (see below). Score confirmed (MEL): not readily (OECD Guideline 301 C, non-GLP) and not inherently (OECD 302B, industrial sludge non-adapted & adapted, non-GLP) biodegradable. Surface water and soil (MEL; non-guideline studies): The half-life in water is estimated to be higher than 60 days, degradation in soil indicated by nitrate formation was slow MEL considered persistent in PBT assessment	Dossiers
	No biodegradation in community wastewater treatment plants (WWTP), but quantitative degradation (80-90 %) in WWTP of a melamine producer.	Review (OECD, 2002)
ENVIRON-MENTAL OCCURRENCE (BLOCK A-B)	According to a Swedish report, both substances are rarely monitored in environmental compartments. As a consequence, no information was found for MCY and information for MEL is sketchy.	Literature (Gustavsson et al., 2017)
	Due to the low retention of MEL in reverse phases, the determination of the substance may encounter analytical problems and the substance has been included in a specific programme to develop reliable analytical methods for the determination in water (no results yet)	Review (LANUV, 2016)
	Average exposure index based on Swedish Product Register data of 3.3 (MCY) and 5.0 (MEL) out of a maximum of 7; a high index of 6 (out of a maximum of 7) was found for both substances for the wastewater compartment	Literature (Gustavsson et al., 2017)
	MEL: detected in all four monitored rivers in the German State of Northrhine-Westphalia and considered ubiquitous; a general precautionary value for surface water of 0.1 µg/L was often exceeded (no further details)	Review (LANUV, 2016)
	MEL: Following a similar incident in 2015, three accidental releases of melamine into the Rhine river were observed at the same site in Germany in February 2016 (600 kg released), May 2016 (700 kg) and August 2016 (100 kg).	Literature (IKSR, 2017)
	MEL: ranked high (rank 8 of 938 substances registered under REACH and considered to possess any environmental emission potential) with respect to its environmental emission potential	Literature (Schulze et al., 2018)
	MEL: considered a substance of concern for drinking water production from European rivers based on presence in the Rhine	Website[114]

[114] http://www.riwa-maas.org/uploads/media/20170320_Mr_Majaz_Malgaj_position_on_substances_of_concern_for_drinking_water_production_from_European_rivers.pdf, accessed October 218.

	river	
	Data from China for MEL: Detected in 13/37 wastewater samples related to MEL factories (unclear whether samples were taken before or after any wastewater treatment): range for nine samples: 22-100 µg/L, range for another four samples: 167-226 766 µg/L Detected in 6/94 irrigation water samples, range: 21-198 µg/L (unclear how sampling locations related to MEL factories) Detected in 1/124 soil samples taken at least 150 km away from MEL-manufacturing sites (0.176 mg/kg) Of 65 soil samples taken about 100 m from MEL factories, MEL was not detected in 52 %, MEL concentrations ranged between 0.1-1 mg/kg (26 %), 1-10 mg/kg (17 %) or were above 10 mg/kg (5 %)	Literature (Qin et al., 2010)
	Detected in Japanese river water (1986-1994), range: <LoD (0.1 µg/kg) – 7.6 µg/kg (no further details)	Review (OECD, 2002)
	Not found in database portal (MEL and MCY)	IPCHEM
OCCUR-RENCE/ ACCU-MULATION IN FOOD/FEED (BLOCK C)	Note: Concentrations in food and feed as a consequence of other pathways of exposure (e.g. adulteration of food/feed, migration from food contact materials as well as from degradation of the pesticide/insecticide cyromazine to melamine) are discussed in EFSA (2010) and are not described here, since they do not cover exposure via the environment	
	The EFSA assessment excluded data on the occurrence in food/feed submitted by Member States since these were influenced by values caused by adulteration; the data submitted by industry were used for the exposure assessment, but very high values were again assumed to be due to adulteration and excluded; handling of non-detects has a large influence on the exposure estimate EFSA considers exposure from the use of MEL as a flame retardant as negligible (due to an assumed low persistence (no justification provided)) and does not consider the occurrence in food/feed due to releases to the environment from manufacture and other industrial/professional uses Note: the data in the assessment do not allow a differentiation of the occurrence in food/feed due to releases to the environment from any occurrence due to contamination via other pathways	Literature (EFSA, 2010)
	Data from China for MEL: Of 246 maize samples, MEL concentrations were: <LoD (23.5 %), <0.1 mg/kg (44 %), 0.1-0.5 mg/kg (31 %) and >0.5 mg/kg (1.5 %); of 168 wheat samples, MEL concentrations were: <LoD (43 %), <0.1 mg/kg (51 %), 0.1-0.5 mg/kg (4 %) and >0.5 mg/kg (2 %); Of 143 soybean samples, MEL concentrations were: <LoD (27 %), <0.1 mg/kg (58 %), 0.1-0.5 mg/kg (13.5 %) and >0.5 mg/kg (1.5 %); unclear for all crop samples how sampling locations related to MEL factories, but authors believe that concentrations reflect baseline levels due to melamine presence in the environment as well as due to the use (of precursors) in pesticides and fertilisers	Literature (Qin et al., 2010)
	MCY: bioaccumulation not expected based on weight of evidence approach MEL: BCF (*Cyprinus carpio*; OECD 305C; non-GLP): <0.38 to <3.8 L/kg;	Dossiers
TOXICITY (RELEVANT ENDPOINT(S))	MCY: Score confirmed: Classification STOT RE 2 in joint submission MEL: Score confirmed: Classification in IARC Group 2B for carcinogenicity, not classified for carcinogenicity in joint submission	Dossier and Literature (Grosse et al., 2017)
	MCY: DNEL (oral, long-term, systemic effects, general population) 15 µg/(kg x d), based on repeated dose toxicity: 28 d, pig, effect	Dossier

	on kidney, applied as 1 mg melamine plus 1 mg cyanuric acid)) MEL: DNEL (oral, long-term, systemic effects), general population: 630 µg/(kg x d), based on repeated dose toxicity: study type and specific effects not obvious in dossier	
	MEL: Proposal for harmonised classification as carcinogen, no documentation available	Website[115]
	MEL: TDI: 200 µg/(kg x d)	Literature (EFSA, 2010)
	MEL: Lowest NOEL of 63 mg/(kg x d) from all toxicity studies; NOEL would fit to the DNEL starting point	Review (OECD, 2002)
ASSESS-MENT	The lack of detailed data on the occurrence in the environment is surprising for a high volume substance (MEL), but may be related to analytical problems. Nonetheless, several sources (including a federal State Agency in Germany) identified MEL in surface waters and another study also identified a high environmental emission scenario of melamine. There are many data on the occurrence of MEL in food/feed. However, it is impossible to identify the cause of the contamination. While it appears reasonable to assume that very high concentrations of MEL in food/feed are due to adulteration, this may not be the case for lower concentrations. These may result from the use of the pesticide/insecticide cyromazine (which degrades to melamine) or from the use of melamine resins in food contact materials. The presence of MEL in food/feed due to exposure via the environment (e.g. use of river water as irrigation water) may represent an additional source. Data from China appear to suggest that MEL may be taken up by crops (although the source of melamine is unclear). The toxicity data (repeated dose toxicity for MCY and suspected carcinogenicity for MEL) are confirmed. Available reference values are lower for MCY than for MEL and the ones for MEL do not consider any potential carcinogenic effects. The EFSA assessment in 2010 was unable to consider the most recent IARC assessment, of which only a summary is currently available (Grosse et al., 2017).	
CONCLU-SION	Monitoring in in STP effluents and/or surface water is recommended as a first step to identify the extent of environmental releases. Monitoring in food/feed should be limited to unprocessed (preventing the impact of any possible adulteration) and unpackaged (preventing the impact of food contact materials) food/feed and include only crops on which cyromazine is not used[116] to check whether melamine enters the food chain due to environmental releases. The data from China suggest that monitoring in maize may be a good first choice.	
MONITO-RING METHODS	Methods for the determination of melamine and and/or cyanuric acid in various food/feed items are described in the literature (see e.g. Muñiz-Valencia et al., 2008; Varelis and Jeskelis, 2008; Cheng et al., 2014; Faustino et al., 2017; Lu et al., 2017).	
CRITICAL FOOD/FEED§	Fish, meat & milk products, fruits and vegetables, grass (Score C = 10 in all items except planktivore fish ('Fish 1') with Score C = 6)	

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed

** Dossier: REACH registration dossier

*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life

§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

[115] https://echa.europa.eu/de/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e181ed61e7, accessed September 2018.

[116] http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.detail&language=EN&selectedID=1189 (accessed October 2018) and links from this dataset provide details.

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Name/synonyms: Diethylmethylbenzenediamine CAS No.: 68479-98-1		In-depth evaluation sheet
Parameter*	**Result**	**Source****
ENVIRONMENTAL RELEASE (BLOCK A)	Tonnage Score confirmed (10 000 t/a maximum) ERC Score confirmed (ERC8C)	Dossier
	Use pattern***: FORM, IND, PROF, CONS	Dossier
	Manufacture of polyurethane products; use in coatings and adhesives/sealants	Dossier
	Norway: substance was among the substances contributing most to the total emissions of 'chronic substances' (i.e. those classified for chronic toxicity) to the Norwegian environment between 2002-2007 based on estimates derived from Norwegian product register data (7 t emitted in 2006, 1 t in 2007)	Statistics Norway (2009)
BIODEGRADATION (BLOCK B)	Score confirmed: 'under test conditions no biodegradation observed' (OECD Guideline 301 D, non-GLP) Soil: no simulation test data available	Dossier
	No additional data identified	
ENVIRONMENTAL OC-CURRENCE (BLOCK A-B)	No data found	
	Not found in database portal	IPCHEM
OCCURRENCE/ ACCUMU-LATION IN FOOD/FEED (BLOCK C)	No data on the occurrence in food/feed	
	BCF (Fish; QSAR: BCFBAF): 2.75 L/kg	Dossier
TOXICITY (RELEVANT ENDPOINT(S))	Score confirmed: STOT RE2 (harmonised classification), also classified in joint classification	Dossier
	DNEL (oral, long-term, systemic effects, general population): 100 µg/(kg x d), basis not specified, derived from BMDL10	Dossier
	CoRAP: Listing due to concerns for suspected reprotoxicity and mutagenicity; substance evaluation not yet finished	ECHA website[117]
	PACT: Listing for possible endocrine disruption; feeds into substance evaluation	ECHA website[118]
ASSESSMENT	Despite its widespread use (including the use in consumer products), no information on the environmental occurrence or the presence in food/feed was found. An estimate from Norway suggests some emissions to the environment, which is in agreement with the Score A assigned. The Toxicity Score is confirmed (harmonised classification for repeated dose toxicity). Additional endpoints (reprotoxicity and mutagenicity as well as endocrine disruption) are currently assessed.	
CONCLUSION	Initial monitoring in STP effluents and/or surface water recommended to gain more insight into contamination pattern in Europe; studies on occurrence in food/feed are currently not recommended.	
MONITORING METHODS	No information found	
CRITICAL FOOD/FEED§	Fish, meat & milk products, fruits and vegetables, grass (Score C = 6 in above ground fruits and vegetables and planktivorous fish; Score C = 10 in all other items)	

117 https://echa.europa.eu/documents/10162/c3962860-1e1a-4d49-a5f7-3ad2f18086e5, accessed July 2018.
118 https://echa.europa.eu/de/pact/-/substance-rev/15004/term?_viewsubstances_WAR_echarevsubstanceportlet_SEARCH_CRITERIA_EC_NUMBER=270-877-4&_viewsubstances_WAR_echarevsubstanceportlet_DISS=true, accessed July 2018.

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed

** Dossier: REACH registration dossier

*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life

§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

References for diethylmethylbenzenediamine

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Name/synonyms: Phenol, isopropylated, phosphate [ip-TPP] CAS No.: 68937-41-7		In-depth evaluation sheet
Parameter*	**Result**	**Source****
ENVIRONMENTAL RELEASE (BLOCK A)	Tonnage Score confirmed (10 000 t/a maximum) ERC Score confirmed (ERC8A)	Dossier
	Use pattern***: MAN, FOR, IND, PROF, CONS, ASL	Dossier
	Used as a plasticiser in PVC products, but also in polyurethanes, textile coatings, adhesives, paints and pigment dispersions as well as lubricants; use as a flame retardant	Reviews (Fisk et al., 2003; Brooke et al., 2009; Sjögren et al., 2010; CalEPA, 2012; Melymuk, 2017)
BIODEGRADATION (BLOCK B)	Score confirmed: 'under test conditions no biodegradation observed' (OECD TG 301 D, GLP: 17.9% within 28 d) Soil/water simulation tests: not available Considered not persistent in PBT assessment due to hydrolysis at pH 7 and pH 9 (but see below)	Dossier
	Not readily biodegradable (0% within 28 days; tris(p-isopropylphenyl) phosphate, CAS No.: 26967-76-0 according to source)	Database (J-Check, 2018)
	In contrast to these data, a review considers these compounds inherently biodegradable	Review (Brooke et al., 2009)
	Hydrolysis of IPPP considered negligible under most environmental conditions	Review (Brooke et al., 2009; NLM, 2018)
ENVIRONMENTAL OCCURRENCE (BLOCK A-B)	No data on the occurrence in Europe	
	Detected in soil at two U.S. Air Force bases (5.8 mg/kg at one base, 0.9 and 2.0 mg/kg in two samples at the other base (USA)	Review (CalEPA, 2012)
	Amount used in Scandinavian countries has steadily increased from 96 t in 2002 to 313 t in 2007	Review (Sjögren et al., 2010)
	Assigned to category D (no human biomonitoring data from Europe, but limited data from outside Europe) in prioritisation background for European human biomonitoring programme (HBM4EU); among the 20 flame retardants (out of 62 screened) that should receive some attention	Review (Melymuk, 2017)
	Identified in environmental prioritisation based on (a) tonnage and (b) aquatic toxicity, but not in a screening risk assessment for the aquatic environment; food chain accumulation not addressed in prioritisation approach	Review (Fisk et al., 2003)
	Relevant metabolites (of ip-TPP containing a single isopropyl group at only one phenyl moiety, i.e. mono-substituted isopropylphenyl diphenyl phosphate (position unspecified)) detected in urine of 15/43 infants (range: <0.07-6.1 ng/mL) and of 347/349 adults (GM: 6.8 ng/mL, range: <LoD-69 ng/mL) in North Carolina (USA), in 22/22 mothers (GM: 0.85 ng/mL, range: 0.67-1.1 ng/mL) and 24/26 children of these mothers (GM: 1.0 ng/mL, range: <0.09-1.6 ng/mL) in New Jersey (USA) and in 28/28 mothers (GM: 2.0 ng/mL, range: 0.56-14.8 ng/mL) and 33/33 children of these mothers (GM: 1.8 ng/mL, range: 0.44-8.5 ng/mL) in California (USA)	Literature (Butt et al., 2014; Hoffman et al., 2015; Butt et al., 2016; Hoffman et al., 2017)
	Additional biomonitoring studies from the USA summarised in a recent review	Review (Saillenfait et al., 2018)
	Not found in database portal	IPCHEM
OCCURRENCE/ ACCUMULATION IN FOOD/FEED (BLOCK C)	No data on the occurrence in food/feed	
	BCF (fish): 776 L/kg (OECD TG 305, GLP), maximum value taken as key value	Dossier
	BCF (fish): 16-43 L/kg (tris(p-isopropylphenyl) phosphate,	Database (J-Check,

	CAS No.: 26967-76-0 according to source)	2018)
TOXICITY (RELEVANT ENDPOINT(S))	Score confirmed: Repr. Cat. 2 (fertility effects) as well as STOT RE 2 (adrenal gland) in joint classification	Dossier
	DNEL (oral, long-term, systemic effects, general population): 40 µg/(kg x d), based on: oral, 90 d, rat, LOAEL 25 mg/(kg x d) / 3 = NOAEL 8.33 mg/(kg x d))	Dossier
	Dossier evaluation under REACH based on testing proposals by the registrant led to the performance of the new 90 d repeated dose toxicity study that is the one used for DNEL derivation A testing proposals for an extended one-generation reproductive toxicity study (EOGRTS) is currently under discussion	Website[119]
ASSESSMENT	The lack of data on occurrence is most likely the result of the complex and variable composition of the substance and its commercial products. Limited analyses of commercial products indicate that substances containing only one isopropyl group are major constituents. The detection of the corresponding metabolites in biomonitoring studies in the USA support this assumption. Detection of metabolites does not necessarily indicate uptake via food but may also result e.g. from intake via house dust. The toxicity Score was confirmed (joint classification for suspected reprotoxicity and repeated dose toxicity). The proposed EOGRTS may shed further light on the potential of the substance as a reproductive toxicant.	
CONCLUSION	Initial monitoring in environmental compartments recommended to gain more insight into contamination pattern in Europe; due to the high log Kow value, monitoring in sewage sludge and/or soil appears more meaningful than monitoring in water; based on metabolites repeatedly detected in US biomonitoring studies, monitoring may first focus on the following mono-substituted isopropyl triphenyl phosphates (i.e. isopropylphenyl diphenyl phosphates): 2-Isopropylphenyl diphenyl phosphate (CAS No.: 64532-94-1) 3-Isopropylphenyl diphenyl phosphate (CAS No.: 69515-46-4) 4-Isopropylphenyl diphenyl phosphate (CAS No.: 55864-04-5) Studies on the occurrence in food/feed are currently not recommended.	
MONITORING METHODS	No information found	
CRITICAL FOOD/FEED§	Fish, meat & milk products, fruits and vegetables, grass (Score C = 10 in all items except below ground crops (potato and carrot) with Score C = 6)	

* ENV: Environmental occurrence (in water, soil etc.); FOOD: Occurrence in food or feed

** Dossier: REACH registration dossier

*** MAN: Manufacture, FORM: Formulation, IND: Industrial uses, PROF: Professional uses, CONS: Consumer use, ASL: Article service life

§ Food/feed items with a Score C of 6 or 10 based on ACC-HUMANsteady modelling

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[119] https://echa.europa.eu/de/information-on-chemicals/testing-proposals/previous/outcome?diss=true&search_criteria_ecnumber=273-066-3&search_criteria_casnumber=68937-41-7&search_criteria_name=Phenol%2C+isopropylated%2C+phosphate+%283%3A1%29, accessed September 2018.

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3.5.3. Summary and discussion

The in-depth evaluation of 10 substances (out of a total of 212 priority substances; melamine and melamine cyanurate assessed together) can be summarised as follows:

- The initial assessment of environmental releases (block A) based on REACH registration data is confirmed for all substances based on a re-examination of these data about 18 months later. In fact, the more recent assessment suggests a higher Score A than originally assigned for two substances.
- The assessment of biodegradation (block B) based on predicted data is confirmed for all substances upon an evaluation of experimental biodegradation data from the REACH registration dossiers. While there are indications that some of the substances may be biodegradable to some extent under certain conditions, such conditions may not exist in all environments.
- Data on the occurrence in environmental compartments in Europe are entirely lacking for two substances and are uncertain (since only few data are available) for another four substances. Considering that all 10 substances have a maximum REACH registration tonnage of 10 000 tpa or more, this finding may be surprising. However, the selection of substances for in-depth evaluation excluded substances that already received some attention (i.e. listed in specific regulatory lists or in EFSA's OpenFoodTox database; see section 2.5.1). The finding of lacking/uncertain data for 6/10 substances might therefore result from the fact that these substances do not appear on relevant lists and thus do not attract much attention for monitoring. It must be noted that four of these six substances are classified, since they are suspected of being CMR substances (see Table 49).

  For four substances (TDCIPP, RDX, sulfolane and NBBS), environmental occurrence has been demonstrated. For two of these substances (RDX and sulfolane), further investigations should clarify whether contamination by these substances is limited to sites of use or is indeed more widespread.
- Data on the occurrence in food/feed (in experimental studies or from dietary surveys) are also limited to these four substances. While the evaluation shows that three of these substances (TDCIPP, RDX and sulfolane) may occur in food/feed, the only experimental study available for NBBS suggests comparatively low uptake into the crops studied. However, the data are considered too limited to allow a final judgement.

  For melamine, there are substantial data on the occurrence in food/feed, but the pathways leading to such contamination (e.g. environmental emissions, food contact materials, adulteration or the degradation of the pesticide cyromazine) may require more attention.
- The initial toxicity assessment based on the classification of substances for relevant endpoints (carcinogenicity, mutagenicity, reprotoxicity and repeated dose toxicity) was confirmed by a re-evaluation of the classification data. Additional analyses of other information showed that four substances are currently investigated further in the substance evaluation instrument of the REACH Regulation. In three cases, this relates to additional endpoints (i.e. beyond those covered by the classification) and in one case this relates to a stricter classification (possible classification in Repr. Cat. 1B instead of Repr. Cat. 2). These findings illustrate that an in-depth evaluation is meaningful even if the toxicity assessment is based on classification information. In none of these four cases, substance evaluation relates to human exposure via the food chain.

Overall, the findings of the in-depth evaluation lead to recommendations for future monitoring activities (see discussion above for melamine). These recommendations are based on the data already available on the occurrence in the environment and in food/feed. For the four substances, for which monitoring in food/feed is recommended, the evaluation in block C also provides indications on which food/feed items to monitor. For the remaining six substances, monitoring in the environment is recommended as a first step to gain more insights in the extent of environmental contamination.

The in-depth evaluation based on all currently available and accessible data did not allow a final judgement as to whether these 10 substances actually represent 'emerging chemical risks' as defined

in section 1. Even for the substance with the largest amount of data on the presence in food (TDCIPP), the data are too limited to fully assess human exposure and, as a consequence, the risk resulting from human exposure via the food chain. This finding is related to the inherent limitations of the term 'emerging risk': a large amount of data (e.g. concentrations in many different food items) is required to finally judge on the presence or absence of risks and such data are generally not available for 'emerging' substances. Conversely, availability of such detailed data requires that many studies and evaluations have been performed for a given substance, which may then no longer be called an 'emerging' substance.

The 10 substances can, therefore, only be considered 'potential emerging chemical risks' or 'emerging chemical issues' (see section 1) due to the lack of reliable data on human exposure via the food chain. However, the in-depth evaluation demonstrated that the overall approach applied in this study produced meaningful results for all other areas (blocks A and B as well as toxicity) and identified relevant data gaps primarily related to the occurrence in the environment.

4. Conclusions

The selection of substances involved a multi-step procedure. Starting from a list of 15 021 substances[120] registered under the REACH Regulation, a substantial number of substances had to be excluded because (a) they were only registered as intermediates handled under strictly controlled conditions and were therefore expected to result in no or only low environmental releases, (b) they lacked crucial data (e.g. a CAS number, information on tonnage and use, or a SMILES notation) or (c) were considered to be outside the applicability domain of the models used in this study. Overall, 2 336 chemicals were selected for further evaluation of their exposure potential, biodegradation, bioaccumulation and toxicity. The methodology for the identification of potential emerging risks proposed in this report is therefore only applicable to 16 % of the substances registered under the REACH Regulation, primarily due to data availability and applicability domain considerations. Nevertheless, the approach chosen ensures that the chemicals selected have relevant data available and are within the applicability domain of the models used in subsequent evaluation steps.

These 2 336 substances were assessed in blocks A (releases to the environment), B (biodegradation), C (bioaccumulation in food) and the toxicity block following the recommendations of the pilot study (Bitsch et al., 2016). In relation to the toxicity endpoints evaluated (carcinogenicity, mutagenicity, reprotoxicity and repeated dose toxicity), the pilot study recommended to evaluate the classification information, since the extraction of experimental toxicity data required extensive resources.

The evaluations showed a good degree of differentiation in all four blocks. About one-third of the substances were assigned a Score A of 6 (sum of ERC Score and Tonnage Score), since this reflects a very common combination of an ERC Score 5 and a Tonnage Score 1. Another third of the substances received lower Scores A and the last third higher Scores A. In relation to biodegradation (block B), the battery evaluation successfully distinguished biodegradable substances (42 %) from poorly biodegradable substances (52 %). Similarly, the evaluation of bioaccumulation in food/feed (block C) differentiated non-bioaccumulative substances (10 %) from bioaccumulative substances (40 %), with about 25 % each in the two intermediate groups. The comparatively high fraction of substances in the high scoring groups is due to the conservative approaches applied (i.e. maximum score in any food/feed item taken as Score C). Such an approach is considered adequate for a screening assessment. Additional comparisons of the results with the screening criteria for bioaccumulation defined in the new ECHA Guidance on PBT/vPvB assessment (ECHA, 2017a) showed a good level of agreement. In relation to toxicity based on classification information, 526 substances were assigned a Toxicity Score of 10 (23 %) and 1 810 substances (77 %) were assigned a Toxicity Score of 1.

Uncertainties in the assessment are associated with block A due to missing information, but – more importantly – due to the fact that the maximum tonnage is not necessarily related to the use resulting in the highest ERC Score (see 'Proposal on possible next steps' in section 5 on how to potentially resolve this issue). Validation of the predicted biodegradation data with key values derived by registrants from experimental data shows a good agreement. However, a considerable fraction of the 2 336 substances was overpredicted (lower degree of biodegradation assumed based on predicted data than assigned based on experimental data). This finding is in line with the conservative evaluation procedure that is considered adequate for a screening assessment. Uncertainty in block C is related to the applicability of the ACC-HUMANsteady model to less well studied substances, e.g. those accumulating by mechanisms other than lipophilicity.

For the assessment of toxicity, a hierarchical approach was applied to ensure that reliable information is given priority. While the majority of classification information retrieved was considered reliable, further checks were performed on 50 substances with other classifications, i.e. classifications submitted under the CLP Regulation, but not included in harmonised classifications or in joint or individual classifications under the REACH Regulation. Overall 526 substances received a Toxicity Score of 10 based on harmonised classifications (N=281, 53 %), IARC classifications (N=24, 4.6 %), joint classifications (N=187, 36 %), individual classifications (N=22, 4.2 %) or other classifications (N=12, 2.3 %). Among these latter 12 substances, the Toxicity Score of 10 was considered to be of low reliability after checking the data for 9 substances, while it was considered high for the remaining 3 substances.

120 As discussed in detail in section 3.1, there is some overlap between different categories so that figures do not add up.

The final evaluation performed after all scores for every block had been assigned to each of the 2 336 substances of the dataset aimed at prioritising substances for further evaluation. For that purpose, different approaches were applied. Based on several different evaluations, Pivot table selections proved to produce the most meaningful results, since they allowed defining criteria that have to be met in any case (i.e. a Toxicity Score of 10 and a Score C > 5) and are – in contrast to weighting scenarios – independent of the distribution of scores. In contrast, weighting scenarios prioritised a substantial fraction of substances that did not meet these criteria. However, weighting scenarios proved to be helpful in defining sub-selections among the prioritised substances (see below).

In total, 267 substances were initially prioritised from the Pivot table selections, from which 50 UVCB substances (mostly petroleum substances) were excluded. Another five substances were removed from the list of priority substances, since the toxicity classification was potentially impacted by an impurity.

This procedure led to 212 priority substances for further evaluation. The confidence in the prioritisation – within the limitations of a screening assessment – is high, since (a) all substances with a Toxicity Score of 10 and a Score C > 5 have been assessed irrespective of their scores in block A and B, (b) additional evaluations suggest that only a small fraction of relevant substances was excluded on the basis of the bioaccumulation assessment alone and (c) the prioritisation accounts for the different levels of reliability associated with the toxicity data. Analyses of these 212 priority substances showed that this study produced valid prioritisation results, since many of the highest ranking substances are also included in several lists concerned with chemical and/or food safety. Furthermore, some of the highest ranking substances in this study were already assessed in-depth by EFSA in relation to their presence in food. For substances included in many of these lists, substance-specific assessments should clarify, whether the risk arising from human exposure via the food chain has been adequately addressed. For the majority of the priority substances, however, it is evident from the nature of the listings as well as from illustrative examples presented in this study that they were not yet assessed with respect to human exposure via the food chain and this is very likely to be the case for the 110 priority substances not included in any list.

Overall, 53 % of the 212 priority substances were assigned a Toxicity Score of 10 based on classifications in REACH registration dossiers. This study therefore identified substances that were not recognised in approaches based on harmonised and IARC classifications only.

The last part of this study involved an in-depth evaluation of a subset of 10 substances (out of the 212 priority substances) that were not already assessed in detail. The weighting scenarios mentioned above proved useful to select these 10 substances from among the 212 priority substances. Within the in-depth evaluation, an evaluation of relevant data in REACH registration dossiers confirmed that the (semi-)automated extraction procedures produced correct results and also identified updated data in some cases. Furthermore, the assessment of biodegradation based on predicted data was confirmed by experimental data for this endpoint. Extensive literature searches identified relevant data showing the environmental occurrence or the occurrence in food/feed for four substances, while data were generally lacking or were considered uncertain for the remaining six substances. These findings formed the basis for recommendations on future monitoring activities. Importantly, some of these 10 substances were included in lists related to chemical and/or food safety, but human exposure via the food chain was not specifically addressed in the respective evaluations. This finding further supports the notion that this pathway was not yet considered for the majority of the 212 substances (however, see Box below). These substances may therefore be considered ‘potential emerging risks’ in the food chain.

Box: Assessment of human exposure via the food chain in REACH registration dossiers

All 212 substances are registered under the REACH Regulation and are classified for human health hazards. Most of them are registered at tonnages of more than 10 tpa and therefore require a chemical safety assessment. A chemical safety assessment typically also includes an evaluation of human exposure via the environment, which includes human exposure via the food chain.

The conclusion that this pathway of exposure was not yet addressed in the majority of cases may therefore not be entirely correct. However, the following issues need to be considered:

- EUSES software is generally used to model human exposure via the food chain. This software has not been updated for a long time and several update needs have been identified that also affect the assessment of human exposure via the food chain (RIVM, 2014; Bitsch et al., 2016). Assessments performed with EUSES software are therefore likely to be associated with considerable uncertainty.
- The assessment of human exposure via the food chain performed in REACH registration dossiers is not publicly available. The extent, quality and results of such assessments could therefore not be evaluated in this study.
- These assessments are only available in text files (i.e. the Chemical Safety Report submitted with the registration). Any evaluation of such assessments therefore involves a substantial amount of manual data evaluation tasks.

Based on these considerations, the conclusion that human exposure via the food chain was not yet addressed may be modified for individual substances upon inspection of the Chemical Safety Report. However, such an evaluation can only be performed by regulatory agencies.

Overall, this study established a link between a chronic health hazard and possible exposure of humans via the food chain. For the majority of these 212 'potential emerging risks' (or 'emerging chemical issues'), such a link has not been previously recognised and substance-specific in-depth assessments are required to clarify whether they actually constitute 'emerging chemical risks'[121]. In some cases, such an in-depth evaluation will come to the conclusion that additional data are needed as was observed for the ten substances evaluated in-depth in this report.

[121] See section 1 for the meaning of these terms.

5. Recommendations

The recommendations given below are based on the experience of substance selection and evaluations of blocks A-C and the toxicity block. It is acknowledged that some of the recommendations affect the current dissemination policy of information generated under the REACH Regulation. Any changes of this policy will need to be discussed with the various stakeholders (e.g. industry and authorities) and are likely to be implemented – if at all – only over a long period of time. The problems in disseminating this information stems from the fact that they may affect proprietary rights of registrants, such as intellectual property rights.

Substance selection

- For substances registered with NONS registrations only, further information on the tonnage and use would be helpful. This information is currently not publicly available, a fact that limits possible assessments for these substances.
- Substances without a CAS number had to be excluded due to a technical limitation (import options of the QSAR Toolbox). An expansion of the QSAR Toolbox to allow importing EC numbers would be helpful to enable the evaluation of a larger number of substances[122].
- A compiled list of registered substances with EC numbers, CAS numbers and validated SMILES notations would be of great benefit for many different screening and research projects.

Block A (releases to the environment)

- The approach used in this study to estimate the potential releases of a substance to the environment suffer from uncertainties related to (a) missing tonnage and use information for some substances and (b) a lacking link between the maximum registration tonnage and the use that results in the highest potential release fraction. Publicly available information on the tonnage for each use of a substance would increase the robustness of assessments like the one presented in this study. It is, however, recognised that such information may be confidential in many cases (see 'Proposal on possible next steps' in this section).
- Alternatively, public dissemination of releases to the environment (as calculated by registrants in the context of a chemical safety assessment) would greatly benefit assessments of the kind presented in this study. Such information is currently considered confidential and not made publicly available. Even information on the overall bands of releases to the environment from all uses combined (e.g. 10-100 kg/a, 100-1 000 kg/a etc.) are expected to provide a more robust picture on environmental releases than the surrogate approaches that had to be used in this study.

Block B (biodegradation)

- Again, public availability of the key values from REACH registration dossiers would greatly benefit more general evaluations, such as the validation of predicted biodegradation as performed in this study. As outlined in this study, confidentiality prevents a more in-depth discussion of specific issues and therefore limits the statistical evaluation. It is noted that the data analysed in this validation represents the largest dataset used so far. The possibility of more in-depth evaluations would therefore be of great interest to the scientific community. In fact, such validation studies will help to improve the adequate application of QSAR battery approaches in risk assessment and help to identify groups of substances that are not well predicted with commonly used BIOWIN models. This is important, because QSAR models are widely used in assessing the biodegradability of substances.

Block C (bioaccumulation)

- ACC-HUMANsteady was extremely useful for the evaluation of bioaccumulation food/feed since it can be operated in batch mode and also allows predictions for many different food items. More up-to-date models with such features would be helpful for comparative evaluations that might identify strength and weaknesses of different modelling approaches.

[122] It is noted, however, that the most recent version of the QSAR Toolbox, which was published after the tasks described in this report were performed, even discontinued the import of CAS number lists (v.4, April 2017).

