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REACH Compliance: Data availability in REACH registrations – Part 3: Evaluation of 100 to 1000 tpa substances

Final Report

For our Environment

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REACH Compliance: Data availability in REACH registrations – Part 3: Evaluation of 100 to 1000 tpa substances

Final report

by

Angelika Oertel, Jakob Menz, Anika Brüning, Sebastian Schmeisser, Anna Lena Kronsbein, Katrin Maul, Paulina Heinze, Agnes Schulte

German Federal Institute for Risk Assessment (BfR), Berlin

On behalf of the German Environment Agency

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Publisher
Umweltbundesamt
Wörlitzer Platz 1
06844 Dessau-Roßlau
Tel: +49 340-2103-0
Fax: +49 340-2103-2285
info@umweltbundesamt.de
Internet: www.umweltbundesamt.de

/umweltbundesamt.de
/umweltbundesamt

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Abstract: REACH Compliance: Data availability in REACH registrations – Part 3: Evaluation of 100 to 1000 tpa substances

The REACH Regulation (Registration, Evaluation, and Authorisation of Chemicals) ensures that data are available for all substances manufactured or imported in quantities of one tonne or more per year (tpa) within the European Economic Area via registration of the chemicals with the European Chemicals Agency (ECHA). These data – information on physico-chemical, toxicological and ecotoxicological properties as well as on exposure – are used to assess the possible hazards for human health and the environment posed by the chemicals and are necessary to derive risk management measures. The objective of the project was to assess the availability and quality of the information on toxicological and ecotoxicological endpoints in lead and individual registration dossiers of the medium tonnage band (100-1000 tpa). Eight endpoints (developmental, reproductive and repeated dose toxicity, mutagenicity, biotic and abiotic degradation, bioaccumulation and ecotoxicity) and the environmental exposure assessment were included in the investigation. While the availability of standard information (guideline studies) was addressed within the screening, data waiving/adaptations were analysed during the formal and refined check. According to the criteria applied within the project, 14 % to 57 % (on average 45 %) of the evaluated data for a specific endpoint were considered "compliant", 9 % to 46 % (on average 24 %) "non-compliant", and 11 % to 76 % (on average 31 %) "complex" (without conclusion within the scope of the project). The results of the project revealed that at least 24 % of the assessed endpoint entries failed to be in compliance with the REACH requirements. Thus, the availability and quality of toxicological and ecotoxicological information provided in registration dossiers may be subjected to improvements.

Kurzbeschreibung: DraftREACH Compliance: Datenverfügbarkeit in REACH-Registrierungen – Teil 3: Bewertung von 100 bis 1000 tpa Stoffen

Die REACH-Verordnung (Registrierung, Bewertung und Zulassung von Chemikalien) stellt sicher, dass Daten zu Chemikalien, die in Mengen von einer Tonne oder mehr pro Jahr (tpa) innerhalb des Europäischen Wirtschaftsraums hergestellt oder importiert werden, durch die Registrierung der Chemikalien bei der Europäischen Chemikalienagentur (ECHA) verfügbar gemacht werden. Diese Daten – Informationen zu physikalisch-chemischen, toxikologischen und ökotoxikologischen Eigenschaften sowie zur Exposition – werden verwendet, um die mögliche Gefährdung der menschlichen Gesundheit und der Umwelt durch Chemikalien zu bewerten sowie gegebenenfalls Risikomanagementmaßnahmen abzuleiten. Ziel des Projekts war es, die Verfügbarkeit und Qualität der Informationen zu toxikologischen und ökotoxikologischen Eigenschaften in federführenden und individuellen Registrierungsdossiers des mittleren Mengenbereichs (100-1000 tpa) zu bewerten. In die Untersuchung wurden acht Endpunkte (Entwicklungs- und Reproduktionstoxizität, Toxizität bei wiederholter Aufnahme, Mutagenität, Biologische und Abiotische Abbaubarkeit, Bioakkumulation und Ökotoxizität) sowie die Umweltexposition einbezogen. Während im Rahmen des Screenings die Verfügbarkeit von Standardinformationen (Guideline-Studien) geprüft wurde, wurden Datenverzicht und Datenanpassungen während der formalen und verfeinerten Prüfung analysiert. Anhand der Kriterien, die im Projekt angewandt wurden, wurden 14 % bis 57 % (Mittelwert 31 %) der ausgewerteten Daten für einen bestimmten Endpunkte als "compliant", 9 % bis 46 % (Mittelwert 24 %) als "non-compliant" und 11 % bis 76 % (Mittelwert 31 %) als "complex" (ohne abschließende Bewertung im Rahmen des Projekts) bewertet. Die Ergebnisse zeigen, dass mindestens 24 % der Endpunkteinträge nicht konform mit den Datenanforderungen unter REACH waren. Demnach sollte die Verfügbarkeit und Qualität toxikologischer und ökotoxikologischer Informationen, die in Registrierungsdossiers bereitgestellt werden, verbessert werden.

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List of abbreviations

Carc	Carcinogens
CAS	Chemical Abstracts Service
CLP	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, … (EC, 2008b)
CSA	Chemical safety assessment
CSR	Chemical safety report
Cytvitro	Cytogenicity/micronucleus test in mammalian cells (study type)
Cytvivo	Cytogenicity/micronucleus test *in vivo* (study type)
EC	European Community
ECHA	European Chemicals Agency
EOGRTS	Extended one-generation reproductive toxicity study
ERC	Environmental release category
ESR	Endpoint study record
Germvivo	Germ cell test *in vivo* (study type)
GMbact	Bacterial gene mutation test (study type)
GMvitro	Gene mutation test *in vitro* (study type)
GMvivo	Gene mutation test *in vivo* (study type)
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
log K_{ow}	10-base logarithm of n-octanol/water partition coefficient
Muta	Germ cell mutagen
n	Number (of)
PROC	Process category
PBT/vPvB	Persistent, bioaccumulative, toxic/very persistent, very bioaccumulative
PEC	Predicted environmental concentration
PNEC	Predicted no effect concentration
QMRF	(Q)SAR Model Reporting Format
QPRF	(Q)SAR Prediction Reporting Format
(Q)SAR	Qualitative or Quantitative Structure-Activity Relationship

Carc	Carcinogens
REACH	Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) … (EC, 2006)
Repro	Reproductive toxicant
PROC	Process category
STOT RE	Specific target organ toxicity – repeated exposure
spERCs	Specific Environmental Release Categories
SVHC	Substances of very high concern
S_w	Water solubility
TMI	Test material information
TG	Test guideline
tpa	Tonne(s) per annum (year)
WoE	Weight of evidence

Summary

Introduction

The European Union's regulatory framework on chemicals aims to ensure the safe use of chemicals for human health and the environment. The Regulation (EG) No 1907/2006 forms the corresponding legal basis and provides a system for the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH (EC, 2006)). REACH requires chemicals manufactured or imported in quantities of one ton per year (tpa) or more to be registered at the European Chemicals Agency (ECHA). A registration shall include information addressing physico-chemical, toxicological and ecotoxicological properties of the chemical which is compiled in different categories (referred to as endpoints) and may be derived from various sources including animal and non-animal testing. The extent of the information requirements thereby depends on the manufactured or imported quantity of the chemical and is laid down in Annexes VII to X of the REACH Regulation. The information on chemicals made available under REACH is essential to identify hazards associated with the chemical, and allows for a suitable exposure and risk assessment for the registered uses concerning human health and the environment. On the basis of this information, for instance, substances of very high concern (SVHC) can be identified that would require further regulatory measures under REACH such as authorisation or restriction of the substance on the European Union's market.

The REACH Compliance project was initiated to give a broad overview on the availability and quality of toxicological and ecotoxicological data across a given tonnage band in a representative number of all lead and individual registrations. Hence, the prime objective of the project was to determine and to document the extent to which the reach requirements have been fulfilled in order to establish a solid basis for discussions with registrants, stakeholders and regulators concerning the implementation of REACH. In addition, the results expected to evolve from this project will be utilised for priority setting for further regulatory actions.

The current report constitutes the third part in a series of publications titled "REACH Compliance project: Data availability of REACH registrations". The first two parts, "Screening of chemicals > 1000 tpa" (Springer et al., 2015) and "Evaluation of data waiving and adaptations for chemicals ≥ 1000 tpa" (Oertel et al., 2018b), have already been published and indicate a need for improvement in REACH registrations of the high tonnage band (≥ 1000 tpa). Recommendations for registrants on how to improve their dossiers were developed based on the project results (Oertel et al., 2018a).

Methodology

The current investigation addresses data availability and quality of toxicological and ecotoxicological information or their respective waiving/adaptations in registration dossiers for substances manufactured or imported in quantities of 100-1000 tpa. Overall, 2053 lead and individual registration dossiers submitted to ECHA until March 2017 were examined.

Consistent with the previous report on ≥ 1000 tpa registrations, the following endpoints were selected: developmental, reproductive and repeated dose toxicity, mutagenicity, biotic and abiotic degradation, bioaccumulation and ecotoxicity. Additionally, the evaluation of the environmental exposure assessment, addressed within the registrant's chemical safety assessment if required, was included in the current project. The methodology developed for the higher tonnage band ≥ 1000 tpa was adapted to the information requirements of the medium tonnage band (100-1000 tpa) according to REACH Annexes VII to IX and revisions were implemented to further increase the final decision rate. As for the previous evaluation, a standardised approach with a tiered procedure was followed to systematically investigate the data availability and quality of the selected endpoints. Therefore, endpoint entries[1] comprising all the available endpoint-specific information for a given substance were subjected to a screening and partly to a formal and a refined check.

Screening

The first evaluation step, the screening, comprised an assessment of the endpoint entries in 2053 registration dossiers with respect to the eight selected endpoints. Herein, it was investigated and documented whether the standard information requirements according to REACH Annexes VII-IX were fulfilled, i.e. whether the respective guideline-conform study was available. If these requirements were not met, the availability of a waiving/adaptation was checked. To this end, the hierarchy of the REACH information requirements was addressed by means of decision trees or questionnaires. Endpoints remained without a final conclusion ("complex") within the screening evaluation if either an in-depth analysis was required or a waiving/adaptation was utilised to comply with the standard information requirements. The latter cases were designated for further assessment within the formal and refined check. An in-depth analysis (e.g. regarding the scientific validity of the information) was outside the scope of the project and the corresponding cases remained complex in this evaluation step and in the project.

Formal check

Of the 2053 dossiers, a representative subset of 500 dossiers was randomly selected. Dossiers that contained waiving/adaptations were subjected to the formal check. The formal check constituted the second evaluation step that included the assessment of the formal conformity of data waiving and adaptations in the registration dossiers. The formal criteria specified in the REACH Annexes VII-IX column 2 or Annex XI were systematically examined using a questionnaire. Data waiving categories evaluated in the formal check included (a) waiving justified by endpoint specific criteria (column 2), (b) testing is technically not possible, and (c) waiving based on limited exposure. Adaptation categories analysed within the formal check included the assessment of surrogate data substantiated by (a) read-across and grouping approaches and (b) Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs).

Refined check

[1] An endpoint entry comprises all the available endpoint-specific information in a given dossier that was subjected to systematic evaluation within the project.

In a subsequent evaluation step, the refined check, additional adaptation and data waiving categories were subjected to an in-depth analysis. These categories comprised (a) weight of evidence (WoE) approaches, (b) waiving with reference to the outcome of the chemical safety assessment and the environmental exposure assessment, and (c) waiving with reference to the chemical structure, depending on the assessed endpoint.

Conclusion categories

A decision based on data availability and quality was made for each of the eight endpoints and assigned to one of the four conclusion categories:

- "Compliant": The endpoint was considered "compliant" if the information requirements according to the assessed criteria of the REACH Compliance project were fulfilled;
- "Non-compliant": The endpoint was considered "non-compliant" if the information requirements according to the assessed criteria of the REACH Compliance project were not fulfilled;
- "Complex": The endpoint was considered "complex" if an endpoint remained without conclusion in one of the evaluation steps and if a final conclusion could ultimately not be reached within the limited scope of the REACH Compliance project;
- "Testing proposal": A testing proposal was provided for the assessed endpoint.

It should be noted that the conclusion categories "compliant" and "non-compliant" within the REACH Compliance projects are not congruent with the outcome of Compliance Checks according to REACH Article 41 (EC, 2006). Due to the principal aim of the project to gain representative results on as many registrations as possible at this tonnage level, the compliance of data waiving/adaptation was analysed, for instance, only with regard to formal requirements but not in terms of scientific quality.

Results and discussion

If not otherwise specified, percentages are given as the average over all eight endpoints.

Screening

Figure 1-1 (left diagram) depicts the screening results. Between 4 % (reproductive toxicity) and 37 % (abiotic degradation) of the assessed endpoint entries were concluded "compliant" within the screening process. On average, 24 % of all assessed endpoint entries were assessed "compliant". In these cases adequate information was provided either as accepted standard guideline tests with the registered substance, as testing proposal for an accepted standard guideline tests with the registered substance, or because testing was not necessary (e.g. substance was already classified or the substance was inorganic, depending on the endpoint). Whereas the latter was mostly relevant for environmental endpoints (17 %), the information requirements for human health endpoints were mostly covered by standard guideline tests (15 %). Taking both human health and environmental endpoints into account, standard guideline tests were available in 12 %, a testing proposal was present in 4 %, and testing was not necessary in 8 % of the assessed endpoint entries. On the other hand, endpoint entries were concluded "non-compliant" in the range of 1 % (bioaccumulation) to 25 % (ecotoxicity) as neither an appropriate study nor suitable surrogate data or a sufficient justification to omit testing was available ("data gap"). On average, 8 % of all assessed endpoint entries were concluded "non-compliant". The remaining endpoint entries (67 % on average) were not concluded within the screening ("complex")

as either surrogate data or a waiving justification were utilised to meet the standard information requirements; or a final conclusion was not possible within the scope of the project. Data waiving/adaptation relevant for concluding the endpoint was applied on average in 57 % of all assessed endpoints and further investigated in the formal or refined check.

Thus, while the screening approach provided only little information on the overall rate of compliance of the endpoints, it uncovered that additional assessment is required for the majority of endpoint entries.

Formal and refined check

Figure 1-1 (right diagram) shows the aggregated final results after screening, formal and refined check for the representative subset of 500 dossiers. The percentage of "compliant" endpoint entries ranged between 14 % (reproductive toxicity) to 57 % (repeated dose toxicity, mutagenicity) with an average of 45 %. Endpoint entries were concluded "non-compliant" in the range of 9 % (reproductive toxicity) to 46 % (ecotoxicity), averaging 24 %. 11 % (mutagenicity) to 76 % (reproductive toxicity) of the assessed endpoint entries remained "complex" (31 % on average). For these endpoint entries, a final decision could not be made due to the limited scope of the current project.

The screening revealed that the standard information requirements were covered by applying data waiving/adaptation for a majority of assessed endpoint entries (57 % on average). Read-across and grouping approaches were the most frequently assessed adaptation (34 % on average). The majority of these approaches were "compliant" for the endpoints because an appropriate justification for using data of a structurally related substance (source substance) with similar physico-chemical, toxicological and ecotoxicological properties was provided and an acceptable experimental study conducted with the source substance was included in the registration (61 % on average). Read-across and grouping approaches allocated to the conclusion category "non-compliant" (17 % on average) failed to provide a sufficient justification (either the justification was not available or insufficient) or the experimental study conducted with the source substance was considered inadequate. Read-across and grouping approaches that remained without conclusion ("complex"; 21 % on average) contained experimental data derived from studies that followed no or a non-standard guideline.

In addition, weight of evidence approaches were frequently used to draw a conclusion on whether or not the substance has dangerous properties (17 %). In a line of evidence, this has to be deduced from the results of at least two experimental studies or surrogate data. Most of the weight of evidence approaches were assessed "complex" because they were solely based on non-standard studies or contained inconsistent study results (48 % on average), 28 % (on average) were assessed "compliant" and 24 % (on average) were considered "non-compliant". The latter decision category was frequently attributed to formal deficiencies of an incorporated read-across and/or (Q)SAR (e.g. no adequate documentation available).

Conclusion

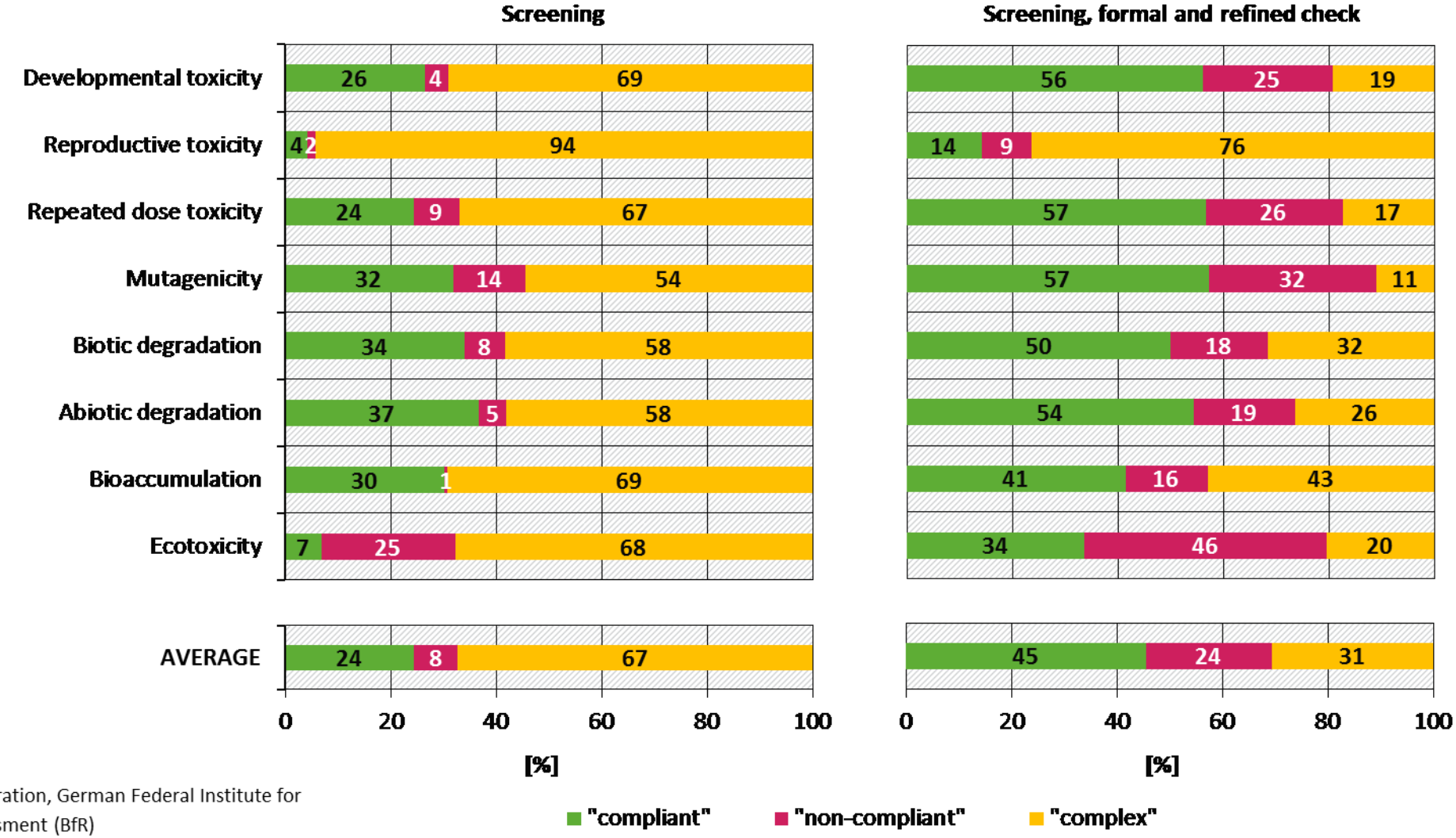
After all three evaluation steps, on average 45 % of the assessed endpoint entries were considered in "compliance" with the REACH requirements in accordance with the criteria defined within the project. The percentage of "non-compliance" ranged from 9 to 46 % (24 % on average). Hence, in at least 46 % of the evaluated dossiers the information requirements under REACH are insufficiently fulfilled for at least one endpoint. A decision on whether or not the endpoint is "compliant" could not be made for 31 % (on average) of all assessed endpoint entries, even after completing all evaluation steps. An in-depth analysis would have been necessary to draw a final conclusion which, however, could not be realised within the limited scope of the project.

The screening uncovered that accepted guideline studies on toxicological and ecotoxicological endpoints (standard information) have been provided as key studies in less than an eighth of all assessed endpoint entries. A number of similar or equivalent guideline studies were, in addition, provided within read-across/grouping and weight of evidence approaches. Thus, standard information in the form of standard guideline studies is available in a limited number of endpoint entries. However, albeit not evaluated in-depth within this project ("complex"), data derived from studies that followed no guideline or a non-standard guideline may also be considered adequate information for the endpoint (i.e. if key parameters foreseen to be investigated in the respective guideline study are adequate and reliable covered). In contrast, data waiving/adaptation has been intensively used. More than half of the evaluated data was provided in the form of a waiving/adaptation. As an alternative approach, data waiving/adaptation, therefore, constituted the predominant strategy to meet the standard information requirements. Read-across and grouping approaches were found to be the most frequently assessed adaptation category.

"Data gaps" within the endpoints of the registration dossiers exist in consequence of a lack of standard information or an insufficiently established data waiving/adaptation. Hence, registrants are encouraged to thoroughly review the information provided in their dossiers and to improve the availability and quality of toxicological and ecotoxicological information if necessary. A special emphasis may thereby be placed on (1) the conditional testing strategy for ecotoxicity depending on the physico-chemical properties of the registered substance, (2) revising and consolidating read-across and grouping approaches according to ECHA's read-across guidance document (quality of studies with the source substance and availability/quality of read-across justifications), (3) reporting of read-across and/or (Q)SAR as incorporated element within a weight of evidence approach.

High-quality data are a prerequisite for hazard identification and subsequent exposure and risk assessment. It is important to ensure that authorities are enabled to identify substances of concern to stipulate further regulatory measures.

Figure 1-1 : **Data availability and quality of human health and environmental endpoints – endpoint conclusions after screening of substances registered at 100 to 1000 tpa (n = 2053 dossiers) and aggregated after screening, formal and refined check (n = 500 dossiers)**



Own illustration, German Federal Institute for Risk Assessment (BfR)

Zusammenfassung

Einleitung

Der regulatorische Rechtsrahmen der Europäischen Union für Chemikalien sollen die sichere Verwendung von Chemikalien in Bezug auf die menschliche Gesundheit und die Umwelt gewährleisten. Die Verordnung (EG) Nr. 1907/2006 bildet hierbei die gesetzliche Grundlage und regelt die Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH (EC, 2006)). REACH sieht dabei vor, dass Hersteller und Importeure ihre Chemikalien ab einem Volumen von mehr als einer Tonne pro Jahr bei der Europäischen Chemikalien Agentur (ECHA) registrieren. Eine solche Registrierung soll Informationen zu physikalisch-chemischen, toxikologischen und ökotoxikologischen Eigenschaften der Substanz enthalten, die in bestimmte Kategorien unterteilt sind (auch als "Endpunkte" bezeichnet) und aus unterschiedlichen Quellen (Tierversuche und Alternativen) stammen können. Der Umfang an Informationen, die geliefert werden müssen, ist in den Anhängen VII-X der REACH Verordnung in Abhängigkeit der jährlich hergestellten oder importierten Menge (Tonnageband) festgelegt. Informationen, die unter REACH verfügbar gemacht werden, dienen in erster Line der Identifizierung von Gefahren, die von Chemikalien ausgehen können und bilden die Grundlage für eine Risikobewertung hinsichtlich der Wahrung menschlicher Gesundheit und des Schutzes der Umwelt. Auf dieser Informationsbasis werden zum Beispiel SVHC-Substanzen (besonders besorgniserregende Stoffe) identifiziert, die weiterer regulatorischer Maßnahmen bedürfen, wie zum Beispiel die Autorisierung oder Beschränkung einer Substanz für den europäischen Markt.

Das Projekt REACH Compliance wurde initiiert, um einen breiten Überblick über die Verfügbarkeit von toxikologischen und ökotoxikologischen Daten aller federführenden ("lead") und individuellen Registrierungen eines jeweiligen Tonnagebandes zu erhalten. Das vorrangige Ziel dieses Projektes war es festzustellen und zu dokumentieren, inwieweit die Anforderungen unter REACH erfüllt wurden, um eine solide Basis zu schaffen, auf der Registranten, Stakeholder und Regulierungsbehörden sich über die Implementierung von REACH austauschen können. Darüber hinaus werden die Ergebnisse dieses Projektes bei der Priorisierung weiterer regulatorischer Maßnahmen Anwendung finden.

Der vorliegende Bericht stellt den dritten Teil der Publikationen zum Projekt "REACH Compliance: Datenverfügbarkeit in Registrierungsdossiers" dar. Die beiden ersten Teile, "Screening of chemicals > 1000 tpa" (Springer et al., 2015) und "Evaluation of data waiving and adaptations for chemicals ≥ 1000 tpa" (Oertel et al., 2018b) sind bereits publiziert und weisen auf einen Verbesserungsbedarf bei Registrierungen hochtonnagiger Stoffe (≥ 1000 tpa) hin. Basierend auf den Projektergebnissen wurden Empfehlungen für die Verbesserung der Registrierungsdossiers entwickelt (Oertel et al., 2018a).

Methoden

In der aktuellen Untersuchung wurden die Verfügbarkeit und Qualität von toxikologischen und ökotoxikologischen Daten bzw. der jeweiligen Datenverzichtserklärungen/Ersatzdaten in Registrierungsdossiers von Substanzen überprüft, die in einer Tonnage von 100-1000 Tonnen pro Jahr (tpa) produziert oder importiert werden. Insgesamt wurden 2053 federführende ("lead") und individuelle Dossiers untersucht, die bis März 2017 bei der ECHA eingereicht wurden.

In Übereinstimmung mit der Untersuchung der ≥ 1000 tpa-Registrierungen wurden folgende Endpunkte betrachtet: Entwicklungs- und Reproduktionstoxizität, Toxizität bei wiederholter Aufnahme, Mutagenität, Biologische und Abiotische Abbaubarkeit, Bioakkumulation und Ökotoxizität. Außerdem wurde die Abschätzung der Umweltexposition untersucht, die, wenn erforderlich, Teil der Stoffsicherheitsbeurteilung ist. Die Methoden, die für die Untersuchung der ≥ 1000 tpa-Stoffe entwickelt wurden, wurden wenn nötig an die Informationsanforderungen der hier untersuchten mittleren Tonnage (100-1000 tpa) angepasst, die in den Anhängen VII bis IX der REACH-Verordnung festgeschrieben sind. Um die finale Entscheidungsrate zu erhöhen, wurden außerdem teilweise Anpassungen der vorherigen Methoden vorgenommen. Wie bei der vorherigen Untersuchung, wurde auch hier eine standardisierte Vorgehensweise benutzt, die auf einem mehrstufigen Verfahren beruht, um die Datenverfügbarkeit und -qualität in den ausgewählten Endpunkten systematisch überprüfen zu können. Dieses mehrstufige Verfahren beinhaltet das Screening, eine formale Prüfung und eine verfeinerte Prüfung.

Screening

Der erste Schritt, das Screening, bestand aus einer Begutachtung aller 2053 Dossiers in allen für dieses Projekt ausgewählten Endpunkten. Hier wurde untersucht und dokumentiert inwieweit die Standard-Informationsanforderungen der REACH-Anhänge VII-IX erfüllt wurden, also ob eine Studie vorhanden war, die nach einer für den jeweiligen Endpunkt akzeptierten Test-Richtlinie durchgeführt wurde. Wenn dies nicht der Fall war, wurde überprüft und dokumentiert, ob ein entsprechender Datenverzicht oder eine Datenanpassung verfügbar war. Zu diesem Zweck wurden entweder Entscheidungsbäume oder Fragenkataloge verwendet, die die Hierarchie der REACH Informationsanforderungen abbilden. Endpunkteinträge, in denen eine ausführlichere Analyse notwendig war oder bei denen Datenverzicht oder -anpassung angewendet wurde, um die Informationsanforderungen zu erfüllen, blieben im Screening ohne finale Entscheidung ("complex").

Endpunkteinträge, in denen Datenverzicht oder -anpassung angewendet wurde, sollten nachfolgend der formalen und verfeinerten Prüfung unterzogen werden. Eine ausführliche Analyse (z.B. bezüglich der wissenschaftlichen Validität) war im Rahmen dieses Projektes nicht möglich und entsprechende Fälle blieben "complex" in der jeweiligen Prüfstufe.

Formale Prüfung

Von den 2053 Dossiers wurde eine repräsentative Zufallsstichprobe von 500 Dossiers gezogen, die weiter untersucht wurde. Die formale Prüfung stellte die zweite Prüfstufe dar, und beinhaltete die Begutachtung der formalen Richtigkeit von Datenverzicht und –anpassungen, die in den Registrierungsdossiers der Stichprobe vorhanden waren. Hierfür wurden die formalen Kriterien für Datenverzicht/-anpassung, die in Spalte 2 der REACH-Anhänge VII-IX und im Anhang XI spezifiziert sind, systematisch mithilfe eines Fragenkataloges untersucht. Die formale Prüfung umfasste folgende Kategorien von Datenverzicht: (a) Endpunktspezifischer Datenverzicht nach Spalte 2, (b) Prüfung ist technisch nicht möglich und (c) Stoffspezifische expositionsabhängige Prüfung. Außerdem wurden folgende Datenanpassungskategorien in der formalen Prüfung untersucht: (a) Stoffgruppen- und Analogieansätze (Grouping/read-across) und (b) Quantitative und Qualitative Struktur-Wirkungs-Beziehungen ((Q)SAR).

Verfeinerte Prüfung

In der letzten Prüfstufe wurden weitere Kategorien von Datenverzicht/-anpassung einer verfeinerten Analyse unterzogen. Zu diesen Kategorien gehörten je nach Endpunkt (a) Beweiskraft der Daten (weight of evidence), (b) Datenverzicht, der sich auf das Ergebnis der Stoffsicherheitsbeurteilung und

der Bewertung der Umweltexposition beruft und/oder (c) Datenverzicht, der sich auf die chemische Struktur der registrierten Substanz bezieht.

Entscheidungskategorien

Für jeden der acht Endpunkte wurde in Abhängigkeit der Datenverfügbarkeit und –qualität eine von 4 Entscheidungskategorien vergeben:

- "Compliant": Ein Endpunkt wurde als "compliant" betrachtet, wenn die Informationsanforderungen gemäß der Kriterien des REACH Compliance Projektes erfüllt waren.
- "Non-compliant": Ein Endpunkt wurde als "non-compliant" betrachtet, wenn die Informationsanforderungen gemäß der Kriterien des REACH Compliance Projektes nicht erfüllt waren.
- "Complex": Ein Endpunkt wurde als "complex" betrachtet, wenn in der jeweiligen Prüfstufe bzw. letztendlich im Rahmen des Projektes keine abschließende Entscheidung getroffen werden konnte.
- "Testing proposal": Für den betrachteten Endpunkt wurde ein Versuchsvorschlag eingereicht.

Es ist zu beachten, dass die Entscheidungskategorien "Compliant" und "Non-compliant" im Projekt REACH Compliance nicht gleichzusetzen sind mit den Ergebnissen der "Compliance Check" Prüfung gemäß Artikel 41 der REACH-Verordnung (EG, 2006). Da das vorrangige Ziel darin bestand ein repräsentatives Ergebnis der untersuchten Tonnage zu erhalten, wurde beispielsweise die Validität von Datenverzicht und Datenanpassungen nur hinsichtlich der formalen Anforderungen, nicht jedoch hinsichtlich der wissenschaftlichen Qualität, analysiert.

Ergebnisse

Die folgenden Prozentangaben beziehen sich, wenn nicht anders angegeben, auf den Durchschnittswert aus allen acht Endpunkten.

Screening

Im linken Diagramm von Figure 1-1 sind die Ergebnisse für alle Endpunkte nach dem Screening dargestellt. Zwischen 4 % (Reproduktionstoxizität) und 37 % (abiotischer Abbau) der untersuchten Endpunkteinträge wurden im Screening als "compliant" bewertet. Im Durchschnitt waren 24 % der betrachteten Endpunkteinträge "compliant". In diesen Fällen konnten adäquate Informationen entweder in Form einer Studie nach akzeptierter Standard-Testrichtlinie oder eines entsprechenden Versuchsvorschlags für die registrierte Substanz vorgewiesen werden, oder eine Studie war nicht notwendig (z.B. weil der Stoff entsprechend eingestuft ist, oder weil er anorganisch ist, abhängig vom Endpunkt). Während letzteres jedoch hauptsächlich für die Umweltendpunkte relevant war (17 %), wurden die Informationsanforderungen in den Gesundheitsendpunkten eher durch Studien nach Standard-Testrichtlinien erfüllt (15 %). Insgesamt waren für die Umwelt- und Gesundheitsendpunkte in 12 % der Fälle Studien nach Standard-Testrichtlinien verfügbar, in 4 % der Fälle wurde ein Versuchsvorschlag eingereicht und in 8 % war eine Studie nicht notwendig.

Auf der anderen Seite wurden zwischen 1 % (Bioakkumulation) und 25 % (Ökotoxizität) der Endpunkteinträge als "non-compliant" bewertet, weil diese eine Datenlücke aufwiesen, d.h. weder eine entsprechende Studie noch geeignete Ersatzdaten oder Begründungen für Datenverzicht vorweisen konnten. Demnach waren durchschnittlich 8 % aller geprüften Endpunkteinträge "non-compliant". Die verbleibenden Endpunkt-Einträge (im Durchschnitt 67 %) konnten in dieser Prüfstufe nicht entschieden werden, weil sie entweder Datenverzichtserklärungen oder -anpassungen enthielten um die Standarddatenanforderungen zu erfüllen, oder sie verblieben "complex" weil eine abschließende Bewertung im Rahmen des Projektes nicht möglich war. Datenverzicht/-anpassung, die relevant für die Beurteilung des jeweiligen Endpunktes war, wurde durchschnittlich in 57 % der untersuchten Endpunkt-Einträge verwendet und in den folgenden Prüfstufen weiter untersucht.

Der Screeningansatz lieferte nur begrenzte Informationen über die endgültige "compliant"-Rate der Endpunkteinträge und zeigte somit vor allem, dass für die Mehrheit der Endpunkteinträge eine zusätzliche Prüfung erforderlich ist.

Formale und verfeinerte Prüfung

Das rechte Diagramm von Figure 1-1 zeigt die abschließenden Ergebnisse nach Screening, formaler und verfeinerter Prüfung für die Zufallsstichprobe (n = 500). Der Prozentsatz an "compliant"-Entscheidungen schwankte zwischen 14 % (Reproduktionstoxizität) und 57 % (Toxizität bei wiederholter Aufnahme, Mutagenität) mit einer durchschnittlichen "compliant"-Rate von 45 %. Im Durchschnitt wurden 24 % der untersuchten Endpunkteinträge als "non-compliant" bewertet, mit einer Schwankung zwischen 9 % (Reproduktionstoxizität) und 46 % (Ökotoxizität). 11 % (Mutagenität) bis 76 % (Reproduktionstoxizität) der untersuchten Endpunkteinträge blieben auch am Ende aller Prüfstufen "complex" (durchschnittlich 31 %), weil eine abschließende Entscheidung im Rahmen dieses Projektes nicht möglich war.

Aus den Screening-Ergebnissen ging hervor, dass bei der Mehrheit der untersuchten Endpunkteinträge die Standardinformationsanforderung durch Datenverzicht bzw. –anpassung abgedeckt wurden (durchschnittlich 57 %). Stoffgruppen- und Analogieansätze (Grouping/Read-across) gehörten zu den Datenanpassungen, die am häufigsten bewertet wurden (34 % im

Durchschnitt). Die Mehrheit dieser Ansätze (durchschnittlich 61 %) konnte als "compliant" bewertet werden, da eine angemessene Begründung dafür vorhanden war, dass Daten einer strukturell ähnlichen Substanz mit ähnlichen physiko-chemischem, toxikologischen und ökotoxikologischen Eigenschaften verwendet wurde, die durch eine entsprechende experimentelle Studie belegt wurden. Stoffgruppen- und Analogieansätze wurden als "non-compliant" bewertet (17 % im Durchschnitt), da entweder keine oder keine ausreichende Begründung vorhanden war, die die Hypothese der Ähnlichkeit der Ersatzstoffe stützt, oder aber die entsprechende experimentelle Studie nicht adäquat war. Stoffgruppen- und Analogieansätze die mit einer experimentellen Studie durchgeführt wurden, die keiner für den jeweiligen Endpunkt akzeptierten Methode entsprach, konnten nicht endgültig entschieden werden und wurden als "complex" bewertet (21 % im Durchschnitt).

Um einen Endpunkt (öko)toxikologisch zu charakterisieren, wurde weiterhin häufig die Datenanpassungskategorie "Beweiskraft der Daten" (weight of evidence) verwendet. In einer Beweiskette muss hier aus mindestens zwei Studien oder Ersatzdateneinträgen abgeleitet werden, ob die registrierte Substanz gefährliche Eigenschaften aufweist oder nicht. Die meisten weight of evidence-Ansätze in diesem Projekt wurden als "complex" bewertet (durchschnittlich 48 %), weil sie z.B. allein aus Studien bestanden die mit keiner akzeptierten Prüfmethode durchgeführt wurden. Durchschnittlich 28 % der Ansätze wurden als "compliant" und 24 % als "non-compliant" bewertet, weil sie Stoffgruppen-/Analogie-Ansätze oder (Q)SARs enthielten die unzureichend begründet oder dokumentiert waren.

Schlussfolgerung

Nach allen drei Prüfstufen konnten durchschnittlich 45 % der untersuchten Endpunkteinträge als "compliant" bewertet werden, also als konform mit den REACH-Anforderungen bzw. den Kriterien die innerhalb des Projektes definiert wurden. Die Rate an Endpunkteinträgen, die nicht konform, also "non-compliant" waren bewegte sich zwischen 9 und 46 % (durchschnittlich 24 %), was allerdings auch bedeutet, dass in mindestens 46 % der untersuchten Dossiers die REACH Informationsanforderungen bei mindestens einem Endpunkt nicht erfüllt waren. Für durchschnittlich 31 % der Endpunkteinträge konnte eine Entscheidung auf "compliant" oder "non-compliant" auch nach allen drei Prüfstufen im begrenzten Rahmen des Projektes nicht getroffen werden.

Das Screening ergab, dass Studien nach akzeptierten Standard-Testrichtlinien für toxikologische und ökotoxikologische Endpunkte (Standardinformation) nur in weniger als 8 % der begutachteten Endpunkteinträge als Schlüsselstudien vorhanden waren. Einige solcher (oder äquivalenter) Studien wurden außerdem im Rahmen von Stoffgruppen- und Analogieansätzen oder weight of evidence-Ansätzen eingereicht. Generell wurden demnach nur in wenigen Endpunkteinträgen die geforderten Standardinformationen in Form von Studien nach Standard-Testrichtlinien bereitgestellt. Dennoch können auch Daten aus Studien die nicht nach akzeptierten Prüfrichtlinien durchgeführt wurden adäquate Informationen für den Endpunkt darstellen ("complex"), auch wenn diese im Zuge des Projektes nicht eingehender untersucht wurden (d.h. adäquate und zuverlässige Adressierung der Schlüsselparameter, die in einer Studie nach der entsprechenden Testrichtlinie untersucht werden sollten). Datenanpassungen und Datenverzicht wurden indes sehr häufig genutzt, um die Standarddatenforderungen zu erfüllen. Mehr als die Hälfte der bewerteten Informationen für einen jeweiligen Endpunkt wurde in dieser Form bereitgestellt. Ersatzdaten und/oder Datenverzicht stellten daher, als alternative Ansätze zu experimentellen Tests, die überwiegende Strategie dar, den Standarddatenforderungen nachzukommen. Stoffgruppen- und Analogieansätze waren dabei die am häufigsten untersuchten Kategorien.

Dennoch existieren Datenlücken innerhalb der Endpunkte der Registrierungsdossiers, die eine Folge fehlender Standarddaten oder unzureichend begründeter oder dokumentierter Ersatzdaten sind. Daher sind Registranten aufgefordert, die Informationen in ihren Dossiers sorgfältig zu überprüfen und zu aktualisieren um, gegebenenfalls, die Datenverfügbarkeit und -qualität in den (öko)toxikologischen Endpunkten zu verbessern. Ein besonderes Augenmerk sollte dabei auf folgende Punkte gelegt werden: (1) die jeweilige Test-Strategie für den Endpunkt Ökotoxizität, bedingt durch die physiko-chemischen Eigenschaften der registrierten Substanz, (2) die Überarbeitung und Konsolidierung der Stoffgruppen- und Analogieansätze gemäß der entsprechenden Leitfäden der ECHA (v.a. bezüglich der Qualität die Studien mit analogen Substanz und dem Vorhandensein/der Qualität der Begründungen) und (3) Verbesserung der Dokumentation von Stoffgruppen- und Analogieansätzen und/oder (Q)SAR als Teil eines weight of evidence-Ansatzes.

Eine optimale Datengrundlage in diesen Endpunkten ist eine elementare Voraussetzung für die Gefahrenermittlung und daran anschließende Expositions- und Risikobewertung. Es ist unabdingbar, dass es Behörden möglich ist, gefährliche Substanzen zu identifizieren um weitere regulatorische Maßnahmen wie Autorisierung oder Beschränkung bedenklicher Stoffe anstrengen zu können.

1 Introduction

Chemical substances, imported or manufactured in the European Union have to be registered according to the REACH Regulation by submitting registration dossiers to the European Chemicals Agency (ECHA). The manufacturers, importers and under specific conditions downstream users have to undertake a chemical safety assessment (CSA), as they are responsible for demonstrating the safe use of substances and products throughout their life cycle. This includes mandatory standard information requirements for registrations that are dependent on the annual tonnage per manufacturer or importer.

The scientific quality of toxicological and ecotoxicological data in the registration dossiers must be appropriate, since this information is essential for the implementation of regulatory measures to protect human health and the environment. In order to ensure the quality of the dossiers and to enable amendment in case of insufficient quality, the REACH Regulation foresees the dossier evaluation by ECHA. For that purpose, at least 5 % of the registration dossiers of each tonnage band are assessed in Compliance Checks. The aim of the REACH Compliance project was to assess the quality of registration dossiers systematically to gain representative information on a high number of dossiers. The assessment within this project is, however, not comparable to a full Compliance Check by ECHA.

1.1 REACH Compliance projects on high tonnage chemicals ≥ 1000 tpa

The data availability and quality of toxicological and ecotoxicological endpoints was systematically assessed in registration dossiers of substances manufactured or imported in quantities of ≥ 1000 tonnes per year (tpa) in the first project "REACH Compliance: Evaluation of data availability from the REACH registrations" (FKZ 3714 67 420). In total, 1814 lead and individual registrations of phase-in substances registered under REACH by 2010 were assessed. In each dossier eight endpoints (developmental and reproductive toxicity, repeated dose toxicity, mutagenicity, biotic and abiotic degradation, bioaccumulation, and ecotoxicity) and environmental exposure assessment were examined by applying extensive decision trees that reflect the information requirements of REACH Annexes VII-X. This procedure was called "screening". If at this stage the available data were found to be in accordance with the information requirements of REACH for the respective endpoint, this endpoint was concluded as "compliant". Data in endpoint entries which did not meet the information requirements for the endpoint of concern were categorised as "non-compliant". No decision was taken for all cases which were too complex to be assessed within the scope of the project. They were documented as "complex".