Block toxicity (based on classification information)

- The C&L Inventory database is extremely useful for assessing the hazards of chemicals. However, from a research perspective, curation of the data would be desirable to enable an assessment of the reliability of the information. As a first step, identification of substances that were classified in individual submissions under REACH in the C&L Inventory would be extremely helpful. This would allow distinguishing such classifications from the bulk of notifications by others, for which the underlying data are not accessible.
- In this context, a limitation of searches in the C&L Inventory to classifications coming from REACH registration dossiers would be extremely helpful (such a limitation is already possible for harmonised classifications).
- It would also be helpful, if classifications affected by impurities could be deselected in the search procedure in the C&L Inventory. In addition, it would be extremely useful, if the inventory could specify, for which endpoint specifically the classification is affected by impurities.
- With respect to other classifications (i.e. other than harmonised classifications or those resulting from registrations under REACH), an evaluation based on the number of notifications is recommended. Classifications supported by only 1 or 2 notifications are not recommended to be used in any evaluations. However, any decision on classification or non-classifications would require an in-depth substance-specific assessment of the underlying toxicological data and is not accessible to semi-automatic evaluations.
- A time stamp ('last updated on…') for entries in the C&L Inventory would greatly increase possibilities for evaluating the data reported. A time stamp for every notification would be the best option, since this would allow differentiating notifications by update dates. As a minimum, a time stamp for the substance-specific entry in the C&L Inventory is required. While this would provide an overall picture, it would not, however, allow differentiating notifications by update dates.
- For prioritisation purposes, the use of classification information from REACH registration dossiers is encouraged, since such classifications (a) are generally considered reliable[123] and (b) considerably increases the number of substances. In the present study, 112/212 (53 %) of the substances were only prioritised due to classifications in REACH registration dossiers.

Checks of classification for toxicity endpoints

- The approach applied identified 12 substances that were assigned a Toxicity Score of 10, but which are currently not classified for any of the four endpoints assessed in any EU legal framework or in REACH registration dossiers. While such a classification is proposed/intended for 3 substances (see section 3.3.5), this is not the case for the remaining 9 substances. More detailed investigations of these compounds and possibly additional research to clarify the concerns are encouraged.

Prioritisation

- Based on the experience with the large dataset evaluated in this study, Pivot table selections appear to be superior to weighting scenarios in prioritisation, since they are not dependent on the distribution of values and allow defining criteria that must definitely be met, thereby preventing the prioritisation of substances that lack critical properties.
- A large number of substances (N=517) was identified that have high scores in all blocks except in the toxicity block. These substances are recommended to be screened in the future in relation to new toxicological data (e.g. classification for any of the four endpoints of interest). These 517 substances are made available to facilitate future evaluations (see section 5).

[123] While the reliability may be questioned in 'negative' cases (i.e. no classification), this statement relates to 'postive' cases (i.e. classifications for CMR properties and repeated dose toxicity) in the context of this study. Thus, there is no reason to assume that a registrant classifies a substance for these endpoints, if there are no reliable data supporting such a classification.

- Furthermore, 74 substances were identified that have high scores in all blocks except in block C (bioaccumulation in food/feed). These substances should be assessed in more detail, if their presence in food or feed is demonstrated. These 74 substances are made available to facilitate future evaluations (see section 5).
- Since these 517 and 74 substances, respectively, were not prioritised, this study did not check the substance type. As a consequence, these substances also refer to some UVCB substances. Before these substances are prioritised in the future based on new information, the substance type may be checked in the REACH registration dossiers.

In-depth evaluation

- Within this study, only 10 out of the 212 priority substances could be evaluated in-depth. The selection of these 10 substances does not imply that the remaining 202 substances are necessarily of a lower priority. In fact, in-depth evaluation of these substances is greatly encouraged.
- For an in-depth evaluation of larger datasets, a publicly available inventory of substances (with CAS numbers) included in IPCHEM would be very helpful. Currently, each substance needs to be searched separately, which is time-consuming for larger lists of substances. Furthermore, the restriction of access to some of the datasets avoids easy evaluation of the data.
- Of these 10 substances, monitoring in food/feed is generally recommended for four substances (tris(1,3-dichloro-2-propyl) phosphate [TDCIPP], CAS No.: 13674-87-8; Hexahydro-1,3,5-trinitro-1,3,5-triazine [RDX; Hexogen], CAS No.: 121-82-4; tetrahydrothiophene-1,1-dioxide [Sulfolane], CAS No.: 126-33-0; N-butylbenzenesulfonamide [NBBS], CAS No.: 3622-84-2), while monitoring in environmental media is generally recommended as a first step for the remaining six substances in order to get more insight into the extent of their environmental occurrence. There are some exceptions from these general recommendations, which are described in more detail in section 3.5.2.
- The approach for the in-depth evaluation was useful in identifying relevant data and data gaps. It is recommended for in-depth evaluations of other priority substances.
- Prior to any in-depth evaluation, the abiotic degradation of a substance should be evaluated to prevent spending resources on substances that are rapidly degraded under environmental conditions. However, abiotic degradation only reflects primary degradation and would need to consider the degradation products (also see discussion in section 2.2.2). Since this potentially involves time-consuming manual evaluation steps, such an evaluation may not be feasible in most instances. In a pragmatic approach, substances showing rapid abiotic degradation are of a lower priority for in-depth evaluation. While specific criteria are lacking, rapid abiotic degradation may be defined by half-lives of less than 2 days (as applied to experimental hydrolysis data in section 3.5.1).

Proposal on possible next steps

As many as 212 'potential emerging risks' have been identified as substances considered (a) to be released to the environment and/or to be poorly biodegradable, (b) to bioaccumulate in food/feed and (c) to possess a chronic human health hazards. An in-depth evaluation carried out on 10 of these substances has shown that even such a detailed evaluation may not allow a conclusion on whether these substances actually qualify as 'emerging risks'. Considering that the limitations experienced in the evaluations of the selected 10 'potential emerging risks' are likely common to most of the 212 substances, it is very important to consider other possible approaches that could facilitate the in-depth evaluation of the 'potential emerging risks'. They are as follows:

- **Option 1:** In-depth evaluation of the remaining 202 priority substances as recommended above (see bullet point 1 in the previous paragraph 'In-depth evaluation') may be performed as a next step. In-depth evaluation consists of scientific literature searches, quality assessment and extraction of experimental data (e.g. for biodegradation) and evaluation steps. Depending on the resources available, an in-depth evaluation may be performed for a sub-selection of the remaining 202 priority substances (e.g. those with the highest ranks in the weighting

scenarios). As discussed above, this may not demonstrate that these substances actually represent 'emerging risks'. However, the in-depth evaluation for 10 substances described in section 3.5.2 identified additional (albeit limited) information that further asserts that some of these substances could pose emerging risks.

- **Option 2:** A qualitative assessment of the occurrence in food/feed and/or environmental media for all 212 substances by non-target (suspect) screening approaches may be a better alternative. Due to the diverse nature of the substances, different analytical methods are likely to be required (such as liquid chromatography and gas chromatography with high-resolution mass spectrometric detection). In contrast to Option 4, such an approach would not aim at analysing representative samples and determining actual concentrations in food/feed items, but rather check whether these substances are detected in different food items. This approach could be focused on unprocessed food/feed items. The goal of this exercise would be to identify additional substances among the 212 that could be the subject of more exhaustive monitoring as described in Option 4. The type and number of samples could be set in agreement with resources available.
- **Option 3:** In the context of an in-depth evaluation, an assessment of Chemical Safety Reports (CSRs) is considered meaningful (see box 'Assessment of human exposure via the food chain in REACH registration dossiers' in section 4). An assessment of CSRs would provide information about the following elements:
  - The tonnage applied in each use, which could overcome the major uncertainty in block A.
  - Confirmation of the assessment based on predicted data in block B using experimental biodegradation data (i.e. the key value derived in the CSRs; see sections 2.2.3 and 3.2.3).
  - Human exposure via the environment (including dietary exposure due to releases to the environment) is typically assessed in the Chemical Safety Reports. While these assessments are likely to be associated with considerable uncertainty (see box 'Assessment of human exposure via the food chain in REACH registration dossiers' in section 4), an evaluation of these assessments of human exposure via the feed/food chain is envisaged to provide some indication of whether the results in block C of this study are meaningful or not (i.e. the relevance of dietary exposure).

  The assessments presented in CSRs are not publicly available and are based on confidential data (e.g. the tonnage per use). Evaluation of the CSRs will therefore require a confirmation by ECHA that access to these CSRs can be granted. Furthermore, the evaluation needs to account for confidentiality issues, which limit the level of detail that can be reported in such evaluations. However, a qualitative judgement (confirmation or not of the results of this study) is considered possible. Due to confidentiality issue and practical considerations, an evaluation of data in the CSRs at ECHA premises in Helsinki is recommended.
- **Option 4:** Monitoring in food/feed for four substances and monitoring in environmental media for six substances in the in-depth evaluation (see bullet point 2 in the previous paragraph 'In-depth evaluation'). Such monitoring requires extensive resources to produce representative data. Depending on the available budget, it may be necessary to limit monitoring activities to one substance (e.g. TDCIPP) and to make use of existing monitoring programmes (i.e. using the same samples analysed for food contaminants with the addition of this one substance in the analysis). Furthermore, it may be appropriate to analyse only raw, unprocessed food/feed items to avoid evaluating a possible entry of the substance during food processing or from food contact materials. This would further decrease the number of samples that need to be analysed. Monitoring in environmental media is not the first priority of EFSA and may not be within the remit of all the competent authorities in the Member States cooperating with EFSA on food/feed-related issues. It is therefore likely that such monitoring campaigns, which also require substantial resources, would need to involve other Commission services and Directorate Generals as well as authorities on environmental safety in the Member States.

  It should be noted that the recommendations on monitoring were derived from the in-depth evaluation of the ten substances. While these ten substances are registered at high tonnages and ranked comparatively high in the weighting scenarios (see section 3.5.1), they are not

considered to be of a higher priority than the remaining 202 priority substances. The monitoring activity under option 4 would therefore only cover few of the 212 substances, or even only one substance.

- Each option has its strengths and weaknesses. The options are not mutually exclusive and can be combined in a meaningful way or followed in a step-wise manner. For example, Option 2 may be run first and Options 1 and/or 3 may then be added only for those substances detected in the non-target screening analyses under Option 2. However, it is also conceivable that Option 2 may be directly followed by Option 4, if e.g. a substance is unequivocally detected in all samples analysed in the non-target screening. Therefore, the results of the first option followed may well decide on the most meaningful next step and this may be different for different substances. In any case, the options followed will depend on the budget available.

Other recommendations

- The procedure developed within this study aimed to identify potential emerging chemical risks in the food chain. Many of the data generated in this study as well as the general approach can be used in other applications as well. Illustrative examples for such applications are discussed in the following box.

Box: Illustrative examples for using the approach and the data generated in this study

This appendix provides illustrative examples how the general approach and the data generated in this study may be used in other applications by different stakeholders. Three stakeholders (authorities, industry and research) were chosen for these illustrative examples but some data may be of interest for other stakeholders as well. Furthermore, some applications are assigned to 'research' (intended to mean academic research), but may equally be useful for researchers in industry and authorities.

Several lists of data were generated in this study that form the basis to illustrate possible applications for the three stakeholders:

- List of all 2 336 substances assessed in this study,
- List of 212 substances identified as priority substances,
- List of 517 substances with scores > 5 in all blocks except the toxicity block,
- List of 74 substances with scores > 5 in all blocks except block C (bioaccumulation in food/ feed).

These lists are provided as supplementary material to this report as a Microsoft Excel® file.

All lists contain the same information, i.e. scores for blocks A, B, C and toxicity as well as additional information, such as physico-chemical properties, tonnage information, toxicity classification and individual scores for all food/feed items assessed in this study.

Since the data contained in these lists may be useful for different stakeholders, possible applications are discussed starting from these lists. Finally, possible applications of the general approach are discussed, focussing using ACC-HUMANsteady modelling for bioaccumulation in food/feed. Figure 46 provides an overview of the possible applications. It must be stressed that these examples are illustrative and non-exhaustive.

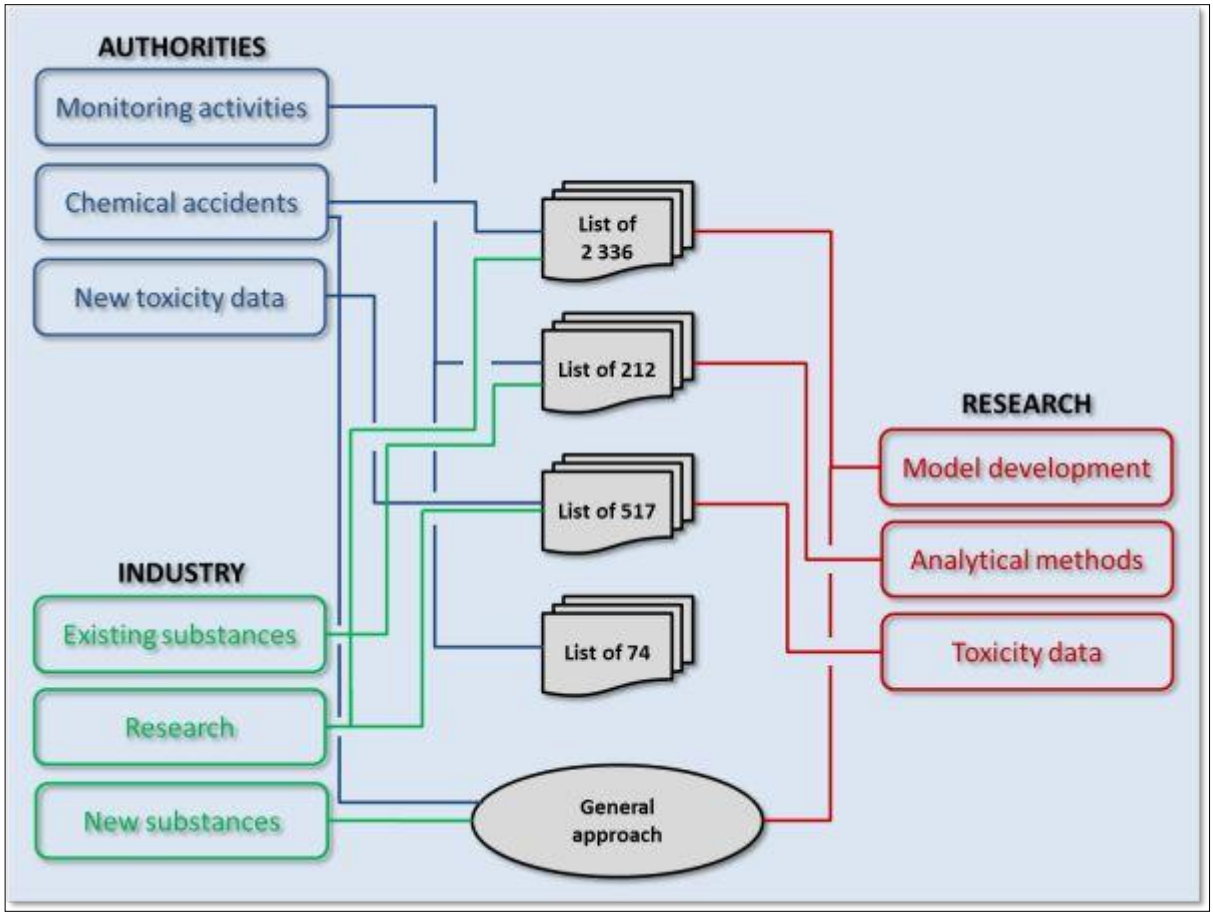

Figure 46: Illustrative examples of using the approach and the data generated in this study

It is essential to read the relevant sections in this report prior to using the data for other applications to fully understand the methodology employed and its limitations.

List of all 2 336 substances assessed in this study

This list contains all 2 336 substances assessed in this study as described in sections 2 and 3 of this report.

Authorities

This list may be useful for authorities in the case of chemical accidents as a simple look-up table. It allows easy identification of substances predicted to possess a potential for accumulation in the food chain and also identifies potentially relevant food/feed items. For example, in the case of identified (accidental) releases of melamine and sulfolane (see in-depth evaluation sheets for these two substances in section 3.5.2) such an approach may have identified the need for additional monitoring in food/feed items. If a substance is not contained in this list, the general approach using ACC-HUMANsteady modelling may be applied (see below).

Research

The list may also be useful for academic research. For example, the scores for block A (environmental releases) may be compared with findings using other approaches to assess potential environmental releases. For example, a recent study (Schulze et al., 2018) assessed the environmental emission potential of a different (though potentially overlapping) set of substances registered under REACH using a different methodology. Furthermore, the list contains scores for predicted biodegradation using the approach described in section 2.2.2. These data may be used for comparisons with other prediction approaches or experimental data (also see the validation exercise in section 3.2.3). Finally, the predicted accumulation potential in food/feed can be compared with predictions in other models or with the screening criteria provided in different regulatory frameworks. A limited comparison with the screening criteria for bioaccumulation in air-breathing (i.e. terrestrial) organisms (ECHA, 2017a) is shown in section 3.2.4, but this may be extended to more detailed evaluations.

Industry

The possible applications described above for research may also be relevant for research carried out in industry. In addition, the list may be useful for industry to identify existing substances that may (or may not) possess a potential for bioaccumulation in the food chain. This may e.g. be one of many building blocks in a weight-of-evidence approach to assess bioaccumulation in aquatic and terrestrial organisms. It must, however, be stressed that the predicted potential for accumulation in the food chain cannot be taken on its own to prove or disprove such a potential. Rather, the predicted potential should be considered as a first indication that may initiate further investigations (e.g. an in-depth evaluation as performed for the 10 substances in section 3.5 or experimental studies).

All stakeholders

Finally, the results of this study may also be used by all stakeholders as a basis for additional evaluations. For example, it is possible to substitute the results in one particular block by other data. If a research group or an authority e.g. believes that they have a better model to predict the biodegradation potential, they may want to substitute the results for block B with their own data.

List of all 212 substances identified as potential emerging risks

This list contains all 212 substances identified as priority substances as described in sections 2.4 and 3.4 of this report. These substances were (a) predicted to be released to the environment and/or to be not readily biodegradable, (b) predicted to possess a potential for bioaccumulation in the food chain and (c) identified to possess a chronic toxicological hazard based on their classification for carcinogenicity, mutagenicity, reprotoxicity or repeated dose toxicity. In addition to the list of 2 336 substances, this list also contains the assessment of other listings, such as inclusion in ECHA's OpenFoodTox database or various ECHA lists, as described in sections 2.5 and 3.5.

Authorities

As already indicated in sections 3.4 and 3.5, this list includes all substances identified as priority substances and these substances are not of a lower priority than the 10 substances selected for in-depth evaluation. Rather, the 10 substances were selected in a pragmatic approach considering the time and budget restraints of this study. As a consequence, all 212 substances may be assessed in more detail and, for example, be included in monitoring activities by authorities. Such monitoring activities may include monitoring in STP effluents and river water to assess their environmental occurrence (or other appropriate compartments depending on the physico-chemical properties of the substance as discussed for two substances in section 3.5.2)), but may also involve monitoring in food/feed if a substance is already known to be present in the environment. It is recognised that the number of substances is high, but the data in this list allow easy selection of substances meeting specific criteria. Thus, it is possible to further prioritise substances for specific needs. For example, the 212 substances are reduced to 17 substances if only substances are considered that (a) have a harmonised classification for carcinogenicity (Cat. 1A, 1B or 2) and (b) have a maximum REACH registration tonnage of 1 000 tpa or more. Most of these substances (12/17) are not included in EFSA's OpenFoodTox database. These substances may therefore be more relevant for further investigations than e.g. substances that are (a) classified for repeated dose toxicity only and (b) have a maximum REACH registration tonnage of 100 tpa or less (N=26). These selection criteria for further prioritisation are only examples. Most importantly, the data included in the list allow selection of substances based on user-defined criteria.

This list of 212 substances may also be used as a starting point for authorities (e.g. ECHA) to check the assessment of human exposure via the food chain in existing Chemical Safety Reports in REACH registration dossiers. In fact, a comparison of the findings of this study with results presented in REACH registration dossiers could provide very valuable insights. For example, if a high ranking substance in this study is found to have comparatively high risks in the assessments performed in the Chemical Safety Report, this may support the evaluation presented here. If, in contrast, the assessment in the Chemical Safety Report concludes that risks are very low, reasons for the discrepancies may be identified. For example, the data presented in the Chemical Safety Report may show that the substance is primarily used in processes with little or no release to the environment.

Research

As another illustrative example, researcher with an interest in the development of new analytical methods may use this list to identify substances predicted (a) to be released to the environment (analytical methods for monitoring in air, water and/or soil/sediment depending on the physico-chemical properties) and (b) to accumulate in food/feed (analytical methods for monitoring in food/feed). Again, the data in this list can be used to further limit the number of substances, e.g. by focussing on those predicted to be released to and persist in the environment (high Score A (or high tonnage) and high Score B). Importantly, the list also contains partition coefficients (log Kow, log Koa and log Kaw) that allow gaining a first evaluation on whether monitoring should focus on aqueous or solid fractions (or fatty tissues in the case of food).

Industry

For industry, this list may be interesting for an assessment of existing substances. The assessment referred to above in relation to all 2 336 substances may focus on these 212 substances, since these were prioritised in the present study. An examination by industry of these 212 substances may include all elements of this assessment and not be limited to bioaccumulation in food/feed (as already discussed above for all 2 336 substances). For example, the present assessment of environmental releases (block A) is limited by the fact that tonnage reflects the overall tonnage without differentiation by the use. As discussed in sections 2.2.1 and 3.2.1, the maximum REACH registration tonnage is not necessarily related to uses responsible for a high ERC Score. In fact, a large fraction of the tonnage may be used in uses associated with low environmental releases for some substances. This limitation has already been identified in the pilot study (Bitsch et al., 2016). Since information on the tonnage per use is only included in the CSRs, which are not publicly available, this limitation still exists in the present study. However, registrants do have access to this information and can review the environmental releases assumed in their CSRs. In some cases, this may support the evaluation of this study, while in other cases such a review may identify overestimates of environmental releases

(e.g. if environmental releases for the uses with the highest tonnage can be demonstrated to be low). Similarly, the predicted biodegradation data may be compared with experimental data. As shown in the limited validation exercise in section 3.2.3, the approach chosen in this study may lead to some overpredictions (i.e. substances predicted to be not or only poorly biodegradable, while in fact they are readily biodegradable). This is meaningful for a screening approach, but the assessment may be refuted by valid experimental data.

List of 517 substances with scores > 5 in all blocks except the toxicity block

This list contains all 517 substances that are not prioritised since they have a Toxicity Score of 1 (i.e. they are currently not classified for any of the relevant endpoints (see sections 2.3 and 3.3 of this report). However, these 517 substances have scores > 5 in all other blocks, i.e. they have a score > 5 in both block A and block B (unlike the prioritisation, which also selected substances with a score > 5 in either block). These substances will therefore become of a high priority, if new data indicate a chronic health hazard (e.g. if they are classified for carcinogenicity in a reliable source).

Authorities

Authorities in EU Member States engaged in the harmonised classification of substances under the CLP Regulation can use this list as a 'watch list'. If one of these substances is newly classified for one of the relevant endpoints (carcinogenicity, mutagenicity, reprotoxicity or repeated dose toxicity), this may initiate further activities, such as an in-depth evaluation as performed for the 10 substances in section 3.5 or monitoring in the environment and/or food/feed).

Research

Researchers engaged in the generation of new toxicity data may use this list as a source of substances that are particularly interesting. For example, *in vitro* testing or high-throughput screening for relevant endpoints may be more meaningful for this set of substances than for substances with little potential for exposure. Again, the data in the list allow further prioritisation based on user-defined criteria, such as the tonnage. In this context, it may be worthwhile to focus efforts on high tonnage substances if endpoints currently not assessed as a standard information requirement under the REACH Regulation are concerned (e.g. endocrine disruption). In contrast, experimental data for the endpoints assessed in this study are required for high tonnage substances under the REACH Regulation. If these endpoints are under investigation (e.g. in a new *in vitro* or high-throughput assay), it may be more meaningful to focus on substances of lower tonnage for which experimental data are not required under the REACH Regulation. Furthermore, limiting the substances to specific molecular weight ranges (if relevant for a specific assay) is possible with the data contained in the list. For example, substances with a molecular weight at or above 500 g/mol may be excluded from further investigations (N=134), since they are predicted to be poorly absorbed according to Lipinski's 'rule of 5' (Lipinski et al., 2001).

Industry

Industry researchers may be interested in this list to identify substances that are worthwhile for further investigations on the toxicity as described in the previous paragraph.

List of 74 substances with scores > 5 in all blocks except block C (bioaccumulation in food/feed)

This list contains all 74 substances that are not prioritised since they have a Score C < 5, while they have scores > 5 in all other blocks, i.e. they have a score > 5 in both block A and block B (unlike the prioritisation, which also selected substances with a score > 5 in block A or block B). These substances will therefore become of a high priority, if data on their occurrence in food/feed become available. If a substance can be demonstrated to be present in food/feed in relevant amounts, this would disprove the assessment in this study.

Authorities

For authorities holding monitoring data on the occurrence of substances in food/feed, this list may be useful. Available monitoring data could be checked against this list to identify substances that may need to receive more attention. For example, this list contains 16 substances that are classified for

CMR endpoints (i.e. not only classified for repeated dose toxicity) in a joint classification. Since they are classified for these endpoints only by registrants without a corresponding harmonised classification, these substances may have gone unnoticed in any schemes based on harmonised classifications only. Even when petroleum products are excluded from this list, 10 substances remain in the selection. Such substances are likely to require further investigation should they be detected in food/feed.

Research and industry

No specific applications for research and industry are identified.

General approach

The general approach further developed from the pilot study (Bitsch et al., 2016) and applied in this study to many more substances has some parallels to similar approaches. For example, the combination of tonnage and use information to predict environmental releases as employed in this study is common approach (see e.g. most recently Schulze et al., 2018). Also, using a battery approach to predict biodegradation is well accepted and generally considered superior to the use of predictions from single models (see e.g. Boethling et al., 2004; Posthumus et al., 2005). While the approach taken for blocks A and B therefore has some parallels with other approaches, the specific methodology is different (e.g. in the scoring applied). This allows comparisons of the results of this study for these blocks with those obtained in other studies as discussed above for the list of all 2 336 substances. With respect to the assessment of toxicity, using classification information is also regularly employed in prioritisation and is indeed one of the key elements in the identification of substances of very high concern under the REACH Regulation.

This study is unique in the approach taken to assess the potential accumulation of a large set of chemicals in the food chain, both in terms of the tools employed (ACC-HUMANsteady modelling rather than simple prioritisation based on partition coefficients) and the scoring approach (based on relative concentrations in different food/feed items). The following illustrative examples therefore focus on the assessment of potential bioaccumulation in food/feed.

In order to use ACC-HUMANsteady[124], substances must be within the applicability domain of the model and several input data need to be generated (preferably with the QSAR Toolbox). Both steps are described in detail in the pilot study (Bitsch et al., 2016) and in section 2.2.4 of this report.

Authorities

As discussed above, ACC-HUMANsteady may be applied to identify substances with a potential for bioaccumulation in food/feed in the context of chemical accidents. While such an assessment has been performed in this study for 2 336 substances, chemical accidents may involve substances not included in the corresponding list. In this case, authorities may perform ACC-HUMANsteady modelling and score the bioaccumulation potential of a substance according to the methods described in section 2.2.4 using the distribution data in Table 25 in section 3.2.4.

It is recognised that users have to familiarise themselves with the software, its handling and its scientific background. This application may only be suitable for people experienced in running modelling tools and with more advanced expertise in using Microsoft Excel®.

Research

Researchers with an interest in model development may be interested in applying ACC-HUMANsteady and compare the results with other models. As already indicated above, this may be done by using the scoring results included in the list of all 2 336 substances. However, researchers may want to compare different tools with another set of substances than assessed in this study or they may e.g. want to use a different scoring approach than applied here.

Industry

For industry, application of ACC-HUMANsteady to new substances may be interesting in order to identify a potential for bioaccumulation in food/feed early in the process. Again, such an assessment may follow the methods described in section 2.2.4 using the distribution data in Table 25 in section

[124] ACC-HUMANsteady is available from http://www.ufz.de/osiris/index.php?en=22157&m=1, last accessed October 2018.

3.2.4. Again, positive results of such an assessment should not be taken as demonstrating such a potential, but rather be interpreted as an indication that further investigations may be meaningful. The extent of such investigations will also depend on other properties of a substance, such as anticipated environmental releases, biodegradability and toxicity.

All stakeholders

As stated above for the results included in the list of all 2 336 substances, results from ACC-HUMANsteady modelling (as applied in this study) may also be combined with other approaches. For example, researchers in authorities, academia or industry may want to use ACC-HUMANsteady for a different set of substances than the one assessed in this study and then combine results with other data for toxicity, environmental releases and biodegradation.

The general approach developed as well as the data generated in this study provide a basis for many more applications. Making available all individual scores ensures flexibility in using the data for a variety of different purposes.

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Abbreviations

AM	Arithmetic mean
BCF	Bioconcentration Factor
BDE	Brominated Diphenyl Ether
BOD	Biochemical Oxygen Demand
BPR	Biocidal Product Regulation
bw	body weight
CAS	Chemical Abstracts Service (number), a unique numerical identifier
CHESAR	Chemical Safety Assessment and Reporting (software)
C&L(I)	Classification and Labelling (Inventory)
CLP	Classification, Labelling and Packaging (Regulation)
COD	Chemical Oxygen Demand
CoRAP	Community Rolling Action Plan
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
DDT	Dichlorodiphenyltrichloroethane
DOC	Dissolved Organic Carbon
dw	dry weight
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
EMA	European Medicines Agency
ERC	Environmental Release Category
EUSES	European Union System for the Evaluation of Substances (software)
FAO	Food and Agriculture Organization of the United Nations
GM	Geometric mean
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
ICH	International Council for Harmonisation
IPCS	International Programme on Chemical Safety
ITER	International Toxicity Estimates for Risk
IUCLID	International Uniform Chemical Information Database (software)
JECFA	Joint Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LO(A)EL	Lowest Observed Adverse Effect Level
MOA	Mode of action
MoU	Memorandum of Understanding
MRL	Maximum Residue Level
NLM	National Library of Medicine (USA)
NO(A)EL	No Observed Adverse Effect Level
NONS	Notified New Substances under previous (pre-REACH) chemicals legislation
OECD	Organisation for Economic Co-operation and Development
PACT	Public Activities Coordination Tool
PAHs	Polycyclic Aromatic Hydrocarbons
PCBs	Polychlorinated Biphenyls (dl-PCBs: dioxin-like PCBs)
PCDD/Fs	Polychlorinated dibenzo-dioxins/furans

PBT	Persistent, bioaccumulative and toxic (substances)
PNECs	Predicted No Effect Concentrations
RAR	Risk Assessment Report
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (Regulation)
RDT	Repeated dose toxicity
SAR	Structure-Activity Relationships
SAs	Structural alerts
SCoFCAH	Standing Committee on the Food Chain and Animal Health
SIDS	Screening Information Datasheets
SMILES	Simplified Molecular Input Line Entry Specification
STOT RE	Specific Target Organ Toxicity – Repeated Exposure
STP	Sewage Treatment Plant
TG	Testing Guideline (OECD)
ThCO2	Theoretical Carbon Dioxide (production)
ThOD	Theoretical Oxygen Demand
tpa	Tonnes per annum
TSCF	Transpiration Stream Concentration Factor
UVCB	Substances of Unknown or Variable composition, Complex reaction products or Biological materials
WFD	Water Framework Directive (EU)
WHO	World Health Organization
WoE	Weight of Evidence
ww	wet weight

Appendix A – Additional information on substance selection

This appendix provides in-depth analyses of the various steps of substance selection and provides illustrative examples.

Substances with a full registration and a CAS number

Figure 47 illustrates the number of registrations differentiated by registration type and availability of a CAS number. In addition, the number of registrations with tonnage information is shown as well as the number of registrations associated with a maximum REACH registration tonnage of 10 000 tonnes per annum (tpa) or more.