In the second project "Availability of human health and environmental data for high-tonnage chemicals under REACH – Phase II: Enhanced REACH Compliance Check" (FKZ 3715 67 4220), the evaluation continued based on the results of the first project (Springer et al., 2015). The analysis of data from registrations of substances ≥ 1000 tpa were extended to three additional work packages. First, it was examined whether the substance identities of lead and member registration dossiers were the same in joint registrations. It was also assessed whether the test material used in key studies was equal to the registered substance. Finally, it was examined whether waiving/adaptations of the standard information requirements were "formally compliant" with regard to the formal criteria defined by REACH.

In a first phase of the third project "Availability of human health and environmental data for high-tonnage chemicals under REACH – finalisation of phase II and working on phase III" (FKZ 3716 67

4220), refined approaches were applied in order to assess so-called "weight of evidence" records and special case groups that remained "complex" within project I. Thus, the first phase of the project III had the following tasks for selected endpoints namely developmental and reproductive toxicity, mutagenicity, ecotoxicity, and environmental exposure assessment:

- developing concepts and checking the endpoints that remained "complex" in the screening (project I; e.g. weight of evidence)
- developing concepts and checking the endpoints that remained "complex" in the formal check (project II) as far as possible

The outcomes of project II and the first phase of project III, all related to registrations of substances ≥ 1000 tpa, are presented in the final report "REACH Compliance: Data Availability in REACH Registrations, Part 2: Evaluation of data waiving and adaptations for chemicals ≥ 1000 tpa." (Oertel et al., 2018b).

1.2 REACH Compliance project III on chemicals 100-1000 tpa

In order to continue the assessment of data quality, the second phase of project III focused on registrations of the tonnage band at 100-1000 tpa. The evaluation strategy developed for ≥ 1000 tpa substances was adapted to registrations of the tonnage band at 100-1000 tpa. A total of 2053 lead and individual registrations of 100-1000 tpa substances were evaluated to estimate the data quality regarding the completeness and appropriateness of available data or their respective substitute data and waiving justifications in comparison to the information requirements of REACH Annexes VII-IX and Annex XI.

In principle, the analysis of registration dossiers in the tonnage band 100-1000 tpa was carried out in the same way (screening, formal check and refined check) and on the same endpoints as for the ≥ 1000 tpa substances. The decision trees developed in project I for the screening of particular endpoints have been adapted to the information requirements of REACH Annexes VII to IX. As in the previous project on substances at ≥ 1000 tpa waiving justifications and read-across approaches were formally examined with regard to the given argumentation and compliance with REACH criteria in order to achieve a high number of concluded endpoints. Finally, approaches for the refined check of "weight of evidence" data were applied for the tonnage band 100-1000 tpa.

2 Methods

2.1 Research approach

The present study aims to evaluate the availability and quality of toxicological and ecotoxicological data with regard to the standard information requirements of the REACH Regulation. The analysis included all lead and individual registration dossiers of phase-in substances manufactured or imported in quantities of 100-1000 tpa.

The fulfilment of standard information requirements was evaluated for selected environmental and human health endpoints (see chapter 2.2) on the basis of REACH Annexes VII to IX. Moreover, adaptations to the standard testing regime and justification of data waiving were analysed with regard to endpoint specific rules of REACH Annexes VII to IX and general rules of REACH Annex XI.

2.2 Scope of evaluation

A list of REACH registrations was provided by ECHA on 9 March 2017. Dossiers for evaluation were selected as follows:

- Full registration according to Article 10 of the REACH Regulation for quantities of 100 to 1000 tpa
- Lead or individual registration
- Former recognised notification under Directive 67/548/EEC (NONS) with a tonnage band increase requiring a REACH registration dossier

Accordingly, a total number of 2053 registration dossiers was selected.

The evaluation was limited to the following human health and environmental endpoints:

Human health:

- Developmental toxicity
- Reproductive toxicity
- Repeated dose toxicity
- Mutagenicity[2]

Environment:

- Biotic degradation
- Abiotic degradation
- Bioaccumulation
- Ecotoxicity

Additionally, the environmental exposure assessment was evaluated in terms of availability and completeness of exposure scenarios in the chemical safety report (CSR).

[2] For reasons of better legibility, the term "mutagenicity" refers to information requirements related to genotoxicity and mutagenicity in the following text.

2.3 General procedure

The registration dossiers were retrieved using the IUCLID 6 (International Uniform Chemical Information Database) software (ECHA, 2016a). The availability and quality of the information was systematically assessed in the technical dossier and/or in the attached CSR or other attached documents (e.g. read-across justification), depending on the particular information requirement being analysed.

The assessment concepts were largely based on the previous REACH Compliance projects on registrations for ≥ 1000 tpa substances (Oertel et al., 2018b; Springer et al., 2015). However, to further increase the final decision rate, some adjustments were implemented under consideration of the deviating information requirements at the lower tonnage band and recently published guidance documents (*e.g.* (ECHA, 2016d; ECHA, 2017f)).

The analysis comprised three steps of evaluation: screening, formal check and refined check (Figure 2-1). By using endpoint specific decision trees, the initial screening step systematically assessed if the standard information required according to column 1 of REACH Annexes VII to IX was available. If the endpoint entry could not be concluded in the screening step ("without conclusion"), *e.g.* due to the presence of data waiving or adaptation, the endpoint evaluation was continued in the next step of the evaluation procedure (formal check and/or the refined check), providing the dossier was part of the selected subset of 500 dossiers.

The formal check evaluated the formal conformity of data waiving and selected approaches for adaptation of the standard testing regime (*e.g.* read-across/grouping and qualitative or quantitative structure-activity-relationships [(Q)SARs]). The refined check consisted of a content-related evaluation of selected case groups that were not addressed or could not be concluded within the previous evaluation steps (*e.g.* weight of evidence [WoE]).

As a result of the three evaluation steps, each examined endpoint within a particular dossier was allocated to one of the following four endpoint conclusion categories:

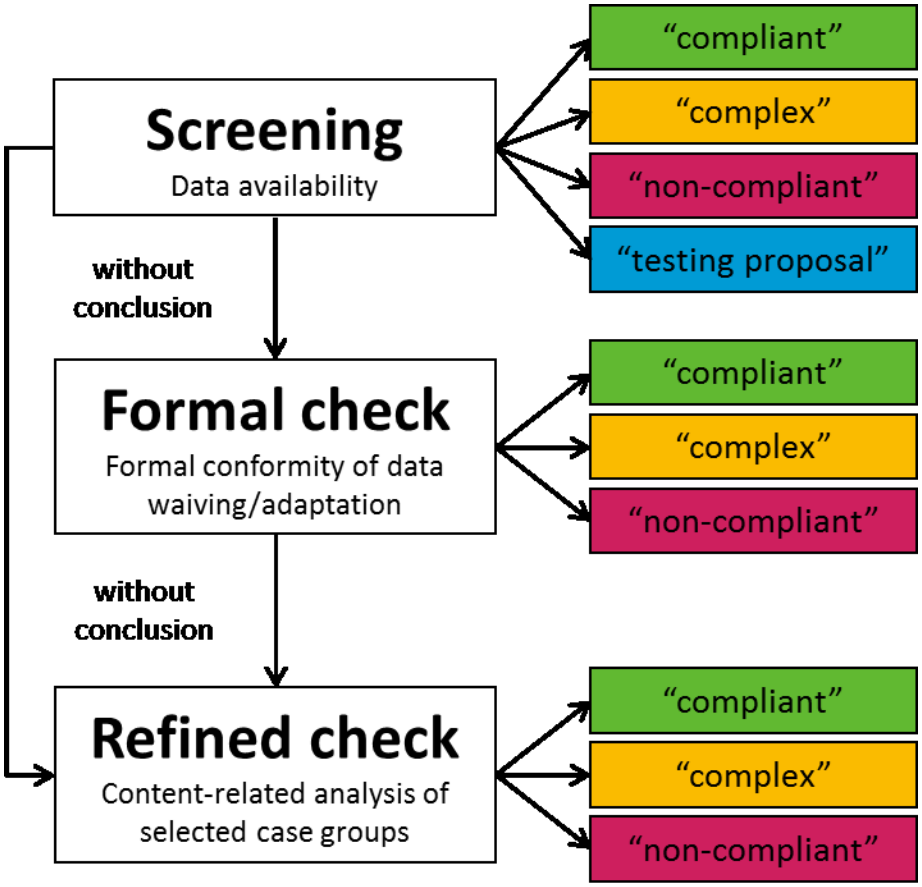
- "Compliant": The endpoint was considered "compliant" if the information requirements according to the assessed criteria of the REACH Compliance project were fulfilled;
- "Non-compliant": The endpoint was considered "non-compliant" if the information requirements according to the assessed criteria of the REACH Compliance project were not fulfilled;
- "Complex": The endpoint was considered "complex" if an endpoint remained without conclusion in one of the evaluation steps and if a final conclusion could ultimately not be reached within the limited scope of the REACH Compliance project;
- "Testing proposal": A testing proposal was provided for the assessed endpoint.

It is important to stress that the conclusion categories "compliant" and "non-compliant" within the REACH Compliance projects are not congruent with the outcome of Compliance Checks according to REACH Article 41 (EC, 2006). For example, due to the principal aim to gain representative results on registrations at this tonnage level and thereby caused limitations on individual examination depth, the compliance of data waiving/adaptation was only analysed with regard to formal requirements but not in terms of scientific quality.

It has to be emphasised that the endpoint conclusion "non-compliant" does not necessarily indicate a true "data gap". For example, a justification for potentially valid data waiving that was considered "non-compliant" if the given justification for data waiving was insufficient according to the specific or general rules for data waiving of REACH Annexes VII-IX or XI. On a case-by-case basis, the endpoint entry could still achieve full compliance with the REACH requirements, e.g. after amendment of inappropriate or incomplete justifications by registrants.

The evaluation process was documented in MS Excel spreadsheets by means of endpoint or case group specific queries with predefined response options.

Figure 2-1: Evaluation steps and endpoint conclusion categories



Own illustration, German Federal Institute for Risk Assessment (BfR)

2.4 Screening

The main objective of the screening step was to determine whether and how the registrant addressed the standard information requirements of the respective endpoint. This could have been done either by providing experimental data from accepted standard test methods or by providing another potentially valid type of information (chapter 2.4.1).

In the first REACH Compliance project, decision trees on each assessed endpoint were developed for substances ≥ 1000 tpa to evaluate the availability of human health and environmental data (Springer et al., 2015). These decision trees consisted of endpoint specific queries that were based on the

information requirements set out in the REACH Annexes VII to X and/or in the respective ECHA guidance documents.

The existing decision trees for substances ≥ 1000 tpa were thoroughly reviewed considering the deviating standard information requirements at the lower tonnage band (REACH Annexes VII to IX) and recently published guidance documents. Additionally, the decision trees for the endpoint ecotoxicity and environmental exposure assessment were amended with additional questions to optimise the conclusion rate (see Annex B). The updated screening concepts are presented in Annex A for human health endpoints and in Annex B for environmental endpoints.

2.4.1 Considered types of information

REACH registration dossiers should contain human health and environmental data in the format of study summaries or robust study summaries. The registrant also has the opportunity to provide a testing proposal or waiving justification for a particular test if certain prerequisites are met. These types of information have to be reported as endpoint study records (ESRs) in the technical dossier of IUCLID and are also part of the CSR.

In each ESR, the registrant has to indicate how the information is used in terms of fulfilling the information requirements for the registered substance with the picklist field *adequacy of study*. Additionally, the registrant has to determine a reliability score between 1 and 4 for each (robust) study summary (ECHA, 2017d; Klimisch et al., 1997).

The evaluation of (robust) study summaries was limited to study records with the indicated adequacy 'key study' or 'weight of evidence'. Key studies with a reliability score of 3 or 4 and supporting studies were excluded from the assessment, since this type of information was considered not sufficiently reliable to fulfil the information requirements (except for weight of evidence approaches). The following types of (robust) study summaries were considered for the screening of data availability:

- Experimental study
- Experimental study planned
- Experimental study planned (based on read-across)
- Read-across based on grouping of substances (category approach)
- Read-across from supporting substance (structural analogue or surrogate)
- (Q)SAR
- Calculation (if not (Q)SAR)

In the absence of a (robust) study summary, it was determined whether a justification for data waiving was presented according to the provisions in column 2 of REACH Annexes VII to IX or Annex XI (sections 2 and 3). The possible rationales for data waiving are implemented in IUCLID as follows:

- Exposure considerations
- Study scientifically not necessary/other information available
- Study technically not feasible
- Study waived due to provisions of other regulation
- Other justification

2.4.2 Acceptance criteria

Each study or waiving record had to fulfil certain criteria on documentation for being acknowledged as relevant piece of information in the screening step. These general acceptance criteria are defined for each assessed information type as followed.

Experimental studies

Although in-depth assessment of the test material identity was not part of the current project, it was briefly checked whether the numerical identifiers (CAS and/or EC number) and/or the IUPAC name and/or synonyms) of used test materials corresponded to the registered substance. If the analysis was not conclusive because of missing or mismatching identifiers, it was checked whether the registrant declared that the identity of test material is 'same as for substance defined in section 1 (if not read-across)' in the attached TMI (test material information). Experimental studies with obviously contradictory or incorrect information on test material were not accepted. In some cases, the registrant may have intended a read-across approach but failed to properly indicate the use of this adaptation strategy. Therefore, if contradictory or incorrect information on test material was provided, the dossier was additionally screened for a suitable read-across justification and, if available, the study was recognised accordingly.

To be recognised as standard information, experimental studies had to be conducted 'according to' or 'equivalent or similar to' the statutory method of Regulation (EC) No 440/2008 (EC, 2008a) or the corresponding OECD test guideline. ECHA suggests acceptable alternatives to the standard methods in the endpoint specific guidance documents (ECHA, 2017a; ECHA, 2017b; ECHA, 2017c).

Inventories of test guidelines considered as equivalent to the statuary method within the REACH Compliance project are provided in Annex A (human health endpoints) and Annex B (environmental endpoints). The correct guideline number and/or title had to be provided for a study to be recognised as standard information. If another accepted guideline was followed these were concluded "compliant". Indicated deviations from the guideline method could not be addressed within the limited scope of the project.

According to REACH, Annex XI 1.1.2., data from other test guidelines or non-standard tests can be considered as equivalent or similar to the standard test method referred to in REACH Article 13(3) if certain conditions are met (*e.g.* adequacy for the purpose of classification and labelling and/or risk assessment). The evaluation of these conditions would have required extensive content-related case-by-case analyses that could not be realised for all relevant dossiers and endpoints in the screening. Therefore, experimental data from other test guidelines than listed under the accepted guidelines for each endpoint in Annex A and Annex B or non-standard tests remained "complex".

Testing proposals

If the registrant identifies the need to perform a test listed in REACH Annex IX or Annex X, a proposal for testing should be provided (EC, 2006). All testing proposals will be reviewed by ECHA to ensure that reliable and adequate data will be produced and to prevent unnecessary animal testing. The quality of testing proposals was not analysed within the REACH Compliance project. The availability of a testing proposal was recorded, provided that the ESR indicated 'experimental study planned' and the proposed method was related to the particular endpoint under evaluation. In some cases, the registrant may have intended a testing proposal, but failed to properly indicate this type of information. If a proposal for testing identified elsewhere in the dossier (e.g. as part of a waiving

justification), this was documented as well. Where a testing proposal was identified, the respective endpoint entry was evaluated "compliant" as final conclusion.

Adaptations to the standard testing regime

If testing does not appear scientifically necessary, the registrant has the opportunity to adapt the standard testing regime in accordance with the general rules set out in section 1 of REACH Annex XI (Testing does not appear scientifically necessary). In this case, existing data and/or information from alternative methods (e.g. WoE, (Q)SARs, grouping/read-across) had to be adequately documented in the format of (robust) study summaries to be recognised as adaptation.

Data waiving

The registrant has the opportunity to waive a test according to the endpoint specific provisions in column 2 of REACH Annexes VII to IX or the general rules for data waiving in section 2 (Testing is technically not possible) and section 3 (Substance-tailored exposure-driven testing) of REACH Annex XI. However, as a minimum requirement, the rationale for data waiving and a corresponding justification had to be provided.

2.4.3 IUCLID data base queries and integrated assessment

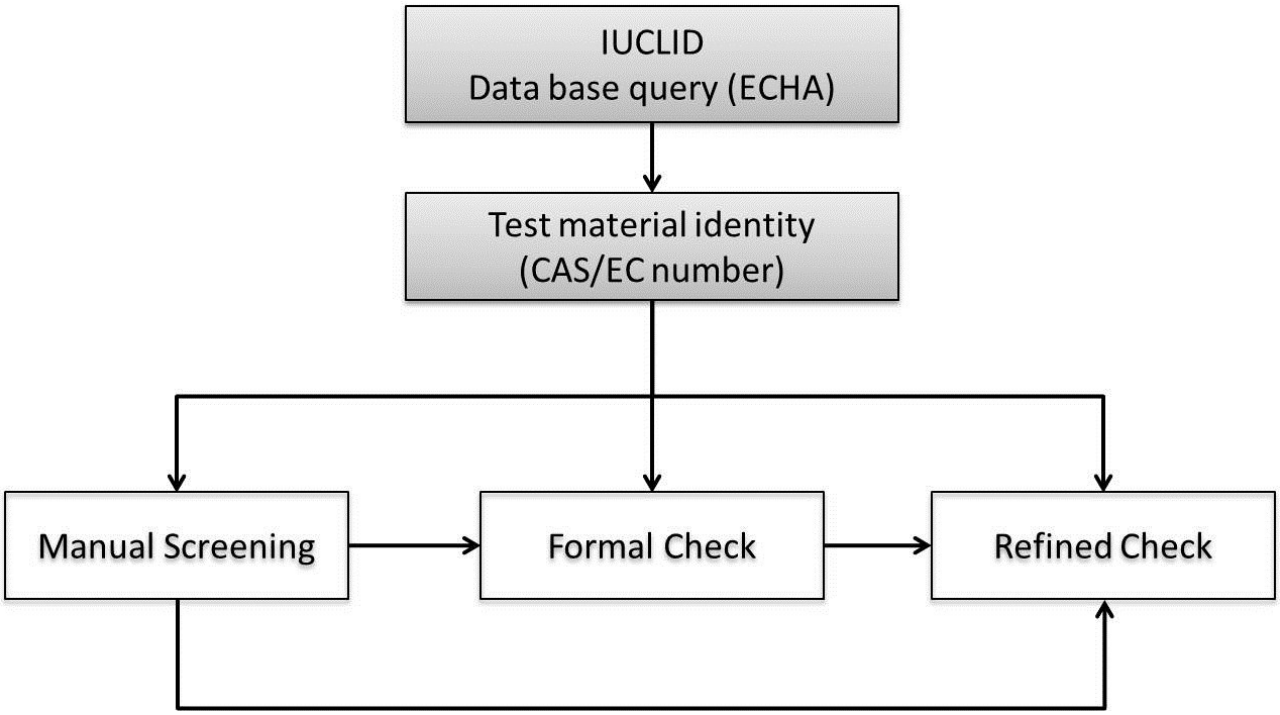
The screening of data availability was partially conducted on the basis of electronic spreadsheets provided by ECHA in April and May 2017. The spreadsheets contained basic information on all relevant ESRs, including type, adequacy, reliability, test material identity and test method of the study.

The data was used to identify registration dossiers which obviously fulfilled the information requirements for a particular endpoint, *e.g.* by providing experimental studies considered at least equivalent or similar to the standard method. Moreover, the data was used to identify dossiers which were obviously "complex" for a particular endpoint, *e.g.* if the complete set of reported experimental studies was considered not equivalent or similar to the standard method.

The electronic spreadsheets were also used to assess whether the test material was identical to the registered substance in terms of CAS and/or EC number (see also section 2.4.2 under the header "Experimental studies").

In many cases it was possible to determine via IT-screening whether a conclusion could be achieved by further manual screening, formal check or refined check. In these cases, the manual dossier evaluation continued with the evaluation step that was considered most expedient (Figure 2-2).

Figure 2-2: IUCLID data base queries and integrated assessment with support from ECHA



Own illustration, German Federal Institute for Risk Assessment (BfR)

2.5 Formal check

2.5.1 Scope and general procedure

The formal check assessed the formal conformity of data waiving justifications and adaptations to the standard testing regime with the provisions of REACH Annexes VII to IX column 2 and REACH Annex XI. The assessment was largely based on the criteria already established for the evaluation of ≥ 1000 tpa substances (Oertel et al., 2018b).

A representative sample of 500 Dossiers out of 2053 Dossiers was selected for all endpoints and further assessed in the formal check and/or the refined check (see also chapter 2.2). The analysis was limited to waiving/adaptation records that impeded a final endpoint conclusion in the screening step and comprised the following approaches for data waiving/adaptation:

- Endpoint specific rules (REACH Annexes VII to IX, column 2)
- (Q)SAR (REACH Annex XI, section 1.3)
- Grouping of substances and read-across (REACH Annex XI, section 1.5)
- Testing is technically not possible (REACH Annex XI, section 2)
- Substance-tailored exposure-driven testing (REACH Annex XI, section 3)

Data waiving approaches that could not be attributed to one of the rules specified in the REACH Annexes and WoE approaches were not part of the formal check since these case groups generally require content-related analyses.

The registrant may use multiple waiving and/or adaptation approaches to address different study types for the same endpoint if the respective standard information requirements involve more than one test (e.g. mutagenicity, ecotoxicity, and biotic degradation). In this case, the formal check of waiving/adaptation records was conducted analogous to the hierarchy of the respective screening decision tree. The evaluation was stopped as soon as the first study type triggered a final endpoint conclusion. If multiple waiving/adaptations were available for a given study type and the primary evaluated waiving/adaptations turned out to be "non-compliant" or "complex", the assessment was extended to include the remaining waiving/adaptations to always allow for a potential "compliant" decision.

2.5.2 Assessment criteria

The formal assessment criteria for endpoint specific waiving approaches according to column 2 of REACH Annexes VII to IX are outlined for each endpoint in Annex A (human health endpoints) and Annex B (environmental endpoints). The assessment criteria for adaptations of the testing regime according to the general rules of REACH Annex XI are presented in Table 2-1 and Table 2-2.

The respective endpoint was concluded "complex" if the experimental study was not considered at least equivalent or similar to the standard test method and if no other valid adaptation was available.

Similar to the preceding project on ≥ 1000 tpa substances, the formal check did not assess the scientific quality of waiving/adaptation approaches (Oertel et al., 2018b). However, if the provided information was considered not appropriate for obvious reasons, *e.g.* a waiving justification that is obviously insufficient or false, a "non-compliant" conclusion for content-related reasons was possible.

Table 2-1: Formal criteria for the assessment of adaptations to the standard testing regime according REACH Annex XI ((Q)SAR) and grouping/read-across)

REACH Reference	Criteria to be addressed in the justification	Additional criteria
Annex XI 1.3.: Qualitative or Quantitative structure-activity relationship ((Q)SAR)	(Q)SAR model is scientifically validated and substance falls within the applicability domain of the (Q)SAR model	▪ Adequate and reliable documentation ▪ Key study with reliability of 1 or 2 ▪ Appropriate documentation of the model and the prediction (e.g. QMRF [a] and QPRF[b])
Annex XI 1.5.: Grouping of substances and read-across approach	Structural similarities are based on: ▪ a common functional group **or** ▪ the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals **or** ▪ a constant pattern in the changing of the potency of the properties across the category	▪ Adequate and reliable documentation ▪ Key study conducted on the analogous (source) substance with reliability of 1 or 2 ▪ Coverage of the key parameters of the corresponding test method ▪ Exposure duration comparable to or longer than the corresponding test method ▪ Appropriate documentation of the read-across justification or grouping approach

[a] (Q)SAR Model Reporting Format
[b] (Q)SAR Prediction Reporting Format

Table 2-2: Formal criteria for the assessment of data waiving according to REACH Annex XI

REACH reference	Criteria to be addressed in the justification	Additional criteria
Annex XI 2.: Testing is technically not possible	Testing might be technically not possible due to specific substance properties: ▪ *e.g.* substance is very volatile or highly reactive or unstable **or** ▪ mixing of the substance with water causes danger of fire or explosion **or** ▪ radiolabelling of the substance required in certain studies may not be possible **or** ▪ relevant concentrations are corrosive (according to Annexes VII to X, introduction, passage 4) **or** ▪ method has technical limitations that do not allow for testing	▪ Verification of physico-chemical properties or respective classification ▪ Available adaptations in the test guideline for critical parameters were considered ▪ Technical limitations described in the test guideline were considered
Annex XI 3.2. a: Substance-tailored exposure-driven testing	▪ Absence or no significant exposure in exposure scenarios of the manufacture and all identified uses **and** ▪ a derived no-effect level (DNEL) or a predicted no effect concentration (PNEC) can be derived **and** ▪ exposures are always well below the DNEL or PNEC	▪ Exposure scenarios are available
Annex XI 3.2. b: Substance-tailored exposure-driven	▪ Substance is not incorporated in an article **and** ▪ strictly controlled conditions as set out in Article 18(4)(a) to (f) apply for all relevant	▪ Non suitable process categories and or environmental release categories for strictly controlled conditions were

REACH reference	Criteria to be addressed in the justification	Additional criteria
testing	scenarios throughout the life cycle	considered as not appropriate
Annex XI 3.2. c: Substance-tailored exposure-driven testing	▪ Substance is incorporated in an article in which it is permanently embedded **and** ▪ the substance is not released during its life-cycle **and** ▪ the exposure of workers, the public or environment is negligible **and** ▪ the substance is handled according to the conditions set out in Article 18(4)(a) to (f) during all manufacturing/production stages including waste management	▪ Non suitable process categories and/or environmental release categories for strictly controlled conditions were considered as not appropriate

2.6 Refined check

The refined check constituted an in-depth analysis on additional adaptation and data waiving categories which could not be addressed or remained without conclusion in the previous evaluation steps. The established concept for the refined check of ≥ 1000 tpa substances (Oertel et al., 2018b) was further optimised and amended with additional case groups to increase the conclusion rate for 100-1000 tpa substances. This resulted in a general assessment concept for weight of evidence data and specific assessment concepts for endpoint-related case groups (see Annex A, Annex B).

2.6.1 Weight of evidence

WoE according to section 1.2 of REACH Annex XI combines two or more independent sources of information. It is usually applied if the available pieces of information do not suffice on a stand-alone basis but are considered adequate in the overall view, or if the individual studies provide conflicting results. The concept of WoE has been formalised to support integrated testing strategies within the REACH standard information requirements (ECHA, 2017a; ECHA, 2017b; ECHA, 2017c). Therefore, an adequate and reliable documentation of the WoE approach is mandatory (ECHA, 2016d).

The initial refined check of WoE analysed whether the included study records fulfilled all necessary formal prerequisites for further content-related analyses (Table 2-3).

A proper documentation of WoE requires at least two accordingly flagged endpoint study records (ECHA, 2017d). However, in this project, the pure intention of the registrant to combine different pieces of information was recognised as WoE approach (Table 2-3, question 1), provided that the line of evidence was documented in a transparent and conclusive way.

The refined check was stopped if the registrant mistakenly reported data waiving as WoE. In this case, the evaluation was continued with screening or formal check, respectively.

The refined check resulted in a “compliant” conclusion if an individual piece of information was obviously sufficient on a stand-alone basis and if other studies did not show conflicting results.

The endpoint was concluded “non-compliant” if the initial analysis revealed major shortcomings in terms of documentation, *e.g.* the absence of a conclusive WoE summary or conflicting information on test material identity (see also chapter 2.4.2).

Table 2-3: Initial refined check of weight of evidence approaches

No.	Question	Assessment criteria
1	Is more than one independent piece of information available?	▪ Endpoint study records - Weight of evidence studies - Key studies - Supporting studies - Other information ▪ Endpoint summary
2	Is data waiving incorrectly flagged as WoE?	▪ Justification for data waiving
3	Is one piece of information obviously sufficient on a stand-alone basis?	▪ Study with a reliability of 1 or 2 ▪ Study considered equivalent or similar to the standard test method ▪ No conflicting results from other studies
4	Is a WoE summary available?	▪ Endpoint summary ▪ ESRs ▪ CSR ▪ Attachments
5	Does the information on test materials correspond to the registered substance (except read-across)?	▪ CAS/EC number and/or substance name ▪ TMI attachment
6 (optional)	Is the entire read-across data formally “compliant”?	▪ Respective criteria of formal check
7 (optional)	Is the entire (Q)SAR data formally “compliant”?	▪ Respective criteria of formal check

3 Results and discussion

The overall results for substances registered in quantities of 100-1000 tpa are presented in section 3.1. In section 3.1.1, the results are shown for the endpoints after the screening and as aggregated results after screening, formal and refined check. In addition, outcomes on the waiving/adaptations are separately summarised in section 3.1.1. In section 3.1.2, the results of the medium tonnage band are compared to the results of the high tonnage band.

The standard information requirements for the medium tonnage band are laid down in REACH VII-IX for human health and environmental endpoints (see Annex A and B). The endpoint specific decisions trees applied in this projects reflect the hierarchical REACH requirements. The results for each individual endpoint are discussed in detail within section 3.2 for human health endpoints and in section 3.3 for environmental endpoints.

3.1 Overall results

3.1.1 Overall results after screening, formal check and refined check

The overall results on data availability and quality for human health and environmental endpoints in registrations of 100-1000 tpa are shown in Figure 3-1. The conclusions on endpoint entries after the screening are presented for the entire sample of 2053 dossiers. The aggregated conclusions after screening, formal and refined check are shown for the representative subset of 500 dossiers that has undergone the full assessment process. Testing proposals were included in the conclusion category "compliant".

If not otherwise specified, percentages are given as the average over all eight endpoints.

Screening (2053 dossiers)

After the screening, 24 % of the assessed endpoint entries were allocated to the category "compliant", ranging from 4 % (reproductive toxicity) to 37 % (abiotic degradation). "Compliant" endpoint conclusions were obtained either if experimental data according to an accepted guideline were available or proposed (testing proposal), or if testing was not required according to endpoint specific criteria laid down in column 2 of REACH Annexes VII-IX (e.g. harmonised classification according to the CLP Regulation; study on ready biodegradability is not needed if the substance is inorganic). Figure 3-2 depicts the percentage of the reasons leading to a "compliant" decision with reference to all endpoint entries in 2053 dossiers. While the standard information requirements for human health endpoints were almost entirely addressed in the form of available or proposed standard guideline tests (21 %), environmental endpoints were covered to a much lesser extent with such information (10 %). Conversely, column 2 arguments led to a "compliant" decision in 17 % of the environmental endpoint entries, whereas this was the case for only 0.4 % of the human health endpoint entries. Considering all endpoints together, standard information derived from accepted guideline tests was only available in 12 % of all endpoint entries and proposed in 4 %.

The category "non-compliant" was assigned for an average of 8 % of the endpoint entries, ranging between 0.5 % (bioaccumulation) to 25 % (ecotoxicity). An endpoint entry was thereby allocated to the category "non-compliant" if neither an appropriate study nor suitable surrogate data or a sufficient justification to omit testing were provided ("data gap").

The majority of the endpoint entries could not be concluded within the screening. On average, 67 % of all assessed endpoint entries were, thus, defined as "complex" with a minimum of 54 % for

mutagenicity and a maximum of 94 % for reproductive toxicity. For the vast majority of these "complex" endpoint entries, data waiving/adaptation was utilised to meet the standard information requirements, i.e. omitting testing was supported by a justification (e.g. column 2 waiving or testing is technically not possible) or surrogate data (e.g. read-across or (Q)SAR data) were submitted. Data waiving/adaptation was frequently used throughout all endpoints (on average 57 %) and designated for further assessment within the formal and refined check. For the other "complex" endpoint entries (on average 10.7 %), a final conclusion was unachievable within the scope of the project as the defined assessment criteria did not allow for a sufficient in-depth analysis that would have been necessary to conclude these endpoints entries. These cases, consequently, remained "complex" and did not undergo further assessment in a subsequent evaluation step. If, for instance, studies that followed no guideline or a non-standard guideline had been submitted to fulfil the information requirements, it could not be assessed as of whether this information is equivalent to data generated by the corresponding standard test method and whether it is adequate for classification, labelling and/or risk assessment purposes. Hereby, the conclusion category "complex" constituted the final conclusion within the project.

Aggregated results after screening, formal and refined check (500 dossiers)

Out of 2053 initially screened dossiers, a subset of 500 dossiers was randomly selected. Endpoint entries not concluded in the screening ("complex") and within the subset of 500 dossiers were subjected to a subsequent formal and/or refined check. Table 3-1 lists the number of dossiers for each endpoint that were selected for further evaluation. On many occasions, multiple waiving/adaptation approaches had been submitted to address a specific endpoint. This was especially the case for endpoints with standard information requirements that include more than one test (e.g. mutagenicity, ecotoxicity).

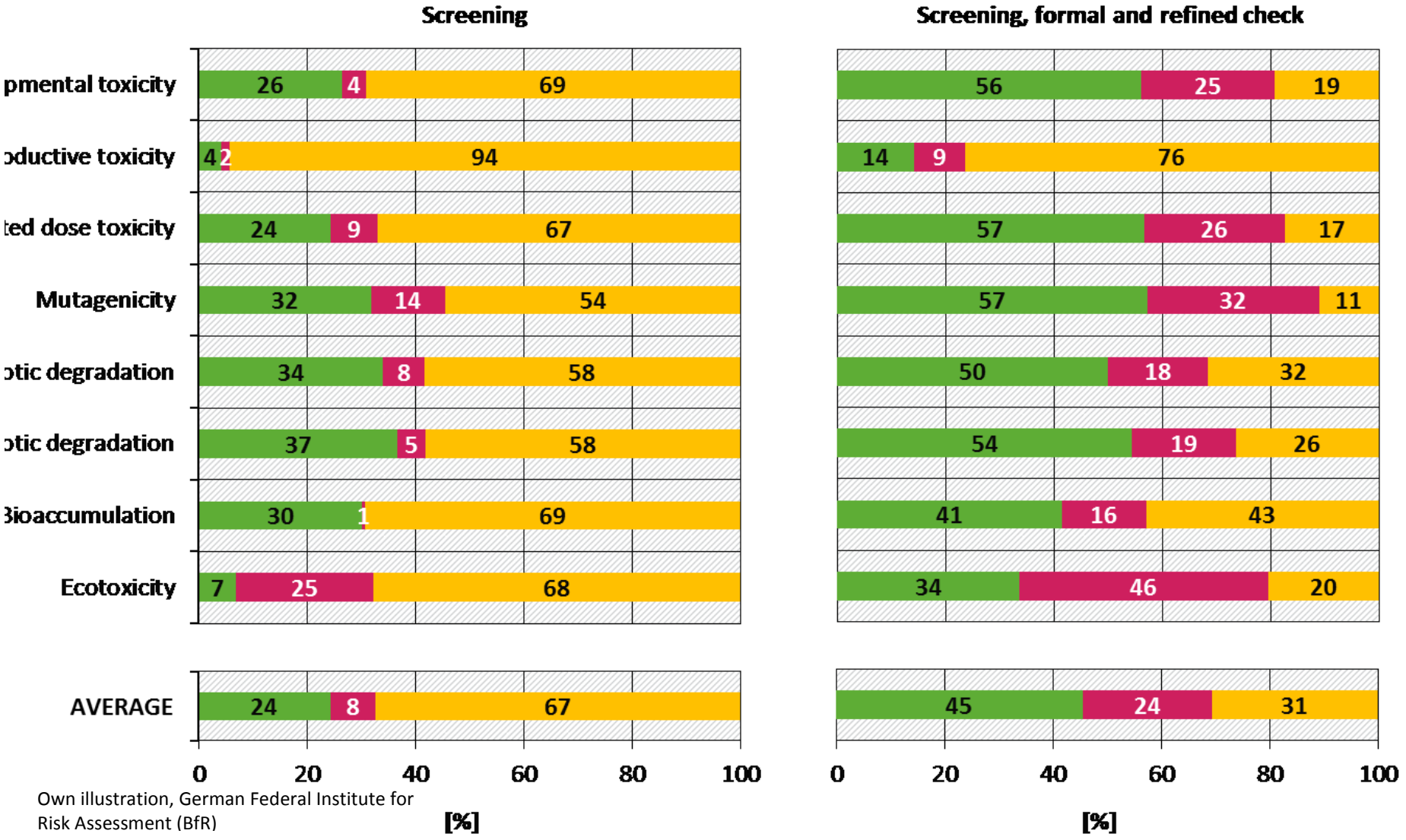
Altogether, i.e. when aggregating the results from screening, formal and refined check, "compliant" conclusions were assigned to 45 % (on average) of the endpoint entries under assessment, ranging from 14 % (reproductive toxicity) to 57 % (repeated dose toxicity, mutagenicity). An endpoint entry was concluded "compliant", if either an experimental study or a testing proposal according to an accepted guideline was available or if appropriate data waiving/adaptation was provided instead. Conversely, the endpoint entries that were assessed "non-compliant" (9 % (reproductive toxicity) to 46 % (ecotoxicity), on average 24 %), neither provided acceptable experimental data nor appropriate surrogate data or a substantiated justification to omit testing. The remaining endpoint entries in the range of 11 % (mutagenicity) to 76 % (reproductive toxicity) were not concluded because the provided information required an in-depth analysis that could not be performed within the limited scope of the project (on average 31 %).

While the rate of "compliant" decisions was notably consistent between most human health endpoints (except reproductive toxicity), mutagenicity and repeated dose toxicity exhibited the highest "compliant"-rate (57 %). Among environmental endpoints, abiotic degradation had the highest number of "compliant" endpoint entries (54 %). With 32 % "non-compliant" decisions, mutagenicity ranked first among human health endpoints. This finding is consistent with ECHA's 2017 dossier evaluation which revealed that mutagenicity was one of the most common non-compliant endpoints (94 times in 139 adopted Compliance Check decisions) (ECHA, 2018b). Similarly, within the REACH Compliance project the rate of "non-compliant" related to environmental endpoints was highest for ecotoxicity (46 %). The results from ECHA's Compliance Check decisions in 2017 showed that long-

term aquatic toxicity testing was frequently requested (73 times in 139 adopted Compliance Check decisions) (ECHA, 2018b).

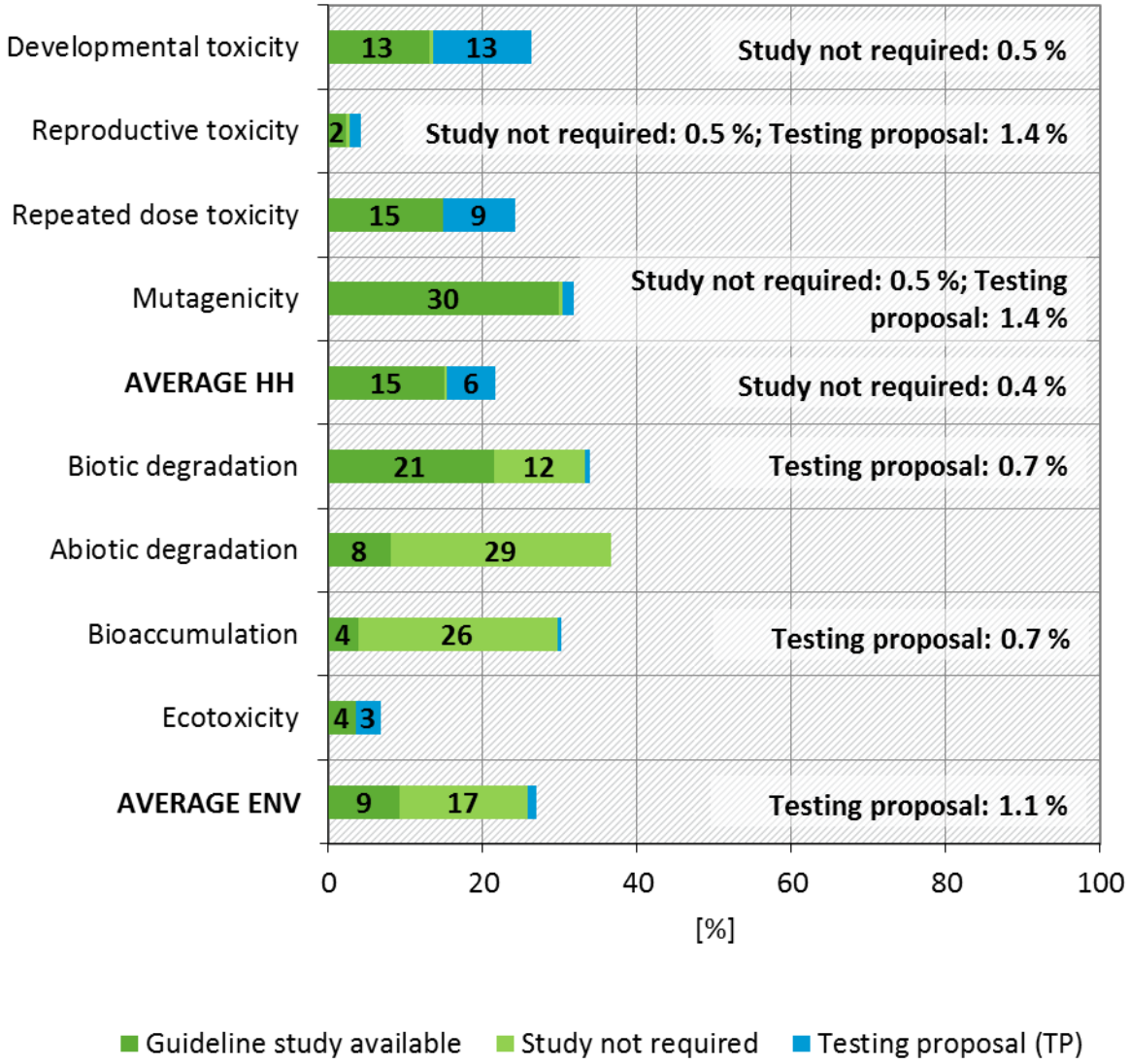
A lack of comparability has to be noted for the project results on the endpoint reproductive toxicity. For most of the dossiers (76 %), an in-depth evaluation would have been necessary to determine the requirement of a higher tier study. This, however, was outside the scope of the current project (see 3.2.4 and A.4).

Figure 3-1: **Data availability and quality of human health and environmental endpoints – endpoint conclusions after screening of substances registered at 100 to 1000 tpa (n = 2053 dossiers) and aggregated after screening, formal and refined check (n = 500 dossiers)**



Own illustration, German Federal Institute for Risk Assessment (BfR)

Figure 3-2: Percentage of available standard information, dispensable testing due to column 2, or available testing proposal in "compliant" endpoint conclusions after screening of substances registered for 100 to 1000 tpa (n = 2053)



Own illustration, German Federal Institute for Risk Assessment (BfR)

Table 3-1: Dossiers assessed in the formal and/or refined check and corresponding number of assessed waiving/adaptation records

Endpoint	Decision level	N dossiers	N waiving/adaptation records
Developmental toxicity	Formal check	257	262
	Refined check	61	61
Reproductive toxicity	Formal check	132	133
	Refined check	31	31
Repeated dose toxicity	Formal check	244	248
	Refined check	47	47
Mutagenicity	Formal check	172	482
	Refined check	76	207
Biotic degradation	Formal check	160	200
	Refined check	107	136
Abiotic degradation	Formal check	181	193
	Refined check	67	67
Bioaccumulation	Formal check	122	133
	Refined check	65	65
Ecotoxicity	Formal check	100*	323
	Refined check	196	356

*additional 38 Dossiers further evaluated in the refined check

Formal and refined check

On average, 57 % of the endpoint entries were further evaluated within the formal and refined check which comprised the assessment of data waiving/adaptation with respect to the formal criteria specified in the REACH Annexes VII-IX column 2 or Annex XI (see section 0 and 2.6). Figure 3-3 shows the percentage of waiving/adaptation records that had been assessed for the respective waiving/adaptation category within a given endpoint (see also Table 3-1).

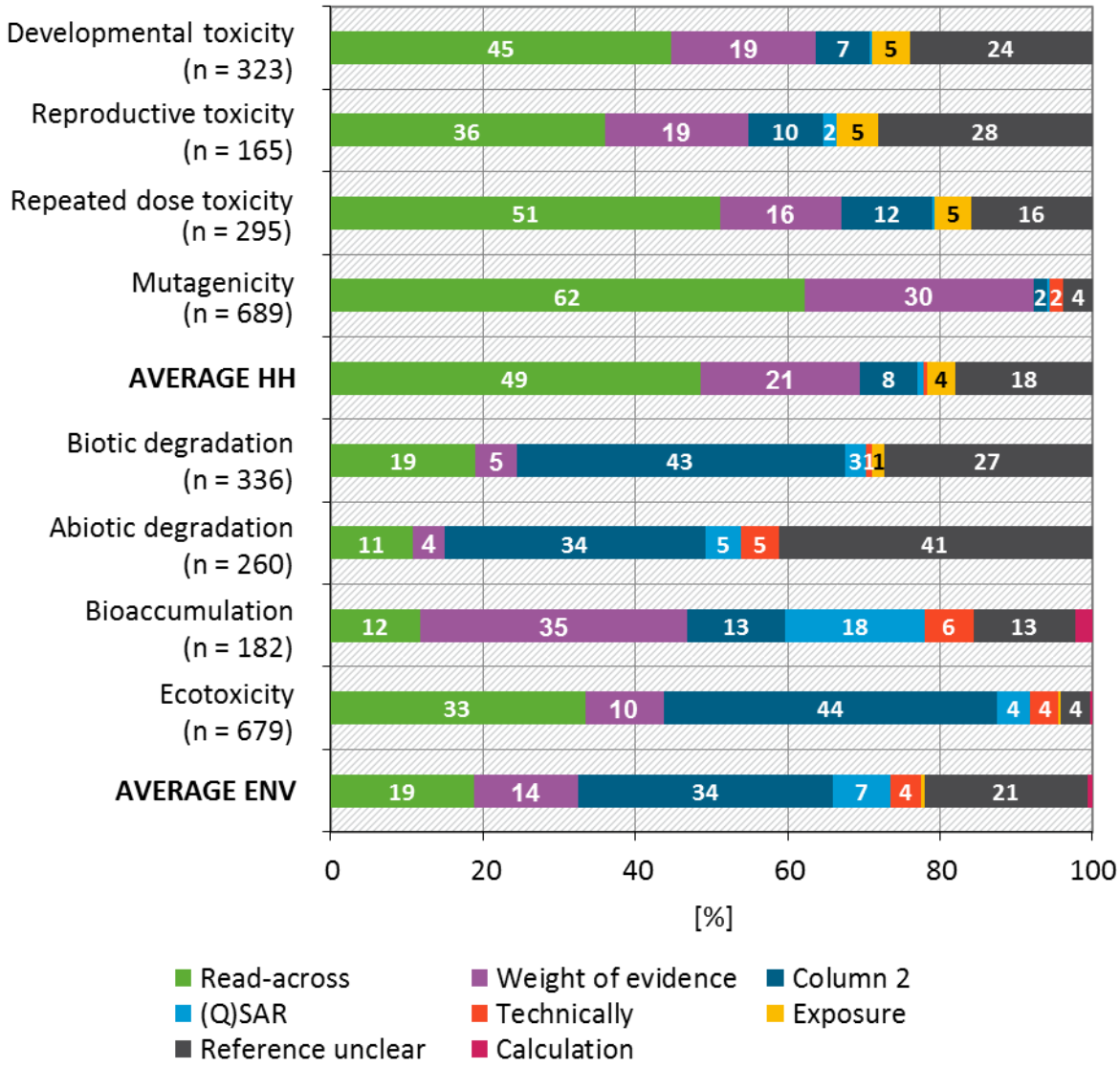
As marked differences were seen between human health and environmental endpoints, average percentage values are depicted separately. Accordingly, read-across (36 % to 62 %, on average 49 %) and weight of evidence (19 % to 30 %, on average 21 %) were the most frequently assessed waiving/adaptation categories amongst all human health endpoints. For environmental endpoints the main waiving/adaptation categories assessed within the project were endpoint specific waiving (column 2) (13 % to 44 %, on average 34 %), reference unclear, i.e. records in which a reference to the REACH Annexes VII-IX and XI was unclear (4 % to 41 %, on average 21 %), and read-across (11 % to

33 %, on average 19 %). Weight of evidence approaches were assessed in 14 % on average for environmental endpoints. Interestingly, assessment of (Q)SARs was mostly necessary for environmental endpoints as opposed to human health endpoints (7 % vs. 0.7 % on average).

The category reference unclear was concluded "non-compliant" or "complex" for the vast majority of the assessed records.

As mentioned above and depicted in Figure 3-2, some of the column 2 waiving rules were already incorporated in the assessment during the screening (e.g. *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study is not needed if the substance has a harmonised classification according to the CLP Regulation either in the carcinogenic category 1A or 1B or germ cell mutagenic category 1A, 1B or 2 (REACH Annex 8.4.2 column 2); bioaccumulation testing is not needed if the substance has a low potential for bioaccumulation demonstrated with log $K_{OW} \leq 3$ (REACH Annex IX 9.3.2 column 2)). In addition, adaptations according to REACH Annex XI 1.1. (use of existing data) are already documented in the screening as non-standard method (no guideline or a non-standard guideline study).

Figure 3-3: Distribution of waiving/adaptation categories assessed during the formal and refined check (n = number of assessed waiving/adaptation records)



Own illustration, German Federal Institute for Risk Assessment (BfR)

The results of the formal and/or refined check are shown in Figure 3-4. "Compliant" endpoint decisions based on the assessment of waiving/adaptations were in the range of 28 % (biotic degradation) to 56 % (mutagenicity), averaging 39 %. "Non-compliant" endpoint decisions ranged from 16 % (reproductive toxicity) to 40 % (bioaccumulation), averaging 28 %. A decision on the endpoint was not possible within the formal and/or refined check in 13 % (mutagenicity) to 54 % (reproductive toxicity) of the evaluated endpoint entries, averaging 33 %. This applied, for instance, to cases where studies that followed no guideline or a non-standard guideline had been utilised as part of

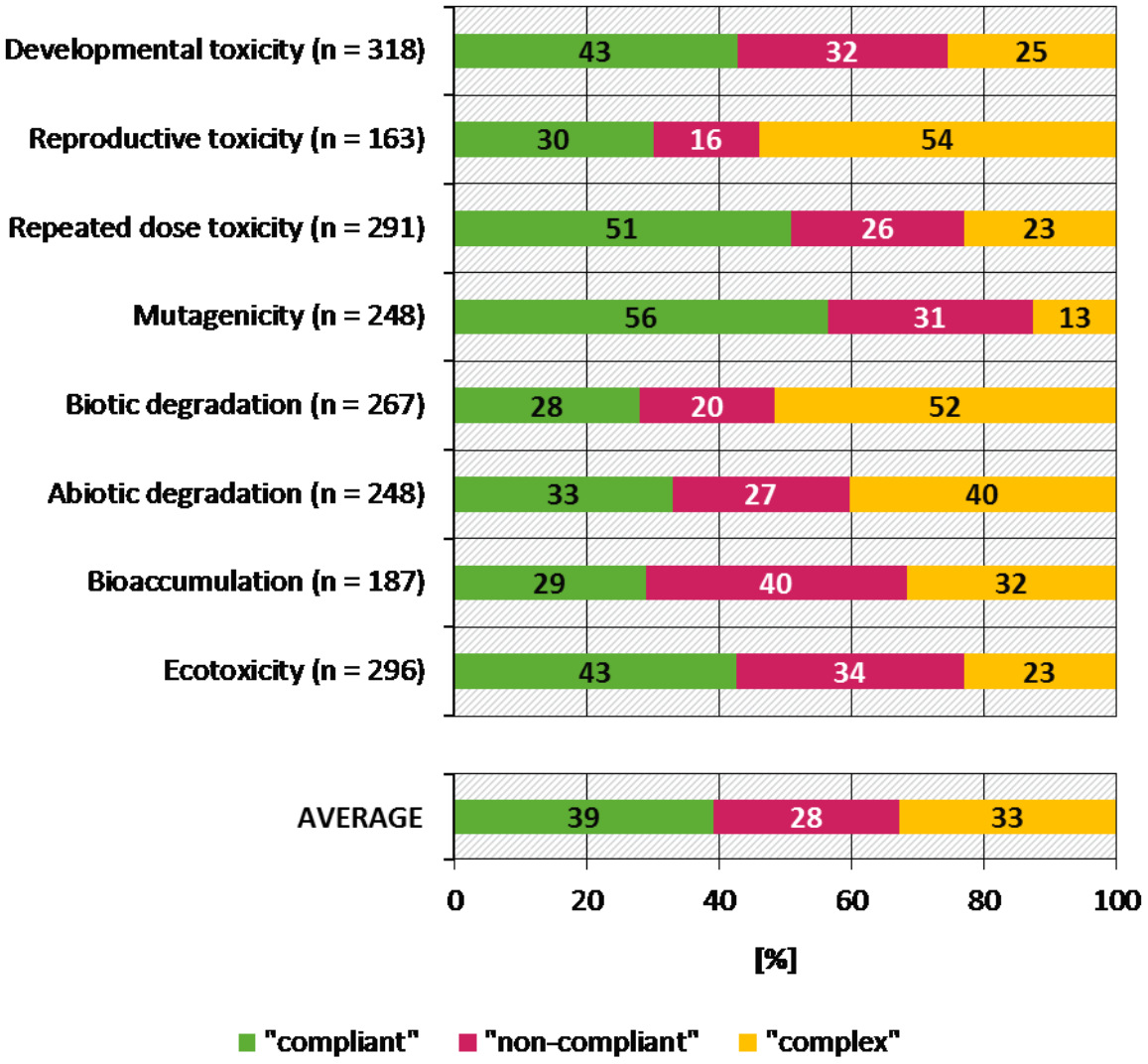
read-across or weight of evidence data. A decision whether or not these studies can be considered valid could not be made within the limited scope of the project.

When analysing the conclusion rates separately for human health and environmental endpoints, it can be noted that the percentage of "compliant" waiving/adaptations related to human health is higher as compared to environmental endpoints (52 % vs. 33 %). This may be due to the fact that some waiving/adaptations were already assessed "compliant" within the screening of environmental endpoints.

A more detailed discussion on the reasons for "compliant", "non-compliant" and "complex" can be found in sections 3.2.1 to 3.2.4 for human health endpoints and in sections 3.3.1 to 3.3.4 for environmental endpoints.

It has to be emphasised that the main focus within the scope of the project was to make a decision on the compliance of the endpoint based on the available information submitted in the dossiers. Hence, the results on waiving/adaptations do not necessarily represent all available waiving/adaptations within the dossiers, i.e. if the decision on a waiving/adaptation record was decisive for the final endpoint conclusion, any additional waiving/adaptation record provided for the endpoint was neglected. However, if a "non-compliant" or "complex" decision on a certain waiving/adaptations was made and additional waiving/adaptations were available for the same endpoint entry or study type, the assessment continued to allow for a potential "compliant" overall decision. Consequently, the formal and/or refined check was terminated if drawing a final conclusion for the endpoint was feasible based on the assessment of the presented waiving/adaptation record.

Figure 3-4: Endpoint conclusions based on the assessment of waiving/adaptations within the formal and refined check (n = number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

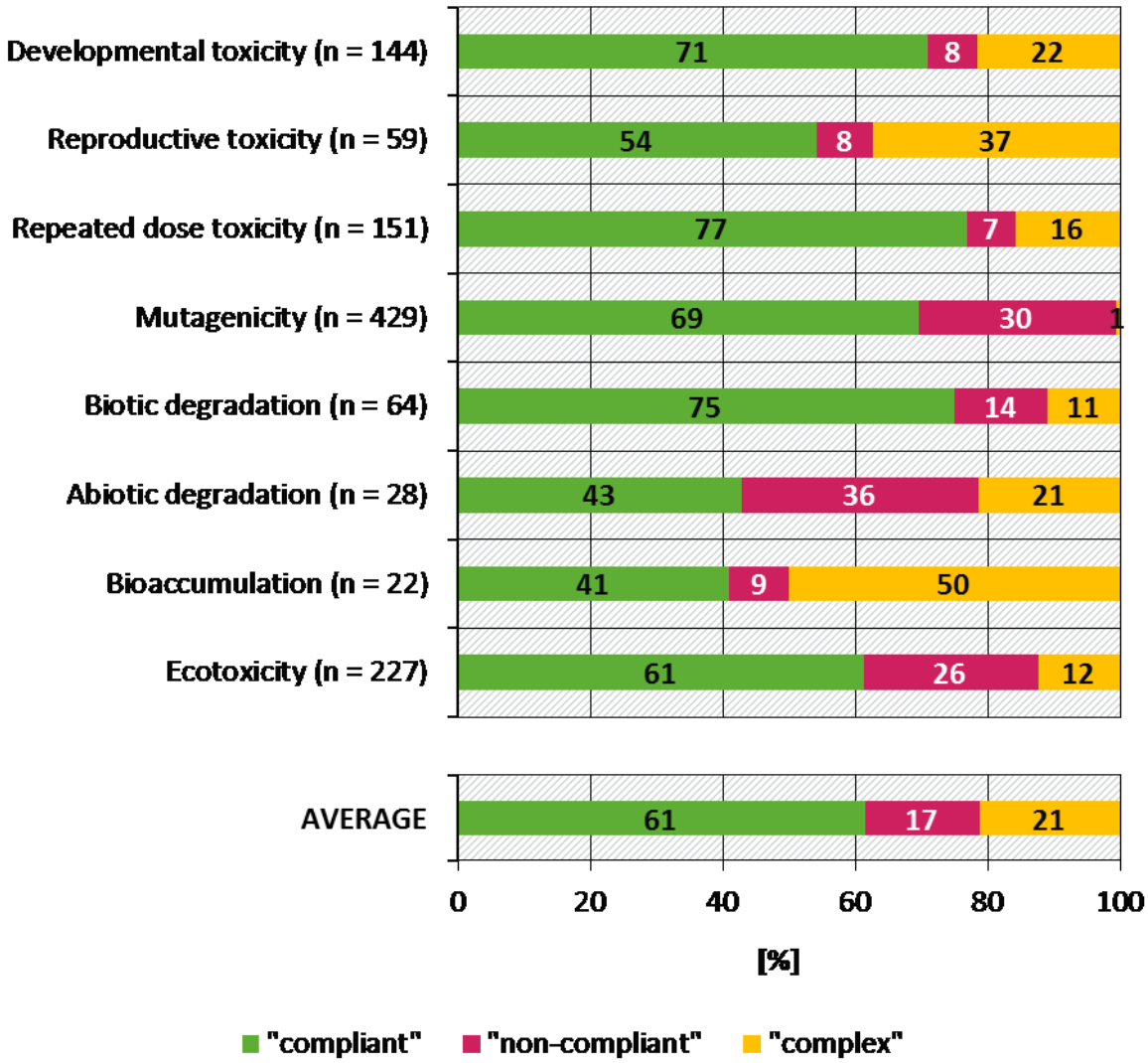
As aforementioned and shown in Figure 3-3, read-across constitute a frequently utilised waiving/adaptation category. With respect to all assessed waiving/adaptation categories within the formal and refined check, the evaluation of read-across was done in 11 % to 62 %, depending on the endpoints and on average in 34 % across all endpoints. The results on read-across approaches assessed within the formal check are depicted in Figure 3-5.

A “compliant” decision was possible if an experimental study according to an accepted guideline and a read-across justification were available. Conversely, the waiving/adaptation record was assessed “non-compliant” if either the experimental study was not accepted with respect to important key parameters of the guideline and/or the read-across justification was not available or insufficient. When interpreting the read-across results, one has to bear in mind that the formal check of read-

across was limited to formal criteria. The scientific validity of the available formally "compliant" read-across approaches would require further in-depth analysis to decide on its compliance.

Read-across approaches were rated "compliant" from 41 % (bioaccumulation) to 77 % (repeated dose toxicity), averaging 61 %, and "non-compliant" from 7 % (repeated dose toxicity) to 36 % (abiotic degradation), averaging 17 %. "Complex" decisions were within the range of 1 % (mutagenicity) to 50 % (bioaccumulation), averaging 21 %. "Complex" read-across approaches were mainly attributed to the use of studies conducted according to no or non-standard guidelines. The validity of these studies could not be assessed within the project scope. Thus, the most frequently assigned decision category on read-across was "compliant".

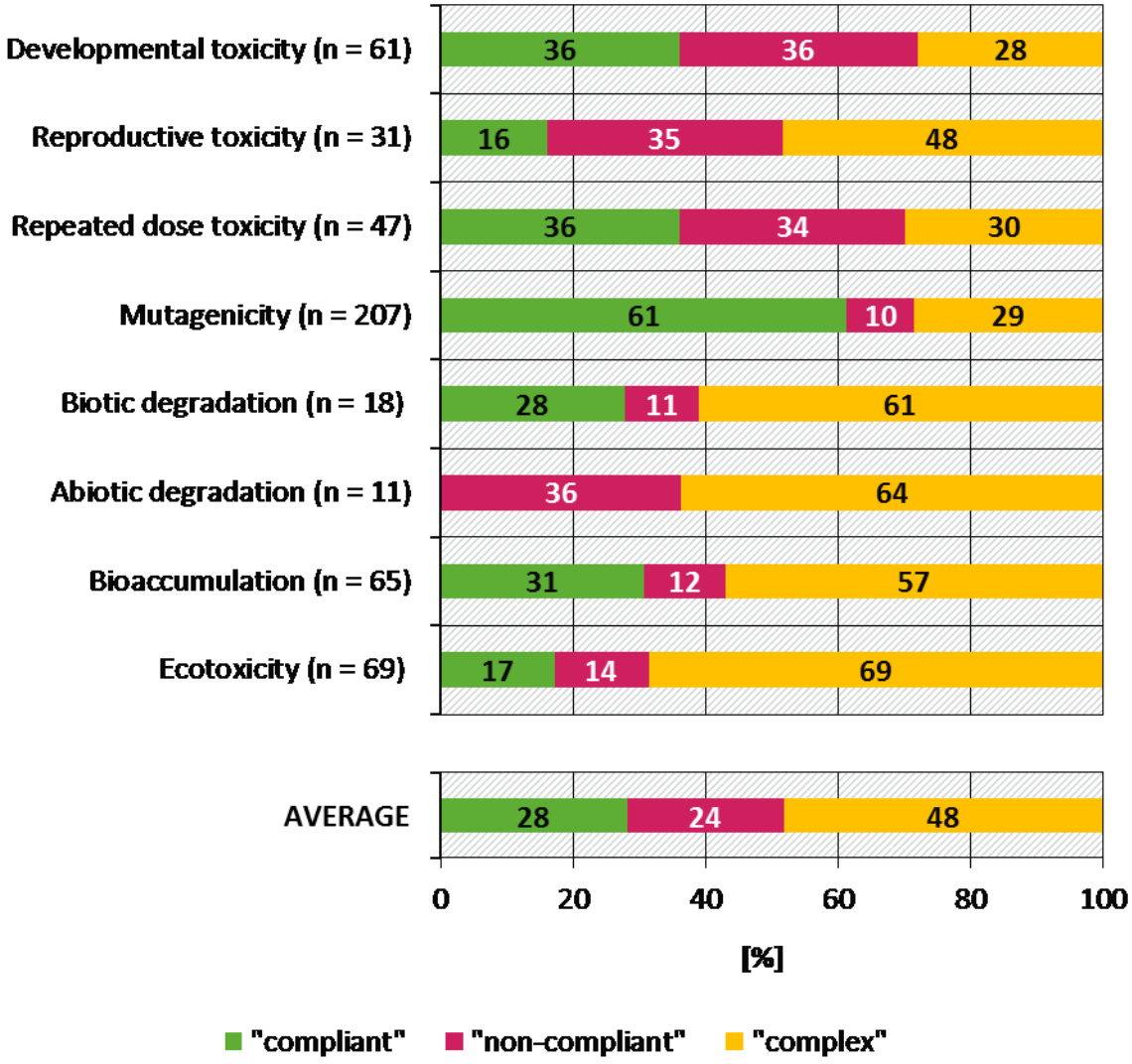
Figure 3-5: Conclusions on read-across records (n = number of waiving/adaptation records)



Own illustration, German Federal Institute for Risk Assessment (BfR)

In relation to all assessed waiving/adaptation categories within the formal and refined check, weight of evidence approaches ranged from 4 % (abiotic degradation) to 35 % (bioaccumulation). In general, weight of evidence approaches are recommended if one piece of information is not sufficient on a stand-alone basis or if conflicting results have to be evaluated to decide whether or not the substance has dangerous properties. A weight of evidence approach requires at least two experimental studies or surrogate data and a line of evidence on how the available results were weighted in the decision making. The results on the assessed weight of evidence records are summarised in Figure 3-6. The number of records assessed within the refined check varied from 11 (abiotic degradation) to 207 (mutagenicity). The percentage of "compliant" decisions varied from 0 % (abiotic degradation) to 61 % (mutagenicity), averaging 28 %. Appart from being obviously sufficient, i.e. fulfilling the criteria set out in section 2.6.1, a certain number of records were assessed "compliant" if a single study was considered sufficient on a stand-alone basis (e.g. an adequate guideline study with the registered substance). As these studies may also be considered key studies, the adaptation was set "compliant" even though a weight of evidence approach requires more than one independent piece of information. A study was defined as sufficient on a stand-alone basis if it was equivalent or similar to the corresponding standard test, assigned with a reliability of 1 or 2 and if it contained non-conflicting data as compared to other information within the weight of evidence. An in-depth assessment of the scientific validity, however, was not within the scope of the project. "Non-compliant" decisions on weight of evidence records ranged from 10 % (mutagenicity) to 36 % (developmental toxicity, abiotic degradation), averaging 24 %. Often, weight of evidence approaches were assessed "non-compliant" because the integrated read-across or (Q)SAR data were insufficiently reported. A decision on the weight of evidence approaches was not possible ("complex") in 48 % on average, ranging from 28 % (developmental toxicity) to 69 % (ecotoxicity). Thus, the most frequently assigned decision category on weight of evidence was "complex".

Figure 3-6: Conclusions on weight of evidence (n = number of waiving/adaptation records)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.1.2 Results of 100-1000 tpa compared to ≥ 1000 tpa

When comparing the results of both tonnage bands, differences regarding the information requirements have to be taken into account. For the endpoints developmental and reproductive toxicity, additional standard information is requested in Annex X (≥ 1000 tpa) as compared to Annex IX (100-1000 tpa). For the endpoints repeated dose toxicity, mutagenicity, abiotic and biotic degradation, bioaccumulation and aquatic ecotoxicity, the standard information requirements are the same for both tonnage bands.

The basic methodology that was used on both tonnage levels is generally comparable. However, on the basis of the experience gained from the evaluation of the high tonnage dossiers, the methodology on screening, formal and refined check was adjusted where useful (see section 2.4.3). For instance, if a

given test material was not identical with the registered substance and the key study was not indicated as read-across, the endpoint entry was concluded "non-compliant" for ≥ 1000 tpa substances. For 100-1000 tpa substances, a formal check was performed in order to find out whether a read-across justification was available or not.

For the medium tonnage band (100-1000 tpa), all endpoints were included in the refined check, whereas for the high tonnage band (≥ 1000 tpa), only developmental and reproductive toxicity, mutagenicity and ecotoxicity were included. Additionally, (Q)SAR data were evaluated for all endpoints for the medium tonnage band, while only being evaluated for the endpoint ecotoxicity and bioaccumulation in the high tonnage band.

These differences have to be kept in mind when comparing and interpreting the results of both tonnage bands.

Figure 3-7 depicts the screening results of the medium and the high tonnage band. While differences between the individual endpoints clearly exist, the average decision-rates are rather similar. Roughly a quarter of the endpoint entries were "compliant" as either standard information according to an accepted test guideline was provided or testing was not required for the registered substance. 8 – 11 % of the endpoint entries were assessed "non-compliant" based on the absence of standard data or an adequate waiving/adaptation. About two third of the endpoint entries could not be decided after screening and remained "complex" (Figure 3-7).

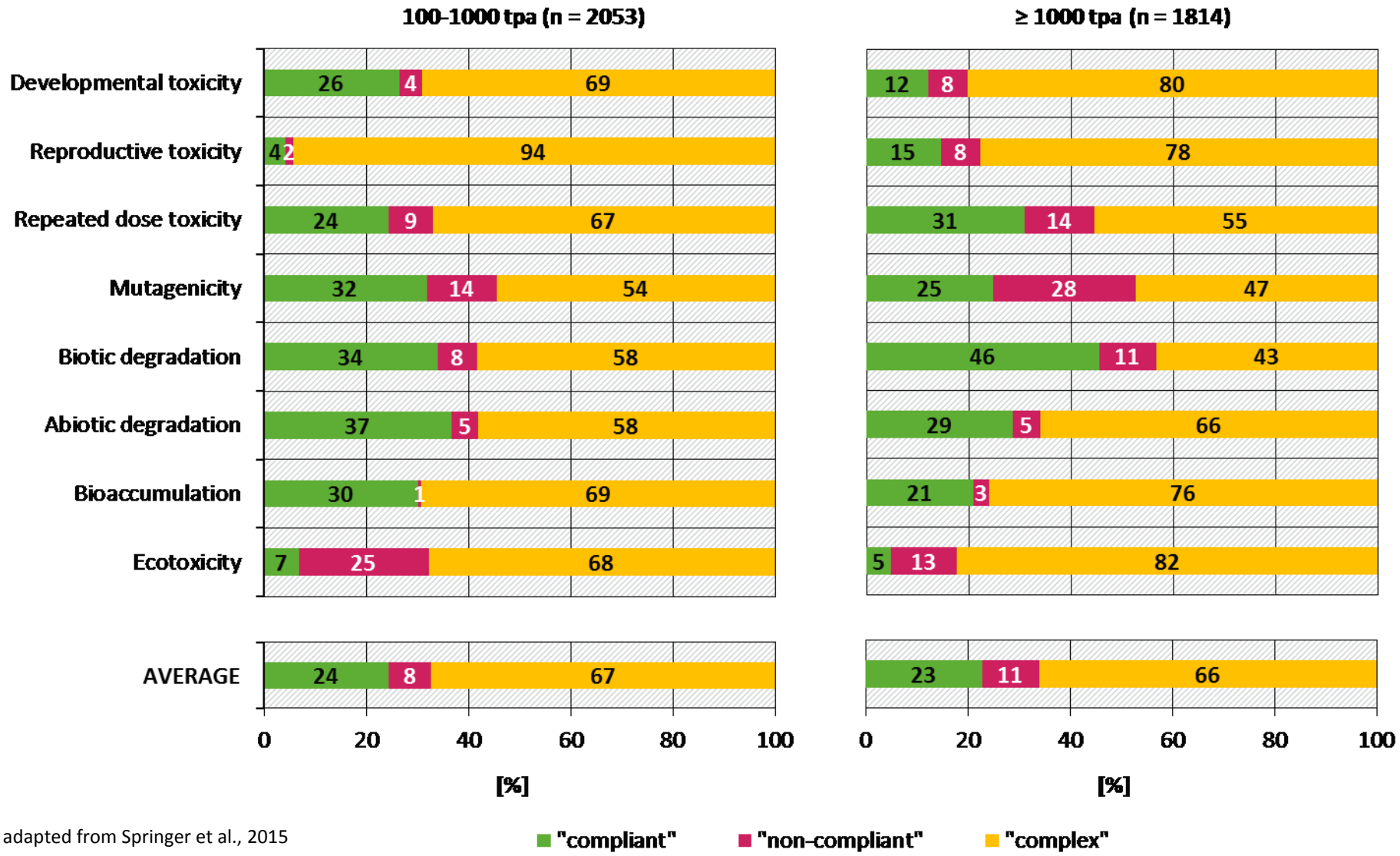
However, differences between the tonnage bands were seen when comparing the aggregated results after screening, formal and refined check. As shown in Figure 3-8, a higher "compliant"-rate (on average 45 %) for the medium tonnage band was achieved as compared to the high tonnage band (on average 34 %). Conversely, the "non-compliant"-rate was lower for the 100-1000 tpa (on average 24 %) compared to ≥ 1000 tpa (on average 33 %). With the exception of reproductive toxicity and biotic degradation, all endpoints displayed an increased "compliant"-rate in the medium tonnage band as compared to the high tonnage band. As mentioned above, the standard information requirements for reproductive toxicity are different between the medium and the high tonnage band. While the conduct of an EOGRTS is mandatory for Annex X substances, it is only conditional for 100-1000 tpa substances depending on the existence of trigger (see A.4). As an in-depth search and evaluation of trigger were not within the scope of the project, a decision could often not be made. Most of the endpoint entries, therefore, remained "complex" (see chapter 3.2.4 and A.4). Consequently, the amount of "complex" endpoint entries is very high for reproductive toxicity in the medium tonnage band as compared to the high tonnage band (76 % vs. 39 %, respectively). Concerning the endpoint biotic degradation, fewer endpoint entries were concluded "compliant" (50 % (34 % in screening)) in the medium tonnage band as compared to the high tonnage band (56 % (46 % in screening)). This may be attributed to a lower quantity of inorganic substances (11.5 %) registered at the 100-1000 tpa as compared to the high tonnage (21.2 %). Testing on biotic degradation does not need to be conducted if the substance is inorganic (REACH Annex 9.2.1.1. column 2). The "compliant"-rate for developmental toxicity was almost three times as high in the medium tonnage band as compared to the high tonnage band (56 % vs. 19 %). Different standard information requirements may, again, be a reason for this. For ≥ 1000 tpa substances, registrants have to provide two prenatal developmental toxicity studies (OECD TG 414) in different species, whereas for 100-1000 tpa substances only one is required.

When comparing the "compliant"-rate of the screening with the final "compliant"-rate following all three evaluation steps, an increase can be noted for both tonnage bands. However, this increase was noticeably higher for the medium tonnage band (+ 21 %-points, on average) in comparison to the high

tonnage band (+ 11 %-points, on average). This "enhancement" might be indicative of an improved application of waiving/adaptation approaches in the medium tonnage band. Accordingly, the "compliant"-rate of read-across was higher in the medium tonnage band (61 %) as compared to the high tonnage band (52 %). The difference was even more evident when comparing the "non-compliant"-rates (Figure 3-9).

The screening procedure for the ≥ 1000 tpa substances was performed on dossiers updated until no later than March 2014 (Springer et al., 2015). Dossier updates after this cut-off date were not considered in the assessment. Even though considerable effort had been undertaken to communicate on how to build a scientifically valid read-across for the ≥ 1000 tpa registration deadline in 2010, it was not until 2015 that the first version of the read-across guidance document (Read-across Assessment Framework (RAAF), (ECHA, 2017f)) was published by ECHA. As the cut-off date for the dossiers of the 100-1000 tpa substances was March 2017, the experience gained in recent years and the availability of guidance documents may have helped registrants to improve the application of read-across in their dossiers. This may be reflected by a better quality of read-across approaches for the medium tonnage band.

Figure 3-7: Data availability and quality of human health and environmental endpoints – endpoint conclusions after screening of substances registered for 100 to 1000 tpa compared to ≥ 1000 tpa

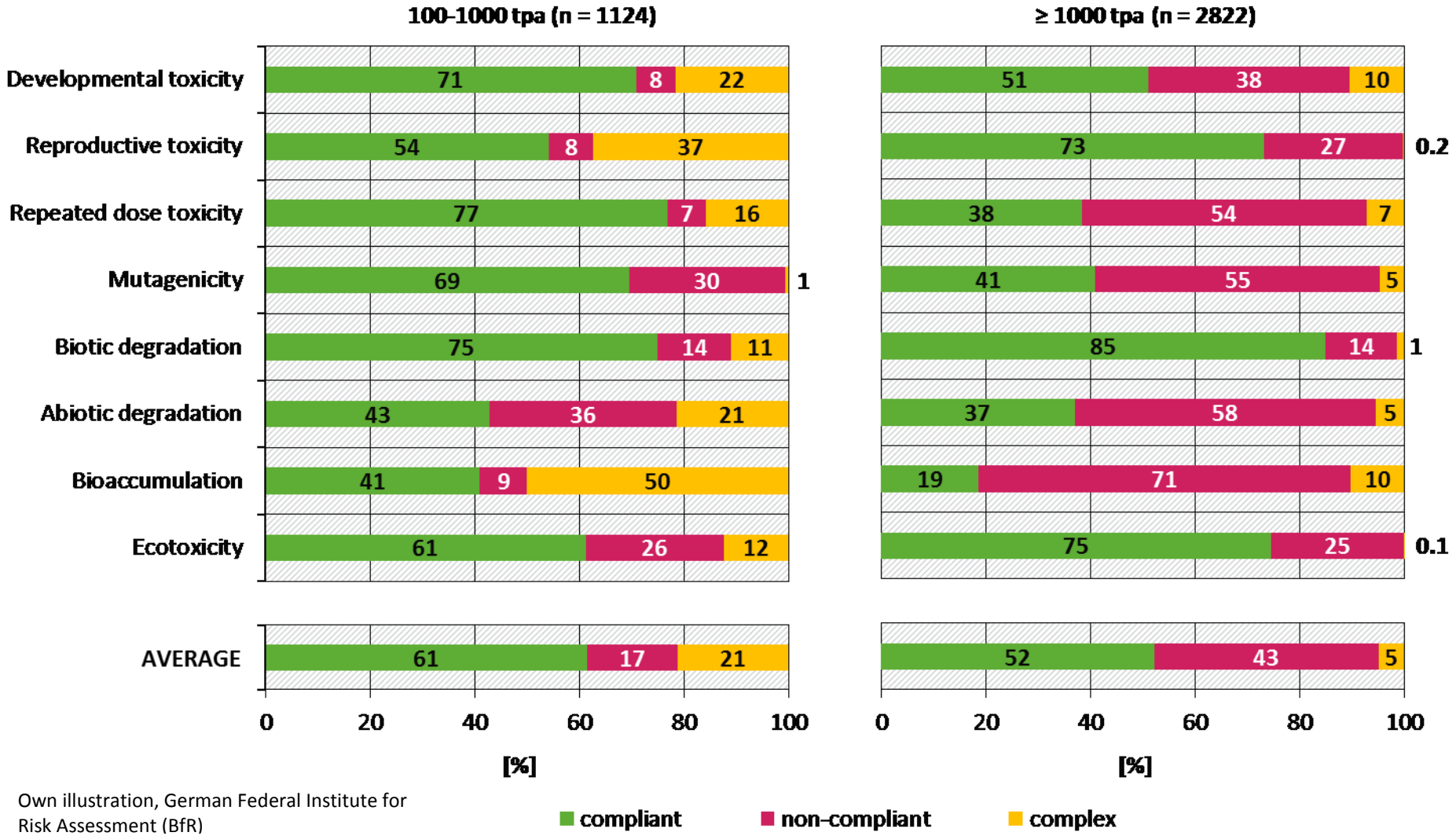


adapted from Springer et al., 2015

Figure 3-8: Data availability and quality of human health and environmental endpoints – final endpoint conclusions after screening, formal check and refined check of substances registered for 100 to 1000 tpa compared to ≥ 1000 tpa

adapted from Oertel et al., 2018b; Springer et al., 2015

Figure 3-9: Conclusions on read-across records for 100 to 1000 tpa compared to ≥ 1000 tpa (n = number of waiving/adaptation records)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.2 Human health endpoints

3.2.1 Repeated dose toxicity

The endpoint repeated dose toxicity provides information about short- and long-term toxicity that can arise from the repeated exposure to a substance over a part of the life-span. Moreover, repeated dose toxicity tests can provide additional information on reproductive toxicity. Findings of adverse effects on reproductive organs in repeated dose toxicity studies or from combined repeated dose toxicity studies with the reproduction/developmental toxicity screening tests (REACH Annex VIII, 8.7.1.) can trigger additional testing on reproductive toxicity (see section 3.2.4).

The standard testing regime according to REACH Annexes VII to IX comprises

- a short-term repeated dose toxicity study (28 days) (REACH Annex VIII 8.6.1.),
- a sub-chronic toxicity study (90 days) (REACH Annex IX 8.6.2.).

Pursuant to column 2 of REACH Annexes VIII to IX, data can be waived according to the endpoint specific rules. For instance, the 28 day-study can be omitted if a sub-chronic (90 days) or chronic (≥ 12 month) study is available. The 90-day study can be omitted if a chronic study is available and/or in general if respective waiving or adaptation options are applied.

Within the screening process, the endpoint repeated dose toxicity was evaluated in 2053 dossiers. Further assessment of the endpoint repeated dose toxicity within the formal and refined check, however, was performed in a representative subset of 500 dossiers.

3.2.1.1 Overall endpoint conclusion

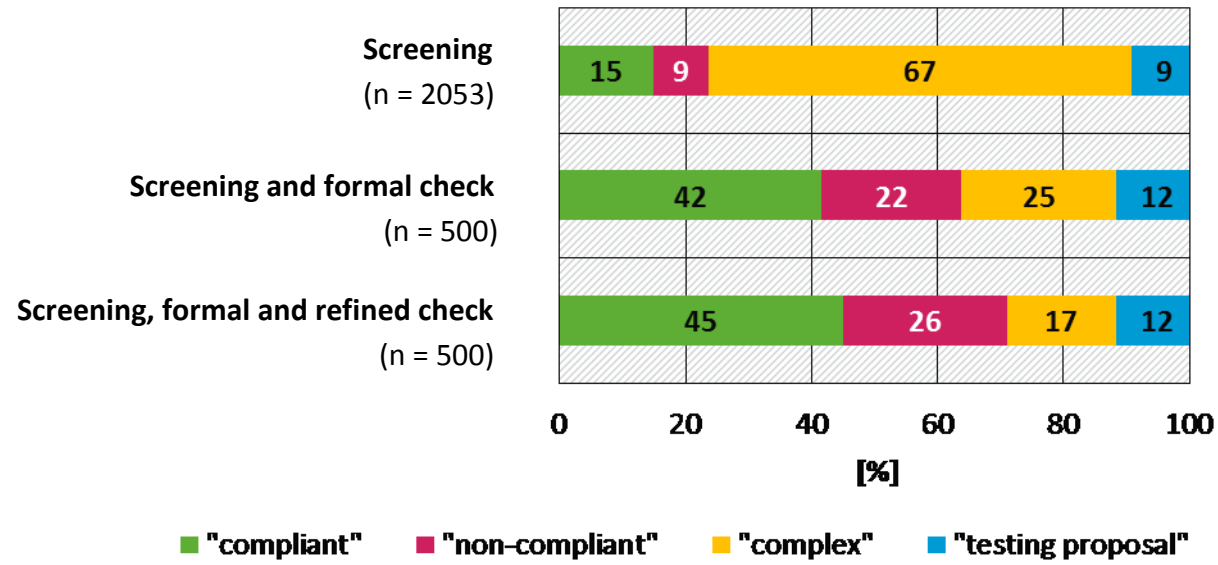
In Figure 3-10 the endpoint conclusions are presented after screening for the total number of 2053 endpoint entries under evaluation compared to the aggregated endpoint conclusions after screening, formal check and refined check for the subset of 500 dossiers.

After screening, 15.0 % of the 2053 endpoint entries that were evaluated could be decided as “compliant” for repeated dose toxicity. 8.7 % were identified as “non-compliant” and 67.0 % remained “complex”. A testing proposal for the standard test according to Annex IX was available in 9.3 % of the endpoint entries.

The subsequent formal check of data waiving and adaptations (e.g. read-across, column 2 waiving) increased the conclusion rate by 26.6 %-points for the “compliant”-decisions, resulting in 41.6 %. However, also the “non-compliant”-rate increased to 22.2 % (+ 13.5 %-points).

The refined check was performed on weight of evidence approaches that were conducted in 47 of the subset of 500 endpoint entries. This additional evaluation step further reduced the former “complex” cases from 24.6 % to 17.4 %. At the same time, the rate of “compliant” decisions increased to 45.0 % (+ 3.4 %-points) and the rate of “non-compliant” decisions increased to 26.0 % (+ 3.2 %-points).

Figure 3-10: Repeated dose toxicity – endpoint conclusions (n = total number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.2.1.2 Screening of data availability

Table 3-2 summarises the endpoint conclusions for repeated dose toxicity after the screening of the total number of dossiers under evaluation and the corresponding reason for the respective decision for the endpoint repeated dose toxicity. From the 2053 endpoint entries that were evaluated, 307 were "compliant" because they contained either a valid sub-chronic study or a valid chronic study (higher tier study, Annex IX 8.6.2. column 2, 2nd bullet point) in rodents. From the remaining endpoint entries, the available information was assessed "non-compliant" in 179 endpoint entries and "complex" in 1376 endpoint entries. A testing proposal to fulfil the standard data requirements for repeated dose toxicity according to Annex IX was available in 191 endpoint entries.

The endpoint conclusion "non-compliant" was allocated due to the fact that a "data gap" was identified, i.e. the absence of a sub-chronic or chronic study and a respective waiving/adaptation (8.7 % of all endpoint conclusions).

The majority of the evaluated endpoint entries remained "complex" after the initial screening. This was predominantly due to waiving/adaptation of the standard data requirement (1270 endpoint entries). Providing that these endpoint entries were included in the representative subset of 500 dossiers, they were further evaluated in the formal check (291 dossiers). The second largest share of "complex" cases (84 endpoint entries) was attributed to the use of non-standard test methods with comparable or longer test duration. Within the scope of the project, non-standard studies could not be evaluated further, because a time-consuming case by case analysis of the test design (in comparison with the standard test design of the respective study) would have been required. These cases remained "complex" as final evaluation. The same applied to "complex" endpoint conclusions due to the use of a standard tests with a non-rodent species (5 endpoint entries), a shorter exposure duration of the standard test (e.g. chronic test < 12 months; 7 endpoint entries), or an administration route other than oral or inhalative (10 endpoint entries).