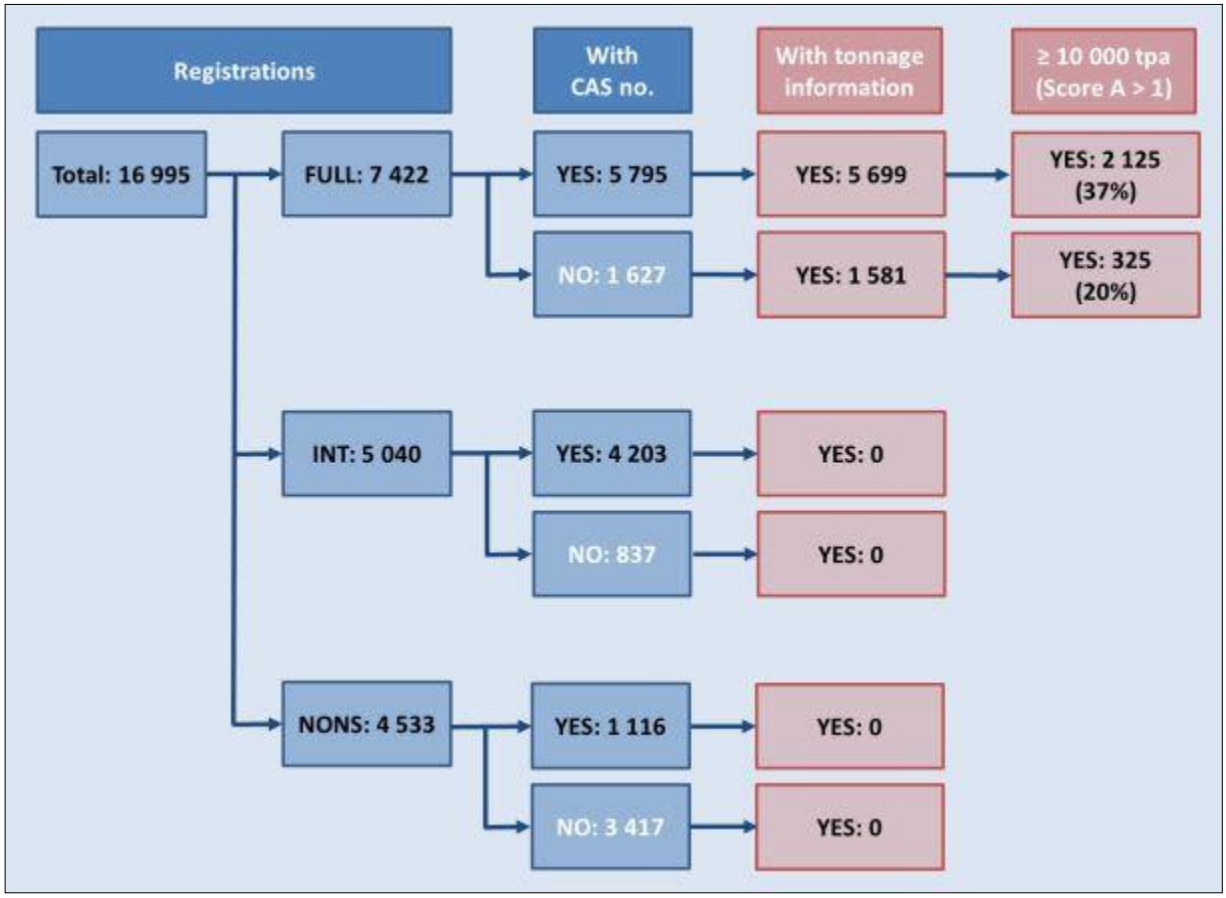


Figure 47: Overview of all registrations under REACH retrieved from ECHA CHEM
Includes duplicate registrations as well as entries with more than one CAS number per substance name
FULL: full registrations; INT: intermediate registrations; NONS: substances notified under Directive 67/548/EEC that are considered registered under REACH

The data show that tonnage information is only available for full registrations, while it is not publicly available for intermediate registrations and NONS. Substances registered with intermediate registrations only are excluded because low emissions to the environment are expected due to their use under strictly controlled conditions.

Lacking CAS number

A total of 1 627 full registrations (1 463 unique substances) are excluded from further evaluation, since a CAS number is missing. Figure 47 shows that the fraction of substances with a maximum REACH registration tonnage of 10 000 tpa or higher is substantially lower among these registrations than among the full registrations with a CAS number. More differentiated analyses indicate that the fraction of full registrations with a maximum REACH registration tonnage yielding very high tonnage

scores of 4 or 5 in block A is also higher among the registrations with a CAS number (8.5 %) than among those without a CAS number (3.1 %; Table 51).

Table 51: Overview of full registrations differentiated by CAS number availability: tonnage and submission type

Registration tonnage and submission type[a]	With CAS No. (n=5 795)	Without CAS No. (n=1 627)
Tonnage		
Tonnage Data Confidential	1.7 %	2.8 %
<10 000 tpa (tonnage score 1)	62 %	77 %
10 000 - < 100 000 tpa (tonnage score 2)	19 %	12 %
100 000 - < 1 000 000 tpa (tonnage score 3)	9.3 %	5.0 %
1 000 000 - < 10 000 000 tpa (tonnage score 4)	5.0 %	2.2 %
10 000 000 tpa or higher (tonnage score 5)	3.5 %	0.9 %
Submission type		
Individual	14 %	41 %
Joint	86 %	59 %

(a): Tonnage score according to Bitsch et al. (2016); the tonnage score for cases of missing data will be discussed in the next interim report.

The data presented in Table 51 also show that the fraction of registrations submitted by consortia ('joint submissions') is higher among the registrations with a CAS than among those without a CAS number.

Further analyses of the 3.1 % registrations without a CAS number but with tonnages of 1 000 000 tpa or higher indicate that these almost exclusively relate to UVCB substances, such as hydrocarbon mixtures, fuels and other petroleum products, reaction masses and substances such as 'Ashes (residues), coal', 'Calcium dihydroxide precipitated with carbon dioxide during sugar juice purification', 'Inorganic residual from kraft or soda pulping separated from green liquor in the chemical recovery cycle', 'Shale oils, heavy' and 'Slags, nickel smelting'.

NONS

The case of NONS is different, since these are excluded primarily for lacking information. In contrast to full and intermediate registrations, CAS numbers are only available for a comparatively small fraction of NONS (1 116/4 533 (25 %); 5 795/7 422 (78 %) for full registrations). A CAS number, however, is required for the evaluation of substances (see section 2.1.2).

Even for those NONS that have a CAS number assigned, no information on the tonnage and on ERCs (Environmental Release Categories) is available. This lack of information would prevent the calculation of a score for block A, unless default values are chosen. The use of default values would assign high scores to these substances, which would increase the risk of high numbers of 'false positives' with respect to block A.

It must be stressed that some substances registered as NONS also have a full registration. These substances were initially registered as NONS but required an update of the registration. The main reason for such updates is an increase in the tonnage. We analysed all substances that have both a NONS and a full registration with respect to the tonnage of the full registration. Since the tonnage of the full registration is usually available and since the full registration tonnage is typically higher than the one of the NONS registration (since a full registration is only required for a NONS in the case of a tonnage increase), such a comparison allows gaining insight into the tonnage of the NONS registration. Due to the lack of a CAS number for the majority of these substances, we compared the registrations based on the EC number (available for all NONS registrations).

Overall, 457 of the 4 533 NONS registrations (11 %) also have a full registration. Table 52 provides an overview of the maximum REACH registration tonnages for these substances.

Table 52: Overview of tonnage information on NONS registrations for substances that also have a full registration

Registration	Number of registrations[(a)]
NONS registrations with a full registration	457
Full registration maximum tonnage confidential	20 (4.4 %)
Full registration maximum tonnage < 10 000 tpa	418 (91 %)
Full registration maximum tonnage ≥ 10 000 tpa	19 (4.1 %)

(a): Number of registrations as evaluated from the extracted information.

These data suggest that NONS registrations primarily relate to substances manufactured in low tonnages. Among the NONS that were updated with a full registration, 91 % of all registrations are below 10 000 tpa, which would result in the minimum score in block A for the tonnage. While 19 registrations are at a maximum tonnage of 10 000 tpa or higher (4.1 %), only two of these[125] have a maximum REACH registration tonnage above 1 000 000 tpa. In contrast, 2 450 of all 7 422 full registrations (33 %) have a maximum tonnage of 10 000 tpa or higher (37 % among the full registrations with a CAS number).

These evaluations support the notion that NONS registrations primarily relate to substances with low tonnages. However, it remains uncertain, whether this can be generalised for all NONS registrations.

We also analysed the information that could be extracted from the QSAR Toolbox for the 1 116 NONS registrations that are assigned a CAS number (corresponding to 1 116 substances). For the majority of substances, no SMILES notation could be assigned in the QSAR Toolbox (604 of the 1 065 datasets retrieved[126]; 57 %) and for most of them, even a name of the substance is missing. No properties could be predicted for these substances. Among the 461 datasets identified by a SMILES notation, 274 datasets (corresponding to the same number of substances) fall within the applicability domain defined in section 2.1.4. Among them, 58 (21 %) also have a full registration and are therefore selected on the basis of the procedure described in sections 2.1.1-2.1.4. Two of these substances were excluded from the final evaluation due to a positive charge and since properties could not be predicted in the QSAR Toolbox (see section 2.1.5). The remaining 56 substances are included in the final set of 2 336 substances that enter the evaluation (see section 3.1.4).

Conclusion

Overall, these evaluations suggest that NONS primarily reflect low tonnage substances that have no CAS number assigned. Even if a CAS number has been assigned, a name and a SMILES notation could often not be identified within the QSAR Toolbox. Of the NONS defined by a CAS number and a SMILES notation, 274 conform to the eligibility criteria and could therefore in principle be evaluated. However, tonnage and use information is missing for most of these substances. As mentioned above, using default worst case scores for such substances will likely lead to many 'false positives' and was therefore judged to be detrimental to the purpose of this study. However, such information is available for 21 % of these substances, since they also have a full registration. These substances are included in the evaluation.

More than 75 % of the full registrations lacking a CAS number have low tonnages. While the loss of these substances is not ideal, the number of substances that would have been eligible and also yield high scores in block A appears to be small on the basis of the analyses presented above.

Substances with a SMILES notation

This selection step removes substances without a SMILES notation from further evaluation. Handling of large datasets requires that this step is performed in an automated way. As described in section 2.1.3, SMILES notations for the substances characterised by their CAS number were retrieved from the QSAR Toolbox. The results presented in section 3.1.2 show that a SMILES notation could not be retrieved for 1 062 (16 %) of the datasets (corresponding to the same number of substances). Moreover, for 117 of these (11 %) a name is missing in the extracted data.

[125] The two NONS registrations with a high tonnage are both UVCB substances (a C18-C50 distillate and a C8-C16 kerosene).
[126] The number of datasets retrieved is lower, since the QSAR Toolbox prevents the export of datasets claimed confidential.

A screening of the remaining 945 datasets (substances with a CAS number and a name, but lacking a SMILES notation) indicated that the substances covered are mostly UVCB substances, are outside the applicability domain (e.g. inorganics) or a combination of both. This finding is not surprising, since it is difficult or impossible to assign a representative SMILES notation to an UVCB substance. In order to analyse this issue statistically, substances were assigned to one of the groups shown in Table 53. The assignment was based on the name given in the dataset (usually the name under which the substance was registered). In some cases, REACH registration dossiers were consulted for clarification. A few substances already contained the description as 'UVCB' in the name, while others were registered as UVCB substances ('confirmed UVCB" in Table 53). Note that many of the other substances are also UVCB substances (e.g. petroleum products), but this was not specifically checked in the REACH registration dossier.

The high number of 945 datasets did not allow a full assessment of all datasets. As a consequence, 18 % of the datasets were not assigned to one of the groups. However, such an analysis was performed for 225 datasets related to substances with a maximum REACH registration tonnage of 100 000 tpa or higher. Such substances would be assigned a score of 3 or higher for the tonnage in block A. The results of these analyses are also shown in Table 53 (the missing 2 % (5 substances) are discussed below).

Table 53: Illustrative examples of substances excluded due to lacking SMILES notation (maximum REACH registration tonnage 100 000 tpa or higher)

Group	All datasets (n=945)	Datasets with maximum tonnage of 100 000 tpa or higher (n=225)[(a)]
Petroleum products, hydrocarbon mixtures, fuels etc.	14 %	44 %
Reaction products and reaction masses	15 %	3 %
Fatty acids and similar with different chain length (no reaction products)	10 %	6 %
Other hydrocarbons with variable carbon chain length or similar	10 %	8 %
Organometallics	3 %	1 %
Polymer(ic)	7 %	4 %
Metals, alloys, residues etc.	5 %	15 %
Inorganics	12 %	12 %
Biologicals and similar	6 %	4 %
Confirmed UVCB	1 %	1 %
Total	**82 %**	**98 %**

(a): Tonnage cut-off refers to the maximum of the REACH registration tonnage.

These data clearly indicate that the vast majority of datasets relate to substances that (a) are potentially UVCB substances (e.g. petroleum products, fatty acids and other hydrocarbons of variable carbon chain length) or (b) are inorganic, organometallic or other substances outside the applicability domain of the models used in this study.

In support of this interpretation, Table 54 provides illustrative examples for these substances with a maximum REACH registration tonnage of 100 000 tpa or more. The names of these substances also illustrate the fact that representative SMILES notations are impossible to establish for many of them.

Table 54: Illustrative examples of substances excluded due to lacking SMILES notation (maximum REACH registration tonnage 100 000 tpa or higher)

CAS no.	Name	Group[(a)]
101316-59-0	distillates (petroleum), hydrodesulfurized middle coker	Petroleum products
101316-72-7	lubricating oils (petroleum), c24-50, solvent-extd., dewaxed, hydrogenated	Petroleum products
101316-84-1	tar, brown-coal, low-temp.	Petroleum products
102242-52-4	fatty acids, c6-24 and c6-24-unsatd., me esters, distn. residues	Fatty acids
1079184-43-2	ethanaminium, 2-hydroxy-n-(2-hydroxyethyl)-n,n-dimethyl-, esters with c16-18 and c18-unsatd. fatty acids, chlorides	Fatty acids
121575-60-8	pitch, coal tar, high-temp., heat-treated	Petroleum products
12737-27-8	chromium iron oxide	Inorganics
1302-93-8	mullite (al6o5(sio4)2)	Inorganics
1410795-90-2	reaction mass of 2,3-dihydroxypropyl formate and 1,3-dihydroxypropan-2-yl formate and 1-(formyloxy)-3-hydroxypropyl formate and 3-(formyloxy)-2-hydroxypropyl formate	Reaction products and reaction masses
142844-00-6	refractories, fibers, aluminosilicate	Inorganics
160901-19-9	alcohols, c12-13, branched and linear, ethoxylated	Other hydrocarbons
32055-14-4	formaldehyde, oligomeric reaction products with aniline and phosgene	Reaction products and reaction masses
65996-65-8	iron ores, agglomerates	Metals, alloys, residues etc.
65997-18-4	frits, chemicals	Inorganics
66071-94-1	corn, steep liquor	Biologicals and similar
67711-95-9	slimes and sludges, copper electrolytic	Metals, alloys, residues etc.
68187-51-9	zinc ferrite brown spinel	Inorganics
68333-89-1	benzene, (1-methylethyl)-, oxidized, polyphenyl residues	Polymer(ic)
68475-76-3	flue dust, portland cement	Inorganics
68476-30-2	fuel oil, no. 2	Petroleum products
68476-80-2	fats and glyceridic oils, vegetable, deodorizer distillates	Biologicals and similar
69011-71-8	aluminum, dross	Metals, alloys, residues etc.
69029-67-0	flue dust, lead-refining	Metals, alloys, residues etc.
70131-50-9	bentonite, acid-leached	Inorganics
8028-48-6	orange, sweet, extract	Biologicals and similar
84604-16-0	saccharomyces cerevisiae, ext.	Biologicals and similar
84625-32-1	eucalyptus, globulus, extract	Biologicals and similar
84696-55-9	tin, melting residues	Metals, alloys, residues etc.
85681-75-0	alkenes, c10-14	Other hydrocarbons
85711-46-2	fatty acids, c14-18 and c16-18 unsatd., maleated	Fatty acids
91722-09-7	slags, steelmaking, converter	Metals, alloys, residues etc.
91770-15-9	kerosine (petroleum), sweetened	Petroleum products
928771-01-1	alkanes, c10-20-branched and linear	Other hydrocarbons
93333-79-0	ashes (residues), plant	Biologicals and similar
93685-99-5	oil shale, thermal processing waste	Inorganics
93819-94-4	zinc bis[o-(6-methylheptyl)] bis[o-(sec-butyl)] bis(dithiophosphate)	Organometallics
97722-02-6	glycerides, tall-oil mono-, di-, and tri-	Other hydrocarbons
97808-88-3	lead, bullion	Inorganics

(a): Fatty acids: Fatty acids and similar with different chain length (no reaction products); other hydrocarbons: Other hydrocarbons with variable carbon change length or similar; Petroleum products: petroleum products, hydrocarbon mixtures, fuels etc.

Overall, 5 of the 225 datasets with a maximum registration tonnage ≥ 100 000 tpa or confidential tonnage information (2 %) could not be assigned to any of the groups and therefore are potentially relevant. Table 55 lists these substances together with the tonnage information retrieved from ECHA CHEM.

Table 55: Information on the 5 substances excluded due to lacking SMILES notation, which are not UVCB substances (maximum REACH registration tonnage ≥ 100 000 tpa or confidential tonnage information)

CAS no.	Name	Tonnage information
1393708-17-2	3-(diethylcarbamoyl)pyridinium-1-yl]propane-1-sulfonate	Tonnage Data Confidential
232938-43-1	benzenesulfonamide, 4-methyl-n-[[[3-[[(4-methylphenyl)-sulfonyl] oxy] phenyl] amino] carbonyl]-	Tonnage Data Confidential
61571-06-0	Tetrahydrothiopyran-3-carboxaldehyde	Tonnage Data Confidential
8013-17-0	Sugar, invert	100 000 tpa
94239-04-0	2-fluoro-6-trifluoromethylpyridine	Tonnage Data Confidential

These substances are all clearly defined, mono-constituent substances except the sugar, which is a multi-constituent substance[127]. Despite the fact that they are not UVCB substances, no SMILES notation could be retrieved from the QSAR Toolbox. Essentially, the QSAR Toolbox retrieves SMILES notations for the imported CAS numbers from databases embedded in the QSAR Toolbox. For the substances discussed here, none of these databases contains a SMILES notation. In addition, no SMILES notation could be retrieved manually for these substances from the EpiSuite™ software or the Danish EPA QSAR database.

As a consequence, these substances are not considered further. Only the sugar, which is highly unlikely to represent a potential emerging risk in the food chain, has a high tonnage. While the tonnage is claimed confidential for the other four compounds, little information is available for these substances, suggesting that they are not produced in very high amounts. The use information in the REACH registration dossiers also suggests limited use of these compounds.

As a final check, US EPA's 'Chemistry Dashboard'[128] was used to check the availability of SMILES notations for these 1 062 substances. A SMILES notation could only be retrieved for 74 of these 1 062 substances (7.0 %) and only 20 of these are assigned a high quality in this database. Six of these 20 substances are ionised. These findings support the data extraction process using the QSAR Toolbox. SMILES notations are also lacking when this additional source is used and the ones retrieved are generally of a low quality and/or refer to substances outside the applicability domain of the models used in block B and C.

Exclusion of substances outside the applicability domain

The distribution of the results for the 5 631 datasets with a SMILES notation (see section 3.1.2) is shown in the following table for the three profilers[129]. Note that results are presented for the three profilers individually (combined results are presented below). Profiling results that define eligible substances according to the criteria defined in section 2.1.4 are highlighted in bold print.

Table 56: Distribution of profiling results of the three QSAR Toolbox profilers

Ionisation at pH 7.4 (ION)		Substance type (ST)		Groups of elements (GoE)	
90-100	35 %	**Discrete chemicals**	**68 %**	**Non-Metal**	**61 %**
80-90	**0.11 %**	Discrete chemical|Dissociating chemical	13 %	**Halogens|Non-Metals**	**9 %**
70-80	**0.20 %**	Discrete chemical|Dissociating chemical|Inorganic	3.1 %	Alkali Earth[(a)]	12 %
60-70	**0.14 %**	Discrete chemical|Inorganic	7.5 %	Transition metals[(a)]	9 %
50-60	**0.14 %**	Mixture	3.1 %	Metalloids|Non-Metals	3 %
40-50	**0.50 %**	Inorganic|Mixture	1.4 %		

[127] Information whether a substance is a mono-conctituent, multi-comstutuent or UVCB substane is available from REACH registration dossiers.
[128] https://comptox.epa.gov/dashboard/dsstoxdb/advanced_search, accessed February 2017.
[129] See section 2.1.4 for details on these profilers.

Ionisation at pH 7.4 (ION)		Substance type (ST)		Groups of elements (GoE)
30-40	**0.36 %**	Anion or cation[(a)]	2.9 %	
20-30	**0.43 %**			
10-20	**0.78 %**			
0-10	**45 %**			
No[(b)]	**17 %**			
Total	100 %		99 %	94 %
Selected	**65 %**		**68 %**	**70 %**

(a): Profiled for this class, but may also be profiled for other classes by the same profiler, e.g. 'Anion|Inorganic|Mixture' in the ST profiler.
(b): No pKa and no pKb value predicted

The data show that 35 % of the datasets are excluded because the substances are predicted to be ionised at pH 7.4 by more than 90 %. The distribution also indicates that the cut-off of 90 % ionisation has little impact, since only few datasets fall within the next classes. In fact, the data indicate a clear dichotomy of datasets: 35 % of the substances are predicted to be ionised to a very large degree, while 45 % are predicted to be ionised to a very low degree, with 17 % showing missing pKa and pKb values. Only 3 % are distributed among the intermediate classes.

A given substance may be assigned to one or more classes of the substance type (ST) and the groups of elements (GoE) profilers. The data in Table 56 only show the resulting classes found most often, i.e. the total only adds up to 99 and 94 %, respectively. With respect to the substance type, 744/5 631 datasets (13 %) of the datasets are profiled as 'Discrete chemical|Dissociating chemical'. It must be noted, however, that in combination with the ionisation (ION) profiler and the groups of elements (GoE) profiler, only 104 datasets meet the selection criteria. Among these 104 datasets, only 2 do not contain an ionised substance.

For datasets to be eligible, the criteria of all three profilers defined in section 2.1.4 must be met. Figure 48 shows the selection process based on the three QSAR Toolbox profilers. It is evident that more than 60 % of the datasets meet the criteria of each individual profiler (also see Table 56 above). Furthermore, more than 50 % of the substances meet the criteria of any two profilers combined (e.g. 2 900/5 631 (52 %) for the ST and ION profilers combined). This fraction decreases to 47 % (2 600/5 631 datasets) when all three profilers are combined.

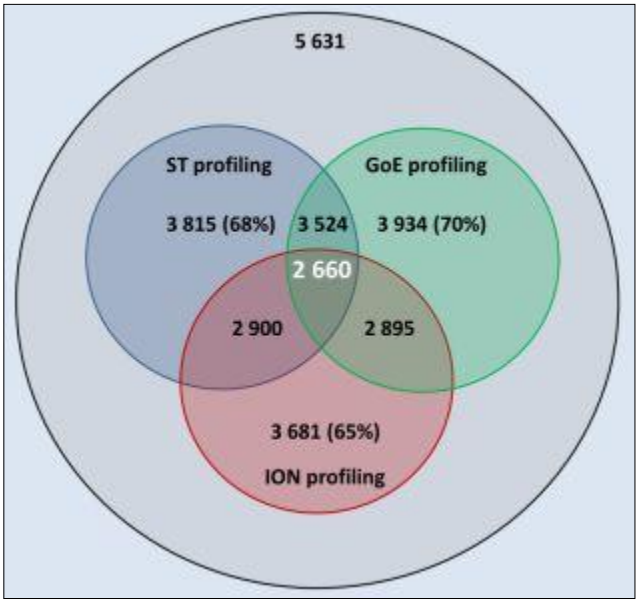


Figure 48: Summary of the selection based on QSAR Toolbox profilers.
QSAR Toolbox profilers: ST – substance type; GE – groups of elements; ION: ionisation at pH 7.4.

Figure 48 above analyses the selection of datasets based on profiling results, while Figure 49 below analyses the exclusion of datasets (i.e. the percentages given relate to the 2 971 excluded datasets). These analyses show that the ION profiler alone leads to the highest reduction in the 2 971 excluded datasets. For example, almost 30 % of the datasets are excluded because the substances are predicted to be ionised at pH 7.4, although these substances meet the criteria of the other two profilers ('ION' in Figure 49). In contrast, less than 10 % of the excluded datasets are excluded because of the ST and GoE profiling results alone, i.e. the criteria of the other two profilers are met ('ST' and 'GoE' in Figure 49). The ION profiler either alone or in combination with any or all of the other profilers leads to the exclusion of 66 % of the datasets (Figure 49).

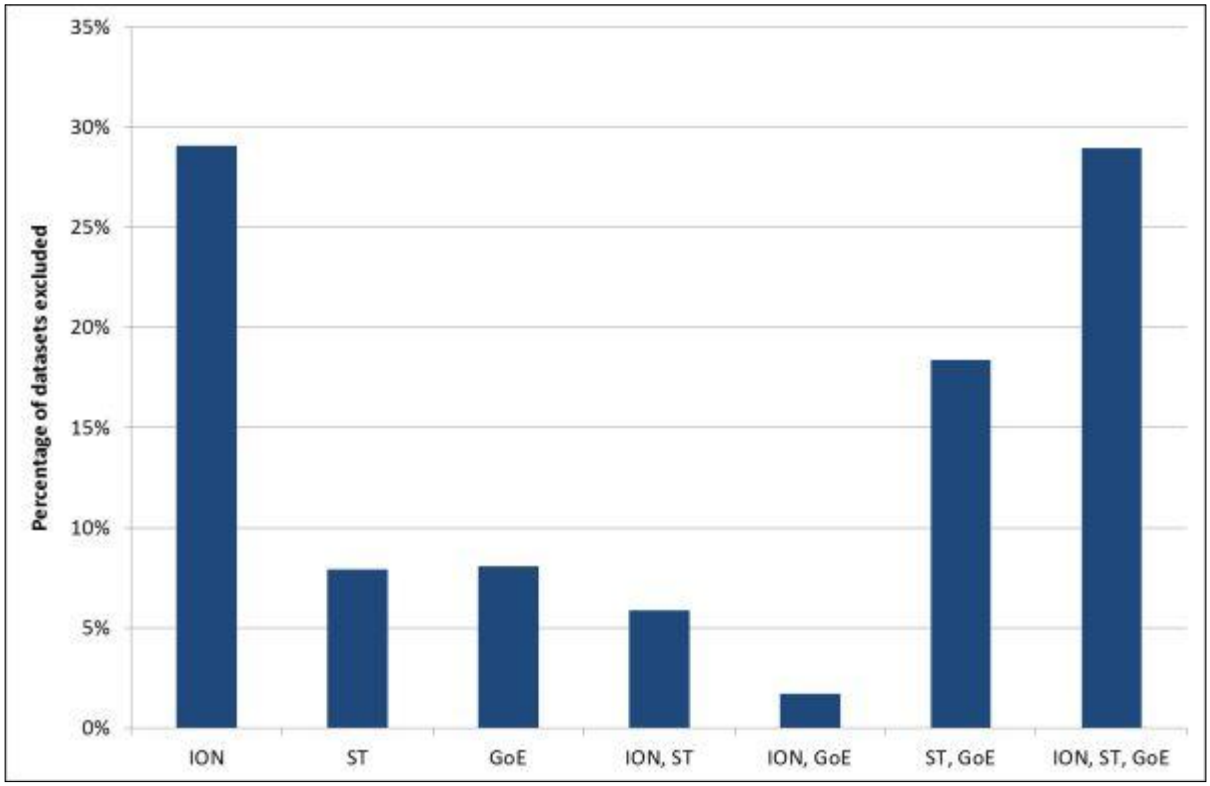


Figure 49: Summary of the exclusion based on QSAR Toolbox profilers.
QSAR Toolbox profilers: ST – substance type; GoE – groups of elements; ION: ionisation at pH 7.4.

Overall, these findings suggest that application of the exclusion criteria lead to a well-founded set of selected substances. In order to further analyse the exclusion process, results from another QSAR Toolbox profiler were used. The ECOSAR profiler assigns chemicals depending on their structure to chemical classes ranging from 'acid halides' to 'vinyl/ally sulfones'. More than 100 classes are implemented in the ECOSAR profiler and any given substance may be assigned to one or several classes (e.g. if it contains several functional groups). If the substance is not assigned to a class defined by a specific structural feature, it is generally assigned to the class 'neutral organics' (e.g. acetone and benzene). Neutral organics represent the class on which most of the models used in this study were originally based.

The data in Table 57 show that one third of the selected datasets are assigned to this class, while less than 1 % of the excluded datasets are. The excluded datasets, on the other hand, contain many datasets assigned to classes of acids, inorganic compounds and/or salts (some double counting occurs in these classes). Almost all of the datasets reflecting an acid functionality according to the ECOSAR profiler are excluded due to a high degree of ionisation predicted by the ION profiler. Note, however, that the selected datasets also include some substances classified with an acid functionality by the ECOSAR profiler (1.2 %). However, these are predicted to be ionised at pH 7.4 to a lower degree.

While some double counting occurs, a large number of datasets are characterised as inorganic and/or salts in the excluded datasets, while none of the selected datasets are assigned to such classes. This

again shows that the approach applied leads to the exclusion of substances outside the applicability domain of the models used in this study.

Table 57: Results of ECOSAR profiling for selected and excluded datasets

ECOSAR class	Selected datasets	Excluded datasets
Neutral organics[(a)]	33 %	0.84 %
Acids[(b)]	1.2 %	19 %
Inorganic compound[(b)]	0	8.8 %
Salts[(c)]	0	15 %
Should not be profiled[(a)]	0	25 %
Not related to an existing ECOSAR class[(a)]	4.5 %	17 %
Not classified[(a)]	0.19 %	2.9 %

(a): Assigned only to this class.
(b): Class starts with this term, but may include other classes, i.e. may involve double counting with other classes evaluated.
(c): Class contains 'salt' anywhere, i.e. may involve double counting with other classes evaluated.

Note that 25 % of the excluded datasets relate to structures that are outside the applicability domain of the ECOSAR profiler ('should not be profiled'). This class is assigned by the profiler, if a metal ion is encountered in the SMILES notation. In agreement with the approach chosen, none of the selected datasets relates to substances containing a metal ion (these were excluded by the GoE profiler). In addition, the excluded datasets also include a high fraction of substances that could not be assigned to one of the ECOSAR profiler classes. Most of these datasets were excluded due to the result of the ionisation profiler either alone or in combination with the other profilers.

Overall, these additional analyses using an independent fourth profiler illustrate that the approach chosen correctly excludes substances outside the applicability domain of the models used for evaluation. Table 58 provides illustrative examples for substances excluded by the ION, ST and GoE profilers. The results of ECOSAR profiling, while not used in the exclusion process, is shown for information.

Table 58: Examples of excluded substances

CAS no.	Name	Profiler[(a)]			
		ION	ST	GT	ECOSAR profiler
2458-08-4	3α,7α-dihydroxy-12-oxo-5β-cholan-24-oic acid	***Acidic [90,100]***| Basic [0,10)	Discrete chemical	Non-Metals	Not related to an existing class
7446-11-9	sulfur trioxide	No pKa value| No pKb value	Discrete chemical| ***Inorganic***	Non-Metals	Inorganic Compound
91770-03-5	fatty acids, tall-oil, reaction products with boric acid and diethanolamine	Acidic [0,10)| Basic [0,10)	Discrete chemical	***Metalloids***| Non-Metals	Amides
2272-11-9	ethanolamine oleate	Acidic [0,10)| ***Acidic [90,100]|*** ***Basic [90,100]|*** No pKb value	***Mixture***	Non-Metals	Aliphatic Amines| Surfactants-Anionic
2489-05-6	silver docosanoate	***Acidic [90,100]|*** No pKb value	Discrete chemical	Non-Metals| ***Transition Metals***	SHOULD NOT BE PROFILED
5188-07-8	sodium methyl mercaptan	Acidic [0,10)| Basic [0,10)	Discrete chemical| ***Dissociating chemical***	***Alkali Earth***| Non-Metals	Salt|Thiols and Mercaptans
2457-01-4	hexanoic acid, 2-ethyl-, barium salt	***Acidic [90,100]|*** No pKb value	Discrete chemical| ***Dissociating chemical***	***Alkaline Earth***| Non-Metals	SHOULD NOT BE PROFILED

(a): Reasons for exclusion are highlighted; the results of ECOSAR profiling were not used in the exclusion procedure, but for validation purposes only (see text for details).

Removal of duplicates and exclusion of non-eligible substances

The removal of duplicates depending on the availability of an EINCES number is straightforward and well justified (see section 2.1.5, step 1). The data in Table 59 show that the majority of duplicate datasets was removed in this step.

Table 59: Summary of the removal of duplicates

Step[a]	Number of datasets
Total entering evaluation	2 657
Removed due to lacking EINECS number (step 1)[b]	196
Removed due to formula/structural inconsistency (step 2)	54
Removed due to identical predictions (step 3)	5
Total removed duplicates (steps 1-3)	255
Total remaining after steps 1-3	2 402

(a): The steps are described in section 2.1.5.
(b): These datasets were only removed when another dataset with an EINCES number for the same substance was available.

To examine the selection based on EINCES numbers assigned, the quality rating within the QSAR Toolbox was checked. The QSAR Toolbox rates the quality of the relations between (a) CAS number and name, (b) name and 2D representation and (c) CAS number and 2D representation. The overall quality of these relations is shown in the QSAR Toolbox in coloured font, with high quality being shown in green, moderate quality in orange and low quality in red.

Figure 50 shows an overview of the information on substance identification for hydroxycitronellal (CAS No.: 107-75-5) that was already discussed in section 3.1.4. The first structure has an EINECS number assigned and was therefore selected. Note that this structure also has a high quality rating in the CAS number and the chemical name fields, while the second (removed) structure has not.