Table 3-2: Repeated dose toxicity – screening: reasons for endpoint conclusions

Conclusion category (n = dossiers (subset))	Question No. (decision tree)	Reason	n dossiers (subset)	% (subset)
"Compliant" n = 307 (77)	1; 2	Chronic/sub-chronic study in rodents available	307 (77)	15.0 (15.4)
"Non-compliant" n = 179 (51)	2; 3a; 5	Standard test and waiving/ is not available	179 (51)	8.7 (10.2)
"Complex" n = 1376 (318)	1a	Only chronic/sub-chronic study in non-rodents available	5 (2)	0.2 (0.4)
	1; 2	Test based on non-standard method	84 (16)	4.1 (3.2)
	3a; 5	Waiving/adaptation of standard information	1270 (291*)	61.9 (58.2)
		Test based on standard method but other route of administration	3 (0)	0.2
		Waiving/adaptation but other route of administration	7 (2)	0.3 (0.4)
		Exposure duration of test not sufficient	7 (3)	0.3 (0.6)
"Testing Proposal" n = 191 (51)		Testing proposal is available	191 (58)	9.3 (11.6)
Total		-	**2053** (500)	**100.0**

*further assessed within formal- and/or refined check

3.2.1.3 Formal check of waiving/adaptation records

In the formal check on the subset of 500 dossiers, most waiving/adaptations identified in the screening were further evaluated. In total, 295 data waiving/adaptation records in 291 endpoint entries have been identified for the endpoint repeated dose toxicity. However, the WoE-records were handled in the refined check, so that the formal check for this endpoint actually comprised 248 records in 244 dossiers. Figure 3-11 shows the frequencies of all waiving/adaptation categories and the respective decisions.

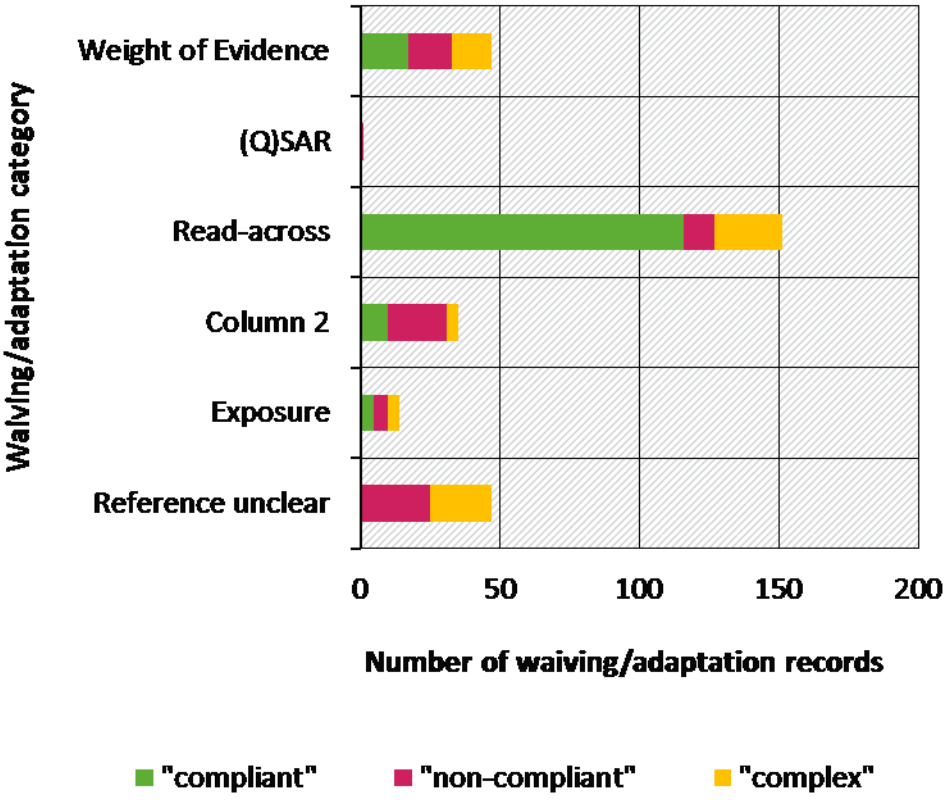
Frequently used categories were read-across and data waiving with reference to the endpoint specific rules of REACH Annexes VII and IX column 2. (Q)SAR was only used in one endpoint entry of the subset of dossiers evaluated in the formal check. In 47 waiving/adaptation records, a clear reference to the endpoint specific or general rules for data waiving according to REACH Annexes VII-IX and XI was not provided (reference unclear).

The fractions of "compliant", "non-compliant" and "complex" decisions varied between the different waiving/adaptation categories (Figure 3-11). The majority of the read-across records was assessed as formally "compliant", whereas for column 2 waiving, the majority of the justifications was "non-compliant". Waiving records without a particular reference to the REACH Annexes (reference unclear) equally resulted in "non-compliant" and "complex" decisions.

Table 3-3 specifies the underlying reasons for the decisions on waiving/adaptation records that were assessed in the formal check and are shown in Figure 3-11.

In the following section, selected waiving/adaptation categories and the attributed reasons for the respective conclusions are explained in detail.

Figure 3-11: Repeated dose toxicity – formal and refined check: conclusions on waiving/adaptation records (n = 295)



Own illustration, German Federal Institute for Risk Assessment (BfR)

Read-across

Out of the 151 read-across records, 116 were formally “compliant”. These approaches provided a plausible justification of the structural similarities between test substance and registered substances and a key study with the source substance that was conducted according to an accepted guideline (see 2.5.2). In contrast, 11 read-across approaches were concluded “non-compliant” because the justification was not available at all or did not plausibly illustrate the structural and toxicological similarities. In a few cases (also in the other endpoints) for example, registrant use a category approach (read-across approach among a number of structurally similar substances), but the test material that was used for read-across was not included in that category. In 24 cases, the read-across record included a non-guideline study on the source substance and was concluded “complex”. Since the evaluation of non-standard test methods requires an in-depth evaluation these dossiers remained finally “complex” and were not further evaluated if no other information was available.

Endpoint specific data waiving (column 2)

Out of the 248 waiving/adaptations that were evaluated in the formal check (excluding WoE), 35 referred to column 2 of REACH Annex IX 8.6.2..

For the endpoint repeated dose toxicity, column 2 comprises 4 possibilities to waive the standard test (see 4 bullet points, Table A3). The existence of a chronic study (2nd bullet point) was already checked in the course of the screening. The justification that the substance undergoes immediate disintegration and there are sufficient data on the cleavage products for systemic effects and effects at the site of uptake (3rd bullet point) was only used in one case and remained "complex" due to the requirement of an in-depth evaluation. For the remaining waiving options (1st and 4th bullet point), a formal check of the criteria was performed. For these justifications, all 3 respective criteria have to be addressed and adequately explained (e.g. that "a reliable 28 days study is available and the 28 days study shows severe toxicity according to criteria for classification as R48 and the NOAEL-28 days allows for extrapolation of the NOAEL-90 days for the same route of exposure). 10 waiving records were found to fulfil these requirements and concluded "compliant". 21 of the 35 column 2 justifications had to be assessed as "non-compliant", since at least one criterion was not addressed. A common argument for waiving the 90-day study was e.g. that the 28-day study, which was not used for classification, showed no endpoint specific toxicity. This argument is only valid if the registrant additionally proves that the substance is: "…unreactive, insoluble and not inhalable and there is no evidence of absorption […] coupled with limited human exposure" (Annex IX 8.6.2. 1st passage, 4th bullet point). When the waiving justification referred to the 1st bullet point, often the NOAEL from 28-day studies was not extrapolated to the 90-day NOAEL or the substance showing severe toxicity was not classified as R48 (STOT RE 2).

Data waiving without reference to REACH Annexes (reference unclear)

Half of the waiving records that could not be assigned to any of the endpoint specific or general rules of REACH Annexes VII-IX and XI (reference unclear) were concluded "non-compliant" because the waiving justification was obviously insufficient or false (25 records). The remaining 22 records in this category often referred to the results of studies on other endpoints in order to justify omission of testing. These justifications were very extensive and would have needed an in-depth evaluation. As a standardised approach cannot be applied, these cases remained "complex" as final evaluation.

Table 3-3: Repeated dose toxicity – formal check: reasons for conclusions on waiving/adaptation records

Waiving/ adaptation category	Conclusion category	Reason	n record	%
Weight of evidence		Refined check (see section 3.2.1.4)	47*	15.9
(Q)SAR	"Non-compliant"	(Q)SAR not adequately documented	1	0.3
Read-across	"Compliant"	Read-across based on standard method and justification available	116	39.3
	"Non-compliant"	Read-across justification not available/not sufficient	11	3.7
	"Complex"	Read-across based on non-standard method	24	8.1
Column 2	"Compliant"	All criteria adequately addressed	10	3.4
	"Non-compliant"	Not all criteria addressed	21	7.1
	"Complex"	In-depth evaluation required	4	1.4
Exposure	"Non-compliant"	Exposure assessment not available	5	1.7
	"Complex"	In-depth evaluation required	5	1.7
	"Complex"	Justification cannot be assigned to the specific criteria of REACH Annex XI 3.2. (a)-(c)	4	1.4
Reference unclear	"Non-compliant"	Waiving justification obviously insufficient or false	25	8.5
	"Complex"	In-depth evaluation required (REACH Annexes VII to IX introduction, last passage could apply)	22	7.5
Total			**295**	**100**

*further assessed in the refined check

3.2.1.4 Refined check of waiving/adaptation records

Weight of evidence

Weight of evidence was also a frequently used waiving/adaptation category (Figure 3-11). The refined check of waiving/adaptation records for repeated dose toxicity comprised 47 weight of evidence approaches. Table 3-4 summarises the reasons for the decisions. Out of the 47 records, 17 were considered "compliant" with the requirements set out in chapter 2.6.1. In the majority of the records (n = 14 out of 17), at least one study (among others) was identified that was obviously sufficient on a stand-alone basis. This study was performed according to an accepted guideline and the results were consistent with other available pieces of information. Only in 3 cases an obviously sufficient WoE-

approach was recognised. There were several possibilities for a WoE-approach to be evaluated "non-compliant". The main reason for a "non-compliant" decision was that a formally "non-compliant" read-across and/or (Q)SAR approach was included (according to the criteria set out in 2.5.2). Rarely, a WoE-summary was not available or only one piece of evidence which was not sufficient on a stand-alone basis.

The decision category "complex" was assigned in 14 cases, mainly because the WoE was entirely based on studies that were conducted with non-standard methods (10 records). The remaining cases mainly showed inconsistent NOAELs and thus an in-depth evaluation would have been required.

Table 3-4: Repeated dose toxicity – refined check: reasons for conclusions on waiving/adaptation records

Adaptation category	Conclusion category	Reason	n record	%
Weight of evidence	"Compliant"	WoE obviously sufficient	3	6.4
	"Compliant"	One piece of evidence is obviously sufficient on a stand-alone basis	14	29.8
	"Non-compliant"	WoE summary not available	2	4.3
	"Non-compliant"	Only one piece of information which is not sufficient on a stand-alone basis	1	2.1
	"Non-compliant"	Read-across data is formally "non-compliant"	8	17.0
	"Non-compliant"	(Q)SAR data is formally "non-compliant"	5	10.7
	"Complex"	WoE entirely based on non-standard methods	10	21.3
	"Complex"	In-depth evaluation required	4	8.5
Total			**47**	**100**

3.2.2 Mutagenicity

According to Annexes VII to IX column 1 of the REACH Regulation, the standard information on mutagenicity for chemicals produced at tonnage levels of 100-1000 tpa are *in vitro* tests concerning gene mutation in bacteria (GMbact) and structural/numerical chromosome aberration in mammalian cells (Cytvitro). Additionally, an *in vitro* gene mutation test in mammalian cells (GMvitro) is necessary if both studies have a negative result. If the results in all three *in vitro* tests are negative, no further testing is required. In case of a positive result in any of the *in vitro* tests, an appropriate follow-up *in vivo* study, addressing the nature of the triggering *in vitro* test, is required.

The standard testing regime according to REACH Annexes VII to IX comprises:

In vitro

- An *in vitro* gene mutation study in bacteria (GMbact) (REACH Annex VII 8.4.1.)

- An *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Cytvitro) (REACH Annex VIII 8.4.2.)
- An *in vitro* gene mutation study in mammalian cells (GMvitro) (REACH Annex VIII 8.4.3), in case of negative results in Annex VII, Section 8.4.1. (GMbact) and Annex VIII, Section 8.4.2. (Cytvitro)

In vivo

- An *in vivo* somatic cell genotoxicity study (Cytvivo/GMvivo) (REACH Annex IX 8.4. column 2), if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII

Column 2 of REACH Annex VIII provides endpoint specific rules that can be applied by registrants to justify a data waiving. For instance, the requirement of providing an in vitro chromosome aberration test in mammalian cells (Cytvitro) and/or an in vitro gene mutation test in mammalian cells (GMvitro) can be omitted if adequate information from in vivo tests addressing the corresponding in vitro endpoint is available.

Within the screening process, the endpoint mutagenicity was evaluated in 2053 dossiers. Further assessment of the endpoint mutagenicity within the formal and refined check, however, was only performed in a representative subset of 500 dossiers.

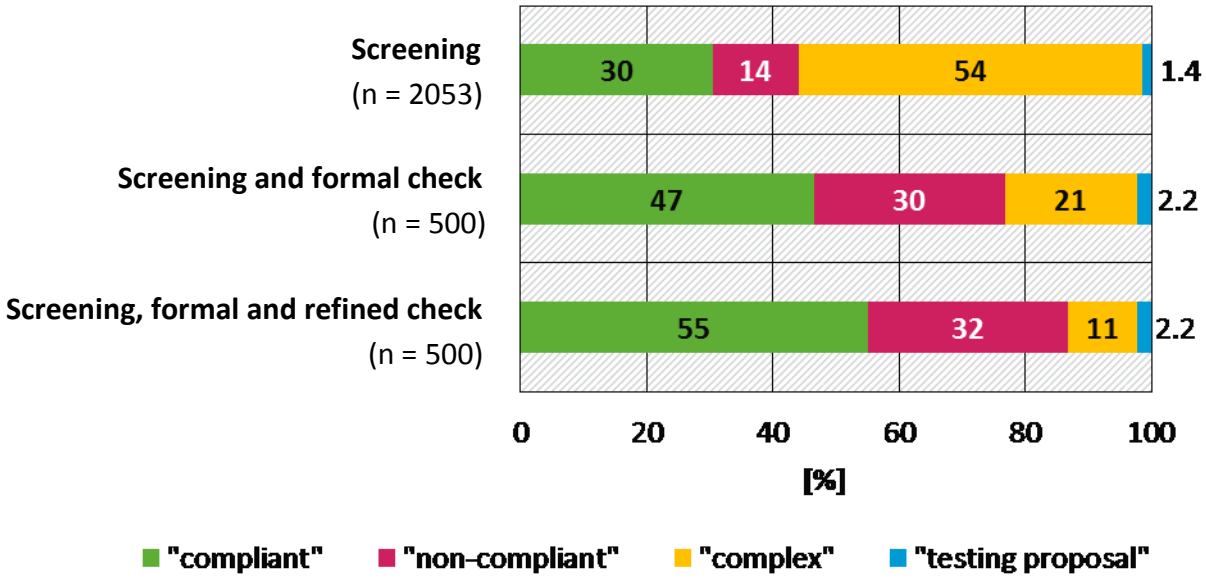
3.2.2.1 Overall endpoint conclusion

Figure 3-12 depicts the endpoint conclusions following the screening process for all evaluated endpoint entries (n = 2053) in comparison to aggregated conclusion rates after formal check and refined check for a representative subset of 500 dossiers.

As the result of the screening process (screening, first bar) with respect to the endpoint mutagenicity, 624 (30.4 %) of the endpoint entries were assigned to the category “compliant”, 283 (13.8 %) to the category “non-compliant”, and 1117 (54.4 %) to the category “complex”. In addition, 29 endpoint entries (1.4 %) contained a testing proposal.

As explained in the method section, only a representative subset of dossiers (n = 500) was assessed within all evaluation levels (screening, formal and refined check). Aggregated conclusion rates of these dossiers for the endpoint mutagenicity are also depicted in Figure 3-12 (screening + formal check, second bar; screening + formal + refined check, third bar). It is noticeable, that the conclusion rate markedly improved with each additional level of evaluation. Accordingly, the aggregated results after screening and formal check revealed 233 “compliant” endpoint entries (46.6 %), 151 “non-compliant” endpoint entries (30.2 %) and 105 “complex” endpoint entries (21 %). Following the conduct of the refined check, these numbers changed to 275 “compliant” endpoint entries (55 %), 159 “non-compliant” endpoint entries (31.8 %) and 55 “complex” endpoint entries (11 %). Amongst the 500 endpoint entries, 11 endpoint entries (2.2 %) contained a testing proposal.

Figure 3-12: Mutagenicity – endpoint conclusions (n = total number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.2.2.2 Screening of data availability

Of the 2053 evaluated endpoint entries, 624 were found "compliant", 283 "non-compliant", 1117 "complex", and 29 contained a testing proposal. Table 3-5 summarises reasons that led to a conclusion within the screening decision level.

The vast majority of endpoint entries allocated to the category "compliant" contained adequate information on all three in vitro test types with test results consistently negative (n = 485). The registrants, thus, fulfilled the standard information requirements by solely providing in vitro tests in these cases. In addition, the availability of adequate information from one in vivo test together with valid information from in vitro tests rendered the corresponding dossiers "compliant" for mutagenicity too. Accordingly, endpoint entries were set "compliant" when adequate information on GMbact and GMvitro with negative results were available in combination with adequate information on Cytvivo (n = 64). The decision "compliant" was also granted to endpoint entries that contained adequate information on GMbact and Cytvitro with negative and positive results, respectively, together with adequate information on Cytvivo (n = 36). Endpoint entries containing information on GMbact in combination with Cytvivo and GMvivo also rendered a dossier "compliant" (n = 28).

In case the standard information requirements were obviously not met due to missing information on required test types ("data gaps"), the dossier was set "non-compliant". The "data gap" for a particular test type that determined the decision is indicated in Table 3-5. Hence, missing information on GMvitro (n = 141) followed by GMvivo (n = 57), GMbact (n = 36), Cytvitro (n = 32), and Cytvivo (n = 9) constituted the decisive criteria that rendered the dossier "non-compliant". It should be, however, noted that endpoint entries can contain "data gaps" for multiple test types for which only one decisive test type is documented in Table 3-5. In 8 cases, no adequate information was provided for all test types.

As aforementioned, the majority of endpoint entries remained "complex" after the screening evaluation (n = 1117). Of these cases, 1029 endpoint entries remained without a final conclusion as waiving and/or adaptation of the standard information requirements were applied for one or more decisive test types. These "complex" endpoint entries were further assessed within the formal- and/or refined check, providing they were part of the selected subset of 500 dossiers (n = 248 out of 1029). The other 88 "complex" endpoint entries either contained studies based on non-standard methods (n = 69) or showed equivocal results (n = 19). These endpoint entries remained "complex" as the scope of the project did not allow for a conclusion in any of the evaluation levels (no formal and/or refined check performed).

Table 3-5: Mutagenicity – screening: reasons for endpoint conclusions

Conclusion category (n = dossiers (subset))	Reason	n dossiers (subset)	% (subset)
"Compliant" n = 624 (135)	GMbact, Cytvitro, and GMvitro are available and have negative results	485 (110)	23.6 (22.0)
	GMbact, GMvitro are available and have negative results, Cytvivo is available	64 (10)	3.1 (2.0)
	GMbact available and negative, Cytvitro available and positive, Cytvivo is available	36 (7)	1.8 (1.4)
	GMbact, Cytvivo, and GMvivo are available	28 (7)	1.4 (1.4)
	GMbact available and negative, Cytvitro available and positive, GMvitro available and positive, Cytvivo and GMvivo available	1 (0)	0.05 (0)
	Substance has a harmonised classification according to the CLP Regulation	10 (1)	0.5 (0.2)
"Non-compliant" n = 283 (82)	GMvitro not addressed	141 (39)	6.9 (7.8)
	GMvivo not addressed	57 (20)	2.8 (4.0)
	GMbact not addressed	36 (11)	1.8 (2.2)
	Cytvitro not addressed	32 (8)	1.6 (1.6)
	Cytvivo not addressed	9 (1)	0.4 (0.2)
	No adequate information for all test types	8 (3)	0.4 (0.6)
"Complex" n = 1117 (272)	Waiving/adaptation for one or more studies available	1029 (248*)	50.1 (49.6)
	Test based on non-standard method	69 (18)	3.4 (3.6)
	In-depth evaluation required - equivocal *in vitro* results	19 (6)	0.9 (1.2)
"Testing Proposal" n = 29 (11)	Testing proposal	29 (11)	1.4 (2.2)
Total	-	**2053** (500)	**100**

*further assessed within formal- and/or refined check

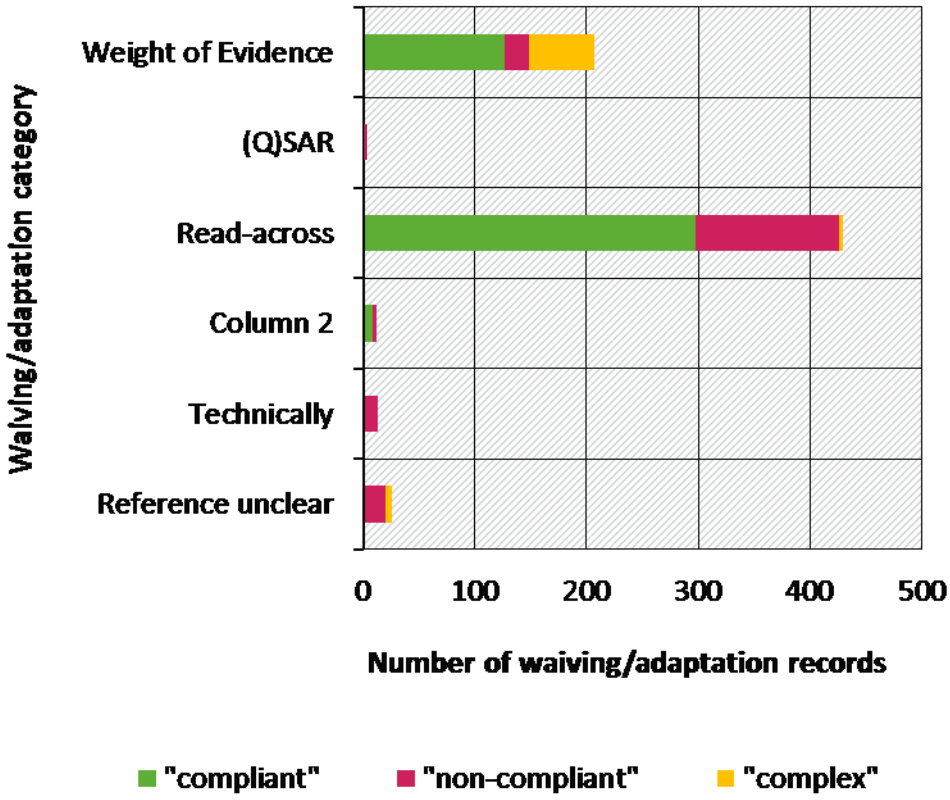
3.2.2.3 Formal check of waiving/adaptation records

Endpoint entries that remained without a final conclusion ("complex") within the screening evaluation and that belonged to the representative subset of 500 dossiers were designated to further assessment. 248 endpoint entries (49.6 %) comprising 774 records for data waiving and/or adaptation were thereby further evaluated. Records that were found not relevant for an endpoint conclusion were exempted from the examination (n = 85). Figure 3-13 depicts the total number of examined waiving/adaptation records (n = 689) for each category with the corresponding decisions. The assessment of WoE approaches conducted within the refined check is already included in Figure 3-13 and further explained in section 0.

For the endpoint mutagenicity, frequently used and examined waiving/adaptation categories incorporated read-across and grouping approaches (n = 429), WoE (n = 207), and data waiving with reference to the endpoint specific rules of REACH Annex VIII 8.4. column 2 (n = 12). A waiving justification lacking a clear reference to the endpoint specific or general rules for data waiving according to REACH Annexes VII-IX and XI (reference unclear) was assessed in 26 records. Waiving/adaptation categories such as (Q)SAR (n = 2) and technically (testing is technically not possible, n = 13) were only assessed in a few cases.

It is to be noted that the formal check was limited to waiving/adaptation records that impeded a final endpoint conclusion in the screening step. Therefore, the number of assessed waiving/adaptation records may differ from the actual number of submitted waiving/adaptation records.

Figure 3-13: Mutagenicity – formal and refined check: conclusions on waiving/adaptation records (n = 689)



Own illustration, German Federal Institute for Risk Assessment (BfR)

Read-across

Read-across adaptations were considered "compliant" if they were based on standard test methods and a justification was available and sufficient (n = 298). The decision "non-compliant" was assigned to adaptations that did not fulfil these criteria (n = 128). In case, the read-across adaptation was based on non-standard test methods, the category "complex" was introduced (n = 3).

Endpoint specific data waiving (column 2)

Data waiving with reference to the endpoint specific rules of REACH Annex VIII was assessed in 12 cases. In three cases, waiving according to column 2 was insufficiently applied, resulting in a "data gap" and a "non-compliant" decision. For example, Cytvitro or GMvitro was waived due to the existence of a corresponding *in vivo* study. However, the assessment of the endpoint entry revealed that an appropriate *in vivo* study was not available. Conversely, if adequate information from *in vivo* studies was available, waiving of the corresponding *in vitro* study was considered "compliant" (n = 9).

Data waiving without reference to REACH Annexes (reference unclear)

Waiving records that could not be assigned to the endpoint specific or general rules of REACH Annexes VII-IX and XI (reference unclear) were considered "non-compliant" in case the waiving justification

was obviously insufficient or false (n = 20). If an in-depth evaluation of the provided justification was required, the assessment was concluded with a "complex" decision (n = 6).

Table 3-6: Mutagenicity – formal check: reasons for conclusions on waiving/adaptation records

Waiving/ adaptation category	Conclusion category	Reason	n record	%
Weight of evidence		Refined check (see section 0)	207*	30.0
(Q)SAR	"Non-compliant"	(Q)SAR model and prediction are not appropriate	2	0.3
Read-across	"Compliant"	Read-across based on standard method and justification available	298	43.3
	"Non-compliant"	Read-across justification not available/not sufficient	128	18.6
	"Complex"	Read-across based on non-standard method	3	0.4
Column 2	"Compliant"	Column 2 waiving sufficiently applied	9	1.3
	"Non-compliant"	Column 2 waiving insufficiently applied	3	0.4
Technically	"Non-compliant"	Justification does not meet requirements of Annex XI 2.	13	1.9
Reference unclear	"Non-compliant"	Waiving justification obviously insufficient or false	20	2.9
	"Complex"	In-depth evaluation required	6	0.9
Total			**689**	**100**

*further assessed in the refined check

3.2.2.4 Refined check of waiving/adaptation records

Within the refined check, 207 adaptations in 76 endpoint entries were further evaluated. For the endpoint mutagenicity, these adaptations comprise solely WoE approaches. Reasons underlying the corresponding decisions are summarised in Table 3-7.

Weight of evidence

As mentioned before and indicated in Figure 3-13 and Table 3-6, WoE approaches were a frequently applied adaptation, ranking second after read-across. Of 234 identified adaptations, 207 were evaluated within the refined check as they turned out critical to draw a final endpoint conclusion. The remaining 27 records did not undergo further examination due to their irrelevance regarding an endpoint conclusion.

Out of 207 WoE adaptations, more than half were allocated to the category "compliant" (n = 127) as they were considered obviously sufficient (n = 81) or a single study was considered sufficient on a

stand-alone basis (n = 46). In the latter case, a study was defined as sufficient on a stand-alone basis if it was equivalent or similar to the corresponding standard test, assigned with a reliability of 1 or 2 and if it contained non-conflicting data as compared to other information within the WoE. Thus, if a WoE for one test type contained only one study considered sufficient on a stand-alone basis, the adaptation was set "compliant" even though a WoE approach requires more than one independent piece of information. Consequently, non-compliance was ascertained if a single piece of information was not sufficient on a stand-alone basis (n = 9). The decision "non-compliant" was also assigned if the WoE was based on a formally insufficient read-across (n = 11) or formally insufficient (Q)SAR application (n = 1). A final decision could not be made if the WoE was entirely based on non-standard test methods (n = 17) or required an in-depth evaluation (n = 42). The latter scenario was given if, for instance, studies with conflicting results were used.

Table 3-7: Mutagenicity – refined check: reasons for conclusions on waiving/adaptation records

Adaptation category	Conclusion category	Reason	n records	%
Weight of evidence	"Compliant"	WoE obviously sufficient	81	39.1
	"Compliant"	One piece of evidence is obviously sufficient on a stand-alone basis	46	22.2
	"Non-compliant"	Read-across data is formally "non-compliant"	11	5.3
	"Non-compliant"	Only one piece of information which is not sufficient on a stand-alone basis	9	4.3
	"Non-compliant"	(Q)SAR data is formally "non-compliant"	1	0.5
	"Complex"	In-depth evaluation required	42	20.3
	"Complex"	WoE entirely based on non-standard methods	17	8.2
Total			**207**	**100**

3.2.3 Developmental toxicity

The endpoint developmental toxicity addresses adverse effects on the normal development of organism. These adverse effects may stem from the exposure of either parent before conception or the developing organism between prenatal development and sexual maturation (ECHA, 2017a).

The standard testing regime according to REACH Annexes VII to IX comprises

- a screening study for reproductive/developmental toxicity (REACH Annex VIII 8.7.1.),
- a prenatal developmental toxicity study (REACH Annex IX 8.6.2.).

According to column 2 of REACH Annex VIII, the screening study does not have to be conducted if a prenatal developmental toxicity study according to OECD TG 414 (OECD, 2001) or an extended one-generation reproductive toxicity study (EOGRTS)/two-generation reproduction toxicity study (OECD TG 443 (OECD, 2012e)/OECD TG 416 (OECD, 1983)) is available.

Within the screening process, the endpoint developmental toxicity was evaluated in 2053 dossiers. Further assessment of the endpoint developmental toxicity within the formal and refined check, however, was only performed in a representative subset of 500 dossiers.

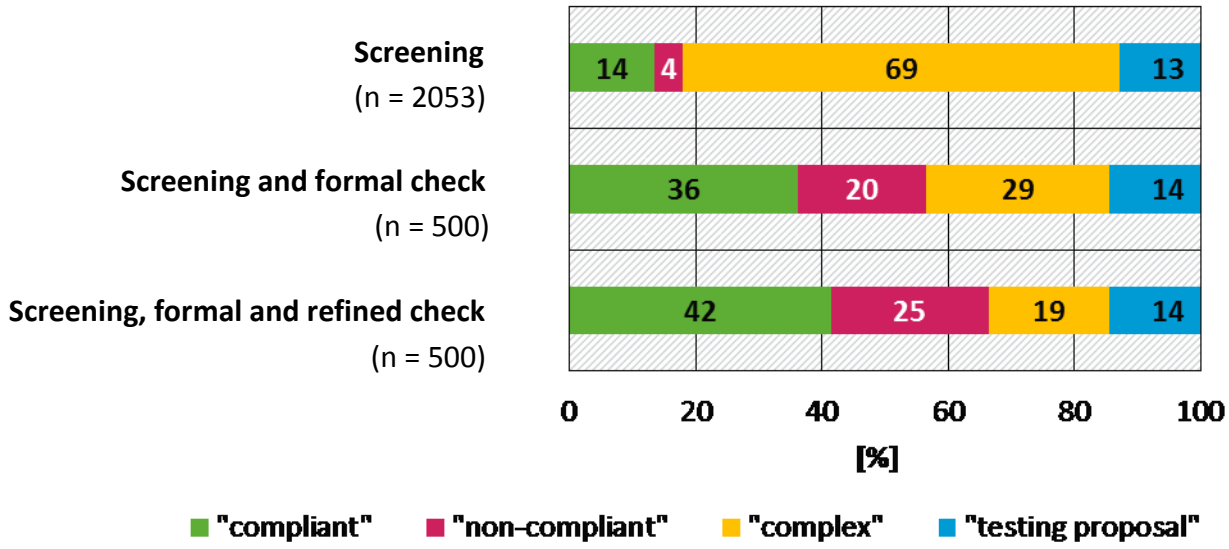
3.2.3.1 Overall endpoint conclusion

Figure 3-14 shows the endpoint conclusions after screening for the initial number of 2053 endpoint entries under evaluation compared to the aggregated results after screening, formal and refined check for a representative subset of 500 dossiers.

After screening, 13.5 % of the endpoint entries could be concluded “compliant”. 4.4 % were identified as “non-compliant” and 69.2 % remained complex. In 12.9 % of the endpoint entries a testing proposal for the OECD TG 414 (OECD, 2001) was provided. The “compliant”-rate almost tripled after the formal check, increasing by 22.7 %-points to 36.2 %. However, also for the “non-compliant” decisions the conclusion rate to increased 20.4 % (+16 %-points).

The refined check on the 61 weight of evidence records that were identified in the subset of 500 endpoint entries further reduced the “complex” cases by 8.8 %-points. This reduction led to an increase in “compliant” decisions to 41.6 % (+ 5.4 %-points) and also the rate of “non-compliant”-decisions increased to 24.8 % (+4.4 %-points). However, still 19.2 % of the cases remained “complex” after this final step out of various reasons explained in the following chapters.

Figure 3-14: Developmental toxicity – endpoint conclusions (n = total number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.2.3.2 Screening of data availability

Table 3-8 comprises all reasons on the basis of which the endpoint conclusions for developmental toxicity were made and shows the distribution of the respective reasons for each decision category. Out of the 2053 endpoint entries that were evaluated in this step, 278 were concluded “compliant”, predominantly because registrants provided the required standard test with rodents or rabbits by oral or inhalative route. In very few cases this test was not required since the substance was classified according to CLP (see footnotes in Table 3-8 for respective classifications).

From the remaining endpoint entries, 91 had to be concluded “non-compliant” and 1420 remained “complex” in this step. Additionally, 264 testing proposals for the standard test (OECD TG 414 (OECD, 2001)) were submitted.

The endpoint conclusion “non-compliant” was based on the non-existence of the standard data requirements and respective data waiving/adaptations (“data gap”).

Most of the evaluated endpoint entries (1328) were “complex” after the screening because they provided waiving/adaptation of the standard data requirements (64.7 % from all endpoint decisions). For the subset of 500 dossiers the waiving/adaptations were further evaluated in the formal or refined check (318 endpoint entries). The second largest share of “complex” cases was attributed to the use of non-standard methods (52 cases). As mentioned before, these cases were not evaluated further and remained “complex” as final evaluation. The remaining endpoint entries also remained “complex” as final evaluation, due to the use of a non-standard route of administration for the test (10 cases) or the waiving/adaptation (29 cases).

Table 3-8: Developmental toxicity – screening: reasons for endpoint conclusions

Conclusion category (n = dossiers (subset))	Question No. (decision tree)	Reason	n dossiers (subset)	% (subset)
"Compliant" n = 278 (67)	1	CLP classified (1)	5 (1)	0.2 (0.2)
	2	CLP classified (2)	4 (0)	0.2 (0)
	3	CLP classified (3)	1 (0)	0.1 (0)
	4	Test based on adequate standard method	268 (66)	13.1 (13.2)
"Non-compliant" n = 91 (23)		Standard test and waiving/adaptation is not available	91 (23)	4.4 (4.6)
"Complex" n = 1420 (338)	4a	Test based on standard method but other route of administation	11 (5)	0.5 (1.0)
	5	Waiving/adaptation of standard information	1328 (318*)	64.7 (63.6)
	5	Waiving/adaptation but other route of administation	29 (5)	1.4 (1.0)
		Test based on non-standard method	52 (10)	2.5 (2.0)
"Testing Proposal" n = 264 (72)		Testing proposal is available	264 (72)	12.9 (14.4)
Total		-	**2053** (500)	**100**

(1) classified as a genotoxic carcinogen (mutagen category 2, H341 and carcinogen category 1A or 1B, H350) or germ cell mutagen (mutagen category 1A or 1B, H340) according to the CLP Regulation

(2) classified as a reproductive toxicant (category 1A or 1B, H360) according to the CLP Regulation affecting fertility (H360F) and the unborn child (H360D) = H360FD and NOAEL is available

(3) classified as a reproductive toxicant (category 1A or 1B, H360D) according to the CLP Regulation affecting the unborn child and NOAEL is available

*further assessed within formal- and/or refined check

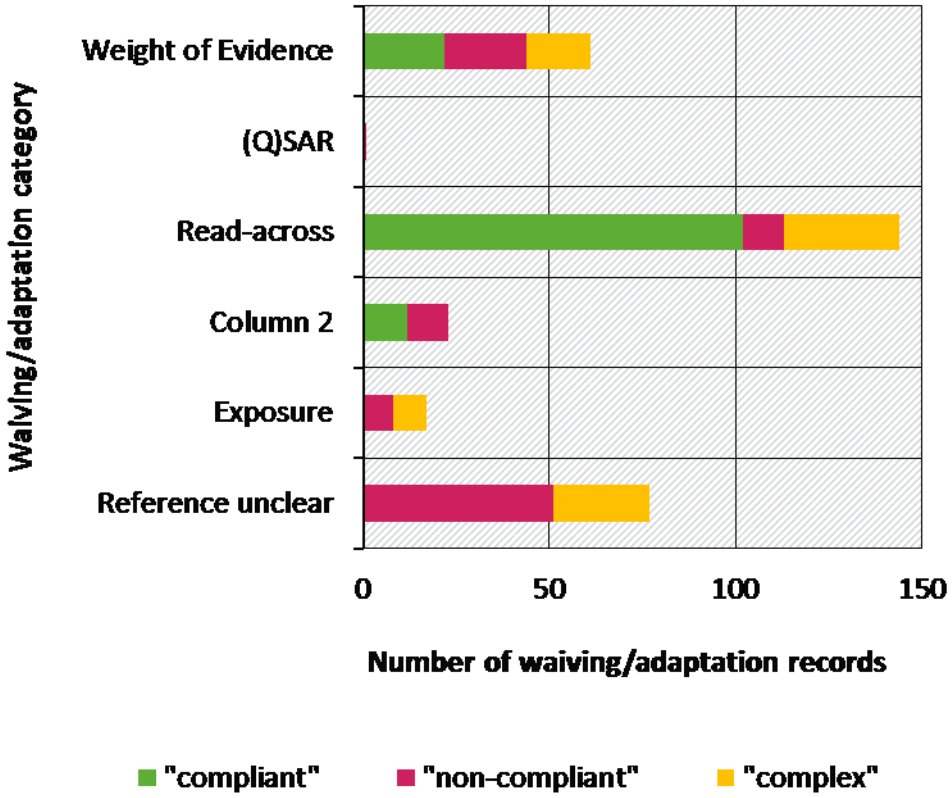
3.2.3.3 Formal check of waiving/adaptation records

For the subset of 500 dossiers, the waiving/adaptations that were identified in the screening were further evaluated in the formal check (323 records in 318 endpoint entries). However, as mentioned before, the WoE-records were handled in the refined check, so that the formal check comprised actually only 262 records in 257 endpoint entries. Figure 3-15 shows the distribution of waiving/adaptation categories and the decision rates for each category.

As for the endpoint repeated dose toxicity and mutagenicity, frequently applied waiving/adaptation categories were read-across and column 2. Again, (Q)SAR was only used in one dossier and waiving without clear reference to general or endpoint specific rules of waiving/adaptation were often identified.

The majority of the read-across records were found to be “compliant”. For exposure based waiving, the majority was assessed “non-compliant”. Around two third of the waiving records without a particular reference to the REACH Annexes (reference unclear) were concluded “non-compliant” and for column 2 waiving records, “compliant” and “non-compliant” decisions were evenly distributed (Figure 3-15).

Figure 3-15: Developmental toxicity – formal and refined check: conclusions on waiving/adaptation records (n = 323)



Own illustration, German Federal Institute for Risk Assessment (BfR)

Table 3-9 comprises the underlying reasons for the endpoint conclusions in the formal check, specified for each waiving/adaptation category. In the following, the most frequently assessed categories and the reasons for their conclusions are specified.

Read-across

Out of the 144 read-across approaches, 102 were formally “compliant” according to the formal criteria described in the methods (2.5.2). In contrast, 11 read-across approaches were concluded “non-compliant” because the justification was not available at all or not sufficient. In 31 cases, the read-across approach included a non-guideline source study and was concluded “complex”.

Endpoint specific data waiving (column 2)

Out of the 262 waiving/adaptations that were evaluated in the formal check, 23 referred to column 2 of REACH Annex IX 8.7.

For the endpoint developmental toxicity, column 2 comprises 4 possibilities to waive the standard test (Table A8). Three of them refer to the classification of the substance which was already documented and concluded in the screening (Table 3-8). The other justification should specify that the substance is of low toxicological activity (regarding all endpoints) and no systemic absorption occurs via relevant routes of exposure and there is no significant human exposure. As for repeated dose toxicity, a proper justification according to column 2 requires the explanation of all three criteria. 12 of 23 justifications could be concluded "compliant". In 11 out of 23 records, the justifications were "non-compliant" because one or two criteria were not addressed. In most of the cases, registrants failed to address human exposure and/or systemic absorption.

Data waiving without reference to REACH Annexes (reference unclear)

77 waiving/adaptation records could not be assigned to the endpoint specific or general rules of REACH Annexes VII-IX and XI (reference unclear). 51 of them were concluded "non-compliant" because the waiving justification was obviously insufficient or false. The remaining 26 records in this category needed in-depth evaluation and thus remained "complex".

Table 3-9: Developmental toxicity – formal check: reasons for conclusions on waiving/adaptation records

Waiving/ adaptation category	Conclusion category	Reason	n record	%
Weight of evidence		Refined check (see section 3.2.3.4)	61*	18.9
(Q)SAR	"Non-compliant"	(Q)SAR not adequately documented	1	0.3
Read-across	"Compliant"	Read-across based on standard method and justification available	102	31.7
	"Non-compliant"	Read-across justification not available/not sufficient	11	3.4
	"Complex"	Read-across based on non-standard method	31	9.6
Column 2	"Compliant"	All criteria adequately addressed	12	3.7
	"Non-compliant"	Not all criteria addressed	11	3.4
Exposure	"Non-compliant"	Justification according to REACH Annex XI 3.2. (a)-(c) not available	8	2.5
	"Complex"	In-depth evaluation required	5	1.6
	"Complex"	Justification cannot be assigned to the specific criteria of REACH Annex XI 3.2. (a)-(c)	4	0.9
Reference unclear	"Non-compliant"	Waiving justification obviously insufficient or false	51	15.8
	"Complex"	In-depth evaluation required (REACH Annexes VII to X introduction, last passage could apply)	26	8.1
Total			**323**	**100**

*further assessed in the refined check

3.2.3.4 Refined check of waiving/adaptation records

Weight of evidence

The refined check on Weight of evidence-approaches comprised 61 waiving/adaptation records (Figure 3-15). Thus, WoE also belongs to the more frequently applied waiving/adaptation categories. Table 3-10 shows the reasons for the respective decisions. Out of the 61 WoE approaches, 22 were "compliant". In contrast to repeated dose toxicity, for instance, the majority of these were obviously sufficient (17 records) to draw a conclusion on this endpoint. In five WoE approaches, different types of studies were available (e.g. other guidelines than OECD TG 414 (OECD, 2001), studies with non-standard test methods), but a single study used in the approach was obviously sufficient on a stand-alone basis (OECD TG 414 (OECD, 2001), results consistent with other studies).