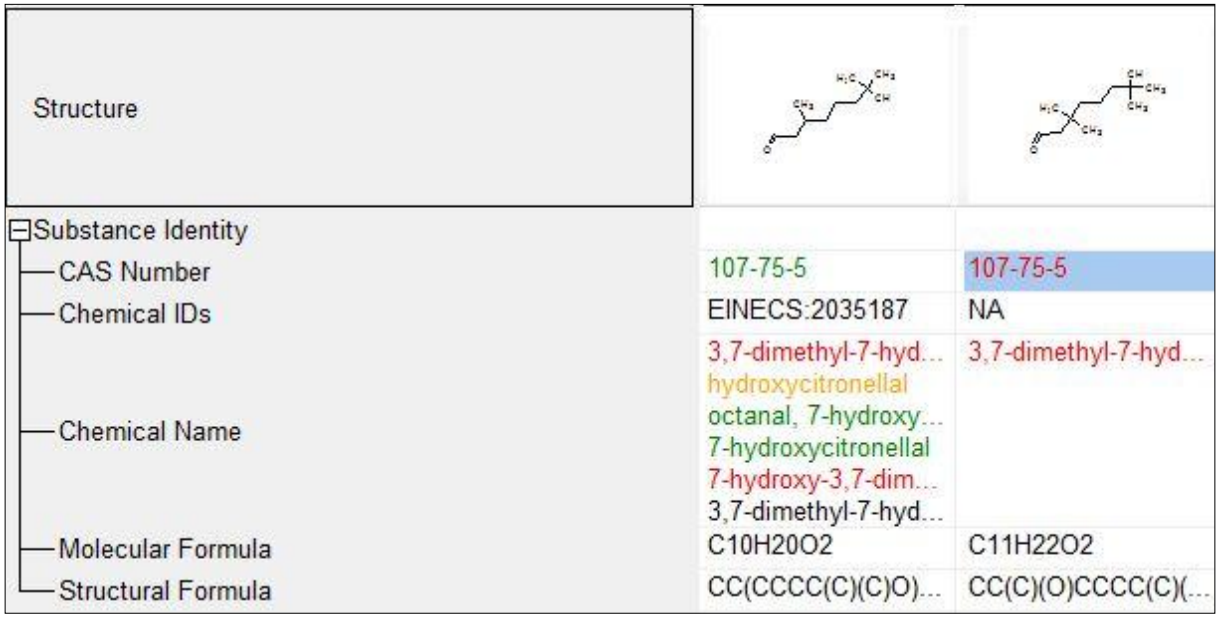
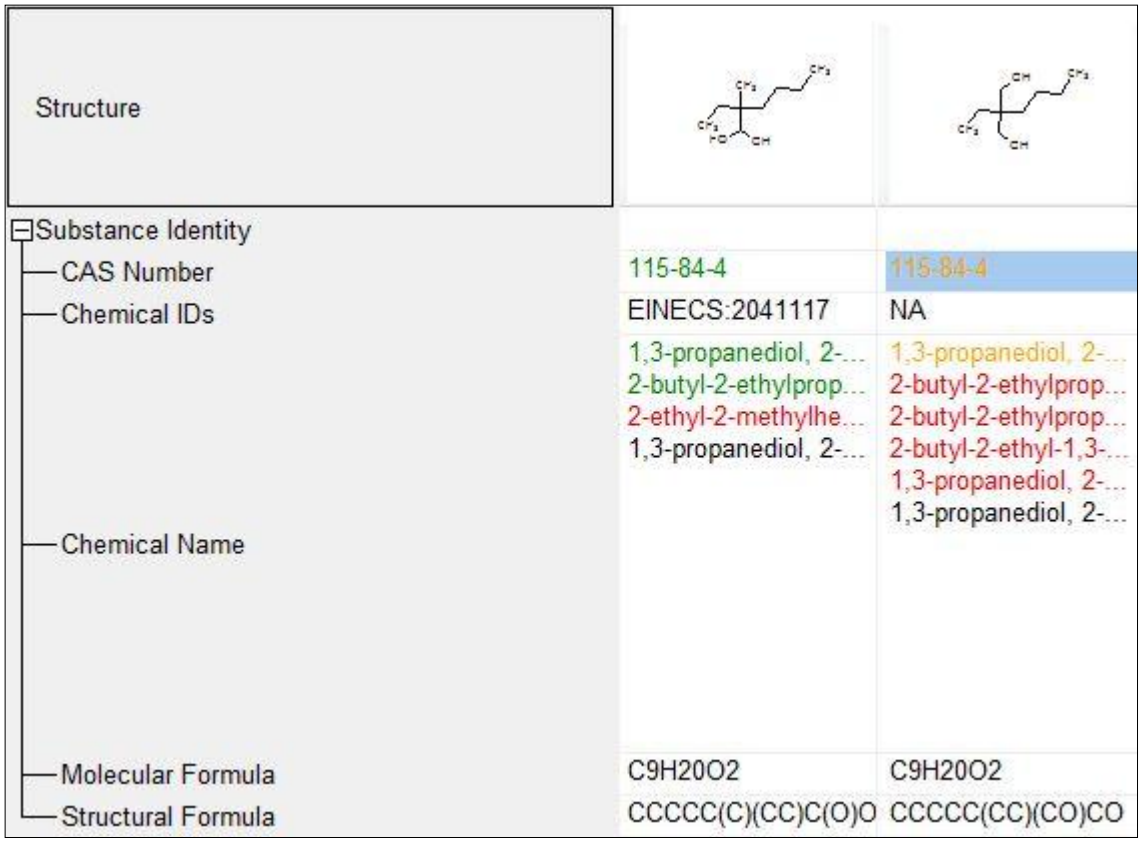


Figure 50: Print screen of information on duplicate datasets in the QSAR Toolbox for CAS number 107-75-5.

The second example shows two datasets for 1,3-propanediol, 2-butyl-2-ethyl- (CAS No.: 115.84-4). Again, the first structure with an EINCES number is assigned a high quality rating, while the second structure is not and was therefore removed from the dataset (Figure 51).



Structure		
Substance Identity		
CAS Number	115-84-4	115-84-4
Chemical IDs	EINECS:2041117	NA
Chemical Name	1,3-propanediol, 2-... 2-butyl-2-ethylprop... 2-ethyl-2-methylhe... 1,3-propanediol, 2-...	1,3-propanediol, 2-... 2-butyl-2-ethylprop... 2-butyl-2-ethylprop... 2-butyl-2-ethyl-1,3-... 1,3-propanediol, 2-... 1,3-propanediol, 2-...
Molecular Formula	C9H20O2	C9H20O2
Structural Formula	CCCCC(C)(CC)C(O)O	CCCCC(CC)(CO)CO

Figure 51: Print screen of information on duplicate datasets in the QSAR Toolbox for CAS number 115-84-4.

There are a few cases, where the quality rating does not support the selection based on the EINECS number. For example, three datasets were retrieved within the QSAR Toolbox for tetrahydromethy-1,3-isobenzofuranedione (CAS No.: 11070-44-3). Figure 52 shows that only the first structure is assigned a high quality in both the CAS number and the chemical name field, while the structure with an EINECS number is assigned only medium quality. Since selection based on the presence of an EINECS number was semi-automatic, the second structure was selected. The differences in physico-chemical parameters between these two structures, however, are small. For example, the log Kow of the first structure (removed) is 2.54, while it is 2.64 for the selected, second structure.

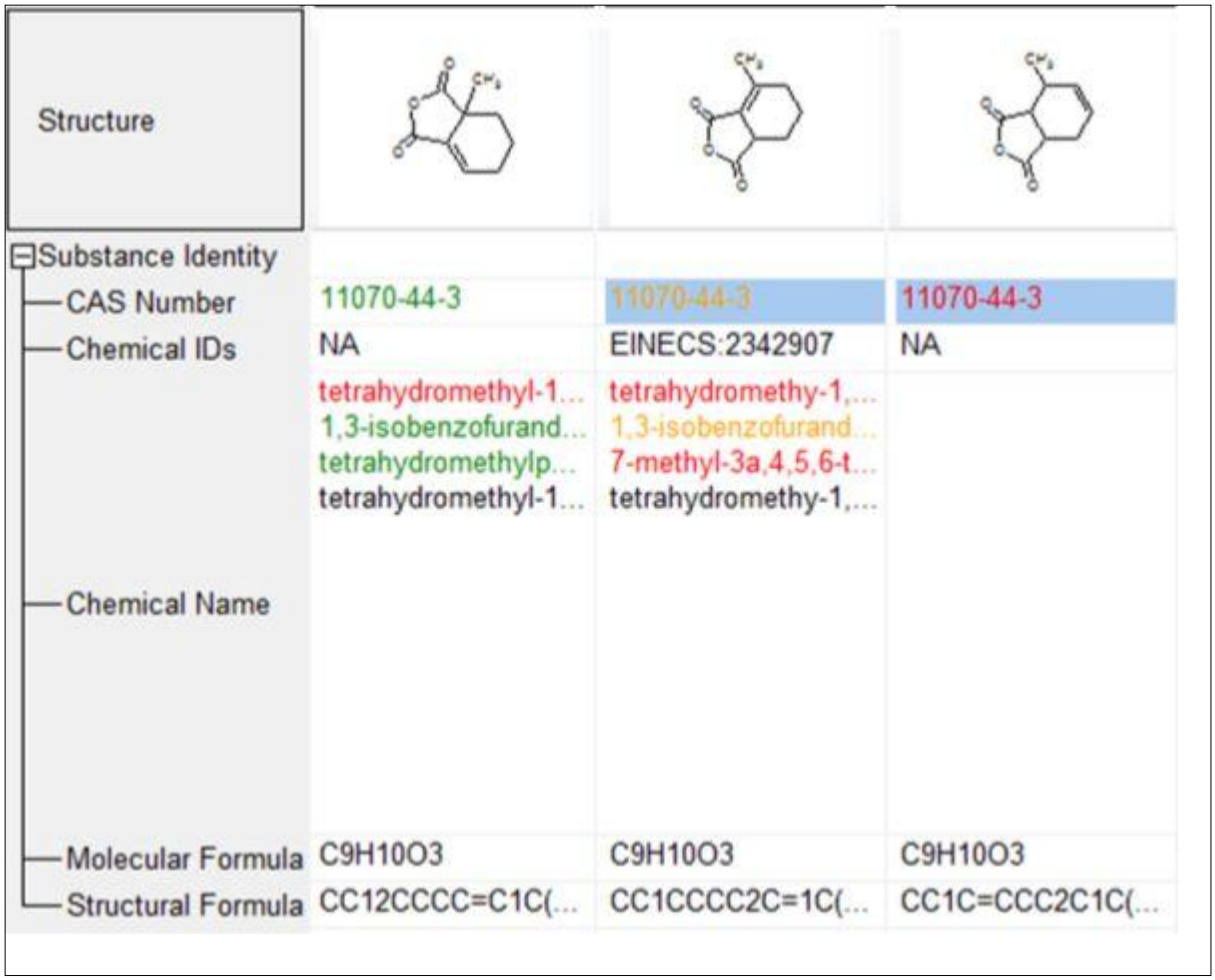


Figure 52: Print screen of information on duplicate datasets in the QSAR Toolbox for CAS number 11070-44-3.

Such cases occur very rarely. The quality for the CAS/2D relationship can also be exported from the QSAR Toolbox, allowing a statistical evaluation. The data in Table 60 show, that 1 684 of the 2 657 datasets (see Table 59) have an EINECS number. Of these, the majority is assigned a 'high quality' for the CAS/2D relationship, while this figure is only 1.4 %

Table 60: Quality summary for datasets with and without EINECS numbers

	With EINECS number (n=1 684)	Without EINECS number (n=973)
High quality	947 (56 %)	14 (1.4 %)
Lower levels of quality[(a)]	14 (0.3 %)	31 (3.2 %)
No quality rating in QSAR Toolbox[(b)]	723 (43 %)	928 (95 %)

(a): For example, 'High quality, conflict', 'Moderate, quality' and 'Low quality, conflict'.
(b): The quality rating is not exported for datasets, for which no experimental data were retrieved, a step that could not be performed for all 2 374 chemicals.

These data support the approach of prioritising datasets with an EINCES number (also see justification in 2.1.5).

The removal of duplicate datasets based on molecular formula and structural features (see section 2.1.5, step 2 required manual inspection of the molecular formulae and SMILES notations given in the datasets. Overall, 54 datasets were removed by these evaluations (Table 59), but none of the 2 374 substances were removed.

The 54 duplicate datasets were removed for a variety of reasons. In contrast to the examples presented in section 3.1.4 and those discussed above, most of these cases did not relate to questions of the most representative substance. Rather, the molecular formula or chemical structure represented by the SMILES notation was not consistent with the substance registered under REACH. While many substance-specific decisions had to be made, the two most common reasons are shown in the following table.

Table 61: Reasons for removal due to formula/structural inconsistency

Reason[(a)]	Percentage[(b)]
Molecular formula/weight did not agree with REACH registration dossier	69 %
Structure was inconsistent with REACH registration dossier	20 %
Other reasons	11 %

(a): REACH registration dossiers were the main source for checking formula/structural consistency, but other sources were occasionally consulted (see section 2.1.5).
(b): Percentage of removed duplicate datasets (step 2).

An example for duplicate datasets removed due to formula inconsistency was already presented in section 3.1.4. Another typical example is presented in Table 62. Three datasets differing in the molecular formula (and molecular weight as well as physico-chemical properties) were retrieved from the QSAR Toolbox for this UVCB substance. The molecular formula in dataset number 2 is clearly outside the range of the formula given in the REACH registration dossier and was therefore removed.

Table 62: Illustrative example of an UVCB substance with three duplicate datasets

Dataset	CAS no.	Name	MF-DS[(a)]	MF-REACH[(a)]	Conclusion
1	67701-27-3	glycerides, c14-18	C51H98O6	C45H86O6-C57H110O6	Retained
2	67701-27-3	glycerides, c14-18	C16H32O4		Removed
3	67701-27-3	glycerides, c14-18	C45H86O6		Removed

(a): Molecular formula given in the datasets (MF-DS) and the REACH registration dossier (MF-REACH).

The molecular formula in datasets 1 and 3 are both within the range given in the REACH registration dossier. However, the molecular formula of dataset 3 is at the lower end of the range given in the REACH registration dossier. Since dataset 1 relates to a substance in the middle of the range given in the REACH registration range, this substances was selected for further evaluation.

Further examination of the information in the REACH registration dossier revealed that this UVCB substance actually refers to glycerol triesters with three variable C14-C18 alkyl chains. Dataset 2, in contrast, relates to a monoalkyl ester. This conclusion was confirmed, when the structures of the SMILES notations were compared.

A last example of duplicate datasets removed on the basis of formula considerations relates to the substance 'benzene, ethenyl-, ar-bromo derivs.' (CAS No.: 125904-11-2). The data for the two duplicate datasets in Table 63 show that the two structures differ in the number of bromine atoms, which results in different log Kow values.

Table 63: Information in two datasets for 'benzene, ethenyl-, ar-bromo derivs.' (CAS No.: 125904-11-2)

Dataset	CAS no.	SMILES	Molecular formula	Log Kow
1	125904-11-2	C=Cc1cc(Br)ccc1Br	C8H6Br2	4.68
2	125904-11-2	C=Cc1ccccc1Br	C8H7Br	3.78

In this case, the REACH registration dossier states that the substance is composed of mono-, di- and tribromostyrene, but provides the molecular formula of dibromostyrene as the most appropriate representation. The dibrominated compound (dataset 1 in Table 63) was therefore selected for further evaluation.

As a general approach, duplicate datasets were removed (a) if the molecular formula/weight was outside or at the lower/upper end of the range reported in the REACH registration dossier and (b) a dataset with a more representative formula was available.

The second group of structural inconsistency (see Table 61) relates to duplicate datasets that have identical molecular formulae/weights. However, the chemical structure represented by the SMILES notation is different. An example for such datasets was given in section 3.1.4. Table 64 shows two more examples for which two duplicate datasets each were retrieved (both substances are registered as UVCB substances). In both cases, the duplicate datasets differ in the position (1 and 2) or presence (3 and 4) of double bonds. Inspection of the REACH registration dossiers for these substances indicated that non-4-ene (dataset 2) is the most representative structure for the first substance and prop-1-ene (dataset 4) is the most representative structure for the second substance. Datasets 1 and 3 were therefore removed.

Table 64: Illustrative examples of two duplicate datasets with differing structures

Dataset	CAS no.	Name	SMILES-DS[(a)]	REACH[(a)]	Conclusion
1	68526-55-6	alkenes, c8-10, c9-rich	CCCCCCCC=C	Non-4-ene	Removed
2	68526-55-6	alkenes, c8-10, c9-rich	CCCCC=CCCC		Retained
3	68606-26-8	hydrocarbons, c3	CCC	Prop-1-ene	Removed
4	68606-26-8	hydrocarbons, c3	CC=C		Retained

(a): SMILES notations given in the datasets (SMILES-DS) and name of representative substance in REACH registration dossier (REACH).

In both examples, the reference substances[130] assigned to the REACH registration substances confirmed the selection made. It is important to note that the name of the substance is not always a reliable indication of the most representative structure. In fact, 'hydrocarbons, c3' may be perfectly described by propane (dataset 3). Inspection of the REACH registration and the assigned reference substance, however, clearly indicate that 'hydrocarbons, c3' is most appropriately described by the unsaturated structure.

These two examples also demonstrate that an informed decision on a representative structure can be made for an UVCB substance in some cases. UVCB substances for which a representative structure could not be identified do, however, exist and were excluded from further evaluation (see below).

Finally, only a very small fraction (5/255 duplicate datasets removed, 2 %) was removed because the duplicates led to identical predictions in critical parameters.

All the steps described above resulted in the removal of duplicate datasets. No substances were excluded during these steps. Rather, the most appropriate structures for a given substance were selected for further evaluation.

This procedure could not always be applied successfully, leading to the exclusion of substances from further evaluation. As shown in section 3.1.4 (Table 14), a total of 66 datasets representing 38 unique substances had to be excluded. Table 65 provides a more detailed overview of the reasons for exclusion.

Table 65: Summary of the excluded datasets and substances

Step[(a)]	Number of datasets	Number of substances
Total remaining after steps 1-3 (see Table 59)	2 402	2 374
Excluded substances (step 4: UVCB substances)	51	23
Excluded substances (step 5: no predictions)	11	11
Excluded substances (step 5: charged substances)	4	4
Total excluded	**66**	**38**
Total remaining	**2 336**	**2 336**

(a): The steps are described in section 2.1.5.

[130] See footnote 23 for details on the use of reference substances.

The majority of datasets (51/66, 77 %) and substances (23/38, 61 %) excluded relate to UVCB substances for which no representative structure could be identified[131]. A typical example is shown in Table 66, representing a substance commonly known as polypropylene glycol. Molecular formulae for the two duplicate datasets differ substantially, as do physico-chemical properties (e.g. log Koa) and predicted values for biodegradation.

Table 66: Illustrative example of an UVCB with two duplicate datasets: substance excluded

Dataset	CAS no.	Name	MF-DS(a)	MF-REACH(a)	Conclusion
1	25322-69-4	propane-1,2-diol, propoxylated	C15H32O6	(C3H6O)n H2O	Excluded
2	25322-69-4	propane-1,2-diol, propoxylated	C3H8O2	n= >1-<4.5	Excluded

(a): Molecular formula given in the datasets (MF-DS) and the REACH registration dossier (MF-REACH).

The data indicate that dataset 2 is outside the range of the REACH registration substance. It represents propylene glycol rather than polypropylene glycol. The compound described in dataset 1 is also outside the range, since it represents a compound with n=5 (5 moles propoxylated rather than less than 4.5 moles as defined in the REACH registration substance). Both datasets and, as a consequence, the substance were therefore excluded from the evaluation.

In this case, a representative structure could probably be defined, e.g. tri- or tetrapropylene glycol. However, manual addition of structures was not within the scope of this project. In addition, while both structures (as well as several others) are given as constituents of the REACH registration substance, the public data do not allow a judgement on their representativeness (i.e. whether they are main constituents).

This case therefore illustrates the difference between UVCB substances that were retained in the evaluation (i.e. a representative structure was defined in the REACH registration dossier (see above for examples)) and UVCB substances that were excluded, because none of the available structures in the duplicate datasets could be identified as representative.

Another example relates to a petroleum product, namely liquefied petroleum gas (LPG; Table 67).

Table 67: Illustrative example of an UVCB with two duplicate datasets: substance excluded

Dataset	CAS no.	Name	MF-DS(a)	MF-REACH(a)	Conclusion
1	68476-85-7	petroleum gases, liquefied	C5H12	Not applicable	Excluded
2	68476-85-7	petroleum gases, liquefied	C4H10		Excluded

(a): Molecular formula given in the datasets (MF-DS) and the REACH registration dossier (MF-REACH).

Both the REACH registration dossier and the reference substance assigned state that a molecular formula is not applicable. The reference substance assigned to the registration substance is described as a 'complex combination of hydrocarbons produced by the distillation of crude oil', consisting of 'hydrocarbons having carbon numbers predominantly in the range of C3 through C7 and boiling in the range of approximately -40°C to 80°C'. While butane and pentane (represented by the two datasets) are within this range, the datasets were excluded due (a) to the complex nature of the substance and (b) the consideration that LPG is outside the applicability domain of the models used (and are likely to be irrelevant for accumulation in food).

A final example illustrates that even substances that appear to be well defined on the basis of the name may be UVCB substances (Table 68).

[131] This includes a single polymer for which the two structures retrieved from the QSAR Toolbox were found not to be adequate (see Table 69) as well as a single mono-constituent substance, for which one structure retieved was not representative, while the other referred to a salt.

Table 68: Illustrative example of an UVCB with two duplicate datasets: substance excluded

Dataset	CAS no.	Name	MF-DS[(a)]	MF-REACH[(a)]	Conclusion
1	11136-60-6	decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate	C24H46O5	Substance is UVCB, consisting of numerous unknown constituents, no definite structural formula can be provided	Excluded
2	11136-60-6	decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate	C32H60O6		Excluded

(a): Molecular formula given in the datasets (MF-DS) and the REACH registration dossier (MF-REACH).

The information in the REACH registration dossier indicates that this in fact is a UVCB substance. The reference substance[132] assigned to this registration substance provides several entries for the molecular formula. While some molecular formulae are provided (C30H56O6; C36H68O6; C32H60O6), most entries stated that the molecular formulae cannot be provided, since this substance is a UVCB substance. Overall, the conclusion in the REACH registration dossier that no definite structure can be provided led to the exclusion of this substance from further evaluation.

In addition to the 23 UVCB substances excluded, 11 substances were excluded since at least one critical parameter could not be predicted. Log Koa could not be predicted for any of the 11 substances and biodegradation predictions were missing for 3 of them. These 11 substances primarily constitute complex organic salts (n=4) or oligosaccharides (n=3). Carbon monoxide, which is clearly irrelevant in the context of this study, was excluded in this step and 3 additional substances registered at low tonnages (see below).

Overall, 87 % of the 38 substances excluded are registered with a maximum tonnage of 10 000 tpa or lower (resulting in a tonnage score in block A of 1 or 2). Of the remaining 5 substances (13 %), 3 are registered at a maximum tonnage of 100 000 tpa, 1 at a maximum tonnage of 1 000 000 tpa and 1 with the tonnage data claimed confidential. These substances would receive a high tonnage score in block A, if they were not excluded (Table 69).

Table 69: Excluded substances that would receive a high tonnage scores in block A

CAS no.	Name	Tonnage [tpa][(a)]	Exclusion justification[(b)]
25322-69-4	propane-1,2-diol, propoxylated	100 000	UCVB; see Table 66
26780-96-1	quinoline, 1,2-dihydro-2,2,4-trimethyl-, homopolymer	100 000	UVCB; no predictions
68476-85-7	petroleum gases, liquefied	1 000 000	UCVB; see Table 67
9003-29-6	butene, homopolymer	100 000	Polymer
47073-92-7	cyanic acid, ethylidenedi-4,1-phenylene ester	TDC	No predictions

(a): Maximum of the REACH registration tonnages (in tonnages per annum, tpa); TDC: Tonnage Data Confidential.
(b): No predictions: values for at least one critical parameter could not be predicted.

Two of these substances were already discussed as illustrative examples above and two more are polymers. While the first one is registered as an UVCB substance and was excluded since critical values could not be predicted, no correct structure could be identified for the second one[133]. In fact, the SMILES notation in one of the datasets for 'butene, homopolymer' represents butane, again demonstrating that incorrect SMILES notations may be retrieved. In any case, polymers are not within the applicability domain of the models used. Finally, the fifth compound was excluded only, because properties could not be predicted. While the tonnage data are claimed confidential (potentially leading to a high tonnage score in block A), this substances was registered by a single company. From the

[132] See footnote 23 for details on the use of reference substances.
[133] Technically, it could have been excluded under step 2; however, step 2 was intended to identify the most appropriate structure and not to exclude substances. Therefore, this substances was assigned to step 4, although it is not registered as a UVCB substance.

information in the REACH registration dossier, the full registration is an update of a NONS registration associated with a tonnage of 1-10 tpa. While the full registration appears to be the result of a tonnage upgrade, it is unlikely that it is produced in very large amounts. No information on the uses is provided in the full registration dossier.

Overall, substance selection results in 2 336 substances to be further assessed in blocks A-C as well as in relation to their toxicity.

Appendix B – Additional information on the validation study

As outlined in section 3.2.3, a single key value was retrieved for the vast majority of the substances for which a key value was available (1 495/1 567 substances, 95 %). For the remaining 72 substances, two (n=67) or three (n=5) different key values were available.

In all but 2 of these 72 cases, the different key values lead to different scores. These two exceptions relate to substances assigned the key values 'inherently biodegradable' and 'inherently biodegradable, fulfilling specific criteria'. While these key values differ, both are assigned a score of 4 according to the scoring system described in Bitsch et al. (2016).

In some of these cases, the difference in scores is only small, e.g. 10 based on one key value and 8 based on the second key value. As outlined in section 2.2.3, the scores for these 72 substances with more than one key value are assigned to the three persistence classes: HIGH (scores 8 and 10), MODERATE (scores 4 and 6) and LOW (scores 1 and 2). Different scores may therefore not lead to a different class assignment. For example, a score of 10 based on one key value and a score of 8 based on the second key value both lead to assignment to the HIGH persistence class. Overall, 53 substances are assigned to different persistence classes based on the different key values, while 19 are not (see section 2.2.3 for the class differentiation).

The principal method for comparing predicted biodegradation data with those from key values was already outlined in section 2.2.3 and 3.2.3. The final assignments to one of the three persistence classes are evaluated in the following way:

- Matching: a substance is assigned to the same class (e.g. LOW) based on predicted data and based on the key value;
- Overprediction: a substance is assigned to a higher persistence class (e.g. HIGH) based on the predicted data than based on the key value (e.g. MODERATE);
- Underprediction: a substance is assigned to a lower persistence class (e.g. LOW) based on the predicted data than based on the key value (e.g. HIGH).

As explained in more detail in section 2.2.3, two assessments were performed, since diverging key values were retrieved for 72 substances that led to different class assignments for 53 substances (3.4 % of the total of 1 567 substances for which a key value was available). While this fraction is low, the evaluations described here aim to analyse, whether there are substantial differences between the two assessment methods. The first assessment is based on the least conservative key value for all of the 53 substances with diverging key values, while the second assessment is based on the most conservative key value for these substances.

The results of these comparisons for 1 567 substances are summarised in Figure 53, which also shows the mean of the two assessments.

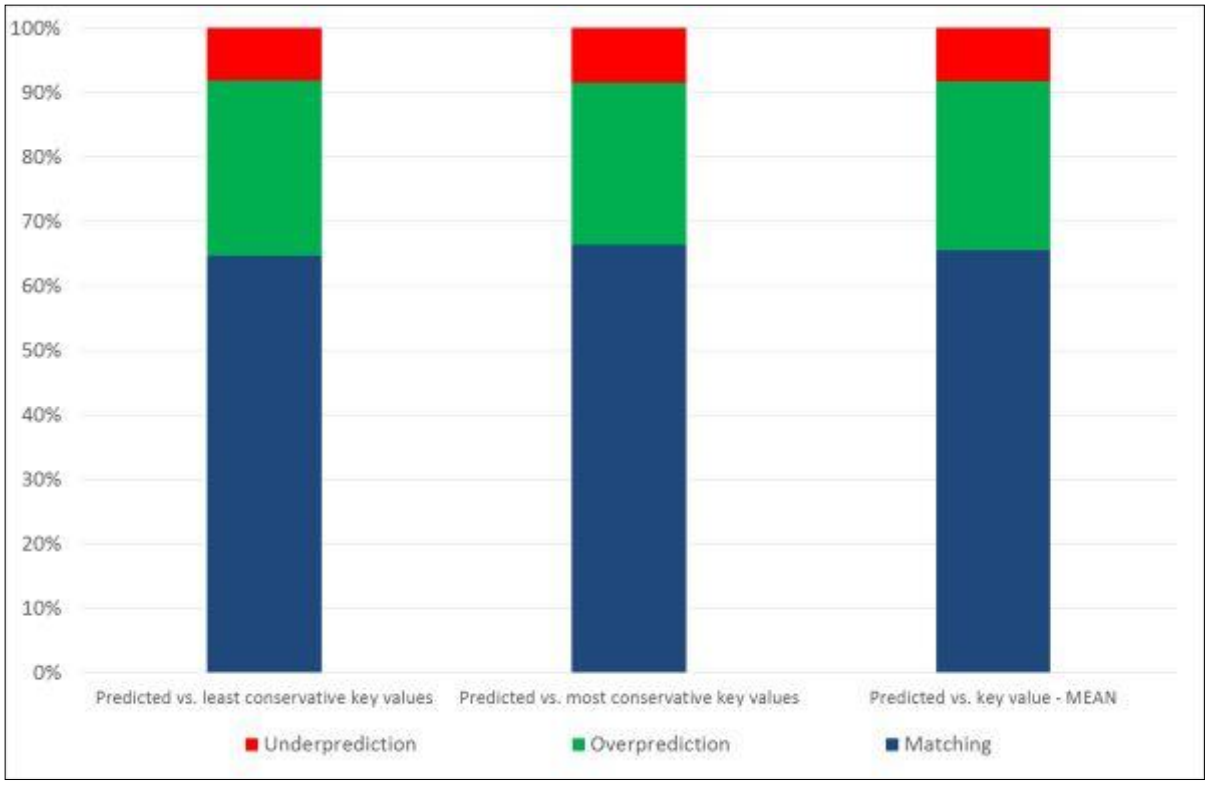


Figure 53: Summary of the validation study based on 1 567 substances based on least conservative and most conservative mean values and the mean of the two assessments

The data illustrate that the differences between the two assessments are very small, which is in agreement with the small fraction of substance with diverging key values (3.4 %). Table 70 shows more detailed data of the results of these comparisons.

Table 70: Details of the results comparing the two assessment methods employed

Comparisons[a]	**Persistence class assignments (predicted-key values)[b]**			**Sum**
MATCHING	**LOW-LOW**	**MODERATE-MODERATE**	**HIGH-HIGH**	
Predicted vs. key values (LC)	38 %	0.77 %	26 %	65 %
Predicted vs. key values (MC)	38 %	0.89 %	27 %	66 %
Predicted vs. key values (mean)	38 %	0.83 %	26 %	66 %
OVERPREDICTION	**MODERATE-LOW**	**HIGH-LOW**	**HIGH-MODERATE**	
Predicted vs. key values (LC)	3.6 %	16 %	7.1 %	27 %
Predicted vs. key values (MC)	3.4 %	14 %	7.3 %	25 %
Predicted vs. key values (mean)	3.5 %	15 %	7.2 %	26 %
UNDERPREDICTION	**LOW-HIGH**	**MODERATE-HIGH**	**LOW- MODERATE**	
Predicted vs. key values (LC)	4.1 %	1.1 %	2.9 %	8.1 %
Predicted vs. key values (MC)	4.3 %	1.1 %	3.1 %	8.6 %
Predicted vs. key values (mean)	4.2 %	1.1 %	3.0 %	8.3 %

All values rounded to two significant figures.

(a): For predicted vs. key value comparisons, values of the assessments based on the least conservative (LC) and the most conservative (MC) key value are shown, as well as the mean from the two assessments.

(b): The first class indicates the one derived from predicted data, while the second class indicates the one based on key values. For example, 3.5 % of the substances are assigned to the MODERATE persistence class based on predicted data, but to the LOW persistence class based on the key values in the evaluation based on means.

These data show that the two assessment methods lead to very similar results in all sub-groups. In the context of this validation study, the differences between the two assessment methods are considered negligible and allow using the mean for the overall evaluation reported in section 3.2.3.

Appendix C – Comparison of results from individual BIOWIN modules with the battery approach using BIOWIN3/5/6

As discussed in sections 2.2.2 and Bitsch et al. (2016), the scoring based on the battery evaluation with BIOWIN3/5/6 is preferred over an evaluation based on individual BIOWIN models. Since a very high number of substances were assessed in this study, additional analyses were performed to compare the results from individual BIOWIN models 3, 5 and 6 with those obtained after application of the battery approach. For this purpose, the results from the individual BIOWIN models were expressed as results from experimental studies based on the approach discussed in section 2.2.2. Table 71 summarises this interpretation of modelled biodegradation data for the BIOWIN models 3, 5 and 6.

Table 71: Interpretation of modelled BIOWIN results

BIOWIN3 result	BIOWIN5 result	BIOWIN6 result	Interpretation
>2.75–5	>=0.5	>=0.5	Readily biodegradable (RB)
>2.25–2.75			Inherently biodegradable (INB)
	<0.5	<0.5	Not readily biodegradable (NRB)
≤2.25			Not inherently biodegradable (NIB)[(a)]

(a): See Table 18 in section 3.2.2 for details; the category NIB also includes those substances predicted to be recalcitrant, since this is also assigned a score of 10.

The results obtained with the individual BIOWIN models were then compared with those of the battery approach. Figure 54 shows the outcome of these comparisons. On the abscissa, results are grouped according to the results from the battery approach. The percentage of substances on the ordinate should be read as e.g. 75 % of all substances screened as readily biodegradable based on BIOWIN 3 alone were actually assigned readily biodegradable based on the battery approach. The multiple bars for score 10 (NIB) mirrors the multiple possible combinations of model outputs leading to score 10 (see Figure 7).