However, the same amount (22 records) of WoE approaches was concluded "non-compliant". In the majority (n = 9) of WoE-records, read-across data was formally "non-compliant". Less often, WoE approaches had to be concluded "non-compliant" because (Q)SAR data were formally "non-compliant" (n = 5), a WoE summary not available (n = 4), or only one piece of information was available, which was not sufficient on a stand-alone basis (n = 4).

The remaining 17 WoE approaches remained "complex" because they were entirely based on non-standard studies or the provided justifications needed in-depth evaluation.

Table 3-10: Developmental toxicity – refined check: reasons for conclusions on waiving/adaptation records

Adaptation category	Conclusion category	Reason	n records	%
Weight of evidence	"Compliant"	WoE obviously sufficient	17	27.9
	"Compliant"	One piece of evidence is obviously sufficient on a stand-alone basis	5	8.2
	"Non-compliant"	WoE summary not available	4	6.6
	"Non-compliant"	Only one piece of information which is not sufficient on a stand-alone basis	4	6.6
	"Non-compliant"	Read-across data is formally "non-compliant"	9	14.7
	"Non-compliant"	(Q)SAR data is formally "non-compliant"	5	8.2
	"Complex"	WoE entirely based on non-standard test methods	6	9.8
	"Complex"	In-depth evaluation required	11	18.0
Total		-	**61**	**100**

3.2.4 Reproductive toxicity

According to ECHA's endpoint specific guidance (ECHA, 2017a), reproductive toxicity comprise every effect of a substance that has the potential to interfere with male and female sexual function and fertility.

The standard testing regime according to REACH Annexes VII to IX comprises

- a screening study for reproductive/developmental toxicity (REACH Annex VIII 8.7.1.),
- an extended one-generation reproductive toxicity study (EOGRTS, REACH Annex IX 8.7.3)
  - only required if available repeated dose toxicity or screening studies indicate adverse effects or other concerns related to reproductive toxicity (REACH Annex IX 8.7.3 column 1)

As for the endpoint developmental toxicity, the screening study does not have to be conducted if a prenatal developmental toxicity study according to OECD TG 414 (OECD, 2001) or an EOGRTS/two-generation reproductive toxicity study (OECD TG 443 (OECD, 2012e))/OECD TG 416 (OECD, 1983) is available (REACH Annex VIII 8.7.1 column 2).

The EOGRTS has to be conducted only if there are triggers in the available repeated dose toxicity or screening studies. These triggers include, but are not limited to reduced mating, fertility or litter size, effects on sperm parameters or oestrous cycle, increased incidence of abortions, changes in anogenital distance and many more.

Within the screening process, the endpoint reproductive toxicity was evaluated in 2053 dossiers. Further assessment of the endpoint reproductive toxicity within the formal and refined check, however, was only performed in a representative subset of 500 dossiers.

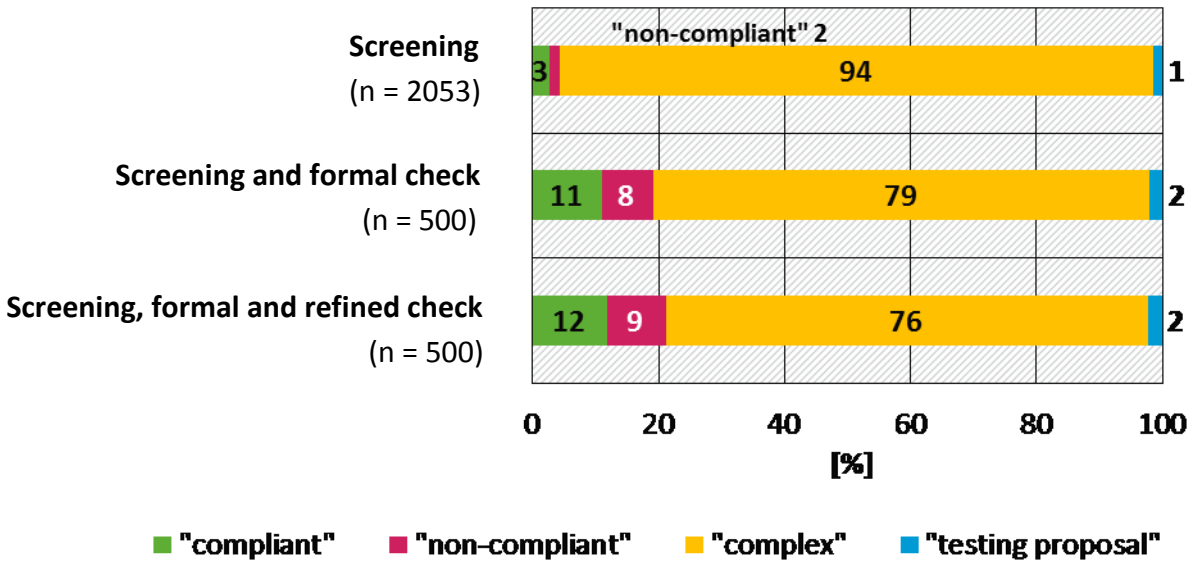
3.2.4.1 Overall endpoint conclusion

Figure 3-16 illustrates the endpoint conclusions after screening for the total number of 2053 dossiers under evaluation in comparison to the aggregated results after screening, formal and refined check for the subset of 500 dossiers.

The results after the screening differ considerably from the other endpoints. Only 2.8 % of the endpoint entries were assessed “compliant” after the screening. 94.3 % remained “complex” and 1.4 % provided a testing proposal for OECD TG 416 (OECD, 1983)/OECD TG 443 (OECD, 2012e). 1.5 % of the endpoint entries for reproductive toxicity contained neither a screening study (OECD TG 421/422 or “compliant” waiving/adaptation) nor a higher tier study according to OECD TG 416/OECD TG 443. These dossiers were concluded “non-compliant” for this endpoint.

After the formal check, the “compliant”-rate increased about 4 times to 11.0 % (+ 8.2 %-points). The rate of “non-compliant” decisions increased by 6.7 %-points to 8.2 % due to inadequate waiving/adaptation approaches. The refined check improved the “compliant”- and “non-compliant”-rate only by 1.0 and 1.0 %-points, the majority of “complex” cases remained “complex” as final evaluation (76.4 %).

Figure 3-16: Reproductive toxicity – endpoint conclusions (n = total number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.2.4.2 Screening of data availability

Table 3-11 shows all reasons for the endpoint decisions after the screening. From 2053 endpoint entries, 57 could be concluded “compliant”, mainly because an OECD TG 416 (OECD, 1983)/OECD TG 443 (OECD, 2012e) was available (47 endpoint entries), the remaining endpoint entries were concluded “compliant” because the corresponding substances were classified as genotoxic carcinogens or reproductive toxicants.

From 2053 dossiers, 31 were concluded “non-compliant” for reproductive toxicity because neither “compliant” information for a screening study (OECD TG 421/422, standard data requirement from Annex VIII) nor a test according to OECD TG 416 or 443 or respective waiving/adaptation was available.

The majority of the evaluated endpoint entries (1473 endpoint entries, 71.9 %) were concluded “complex” for this endpoint after the screening because they contained waiving/adaptations for the higher tier study. For the subset of 500 dossiers, the waiving/adaptations (163 endpoint entries) were further evaluated in the formal or refined check.

395 of the 2053 endpoint entries contained adequate information on the screening study (i.e. study or “compliant” waiving/adaptation for OECD TG 421/422), but no higher tier study. For these endpoint entries an in-depth evaluation regarding the conduct of an OECD TG 416/443 study would be required, i.e. an examination of triggers in repeated dose toxicity or screening studies. Since it was not foreseen to evaluate these triggers within the scope of the project, these endpoint entries remained “complex” as final conclusion. 68 endpoint entries additionally remain “complex” because the available tests on reproductive toxicity were based on non-standard methods.

In 2053 endpoint entries 29 (1.4 %) testing proposals for the standard test for reproductive toxicity have been submitted. The number initially sounds low compared to the other endpoints; however, the requirement of this test in this tonnage band is indeterminate, unless the available repeated dose toxicity /screening studies are evaluated.

Table 3-11: Reproductive toxicity – screening: reasons for endpoint conclusions

Conclusion category (n = dossiers (subset))	Question No. (decision tree)	Reason	n dossiers (subset)	% (subset)
"Compliant" n = 57 (11)	1	CLP classified (1)	5 (1)	0.2 (0.2)
	2	CLP classified (2)	5 (1)	0.2 (0.2)
	4	Test based on adequate standard method	47 (9)	2.3 (1.8)
"Non-compliant" n = 31 (26)		Standard test and waiving/adaptation for OECD TG 421/422 and OECD TG 416/443 is not available	31 (26)	1.5 (5.2)
"Complex" n = 1970 (481)	5, 6	Waiving/adaptation of standard information	1473 (163*)	71.9 (32.6)
	5, 6	Information on OECD TG 421/422 available, in-depth evaluation regarding conduct of OECD TG 416/443 required	395 (273)	19.3 (54.6)
	4	Test based on non-standard method	68 (16)	3.3 (3.2)
"Testing Proposal" n = 26 (8)		Testing proposal is available	29 (11)	1.4 (2.2)
Total		-	**2053** (500)	**100**

(1) classified as a genotoxic carcinogen (mutagen category 2, H341 and carcinogen category 1A or 1B, H350) or germ cell mutagen (mutagen category 1A or 1B, H340) according to the CLP Regulation

(2) classified as a reproductive toxicant (category 1A or 1B, H360) according to the CLP Regulation affecting fertility (H360F) and the unborn child (H360D) = H360FD and NOAEL is available

* further assessed within formal- and/or refined check

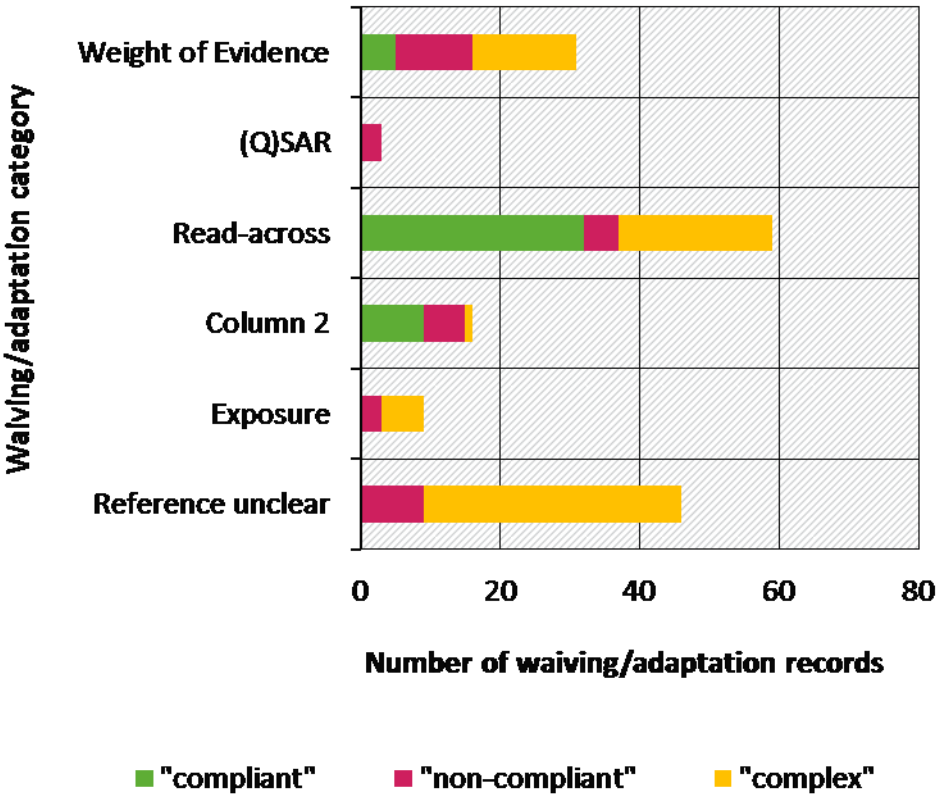
There is a variation in the distribution of the different reasons for "complex" decisions between the subset of 500 dossiers (number in brackets) and the original number of 2053 dossiers (Table 3-11). From the 2053 endpoint entries, 72 % contain a waiving/adaptation, for the subset it is only 33 %. In the formal check, waiving categories could only be defined according the content of the justification (column 2, exposure, reference unclear). However, the initial screening of study information did not include the justifications, only the information, that there is a waiving. In the formal check, which was only performed for the subset, some of the evaluated justifications contained no actual waiving, but information on trigger in different studies. These justifications were not counted as waiving but set "complex" retrospectively in the screening (reason: "Information on OECD TG 421/422 available, in-depth evaluation regarding conduct of OECD TG 416/443 required", Table 3-11).

3.2.4.3 Formal check of waiving/adaptation records

For the subset of 500 dossiers, 173 records in 163 endpoint entries entered the formal check. 9 waiving/adaptation records were not examined because they included an in-depth evaluation of trigger, they were exempted from the evaluation, counted as "complex" as final evaluation and are not considered in Figure 3-17 and Table 3-12. As mentioned before, WoE approaches (31 records) were evaluated in the refined check.

Consequently, 133 waiving adaptation records (164 waiving/adaptations records less 31 WoE-records) were actually evaluated in the formal check. The formal check comprised (Q)SAR, read-across, endpoint specific waiving according to column 2, exposure related waiving and waiving without clear reference to general or endpoint specific rules (reference unclear). As for the preceding human health endpoints, read-across or grouping approaches (n = 59) were among the most abundant waiving/adaptation categories that were evaluated for this endpoint. Records lacking a clear reference to the endpoint specific or general rules for data waiving according to REACH Annexes VII-IX and XI (reference unclear, n = 46) and data waiving with reference to the endpoint specific rules of REACH Annex VIII 8.4. column 2 (n = 16) were also frequent. Exposure based waiving and (Q)SAR were used very rarely (9 and 1 records) (Figure 3-17). For read-across and waiving according to column 2 more than half of the waiving/adaptation records could be concluded formally "compliant", for the other categories in the formal check, however, "non-compliant" and "complex" decisions prevail.

Figure 3-17: Reproductive toxicity – formal and refined check: conclusions on waiving/adaptation records (n = 164)



Own illustration, German Federal Institute for Risk Assessment (BfR)

Table 3-12 includes the reasons for the endpoint conclusions in the formal check, specified for each waiving/adaptation category. In the following, the most frequently assessed categories and the reasons for their conclusions are specified.

Read-across

From 59 read-across records, 32 met the formal criteria described in the methods (2.5.2) and were concluded "compliant". Only 5 read-across approaches had to be assessed "non-compliant" because a justification was not available or not sufficient. In 22 cases, the read-across approach included a non-guideline source study and was concluded "complex".

Endpoint specific data waiving (column 2)

16 of the waiving/adaptations that were evaluated in the formal check referred to column 2 of REACH Annex IX 8.7.

For the endpoint reproductive toxicity, waiving according to column 2 is similar to the endpoint developmental toxicity. Three of the waiving options refer to the classification of the substance and were already documented and concluded in the screening (Table 3-11). The other waiving possibility comprises three criteria: the substance is of low toxicological activity (regarding all endpoints) and no systemic absorption occurs via relevant routes of exposure and there is no significant human exposure. Again, the justification to waive the standard test according to column 2 requires a detailed explanation whether and how all three criteria apply. 9 justifications met these requirements and could be concluded "compliant". In 6 records the justifications were "non-compliant" because one or two criteria were not addressed. As for developmental toxicity, registrants mostly failed to address human exposure and/or systemic absorption.

Data waiving without reference to REACH Annexes (reference unclear)

9 waiving/adaptation records of this category were concluded "non-compliant" because the waiving justification was obviously insufficient or false. The remaining 37 records of this category needed in-depth evaluation and thus remained "complex".

Table 3-12: Reproductive toxicity – formal check: reasons for conclusions on waiving/adaptation records

Waiving/ adaptation category	Conclusion category	Reason	n record	%
Weight of evidence		Refined check (see section 3.2.4.4)	31*	18.9
(Q)SAR	"Non-compliant"	(Q)SAR not adequately documented	3	1.8
Read-across	"Compliant"	Read-across based on standard method and justification available	32	19.5
	"Non-compliant"	Read-across justification not available/not sufficient	5	3.1
	"Complex"	Read-across not based on standard method	22	13.4
Column 2	"Compliant"	All criteria adequately addressed	9	5.5
	"Non-compliant"	Not all criteria addressed	6	3.7
	"Complex"	In-depth evaluation required	1	0.6
Exposure	"Non-compliant"	Exposure assessment not available	3	1.8
	"Complex"	In-depth evaluation required	3	1.8
	"Complex"	Justification cannot be assigned to the specific criteria of REACH Annex XI 3.2. (a)-(c)	3	1.8
Reference unclear	"Non-compliant"	Waiving justification obviously insufficient or false	9	5.5
	"Complex"	In-depth evaluation required (REACH Annexes VII to X introduction, last passage could apply)	37	22.6
Total			**164**	**100.0**

*further assessed in the refined check

3.2.4.4 Refined check of waiving/adaptation records

Weight of evidence

Also in the endpoint reproductive toxicity weight of evidence approaches were applied frequently. As mentioned before, weight of evidence records were evaluated in the refined check. For reproductive toxicity, 31 WoE approaches were identified and assessed. The distribution of decisions for this waiving/adaptation category is shown in Figure 3-17 and the reasons for the decisions are compiled in Table 3-13. Only five of the approaches were "compliant". They contained a study which was sufficient on a stand-alone basis because it was conducted according to the required test guideline (OECD TG 416 (OECD, 1983)/OECD TG 433 (OECD, 2012e)) and the results were consistent to the

results of the other studies in this approach. 15 approaches were concluded "complex", because they either required in-depth evaluation (3 records) or they were entirely based on studies with non-standard test methods (12 records).

11 of the 31 WoE approaches were assessed "non-compliant", mostly, because they contained "non-compliant" read-across or (Q)SAR data or the summary was not available.

Table 3-13: Reproductive toxicity – refined check: reasons for conclusions on waiving/adaptation records

Adaptation category	Conclusion category	Reason	n records	%
Weight of evidence	"Compliant"	One piece of evidence is obviously sufficient on a stand-alone basis	5	16.1
	"Non-compliant"	WoE summary not available	3	9.7
	"Non-compliant"	Only one piece of information which is not sufficient on a stand-alone basis	1	3.2
	"Non-compliant"	Read-across data is formally "non-compliant"	3	9.7
	"Non-compliant"	(Q)SAR data is formally "non-compliant"	4	12.9
	"Complex"	WoE entirely based on non-standard test methods	12	38.7
	"Complex"	In-depth evaluation required	3	9.7
Total		-	**31**	**100**

3.3 Environmental endpoints

3.3.1 Biotic degradation

The endpoint biotic degradation is essential for predicting environmental fate of the substance and for identifying PBT or vPvB substances. Therefore, missing information on biotic degradation can significantly impact the outcome of CSA with regard to both environmental and human health associated protection goals.

The standard testing regime according to REACH Annexes VII to IX includes

- a screening test on ready biodegradability (REACH Annex VII 9.2.1.1.),
- a simulation test on ultimate degradation in surface water (REACH Annex IX 9.2.1.2.),
- a simulation test on ultimate degradation in soil (REACH Annex IX 9.2.1.3.),
- a simulation test on ultimate degradation in sediment (REACH Annex IX 9.2.1.4.),
- and the identification of degradation products (REACH Annex IX 9.2.3.).

Column 2 of REACH Annexes VII to IX also provides endpoint specific rules that can be applied by registrants to justify data waiving. For instance, a screening test on ready biodegradability is generally not required for inorganic substances, since biotic degradation processes are only considered relevant to organic compounds. Moreover, simulation testing and identification of degradation products is generally not required for readily biodegradable substances, because a rapid mineralisation is expected upon release of the substance.

Within the screening process, the endpoint biotic degradation was evaluated in 2053 dossiers. Further assessment of the endpoint biotic degradation within the formal and refined check, however, was only performed in a representative subset of 500 dossiers.

3.3.1.1 Overall endpoint conclusion

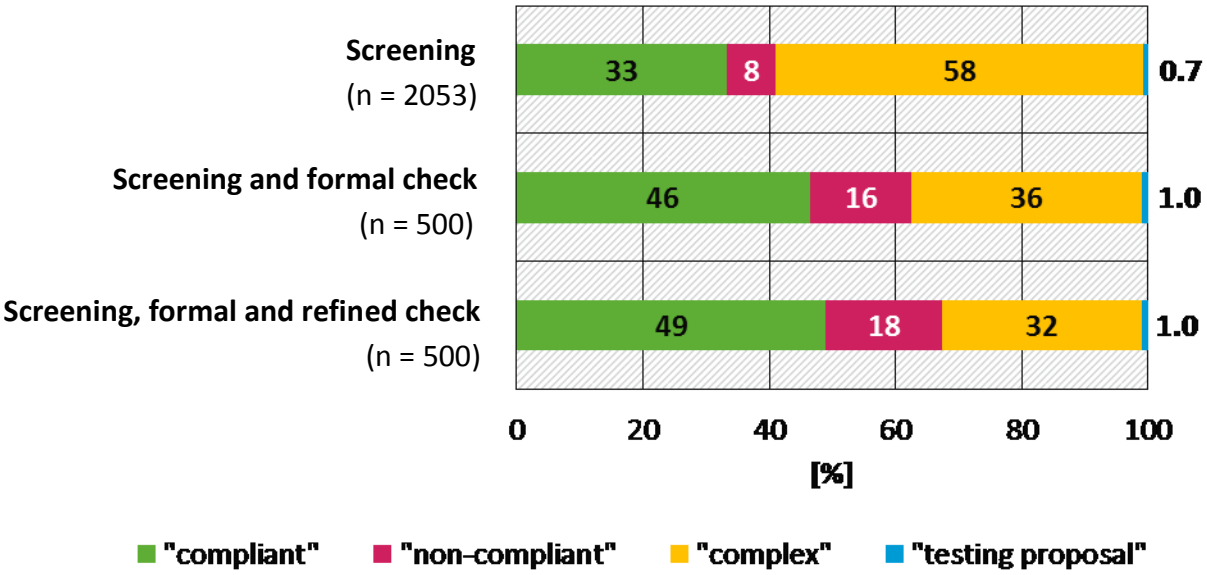
Figure 3-18 shows the endpoint conclusions after screening for the total number of dossiers under evaluation (n = 2053) in comparison to the aggregated conclusion rates after formal and refined check for a representative subset of 500 dossiers.

The screening resulted in 33.3 % “compliant”, 7.6 % “non-compliant” and 58.4 % “complex” endpoint conclusions. Testing proposals for Annex IX information requirements were identified in 0.7 % of assessed endpoint entries.

The subsequent formal check of data waiving/adaptation approaches resulted in an increase of the conclusion rate by 21.8 %-points. The aggregated endpoint conclusion after screening and formal check was “compliant” for 46.4 % of endpoint entries and “non-compliant” for 16.2 % of endpoint entries.

The refined check for biotic degradation comprised weight of evidence approaches and data waiving with reference to CSA (Annex B.1.3). These additional assessments led to a further reduction of “complex” endpoint conclusions by 4.8 %-points. The aggregated endpoint conclusions after screening, formal check and refined check consisted of 49 % “compliant”, 18.4 % “non-compliant” and 31.6 % “complex” cases.

Figure 3-18: Biotic degradation – endpoint conclusions (n = total number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.3.1.2 Screening of data availability

Table 3-14 summarises all endpoint conclusions for biotic degradation after the screening of data availability in 2053 registration dossiers. The available information on biotic degradation was assessed as "compliant" in 684 dossiers, as "non-compliant" in 157 dossiers and as "complex" in 1198 dossiers. Testing proposals for Annex IX information requirements were identified in 14 endpoint entries.

The endpoint conclusion "compliant" was mainly attributed to the registration of an inorganic substance (236 endpoint entries) or the availability of a standard screening test according to OECD TG 301 (OECD, 1992b) which demonstrated that the substance is readily biodegradable (432 endpoint entries). Remarkably, only 9 endpoint entries were assessed as "compliant" on the basis of available Annex IX standard information (i.e. simulation test according to OECD TG 307, 308 or 309 and identification of degradation products). Given that 926 endpoint entries concluded that the registered substance is not readily biodegradable, the low availability of Annex IX standard information raises the question whether biotic degradation products have sufficiently been addressed in the CSA of the respective substances.

The largest share of "non-compliant" endpoint conclusions was caused by a missing waiving justification for a simulation test (121 endpoint entries). For instance, data waiving was often justified either for simulation testing in surface water or for simulation testing in sediment. However, in the absence of suitable data from simulation testing, a waiving justification is usually required for both compartments. The second largest share of "non-compliant" endpoint conclusions resulted from missing information on ready biodegradability (36 endpoint entries). This also included 25 studies with inconsistent information on test material identity.

The majority of evaluated endpoint entries remained "complex" after screening. This was mainly attributed to the waiving/adaptation of simulation testing (764 endpoint entries). 423 endpoint entries were not concluded either because the ready biodegradability testing was omitted (378 endpoint entries) or because the suitability of applied methods for screening biodegradation testing was not evident (45 endpoint entries). For instance, the method according to OECD TG 301 B (OECD, 1992b) was frequently applied to substances with an estimated Henry's law constant (K_H) > 10 Pa m^3 mol^{-1}, even though this method should not be used for volatile substances (OECD, 1992b). These cases were evaluated as "complex" because an in-depth analysis of additional data would have been needed to assess the validity of the study.

Table 3-14: Biotic degradation – screening: reasons for endpoint conclusions

Conclusion category (n = dossiers (subset))	Question No. (decision tree)	Reason	n dossiers (subset)	% (subset)
"Compliant" n = 684 (170)	1	Substance is inorganic	236 (62)	11.5 (12.4)
	4	Screening test is based on adequate standard method	432 (103)	21.0 (20.6)
	8	Waiving of simulation testing is justified according to Annex IX 9.2.1.2. column 2 (Sw < 1 mg/L)	7 (1)	0.3 (0.2)
	11	Degradation products were identified	9 (4)	0.4 (0.8)
"Complex" n = 1198 (287)	4	Waiving/adaptation of screening information or suitability of test method is unclear	423 (106*)	20.6 (21.6)
	8	Waiving/adaptation of simulation testing without reference to Annex IX 9.2.1.2. column 2 (Sw < 1 mg/L)	764 (179*)	37.2 (35.8)
	10	Simulation test based on non-standard method	11 (2)	0.5 (0.4)
"Non-compliant" n = 157 (38)	2	Screening information on ready biodegradability is not available	36 (8)	1.8 (1.6)
	7	Waiving/adaptation for simulation testing is not available	121 (30)	5.9 (1.6)
	11	Degradation products were not identified	0 (0)	0 (0)
"Testing Proposal" n = 14 (5)	2	Testing proposal is available	14 (5)	0.7 (1)
Total		-	**2053** (500)	**100**

* further assessed within formal- and/or refined check (except for 18 dossiers)

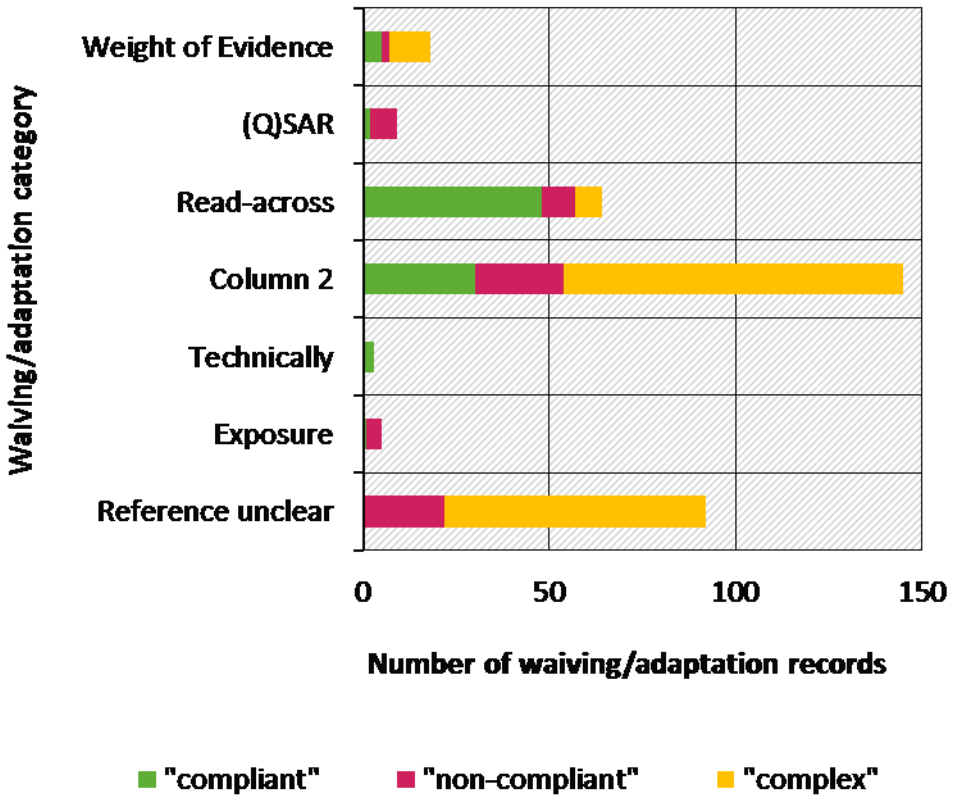
3.3.1.3 Formal check of waiving/adaptation records

The subset of 500 dossiers included 267 endpoint entries and 336 waiving/adaptation records for the endpoint biotic degradation that were subject of the formal and/or refined check of data waiving/adaptation.

Figure 3-19 shows the total number of assessed waiving/adaptation records and the distribution of decisions for each waiving/adaptation category after formal check and refined check. Data waiving with reference to the endpoint specific rules of REACH Annexes VII and IX (column 2) was the most influential waiving/adaptation category, followed by read-across, WoE, and (Q)SAR. Moreover, a large number of waiving records did not provide a clear reference to the endpoint specific or general rules for data waiving according to REACH Annexes VII-IX and XI (Reference unclear).

Table 3-15 summarises decisions and underlying reasons on waiving/adaptation records and their relative contribution to the total number of decisions in the formal check.

Figure 3-19: Biotic degradation – formal and refined check: conclusions on waiving/adaptation records (n = 336)



Own illustration, German Federal Institute for Risk Assessment (BfR)

It is to be noted that the formal check was limited to waiving/adaptation records that impeded a final endpoint conclusion in the screening step. Consequently, the number of assessed waiving/adaptation records differs from the actual number of submitted waiving/adaptation records.

Read-across

Out of 64 assessed read-across approaches, 48 had a plausible justification of structural similarities and referenced a source study that was based on an accepted guideline. This was contrasted by nine "non-compliant" cases that did not provide a plausible justification of structural similarities or referenced a source study in the endpoint summary that was not adequately documented as (robust) study summary. In seven cases, the read-across approach included a non-guideline source study and was concluded "complex".

Endpoint specific data waiving (column 2)

The distribution of endpoint specific waiving justifications (column 2) in the formal check should be interpreted with caution, since the majority of endpoint specific waiving records was already conclusively assessed in the screening step (e.g. inorganic or readily biodegradable substances).

Out of 145 endpoint specific waiving justifications that were assessed in the formal check, 118 referred to the outcome of the CSA (e.g. "CSA does not indicate the need to investigate further the degradation of the substance"). These waiving records remained without conclusion in the formal check and were further assessed in the refined check.

Exposure considerations form the second largest subset of endpoint specific waiving justifications (e.g. "direct and indirect exposure of soil is unlikely"). Within this group, 9 out of 27 assessed records were concluded "non-compliant" because the waiving justification was not supported by a thorough exposure assessment.

Data waiving without reference to REACH Annexes (reference unclear)

A large share of waiving records that could not be assigned to the endpoint specific or general rules of REACH Annexes VII-IX and XI (reference unclear) was assessed "non-compliant" due to an obviously insufficient justification (22 records). The remaining 70 records in this category mainly referred to the results of screening or inherent biodegradation studies in order to justify waiving of simulation testing. However, since in-depth analyses would be required to conclude on these cases, the assessment was concluded with a "complex" decision.

Table 3-15: Biotic degradation – formal check: reasons for conclusions on waiving/adaptation records

Waiving/ adaptation category	Conclusion category	Reason	n record	%
Weight of evidence		Refined check (see section 3.3.1.4)	18*	5.4
(Q)SAR	"Compliant"	Model is scientifically validated and the substance falls within the applicability domain	2	0.6
	"Non-compliant"	(Q)SAR not adequately documented	7	2.1
Read-across	"Compliant"	Read-across based on standard method and justification available	48	14.3
	"Non-compliant"	Read-across justification not available/not sufficient	8	2.4
	"Non-compliant"	ESR or key study not available	1	0.3
	"Complex"	Read-across based on non-standard method	7	2.1
Column 2	"Compliant"	Exposure scenarios available	18	5.4
	"Non-compliant"	Exposure scenarios not available	9	2.7
		Refined check (see section 3.3.1.4) - Justification according to REACH Annex IX 9.2. column 2 (CSA)	118*	35.1
Technically	"Compliant"	Justification according to Reach Annex XI 2. first sentence	3	0.9
Exposure	"Compliant"	Justification according to REACH Annex XI 3.2. (a)-(c)	1	0.3
	"Non-compliant"	Justification according to REACH Annex XI 3.2. (a)-(c) not available	3	0.9
	"Non-compliant"	Exposure assessment not available	1	0.3
Reference unclear	"Non-compliant"	Waiving justification obviously insufficient or false	22	6.5
	"Complex"	In-depth evaluation required (REACH Annexes VII to IX introduction, last passage could apply)	70	20.8
Total			**336**	**100**

*further evaluated in the refined check

3.3.1.4 Refined check of waiving/adaptation records

The refined check for biotic degradation comprised 136 records in 107 endpoint entries. Table 3-16 summarises all decisions on waiving/adaptation records that were obtained from this refined check.

Weight of evidence

In 5 out of 18 assessed WoE approaches, the evidence was sufficient to draw a conclusion on the ready biodegradability of the substance ("compliant"). In two cases, WoE was assessed as "non-compliant" because (Q)SAR predictions without adequate documentation had been included. WoE remained "complex" after refined check in 11 out of 18 assessed WoE approaches. This was mainly attributed to a submission of non-guideline (read-across) studies or the incomplete reporting of study design. In two cases, the registrant provided more than ten independent pieces of information and therefore content-related analysis of the entire information was not possible within the project.

Endpoint specific data waiving – reference to CSA

Waiving of simulation testing with reference to the outcome of the CSA is only applicable if the available screening information is sufficient to demonstrate the absence of a significant risk and to conclude on PBT/vPvB properties of the substance.

In total, 118 records in 89 endpoint entries referred to the CSA in order to justify waiving of simulation testing.

In 12 out of 118 assessed records, the waiving approach was "compliant" because the risk characterisation did not indicate a significant risk and additional proof for "*not P/vP*" was provided (e.g. a positive enhanced ready biodegradation test).

In 14 out of 118 cases, the waiving approach was assessed "non-compliant" because further simulation testing was required to conclude on persistent, bioaccumulative, toxic/very persistent, very bioaccumulative properties (PBT/vPvB). This applied, for instance, if the available information provided clear indications for potential P/vP and (potential) B/vB properties. There was also one "non-compliant" case, in which the ratio of the predicted environmental concentration and predicted no effect concentration was greater than one (PEC/PNEC > 1). Hence, the registrant apparently failed to demonstrate the safe use of his substance.

The vast majority of assessed waiving approaches (91 records) still remained "complex" after the refined check, mainly because the substance fulfilled the criteria of "*potentially P/vP*" but was assessed as "*not B*" by the registrant. In these cases, further analyses would have been required to decide whether additional information on biotic degradation needs to be generated. For instance, the PBT/vPvB assessment should also address degradation products if the available information indicates that relevant degradation products are formed (ECHA, 2017e). However, to assess whether this obligation has been fulfilled in-depth analyses would have been needed that could not be realised to the required extent.

Table 3-16: Biotic degradation – refined check: reasons for conclusions on waiving/adaptation records

Adaptation Category	Decision	Reason	N	%
Weight of evidence	"Compliant"	WoE is obviously sufficient	5	3.7
	"Non-compliant"	(Q)SAR data is formally "non-compliant"	2	1.5
	"Complex"	In-depth evaluation required	11	8.1
Column 2 - CSA	"Compliant"	Substance is "*not P/vP*"	12	8.8
	"Non-compliant"	Further simulation testing required to conclude on PBT/vPvB	14	10.3
	"Non-compliant"	PEC/PNEC is > 1	1	0.7
	"Complex"	In-depth evaluation of CSA required	91	66.9
Total			**136**	**100**

3.3.2 Abiotic Degradation

The endpoint abiotic degradation describes degradation processes other than biodegradation such as hydrolysis, oxidation and photolysis (ECHA, 2017b). This information is required to predict primary degradation of the substance in the environment and to determine whether relevant transformation products are formed.

The standard testing regime according to REACH Annexes VII to IX includes a study of

- hydrolysis as a function of pH (REACH Annex VIII 9.2.2.1.).

According to the specific rules for adaptation of the standard testing regime, the study does not need to be conducted if the substance is readily biodegradable or highly insoluble in water.

Within the screening process, the endpoint abiotic degradation was evaluated in 2053 dossiers. Further assessment of the endpoint abiotic degradation within the formal and refined check, however, was only performed in a representative subset of 500 dossiers.

3.3.2.1 Overall endpoint conclusion

Figure 3-20 shows the screening-level distribution of endpoint conclusions for the total number of dossiers under evaluation (n = 2053) in comparison to the aggregated conclusion rates after formal and refined check for a representative subset of 500 dossiers.

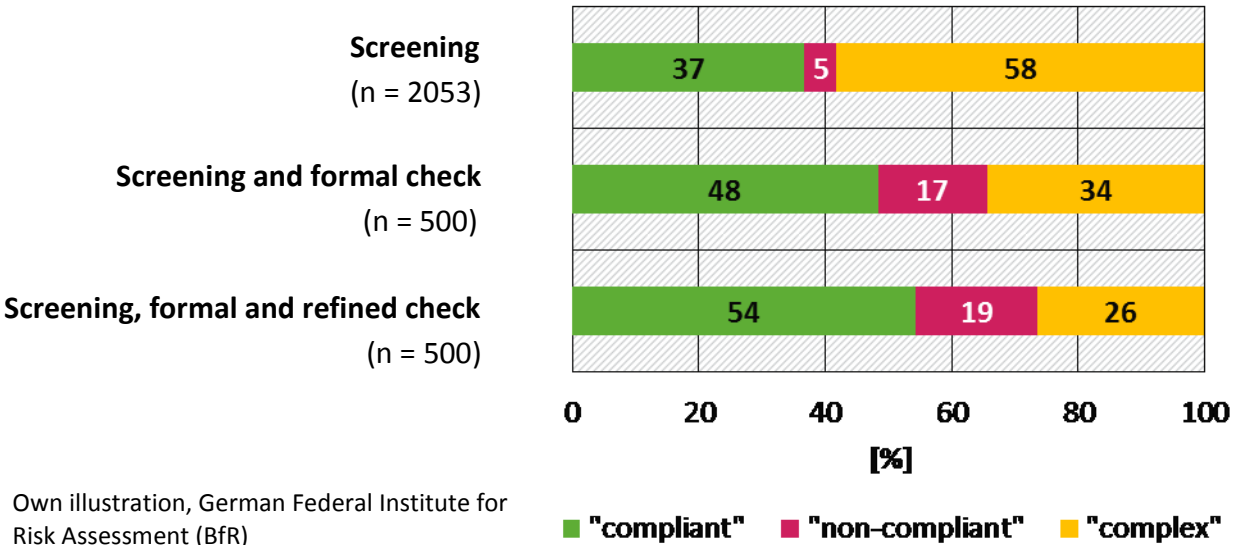
The screening resulted in 36.7 % “compliant”, 5.1 % “non-compliant” and 58.2 % “complex” endpoint conclusions. Testing proposals were not available since these are generally not admissible for Annex VII and VIII endpoints.

The subsequent formal check of data waiving/adaptation approaches resulted in a significant increase of the conclusion rate (23.8 %-points). The aggregated endpoint conclusion after screening and formal check was “compliant” for 48.4 % of endpoint entries and “non-compliant” for 17.2 % of endpoint entries.

The refined check of abiotic degradation comprised weight of evidence approaches and data waiving with reference to the chemical structure. This refined assessment led to a further reduction of “complex” endpoint entries by 8.0 %-points. The aggregated endpoint conclusion after screening, formal check and refined check consisted of 54.4 % “compliant”, 19.4 % “non-compliant” and 26.4 % “complex” cases.

Figure 3-21 shows the total number of assessed waiving/adaptation records and the distribution of decisions for each waiving/adaptation category after formal and refined check. Data waiving with reference to the endpoint specific rules of REACH Annexes VII and IX (column 2) was the most influential waiving/adaptation category, followed by read-across approaches and technical waiving justifications (technically). A large number of waiving records did not provide a clear reference to the endpoint specific or general rules for data waiving according to REACH Annexes VII-IX and XI (Reference unclear).

Figure 3-20: Abiotic degradation – endpoint conclusions (n = total number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.3.2.2 Screening of data availability

Table 3-17 summarises all endpoint conclusions for abiotic degradation after the screening of data availability. The available information on abiotic degradation was assessed as "compliant" in 754 dossiers, as "non-compliant" in 104 dossiers and as "complex" in 1195 dossiers.

The endpoint conclusion "compliant" was mainly attributed to data waiving in accordance with the endpoint specific rules for hydrolysis testing (587 endpoint entries). This meant that the registrant provided plausible evidence that the substance is readily biodegradable and/or highly insoluble in water. Another 167 endpoint entries were assessed as "compliant" on the basis of experimental data either from a hydrolysis pre-test (151 endpoint entries) or from a main hydrolysis test (16 endpoint entries).

The largest share of "non-compliant" endpoint conclusions was attributed to shortcomings in the execution or reporting of experimental studies. In 37 cases, a main hydrolysis test was available for all relevant pH values and temperatures but the registrant failed to provide information on degradation products. In 25 cases, the provided data did not cover all relevant pH values and temperatures. In 42 cases, neither experimental data nor any other acceptable information on hydrolysis was provided.

The majority of evaluated endpoint entries remained "complex" after screening. This was mainly attributed to 709 waiving/adaptation approaches that did not refer to ready biodegradability or water solubility. Moreover, in 322 endpoint entries, the registrant justified data waiving with ready biodegradability or low water solubility but the respective data did not allow a clear-cut decision. For instance, many registrants applied read-across to demonstrate that their substance is ready biodegradable. These cases required further assessment of the read-across approach in the formal check to draw a final conclusion. In addition, 131 endpoint entries remained "complex" due to the registration of an adsorptive (log KOW > 4) or inorganic substance.

Table 3-17: Abiotic degradation – screening: reasons for endpoint conclusions

Conclusion category (n = dossiers (subset))	Question No. (decision tree)	Reason	n dossiers (subset)	% (subset)
"Compliant" n = 754 (190)	2	Waiving refers to Annex VIII 9.2.2.1. column 2 (substance is readily biodegradable or Sw < 1 mg/L)	587 (147)	28.6 (29.4)
	5	Extrapolated half-lives from the hydrolysis pre-test are < 1 day or > 1 year at all relevant pH values	151 (40)	7.4 (8.0)
	8	Degradation products (> 10 %) have been identified in standard hydrolysis main test	16 (3)	0.8 (0.6)
"Non-compliant" n = 104 (30)	7	Results from hydrolysis test do not cover the relevant pH values and temperatures	25 (4)	1.2 (0.8)
	8	Degradation products (> 10 %) have not been identified in standard hydrolysis main test	37 (11)	1.8 (2.2)
	9	Results from standard hydrolysis main test are not available	42 (15)	2.0 (3.0)
"Complex" n = 1195 (280)	2	Waiving does not refer to Annex VIII 9.2.2.1. column 2 (substance is readily biodegradable or Sw < 1mg/L)	1031 (248*)	50.2 (49.6)
	3	The substance is adsorptive (log K_{OW} > 4) or inorganic	131 (30)	6.4 (6.0)
	9	Test based on non-standard method	33 (2)	1.6 (0.4)
"Testing proposal" n = 0 (0)	4	Testing proposal is available	0 (0)	0 (0)
Total			**2053** (500)	**100**

*further assessed within formal- and/or refined check

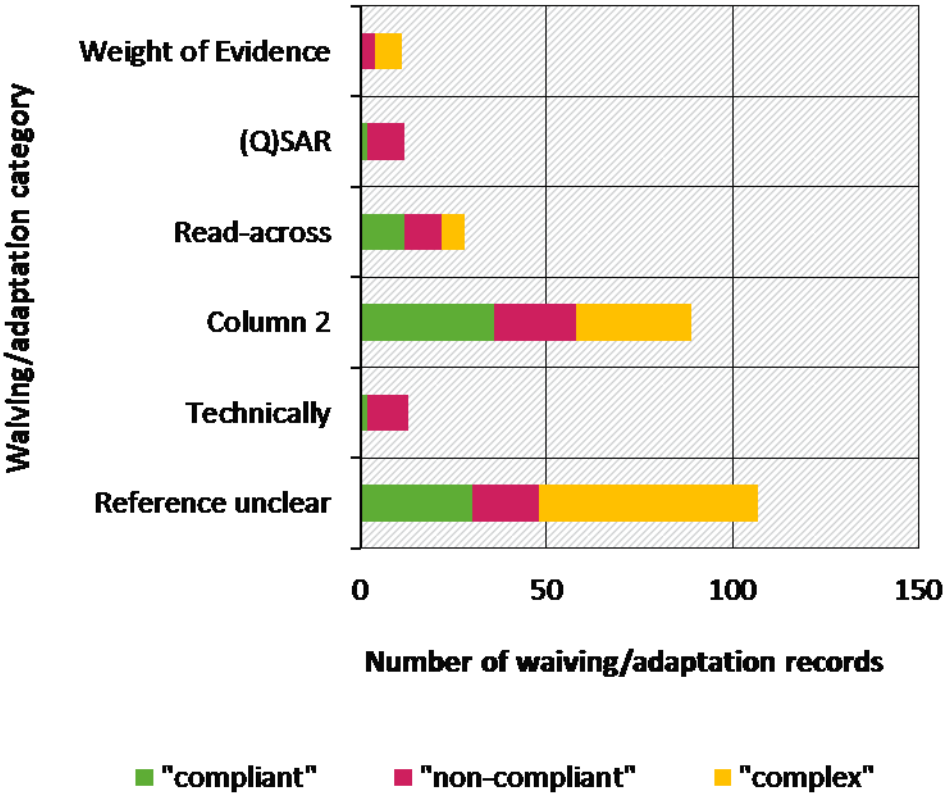
3.3.2.3 Formal check of waiving/adaptation records

The subset of 500 dossiers included 260 entries for the endpoint abiotic degradation that were subject of the formal and/or refined check of data waiving/adaptation. The formal check comprised 249 adaptation/waiving records in 249 endpoint entries. The refined check was conducted on 67 adaptation/waiving records in 67 endpoint entries.

Table 3-18 summarises decisions gained in the formal check and the underlying reasons on waiving/adaptation records and their relative contribution to the total number of decisions in the formal check.

It is to be noted that the formal check was limited to waiving/adaptation records that impeded a final endpoint conclusion in the screening step. Therefore, the number of assessed waiving/adaptation records differs from the actual number of submitted waiving/adaptation records.

Figure 3-21: Abiotic degradation – formal and refined check: conclusions on waiving/adaptation records (n = 260)



Own illustration, German Federal Institute for Risk Assessment (BfR)

Endpoint specific data waiving

The distribution of endpoint specific waiving justifications (column 2) in the formal check should be interpreted with caution, since the majority of endpoint specific waiving records was already

conclusively assessed as “compliant” in the screening step (e.g. readily biodegradable or highly insoluble substances).

Out of 89 endpoint specific waiving justifications that were assessed in the formal check, 72 justifications stated that the substance is ready biodegradable and 17 stated that the substance is highly insoluble. In 36 cases, the waiving approach was assessed “compliant”, because the provided adaptation (e.g. read-across) for ready biodegradability fulfilled the formal requirements. This was contrasted by 22 waiving justifications that were obviously not supported by the submitted data. Moreover, 31 cases remained “complex” because the provided data on biodegradation and water solubility would have required in-depth analysis to draw a conclusion.

Data waiving without reference to REACH Annexes

There was a considerable number of waiving justifications that could not be assigned to the endpoint specific or general rules for adaptation of REACH Annexes VII-IX and XI (reference unclear). Out of 107 waiving/adaptation records without direct or indirect reference to specific waiving options, 12 were assessed “non-compliant” because a waiving justification that is obviously insufficient or false was provided. Another 56 waiving/adaptation records remained without conclusion, because waiving was justified with the absence of hydrolysable functional groups in the chemical structure of the registered substance. These cases were subjected to further assessment in the refined check. The remaining 39 waiving justifications could not be assessed by standardised approaches and the formal check was therefore concluded “complex”.

Table 3-18: Abiotic degradation – formal check: reasons for conclusions on waiving/adaptations records

Waiving/ adaptation category	Conclusion category	Reason	n records	%
Weight of evidence		Refined check (see section 3.3.2.4)	11*	4.2
(Q)SAR	"Compliant"	Model is scientifically validated and the substance falls within the applicability domain	2	0.8
	"Non-compliant"	(Q)SAR not adequately documented	10	3.8
Read-Across	"Compliant"	Read-across based on standard method and justification available	12	4.6
	"Non-compliant"	Read-across justification not available/not sufficient	8	3.1
	"Non-compliant"	ESR or key study not available	2	0.8
	"Complex"	Read-across based on non-standard method	6	2.3
Column 2	"Compliant"	Screening biodegradation test is formally "compliant"	36	13.8
	"Non-compliant"	Screening biodegradation test is formally "non-compliant"	6	2.3
	"Non-compliant"	Sw is not < 1 mg/L	14	5.4
	"Non-compliant"	Screening information on ready biodegradability is not available	2	0.8
	"Complex"	Water solubility unclear	3	1.2
	"Complex"	Ready biodegradability unclear	28	10.8
Technically	"Compliant"	Justification according to Annex XI 2. 2nd sentence	2	0.8
	"Non-compliant"	Justification does not meet requirements of Annex XI 2.	11	4.2
Reference unclear	"Non-compliant"	Waiving justification obviously insufficient or false	12	4.6
	"Complex"	In-depth evaluation required (REACH Annexes VII to X introduction, last passage could apply)	39	15.0
	"Without conclusion"	Waiving with reference to the chemical structure	56*	21.5
Total			**260**	**100**

*further assessed in the refined check

3.3.2.4 Refined check of waiving/adaptation records

The refined check for abiotic degradation comprised 67 records in 67 endpoint entries. Table 3-19 summarises all decisions on waiving/adaptation records that were obtained from this refined check.

Weight of evidence

In four out of 11 assessed WoE approaches the evidence was obviously not sufficient to draw a conclusion ("non-compliant"). Seven WoE approaches remained "complex" in the refined check since further in-depth analyses would have been required.

Waiving with reference to the chemical structure

According to ECHA, structure-activity relationships (SARs) that are based on qualitative information can be used to describe the degradation characteristics of a substance. In this sense, hydrolysis testing was frequently omitted on the ground that the chemical structure of the registered substance does not contain hydrolysable functional groups.

The plausibility of such SAR statements was briefly assessed in the refined check using the HYDROWIN™ v.2.00 module of US EPA's EPI Suite (US EPA, 2012). Out of 56 assessed waiving records, 30 were "compliant", because the software did not detect a hydrolysable functional group. In six cases, the waiving approach was "non-compliant", because a hydrolysable function was detected although the registrant stated that the substance is unlikely to undergo hydrolysis. The remaining waiving records were concluded "complex" either because the substance consisted of multiple constituents or because the software uncovered that insufficient data is currently available to predict hydrolysis of the respective structure type.

Table 3-19: Abiotic degradation – refined check: reasons for conclusions on waiving/adaptation records

Adaptation category	Decision	Reason	N	%
Weight of evidence	"Non-compliant"	Read-across data is formally "non-compliant"	2	3.0
	"Non-compliant"	Test material does not correspond to the registered substance	1	1.5
	"Non-compliant"	(Q)SAR data is formally "non-compliant"	1	1.5
	"Complex"	In-depth evaluation required	7	10.4
Reference unclear – structure	"Compliant"	Hydrolysable function not detected	30	44.8
	"Non-compliant"	Hydrolysable function detected	6	9.0
	"Complex"	UVCB/multi-constituent substance	16	23.9
	"Complex"	Model not applicable (insufficient data)	4	6.0
Total			**67**	**100**

3.3.3 Bioaccumulation

Bioaccumulation testing in aquatic species, preferably fish, enables the prediction of the environmental fate and behaviour of a substance in the environment. The outcome of this endpoint is important to assess the PBT- and/or vPvB-properties of substances. The following standard testing regime is foreseen for substances ≥ 100 tpa:

- Bioaccumulation testing in aquatic species, preferably fish; according to OECD TG 305 (OECD, 2012d) (REACH Annex IX 9.3.2.)

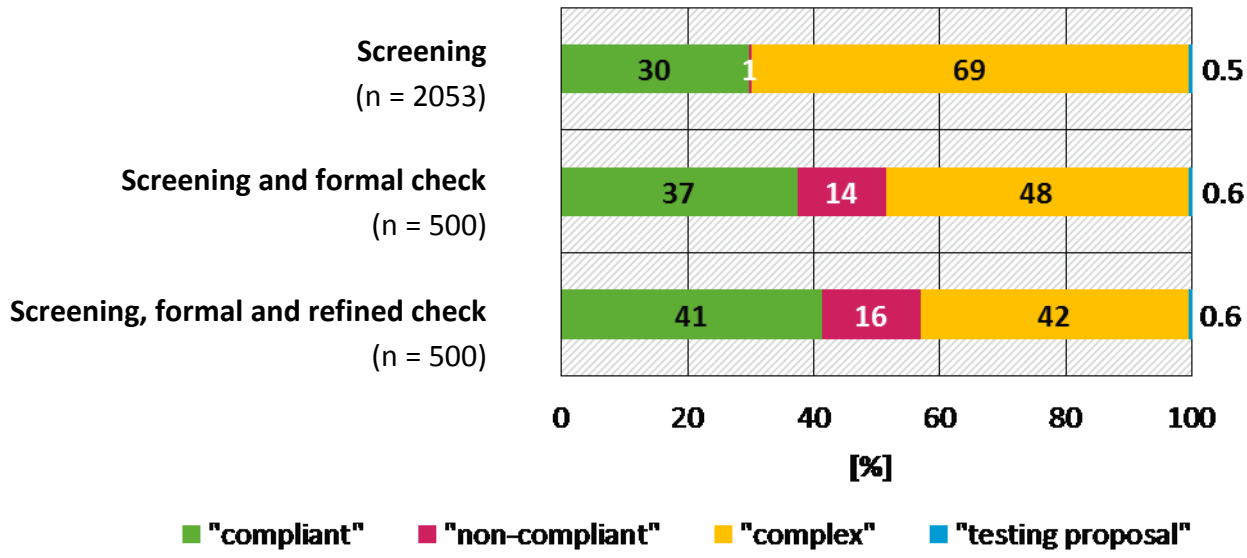
It is possible to omit bioaccumulation testing if: (a) the substance has a low potential for bioaccumulation (for instance log K_{OW} of the substance is ≤ 3) and/or, (b) the substance has a low potential to cross biological membranes or, (c) direct and indirect exposure of the aquatic compartment is unlikely (REACH Annex IX 9.3.2. column 2).

Within the screening process, the endpoint bioaccumulation was evaluated in 2053 dossiers. Further assessment of the endpoint bioaccumulation within the formal and refined check, however, was only performed in a representative subset of 500 dossiers.

3.3.3.1 Overall endpoint conclusion

The overall endpoint conclusions on bioaccumulation after screening and aggregated conclusions after the formal check and refined check are shown in Figure 3-22. Almost one-third of the endpoint entries were “compliant” either by providing the experimental study according to OECD TG 305 or a similar study or a waiving justification referring to a log KOW ≤ 3. Only 0.5 % of the endpoint entries were concluded “non-compliant” because a waiving justification was not available or false (8 endpoint entries, 0.4 %). The endpoint entry was also set “non-compliant” if the available test was not performed according to OECD TG 305 or another accepted method (2 endpoint entries, 0.1 %). The majority of the endpoint entries (69 %) could not be concluded within the screening because a waiving/adaptation was provided (“complex”).

Figure 3-22: Bioaccumulation – endpoint conclusions (n = total number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.3.3.2 Screening of data availability

The screening of the information requirements on the endpoint bioaccumulation was based on the decision tree developed in the first project (Springer et al., 2015). The decision tree and its questions can be found in Annex B.3. The reasons for the endpoint conclusions are given in Table 3-20 and are deduced from the respective answers of the questions in the decision tree.

The main assessment criteria for the endpoint bioaccumulation were the availability of bioaccumulation studies or waiving justifications with reference to the column 2 criterion "the substance has a low potential for bioaccumulation" because the octanol-water partition coefficient log K_{OW} is smaller or equal than 3. The endpoint bioaccumulation was mainly "compliant" (530 endpoint entries, 25.8 %) because the conduct of a study was dispensable due to a log $K_{OW} \leq 3$. An experimental study according to OECD TG 305 (OECD, 2012d), OECD TG 305C (OECD, 1981a) or OECD TG 305E (OECD, 1981b) was provided in 79 cases (3.8 %) which rendered the registration dossier "compliant" for this endpoint. A testing proposal was submitted in 11 endpoint entries (0.5 %).

The results for the endpoint bioaccumulation indicate that the majority of registrants (790 endpoint entries, 38.5 %) provided waiving/adaptations. In case, the substance was inorganic (274 endpoint entries, 13.3 %), ionisable (200 endpoint entries, 9.7 %) or hydrolytically unstable (122 endpoint entries, 5.9 %), the endpoint could not be concluded because an in-depth evaluation would be required and remained "complex".

Table 3-20: Bioaccumulation – screening: reasons for endpoint conclusions

Conclusion category (n = dossiers (subset))	Question No. (decision tree)	Reason	n dossiers (subset)	% (subset)
"Compliant" n = 609 (153)	7	Waiving refers to REACH Annex IX 9.3.2 column 2 (log K_{OW} ≤ 3)	530 (130)	25.8 (26)
	4	The test is conducted according to OECD TG 305	79 (23)	3.8 (4.6)
"Non-compliant" n = 10 (4)	6	Waiving justification is not available or false	8 (3)	0.4 (0.6)
	5	The test is not performed according to OECD TG 305 or another accepted method	2 (1)	0.1 (0.2)
"Complex" n = 1424 (340)	7	Waiving does not refer to REACH Annex IX 9.3.2. column 2 (log K_{OW} ≤ 3)	790 (187*)	38.5 (37.4)
	1	Substance is inorganic	274 (68)	13.3 (13.6)
	2	Substance is ionisable at environmentally relevant pH values	200 (51)	9.7 (10.2)
	2	Substance is hydrolytically unstable	122 (29)	5.9 (5.8)
	5	Test based on non-standard method	37 (5)	1.8 (1.0)
Testing proposal n = 11 (3)	3	Testing proposal is available	11 (3)	0.5 (0.6)
Total			**2053** (500)	**100**

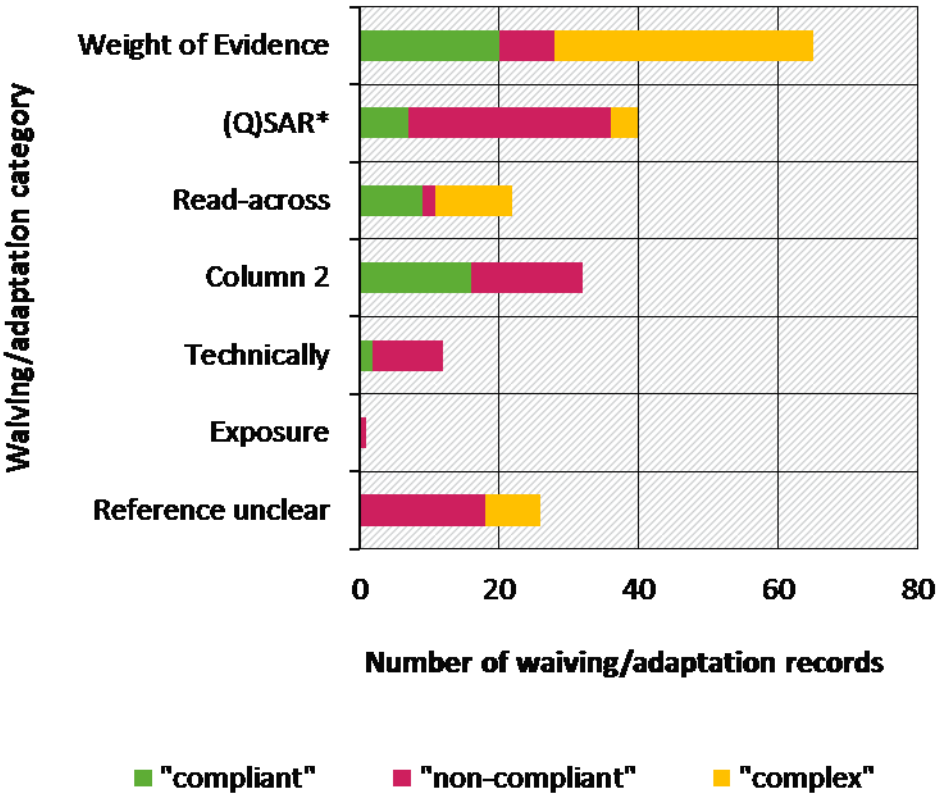
*further assessed within formal- and/or refined check

3.3.3.3 Formal check of waiving/adaptation records

The screening revealed in 187 endpoint entries out of the subset of 500 dossiers that "waiving does not refer to REACH Annex IX 9.3.2 column 2 (log K_{OW} ≤ 3)". Overall 198 other waiving/adaptation records were available in 187 endpoint entries. Available waiving justifications with reference to REACH Annex IX 9.3.2 column 2 (log K_{OW} ≤ 3) were already assessed within the screening (see section 3.3.3.2).

Conclusions on waiving/adaptation records for the endpoint bioaccumulation are illustrated in Figure 3-23 and the detailed reasons for conclusions are presented in Table 3-21. The most frequently used waiving/adaptation category was weight of evidence (65 waiving/adaptation records). The results of WoE are also included in Figure 3-23 and are presented and discussed in section 3.3.3.4.

Figure 3-23: Bioaccumulation – formal check and refined check: conclusions on waiving/adaptation records (n = 198)



Own illustration, German Federal Institute for Risk Assessment (BfR)

*4 waiving/adaptation records based on a calculation included

Read-across

Read-across approaches were applied in 22 waiving/adaptation records (11.1 %). It was concluded that 9 (4.5 %) of the waiving/adaptation records were "compliant" because a key study based on an accepted standard method and an appropriate read-across justification was available. Read-across justifications were not available in 2 waiving/adaptation records (1 %) and accordingly assessed "non-compliant". For the remaining 11 read-across approaches (5.6 %), a conclusion could not be made because a non-guideline study was indicated as key study.

(Q)SAR

(Q)SAR data were submitted in 36 waiving/adaptation records. It was assessed whether both the model and prediction were appropriately reported (e.g. QMRF and QPRF) providing that the model is validated and the registered substance is included in the applicability domain. The results show that 24 waiving/adaptation records on (Q)SARs were formally "non-compliant" because the provided information was insufficient regarding the model and the prediction reported. For additional 5 waiving/adaptation records, the (Q)SAR data were not documented as an ESR and/or key study.

"Compliant" (Q)SAR data were appropriately reported in 7 waiving/adaptation records showing that the model is scientifically validated and the substance falls within the applicability domain.

Calculation

A calculation was applied in four waiving/adaptation records and remained "complex".

Endpoint specific data waiving (column 2)

A major part of endpoint specific data waiving was already evaluated within the screening (see section 3.3.3.2). Taking this into account, endpoint specific data waiving was the most frequently applied waiving/adaptation category (see section 3.3.3.2).

Waiving with reference to the column 2 "direct and indirect exposure of the aquatic compartment is unlikely" was assessed in 16 waiving/adaptation records as "compliant" because exposure scenarios were available. Conversely, five endpoint entries were set "non-compliant" due to the absence of exposure scenarios.

Waiving justified with a low potential for bioaccumulation was "non-compliant" for eight waiving/adaptation records because the log KOW was not ≤ 3 and for further 3 waiving/adaptation records the given information was not adequately documented.

Testing technically not possible (technically)

Waiving with reference to "Testing is technically not possible" (REACH Annex XI 2.) was given in 12 waiving/adaptation records with the majority of them being "non-compliant" (10 waiving/adaptation records, 5.1 %).

The last revision of OECD TG 305 (OECD, 2012c) included a dietary study which is also suitable for substances with very low water solubility. Consequently, omitting testing according to REACH Annex XI 2. could not be justified with a low water solubility of the substance in 6 waiving/adaptation records.

Three "non-compliant" waiving/adaptation records contained an inappropriate justification stating the substance is a multi-constituent substance or a UVCB (chemical substances of Unknown or Variable composition, Complex reaction products and Biological materials). The OECD TG 305 specifies considerations for multi-constituent substances or UVCBs such as, for instance, analytical methods, different water solubilities of constituents should be taken into account.

The one remaining "non-compliant" waiving/adaptation was unjustified because degradability of the substance is not a reason for omitting testing. Instead, degradation of the substance in the test system should be avoided.

However, a minor number of two waiving/adaptations were assessed "compliant" in line with REACH Annex XI 2. 2nd sentence. Omitting testing was justified for volatile substance because a constant concentration that remains in aqueous solution is not possible during testing.

Data waiving without reference to REACH Annexes (reference unclear)

A reference to REACH Annexes IX and XI could not be deduced for 8 waiving/adaptation records. These records require an in-depth evaluation to determine whether waiving is justified for other reasons than laid down in REACH Annexes IX and XI (REACH Annex IX introduction, last paragraph).

Obviously, 18 waiving/adaptation records (9.1 %) were assessed "non-compliant" because a substantial justification to omit bioaccumulation testing could not be identified.

Table 3-21: Bioaccumulation – formal check: reasons for conclusions on waiving/adaptation records

Waiving/ adaptation category	Conclusion category	Reason	n record	%
Weight of evidence		Refined check (see section 3.3.3.4)	65*	32.8
(Q)SAR	"Compliant"	Model is scientifically validated and the substance falls within the applicability domain	7	3.5
	"Non-compliant"	(Q)SAR model and prediction are not appropriate reported	24	12.1
	"Non-compliant"	ESR or key study not available	5	2.5
Read-across	"Compliant"	Read-across based on standard method and justification available	9	4.5
	"Non-compliant"	Read-across justification not available/not sufficient	2	1.0
	"Complex"	Read-across based on non-standard method	11	5.6
Column 2	"Compliant"	Exposure scenarios available	16	8.1
	"Non-compliant"	Log K_{OW} is not ≤ 3	8	4.0
	"Non-compliant"	Exposure scenarios not available	5	2.5
	"Non-compliant"	Log K_{OW} is not adequately documented	3	1.5
Technically	"Compliant"	Justification according to REACH Annex XI 2. second sentence	2	1.0
	"Non-compliant"	Justification does not meet requirements of REACH Annex XI 2.	10	5.1
Exposure	"Non-compliant"	Criteria of Annex XI 3.2. (a) incompletely addressed	1	0.5
Reference unclear	"Non-compliant"	Waiving justification obviously insufficient or false	18	9.1
	"Complex"	Reference to REACH Annexes IX/XI unclear	8	4.0
Calculation	"Complex"	Calculation	4	2.0
Total			**198**	**100**

*further assessed in the refined check

3.3.3.4 Refined check of waiving/adaptation records

Weight of evidence

Reasons for decisions on the 65 WoE approaches are given in Table 3-22. An in-depth evaluation is required for 37 WoE-records (57 %) which allocated the endpoint entries to the "complex" category.

The WoE approach was obviously sufficient in 20 waiving/adaptation records (30.8 %). Interestingly, the majority of (Q)SAR models reported as part of a WoE approach were formally "compliant" (20 waiving/adaptation records included (Q)SAR). The same was true for seven waiving/adaptation records containing a read-across approach. These endpoint entries were set "compliant".

On the contrary, WoE was assessed in eight waiving/adaptation records as "non-compliant" if the included (Q)SAR data were formally "non-compliant" (seven waiving/adaptation records, 10.8 %) or the ESR or key study was not available (one waiving/adaptation records, 1.5 %). The majority (37) of WoE approaches require an in-depth evaluation (59.9 %).

Table 3-22: Bioaccumulation – refined check: reasons for conclusions on waiving/adaptation records

Adaptation category	Conclusion category	Reason	n record	%
Weight of evidence	"Compliant"	WoE obviously sufficient	20	30.8
	"Non-compliant"	ESR or key study not available	1	1.5
	"Non-compliant"	(Q)SAR data is formally "non-compliant"	7	10.8
	"Complex"	In-depth evaluation required	37	56.9
Total			**65**	**100**

3.3.4 Ecotoxicity

Aquatic toxicity testing on algae, invertebrates and fish is part of the standard information requirements for the endpoint ecotoxicity to assess the hazards and risks arising from chemical exposure to freshwater systems. Aquatic toxicity is described as the property of a substance to be detrimental to an organism after short-term and/or long-term exposure (ECHA, 2017b). Aquatic toxicity is mainly determined by short- and long-term toxicity tests on invertebrates (preferably Daphnia) as well as fish and algae. This information is most important for the environmental hazard assessment, i.e. classification, PBT and/or vPvB assessment and derivation of the PNEC. In addition, results of aquatic toxicity testing can trigger further testing such as, for instance, bioaccumulation (ECHA, 2017e). Short-term tests with invertebrates and fish are required for substances manufactured or imported at a quantity of 1 tpa and 10 tpa and more, respectively (REACH Annex VII 9.1.1. and Annex VIII 9.1.3.). Long-term testing on invertebrates and fish, however, is a standard information requirement for the lower tonnage bands if the substance is poorly water-soluble (1-10 tpa: REACH Annex VII 9.1.1. and 10-100tpa: Annex VIII 9.1.3.). For substances produced or imported in quantities of 100 tpa and more, long-term toxicity testing with invertebrates and fish is required if the CSA

according to REACH Annex I indicates the need to further investigate the effects on aquatic organisms (REACH Annex IX 9.1.).

The standard testing regime for short-term and long-term toxicity testing with invertebrates and fish for ≥ 100 tpa substances according to REACH Annexes VII to IX includes:

- Short-term toxicity testing on invertebrates (preferred species *Daphnia*) according to OECD TG 202 (OECD, 2004b) (REACH Annex VII 9.1.1.)
- Long-term toxicity testing on invertebrates if the substance is poorly water soluble OECD TG 211 (OECD, 2012a) (REACH Annex VII 9.1.1.)
- Long-term toxicity testing on invertebrates if the CSA indicates a need to further investigate the effects on vertebrates according to OECD TG 211 (OECD, 2012a) (REACH Annex IX 9.1.)
- Short-term toxicity testing on fish according to OECD TG 203 (OECD, 1992a)
- Long-term toxicity testing on fish if the substance is poorly water soluble according to OECD TG 210 (OECD, 2013b), OECD TG 212 (OECD, 1998) or OECD TG 215 (OECD, 2000b)(REACH Annex VIII 9.1.3.)
- Long-term toxicity testing on fish if the CSA indicate a need to further investigate the effects on fish according to OECD TG 210 (OECD, 2013b), OECD TG 212 (OECD, 1998) or OECD TG 215 (OECD, 2000b)(REACH Annex VII 9.1.1.1. and Annex IX 9.1.)

Short-term toxicity testing on invertebrates and/or fish can be omitted if the respective long-term aquatic study is available (REACH Annex VII 9.1.1. column 2, Annex VIII 9.1.3. column 2). Refraining from short-term aquatic toxicity testing is also possible if mitigating factors indicate that aquatic toxicity is unlikely to occur. Therefore, the mitigating factors should be substantiated in detail. If the substance is highly insoluble in water this should be demonstrated by

- a transformation/ dissolution protocol for inorganic substances,
- components of the substance should be identified in the water accommodated fraction or
- long-term toxicity testing should be required (see above).

Within the screening process, the endpoint ecotoxicity was evaluated in 2053 dossiers. Further assessment of the endpoint ecotoxicity within the formal and refined check, however, was only performed in a representative subset of 500 dossiers.

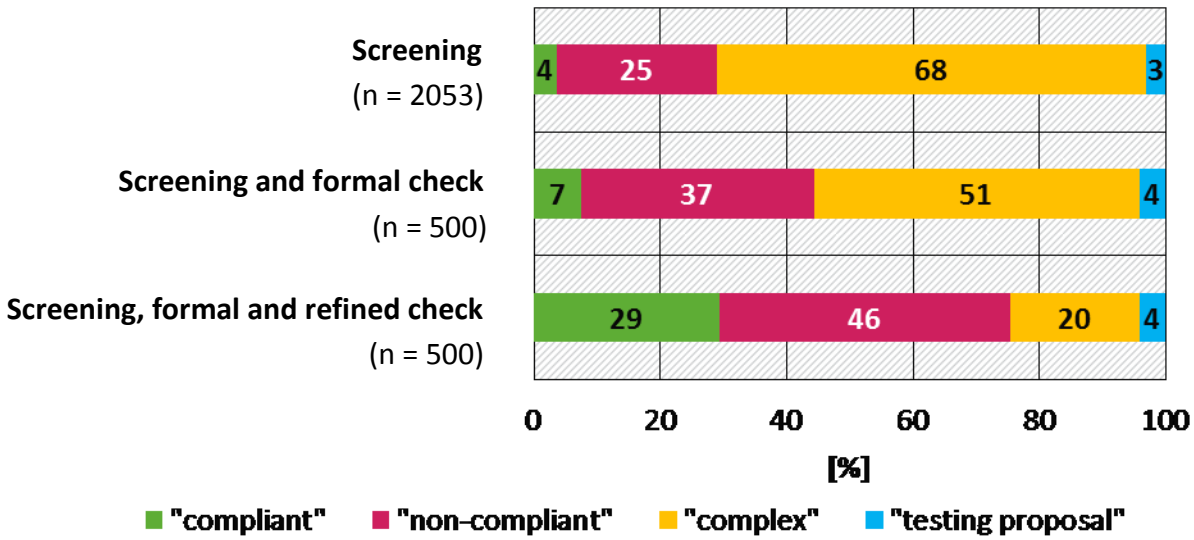
3.3.4.1 Overall endpoint conclusion

The overall results for the endpoint ecotoxicity are shown in Figure 3-24. The decision rate increased after each evaluation step from 32 % after screening, to 49 % after formal check and to 80 % after the refined check. For 20 % of the dossiers, a conclusion for the endpoint ecotoxicity was not possible because an in-depth evaluation would have been required.

Conversely, the proportion of "compliant" and "non-compliant" endpoint conclusions on ecotoxicity increased from 4 % and 25 % after screening up to 29 % and 46 % after screening, formal and refined check.

Testing proposals were present in 3 % of the endpoint entries (66 of 2053 dossiers) for ecotoxicity after screening. Within the subset of 500 dossiers, 21 testing proposals (4 %) were included.

Figure 3-24: Ecotoxicity – endpoint conclusions (n = total number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.3.4.2 Screening of data availability

The detailed results of the screening and the respective reasons for decision making are described in Table 3-23. In 4 % of the endpoint entries, the assessed information was rated as "compliant", in 25 % as "non-compliant", in 68 % as "complex", and in 3 % a testing proposal was available.

Screening of dossiers for the endpoint ecotoxicity revealed that in 52 endpoint entries (2.5 %) both chronic tests according to an accepted guideline (see Annex B.4) were available, allowing for a "compliant" evaluation. If both acute tests according to an accepted guideline were presented, the ratio of LC_{50} and EC_{50} was used to determine which species is more sensitive. The endpoint ecotoxicity was considered "compliant" when both acute tests were available and a long-term test was performed with the more sensitive species. In one endpoint entry (0.1 %), fish was, when exposed to the registered substance, the more sensitive species and the long-term fish study was available. In comparison, in 20 endpoint entries (1.0 %) it was shown that daphnia was the most sensitive species and accordingly the long-term study with invertebrate was provided.

In addition to the availability of short-term experimental studies, it was examined whether the registrants have considered the obligation that due to poor water solubility (Sw ≤ 1 mg/L) long-term studies are required. In column 1 of REACH Annex VII 9.1.1. and VIII 9.1.3. it is specified that "the registrant may consider long-term toxicity testing instead of short-term" and column 2 "The long-term aquatic toxicity study on fish (REACH Annex IX 9.1.6.) shall be considered if the substance is poorly water-soluble". Generally, if the substance is poorly water soluble it is not possible to investigate the sensitivity of the tested species. Consequently, long-term tests using both species are required. In contrast to the preceding project, this requirement was included in the decision tree for the screening in order to increase the decision rate. The results showed that the registrants frequently did not consider the water solubility as a trigger for chronic toxicity testing (479 endpoint entries, 23.4 %). Accordingly, a chronic test using either fish or invertebrates was not available in 254 endpoint entries

(12.4 %) and 6 endpoint entries (0.3 %), respectively, while in 219 endpoint entries (10.7 %) both chronic tests were not provided. These endpoint entries were concluded "non-compliant".

REACH Annexes VII and VIII integrate two complementary concepts on how water solubility should be handled in aquatic toxicity testing. The first concept on poorly water soluble substances states that long-term toxicity testing on invertebrates shall be considered (REACH Annex VII 9.1.1. column 2 and Annex VIII 9.1.3. column 2 triggers testing according to Annex IX 9.1.5. column 1 and Annex IX 9.1.6. column 1). The concept of "highly insoluble substances" requires substance specific assessment indicating that aquatic toxicity is unlikely to occur at the limit of water solubility in order to justify waiving according to REACH Annex VII 9.1.3. column 2 and/or VIII 9.1.3. column 2. Substances should be assessed for that purpose with information obtained from transformation/dissolution studies or from identified substances of the water accommodated fraction (ECHA, 2016e). If it is not possible to demonstrate that aquatic toxicity is unlikely to occur, long-term testing is mandatory as foreseen for poorly soluble substances. In this case, the substance is treated as a "poorly water soluble substance".

In 37 endpoint entries (1.8 %), the provided guideline was not accepted and a waiving justification was also not available. These endpoint entries were concluded "non-compliant" as well. In 12 of these endpoint entries, e.g. the provided OCEC TG 204 (OECD, 1984) was inadequate to fulfil the standard information requirements for long-term aquatic toxicity on fish (ECHA, 2017b) (see also section 3.3.4.3, read-across with not accepted guideline studies). Instead, a key study according to OECD TG 204 (OECD, 1984) could be used to fulfill the information requirement for short-term toxicity testing on fish as foreseen in Annex VIII 9.1.3. column 1. Some short-term fish studies according to OECD TG 203 (OECD, 1992a) or DIN 38412-15 (DIN, 1982b) were conducted with a test duration of only 48 hours instead of 96 hours which was obviously not sufficient to meet the standard information requirements of the endpoint ecotoxicity in 15 dossiers. Also, some short-term invertebrate studies were conducted with an insufficiently short test duration of 24 hours instead of 48 hours and additional information on a 48 hours invertebrates study (e.g. read-across) or a long-term invertebrate study, e.g. OECD TG 211 (OECD, 2012a) was not provided (ECHA, 2017b).

If a non-guideline test was submitted instead of the standard method, the endpoint entries remained "complex" as this would require an in-depth analysis regarding the adequacy of the study with respect to REACH Annex XI. In 99 endpoint entries (4.8 %) at least one study was conducted either with another guideline or no guideline followed.

A conclusion on the endpoint was also not possible in 58 endpoint entries (2.8 %) because the water solubility of the substance was larger than 1 mg/L and the ratio EC_{50}/LC_{50} was between 0.2 and 5. Waiving/adaptations were presented in 1233 endpoint entries (60.1 %). Within the subset of 500 dossiers, 282 waiving/adaptations were available at least for one of the four tests for ecotoxicity (Table 3-23). These waiving/adaptations were further evaluated in the formal check and/or refined check (see section 3.3.4.3 and 3.3.4.4).

Table 3-23: Ecotoxicity – screening: reasons for endpoint conclusions

Conclusion category (n = dossiers (subset))	Question No. (decision tree)	Reason	n dossiers (subset)	% (subset)
"Compliant" n = 73 (21)	1	Both long-term studies are available	52 (17)	2.5 (3.4)
	10	EC_{50}/LC_{50} > 5 and a long-term fish study is available	1 (0)	0.1 (0)
	11	EC_{50}/LC_{50} < 0.2 and a long-term invertebrate study is available	20 (4)	1.0 (0.8)
"Non-compliant" n = 522 (128)	5	A waiving justification is not available	6 (3)	0.3 (0.6)
	1; 7; 12; 5	Sw < 1 mg/L and a long-term invertebrate study is not available	6 (2)	0.3 (0.4)
	1; 7; 12; 5	Sw < 1 mg/L and long-term fish study is not available	254 (57)	12.4 (11.4)
	1; 7; 12; 5	Sw < 1 mg/L and both long-term studies are not available	219 (58)	10.7 (11.6)
	12	A not accepted guideline is provided and a waiving justification was not available	37 (8)	1.8 (1.6)
"Complex" n = 1392 (330)	5	Waiving/adaptation of standard information	1233 (282*)	60.1 (56.4)
	12	Test(s) based on non-standard method	99 (34)	4.8 (6.8)
	9	Water solubility of the substance is > 1 mg/L and $EC_{50}/LC_{50} \geq 0.2 - \leq 5$	58 (14*)	2.8 (2.8)
	6	Long-term studies are exclusively justified by (Q)SAR	2(0)	0.1 (0)
Testing proposal n = 66 (21)	1	Testing proposal is available	66 (21)	3.2 (4.2)
Total			**2053** (500)	**100**

*further assessed within formal- and/or refined check

3.3.4.3 Formal check of waiving/adaptation records

Within the subset of 500 dossiers, waiving/adaptations were present in 282 dossiers to fulfill the information requirements according to REACH Annexes VII to IX and XI for ecotoxicity. A formal check was conducted in 138 endpoint entries on 323 waiving/adaptation records and a refined check in 196 endpoint entries on 356 records (in 38 endpoint entries both evaluation steps were conducted).

The results of the assessment on the waiving/adaptation records after formal and refined check for the endpoint ecotoxicity are presented in Figure 3-25 and the respective reasons for decisions are given in Table 3-24.

(Q)SAR

The applied (Q)SAR models and predictions were assessed as "non-compliant" in 21 of the waiving/adaptation records. The models and predictions were not appropriately reported and therefore information on the validity of the model cannot be deduced. Nine (Q)SAR records were assessed as "compliant". The (Q)SAR Model Reporting Format (QMRF) and (Q)SAR Predication Reporting Format (QPRF) were appropriate documented, information on the validation criteria was included and the registered substance was embedded in the applicability domain of the model.

Read-across

With 227 records, read-across was one of the most frequently applied waiving/adaptation category. 139 of the records were assessed as "compliant", 60 as "non-compliant" and 28 remained without a conclusion ("complex") because a non-standard method was submitted. "Compliant" read-across approaches comprised short-term and/or long-term aquatic toxicity testing according to an accepted guideline (Annex B.4) with a read-across justification available. Reasons for "non-compliant" read-across approaches were, on the one hand, that a provided OECD TG 204 (OECD, 1984) was not accepted for long-term toxicity testing on fish (seven records), that the test duration was too short (one record), bioaccumulation testing according to OECD TG 305 (OECD, 2012d) was submitted instead (one record), or that an ESR was not available (four records). On the other hand, a read-across justification was either not available (18 records) or obviously insufficient (29 records).

Endpoint specific data waiving (column 2)

Another frequently used waiving/adaptation category was endpoint-specific waiving according to Annexes VII-IX column 2. However, endpoint-specific criteria were also part of the screening (see section 3.3.4.2.) and the refined check (see section 3.3.4.4). REACH Annexes VII and VIII column 2 require long-term aquatic toxicity testing for poorly water-soluble substances instead of short-term aquatic toxicity testing. This criterion was incorporated in the screening (see section 3.3.4.2). Waiving/adaptation with reference to Annex IX 9.1. column 2 (CSA) is included in section 3.3.4.4. It should be noted that the results are already depicted in Figure 3-25 under the waiving/adaptation category "column 2" and are discussed in section 3.3.4.4.

Within the formal check, the column 2 criterion was assessed, that was used to omit short-term aquatic toxicity because the respective long-term toxicity test is present. Usually, this waiving justification was applied correctly and could be assessed as "compliant". Long-term toxicity testing with invertebrates was provided in three endpoint entries instead of the short-term toxicity testing and at the same time justified with reference to REACH Annex VII 9.1.1. column 2.

The waiving justification "There are mitigating factors indicating that aquatic toxicity is unlikely to occur (highly insoluble in water, unlikely to cross biological membranes)" was sufficiently justified in 8 waiving/adaptation records and was assessed as "compliant".

Testing technically not possible (technically)

In line with REACH Annex XI it is possible to refrain from long-term toxicity testing if the substance is highly insoluble. As a requirement, evidence should be provided that the substance is highly insoluble. A transformation/dissolution protocol or similar information was presented in 16 waiving/adaptation records. Since an in-depth evaluation would have been required, these records remained "complex". Nine waiving/adaptation records with reference to REACH Annex XI 2. were "non-compliant" as the substances had difficult properties (e.g. substance is volatile) which require an adaptation of the test method according to OECD 23 (OECD, 2000a) and Table R.7.8-3 in ECHA (2017b).