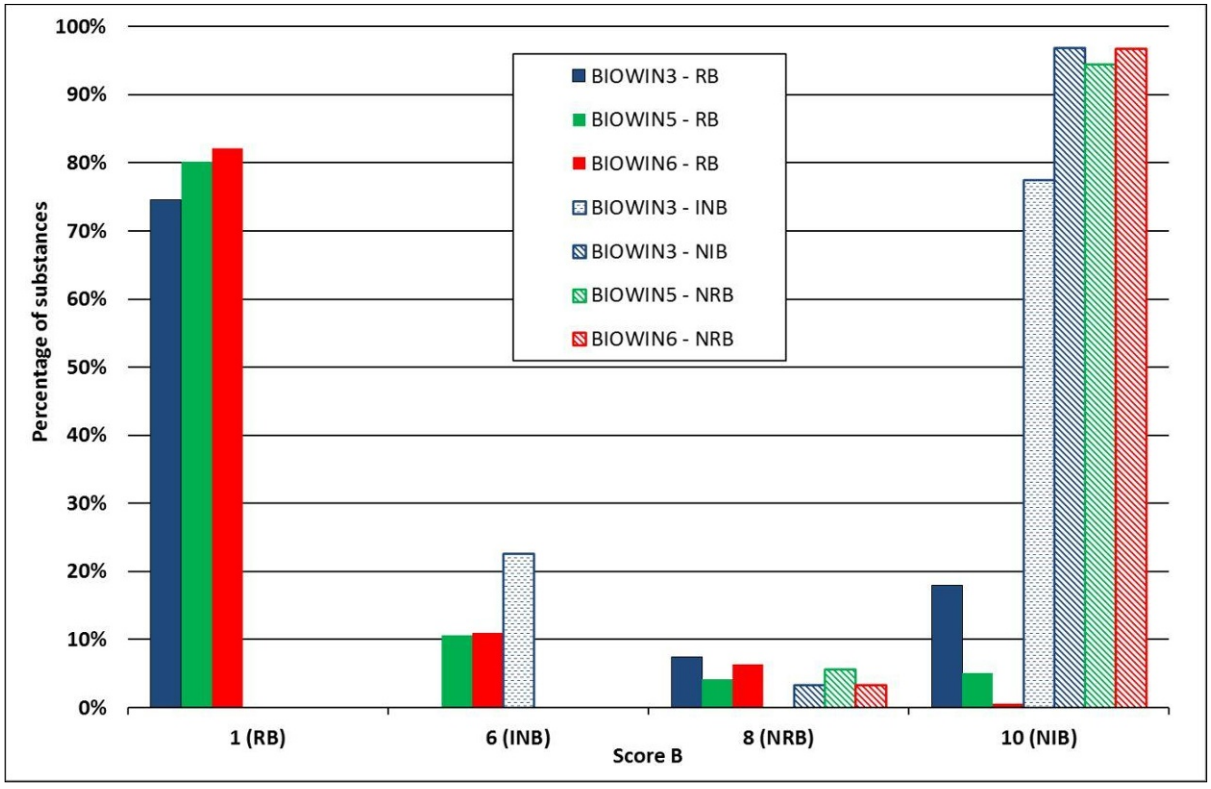


Figure 54: Comparison of results from individual BIOWIN models with results obtained in the battery approach

These data show that the majority of substances predicted to be readily biodegradable by the individual models are also predicted to be readily biodegradable in the battery approach (Score B of 1; 75 % (BIOWIN3) to 82 % (BIOWIN6)). However, a notable fraction of 18-25 % is predicted to be readily biodegradable by the individual models, but is evaluated as being less biodegradable in the battery approach. While most of these substances are evaluated in the battery approach as inherently biodegradable (Score B of 6) for BIOWIN5 and BIOWIN6, the majority of the substances are evaluated in the battery approach as not inherently biodegradable in the case of BIOWIN3 (Score B of 10).

BIOWIN3 is the only model that predicts inherently biodegradable substances. However, only 23 % of these are actually a corresponding Score B of 6 in the battery approach. All other substances predicted by BIOWIN3 to be inherently biodegradable are evaluated in the battery approach as being not inherently biodegradable (77 %), because they are predicted not to be readily biodegradable in BIOWIN5, BIOWIN6 or both BIOWIN5 and BIOWIN6. This reflects the scoring applied in the battery evaluation (see Figure 7 in section 2.2.2), which contains a conservative element appropriate for a screening assessment.

More than 90 % of the substances predicted in BIOWIN3 as not inherently biodegradable[134] are evaluated as not inherently biodegradable in the battery approach. BIOWIN5 and BIOWIN6 only differentiate between 'readily biodegradable' and 'not readily biodegradable'. Less than 10 % of the substances predicted by individual BIOWIN5 and BIOWIN6 models as not readily biodegradable are evaluated as not readily biodegradable in the battery evaluation. The overwhelming majority of these substances are assessed as not inherently biodegradable, but this of course implies that they are not readily biodegradable as well.

[134] As noted earlier, this category also includes substances that are recalcitrant to biodegradation.

Appendix D – Exploratory data analysis of ACC-HUMANsteady data input and data output

ACC-HUMANsteady data input: molecular weight, log Kow, log Koa and log Kaw

The following figures (Figure 55 to Figure 58) illustrate the relative frequency distributions of several input parameters for the dataset of 2 336 substances. The figures intent to graphically characterise the input data of parameters molecular weight, log Kow, log Koa and log Kaw. The input parameters were used in ACC-HUMANsteady to predict potential bioaccumulation in different food and feed items.

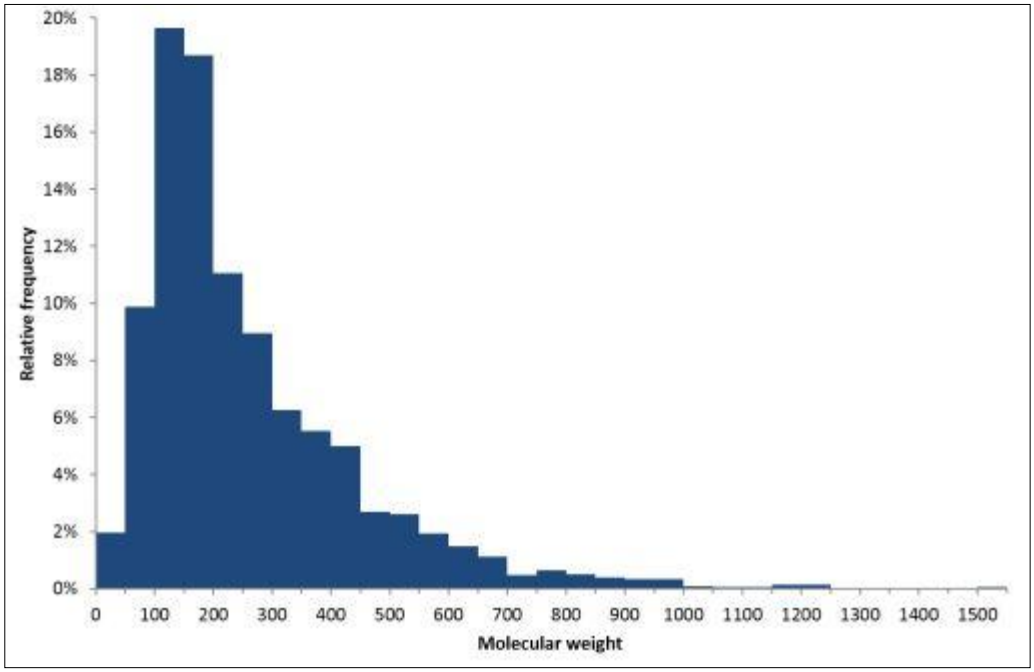


Figure 55: Frequency distribution of the molecular weight of 2 336 substances selected

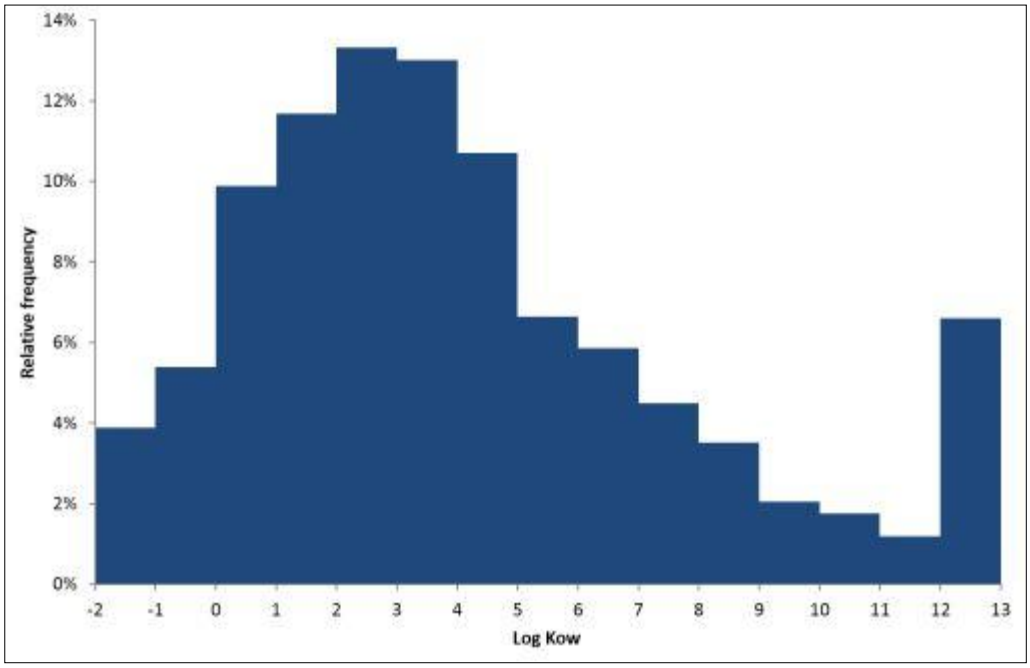


Figure 56: Frequency distribution of the log Kow of 2 336 substances selected
Note, the cut-off value of the upper end was set to 12 and is clearly indicated by the peak at log Kow 12-13 in this figure.

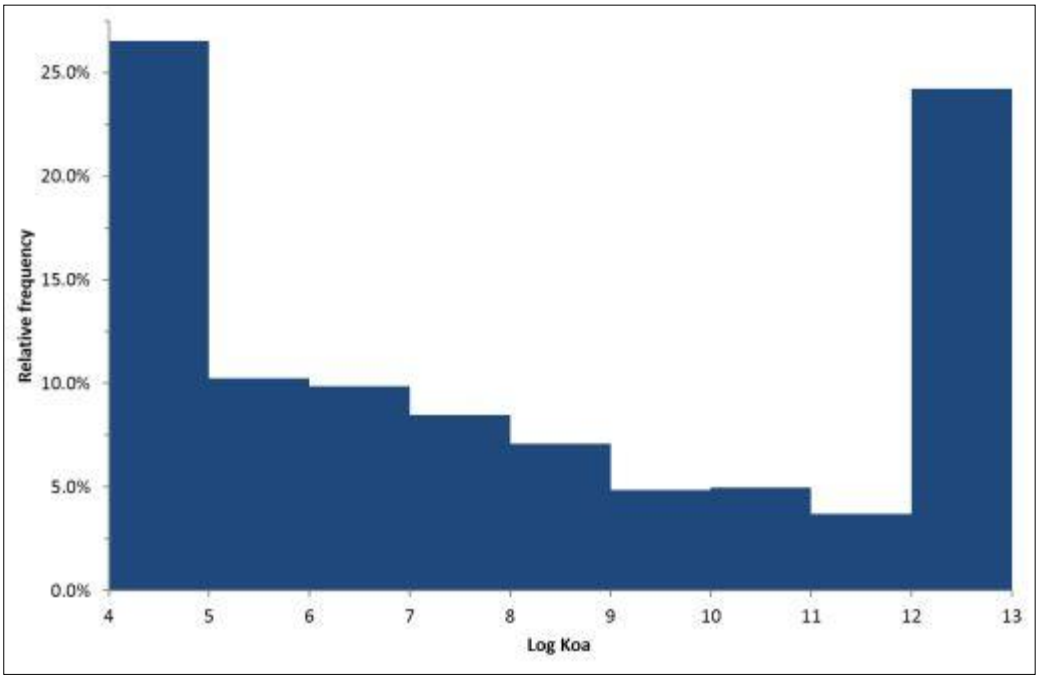


Figure 57: Frequency distribution of the log Koa of 2 336 substances selected
Note, the cut-off value of the lower and upper end was set to 4 and 12, respectively, and is clearly indicated by the peak at log Koa 4-5 and 12-13 in this figure.

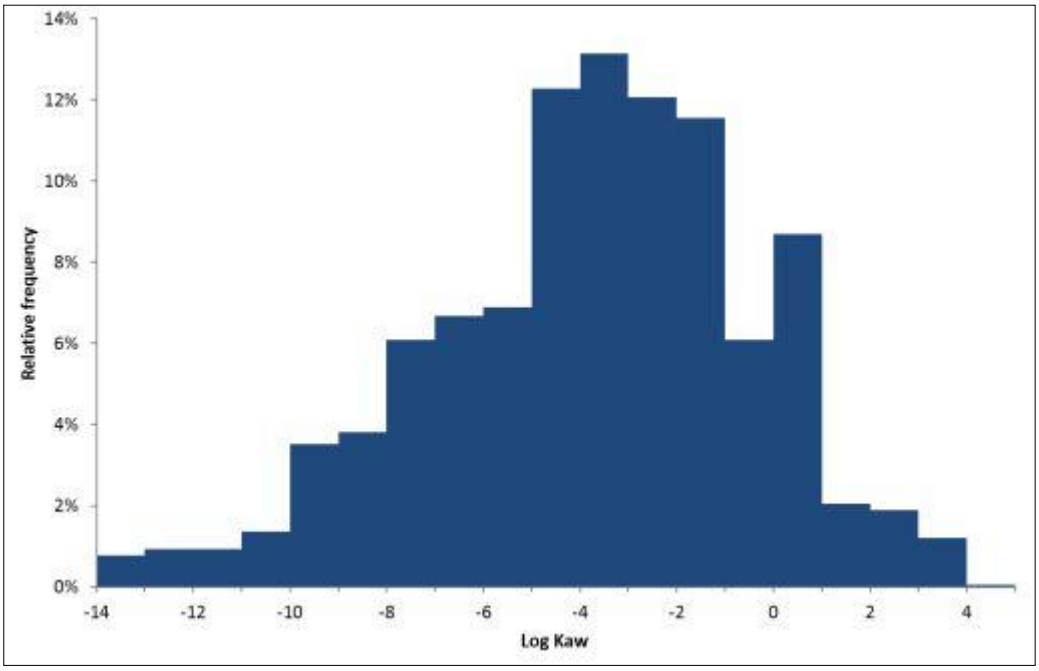
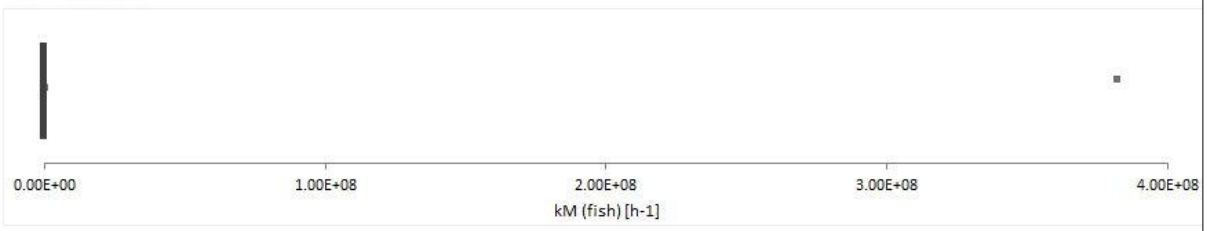


Figure 58: Frequency distribution of the log Kaw of 2 336 substances selected

ACC-HUMANsteady data input: biotransformation in fish

For biotransformation, metabolism rate constants in fish (k_M [1/h]) show a few very high values that prevent a meaningful histogram of the data. Statistical descriptors are shown in the following figure.

Descriptives



N	2336

	Minimum	1st quartile	Median	3rd quartile	Maximum
kM (fish) [h-1]	2.31E-08	1.45E-02	9.32E-02	6.22E-01	3.83E+08

Quantile	kM (fish) [h-1]
0.100	1.50E-03
0.200	8.30E-03
0.300	2.29E-02
0.400	4.60E-02
0.500	9.32E-02
0.600	2.11E-01
0.700	4.32E-01
0.800	9.93E-01
0.900	3.43E+00

Figure 59: Statistical descriptors of the metabolism rate constants in fish (kM [1/h] of 2 336 substances selected
Note the binary distribution with very few high values and the bulk of the substances at low values.

ACC-HUMANsteady data output

Figure 60 and Figure 61 compare two different bioaccumulation factors (BAF) generated with the QSAR Toolbox module BCFBAF in EPISuite™ with concentrations in Fish 2 predicted by ACC-HUMANsteady depending on log Kow or log Koa, respectively. The two bioaccumulation factors were (a) bioaccumulation factors with no biotransformation involved and (b) bioaccumulation factors taking biotransformation into account. Both BAFs were generated with the QSAR Toolbox module BCFBAF in EPISuite™.

The following figures (Figure 62 to Figure 68) are illustrations of the exploratory data analysis of ACC-HUMANsteady predictions for 2 336 substances. The potential of bioaccumulation in different food and feed items is represented by the predicted log concentrations. The graphical illustrations give insight into the implemented partitioning behaviours of substances depending on log Kow, log Koa or log k_M (log of metabolism rate constants), resulting in a wide range of predicted concentrations of substances in food and feed.

A detailed discussion of ACC-HUMANsteady modelling of the various partitioning processes is beyond the scope of this study. However, the plots illustrate the following:

- For any given log Kow, log Koa or log k_M value, the concentrations modelled in any food item generally varies over several orders of magnitude. This demonstrates that these concentrations are not predicted on the basis of a single input value, but reflect the overall partitioning behaviour.
- This general observation notwithstanding, predicted concentrations in food items tend to increase with increasing log Koa (reflecting decreasing volatilisation), but show a less clear trend with increasing log Kow (in particular for fish). With respect to log Kow, there appear to be differences between below-ground vegetables (decreasing concentrations with increasing log Kow) and above-ground fruits and vegetables.
- The impact of biotransformation is evident to a certain extent, but again the predicted concentrations range over several orders of magnitude at any given log k_M value.
- Predicted BAF in fish obviously do not take volatilisation into account (independence of log Koa).

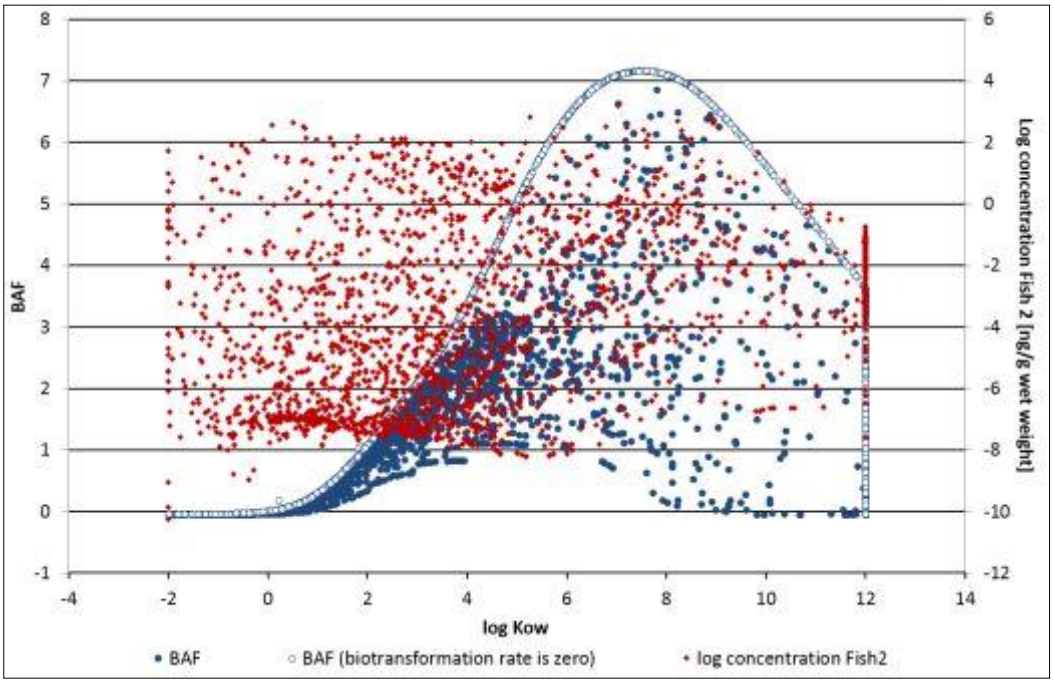


Figure 60: Log BAFs and Fish 2 concentrations plotted against log Kow. Bioaccumulation factors (BAFs) were generated with the QSAR Toolbox module BCFBAF in EPISuite™. Log Kow cut-off values were set to -2 and 12.
Note how BAF with no biotransformation is clearly depending on log Kow in contrast to BAF with biotransformation. Predicted concentrations for Fish 2 do not depend on log Kow at all (compare also Bitsch et al. (2016)).

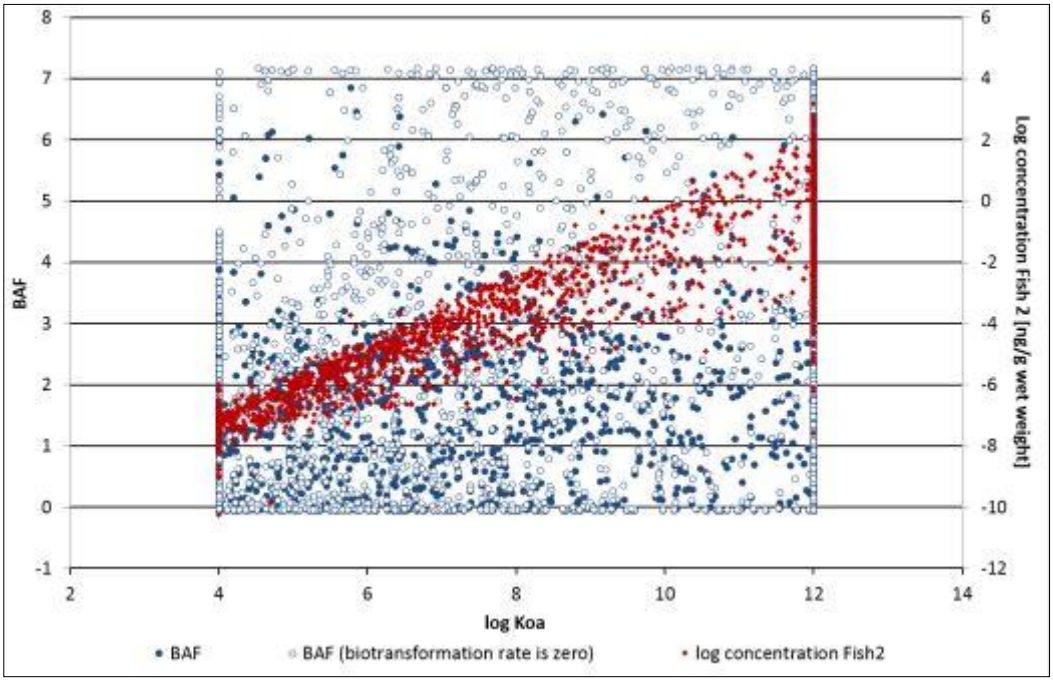


Figure 61: Log BAFs and Fish 2 concentrations plotted against log Koa. Bioaccumulation factors (BAFs) were generated with the QSAR Toolbox module BCFBAF in EPISuite™. Log Koa cut-off vales were set to 4 and 12.
Note, BAF with no biotransformation and BAF with biotransformation do not depend on log Koa. In contrast, predicted concentrations for Fish 2 (which consider biotransformation) correlate with log Koa to some extent (compare also Bitsch et al. (2016)).

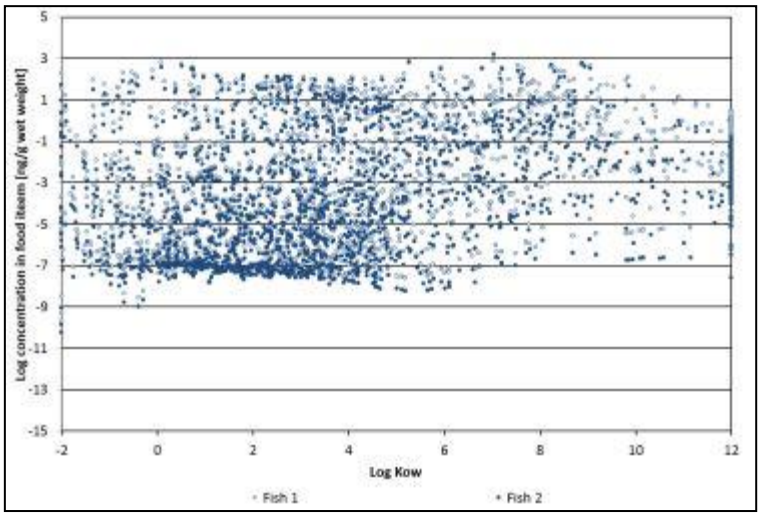


Figure 62: ACC-HUMANsteady predictions of chemical bioaccumulation – depicted as log concentrations – in food category 'Fish' depending on log Kow

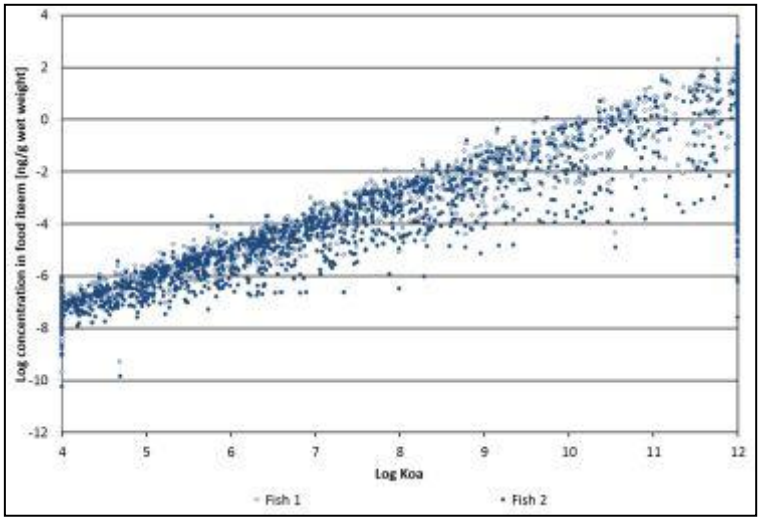
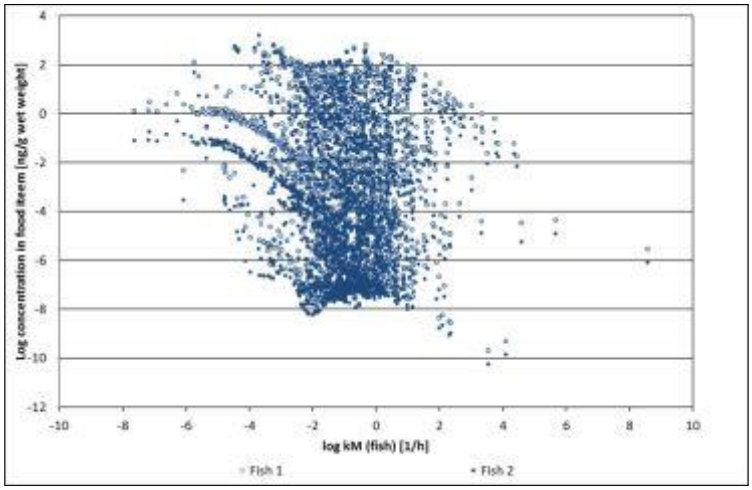


Figure 63: ACC-HUMANsteady predictions of chemical bioaccumulation – depicted as log concentrations – in food category 'Fish' depending on log Koa



ACC-HUMANsteady predictions of chemical bioaccumulation – depicted as log concentrations – in food category 'Fish' depending on log kM [1/h]

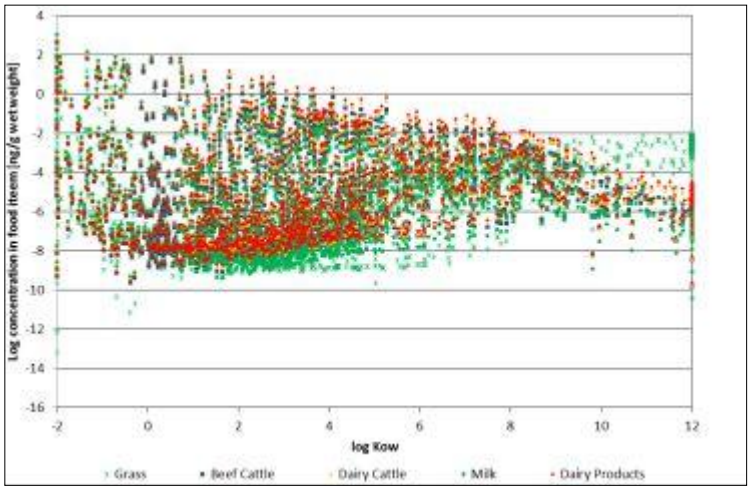


Figure 64: ACC-HUMANsteady predictions of chemical bioaccumulation – depicted as log concentrations – in food category 'Meat and milk products' and 'Grass' (feed item) depending on log Kow

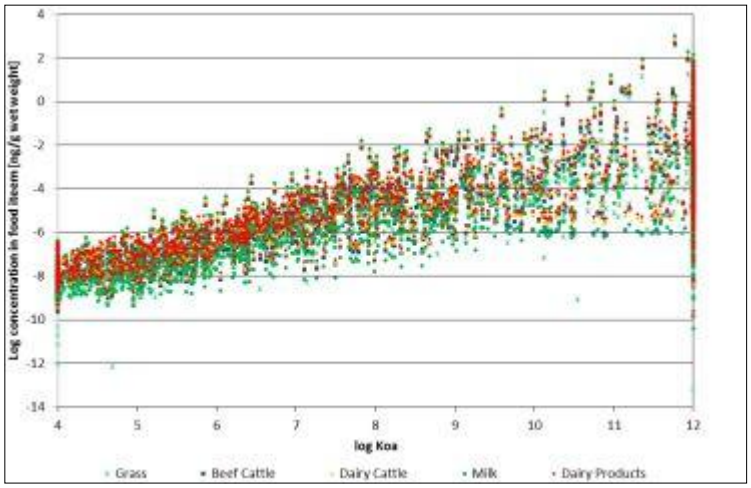


Figure 65: ACC-HUMANsteady predictions of chemical bioaccumulation – depicted as log concentrations – in food category 'Meat and milk products' and 'Grass' (feed item) depending on log Koa

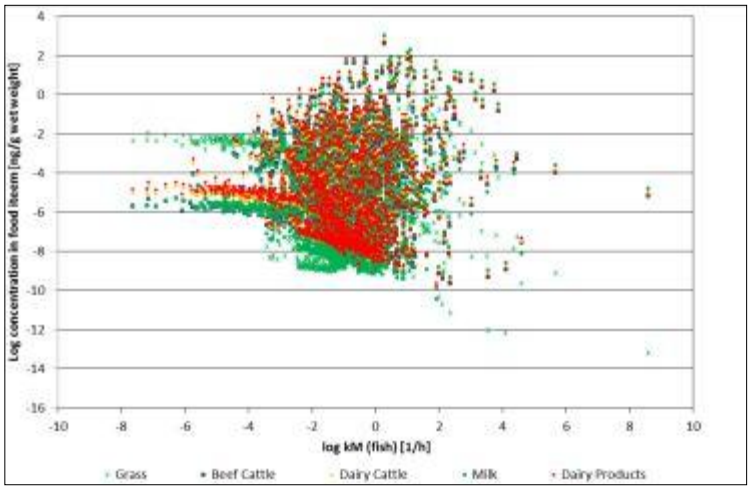


Figure 66: ACC-HUMANsteady predictions of chemical bioaccumulation – depicted as log concentrations – in food category 'Meat and milk products' and 'Grass' (feed item) depending on log kM

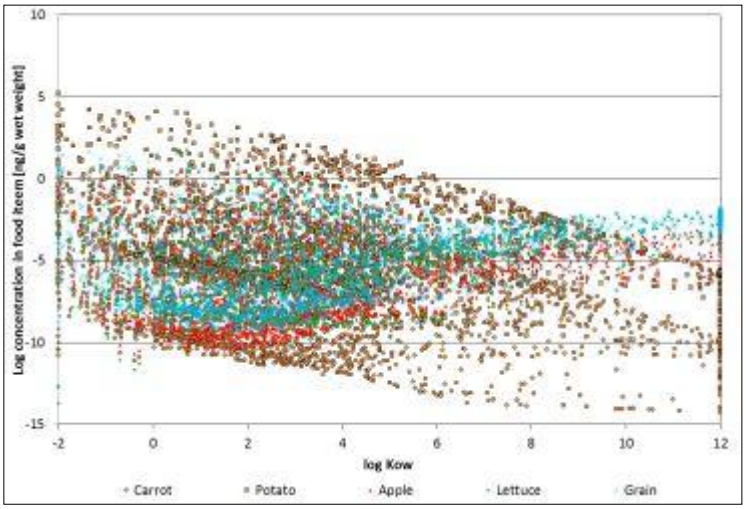


Figure 67: ACC-HUMANsteady predictions of chemical bioaccumulation – depicted as log concentrations – in food category 'Fruits and vegetables' depending on log Kow

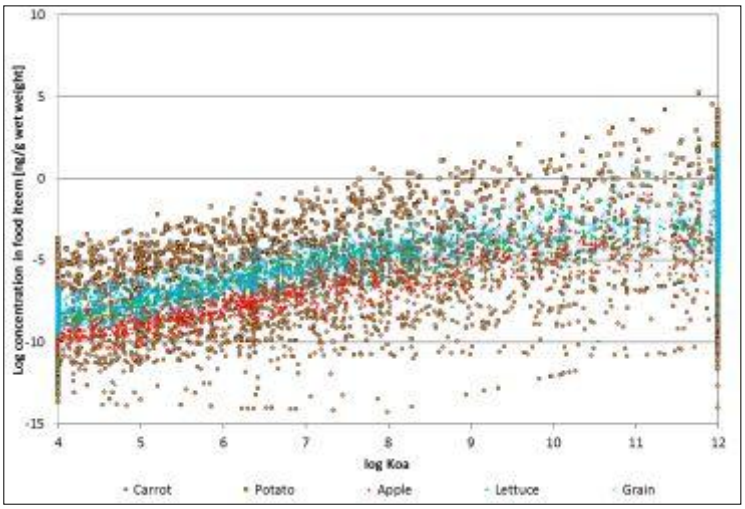


Figure 68: ACC-HUMANsteady predictions of chemical bioaccumulation – depicted as log concentrations – in food category 'Fruits and vegetables' depending on log Koa

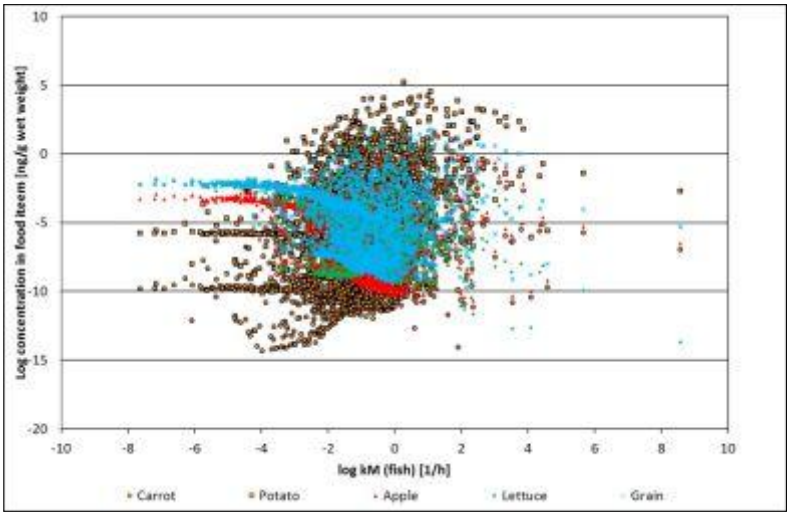


Figure 69: ACC-HUMANsteady predictions of chemical bioaccumulation – depicted as log concentrations – in food category 'Fruits and vegetables' depending on log kM

Correlation of scores between different food items

Coefficients of determination (R^2, i.e. the square of the Pearson correlation coefficient) for scores obtained in different food items were calculated. In order to highlight the findings, the following colour codes were used for R^2 values:

Green and bold: 0.9 or higher

Orange: 0.8 - < 0.9

Note that all values were rounded to two significant figures, but unrounded values were used for evaluation. For example, the R^2 value for the correlation between scores in 'beef cattle' and in 'Milk' is actually 0.896 and therefore highlighted in orange.