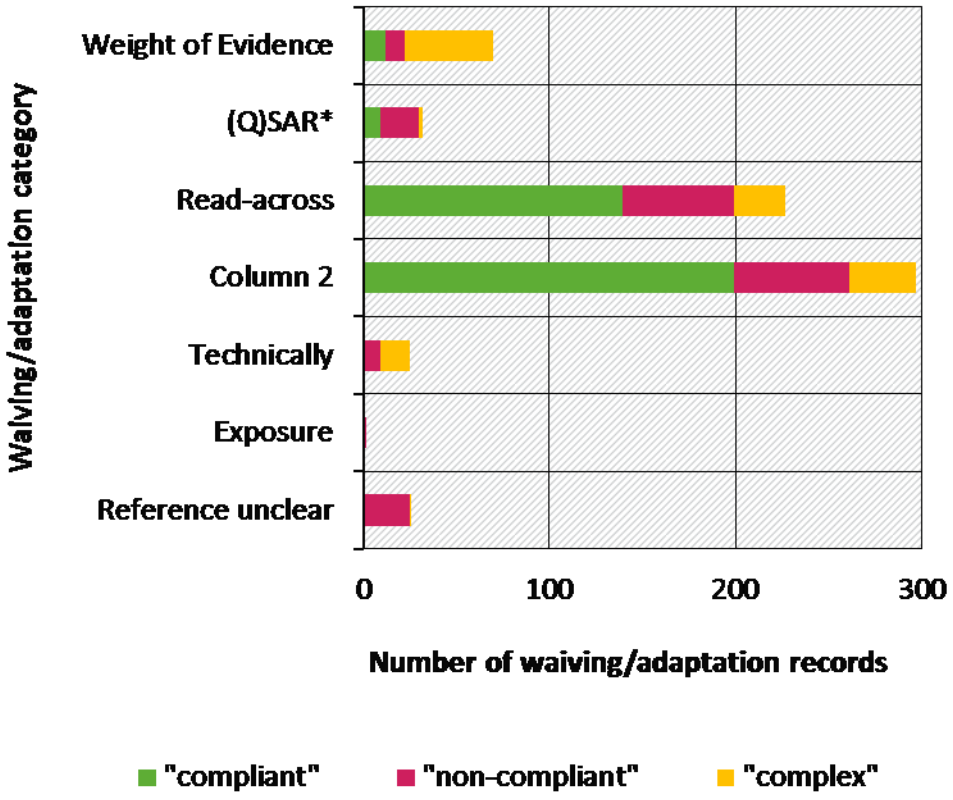
Substance-tailored exposure driven testing (exposure)

A waiving justification according to REACH Annex XI 3.2. (b) was provided in two waiving/adaptation records. These were assessed as "non-compliant" because strictly controlled conditions were not documented for all scenarios throughout the life cycle as set out in REACH Article 18(4) (a) to (f).

Data waiving without reference to REACH Annexes (reference unclear)

The waiving/adaptation justification was obviously insufficient in 25 records. In eight of them, the registrants stated that long-term toxicity testing is not required because short-term toxicity testing was already provided as REACH Annex VII and/or VIII requirements. In these cases REACH Annex XI 9.1.5. column 1 and/or 9.1.6. column 1 "unless already provided as part of Annex VII/VIII requirements" may have been misinterpreted. One waiving/adaptation record requires further evaluation because reference to REACH Annexes VII-IX/XI is unclear.

Figure 3-25: Ecotoxicity – formal and refined check: conclusions on waiving/adaptation records (n = 679)



Own illustration, German Federal Institute for Risk Assessment (BfR)

*2 waiving/adaptation records based on a calculation included

Table 3-24: Ecotoxicity – formal check: reasons for conclusions on waiving/adaptation records

Waiving/ adaptation category	Conclusion category	Reason	n record	%
Weight of evidence		Refined check (see section 3.3.4.4)	70*	10.3
(Q)SAR	"Compliant"	Model is scientifically validated and the substance falls within the applicability domain	9	1.3
	"Non-compliant"	(Q)SAR not adequately documented	21	3.1
Read-across	"Compliant"	Read-across based on standard method and justification available	139	20.5
	"Non-compliant"	Read-across justification not available/not sufficient	47	6.9
	"Non-compliant"	Read-across based on a not accepted guideline or test duration too short	9	1.3
	"Non-compliant"	ESR or key study not available	4	0.6
	"Complex"	Read-across based on non-standard method	28	4.1
Column 2	"Compliant"	Mitigating factors indicating that aquatic toxicity is unlikely to occur	8	1.2
	"Compliant"	Long-term toxicity testing were provided instead of short-term toxicity testing	3	0.4
		Refined check (see section 3.3.4.4)	286*	42.1
Technically	"Non-compliant"	Justification does not meet requirements of REACH Annex XI 2.	9	1.3
	"Complex"	Substance is highly insoluble and a transformation/dissolution protocol is available	16	2.4
Exposure	"Non-compliant"	Justification according to REACH Annex XI 3.2. (a)-(c) insufficient	2	0.3
Reference unclear	"Non-compliant"	Waiving justification obviously insufficient or false	25	3.7
	"Complex"	Reference to REACH Annexes VII-IX/XI unclear	1	0.1
Calculation	"Complex"	Based on a calculation	2	0.3
Total			**679**	**100**

*further assessed in the refined check

3.3.4.4 Refined check of waiving/adaptation records

Weight of evidence

WoE approaches were concluded to be sufficient in 12 waiving/adaptation records ("compliant"). "Non-compliant" conclusions on the waiving/adaptation (10 records) were either related to read-across or (Q)SAR data that were formally "non-compliant" (one and six records) or an insufficient guideline was provided (three records). 48 WoE approaches could not be concluded because the assessment would have required in-depth evaluation. These cases mostly included non-guideline studies or a calculation at least for one study (30 records). The remaining cases used a species sensitivity distribution for PNEC derivation (14 records) or require further analysis (four records).

Endpoint specific data waiving (column 2) – Reference to CSA

Within the refined check, it was examined whether the outcome of the CSA provides an indication for whether or not long-term testing is required. The detailed results on 286 waiving/adaptation records of the refined check are listed in Table 3-25. Overall, 188 waiving/adaptation records with reference to the CSA were "compliant", 62 "non-compliant", and 36 "complex".

The results show that waiving with reference to the CSA was correctly applied in 188 records. If the the substance does not meet any criteria of the hazard classes or categories (physical, health or environmental) set out in REACH Article 14(4), and is not assessed as PBT/vPvB substance, exposure assessment is not an obligatory part of the CSA. Therefore, these cases were considered "compliant". The waiving justification with reference to the CSA was assessed "compliant" because exposure assessment was not required (57 records) or the PEC/PNEC ratio was smaller than one and/or a risk was also not indicated by other means (131 records).

An in-depth analysis was required for 36 records because, e.g., a species sensitivity distribution was applied. The evaluation was also not possible if too many exposure scenarios were presented. In some endpoint entries the application factor for PNEC derivation was adjusted and a justification was provided. These records remained without conclusion ("complex") within the scope of the project.

Waiving with reference to the CSA was assessed as "non-compliant" (six records) if the exposure assessment was not available although it was mandatory due to the fact that the substance was classified (23 records) or if it was not complete (23 records). Occasionally, in six waiving/adaptation records, a risk was indicated by the outcome of the CSA and therefore long-term toxicity testing is required to refine the risk assessment (or to define appropriate risk management measures). Other reasons for "non-compliant" records were the application of a wrong application factor (six records) or information is available that one species is more sensitive (four records).

Table 3-25: Ecotoxicity – refined check: reasons for conclusions on waiving/adaptation records

Waiving/ adaptation category	Conclusion category	Reason	n records	%
Weight of evidence	"Compliant"	WoE is obviously sufficient	12	3.4
	"Non-compliant"	Read-across data is formally "non-compliant"	1	0.3
	"Non-compliant"	(Q)SAR data is formally "non-compliant"	6	1.7
	"Non-compliant"	WoE included not accepted guideline (OECD TG 204)	3	0.8
	"Complex"	Test based on non-standard method included	27	7.6
	"Complex"	Species sensitivity distribution was provided for PNEC derivation	14	3.9
	"Complex"	Calculation included	3	0.8
	"Complex"	In-depth evaluation required	4	1.1
Column 2 – CSA	"Compliant"	Environmental exposure assessment not required	57	16.0
	"Compliant"	Long-term testing not indicated by the outcome of the CSA	131	36.8
	"Non-compliant"	Environmental exposure assessment either not available or not complete	46	12.9
	"Non-compliant"	Long-term testing is indicated (e.g. PEC/PNEC > 1)	6	1.7
	"Non-compliant"	Application factor for PNEC derivation not appropriate	6	1.7
	"Non-compliant"	Information is available that one species is more sensitive	4	1.1
	"Complex"	In-depth evaluation required	36	10.1
Total			**356**	**100**

3.3.5 Environmental exposure

Exposure assessment is mandatory if the "the substance meets the criteria for at least one of the hazard classes or categories (physical, health or environmental), or is assessed as having any of the properties (PBT/vPvB) set out in Article 14(4) of REACH" (ECHA, 2016b). In this context, the CSA shall include the exposure assessment and a risk assessment (REACH Annex I 0.6.3.). Subsequently, the exposure assessment must cover any hazards on human health and the environmental compartments. In general, an environmental exposure assessment is obligatory if at least one of REACH Article 14(4) hazard classes, categories or properties are applicable for the substance and if adverse effects have been observed in ecotoxicity testing at the highest practicable and biologically appropriate concentration. In practice, if no adverse effects have been observed at the highest recommended concentration and a PNEC could not be derived, an exposure assessment for the respective environmental compartment is not needed. OECD TG 202 and OECD TG 203 define 100 mg/L as the highest practicable and biologically appropriate concentration in a limit test for acute aquatic toxicity (ECHA, 2016c).

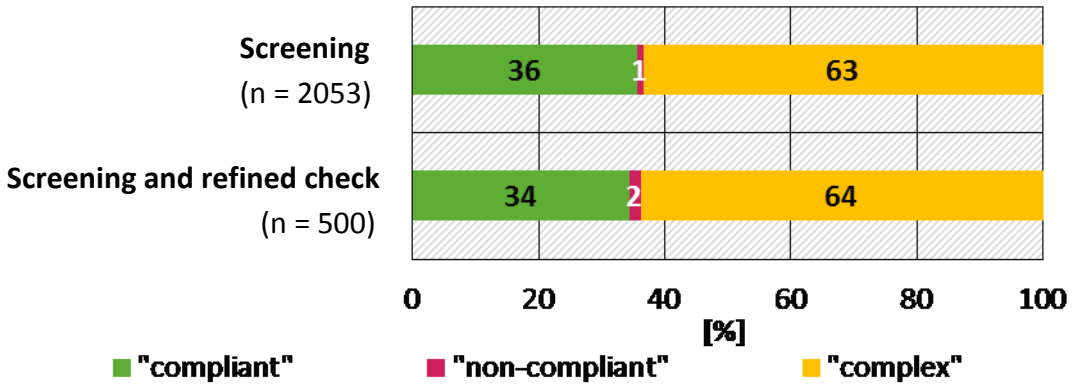
A quantitative environmental exposure assessment includes exposure scenarios for manufacture and each identified use and the aggregated exposure assessment. For substances registered at 100-1000 tpa an assessment of human exposure via the environment is mandatory if the substance has certain CMR-properties. A qualitative exposure assessment has to be done for substances with PBT and/or vPvB properties.

3.3.5.1 Overall results

The overall results on the exposure assessment are presented in Figure 3-26. After screening of the environmental exposure assessment, 35 % of the endpoint entries were concluded "compliant" because none of the REACH Article 14(4) hazard classes, categories or properties applied for the respective substances. One percent of the endpoint entries were "non-compliant" because an exposure assessment was not available although obligatory. In 63 % of the endpoint entries, a qualitative or quantitative exposure assessment was available, however, within the scope of the screening it was not possible to conclude on these records ("complex").

Endpoint entries that remained "complex" for this endpoint after the screening were included in the refined check if they were part of the subset (500 dossiers) (see section 3.3.5.3).

Figure 3-26: Environmental exposure – endpoint conclusions (n = total number of dossiers)



Own illustration, German Federal Institute for Risk Assessment (BfR)

3.3.5.2 Screening of data availability

The reasons for conclusions after screening of the environmental exposure assessment are summarised in Table 3-26. The environmental exposure assessment was assessed "compliant" in 722 endpoint entries (35.2 %) because the substance was neither classified nor PBT/vPvB (REACH Article 14(4)) and accordingly an exposure assessment is not required. Further nine dossiers were "compliant" for the environmental exposure because they were exempted from the exposure assessment (e.g. registration of a monomer and none identified uses).

A qualitative exposure assessment was presented in 23 dossiers (1 %). An in-depth analysis would have been required for decision making and accordingly these dossiers remain "complex" for the environmental exposure.

The available quantitative exposure assessments require further in-depth analysis as well. Within the screening, the completeness of the environmental exposure assessment was confirmed in 573 dossiers (27.9 %). However, these dossiers still require an in-depth analysis. The completeness check and an in-depth evaluation are required for additional 701 (34.1 %).

Exposure assessment was not available in 23 dossiers (1 %), although a classification according to REACH Article 14(4) was notified. Accordingly, these were categorised "non-compliant" for environmental exposure.

Within the screening of the environmental exposure assessment, seven out of 2053 substances with PBT/vPvB properties were identified (0.32 %) and additional three (0.15 %) were considered PBT/vPvB. This is consistent with the ≥ 1000 tpa registrations recognising 0.3 % of substances as PBT/vPvB-substances (five out of 1814 substances). Publically available data show that approximately 0.5 % of the substances with a concern under REACH have PBT/vPvB properties (ECHA, 2018a). However, these percentages may be an underestimation of the actual situation. According to a publication by Strempel *et al.*, approximately 3 % of the European Inventory of Existing Commercial Chemical Substances (EINECS) might have PBT/vPvB properties (Strempel et al., 2012). In the light of missing information due to "data gaps" (24 %; Figure 3-1), the proportion of so far identified PBT/vPvB-substances may be higher.

Table 3-26: Environmental exposure assessment – screening: reasons for conclusions

Conclusion category (n = dossiers (subset))	Question No. (decision tree)	Reason	n dossiers (subset)	% (subset)
"Compliant" n = 731 (171)	1-7	The substance is not classified and is not PBT or vPvB	722 (170)	35.2 (34)
	-	Exemption from exposure assessment (e.g. registration of a monomer and none identified uses)	9 (1)	0.4 (0.2)
"Complex" n = 1299 (325)	8	A qualitative environmental exposure assessment is available	25 (6)	1.2 (1.2)
	9 a-e	Requirements on environmental exposure assessment require in-depth analysis	701 (182*)	34.1 (36.4)
	9 a-e	Environmental exposure assessment is complete, refined check	573 (137*)	27.9 (27.4)
"Non-compliant" n = 23 (4)	9	Exposure assessment is not available, although a classification according to REACH Article 14(4) Regulation is notified	23 (4)	1.1 (0.8)
Total			**2053** (500)	**100**

*further evaluated in the refined check

3.3.5.3 Refined check

Within the subset of 500 dossiers, the 319 "complex" endpoint entries were selected for further analysis. For these endpoint entries a quantitative exposure assessment was mandatory and available.

As an additional prerequisite, standard information according to REACH Annexes VII to IX column 1 or the respective adaptations/waiving (REACH Annexes VII to IX column 2 or Annex XI) have to be available for the environmental endpoints biotic and abiotic degradation and ecotoxicity. Table 3-27 provides reasons for decisions after the refined check of the environmental exposure assessment. Applying these acceptability criteria, 35 dossiers were selected because they were "compliant" for the endpoints biotic, abiotic degradation and ecotoxicity. 30 of these dossiers contained a formally complete environmental exposure assessment and were evaluated further. Five endpoint entries (14.3 %) were "non-compliant" because the environmental exposure assessment was not complete.

However, the majority of the 35 selected dossiers were concluded "complex" for environmental exposure (26 dossiers) in the refined check. In six (17.1 %) of the 26 dossiers, for example, more than one hazard profile was relevant. In four dossiers (11.4 %) at least one of the Tier 1 physico-chemical parameters would have required an in-depth evaluation and therefore the environmental exposure assessment remained "complex".

In the remaining dossiers (except for one), the provided quantities and emission days for manufacture and each identified use were available. However, the environmental exposure assessments presented variations of the environmental release categories (ERCs) either because specific environmental release categories (spERC) were used (10 dossiers, 28.6 %) or the default values of the ERCs were

adapted and a justification was provided (3 dossiers, 8.6 %). These adaptations of the default parameters for the environmental exposure assessment require an in-depth analysis. An in-depth evaluation is required for additional three dossiers (8.6 %).

Finally, the correct assignment of PROCs and ERCs and the completeness of assessed life cycles were assessed "compliant" for one dossier (2.9 %).

Since only a limited number of 35 dossiers fulfilled the preselection criteria on completeness and the endpoints biotic and abiotic degradation and ecotoxicity being assessed "compliant", the results of the refined check should be interpreted in a qualitative manner.

"Complex" decisions are an indicator for extensive exposure scenarios which could not be resolved within the scope of the project. In order to cope with the growing complexity of quantitative environmental exposure assessment an extended and comprehensive case-by-case analysis is needed. Therefore, an interpretation of the results should be made carefully. "Complex" decisions suggest that evaluation of quantitative exposure assessment generally requires a comprehensive in-depth analysis.

Furthermore, the limited number of dossiers that fulfilled the preselection criteria emphasise the importance of each piece of information for a sound exposure assessment and subsequent risk assessment. False input parameters could induce an error propagation underestimating potential environmental risks.

Table 3-27: Environmental exposure assessment – refined check: reasons for conclusions

Conclusion category	Reason	n dossier	%
"Compliant"	All requirements fulfilled	1	2.9
"Complex"	More than one hazard profile is relevant	6	17.1
	Tier 1 parameter "complex"	4	11.4
	spERCs	10	28,6
	ERC not applied with default values parameter	3	8.6
	In-depth evaluation required	3	8.6
"Non-compliant"	Exposure assessment not complete	5	14.3
	Different reasons	3	8.6
Total		**35**	**100**

4 Conclusions and outlook

Three evaluation steps were conducted to assess the availability and quality of the information provided by registrants to meet the standard information requirements under REACH. If not otherwise specified, percentages are given as the average over all eight endpoints. With respect to the defined criteria of the current project, compliance with the requirements under REACH was ascertained in only less than half (45 %) of the assessed endpoint entries. 24 % were considered "non-compliant" and 31 % remained without a final conclusion ("complex").

Even though the outcome of the screening must be considered preliminary with only little information on the overall rate of compliance of the endpoints, it nevertheless revealed some interesting aspects. The result of the screening, for instance, demonstrated that roughly a quarter of the assessed endpoint entries (24 %) in the tonnage band 100-1000 tpa contained adequate information either because standard guideline tests on the registered substance were available, a testing proposal for a standard guideline tests on the registered substance was submitted, or testing was not necessary. Whereas the latter was mostly relevant for environmental endpoints (17 %), the information requirements for human health endpoints were mostly covered by standard guideline tests (15 %). Taking both human health and environmental endpoints into account, standard guideline tests were available in 12 %, a testing proposal was present in 4 %, and testing was not necessary in 8 % of the assessed endpoint entries. For these endpoints, the corresponding dossiers are obviously in "compliance" with the standard information requirements and thus, an explicit need for a dossier up-date and the generation of new data could not be identified. However, given the fact that an assessment concerning the scientific validity of the submitted standard tests was not within the scope of the current project, a certain percentage of these endpoints may still contain shortcomings.

The preliminary results of the screening also uncovered that the information requirements were obviously not met on average in 8 % of all assessed endpoint entries. The dossiers were "non-compliant" for the addressed endpoints in case the corresponding registrants failed to provide any appropriate information such as standard guideline tests, suitable surrogate data, or a sufficient justification as to why testing can be omitted. A striking example of such inappropriate submitted information was revealed during the screening process for the endpoint ecotoxicity. Hereby, registrants frequently failed to consider physico-chemical properties for triggering chronic toxicity testing, thus rendering 24 % of the endpoint entries "non-compliant". Hence, it can be concluded that these "data gap"-containing dossiers are of insufficient and unacceptable quality for the assessed endpoint entries and a dossier up-date is strictly required.

Most importantly, the screening showed that approximately two-thirds of the assessed endpoint entries (67 %) required further assessment which was documented with the category "complex" within the screening. For a number of endpoint entries (10.7 %), an in-depth assessment was outside the scope of the project. Hence, these cases remained "complex" without any further assessment (e.g. studies that followed no guideline or a non-standard guideline). The vast majority of endpoint entries (57 %; on average 1161 endpoint entries in 2053 dossiers) remained "complex" due to the use of data waiving/adaptation as an alternative approach to fulfil the standard information requirements. Thus, proposing a waiving and/or an adaptation of data constituted the predominant strategy to meet the standard information requirements of the medium tonnage band (100-1000 tpa) under REACH. This is consistent with the REACH-specific obligation to consider animal testing as a last resort to obtain missing information. The formal conformity of these waiving/adaptations was assessed during the

formal and refined check. However, it should be stressed that the evaluation criteria, defined and applied for waiving/adaptation categories within the current project, cover only the formal requirements pursuant to the REACH Annexes VII-IX/XI. An evaluation addressing the scientific validity of data waiving/adaptation, routinely performed within ECHA's dossier evaluation, was beyond the scope of the current project. Consequently, a certain number of waiving/adaptation records assessed "compliant" within the project may presumably not be accepted during ECHA's Compliance Check procedure. Irrespectively of the limitations of the formal conformity check within the project, "non-compliance" could be assigned to 28 % (on average) of the endpoint entries based on the evaluation of the waiving/adaptation. In these cases, the waiving/adaptation of data was found obviously inadequate.

Read-across and grouping approaches were amongst the most frequently used adaptations which is in line with ECHA's experience (ECHA, 2017f). The majority (61 %) of the read-across records were considered "compliant" which appears to be in contrast with the lower acceptance rate of read-across within ECHA's dossier evaluation (Ball et al., 2016) but can be explained by the aforementioned differences in the evaluation depth. A "non-compliant" decision, assigned to 17 % of the assessed read-across and grouping records, was frequently attributed to shortcomings such as (1) insufficient coverage of important key parameters within an experimental study conducted with the source substance, or (2) an unavailable read-across justification, or (3) an obviously insufficient read-across justification.

Weight of evidence was another frequently used adaptation category. Unlike the results of the read-across assessment though, weight of evidence approaches remained without a final conclusion for the majority of the assessed records (48 %). Given that the scientific validity of studies was not examined in the project, weight of evidence approaches that were solely based on non-standard studies or that contained inconsistent study results were set "complex". "Non-compliant" decisions, found in 24 % of the assessed records, were frequently attributed to formal deficiencies of an incorporated read-across and/or (Q)SAR (e.g. no adequate documentation available).

With respect to the overall results obtained as aggregated percentages following all three evaluation steps, 45 % of the assessed endpoint entries were considered "compliant" with the REACH requirements according to the criteria defined within the project. However, taking into account that the percentage of "non-compliant" decisions ranged between 9 % and 46 % (24 % on average), it can be concluded that in at least 46 % of the evaluated dossiers the information requirements under REACH are insufficiently fulfilled for at least one endpoint. A decision on whether or not the endpoint is "compliant" could not be reached for about one-third of all assessed endpoint entries (31 %), even after completing all evaluation steps. An in-depth analysis would have been necessary to draw a final conclusion which, however, could not be realised within the limited scope of the project.

In conclusion, accepted guideline studies on toxicological and ecotoxicological endpoints (standard information) have been provided as key studies in less than an eighth of all assessed endpoint entries. A number of similar or equivalent guideline studies were, in addition, provided within read-across/grouping and weight of evidence approaches. Thus, standard information provided as standard guideline studies is available in a limited number of endpoint entries. However, albeit not evaluated in-depth within this project ("complex"), data derived from studies that followed no guideline or a non-standard guideline may also be considered adequate information for the endpoint (i.e. adequate and reliable coverage of key parameters foreseen to be investigated in the respective guideline study). In contrast, data waiving/adaptation has been intensively used, suggesting that registrants are aware of their obligation to conduct animal studies only as a last resort.

"Data gaps" within the endpoints of the registration dossiers exist in consequence of a lack of standard information or an insufficiently established data waiving/adaptation. Hence, registrants are encouraged to thoroughly review the information provided in their dossiers and to improve the availability and quality of toxicological and ecotoxicological information if necessary. A special emphasis may thereby be placed on (1) the conditional testing strategy for ecotoxicity depending on the physico-chemical properties of the registered substance, (2) revising and consolidating the read-across and grouping approach according to ECHA's read-across guidance document (quality of studies with the source substance and availability/quality of read-across justifications), (3) reporting of read-across and/or (Q)SAR as incorporated element within a weight of evidence approach.

Differences between the medium tonnage band (100-1000 tpa) and the high tonnage band (≥ 1000 tpa) became apparent when comparing the aggregated results of both tonnage bands. A higher "compliant"-rate was noted in the medium tonnage band (45 %) compared against the high tonnage band (34 %). While adjustments of the methodology and different tonnage-dependent REACH requirements of specific endpoints have to be taken into consideration, an improvement in the quality of adaptations, particularly for read-across and grouping, was a noticeable reason for the overall higher "compliant"-rate.

High-quality data are a prerequisite for hazard identification and subsequent exposure and risk assessment. It is important to ensure that authorities are enabled to identify substances of concern to stipulate further regulatory measures.

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A Human health: Endpoint specific evaluation methods

A.1 General settings for evaluation

A.1.1 Data considered for evaluation

ECHA additionally provided lists of exported study data and hazard information of the registration dossiers in IUCLID for the considered human health and environmental endpoints between April and May 2017.

For human health endpoints the exported information of selected IUCLID fields was used to support the evaluation of the available study data. The following IUCLID fields were considered:

- Study type
- Endpoint (code)
- Type of information (code)
- Adequacy of study (code)
- Reliability (code)
- Data waiving (code)
- Justification data waiving
- Guideline
- Species (code/other)
- Strain (code)
- Test results (in vitro/in vivo: genotoxicity (code))
- Duration of treatment exposure
- Frequency of treatment
- Route of administration (code/other)

'Study type' specified the endpoint analysed within the scope of the project, *e.g.* 'toxicity to reproduction' or 'repeated dose toxicity dermal'. 'Endpoint (code)' gave information about the available study type, *e.g.* 'two generation reproductive toxicity' or 'chronic toxicity: dermal'.

For 'type of information' the following entries were included in the evaluation:

- (Q)SAR
- experimental study
- experimental study planned = testing proposal
- read-across from supporting substance (structural analogue or surrogate) or read-across based on grouping of substances (category approach) = read-across
- empty = data waiving/adaptation

As mentioned before, 'adequacy of study' had to be declared as 'key study' or 'weight of evidence' (see 2.4.1).

A.2 Repeated dose toxicity

Repeated dose toxicity studies provide information on toxicological effects which are likely caused by the repeated exposure to a substance. Additionally, these studies may also give information on *e.g.* reproductive toxicity, although they are not especially designed for this endpoint. The studies should enable a threshold definition with regard to human exposure. Concerning the appropriate route of administration the most likely route of human exposure should be considered (ECHA, 2017a).

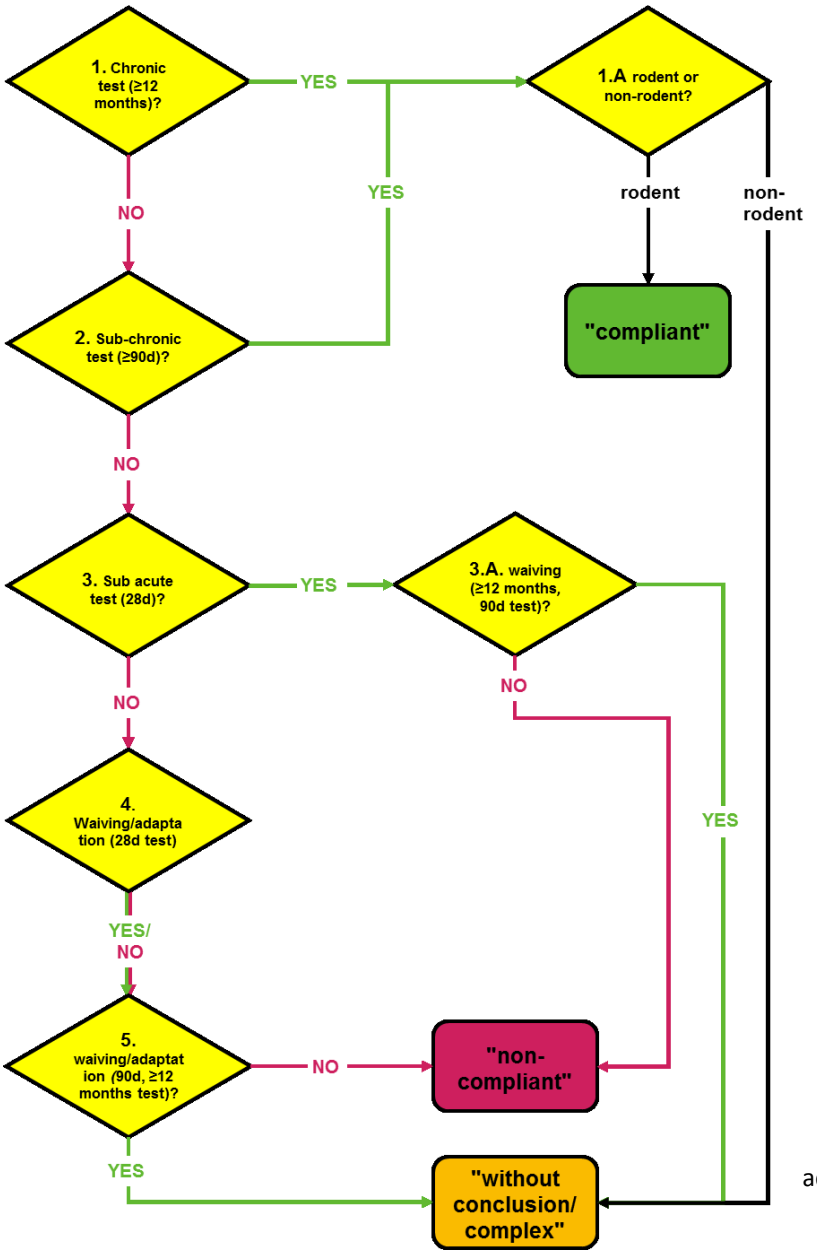
A.2.1 Screening

The screening was based on the decision tree presented in Figure A1. The standard information requirements for the tonnage level 100 to 1000 tpa are:

- a sub-acute repeated dose toxicity study (28 days) in one species
- a sub-chronic repeated dose toxicity study (90 days) in one species

A 28-day test is not required if already provided at REACH Annex VIII level or if a 90-day study is available or proposed. Both tests can be omitted, if a long-term repeated toxicity study (chronic, ≥ 12 months) is available and/or respective waiving or adaptation options are applied.

Figure A1: Decision tree of the endpoint repeated dose toxicity



adapted from Springer et al. (2015)

The following textboxes sum up the questions and answer options of the decision tree and give further information regarding the screening approach where necessary.

Question No. 1

Is a chronic toxicity study (≥ 12 months) available?

Answer Yes: Continuation with question 1.A[a]

Answer No: Continuation with question 2

[a] If a chronic toxicity study is available, waiving or adaptation of the standard information is formally required. However, within the scope of the project no further requirements are evaluated.

Question No. 1.A

Has the chronic or sub-chronic toxicity study been conducted in rodents or non-rodents?

Answer rodent: Categorisation as "compliant"

Answer non-rodent: Categorisation as "without conclusion"[b]

[b] Rodents are the default experimental species for repeated dose toxicity testing. Depending on the substance, other animal models might be more suitable. This requires a more detailed assessment, consequently non-rodent studies are categorised as "without conclusion".

Question No. 2

Is a sub-chronic toxicity study (≥ 90 days) available?

Answer Yes: Continuation with question 1.A

Answer No: Continuation with question 3

Question No. 3

Is a subacute toxicity study (28 days) available?

Answer Yes: Continuation with question 3.A[c]

Answer No: Continuation with question 4

Question No. 3.A

Is a waiving or adaptation option available for the sub-chronic or chronic study (90 d test, ≥ 12 months)?

Answer Yes: Categorisation as "without conclusion"

Answer No: Categorisation as "non-compliant"

[c] The route of exposure has to be identical for the 28-day study and the waiving/adaptation of the 90-day study. The category of waiving/adaptation is specified in the memo field of the excel data sheet.

Question No. 4

Is a waiving or adaptation option available for the sub-acute toxicity study (28 d test)?

Answer Yes: Continuation with question 5

Answer No: Continuation with question 5

Question No. 5

Is a waiving or adaptation option available for sub-chronic or chronic study (90 d test, ≥ 12 months)?

Answer Yes: Categorisation as "without conclusion"[d]

Answer No: Categorisation as "non-compliant"

[d] Due to the standard information requirements (28-day and 90-day study) two declarations of waiving/adaptation are expected. But the provision of one waiving/adaptation is accepted within the scope of the screening. The category of waiving/adaptation is specified in the memo field of the excel data sheet.

Table A1 lists the OECD and EU test guidelines and the respective US EPA analogues for repeated dose toxicity studies that are accepted under REACH. Within the screening step of the project, studies that

were conducted according to theses test methods were accepted to fulfil the standard information requirements. There are route-specific studies for the endpoint Repeated dose toxicity. Thus, the registrant has to choose accordingly. During IT-screening, if the 'route' flag did not correspond to the respective test guideline (*e.g.* route of administration for OECD TG 408 had to be oral, Table A1) the endpoint study record was not further considered. If a study was flagged as an accepted guideline, but the exposure duration was shorter, this study was considered as "complex", since in-depth analysis would be needed. "[…] the oral route (gavage, in diet, or in drinking water) is the "default" route, except for gases.[…] If another route of administration other than oral is used, the registrant should provide justification and reasoning for its selection."(ECHA, 2017a). For endpoint entries with the route choice "inhalation", it was randomly checked if aggregate state of the substance is gaseous. This analysis showed that the inhalative route was correctly chosen for all selected endpoint entries. Consequently, inhalative route was also accepted as default route. If, however, the dermal route was chosen, the endpoint remained "complex". "Non-physiological routes of human exposure, such as [intravenous, intramuscular, subcutaneous, intraperitoneal] are usually considered not appropriate routes of administration for animal testing to be requested for the REACH Regulation."(ECHA, 2017a). Therefore, endpoint entries with studies using these routes remained "complex".

Table A1: Repeated dose toxicity - Overview of the accepted test methods for the endpoint

Category[a]	Test method[b]	OECD TG[b]	EU method[c]	US EPA analogue[d]		Route	Remarks
				OCSPP	OPPT		
Chronic toxicity studies	Chronic toxicity studies	452	B.30	870.4100	798.3260	Oral[e]	Updated EU method (03/2014)[f]
	Combined chronic toxicity/carcinogenicity studies	453	B.33	870.4300	798.3320	Oral[e]	Updated EU method (03/2014)[f]
Sub-chronic toxicity studies	Repeated dose 90-day oral toxicity study in rodents	408	B.26	870.3100	798.2650	Oral	
	Repeated dose 90-day oral toxicity study in non-rodents	409	B.27	870.3150		Oral	
	Sub-chronic dermal toxicity: 90-day study	411	B.28	870.3250	798.2250	Dermal	
	90-day (sub-chronic) inhalation toxicity study	413	B.29	870.3465	798.2450	Inhalation	Updated EU method (03/2014)[f]
Subacute toxicity studies	Repeated dose 28-day oral toxicity study in rodents	407	B.07	870.3050		Oral	Updated EU method (03/2014)[f]
	Repeated dose dermal toxicity: 21/28-day study	410	B.09	870.3200		Dermal	
	28-day (subacute) inhalation toxicity study	412	B.08			Inhalation	Updated EU method (03/2014)[f]
	Delayed neurotoxicity of organophosphorus substances 28-day repeated dose study	419	B.38	870.6100	798.6450, 798.6540, 798.6560	Oral	
	Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test	422	B.33	870.3650		Oral[e]	

According to [a] Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance (ECHA, 2017a); [b] OECD Guidelines for the Testing of Chemicals, Section 4 – Health Effects (OECD, 2015); [c] Council Regulation (EC) No 440/2008 (EC, 2008a); [d] OCSPP Harmonized Test Guidelines, series 870 –Health effects test guidelines (OCSPP, 2015)
[e] preferred administration route, while dermal and inhalation are also possible but require modifications; [f] EU method was updated (EU, 2014)

Table A2: Repeated dose toxicity - Subordinate test method that may provide additional supporting information on the endpoint

Category[a]	Test method[b]	OECD TG[b]	EU method[c]	US EPA analogue[d]		Route	Remarks
				OCSPP	OPPT		
Subacute toxicity study	Neurotoxicity study in rodents	424	B.43	870.6200	798.6050, 798.6200, 798.6400	Oral[e]	

According to [a] Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance (ECHA, 2017a); [b] OECD Guidelines for the Testing of Chemicals, Section 4 – Health Effects (OECD, 2015); [c] Council Regulation (EC) No 440/2008 (EC, 2008a); [d] OCSPP Harmonized Test Guidelines, series 870 –Health effects test guidelines (OCSPP, 2015)
[e] preferred administration route, while dermal and inhalation are also possible but require modifications

Studies referring to other guidelines like OECD test guideline for reproductive and developmental toxicity (OECD TG 414 (OECD, 2001), 415, 416 (OECD, 1983), 421 (OECD, 2016a) or 426) or for carcinogenicity (OECD TG 451 (OECD, 2009b)) can provide information on repeated dose toxicity. However, in these studies not all of the required test parameters and/or organs may have been evaluated (ECHA, 2017a). Since expert judgement would have been needed to evaluate the suitability of these studies, the memo "other guide" was assigned and the endpoint was concluded "complex", if no other accepted information was available. Correspondingly, studies which were not conducted according to any guideline or where the guideline information was missing were assigned with the memo "no guide" and concluded "complex" if no other accepted information was available. Studies conducted with non-rodent species (e.g. rabbit, dog) are treated likewise.

A.2.2 Formal check

The endpoint specific formal check corresponded to the one of the former project (Oertel et al., 2018b). The formal criteria for using the waiving options (set out in REACH Annexes VII to IX) that were examined within this project are summed up in Table A3.

Table A3: Repeated dose toxicity – Formal check of endpoint-specific justifications for data waiving

Standard information requirement (column 1)	REACH reference (column 2)	Required justification	Additional criteria
REACH Annex IX, 8.6.1. Short-term (28 days) study	(no waiving according to column 2 possible, only options of Annex XI apply)	90-day study available	90-day study available: ▪ key study with a reliability of 1 or 2 **or** ▪ WoE
REACH Annex IX, 8.6.2. Sub-chronic (90 days) study	REACH Annex IX 8.6.2. column 2, 1st passage, 1st bullet point	▪ reliable 28-day study available **and** ▪ that shows severe toxicity according to the criteria for classifying substance as R48[a] **and** ▪ NO(A)EL-28-days allows for extrapolation towards the NO(A)EL-90-days for the same route of exposure	criteria are explained in waiving justification **and** 28-day study available: ▪ key study with a reliability of 1 or 2 **or** ▪ WoE
	REACH Annex IX 8.6.2. column 2, 1st passage, 3rd bullet point	▪ substance undergoes immediate disintegration **and** ▪ sufficient data on cleavage products are available and (for systemic and local effects)	criteria are explained in waiving justification
	REACH Annex IX 8.6.2. column 2, 1st passage, 4th bullet point	▪ substance is unreactive, insoluble and not inhalable **and** ▪ no evidence of absorption **and** ▪ no evidence of toxicity in a 28-day "limit test"	criteria are explained in waiving justification **and** 28-day study "limit test" available: ▪ key study with a reliability of 1 or 2 **or** ▪ WoE

[a] R48 = Classification under Directive 67/548/EEC, corresponds to hazard class-and-category STOT RE 1/STOT RE 2 (specific target organ toxicity – repeated exposure) (CLP-Verordung No 1272/2008 (EC, 2008b))

REACH Annex IX, 8.6.2. column 2, 1st passage, 2nd bullet point (reliable chronic study is available and appropriate species was used and appropriate route of exposure was used) was already evaluated in the screening (Figure A1).

A.2.3 Refined check

The refined check was performed on all weight of evidence approaches and the methods correspond to 2.6.1.

A.3 Mutagenicity

Mutagenicity, describes the induction of irreversible transmissible changes (mutations) in the amount or structure of the genetic material. These changes can apply to a single gene or gene segment, a block of genes or chromosomes. Clastogenicity refers to structural chromosome aberrations. Aneugenicity on the other hand refers to an alteration of the chromosome number (loss or gain) in cells. In principle, exposure to mutagenic substances may result in increased frequencies of mutations.

Mutagenicity tests:

- Examine the induction of heritable DNA mutations following substance exposure
- Types of mutations: gene mutations (base substitutions and deletions/additions), chromosomal mutations (breaks and rearrangements; clastogenicity), and genome mutations (loss or gain of chromosomes; aneugenicity)

Genotoxicity is a superordinate term which additionally considers alterations of the DNA that may or may not result in mutations such as DNA damages via e.g. DNA strand breaks.

Indicator tests:

- Examine the induction of potentially reversible alterations to the genetic material following substance exposure (broader spectrum of effects, e.g. DNA strand breaks, DNA adducts, mitotic recombination, etc.)
- Effects can be repaired, can lead to apoptosis, or can be inherited

Thus, all mutagens are genotoxic, but not all genotoxic substances are mutagens.

The key question under REACH is whether a substance is a mutagen. The aim of genotoxicity testing is the detection of substances which cause genetic alterations in somatic and/or germ cells. Genetic alteration in somatic cells can cause cancer. Genetic alterations in germ cells can be passed on to the next generation. DNA damage in germ cells is related to e.g. spontaneous abortions or malformations. Germ cell mutagens are in all (known) cases also mutagenic in somatic cells *in vivo*, and vice versa substances that are not mutagenic in somatic cells *in vivo* are most likely not mutagenic in germ cells.

The standard information requirements, the specific rules for adaptation from column 1 (REACH Annexes VII to X column 2), and the integrated mutagenicity testing strategy are described in detail in ECHA's Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance (ECHA, 2017a). To fully assess the mutagenic potential of a given substance, information on the induction of gene mutations, chromosomal mutations, and genome mutations is required.

According to the REACH Regulation, the following test types were examined:

- GMbact
- Cytvitro
- GMvitro
- Cytvivo
- GMvivo
- Germvivo

Results of the test types could have been "negative", "positive" or "ambiguous". If there was more than one relevant ESR for one test type with positive and negative results, the overall result was concluded

as “ambiguous”. Endpoint entries containing an “ambiguous” test type required expert judgement and therefore remained “complex” within the scope of this project.

If there was no harmonised classification according to the CLP Regulation the registrant had to submit the following data (standard information requirements):

- *In vitro* gene mutation study in bacteria (GMbact, REACH Annex VII 8.4.1.)
- *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Cytvitro, REACH Annex VIII 8.4.2.)
- *In vitro* gene mutation study in mammalian cells (GMvitro, REACH Annex VIII 8.4.3.), if a negative result in REACH Annex VII 8.4.1. and Annex VIII 8.4.2.

In case of a positive *in vitro* test a corresponding *in vivo* test is required, *e.g.* a GMvivo is necessary if the GMbact or GMvitro was positive. In case of a positive test result from an *in vivo* soma cell test, the potential for germ cell mutagenicity should be considered according to REACH Annex IX 8.4. column 2 (EC, 2006). However, *in vivo* germ cell tests (Germvivo) are not regarded as standard information requirement and thus, do not determine the decision in regard to overall endpoint compliance. The availability and the outcome of *in vivo* germ cell tests have nevertheless been documented within the screening process.