Table 72 presents the R^2 values in a correlation matrix, which can be summarised as follows:

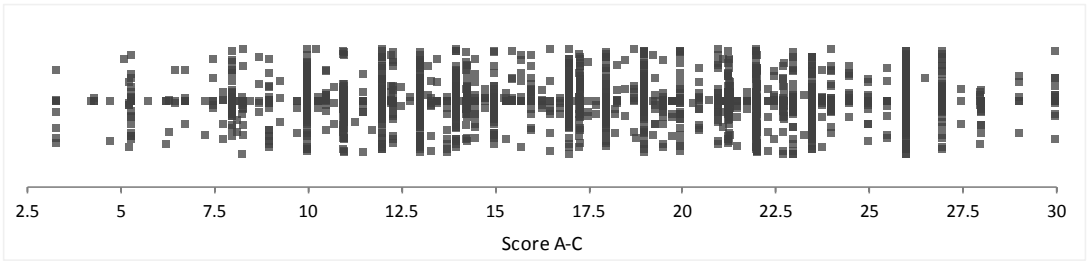
- A strong correlation generally exists between scores for food items in the same category, i.e. both fish species and all meat and milk products).
- The exception is the category 'Fruits & vegetables', which shows a more differentiated pattern. A strong correlation exists both for above-ground crops (apple, grain, lettuce and grass) and below-ground crops (potato and carrot), but not between food items from both sub-categories (see e.g. apple-potato or lettuce carrot).
- The correlation between scores in fruits and vegetables and those in fish or meat and milk products is generally weak.

Table 72: Correlation matrix (R^2) for scores in different food items

	Fish		Meat & milk products				Fruits & vegetables					
	Fish 1	Fish 2	Beef Cattle	Dairy cattle	Milk	Dairy products	Apple	Grain	Potato	Lettuce	Carrot	Grass
Fish 1		**0.92**	0.75	0.77	0.73	0.78	0.74	0.75	0.45	0.73	0.48	0.72
Fish 2			0.79	0.81	0.75	0.82	0.70	0.71	0.52	0.69	0.55	0.69
Beef Cattle				**0.95**	0.90	**0.94**	0.64	0.64	0.65	0.58	0.67	0.62
Dairy cattle					**0.92**	**0.98**	0.69	0.70	0.62	0.62	0.65	0.67
Milk						**0.90**	0.66	0.67	0.67	0.59	0.70	0.65
Dairy Products							0.70	0.71	0.60	0.63	0.63	0.68
Apple								**0.99**	0.31	0.84	0.35	0.86
Grain									0.33	0.85	0.36	0.88
Potato										0.26	**0.97**	0.31
Lettuce											0.29	**0.91**
Carrot												0.35
Grass												

Appendix E – Statistical descriptors for Score A-C

Descriptives



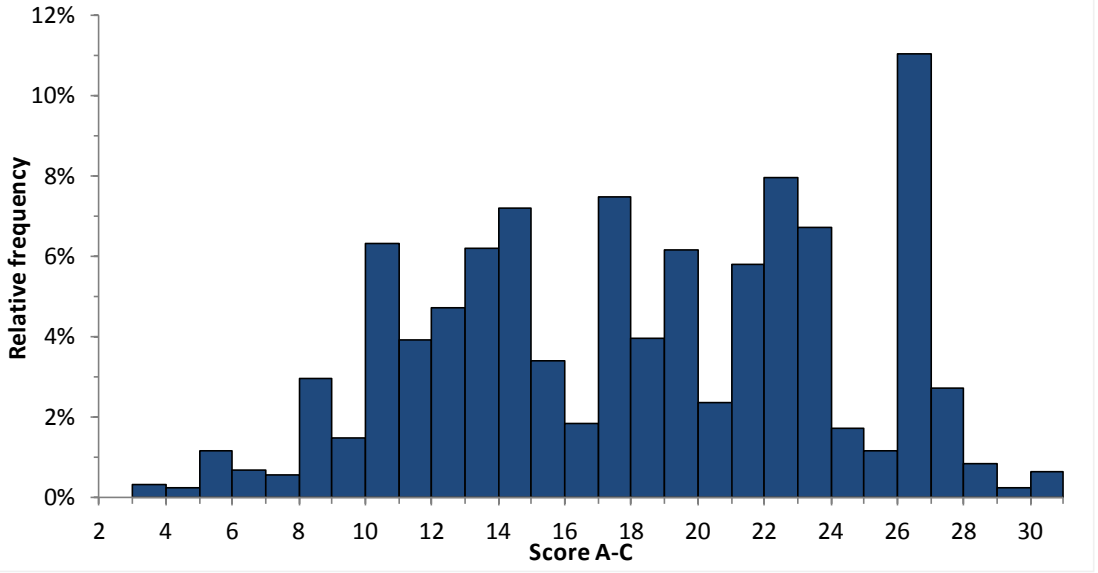
N	2336

	Mean	Mean SE	Geometric mean	SD
Score A-C	17.9	0.124	16.7	5.99

	Minimum	1st	Median	3rd	Maximum
Score A-C	3.30	13.0	18.0	23.0	30.0

Quantile	Score A-C
0.100	10.0
0.200	12.0
0.300	14.0
0.400	16.0
0.500	18.0
0.600	20.0
0.700	22.0
0.800	23.5
0.900	26.0

Descriptives



Appendix F – Overview classification categories

While the selection of substances presented in the report was based on all 4 classification endpoints, the specific endpoints are investigated in more detail in this appendix. The comparison was made for the categories harmonised, joint and single classification only. It was compared whether the substance is classified for a given endpoint in both types or not and is classified in only one of the two. It should be noted that in the following tables and figures the group 'single classification' contains individual and other classifications without any differentiation of other classifications by reliability. Classifications from IARC are limited to carcinogenicity and is only available for a limited number of substances. Therefore, it has not been included in the comparison.

Overview substances with carcinogenicity classification

For carcinogenicity three comparisons were performed (see Table 73 and Figure 70). The outcome "no classification" is nearly identical in all 3 comparisons (1979 to 2071) as well as the number of identical classifications (177 to 197). Only single classification is more often available compared to the other. A few joint classifications have classifications for this endpoint when there is no harmonised classification, while this is more often the case for single classifications.

Table 73: Differences in classification for carcinogenicity of the selected 2 336 substances

Classification	A: Harmonised versus B: Joint	A: Joint versus B: single*	A: Harmonised versus B: single*
A and B same	197	194	177
A and B no	2071	1979	2000
Only A	15	56	35
Only B	53	107	124

* Contains individual and other classifications

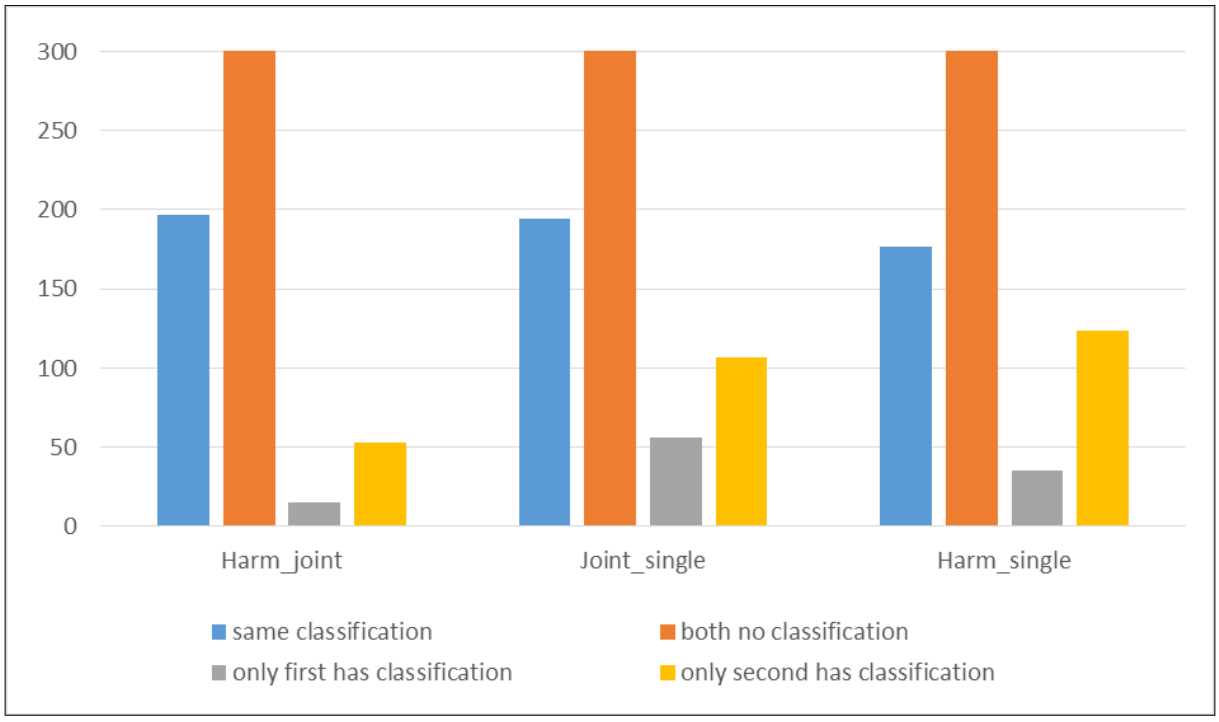


Figure 70: Differences in classification for carcinogenicity of the selected 2 336 substances (scale of y-axes cut at 300)

Overview substances with mutagenicity classification

For mutagenicity, again three comparisons were performed (see Table 74 and Figure 71). A similar pattern as for carcinogenicity was observed. However, the total numbers of classifications (same or different) is lower. The same outcome "no classification" is nearly identical in all 3 comparisons and between 79 and 101 have both a classification.

Table 74: Differences in classification for mutagenicity of the selected 2 336 substances

Classification	A: Harmonised versus B: Joint	A: Joint versus B: single*	A: Harmonised versus B: single*
A and B same	101	97	79
A and B no	2188	2091	2106
Only A	7	44	29
Only B	40	104	122

* Contains individual and other classifications

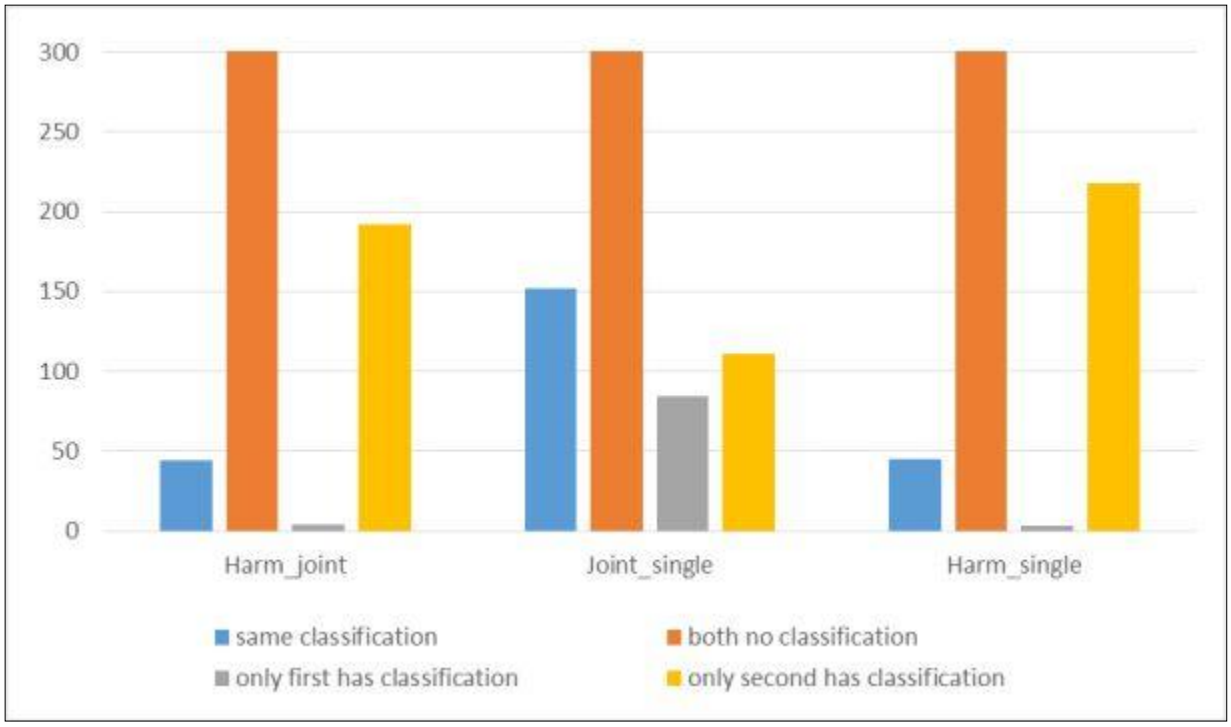


Figure 71: Differences in classification for mutagenicity of the selected 2 336 substances (scale of y-axes cut at 300)

Overview substances with reprotoxicity classification

For reprotoxicity three comparisons were performed (see Table 75 and Figure 72). Classifications from joint and single classifications are more often available than only harmonised classifications. For joint and single classification, the number of substances having only one type of classification is more equal compared to the other endpoints (repro: 84 to 114; cancer: 56 to 107, muta: 44 to 104, STOT RE: 73 to 167). The number of substances having a harmonised classification but no joint or single classification is low (4 and 3).

Table 75: Differences in classification for reprotoxicity of the selected 2 336 substances

Classification	A: Harmonised versus B: Joint	A: Joint versus B: single*	A: Harmonised versus B: single*
A and B same	44	152	45
A and B no	2096	1989	2070
Only A	4	84	3
Only B	192	111	218

* Contains individual and other classifications

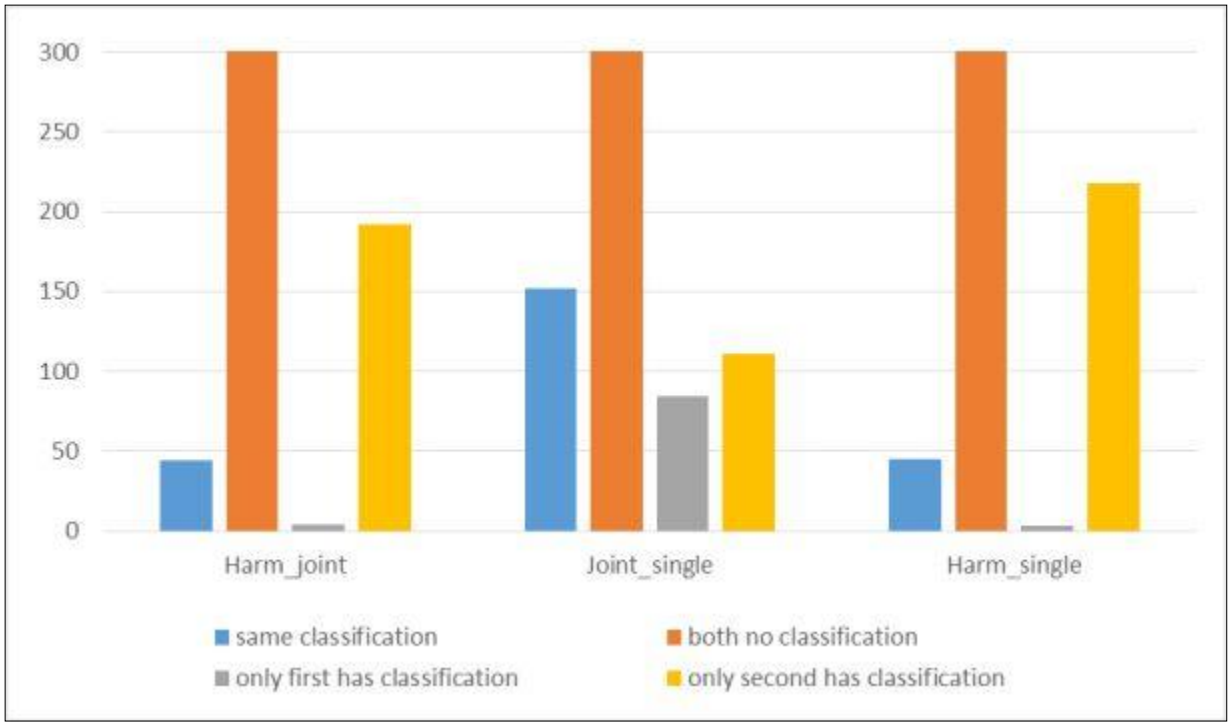


Figure 72: Differences in classification for reprotoxicity of the selected 2 336 substances (scale of y-axes cut at 300)

Overview substances with STOT RE classification

STOT RE shows a slightly different picture compared to the other three endpoints. Here the deviation from harmonised classification is the highest. This may be related to the fact that the endpoint contains some subjective elements is the assessment of adversity and severity. Compared to joint classifications, single classifications deviate more often from harmonised (300 vs. 207). The number of substances having a harmonised classification but no joint or single classification is low (4 and 3).

Table 76: Differences in classification for STOT RE of the selected substances

Classification	A: harmonised versus B: Joint	A: Joint versus B: single*	A: harmonised versus B: single*
A and B same	41	175	42
A and B no	2084	1921	1991
Only A	4	73	3
Only B	207	167	300

* Contains individual and other classifications

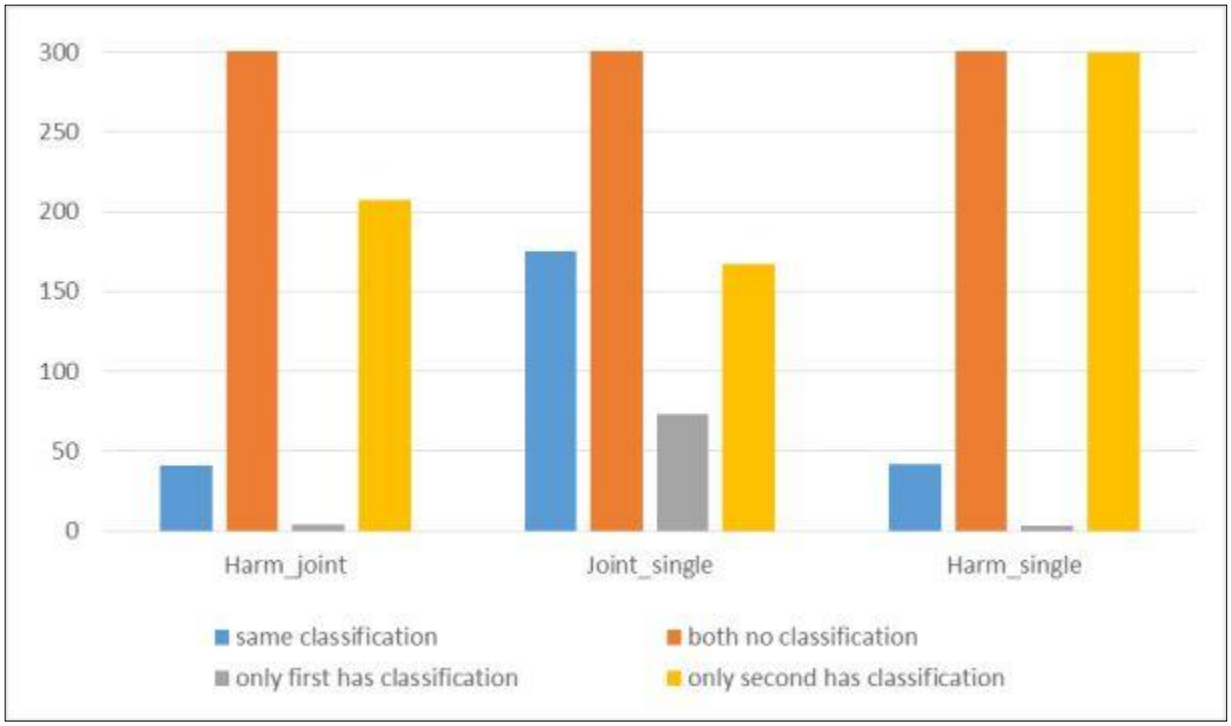


Figure 73: Distribution of the 2 336 selected substances among four groups for Score A-C by Score B and Score C. (scale of y-axes cut at 300)

In conclusion, for all four endpoints there is a great agreement of substances being classified or not. The groups joint and single classification more often have a classification compared to the harmonised classification. For the endpoint repeated dose toxicity the highest numbers are observed.

Appendix G – Detailed results for block A and block B for prioritised substances

Scores A and B are combined by an OR operator in the Pivot table selection. Table 77 provides additional data for these two blocks on the 267 initial priority substances. These data illustrate that:

- 111/267 substances (42 %) have both a Score A > 5 and a Score B > 5,
- an additional 101/267 substances (38 %) are predicted to be not readily biodegradable (Score B > 5), with the majority being predicted not to be biodegradable at all (Score B = 10, N=93),
- an additional 26/267 substances (9.7 %) are assigned very high Scores A above 7,
- there are only few substances which are predicted to be biodegradable at least to some degree (Score B = 1-8 and have Scores A ≤ 5 (N=9, 3.4 %).

These data indicate that the majority of priority substances selected in this step are chemicals predicted to be (a) substantially released to the environment and/or (b) persistent due to little or no biodegradation. Overall, 192/267 substances (72 %) are predicted not to be biodegradable (Score B =10).

Table 77: Number of substances differentiated by Score A and Score B[(a)] among the 267 substances initially prioritised

Score B	Score A < 3	Score A = 3-5[(b)]	Score A = 5-7[(b)]	Score A > 7	Totals
1	0	1[(c)]	28	26	55
6	2	0	**4**	**1**	7
8	2	4	**6**	**1**	13
10	57	36	**64**	**35**	192
Totals	61	41	102	63	267

(a): The 111 substances with both Score A > 5 and Score B > 5 are highlighted.
(b): No substance is assigned a Score A of 5.
(c): Hydroquinone identified in step 2.

Note that the one substances with a Score B of 1 and a Score A of 3-5 represents hydroquinone, which was prioritised in step 2 in section 3.4.4, since Score A is potentially an underestimate.

Table 78 shows that the majority of substances (179/267, 67 %) have maximum REACH registration tonnages of 1 000 tonnes per annum or more (including those with confidential tonnage data). Among the 88 substances with lower tonnages, 77 (87 %) are predicted to be non-biodegradable (Score B = 10).

Table 78: Number of substances differentiated by maximum REACH registration tonnage (T; in tonnes per annum) and Score B among the 267 substances initially prioritised

Score B	T ≤ 100	T 1 000-10 000	T ≥ 100 000	TDC[(a)]	Totals
1	7	17	28	3	55
6	1	5	1	0	7
8	3	8	2	0	13
10	77	73	39	3	192
Totals	88	103	70	6	267

(a): TDC: Tonnage data confidential

More than half of the 55 substances predicted to be readily biodegradable (N=28, 51 %) are registered with maximum REACH registration tonnages of 100 000 tpa or more (16 of these are in fact registered at maximum REACH registration tonnages of 1 000 000 tpa or more).

Only seven substances (2.6 %) are predicted to be readily biodegradable (Score B = 1) and are

registered at low tonnages (maximum REACH registration tonnages ≤ 100 tonnes per annum). By definition, these have an ERC Score of 5 (in order to reach a Score A of 6). None of these seven substances have an ERC Score of 5 based on a default ERC Score (assigned in the case of missing data; see section 2.2.1), but rather based on ERC categories assigned. Table 79 provides information on the maximum REACH registration tonnage for these seven substances both at the time of the original evaluation (February 2017) and at a re-evaluation about 8 months later. The re-evaluation identified 2 substances for which the tonnage increased in this relatively short period.

Table 79: Details for 7 initial priority substances with a tonnage ≤ 100 tonnes per annum and a Score B of 1

CAS No.	Name	Maximum tonnage [tpa]	
		Original evaluation	Re-evaluation
78-50-2	Trioctylphosphine oxide	100	100
151-56-4	Ethyleneimine	10	1 000
288-32-4	Imidazole	10	100
68814-89-1	Extracts (petroleum), heavy paraffinic distillates, solvent-deasphalted	10	10
70969-70-9	2-ethylhexyl 3,5,5-trimethylhexanoate	100	100
75-12-7	Formamide	100	100
84-69-5	Diisobutyl phthalate	10	100

These examples illustrate that tonnage may change over time. However, the increases in tonnage observed for 2 substances are comparatively small and the Tonnage Score of 1 for these two substances would not change. Changes may also occur with respect to the use pattern, but analyses of such changes would require repeating the extractions and evaluations described in section 2.2.1 and were not performed for this evaluation.

Overall, the 267 initial priority substances are characterised by a high fraction of substances that are predicted to be persistent due to little or no biodegradation (N=212, 79 %), with the remainder being selected due to Scores A above 5 (N=55, 21 %).

Similar evaluations were performed for the 212 substances finally included in the priority list for further evaluation (i.e. after the exclusion of substances described in section 3.4.4). Table 80 shows that

- 75 substances have both a Score A > 5 and a Score B > 5 (35 %), which represents a lower fraction than in the set of 267 substances (42 %),
- an additional 96/212 substances (45 %) are predicted to be not readily biodegradable (Score B > 5), with the majority being predicted not to be biodegradable at all (Score B = 10, N=90); this fraction is higher than in the set of 267 substances (38 %),
- an additional 13/212 substances (6.1 %) are assigned very high Scores A above 7,
- there are only few substances which are predicted to be biodegradable to at least some degree (Score B = 1-8 and have Scores A < 5 (N=7, 3.3 %).

Overall, these data demonstrate that the fraction of substances with very high Scores A is reduced, a finding that is due to the exclusion of petroleum substances. The 48 excluded petroleum substances all have a Score A of 6-10, with 40 of them having a Score A > 7.

Overall, 155/212 substances (73 %) are predicted not to be biodegradable (Score B =10). This fraction is almost identical to the one observed for the set of 267 substances (72 %). This further illustrates that the changes observed only relate to block A.

Table 80: Number of substances differentiated by Score A and Score B[(a)] among the 212 priority substances selected for further evaluation

Score B	Score A < 3	Score A = 3-5[(b)]	Score A = 5-7[(b)]	Score A > 7	Totals
1	0	1[(c)]	27	13	41
6	2	0	**4**	**0**	6
8	2	2	**6**	**0**	10
10	57	33	**55**	**10**	155
Totals	61	36	92	23	212

(a): The 75 substances with both Score A > 5 and Score B > 5 are highlighted.
(b): No substance is assigned a Score A of 5.
(c): Hydroquinone identified in step 2.

Table 81 shows that the majority of substances (129/212, 61 %) have maximum REACH registration tonnages of 1 000 tonnes per annum or more (including those with confidential tonnage data). This represents only a slight decrease compared to the 267 substances initially prioritised 179/267, 67 %). However, the fraction with maximum REACH registration tonnages ≥ 100 000 (29/212, 14 %) is substantially lower compared to the set of substances initially prioritised in the Pivot table selection (70/267, 26 %). As noted above, this decrease results from the exclusion of substances representing petroleum products.

Among the 83 substances with lower tonnages, 73 (88 %) are predicted to be non-biodegradable (Score B = 10), a fraction that is similar to the one in the set of 267 substances (87 %).

Table 81: Number of substances differentiated by maximum REACH registration tonnage (T; in tonnes per annum) and Score B among the 212 priority substances selected for further evaluation

Score B	T ≤ 100	T 1 000-10 000	T ≥ 100 000	TDC[(a)]	Totals
1	6	17	15	3	41
6	1	5	0	0	6
8	3	7	0	0	10
10	73	65	14	3	155
Totals	83	94	29	6	212

(a): TDC: Tonnage data confidential

Overall, these evaluations show that the 212 priority substances for further evaluation are characterised by a high fraction of substances that are predicted to be persistent due to little or no biodegradation (N=171, 81 %). This fraction is similar to the one observed for the set of 267 prioritised in the Pivot table selection (212/267, 79 %). The remaining 41 substances are selected due to Scores A above 5 with the only exception of hydroquinone that was selected in step 2, since Score A may represent an underestimate (see section 3.4.4). The exclusion of substances representing petroleum products reduces the fraction of substances registered at very high tonnages, while the fraction of those predicted not to be readily biodegradable remains at a high level.

Appendix H – Comparison of Scores B and Scores C

The scores derived in the individual blocks are largely considered to be independent of each other, making the approach used in this study more powerful. For example, no correlation is expected to exist between releases to the environment (block A) and biodegradation (block B). However, some dependency may exist between biodegradation (blocks B) and bioaccumulation (block C), since substances showing little tendency to be biodegraded by microorganisms in the environment may also be more resistant to metabolism by plants and livestock.

In order to analyse the assumed independency of the scores in the different blocks in more detail, correlation coefficients (R) were calculated for the different combinations of scores for all 2 336 substances. Since the Pivot table selection in section 3.4.2 involves the combination of Score A and Score B by an OR operator, correlations coefficients for the maximum of Score A and Score B with either Score C or the Toxicity Score were also calculated. The results are shown in the following table.

Table 82: Correlation coefficients (R) for scores

Correlation	Correlation coefficient (R)
Score A - Score B	−0.285
Score A - Score C	−0.216
Score A - Toxicity Score	0.150
Score B - Score C	0.353
Score B - Toxicity Score	0.021
Score C - Toxicity Score	−0.158
MAX(Score A, Score B) - Score C	0.165
MAX(Score A, Score B) - Toxicity Score	0.137

The data show indeed a poor correlation between the scores in the different blocks. The highest correlation coefficient is observed between the scores in block B and the ones in block C. For reasons discussed above, this finding is not surprising, but the correlation coefficient is still low. Nonetheless, the correlation of the scores in these two blocks was examined in some more detail. The following table shows the number of substances (out of the total of 2 336 substances) with different combinations of scores B and scores C.

Table 83: Number of substances (N=2 336) with different combinations of scores in blocks B and C[(a)]

Score B	Score C			
	10	6	3	1
10	**622**	**257**	*195*	*35*
8	**35**	**24**	*40*	*14*
6	**65**	**27**	*34*	*5*
1	*216*	*283*	**294**	**190**

(a): Values showing agreement (e.g. persistent in the environment – bioaccumulating in food) are set in bold, values showing disagreement (e.g. persistent in the environment – not bioaccumulating in food) are shown in italics.

If these data are aggregated using scores B > 5 to mark persistence in the environment and scores C > 5 to mark a bioaccumulation potential (see chapter 3.4), the findings can be summarised as follows:

- Of the 1 353 substances predicted to be persistent in the environment (Score B > 5),
  - 1 030 substance (76 %) are also predicted to bioaccumulate in food, with the majority being assigned a score of 10 in both blocks (N=622);
  - 323 substances (24 %) are predicted not to bioaccumulate, with the majority of these being assigned a Score C of 3 (N=269);

- Of the 983 substances predicted to be readily biodegradable (Score B = 1),
  - 499 substances (51 %) are predicted to bioaccumulate in food;
  - 484 substances (49 %) are predicted not to bioaccumulate in food.

These data suggest that poor biodegradation is a better predictor of the bioaccumulation potential in food than ready biodegradation. However, the correlation coefficient between Score B and Score C for the 1 353 substances predicted to be persistent in the environment (Score B > 5) is even lower than for all substances (R=0.109 *vs.* R=0.353). It is also remarkable, that a substance predicted to be readily biodegradable has an almost equal likelihood of being evaluated as bioaccumulative or not.

While this analysis suggests that the scores in these two blocks may not be completely independent, the correlation is poor and there are substantial deviations from an assumed dependency of biodegradation and bioaccumulation. As shown above, there are 499 substances that are predicted to be readily biodegradable, but are also predicted to bioaccumulate in food. The majority of these 499 substances (N=294, 59 %) also meet the criteria for bioaccumulation in 'air-breathing organisms' according to the ECHA Guidance on PBT/vPvB assessment (ECHA, 2017a).

Overall, this evaluation shows that there is generally no correlation between most of the scores. While there is some correlation between scores B and C, the overall correlation is poor. Some correlation may exist for substances predicted not to be biodegradable at all. However, even for the 1 109 substances predicted not to be biodegradable (Score B = 10), 230 (21 %) are predicted not to bioaccumulate in food (see Table 83).

Appendix I – Substance type information for prioritised substances

As discussed in section 3.4.4, 267 substances were prioritised for further evaluation. Five substances were excluded from the prioritisation due to the impact of impurities, while another 48 substances were excluded since these represented petroleum products. Additional analyses were performed for the remaining 214 prioritised substances.

For this purpose, information on the 'type of substance'[135] was manually extracted from the REACH registration dossier[136]. This information is contained in two structured fields in the IUCLID software, which describe (a) the composition (e.g. mono-constituent substance) and (b) the origin of the substance (e.g. organic or petroleum product). This information is also disseminated in ECHA CHEM and can therefore be evaluated on the basis of public data.

The IUCLID software provides pick lists for both of these structured fields with a limited number of possible entries as shown in the following figure.

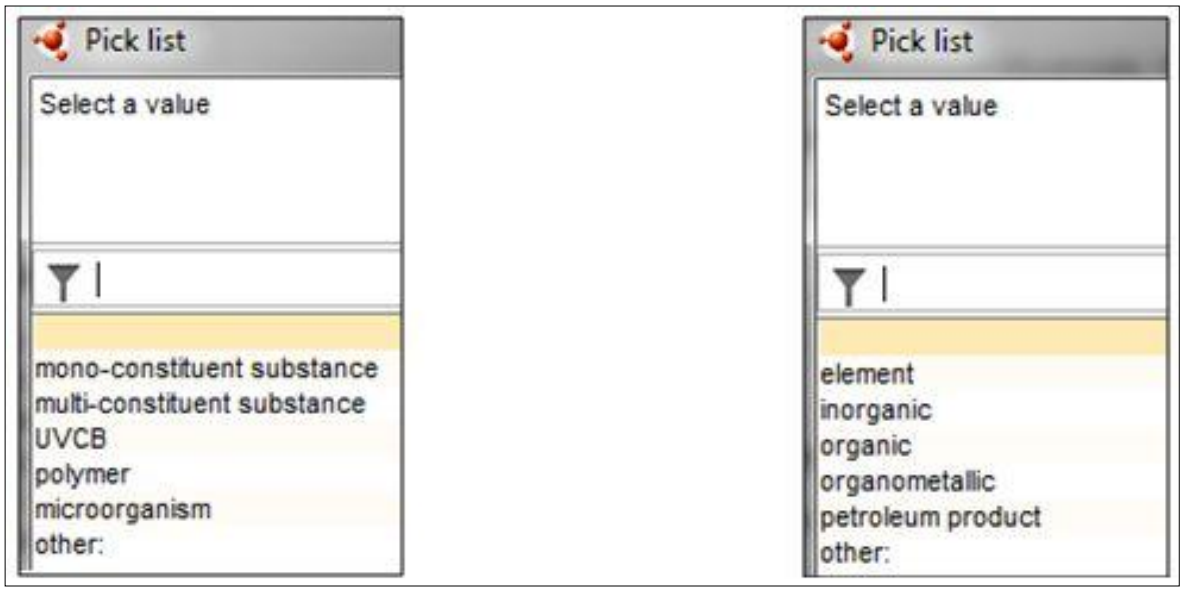


Figure 74: Composition (left) and origin (right) pick lists in IUCLID software

Any given substance is assigned values for the composition and the origin. For example, a mono-constituent substance can be inorganic, organic, organometallic etc. All 214 substances prioritised were evaluated with respect to this information. The statistics of this evaluation are shown in the following table.

Table 84: Composition information on the 214 prioritised substances

Composition	N (%)[(a)]
Mono-constituent	196 (92 %)
Multi-constituent	9 (4.2 %)
UVCB	9 (4.2 %)

(a): All percentage values rounded to two significant figures.

The data show that the fraction of multi-constituent and UVCB substances is relatively small. This finding was expected, since much effort was put into the exclusion of such substances during substance selection. For example, many substances that were lacking a SMILES notation and were

[135] This is the heading in the IUCLID software that is used to prepare registration dossiers; both "type of substance' and 'origin' information is provided under this heading.

[136] If several registration dossiers existed, the one used for tonnage and ERC information was selected, i.e. usually the one with a full registration representing the highest aggregated tonnage (see section 2).

therefore excluded during substance selection represented UVCB substances (see section 3.1.2 and Appendix A). It must be noted that multi-constituent substances generally do not pose a problem in the evaluation, since the SMILES notation represents a structure that is contained in the substance. For example, hexabromocyclododecane (CAS No.: 25637-99-4) is registered as a multi-constituent substance, apparently due to the presence of three different stereoisomers in the commercial product. As another example, tert-butyl-4-methoxyphenol (CAS No.: 25013-16-5) is registered as a multi-constituent substance, since it contains both 3-tert-butyl-4-methoxyphenol (CAS No.: 88-32-4) and 2-tert-butyl-4-methoxyphenol (CAS No.: 121-00-6). The SMILES notation retrieved for this substance represents 2-tert-butyl-4-methoxyphenol, which is one of the two constituents of the registered substance.

However, the case is different for UVCB substances, which may be described by a SMILES notation that is inadequate. As discussed in section 3.4.4, this was the case for many petroleum products. Therefore, information on the 'origin' (see above) was retrieved for the 9 UVCB substances among the 214 prioritised substances and comparisons of the structures defined by the SMILES notation with the registered substance were performed in more detail. All these 9 UVCB substances are registered as 'organic' and none of them is registered as 'petroleum product' (see Figure 74 above for these descriptors). This finding is not surprising, since petroleum products were already excluded as described in section 3.4.4.

Among the 9 organic UVCB substances, the structure defined by the SMILES notation was found to be representative of the UVCB substance in 7 cases, while it was found to be not representative in the remaining 2 cases. Table 85 shows some of these cases for illustrative purposes.

Table 85: Examples UVCB substances that are registered as organics the 212 (potential) priority substances

CAS No.	REACH registration name	Evaluation and conclusion
68937-41-7	Phenol, isopropylated, phosphate (3:1)	Molecular weight of structure (452.5 g/mol) well within range given for UVCB substance (326.3 -705 g/mol) SMILES notation in the REACH registration dossier for the reference substance[137] identical to the one used in the assessment ➔ Structure representative
192268-65-8	A mixture of: triphenylthiophosphate and tertiary butylated phenyl derivatives	Identical structure included in document justifying the listing of the substance for substance evaluation under REACH[138]; one t-butylated phenyl at defined position in structure represented by SMILES notation, while mixture may contain one or several tertiary butyl groups ➔ Structure representative
121158-58-5	Phenol, dodecyl-, branched-	The structure represented by the SMILES notation has a linear C12 alkyl chain (at meta position), while the name clearly indicates that the C12 alkyl chain is branched in the registered substance; the substance is also a UVCB substance, since it has branched alkyl chains of varying lengths (although C12-rich) ➔ Structure **not** representative

These examples are typical for the 9 UVCB substances registered as organics. It is evident that a structure defined by the SMILES notation (as used in this study) may well represent a UVCB substance.

[137] More than 3 500 reference substances are available for the IUCLID software to assign a specified substance (identified e.g. by CAS and EC numbers as well as IUPAC names) to the substance registered. In many cases, additional identifiers such as the SMILES notation or the molecular formula are also included; see https://iuclid6.echa.europa.eu/de/get-reference-substances, accessed February 2018.

[138] See https://echa.europa.eu/documents/10162/5851eb8f-0420-417e-8ede-cb2e75b91950, accessed February 2018.

Overall, the evaluation shows that of the 9 UVCB substances among the 214 priority substances,

- 2 structures are not representative of the UVCB substance;
- 7 structures are representative of the UVCB substance.

Table 86 summarises the information for all 9 UVCB substances.

Table 86: Information on 9 UVCB substances among the 212 (potential) priority substances with conclusion on representativeness of the structure evaluated

CAS No.	REACH registration name	Origin	Conclusion
68937-41-7	Phenol, isopropylated, phosphate (3:1)	Organic	Structure representative
192268-65-8	A mixture of: triphenylthiophosphate and tertiary butylated phenyl derivatives	Organic	Structure representative
25155-23-1	Trixylyl phosphate	Organic	Structure representative
90529-77-4	Reaction products of 2-(chloromethyl)oxirane and glycerol	Organic	Structure representative
68610-51-5	Phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene	Organic	Structure NOT representative
121158-58-5	Phenol, dodecyl-, branched	Organic	Structure NOT representative
51240-95-0	1,1,3,3-tetramethylbutyl peroxyneodecanoate	Organic	Structure representative
26761-45-5	2,3-epoxypropyl neodecanoate	Organic	Structure representative
63449-39-8	Paraffin waxes and Hydrocarbon waxes, chloro	Organic	Structure representative

Appendix J – Selection of substances assigned an initial Toxicity Score of 1 for evaluation of toxicity data

As discussed in section 3.3.5, 183 substances have 'other classifications' for any of the four endpoints but the information was considered not reliable enough to be assigned an initial Toxicity Score of 10 (since such a classification was not supported by more than two notifications). It must again be stressed that these substances have no harmonised classification, IARC classification or classification from REACH registration dossiers for any of the four endpoints (although all these substances are already registered under the REACH Regulation). These 183 substances were assigned an initial Toxicity Score of 1 and flagged 'OTH-NO' (for 'other classification – no toxicity in reliable classifications') in the evaluation of classification information. This section evaluates these 183 substances in more detail in order to (a) assess the impact should these substances – in contrast to expectation – turn out to possess a toxic hazard in relation to the four endpoints considered and (b) identify the most relevant substances for which toxicity data are checked.

Figure 75 shows a Venn chart combining the toxicity score with those from the other blocks. Overall, 115/183 substances (63 %) are assigned a Score C > 5 and this figure is only slightly reduced if the criteria of the Pivot table selection for Score A and B are applied (N=113, 62 %). As outlined above for the substances prioritised in the Pivot table selection (see section 3.4.2), this is due to high number of substances with Score A > 5 or Score B > 5.

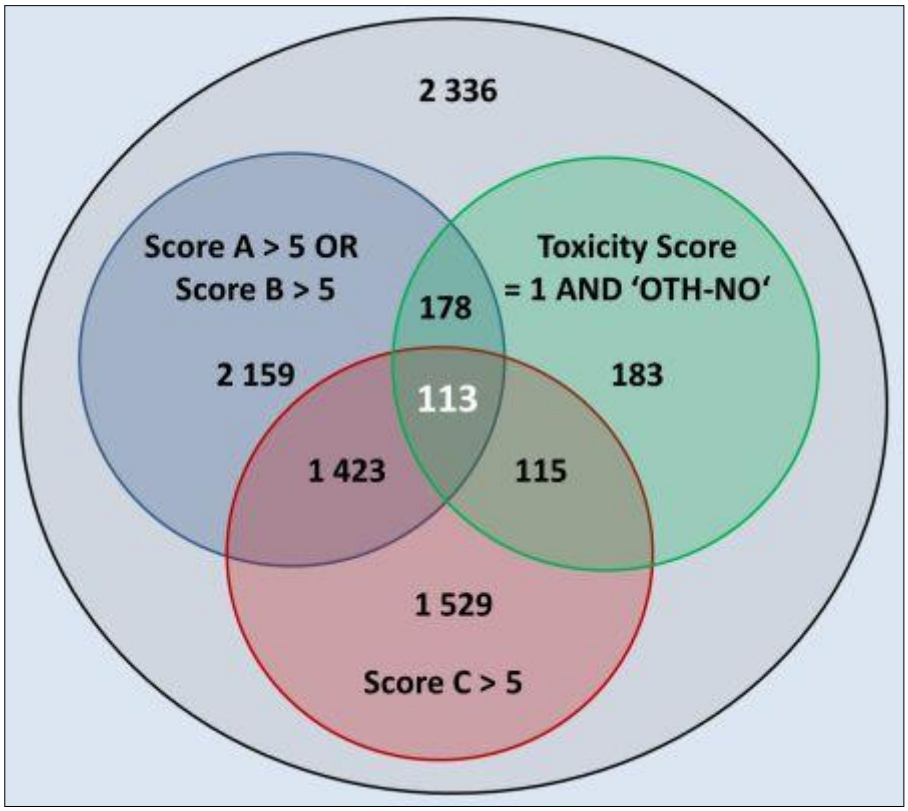


Figure 75: Number of substances with unreliable classification information for toxicity meeting the other criteria of the Pivot table selection for the 2 336 substances in the dataset.

Since the toxicity information is considered unreliable, prioritisation of all these 115 (or 113) substances is clearly not indicated. In addition, this would make a substantial contribution to the priority substances selected. Even if a toxic hazard is confirmed for any of these substances, the assigned Toxicity Score of 10 would still remain somewhat uncertain, since this substance has not been classified for the four endpoints in the REACH registration dossiers (or the harmonised and IARC classifications), i.e. there are always data to the contrary. Nonetheless, ignoring these substances completely may overlook some potential emerging chemical risks.

In a balanced approach, substances that have very high scores in blocks A, B and C are therefore selected, for which the toxicity data for the endpoints identified in the 'other classification' (supported by only one or two notifications, see section 3.3.5) were checked (see section 3.3.5 and Appendix K). The focus is on substances with very high scores in blocks A-C, since overlooking a toxic hazard would be most critical for these substances. The criteria of the Pivot table selection are adapted to stricter cut-off values for this purpose:

Score A ≥ 6 AND Score B ≥ 8 AND Score C = 10

Figure 76 shows the Venn chart with the application of these stricter criteria for blocks A, B and C to all 183 substances with 'other classifications' supported by only one or two notifications.

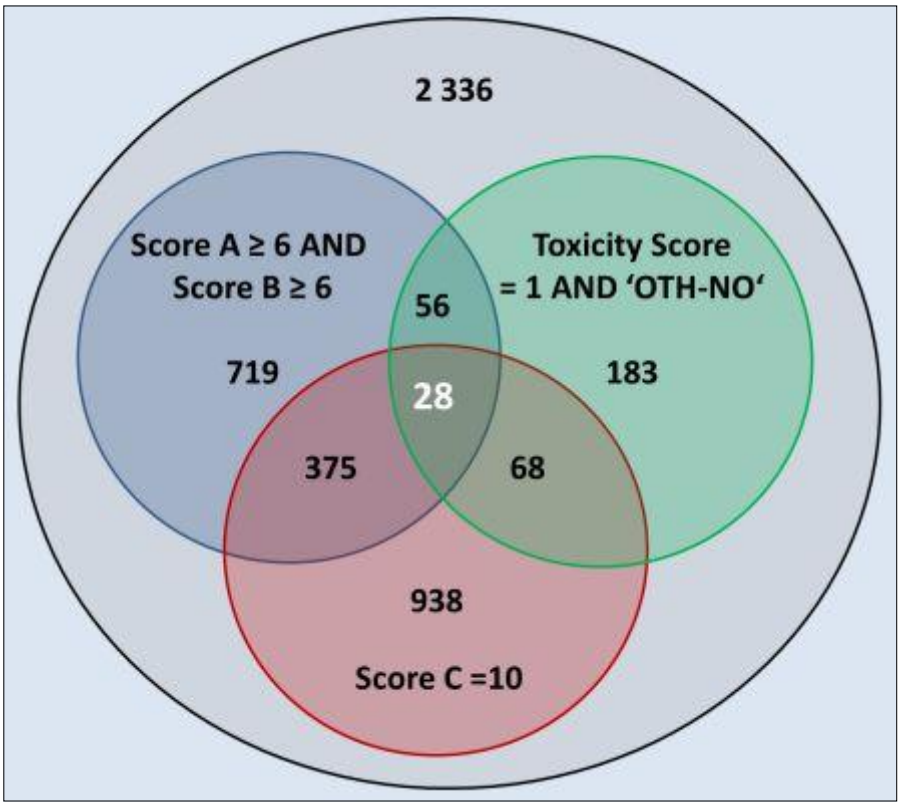


Figure 76: Number of substances with unreliable classification information for toxicity meeting stricter criteria for blocks A, B and C of the Pivot table selection.

Overall, 28 substances among these 183 substances meet the stricter criteria for the Pivot table selection and were therefore selected for checking the toxicity data.

Figure 77 illustrates the (groups of) endpoints for which these 28 substances are classified. The distribution for the 115 and 183 substances discussed above is shown for comparison.

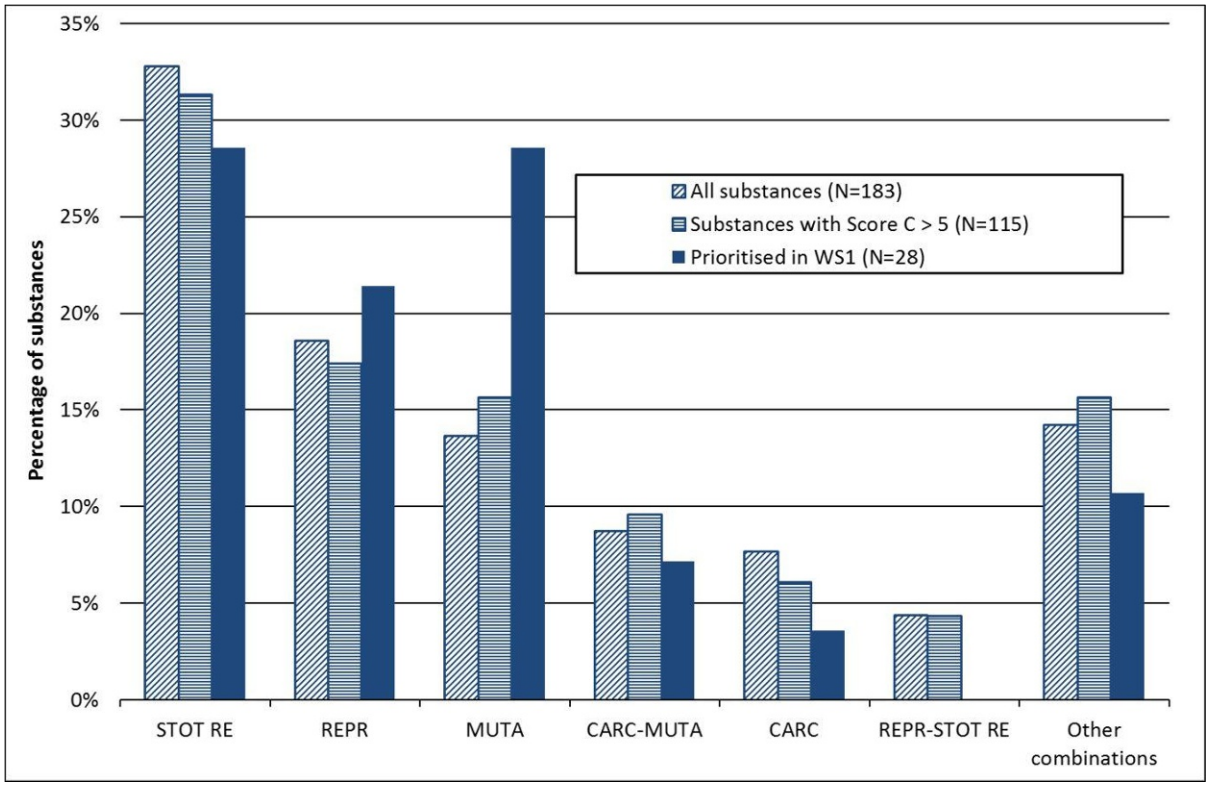


Figure 77: Endpoints for 'other classification': substances with unreliable classification information (2 notifications per endpoint or less).
STOT RE: Systemic target organ toxicity – repeated exposure; REPR: reprotoxicity; MUTA: mutagenicity; CARC: carcinogenicity

The data show that the fraction of substances classified for mutagenicity and reprotoxicity is higher among these 28 substances than in the other two groups. There is no obvious reason for this difference, which is most likely a chance finding.

Some of the 28 substances have 'other classifications' for multiple endpoints. Therefore, toxicity data for 35 endpoints for these 28 substances were checked.

Appendix K – Documentation of the evaluation of toxicity data

The following tables contain the documentation of the data retrieved and evaluated for the 50 substances assigned initial toxicity scores considered less reliable. Table 87 contains the information for the 22 substances with an initial Toxicity Score of 10 and Table 88 contains the information for the 28 substances assigned an initial Toxicity Score of 1. Since none of the classifications for the 50 substances was impacted by impurities according to the information in the C&L Inventory database, this information is not included in the tables.

Please refer to section 2.3.5 the data sources evaluated and shown in the following table. As explained that section, the overall assessment involves some expert judgement and must be considered uncertain in most cases, since a full substance-specific assessment could not be performed in the context of this study. If the initial toxicity score is not confirmed, a brief reasoning for this conclusion is provided in the column 'Other sources (via eChemPortal) for endpoint-specific data', which basically summarises the main reason. This reasoning is included in this column only, but is intended to reflect the data presented in all columns).

The following abbreviations are used in the tables.

ALB	Albumin
ALP	Alkaline phosphatase
EOGRTS	Extended One-Generation Reproductive Toxicity Study
TG	Testing guideline
KEY	Key study
GLP	Good laboratory practice
RL	Reliability
SUP	Supporting study
MN	Micronucleus
NEG	Negative
POS	Positive
WoE	Weight of evidence
CA	Chromosome aberration
SCE	Sister chromatid exchange
MLA	Mouse lymphoma assay
HGPRT (HPRT)	Hypoxanthine-guanine phosphoribosyltransferase
TP	Total protein
TC	Total cholesterol
HDL	High-density lipoprotein
Reg	Registration
1-Gen	1-Generation
2-Gen	2-Generation
ICH S5 (R2)	International conference on harmonization Detection of toxicity to reproduction for medicinal products & toxicity to male fertility S5(r2)
CLH	Harmonised classification and labelling
CORAP	Community Rolling Action Plan
BPC	Biocidal Products Committee
NTP	National Toxicology Program
wk	Week
d	Day
a	Year

Table 87: Substances with an initial Toxicity Score of 10

CAS No.	Endpoint	ECHA CHEM	REACH registration dossier for endpoint-specific data	Other sources (via eChemPortal) for endpoint-specific data	Final Toxicity Score
119313-12-1	REPRO	Harmonised classification proposed, Score confirmed			10
4433-79-8	STOT RE	No additional information	1 rat, oral, OECD TG 407 (KEY, GLP, RL 1): NOEL 20 mg/kg x d, but no specific effects at 100 mg/kg x d, Score questionable	J-CHECK: 1 rat, oral, OECD TG 422 (GLP): NOAEL 40 mg/kg x d, NOEL 8 mg/kg x d, Score confirmed	10
5307-14-2	CARC	No additional information	1 rat, oral (KEY, RL 2), 78+27 weeks 1 rat, oral (SUP, RL 2), female only, 78+27 weeks 1 mouse, oral (SUP, RL 2), 78+12 weeks All considered negative Score not confirmed	INCHEM: IARC Group 3 NICNAS IMAP: increased incidence of hepatocarcinomas in female mice, but in conclusion substance not considered carcinogenic Score not confirmed (IARC Group 3)	1
5307-14-2	MUTA	No additional information	In vitro: NEG in 1 Ames (KEY, RL 2); POS/NEG in numerous SUP studies In vivo: NEG in 1 MN (KEY, RL 2) Score not confirmed	NICNAS IMAP: In vitro: POS in 4 studies (1 Ames, a SCE, 2 CA) In vivo: NEG in 3 studies (SCE (bone marrow), MN, DLA) Score not confirmed (in vivo negative)	1
6786-83-0	CARC	SVHC identification as CARC based on impurities >0.1%	No CARC study available, registered with impurity <0.1% Score not confirmed	NICNAS IMAP: No experimental data but judged carcinogenic, based on read across and impurities CESAR: 'belong(s) to the class of triarylmethane colorants, where some members of which have demonstrated concerns for carcinogenicity' Score confirmed, but may be related to impurities	10
6786-83-0	MUTA	No additional information.	In vitro: NEG in 1 Ames (WoE, RL 2) NEG in 1 CA (WoE, RL 2) Score not confirmed	NICNAS IMAP: No experimental data but judged genotoxic, based on structural alerts Score confirmed	10
26523-78-4 (no longer registered under this CAS no.; now EC no. 701-028-2)	REPRO	CLH proposal and decision (skin sensitisation, aquatic toxicity); background document presents reprotoxicity data from older evaluation with conclusion of no	1 rat, oral, OECD TG 421 (KEY, GLP, RL 1,), negative, NOAEL 200 mg/kg x d 1 rat, oral, no OECD TG 2-Gen (KEY, RL 2), negative, NOAEL 167 mg/kg x d Score not confirmed	HPVIS: HPV testing plan 1 rat, combined chronic and reprotoxicity, negative, NOAEL 167 mg/kg x d INERIS-PSC: No studies available, but discussion of hydrolysis product nonylphenol (classified as Repr. Cat. 2) CCR: Developmental toxicity negative (no further information) US EPA: substance contains residual nonylphenol	1

CAS No.	Endpoint	ECHA CHEM	REACH registration dossier for endpoint-specific data	Other sources (via eChemPortal) for endpoint-specific data	Final Toxicity Score
		classification (despite some effects)		Score not confirmed (CLH proposal and overall data)	
103-90-2	CARC	No additional information.	No carcinogenicity study available Score not confirmed	ENVICHEM: No adequate evidence for carcinogenicity to humans INCHEM - IARC: IARC classification group 3 NTP study: equivocal evidence of carcinogenic activity of acetaminophen in female F344/N rats based on increased incidences of mono-nuclear cell leukaemia. No evidence in male rats and male and female mice Score not confirmed (IARC Group 3)	1
103-90-2	MUTA	No additional information.	In vitro: NEG in 1 Ames (WoE, RL 2) NEG in 1 SCE (WoE, RL 2) Score not confirmed	ENVICHEM: in vivo POS in MN in vitro POS in SCE and CA INCHEM - IARC: cytogenetic effects inconclusive, in vivo POS in SCE, DSB and CA, NEG in MN in vitro POS in SCE, MN and CA, NEG in Ames NTP study: NEG in 1 Ames, POS in SCE and CA Score confirmed	10
103-90-2	STOT RE	No additional information.	4 WoE studies: 1 rat oral 10 d (WoE, RL 2) LOAEL 1000 mg/kg x d Liver - hepatitis (hepatocellular necrosis), significant reduction in ALP, TP, ALB, TC and HDL 1 rat oral 14 d (WoE, RL 2) LOEL 1 250 mg/kg diet, effects on food consumption, body weight 1 mouse oral 13 wk (WoE, RL 2) LOEL 2500 mg/kg x d, effects on food consumption, body weight, organ weight 1 rat oral 30 d (WoE, RL 2) TDLo 15000 mg/kg x d, kidney, ureter, bladder - renal function 1 rat, oral, no OECD TG 1-Gen (WoE, RL 2), negative, NOAEL 1430 mg/kg x d 1 rat, oral, no OECD TG, fertility, 5d study (WoE, RL 2), equivocal LOEL 400 mg/kg x d (only one dose tested, testes weight decreased) Score not confirmed	ENVICHEM: 2 mouse studies 40-41 wk, 1000 or 5000 ppm and 1.1% or 1.25% in diet, liver effects US EPA SRS: NTP studies rat and mouse 2 wk and 13 wk: NOEL 6250 ppm mainly liver and kidney effects Score not confirmed (high NO(A)ELs)	1
2386-87-0	MUTA	No information on CLH, Substance evaluation conclusion MUTA Cat 2 justified	In vitro: 6 studies WoE POS AMES (GLP, RL 1), POS MLA (GLP, RL 1) NEG HGPRT (RL 2), POS SCE (RL 2), equivocal UDS (RL 2) In vivo: 1 ambiguous (KEY, GLP, RL 1) new study after final decision, 1 NEG UDS (WoE, GLP, RL 1), 1 NEG MN	NICNAS IMAP: positive results in several different test systems in vitro (partly results for similar substances), but no data in vivo. Score confirmed.	10

CAS No.	Endpoint	ECHA CHEM	REACH registration dossier for endpoint-specific data	Other sources (via eChemPortal) for endpoint-specific data	Final Toxicity Score
			(WoE, GLP, RL 2,) Dossier suggests that the 'in vitro studies therefore indicate a genotoxic potential for the substance', but considered data insufficient for classification Score confirmed		
2386-87-0	STOT RE	No information on CLH, Substance evaluation conclusion STOT RE 2 justified	1 rat, oral, OECD TG 408 90d (KEY, GLP, RL 1): NOEL 5 mg/kg x d, but no specific effects at 50 mg/kg x d (organ weights, degeneration of olfactory epithelium in nasal tissues), 1 rat, oral, OECD TG 407 28 d (SUP, GLP, RL 1): LOAEL 100 mg/kg x d (liver weight) Score confirmed	NICNAS IMAP: 1 rat, oral, 13 wk: NOAEL 62.5 mg/kg x d, diffuse hyperplasia and hyperkeratosis in the stratified squamous epithelium of the forestomach at 125 mg/kg x d 1 mouse, oral, 13 wk: LOAEL 62.5 mg/kg x d, diffuse hyperplasia and hyperkeratosis in the stratified squamous epithelium of the forestomach in all dose groups Score confirmed	10
101357-15-7	MUTA	No information on CLH, CORAP identification but not for endpoint	In vitro: NEG in 1 Ames (KEY, GLP, RL 1), NEG in 1 CA (KEY, GLP, RL 2), NEG in 1 HPRT gene mutation (KEY, GLP, RL 1), (ECHA requested an additional strain to be tested in AMES) Score not confirmed	No information available. Score not confirmed (overall negative)	1
101357-15-7	STOT RE	No information on CLH, CORAP identification but not for endpoint	1 rat, oral, OECD TG 407 28 d (KEY, GLP, RL 1): NOAEL 150 mg/kg x d, but no specific effects at 1000 mg/kg x d (haematological effects, changes in spleen weight), according to registrant criteria for STOT RE are not met Score not confirmed	No information available. Score not confirmed (high NOAEL)	1
28768-32-3	MUTA	No information on CLH, CORAP testing requirement for in vivo genotoxicity due to concerns for this endpoint	In vitro: 1 POS AMES (RA, KEY, RL 2), 1 POS MLA (RA, KEY, GLP, RL 2) 4 SUP RA studies NEG but 2 have RL 3 In vivo: 1 NEG MN (RA, KEY RL 1) 1 POS CA (RA, KEY, GLP RL 1) 4 SUP studies from RA 2 NEG, 1 POS, 1 ambiguous Based on results from somatic mutagenicity tests the registrant has self-classified the substance as Muta. Cat. 2 (according to CORAP) Score confirmed	No information available. Score not confirmed (confirmed based on data from REACH registration dossier; see column to the left)	10
99-57-0	CARC	No additional information.	No CARC study available Score not confirmed	INCHEM-IARC: IARC classification group 3 No significant increase in the incidence of tumours was observed in mice or in female rats. The incidence of renal-cell adenomas was increased in male rats.	1

CAS No.	Endpoint	ECHA CHEM	REACH registration dossier for endpoint-specific data	Other sources (via eChemPortal) for endpoint-specific data	Final Toxicity Score
				NICNAS IMAP: incidences of preputial gland adenomas or carcinomas, or both, in male rat Haemangiomas or haemangiosarcomas, or both, in mice chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence Score not confirmed (IARC Group 3 and overall data)	
99-57-0	MUTA	No additional information.	In vitro: 1 NEG AMES (KEY, RL 2), 1 NEG QSAR (KEY, RL 2) In vivo: No studies available Score not confirmed	INCHEM-IARC: POS in several in vitro studies (AMES, CA, SCE), NEG in vivo (MN, CA DLM) NICNAS IMAP: some evidence in vitro but NEG in vivo. Overall result: The chemical is not expected to be genotoxic. Score not confirmed (in vivo negative)	1
128-37-0	CARC	No information on CLH, CORAP identification but not for endpoint	1 rat, oral, 2-Gen CARC study (KEY, GLP, RL2), pre-neoplastic changes in the liver Several other SUP studies: General outcome non-genotoxic mode of action, not relevant for C&L Score not confirmed	INCHEM-IARC: IARC classification group 3; pulmonary tumours in female mice were not confirmed in other study, no dose related increase in pituitary adenomas in female rats, not confirmed in other study INCHEM-OECD SIDS: Not a genotoxic carcinogen, but non-genotoxic mechanisms cannot be completely ruled out EFSA OpenFoodTox: any carcinogenicity would be thresholded Score not confirmed (IARC Group 3 and overall data)	1
128-37-0	MUTA	No information on CLH, CORAP identification but not for endpoint	In vitro: 1 NEG AMES (KEY, RL 2, opt-out), 1 NEG rat liver cell line gene mutation (KEY, RL 2, opt-out), 1 NEG CA (KEY, RL 2, opt-out) Several other SUP and WoE studies: No point mutation, not clastogenic In vivo: 1 NEG MN (KEY, RL 2 opt-out), 1 NEG CA (KEY, RL 2, opt-out) Several other SUP and WoE studies: No point mutation, not clastogenic Score not confirmed	INCHEM-IARC:NEG in several in vitro studies (AMES, CA), 1 POS mammalian cells mutation, DNA binding in rats positive, NEG in other (MN, DLM) INCHEM-OECD SIDS: Not a genotoxic carcinogen EFSA OpenFoodTox: not of concern with respect to genotoxicity Score not confirmed (in vivo negative and overall data)	1
128-37-0	REPRO	No information on CLH, CORAP identification for	1 rat, oral, 2-Gen (KEY, GLP, RL 1 opt-out), negative, NOAEL 500 mg/kg x d 1 rat, oral, 2-Gen OECD TG 416 (WoE, RL 2), negative,	INCHEM-OECD SIDS: same NOAEL of 25 mg/kg x d EFSA OpenFoodTox: old ADI based on reproduction and other endpoints	1

CAS No.	Endpoint	ECHA CHEM	REACH registration dossier for endpoint-specific data	Other sources (via eChemPortal) for endpoint-specific data	Final Toxicity Score
		endocrine	NOAEL 25 mg/kg x d, at 100 mg/kg x d lower numbers of litters of ten or more pups at birth Several other SUP and WoE studies: judged negative Score not confirmed	Score not confirmed (unclear whether results are sufficient for classification)	
128-37-0	STOT RE	No information on CLH, CORAP identification but not for endpoint	1 rat oral 2-Gen carcinogenicity study available (KEY, RL 2, opt-out and WoE RL 2), NOAEL 25 mg/kg, no classification for STOT RE required Several other SUP and WoE studies: Score not confirmed	INCHEM-OECD SIDS: same NOAEL of 25 mg/kg x d EFSA OpenFoodTox: same NOAEL of 25 mg/kg x d Score not confirmed (unclear whether results are sufficient for classification)	1
121-30-2	STOT RE	No additional information.	No study available (Reg 1-10 tpa as well as one intermediate)¸second intermediate registration contains 1 study, rat, oral (RL4); not enough detail Score not confirmed	No information available Score not confirmed (data insufficient for classification)	1
9016-45-9	REPRO	No additional information.	No study available (Reg 1-10 tpa) Score not confirmed	NICNAS IMAP: nonylphenol ethoxylate NPE-9 (CAS 26571-11-9) positive (spermicide); no effects observed in other tested NPEs Own comment: Potentially Repr. Cat. 2 classification due to degradation to p-nonylphenol Score not confirmed (unclear whether results are sufficient for classification of this substance)	1
9016-45-9	STOT RE	No additional information.	No study available (Reg 1-10 tpa) Score not confirmed	J-check: 1 oral rat OECD TG 407 (RL 1), NOEL 1000 mg/kg x d NICNAS IMAP: several studies are available for different ethoxylates, effects on organ weights observed at 200 mg/kg x d CESAR: 1 oral rat & 1 oral dog subchronic and chronic study, all NOEL 40 mg/kg x d Score not confirmed (unclear whether results are sufficient for classification)	1
103-95-7	REPRO	No additional information.	1 rat, oral, OECD TG 415 1-Gen (KEY, GLP, RL 1), judged negative as observed effects on sperm analyses and histopathological changes to the epididymides at 150, reproductive organ weights were reduced at 75 & 150 but also reduction in body weight and other organ weights, NOAEL 25 mg/kg x d Specific studies on reproductive toxicity (2 x WoE) with no indication for effects on males at 300 mg/kg and species differences on hepatocyte metabolism Score not confirmed	No information available Own comment: Evaluated as food flavouring -> EFSA OpenFoodTox Score not confirmed (unclear whether results are sufficient for classification)	1

CAS No.	Endpoint	ECHA CHEM	REACH registration dossier for endpoint-specific data	Other sources (via eChemPortal) for endpoint-specific data	Final Toxicity Score
121-73-3	CARC	No additional information.	No study available (Reg 1-10 tpa) Score not confirmed	No information available Score not confirmed (no data retrieved)	1
121-73-3	STOT RE	No additional information.	No oral study with RL 1 and 2 available (KEY, RL 4), low LOAEL 1 mg/kg x d Score not confirmed	US HPVIS: 1 rat, inhal OECD 413 (GLP, RL1) NOAEL <1.5 ppm 1 rat, inhal OECD 412 (GLP, RL1) NOAEL <5 mg/m3 = 0.78 ppm Inhalation studies with effects at the lowest concentration tested similar to the ones observed in the oral studies Overall conclusion: score confirmed taking oral and inhalation studies into account	10
33704-61-9	STOT RE	No additional information.	1 rat, oral, OECD TG 408 (KEY, GLP, RL 1), NOAEL 10 mg/kg x d; at 50 mg/kg x d effects on clinical signs, increase in organ weight, changes in urine, histological changes. Score confirmed	No additional information. Score not confirmed (confirmed based on data from REACH registration dossier; see column to the left)	10
104-40-5	REPRO	No additional information.	1 rat, oral, developmental toxicity study (KEY, RL 2), negative, LOEL 1.25 mg/kg x d effect decreased dam food consumption Score not confirmed	INERIS-PSC: INRS In rats after oral exposure effects on fertility observed (reported in French summary) NICNAS IMAP: mixed nonylphenol and 4-nonylphenol branched are classified as Rrepr. Cat. 2 No test reported for p-nonylphenol, unbranched Score confirmed	10
120-93-4	REPRO	No information on CLH, testing proposal repro/pre-natal developmental toxixity No more information	1 rat, oral, OECD 422 (KEY, GLP, RL 1), negative, NOAEL 155-214 mg/kg x d no effects on reproduction and development, except high dose group pup viability was outside control range but 7 o 11 dead offspring came from one litter. According to the authors, a relationship to the treatment cannot be excluded 1 study showing effects considered unreliable (RL3) based e.g. on unclear identity of test substance and unsuitable route of test substance administration Score not confirmed	HSDB: 1 oral female rat single dose teratogenicity: negative Score not confirmed (negative results)	1
88-19-7	CARC	No additional information.	1 rat oral 2-Gen carc. study (KEY, RL 2), Urinary bladder tumours in single animals, not dose related, not statistically significant Score not confirmed	INCHEM-OECD SIDS: 1 rat oral 2-Gen carc. study negative, 2 rat oral 2 year carc. studies negative, 1 life-time feeding study and 1 rat oral 2-Gen carc. study unreliable due to poor reporting Score not confirmed (negative results)	1
111-90-0	REPRO	No additional	1 rat oral 2-Gen OECD TG 416 (KEY, GLP, RL 1),	OECD HPV-OECD SIDS: Effect on sperm motility was	1

CAS No.	Endpoint	ECHA CHEM	REACH registration dossier for endpoint-specific data	Other sources (via eChemPortal) for endpoint-specific data	Final Toxicity Score
		information.	decrease in sperm motility, not judged relevant for classification as a reproductive toxicant 1 SUP study: rat oral ICH S5 (R2) Add. (SUP, GLP RL2), No effect on gonadal function, mating performance and fertility, NOAEL 2000 mg/kg x d Studies on Dev tox: 1 rat KEY (see above ICH S5 R2) and 3 SUP (all RL2) all negative Score not confirmed	discussed to be related to impurities, but could not be ruled out completely, no other effects observed NICNAS IMAP: No information, only Tier 1 assessment Score not confirmed (unclear whether results are sufficient for classification and potential impact of impurities)	
111-90-0	STOT RE	No additional information.	1 dog, oral, OECD 409 (KEY, GLP, RL 1), negative, NOAEL 1000 mg/kg x d 7 SUP studies: 5 RL2, 2 RL4, different exposure durations (8d - 90d) and species (rat, mouse, pig), NOAEL from 167-1340 mg/kg x d and 3%) Score not confirmed	OECD HPV-OECD SIDS: Effect observed only observed at doses >800 mg/kg in various studies from 30 d to 2 years NICNAS IMAP: No information, only Tier 1 assessment Score not confirmed (high NOAEL/LOAELs)	1
56-81-5	STOT RE	No additional information.	1 rat oral 2-a feeding study (KEY, RL 2), NOAEL 8000 mg/kg x d 1 rat oral 90 d feeding study (KEY, RL 2), NOAEL approx. 4500 mg/kg x d Score not confirmed	INCHEM-OECD SIDS: Effect only observed at doses >10000 mg/kg in 2 a study EFSA OpenFoodTox: Effect observed only observed at doses >6000 mg/kg in various studies from 20 weeks to 2 years NICNAS IMAP: No information, only Tier 1 assessment Score not confirmed (high NOAEL/LOAELs)	1
91-64-5	CARC	Withdrawn CLH intention, but endpoint unclear	1 rat oral CARC study (KEY, RL 2), increased mortality was attributed to increased severity of age-related spontaneous chronic progressive nephropathy in male rats. The incidence of renal tubule adenomas, based on single sections, was not significantly increased, there was an increase in the nine-month 100 mg/kg bw dose group after step-sectioning of the kidney Score not confirmed	INCHEM-IARC: IARC classification group 3 1 mice strain increases in lung tumours (adenomas and carcinomas) in m + f, hepatocellular adenomas in f, another strain negative, 1 rat renal tubule adenomas in m after step-sectioning of the kidney: *limited evidence* in experimental animals EFSA OpenFoodTox: study on DNA-adduct formation in kidney and liver of rats demonstrate that coumarin does not bind covalently to DNA, supporting a non-genotoxic mode of action for tumour induction. Score not confirmed (IARC Group 3 and overall data)	1
91-64-5	STOT RE	Withdrawn CLH intention, but endpoint unclear	1 mice oral 13 wk study (KEY, RL 2), NOAEL >138 mg/kg x d 1 rat 2 a study (KEY, RL2, opt out) no NOAEL reported, but NOEL 42 mg/kg x d for male and 50 mg/kg x d for female, but limited information reported Score not confirmed	EFSA OpenFoodTox: NOAEL from 2 a rat, dog and mice study was 10 mg/kg x d Score confirmed	10

Table 88: Substances with an initial Toxicity Score of 1

CAS No.	Endpoint	ECHA CHEM	REACH registration dossier for endpoint-specific data	Other sources (via eChemPortal) for endpoint-specific data	Final Toxicity Score
51-03-6	REPRO	No information on CLH, CORAP identification but not for endpoint, Dossier evaluation requested robust study summaries with more information BPC opinion: No CLH proposal for this endpoint, but as Carc. Cat. 2 BPC Assessment report: Not considered as toxic to reproduction	1 rat oral 2-Gen OECD TG 416 (KEY, GLP, RL 1), no significant adverse effect level for parental toxicity and pup development, NOAEL 100 mg/kg x d Score confirmed	EPA HHBP: Guideline studies:1 rat oral 2-Gen study negative, Dev tox in rat and rabbit negative Non-guideline studies: 2 Gen study mice NOAEL offspring 2000 ppm Reduction in litter size and litter weight in F2 generation and decreased weight of the F1 and F2 pups during lactation. INCHEM-IARC: Treatment of rats with high doses of piperonyl butoxide during organogenesis did not affect foetal development; however, its continued administration at high dose levels for three generations caused reduction in the number of pregnancies and offspring. Score confirmed for endpoint REPRO, but change in score based on Carc. Cat. 2 proposal for BPC, i.e. other endpoint	10
63449-39-8	CARC	No information on CLH Dossier evaluation with regard to aquatic toxicity classification	1 rat oral CARC studies (KEY, GLP, RL 2), incidence of adrenal medullary phaeochromocytomas was increase in treated female rats compared to controls, although there was no evidence of hyperplasia. The increase was statistically significantly different in the group receiving 900 mg/kg bw. Conclusion from author: Not anticipated to be carcinogenic 1 mice oral CARC studies (KEY, GLP, RL 2), increased incidence of malignant lymphoma in male mice reported at the highest dose tested, 5000 mg/kg/day. Conclusion from author: Significance for human health unclear Score confirmed	CESAR: NTP study in rats and mice: statistically significant increase in incidence of malignant lymphomas in male mice, a marginal (not statistically significant) increase of hepatocellular carcinomas in female mice, and adenomas or carcinomas (in both males and females). Positive trend for increased incidence of phaeochromocytomas of the adrenal medulla with increased dose in female rats. NTP evaluation: no evidence of carcinogenicity for male F344/N rats, equivocal evidence of carcinogenicity for female F344/N rats and female B6C3F1 mice, and clear evidence of carcinogenicity for male B6C3F1 mice. INERIS-PSC/ INCHEM: IPCS EHC 181:Long-term carcinogenicity studies by oral gavage in rats and mice have been conducted on a long chain chlorinated paraffin (C23; 43% Cl). The incidences of malignant lymphomas in male mice and tumours of the adrenal gland in female rats were increased.	10

				INCHEM: IARC evaluation Category chlorinated paraffins Group 2B OECD HPV: same NTP study (see above), "These changes were only observed at exposure levels that are so high (5000 mg/kg bw/day) that the relevance of this property to a human health is doubtful." Score not confirmed (IARC Group 2B)	
63449-39-8	STOT RE	No information on CLH Dossier evaluation with regard to aquatic toxicity classification	1 rat, m?, oral 13 wk study (KEY, GLP, RL 2), NOAEL 900 mg/kg x d for m/f, effects on liver at 3750 mg/kg x d 1 rat, m/f, oral 13 wk study (KEY, GLP, RL 2), NOAEL 900 mg/kg x d for m LOAEL of 100 mg/kg x d for f, effects on liver 8 SUP studies: rat, mouse RL1-2, 14 d – 13 wk, no specific effects, NOAEL in the same range as for KEY Score confirmed	CESAR: 1 mice, m/f, oral 13 wk study NOEL 7500 mg/kg x d, 1 rat, m/f, oral 13 wk study LOEL 235 mg/kg x d for f 1 rat, m/f, oral, 2 a, LOEL 100 mg/kg x d for f INERIS-PSC: IPCS EHC 181: Same studies also LOAEL of 100 mg/kg x d OECD HPV: same as in registration dossier Score confirmed	1
64742-42-3	STOT RE	No additional information	1 rat oral 90 d (KEY, RA, GLP, RL 2) low melting point wax NOAEL 2%, no effects observed, other waxes have lower NOAEL <0.2% Score confirmed	HPVIS: Group waxes and related materials, no direct, lists same study as in registration dossier NICNAS IMAP: No specific data available, read-across to diff. paraffin waxes and low-viscosity and low molecular weight white mineral oils. Conclusion: An overall NOAEL of 2.0 % (about 1100 mg/kg x d) for the microcrystalline waxes was reported. Score confirmed	1
6683-19-8	CARC	No information on CLH Dossier evaluation with regard to aquatic long term toxicity testing	1 mouse oral CARC studies OECD TG 451 (KEY, RL 2), negative, not carcinogenic up to 1000 ppm 1 rat oral CARC studies OECD TG 453 (KEY, RL 2), negative, no increased tumour incidence in treated rats compared to control rats. The incidence of pancreatic islet cell adenomas, in male rats from the 10000 ppm dosage group was slightly above that of the control group. However, the increase was not statistically significant and considered unlikely to be of biological importance. No effect was seen in female rats. Score confirmed	HPVIS: Same studies as in registration dossier CCR: negative in screening on carcinogenicity (CASETOX v1.56 TOPKAT v6.2) Score confirmed	1
793-24-8	STOT RE	No additional information	1 rat oral 28d Japanese guideline (KEY, GLP, RL 2) NOAEL 20mg/kg x d reversible periportal fatty changes of the liver without an increase of liver weight, increased total serum protein 1 rat oral 2a OECD TG 452 (KEY, RL 2) NOEL 50 ppm	JECDB: reproduction/developmental toxicity screening test OECD TG 401 NOEL 6 mg/kg x d liver weight increase INCHEM OECD SIDS: Same studies as in registration dossier, higher NOAELs when administered in feed	1

			(2.6 mg/kg x d m, 3.2 mg/kg x d f)reduced body weight in females, increased food consumption in females and increased liver weight 3 SUP studies: RL1-2, rat 48 d NOAEL 6 mg/kg x d effects on liver rat 13 wk NOAEL 250 ppm transient mild anaemia f rat 2 a NOAEL 300 ppm body weight, liver weight Score confirmed	compared to gavage, due to limited bioavailability Score confirmed	
106-50-3	STOT RE	No information on CLH Dossier evaluation with regard to aquatic long term toxicity testing, testing proposal on long term fish	1 rat oral 90d OECD TG 408 (KEY, GLP, RL 1) NOEL 4 mg/kg x d As the increased body weight-related liver and kidney effects had no associated pathological changes (and are considered and adaptive response to dosing); NOAEL 16 mg/kg x d increased mean absolute and bodyweight-related liver weights in males, and increased mean absolute and bodyweight-related kidney weights in females. No associated pathological changes. 11 SUP studies with different duration, exposure (gavage or feed) and species: No specific effects identified, mostly body weight or organ weight, except myocardial changes at 10 mg/kg x d in rabbit. However, study was RL 4. Score confirmed	NICNAS IMAP: Same study as in registration dossier, 13-wk study (OECD TG 408), SD rats but NOAEL 4 mg/kg x d based on increased absolute and relative liver weights in males 13-wk neurotoxicity study, Fischer 344 rats NOAEL 16 mg/kg x d 12-wk study, Fischer 344 rats NOAEL 50 mg/kg x d 80-wk study, Fischer 344 rats LOEL 25 mg/kg x d slightly decreased body weight in female rats at 0.1% Score confirmed	1
1163-19-5	MUTA	SVHC identification based on PBT properties; no classification proposed in former EU Risk Assessment Report	In vitro: 1 NEG AMES (KEY, RL 1), 1 NEG mouse lymphoma cell line gene mutation (KEY, RL 1), 1 NEG CA/SCE (KEY, RL 1) In vivo: 1 NEG rat cytogenetic evaluation of bone marrow (KEY, RL 2) Score confirmed	NICNAS PEC: No indication of mutagenic effect US EPA IRIS: same studies as in registration dossier CESAR: same studies as in registration dossier EFSA OpenFoodTox: Category PBDEs in food, DNA damage due to induction of ROS, but no specific investigation on the substance Score confirmed	1
1163-19-5	REPRO	SVHC identification based on PBT properties ; no classification proposed in former EU Risk Assessment Report	1 rat oral 1-Gen OECD TG 415 (KEY, RL 2), no significant adverse effects, NOEL >100 mg/kg x d Score confirmed	NICNAS PEC: No indication of reprotoxic effect US EPA IRIS: Significant dose-related disruption in habituation (changes in locomotion, rearing, and total activity) at 8 wk in rats, following a single exposure to 6.7 and 20.1 mg/kg on PND 3; similar effects in mice Mouse oral PND21-70: NOAEL 100 mg/kg x d Significant dose-related disruption in habituation (changes in locomotion, rearing, and total activity) at 2 months in rats, following exposure to 6.7 and 20.1 mg/kg on PND 3 EFSA OpenFoodTox: substance generally did not	1

				cause reproductive or developmental effect at doses up to 500 mg/kg x d CESAR: same studies as in registration dossier Score confirmed	
1163-19-5	STOT RE	SVHC identification based on PBT properties; no classification proposed in former EU Risk Assessment Report	1 rat oral 14d (KEY, RL 2) NOEL 100000 ppm in diet (10%) 1 rat oral 90d EPA OPPTS 870.3100 (KEY, RL 2) NOAEL > 50000 ppm Score confirmed	NICNAS PEC: No indication of specific organ toxicity from repeated dose studies US EPA IRIS: same studies as in registration dossier, additional studies in rats and mice with no indication of organ specific effects EFSA OpenFoodTox: neurodevelopmental effects at low doses (LOEL: 20 mg/kg x d), but based on single exposure and non-guideline study CESAR: same studies as in registration dossier Score confirmed	1
27138-31-4	REPRO	CORAP identification for CMR, reprotox based on effects in OECD 414 that should be evaluated in SEV	1 rat oral 2-Gen OECD TG 416 (KEY, GLP, RL 1), no significant adverse effects, NOEL 10 000 ppm for reproductive parameters, NOAEL for developing offspring 3300 ppm 1 rat oral 1-Gen study (SUP, RL 4) dose-range finder for 2-Gen study NOAEC 15000 ppm for P0, NOAEC 7500 ppm for F1 1 rat oral OECD TG 414 (KEY, GLP, RL 1) NOAEL 250 mg/kg x d fetal/pup body weight changes, external malformations Score confirmed	HPVIS: Same studies as in registration dossier Score confirmed	1
6535-46-2	MUTA	No information on CLH Dossier evaluation with regard to PC data request	In vitro: 1 NEG AMES (Key, GLP, RL 1), 1 NEG MN V79 cells (Chinese hamster cell line) (KEY, GLP, RL 1), 1 NEG HPRT V79 cells (Chinese hamster cell line (KEY, GLP, RL 1) 5 SUP studies: all with negative results (4 AMES, RL 1-2, 1 AMES RL 3) Score confirmed	No additional information Score confirmed	1
68411-46-1	STOT RE	No information on CLH Dossier evaluation with regard to sub-stance identity CORAP identifica-tion, but based on PBT Testing proposal	1 rat oral 90 d, OECD TG 408 (KEY, GLP, RL 2), NOEL < 100 mg/kg x d increased liver weight, histopathology findings in liver (centrilobular hypertrophy grade, single cell necrosis, midzonal fatty change) and thyroid (hypertrophy, altered colloid) 1 rat oral 28d m, 53 d f, OECD TG 422 (KEY, RA, GLP, RL 1), NOAEL 25 mg/kg x d morphologic liver findings, changes in clinical biochemistry parameters as high dose animals, relative liver weight increase of 24% and 17%	No additional information Score confirmed	1

		for EOGRTS (previous 90d and 2-Gen study)	for males and females 1 rat oral 28d, (KEY, GLP, RL 1) NOAEL 25 mg/kg x d, effects on liver Score confirmed		
67-68-5	CARC	No additional information	7 SUP studies with emphasis on use of DMSO as solvent in carcinogenicity studies: No specific effects after dermal treatment or subcutaneous injection Score confirmed	HPVIS: same studies as in registration dossier Score confirmed	1
67-68-5	MUTA	No additional information	In vitro: 1 NEG AMES (KEY, RL 2), 1 NEG CA Chinese hamster ovary cells (KEY, RL 2), 1 NEG SCE Chinese hamster ovary cells (KEY, RL 2) 4 SUP studies: 3 with negative result (1 AMES, 1 DNA repair, 1 chromosome gain), 1 POS prophage-induction assay 3 WoE studies Mammalian cell gene mutation: negative In vivo: 1 NEG MN (KEY, GLP, RL 1) 5 SUP studies: all negative Score confirmed	HPVIS: same studies as in registration dossier OECD HPV: same studies as in registration dossier Score confirmed	1
67-68-5	STOT RE	No additional information	1 rat oral 78 wk, OECD TG 452 (KEY, RL 2), NOAEL 3300 mg/kg x d slight depression of the body-weight gain 1 dog oral 2 a, OECD TG 452 (KEY, RL 2), NOAEL 1100 mg/kg x d but changes in the lens of eye at all dose levels 1 monkey oral 87 wk, OECD TG 452 (KEY, RL 2), NOAEL 2970 mg/kg x d effects on body weight, food consumption (anorexia), ptyalism and emesis 1 rat oral OECD 421 (SUP, GLP, RL 2), NOAEL >1100 mg/kg x d, no effects observed Score confirmed	HPVIS: same studies as in registration dossier OECD HPV: same studies as in registration dossier Score confirmed	1
130-26-7	REPRO	No additional information	3 WoE entry: read-across with negative outcome, 2 non-guideline studies RL 2 and 4 negative. QSAR also for dev tox, 1 rat oral (WoE, RL2) LOEL 120 mg/kg retardation of ossification in 5th sternebra, proximal phalanx, and caudal vertebrae. Note: According to the limited reporting, the LOEL should be the NOEL. Score confirmed	No additional information Score confirmed	1
131-57-7	STOT RE	CORAP identification but not for endpoint, as possible endocrine disruptor	1 rat oral 90d OECD TG 408 (KEY, GLP, RL 1), NOAEL 6250 ppm (approx. 400 mg/kg x d) microscopic kidney lesions in mid dose group 1 mouse oral 90d OECD TG 40 (sup, GLP, RL 1), NOAEL 25000 ppm microscopic kidney lesions in mid dose group	US EPA SRS: NTP 2 and 13 wk studies in rats and mice: rat 2 wk liver effects at 6250 ppm, 13 wk kidney effects Mouse 2 wk liver effects, 13 wk kidney effects at 50000 ppm	1

			1 rat oral 28d (SUP, RL 2), NOAEL >10000 ppm, no effects observed Score confirmed	Overall NOAEL 6250 ppm for microscopic lesions Dermal studies showed a NOAEL <(<23 mg/kg x d, (<23 mg/kg/day 1 mice continuous breeding study (1.25-5% in feed) minimal effects on fertility in the F1 generation but F2 pup weights were significantly Score confirmed	
17354-14-2	MUTA	No additional information	In vitro: 1 AMES NEG in 3 strains, POS in TA98 +S9 (KEY, GLP, RL 1), 1 NEG HPRT Chinese hamster ovary cells (KEY, GLP, RL 1), 1 AMES NEG in 4 strains, POS in TA98 +S9 (KEY, GLP, RL 1) Score not confirmed	NICNAS IMAP: No substance specific data, but a genotoxic mode of action cannot be ruled out for any of the chemicals in this group Score not confirmed (positive in vitro)	10
2440-22-4	STOT RE	No information on CLH Dossier evaluation with regard to aquatic long term toxicity testing and other env endpoints and in vitro gene mutation in mammalian cells CORAP / substance evaluation: Result No need for regulatory follow-up action at EU level	1 rat oral 90d (KEY, RL 2), NOEL 0.2% in feed (approx. 100 mg/kg x d) m/f: Increase in relative liver weight with hepatocyte hypertrophy and increase in relative kidney weight, m: nephropathy; slight reduction in relative testes weight without histopathology findings, f: slight increase in relative adrenal weight without histopathology findings 1 rat oral 2a OECD TG 452 (KEY, RL 1), NOEL 1000 ppm (approx. 50 mg/kg x d) reduction of body weight gain 1 dog oral 90d + 28d recovery (KEY, RL 1), NOEL 1000 ppm (approx. 33 mg/kg x d)reversible increase in relative liver weight with increased ALT and GGT levels 3 SUP studies: 2 RL 3 and 1 RL 4 without additional relevant findings Score confirmed	HPVIS: same studies as in registration dossier J-CHECK: 1 rat oral OECD 422 (GLP): NOAEL 100 mg/kg x d hydropic change and regeneration of renal proximal tubules in the females NOAEL 300 mg/kg x d for reproductive/developmental toxicity Score confirmed	1
32724-62-2	MUTA	No additional information	In vitro: 1 NEG AMES (KEY, RL 2), 1 NEG CA CHL/IU cells (KEY, RA, RL 2), 1 NEG HPRT V79 cells (Key, RA, RL 2) 1 NEG AMES (SUP, RA, GLP, RL1), Score confirmed	No additional information Score confirmed	1
3468-63-1	CARC	No information on CLH CORAP / substance evaluation: Identification based on CMR properties, lack of information	1 rat dermal (SUP, RL 4) NOAEC > 143.7 mg total dose no increase in incidence of neoplasia 1 rat oral 78 wk (SUP, RA, RL 4) treatment-related increase of benign liver tumours in females is questionable 1 mouse oral 2a OECD TG 453 (SUP, RA, RL 2) Increased incidence of renal cortex tubule adenoma and	No additional information Score confirmed	1

		from existing studies	of thyroid follicular cell adenoma in males leads to NPT conclusion 'some evidence of carcinogenic activity' of PR3 in male mice; female mice 'no evidence of carcinogenic activity' 1 rat oral 2a OECD TG 453 (SUP, RA, RL 2) Increased incidence of adenoma in several organs in males and females; reporting of studies is a copy from NTP report Score confirmed		
3468-63-1	MUTA	No information on CLH CORAP / substance evaluation: Identification based on CMR properties, lack of information from existing studies	In vitro: 1 POS AMES (Key, GLP, RL 1), 1 NEG CA CHL/IU cells (Key, RL 2), 1 NEG HGPRT V79 cells (Key, RL 2) 8 SUP studies: 7 POS AMES (RL 2-3), 1 NEG Ames (RL 2) In vivo: 1 NEG rat oral DNA repair UDS OECD TG 486 (Key, GLP, RL 1) 1 NEG hamster CA OECD TG 475 (SUP, RL2) Score confirmed	No additional information Score confirmed	1
36968-27-1	MUTA	No additional information	In vitro: 2 NEG AMES (Key, GLP, RL 1), 21 other KEY studies from read-across: 11 NEG AMES; 4 NEG CA, 1 NEG MN, 5 NEG HGPT, In vivo: 1 NEG rat oral DNA repair UDS OECD TG 486 (Key, GLP, RL 1) Score confirmed	No additional information Score confirmed	1
505-32-8	REPRO	No additional information	1 rat oral 1-Gen OECD TG 415 (SUP, GLP, RL 1), NOAEL 500 mg/kg x d Reproduction parameters affected at 1000 mg/kg x d; LOAEL 250 mg/kg x d effects on kidney Score confirmed	OECD HPV: same study as in registration dossier EFSA OpenFoodTox: Flav Group 18 Group evaluation and revisions (latest 2015) did not report the study from registration dossier Score confirmed	1
518-47-8	MUTA	No additional information	In vitro: 1 NEG AMES (Key, RL 2) 8 SUP studies: 4 NEG AMES (RL 2), 3 NEG CA (RL 2), 1 NEG –S9, POS +S9 MLA (RL 2) Score confirmed	US EPA SRS: NTP: study was considered inadequate and no technical report was prepared. NICNAS IMAP: same studies as in registration dossier, evaluation: not expected to be genotoxic Score confirmed	1
57-88-5	REPRO	No additional information	No study for tox to reproduction 4 WoE for dev tox: All non-guideline, some indication of effect after (subcut.) injections and oral application: increase in total number of abnormal palates, lower body weight of foetuses, increased resorption and increased number of foetuses with oral clefts Score confirmed	INCHEM: IARC evaluation group 3, no information on reprotoxicity Score confirmed	1
591-27-5	STOT RE	No additional	1 rat oral 90d (KEY, RL 2), NOEL 20 mg/kg x d) dose	JECDB: 1 rat oral 28 d Japanese guideline (GLP)	1

		information	related thyroid hyperactivity and the presence of the test substance in the renal tubules 3 SUP studies: 1 rat oral 90 d LOEL 250 mg/kg x d reduction in body weight, 1 rat (newborn) oral 18 d NOEL 80 mg/kg x d effects on general behaviour, body weight and organ weights 1 rat oral 28 d NOAEL 240 mg/kg x d based on anaemia, hepatotoxicity and renal toxicity, in addition to tremors, depression of body weight gain and histopathological changes in thyroid gland 1 rat dermal 2a (KEY, RL2) NOAEL 0.5 ml = 500 mg/kg x d effect on body weight, food consumption, haematology and pathology Score confirmed	NOEL <80 mg/kg x d brownish black urine and increase in volume with water consumption. NICNAS IMAP: same studies as in registration dossier Score confirmed	
597-82-0	REPRO	No information on CLH CORAP / substance evaluation: Based on PBT criteria, but it is mentioned that reproductive effects (decreased viability in offspring) had been observed in OECD TG 421 study Conclusion: no indications for concern with respect to mutagenicity, carcinogenicity, reproduction toxicity or STOT. Testing proposal: EOGRTS	1 rat oral OECD TG 421 (KEY, RA, GLP, RL 2), P NOAEL 250 mg/kg x d lower food consumption and the occasional lower mean body weight gain, P NOEL >250 mg/kg x d fertility index, viability index; F1 NOAEL >250 mg/kg x d absence of adverse findings 1 rat oral OECD TG 422 (KEY, GLP, RL 1), P NOAEL 25 mg/kg x d clinical, signs, haematology, clinical biochemistry, F NOAEL 25 mg/kg x d for reproductive and developmental toxicity Score confirmed	No additional information Score confirmed	1
6410-32-8	MUTA	No additional information	In vitro: 2 NEG AMES (Key, GLP, RL 1), 21 other KEY studies from read-across: 11 NEG AMES; 4 NEG CA, 1 NEG MN, 5 NEG HGPT, In vivo: 1 NEG rat oral DNA repair UDS OECD TG 486 (Key, GLP, RL 1) Score confirmed	No additional information Score confirmed	1

6448-95-9	MUTA	No additional information	In vitro: 2 NEG AMES; 1 NEG CA (Key, GLP, RL 1), 20 other KEY studies from read-across: 11 NEG AMES; 3 NEG CA, 1 NEG MN, 5 NEG HGPT In vivo: 1 NEG rat oral DNA repair UDS OECD TG 486 (Key, GLP, RL 1) Score confirmed	JECDB: 1 POS AMES OECD TG 471 (GLP), 1 NEG CA OEC D TG 473 (GLP) Score confirmed	1
67990-05-0	MUTA	No additional information	In vitro: 2 NEG AMES (Key, GLP, RL 1), 21 other KEY studies from read-across: 11 NEG AMES; 4 NEG CA, 1 NEG MN, 5 NEG HGPT, In vivo: 1 NEG rat oral DNA repair UDS OECD TG 486 (Key, GLP, RL 1) Score confirmed	No additional information Score confirmed	1
70879-65-1	CARC	No additional information	No study available in registration dossier Score confirmed	No additional information Score confirmed	1
70879-65-1	MUTA	No additional information	In vitro: 1 NEG AMES (WoE, RL 4), 2 WoE studies from read-across: 1 NEG AMES; 1 NEG CA Score confirmed	NICNAS IMAP: not possible to draw a definite conclusion, no substance specific data, but a genotoxic mode of action cannot be ruled out for any of the chemicals in this group Score confirmed	1
85-60-9	STOT RE	No information on CLH Dossier evaluation: Request of ecotox studies and 1 pre-natal dev tox OECD TG 414 CORAP / substance evaluation: Selection in a group of hindered phenols, based on PBT criteria and endocrine disruption	1 rat oral 90d (KEY, RL 2), NOAEL 100 ppm changes in SGOT and SGPT, liver weights, and in liver and lymph node tissue 1 SUP studies: 1 rat oral 28 d NOEL <1000 ppm liver identified as target organ 1 rat oral OECD TG 421 (KEY, GLP, RL 1) NOAEL 1000 mg/kg x d overall effects clinical signs; mortality; body weight; food consumption; water consumption; gross pathology; organ weights; histopathology Score confirmed	HPVIS: same studies as in registration dossier Score confirmed	1