A.3.1 Screening

For an efficient use of the IUCLID export that ECHA provided, the decision tree developed in the first REACH Compliance project (Springer et al., 2015) was changed into a list of questions. The following text boxes explain the single questions.

Question No.1
Is the substance listed in Annex VI of the CLP Regulation as a carcinogen category 1A or 1B (H350) or a germ cell mutagen category 1A or 1B (H340)?[a]

[a] If the substance is already classified as described above, waiving or adaptation of the standard information is formally required. However, within the scope of the project no further requirements were evaluated.

Question No. 2
Is an in vivo test for germ cells (Germvivo) available?
Question No. 2A
Is a waiving or adaptation option for Germvivo available?
Question No. 2.B
What is the result of the Germvivo?[b, c]

[b] A negative germ cell test does not exclude that soma cells are affected by the substance. At least the standard information requirements have to be fulfilled.

[c] If the germ cell test was positive, it is assumed that the substance also affects soma cells, but no additional testing, except the GMbact (test or adaptation), is required. Waiving or adaptation of the standard information is formally required. However, within the scope of the project no further requirements were evaluated.

Question No. 3
Is an in vivo test for soma cells (GMvivo) available?[d]
Question No. 3.A
Is a waiving or adaptation option for GMvivo available?
Question No. 3.B
What is the result of the GMvivo?
Question No. 4
Is an in vivo test for soma cells (Cytvivo) available?[d]
Question No. 4.A
Is a waiving or adaptation option for Cytvivo available?
Question No. 4.B
What is the result of the Cytvivo?

[d] Waiving or adaptation for the *in vitro* standard information is formally required. Within the scope of the project the waiving/adaptation option was only documented during the formal check if it was available.

Question No. 5
Is an *in vitro* gene mutation study in mammalian cells (GMvitro) available?
Question No. 5.A
Is a waiving or adaptation option for GMvitro available?
Question No. 5.B
What is the result of the GMvitro?
Question No. 6
Is an *in vitro* cytogenicity study in mammalian cells or in vitro micronucleus study (Cytvitro) available?
Question No. 6.A
Is a waiving or adaptation option for Cytvitro available?
Question No. 6.B
What is the result of the Cytvitro?
Question No. 7
Is a bacterial test (GMbact) available?
Question No. 7.A
Is a waiving or adaptation option for GMbact available?[e]
Question No. 7.B
What is the result of the GMbact?

[e] Adaptation is only possible according to Annex XI column 2 of Annexes VII to IX does not contain waiving possibilities for GMbact. The category of adaptation was specified in the memo field of the excel data sheet.

Table A4 lists the OECD and EU test guidelines for genotoxicity studies accepted under REACH as well as the respective US EPA analogues. Within the screening step of the project, studies that were conducted according to the listed test methods were accepted to fulfil the standard information requirements.

Table A4: Mutagenicity - Overview of the accepted test methods for the endpoint[a]

Category[b]		Test method[c]	OECD TG[d]	EU method[e]	US EPA analogue[f]		Remarks
					OCSPP	OPPT	
In vitro							
Gene mutation, bacteria	GMbact	Bacterial reverse mutation test (until 1997)	471			798.5265	
		Genetic toxicology: *Escherichia coli*, Reverse assay (until 1997)	472			798.5100	If study is older than 1981, data is not accepted
		Bacterial reverse mutation test (since 1997)	471	B.13/14	870.5100	798.5100; 798.5265	
Gene mutation, mammalian cells	GMvitro	*In vitro* mammalian cell gene mutation test – HPRT, XPRT or TK test (until 2015)	476	B.17	870.5300	798.5300	
		In vitro mammalian cell gene mutation test – HPRT or XPRT test (since 2015)	476	Is not yet available			
		In vitro mammalian cell gene mutation test – TK test (since 2015)	490	Is not yet available			
Chromosomal effects, mammalian cells	Cytvitro	*In vitro* mammalian chromosome aberration test	473	B.10	870.5375	798.5375	Updated EU method (04/2017)[f]
		In vitro mammalian micronucleus test	487	B.49			Updated EU method (04/2017)[f]
In vivo							
Gene mutation,	GMvivo	Transgenic rodent	488	B.58			Updated EU method

soma cells		somatic and germ cell gene mutation assays					(08/2014)[g]
		In vivo mammalian alkaline comet assay [h]	489	B.62			Updated EU method (04/2017)[f]
		Unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo* [h, i]	486	B.39			
Chromosomal effects, soma cells	Cytvivo	Mammalian erythrocyte micronucleus test	474	B.12	870.5395	798.5395	Updated EU method (04/2017)[f]
		Mammalian bone marrow chromosomal aberration test	475	B.11	870.5385	798.5385	Updated EU method (04/2017)[f]
		In vivo mammalian alkaline comet assay	489	B.62			Updated EU method (04/2017)[f]
Germ cell mutations	Germvivo	Rodent dominant lethal test	478	B.22	870.5450	798.5450	
		Mammalian spermatogonial chromosomal aberration test	483	B.23	870.5380	798.5380	
		Transgenic rodent somatic and germ cell gene mutation assays	488	B.58			Updated EU method (08/2014)[g]

[a] includes also genotoxicity studies which are not necessarily associated with mutagenicity
According to [a] Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance (ECHA, 2017a); [b] OECD Guidelines for the Testing of Chemicals, Section 4 – Health Effects (OECD, 2015); [c] Council Regulation (EC) No 440/2008 (EC, 2008a); [d] OCSPP Harmonized Test Guidelines, series 870 –Health effects test guidelines (OCSPP, 2015);
EU method was updated [f] (http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R0735), [g] (http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014R0900) [h] According to ECHA's Guidance on information requirements and chemical safety assessment Chapter R.7a (Section R.7.7.6.3, Testing strategy for mutagenicity, version 6.0, July 2017), indicator assays such as the *in vivo* comet assay or the *in vivo* unscheduled DNA synthesis (UDS) assay do not provide adequate information to conclude on the induction of gene mutation. Hence, an adaptation of the standard information requirements according to REACH VIII Annex 8.4.3. column 2 using one of these tests may not be sufficient. However, within the REACH-compliance project both tests were considered adequate information on *in vivo* mammalian gene mutation. [i] According to the Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance, the use of the *in vivo* UDS indicator test should

always be justified on a case-by-case basis and may only be sufficient under certain circumstances (considering target organ and substance-specific factors). Within the scope of the project, the UDS test was accepted without an in-depth analysis of its adequacy.

A.3.2 Formal check

Table A5 summarises the formal criteria of the former project (Oertel et al., 2018b) which were used for evaluating the waiving options set out in the REACH Annexes VII to IX.

Table A5: Mutagenicity – Formal check of endpoint-specific justifications for data waiving

Standard information requirement (column 1)	REACH reference (column 2)	Required justification	Additional criteria
***In vitro* tests**			
Annex VII, 8.4.1. GMbact	(no waiving according to column 2 possible, only options of Annex XI apply)		
Annex VIII, 8.4.2. Cytvitro	Annex VIII 8.4.2. column 2 1st bullet point	Adequate data for *in vivo* cytogenicity test are available	Cytvivo study available: ▪ key study with a reliability of 1 or 2 or ▪ WoE
	Annex VIII 8.4.2 column 2 2nd bullet point	Known to be carcinogenic cat. 1A or 1B or germ cell mutagenic cat. 1A, 1B or 2	criterion is explained in waiving justification (evaluation of harmonised or self-classification required)
Annex VIII, 8.4.3. GMvitro	Annex VIII 8.4.3 column 2	Adequate data for *in vivo* mammalian gene mutation test are available	GMvivo study available: ▪ key study with a reliability of 1 or 2 or ▪ WoE
***In vivo* tests**			
If *in vitro* tests were positive: Annex IX, 8.4. column 2 first passage: *in vivo* tests	(only options of Annex XI apply)		

In case of a positive *in vivo* soma cell test "the potential for germ cell mutagenicity should be considered" according to REACH Annex IX 8.4. column 2 (EC, 2006). However, an *in vivo* germ cell test (Germvivo) is not considered as standard information requirement. Therefore, registrants do not need a waiving justification for omitting Germvivo.

A.3.3 Refined check

The refined check was performed on all weight of evidence approaches and the methods correspond to 2.6.1.

It is important to stress that due to the fundamental differences in genetic alterations that are specifically addressed with the appropriate test type, a separate weight of evidence analysis should be carried out on each test type and each endpoint related to mutagenicity. Combining results from different test types and endpoints in one overall weight of evidence analysis, therefore, should not be done (ECHA, 2017a).

A.4 Toxicity to reproduction (Developmental Toxicity + Reproductive toxicity)

Within the REACH annexes the endpoint 'reproductive toxicity' is split into:

- 'reproductive toxicity/fertility' and
- 'developmental toxicity/teratogenicity'

Those two endpoints were treated separately in this project as they have individual information requirements, which are also reflected in separate IUCLID subsections. Studies on reproductive toxicity (reproductive toxicity) address toxic effects of a substance on fertility of adults, covering all effects on the reproductive cycle, i.e. functional fertility, morphological and histological changes related to reproductive organs as well as the ability to produce offspring and to nurse them. Furthermore, developmental impairments of the progeny caused by toxic effects of a substance can be identified by these studies. Toxicity to fertility includes, inter alia, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive (oestrus) cycle normality, sexual behavior, fertility, gestation length, parturition, pregnancy outcomes, and premature reproductive senescence.

Standard information requirements for reproductive toxicity in the tonnage band of 100-1000 tpa are:

- Screening for reproductive/developmental toxicity (Annex VIII 8.7.1.)
- Extended one-generation reproductive toxicity study (Annex IX 8.7.3.)
    - only required if available repeated dose toxicity studies indicate adverse effects or other concerns related to reproductive toxicity (Annex IX, 8.7.3. column 1)

Developmental toxicity involves effects on normal development of a born or unborn organism that results from exposure of the adult during pregnancy or the developing organism at any point of its life span with manifestations like death of the developing organism, structural abnormalities, altered growth, and functional deficiencies (ECHA, 2017a).

Standard information requirements for developmental toxicity in the tonnage band of 100-1000 tpa are:

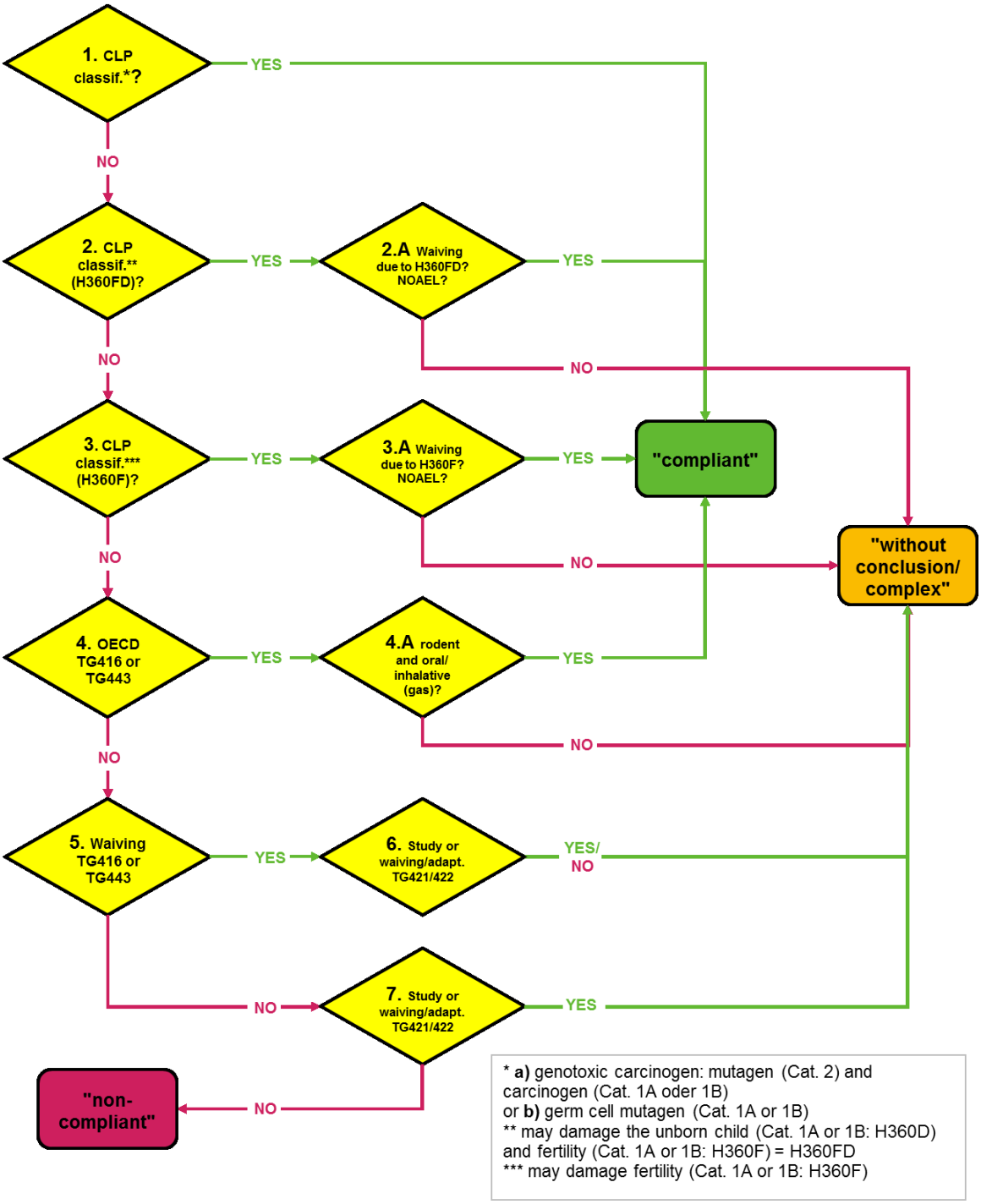
- Screening for reproductive/developmental toxicity (Annex VIII, 8.7.1.)
- Prenatal developmental toxicity study in one species (Annex IX, 8.7.2.)

Contrary to the requirements for ≥ 1000 tpa, OECD TG 414 (OECD, 2001) on a second species is only required if it is 'triggered'. These triggers are findings in the first OECD TG 414 (OECD, 2001) and other relevant data.

A.4.1 Screening

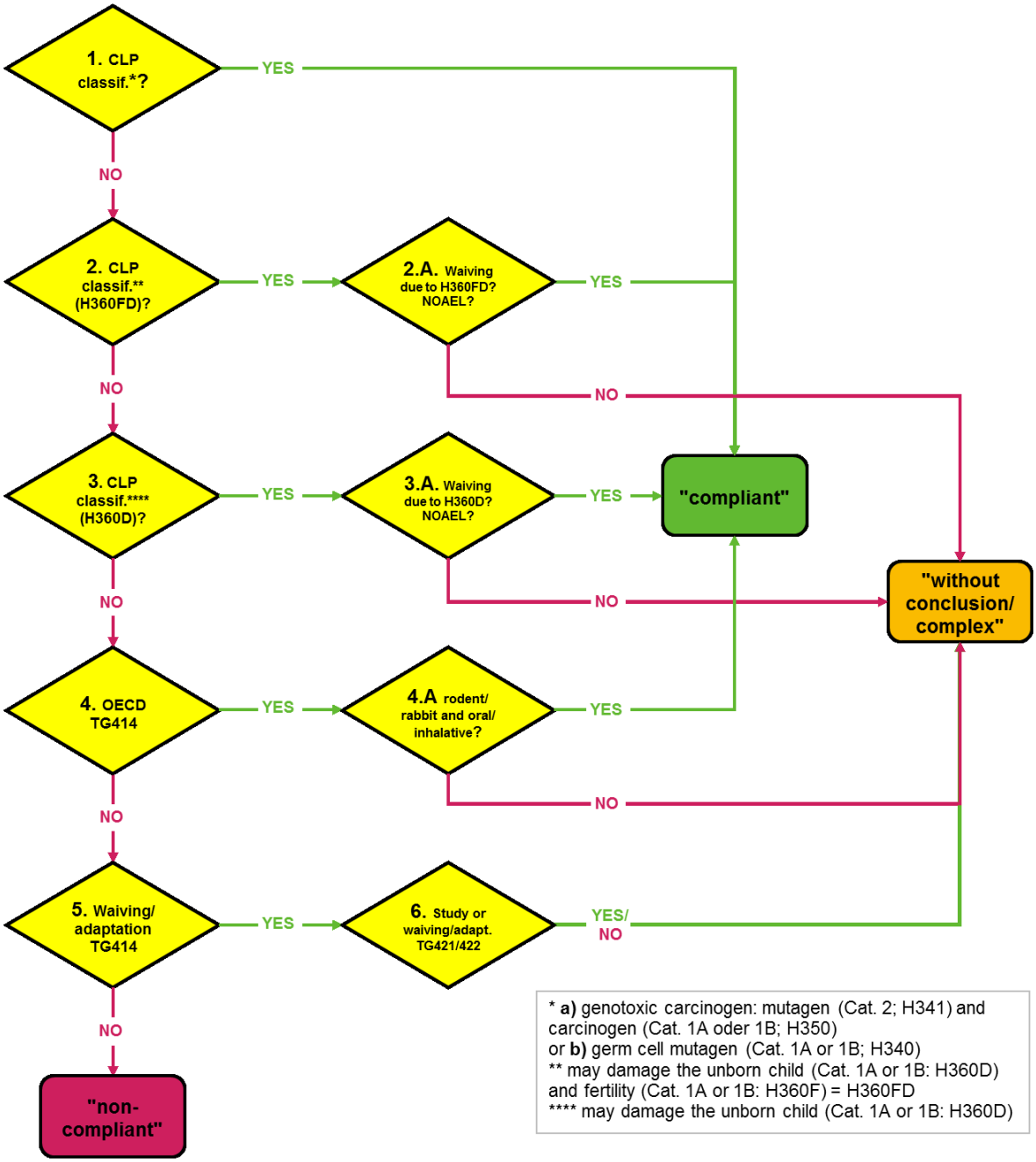
For the current project the endpoints reproductive toxicity and developmental toxicity were evaluated separately. The decisions trees are presented in Figure A2 and Figure A3. The subsequent text boxes explain the questions and answer options, either for reproductive or developmental toxicity. If not noted, the question was valid for both endpoints.

Figure A2: Decision tree of the endpoint reproductive toxicity



adapted from Springer et al. (2015)

Figure A3: Decision tree of the endpoint developmental toxicity



adapted from Springer et al. (2015)

Question No. 1

Is the substance classified as a genotoxic carcinogen (mutagen category 2, H341 and carcinogen category 1A or 1B, H350) or a germ cell mutagen (mutagen category 1A or 1B, H340) according to the CLP Regulation?

Answer Yes: Categorisation as "compliant"[a]

Answer No: Continuation with question 2

[a] If the substance is already classified as described above, waiving or adaptation of the standard information is formally required. However, within the scope of the project no further requirements are evaluated. Furthermore, appropriate risk management measures are not included in the screening.

Question No. 2

Is the substance classified as a reproductive toxicant (category 1A or 1B, H360) according to the CLP Regulation affecting fertility and the unborn child (H360FD)?

Answer Yes: Continuation with question 2.A

Answer No: Continuation with question 3

Question No. 2.A

Is a waiving due to H360FD available? Is a NOAEL available to represent a robust risk assessment and on which study is it based?

Answer Yes: Categorisation as "compliant"

Answer Yes, but no NOAEL: Categorisation as "without conclusion"

Answer No: Categorisation as "without conclusion"

Answer No, but NOAEL: Categorisation as "compliant"[b]

[b] The waiving due to the respective classification is formally required but is not decisive for the screening.

Question No. 3 – reproductive toxicity

Is the substance classified as a reproductive toxicant (category 1A or 1B, H360F) according to the CLP Regulation affecting fertility?

Answer Yes: Continuation with question 3.A

Answer No: Continuation with question 4

Question No. 3 – developmental toxicity

Is the substance classified as a reproductive toxicant (category 1A or 1B, H360D) according to the CLP Regulation affecting the unborn child?

Answer Yes: Continuation with question 3.A

Answer No: Continuation with question 4

Question No. 3.A – reproductive toxicity

Is a waiving due to H360F available? Is a NOAEL available to represent a robust risk assessment and on which study is it based?

Answer Yes: Categorisation as "compliant"

Answer Yes, but no NOAEL: Categorisation as "without conclusion"

Answer No: Categorisation as "without conclusion"

Answer No, but NOAEL: Categorisation as "compliant"[c]

[c] The waiving due to the respective classification is formally required but is not decisive for the screening.

Question No. 3.A – developmental toxicity

Is a waiving due to H360D available? Is a NOAEL available to represent a robust risk assessment and on which study is it based?

Answer Yes: Categorisation as "compliant"
Answer Yes, but no NOAEL: Categorisation as "without conclusion"
Answer No: Categorisation as "without conclusion"
Answer No, but NOAEL: Categorisation as "compliant"[d]

[d] The waiving due to the respective classification is formally required but is not decisive for the screening.

Question No. 4 – reproductive toxicity

Is a study on reproductive toxicity (OECD TG 416 (OECD, 1983) or OECD TG 443 (OECD, 2012e)) available?

Answer Yes: Continuation with question 4.A
Answer No: Continuation with question 5

Question No. 4 – developmental toxicity

Is a study on developmental toxicity (OECD TG 414 (OECD, 2001)) available?

Answer Yes: Continuation with question 4.A
Answer No: Continuation with question 5

Question No. 4.A

Is the study conducted on rodent (reproductive toxicity) or rodent/rabbit (developmental toxicity) and is the oral or the inhalative administration route chosen?

Answer Yes: Categorisation as "compliant"
Answer No: Categorisation as "without conclusion"[e]

[e] Preferred species is rat (reproductive toxicity) and rat/rabbit (developmental toxicity), preferred route is oral or inhalative for gases. Other species are possible. The route has to be the most appropriate having regard to the likely route of human exposure. Within the scope of the screening other species than rodent and other routes than the preferred ones are categorised as "without conclusion".

Question No. 5 – reproductive toxicity

Is a waiving or adaptation option for the OECD TG 416 (OECD, 1983)/443 (reproductive toxicity (OECD, 2012e)) available?

Answer Yes: Continuation with question Q6[f]
Answer No: Continuation with question Q7[f]

Question No. 5 – developmental toxicity

Is a waiving or adaptation option for the OECD TG 414 (developmental toxicity (OECD, 2001)) available?

Answer Yes: Continuation with question Q6[f]
Answer No: Categorisation as "non-compliant"

[f] The adaptation or waiving category is specified in the memo field of the excel data sheet.

Question No. 6

Is a screening test available (OECD TG 421 (OECD, 2016a) or OECD TG 422 (OECD, 2016b)) or is a waiving/adaptation option for the OECD TG 421 or 422 available?

Answer Yes/No: Categorisations as "without conclusion"

Question No. 7 – reproductive toxicity

Is a screening test available (OECD TG 421 (OECD, 2016a) or OECD TG 422 (OECD, 2016b)) or is a waiving/adaptation option for the OECD TG 421 or 422 available?

Answer Yes: Categorisation as "without conclusion"

Answer No: Categorisation as "non-compliant"

Table A6 shows the OECD and EU guidelines and the respective US EPA analogues for toxicity to reproduction studies accepted under REACH. Within the screening step of the project, studies that were conducted according to these test methods were accepted to fulfil the standard information requirements. The evaluation of the appropriate route of administration was not part of the screening. "[…] the oral route (gavage, in diet, or in drinking water) is the "default" route, except for gases.[…] If another route of administration other than oral is used, the registrant should provide justification and reasoning for its selection." (ECHA, 2017b). For endpoint entries with the route choice "inhalation", it was randomly checked if aggregate state of the substance is gaseous. This analysis showed that the inhalative route was correctly chosen for all selected endpoint entries. Consequently, inhalative route was also accepted as default route. If, however, the dermal route was chosen, the endpoint remained "complex". "Non-physiological routes of human exposure, such as [intravenous, intramuscular, subcutaneous, intraperitoneal] are usually considered not appropriate routes of administration for animal testing to be requested for the REACH Regulation." (ECHA, 2017b). Therefore, endpoint entries with studies using these routes remained "complex".

Table A6: Reproductive and developmental toxicity – overview of the accepted test methods for the endpoints

Category[a]	Test method[b]	OECD TG[b]	EU method[c]	US EPA analogue[d]		Remarks
				OCSPP	OPPT	
Developmental toxicity / reproductive toxicity - Screening	Reproduction/developmental toxicity screening test	421		870.3550		
	Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test	422	B.33	870.3650		
Developmental toxicity	Prenatal developmental toxicity study	414	B.31	870.3700	798.4900	
Reproductive toxicity	Two-generation reproduction toxicity study	416	B.35	870.3800	798.4700	
	Extended one-generation reproductive toxicity study	443	B.56			Updated EU method (08/2014)[e]

According to [a] Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance (ECHA, 2017a); [b] OECD Guidelines for the Testing of Chemicals, Section 4 – Health Effects (OECD, 2015); [c] Council Regulation (EC) No 440/2008 (EC, 2008a); [d] OCSPP Harmonized Test Guidelines, series 870 –Health effects test guidelines (OCSPP, 2015);
[e] EU method was updated (EU, 2014)

Table A7: Reproductive and developmental toxicity - Subordinate test methods that may provide additional supporting information on the endpoints

Category[a]	Test method[b]	OECD TG[b]	EU method[c]	US EPA analogue[d]		Remarks
				OCSPP	OPPT	
Develop-mental toxicity	Developmental neurotoxicity study	426	B.53			Updated EU method (08/2014)[e]
Reproductive toxicity	One-generation reproduction toxicity study	415	B.34			

According to [a] Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance (ECHA, 2017a); [b] OECD Guidelines for the Testing of Chemicals, Section 4 – Health Effects (OECD, 2015); [c] Council Regulation (EC) No 440/2008 (EC, 2008a); [d] OCSPP Harmonized Test Guidelines, series 870 –Health effects test guidelines (OCSPP, 2015)
[e] EU method was updated (http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014R0900)

Studies referring to guidelines other than mentioned in Table A6, *e.g.* OECD guidelines for further endpoints, guidelines from FDA or ICH or studies mentioned in

Table A7, may provide information on reproductive or developmental toxicity. However, in these studies not all of the required test parameters and/or organs may have been evaluated (ECHA, 2017a). Since expert judgement would have been needed to assess the suitability of these studies, the memo "other guide" was assigned and the endpoint was concluded "complex", if no other accepted information was available. Consequently, studies which were not conducted according to any guideline or where the guideline information was missing were assigned with the memo "no guide" and concluded "complex" if no other accepted information was available. Studies conducted with non-rodent species, *e.g.* dog (reproductive toxicity and developmental toxicity) or rabbit (reproductive toxicity) also would have needed expert judgement and therefore remained complex.

A.4.2 Formal check

Table A8: Reproductive and developmental toxicity – formal check of endpoint-specific justifications for data waiving

Standard information requirement (column 1)	REACH reference (column 2)	Required justification	Additional criteria
Annex VIII, 8.7.1. Reproductive toxicity & developmental toxicity Screening study	Annex VIII 8.7.1. column 2, 1st passage, 1st bullet point	*known genotoxic carcinogen*	criterion is explained in waiving justification
	Annex VIII 8.7.1. column 2, 1st passage, 2nd bullet point	*known germ cell mutagen*	criterion is explained in waiving justification
	Annex VIII 8.7.1. column 2, 1st passage, 3rd bullet point	*no relevant human exposure (referenced to Annex XI, section 3)*	refined check
	Annex VIII 8.7.1. column 2, 1st passage, 4th bullet point	▪ *prenatal developmental toxicity study* ▪ *extended one-generation reproductive toxicity study* ***or*** ▪ *a two-generation reproductive toxicity study available*	criteria are explained in waiving justification **and** study available: ▪ key study with a reliability of 1 or 2 **or** ▪ WoE
	Annex VIII 8.7.1. column 2, 2nd passage	*Criteria for classification as toxic for reproduction cat. 1A or 1B (H360F) are met*	criterion is explained in waiving justification
	Annex VIII 8.7.1. column 2, 3rd passage	*Criteria for classification as toxic for reproduction cat. 1A or 1B (H360D) are met*	criterion is explained in waiving justification
	Annex VIII 8.7.1. column 2, 4th passage	*testing proposal for extended one-generation reproductive toxicity or prenatal developmental toxicity study*	criterion is explained in waiving justification
Annex IX, 8.7. Reproductive toxicity & developmental toxicity	Annex IX 8.7. column 2, 1st passage, 1st bullet point	*known genotoxic carcinogen*	criterion is explained in waiving justification
	Annex IX 8.7. column 2, 1st passage, 2nd bullet point	*known germ cell mutagen*	criterion is explained in waiving justification
	Annex IX 8.7. column 2, 1st passage, 3rd bullet point	▪ *low toxicological activity* ***and*** ▪ *no systemic absorption via relevant routes of exposure* ***and*** ▪ *no or no significant human exposure*	criteria are explained in waiving justification
	Annex IX 8.7. column 2, 2nd passage	*Criteria for classification as toxic for reproduction cat. 1A or 1B (H360F) are met*	criterion is explained in waiving justification
	Annex IX 8.7. column 2, 3rd passage	*Criteria for classification as toxic for reproduction cat. 1A or 1B (H360D) are met*	criterion is explained in waiving justification

It has to be noted that if a substance was classified (Muta 2, H341 and Carc 1A/B, H350; Muta 1A/B, H340; Repro 1A/B, H360FD) and the respective study was not required, the endpoint entry will usually already be concluded "compliant" in the screening (see Figure A2 and Figure A3).

Formal check – reproductive toxicity

For the endpoint reproductive toxicity special features have to be taken into account based on the standard information requirements for 100-1000 tpa. For this tonnage band an EOGRTS (OECD TG 443 (OECD, 2012e)) or a OECD TG 416 (OECD, 1983) only has to be provided if there are adverse effects on reproduction (Trigger) in the available repeated dose toxicity or screening (OECD TG 421 (OECD, 2016a)/OECD TG 422 (OECD, 2016b)) studies. Accordingly, if no information at all is available for this endpoint (no OECD TG 443 (OECD, 2012e) and no waiving/adaptation) or if a waiving according to column 2 or REACH Annex XI is assessed "non-compliant" in the formal check, the endpoint entrie will be concluded "complex" in the final evaluation. As the requirement of the test can only be determined after evaluation of possible adverse effects on reproduction in the respective repeated dose toxicity /screening studies, an in-depth analysis would be required, which was not within the scope of the project. If no repeated dose toxicity or screening studies are available, the dossier also remains "complex" for this endpoint, since a final evaluation is not possible. However, some registrants create waiving records with justifications addressing these column 1-arguments (column 1). If the absence of trigger is explicated in that waiving justification and a reliable repeated dose toxicity /screening study (or "compliant" read-across-/WoE record) is available, it is rated as "compliant". When registrants report the existence of trigger, but nevertheless omit the standard test, they are rated as "non-compliant", as in this case the OECD TG 443 (OECD, 2012e) is formally required (see chapter 0 and 3.2.4.3 for detailed information).

A.4.3 Refined check

The refined check was performed on all weight of evidence approaches and the methods of evaluation correspond to 2.6.1.

Remaining endpoint entries that can only be evaluated according to the trigger in the repeated dose toxicity or screening studies ("Trigger") are not examined further and remain "complex" (see 3.2.4.4).

B Environment: Endpoint specific evaluation methods

B.1 Biotic Degradation

B.1.1 Screening

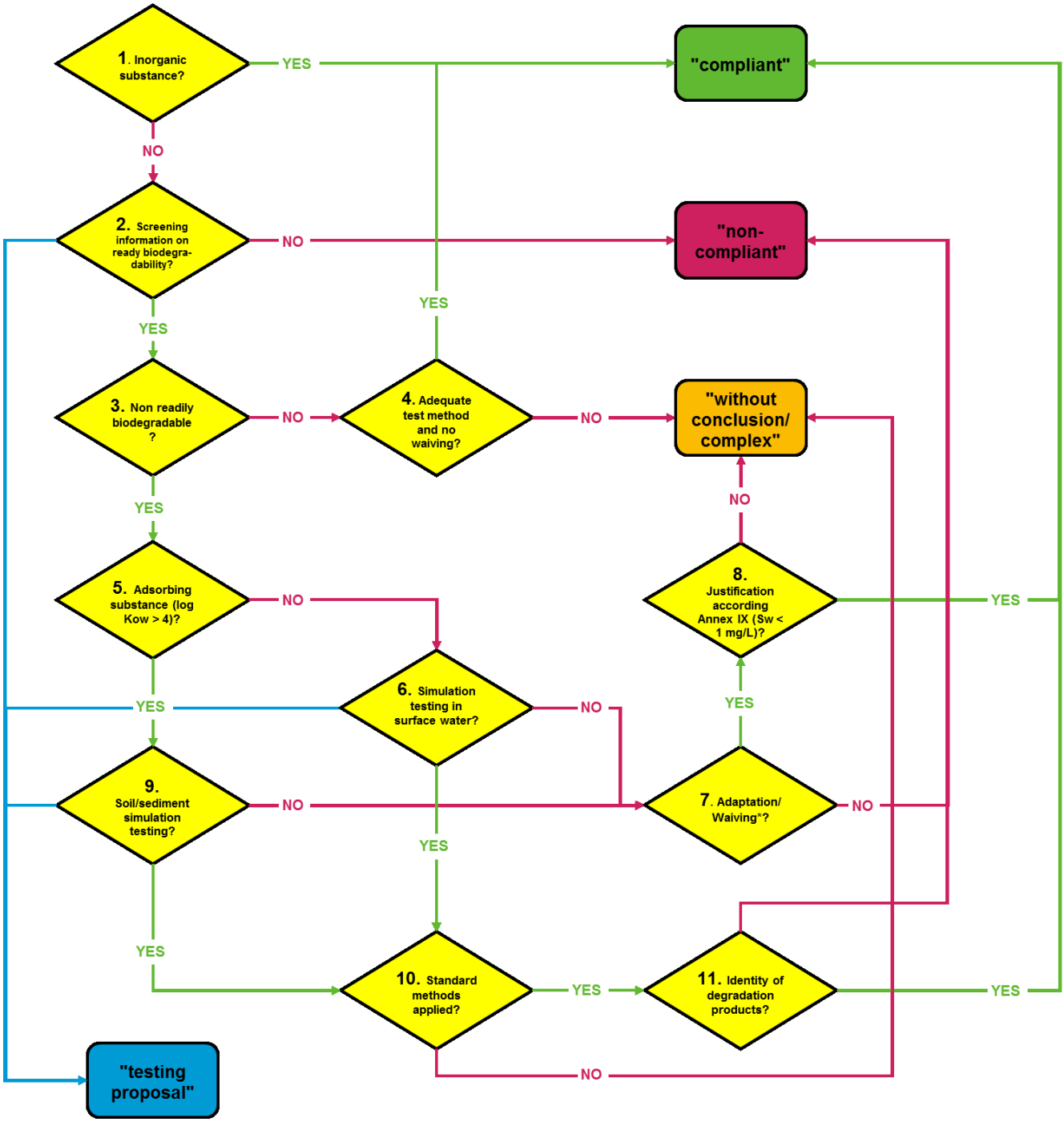
The screening of data availability for the endpoint biotic degradation was based on the same decision tree that was developed within the first part of the REACH compliance Project for the screening of ≥1000 tpa substances (Figure A4). The exact queries of the decision tree are summarised in the text box beneath. A more detailed description of the screening method can be found in the report on the first part of the REACH compliance Project (Springer et al., 2015).

In the case of a readily biodegradable substance, it was assessed whether an adequate standard method was used (question 4). According to OECD TG 301 (OECD, 1992b) and OECD TG 310 (OECD, 2006), not all test methods are equally suited for poorly water soluble, volatile or adsorptive substances. The applicability of test methods was therefore evaluated with respect to the physico-chemical properties of the test material (Table A9).

The volatility of the substance was preferentially assessed by means of the Henry's law constant (K_H) provided by the registrant. However, since this endpoint is not part of the REACH standard information requirements, the data was frequently not available. Therefore, in the absence of the Henry's law constant, a surrogate value was estimated by the project staff using an appropriate calculation or (Q)SAR method according to ECHA (2017a) .

Questions used in the decision tree of the endpoint biotic degradation
Question 1: Is the substance inorganic?
Question 2: Is information available regarding ready biodegradability?
Question 3: Is the substance not readily biodegradable?
Question 4: Is an adequate standard method and no waiving applied?
Question 5: Is the substance highly adsorptive (log K_{OW} > 4)?
Question 6: Is a simulation test in surface water available?
Question 7: Is waiving/adaptation available?
Question 8: Is waiving justified with Sw < 1 mg/L according to Annex IX 9.2.1.2. column 2?
Question 9: Is a simulation test in sediment or soil available?
Question 10: Is a standard-method applied?
Question 11: Are degradation products identified?

Figure A4: Decision tree of the endpoint biotic degradation



adapted from Springer et al. (2015)

Table A9: Test methods, degradation pass levels and suitability of standard test methods on ready biodegradability according to OECD (OECD, 1992b; OECD, 2006) and EU test methods (EC, 2008a)

Test method		Degradation pass level	Suitability of test method according to OECD 301 and 310		
OECD	EU		Poorly soluble	Volatile	Adsorptive
			S_w < 100 mg/L	K_H > 10 Pa m^3 mol^{-1}	log K_{OW} > 4
301 A	C.4 A	> 70 % (DOC)	-	-	+/- (-)
301 B	C.4 C	> 60 % ($ThCO_2$)	+	-	+
301 C	C.4 F	> 60 % (ThOD)	+	+/- (+)	+
301 D	C.4 E	> 60 % (ThOD)	+/- (+)	+	+
301 E	C.4 B	> 70 % (DOC)	-	-	+/- (-)
301 F	C.4 D	> 60 % (ThOD)	+	+/- (+)	+
310	C.29	> 60 % (ThIC)	+	+	+/- (+)

In brackets: Suitability of test method according to ECHA guidance R.7b (ECHA, 2017b). S_W – Water solubility; K_H – Henry's law constant; K_{OW} –Partition coefficient, n-octanol-water; DOC – Dissolved Organic Carbon; ThOD – Theoretical Oxygen Demand; $ThCO_2$ – Theoretical CO_2 production; ThIC – Theoretical Inorganic Carbon production.

B.1.2 Formal check

The identified endpoint-specific approaches for data waiving were assessed with respect to the specific rules outlined in column 2 of REACH Annex IX (

Table A10). A more detailed description of the formal check approach is included in the second report on the REACH compliance Project (Oertel et al., 2018b).

Table A10: Biotic degradation – formal check of endpoint-specific justifications for data waiving

Standard information requirement (column 1)	REACH reference (column 2)	Required justification	Additional criteria
Annex IX, 9.2. Degradation	Annex IX, 9.2.	The CSA according to REACH Annex I does not indicate the need to investigate further the degradation of the substance	▪ Refined check
Annex IX, 9.2.1.2. Simulation testing on ultimate degradation in surface water	Annex IX, 9.2.1.2. 1st bullet point	The substance is highly insoluble in water	▪ Adequate documentation of water solubility ▪ Key study with a reliability 1 or 2 or WoE ▪ Sw < 1 mg/L
	Annex IX, 9.2.1.2. 2nd bullet point	The substance is readily biodegradable	▪ Adequate documentation of ready biodegradability ▪ Key study with a reliability 1 or 2 or WoE ▪ Pass level for ready biodegradability
Annex IX, 9.2.1.3. Soil simulation testing	Annex IX, 9.2.1.3., 1st bullet point	The substance is readily biodegradable	▪ Adequate documentation of ready biodegradability ▪ Key study with a reliability 1 or 2 or WoE ▪ Pass level for ready biodegradability
	Annex IX, 9.2.1.3., 2nd bullet point	Direct and indirect exposure of soil is unlikely	▪ Exposure scenarios or qualitative exposure assessment available
Annex IX, 9.2.1.4. Sediment simulation testing	Annex IX, 9.2.1.4., 1st bullet point	The substance is readily biodegradable	▪ Adequate documentation of ready biodegradability ▪ Key study with a reliability 1 or 2 or WoE ▪ Pass level for ready biodegradability
	Annex IX, 9.2.1.4., 2nd bullet point	Direct and indirect exposure of sediment is unlikely	▪ Exposure scenarios or qualitative exposure assessment available
Annex IX, 9.2.3 Identification of degradation products	Annex IX, 9.2.3	The substance is readily biodegradable	▪ Adequate documentation of ready biodegradability ▪ Key study with a reliability 1 or 2 or WoE ▪ Pass level for ready biodegradability

B.1.3 Refined check

Waiving of simulation testing with reference to CSA

This case group comprises all cases of data waiving that could be directly or indirectly allocated to section 9.2 of REACH Annex IX (column 2):

"Further biotic degradation testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance and its degradation products. The choice of the appropriate test(s) depends on the results of the chemical safety assessment and may include simulation testing in appropriate media (e.g. water, sediment or soil)"

Consequently, waiving of simulation testing with reference to the CSA is only applicable if the available screening information is sufficient to demonstrate the absence of a significant risk and to conclude on PBT/vPvB properties of the substance. The refined check of biotic degradation followed a stepwise approach to assess whether these conditions were met (Table A11).

Further simulation testing of the biodegradability of the substance may be required if the risk characterisation indicates a potential risk for one or more environmental compartments (ECHA, 2017b). Therefore, questions 1 and 2 address the completeness and the outcome of the risk characterisation with a specific focus on the environmental compartment for which simulation testing was omitted.

If the registrant cannot derive a definitive conclusion in the PBT/vPvB assessment using the relevant available information, the registrant must generate the necessary information. Alternatively, the substance may be considered and managed "*as if it is a PBT or vPvB*" (ECHA, 2017b). The fulfilment of this obligation is assessed by Questions 3 to 5.

The identification of degradation products is usually required if the substance is not readily biodegradable (REACH Annex IX, 9.2.3.). Moreover, degradation products should be addressed in the PBT/vPvB assessment if the available information indicates that relevant degradation products are formed (ECHA, 2017e). Therefore, question 6 was applied to document the availability of other information on potential biotic degradation products.

Table A11: Biotic degradation - refined check of data waiving with reference to CSA

No.	Question	Assessment criteria and scope
1	Are the required exposure scenarios available for all identified uses?	Environmental compartment for which simulation testing was omitted
2	Is PEC/PNEC < 1 for all relevant exposure scenarios?	Environmental compartment for which simulation testing was omitted
3a	Is there other information than positive ready biodegradation test which provides proof for "*not P/vP*"?	E.g. positive enhanced ready biodegradation test, inherent test
3b	Is there other information than negative ready biodegradation test which provides proof for "*potentially P/vP*"?	E.g. negative enhanced ready biodegradation test, inherent test
3c	Is there other information useful in a weight-of-evidence approach?	E.g. abiotic degradation, (Q)SARs, monitoring data
4	Is further simulation testing required to conclude on PBT/vPvB?	Table R.11-4, R.11.4.1.4.3 (ECHA, 2017e)
5	Is the substance considered "*as if PBT/vPvB*"?	Conclusion on PBT/vPvB in IUCLID and CSR
6	Is other information on potential biotic degradation products available?	e.g. (Q)SAR

B.2 Abiotic Degradation

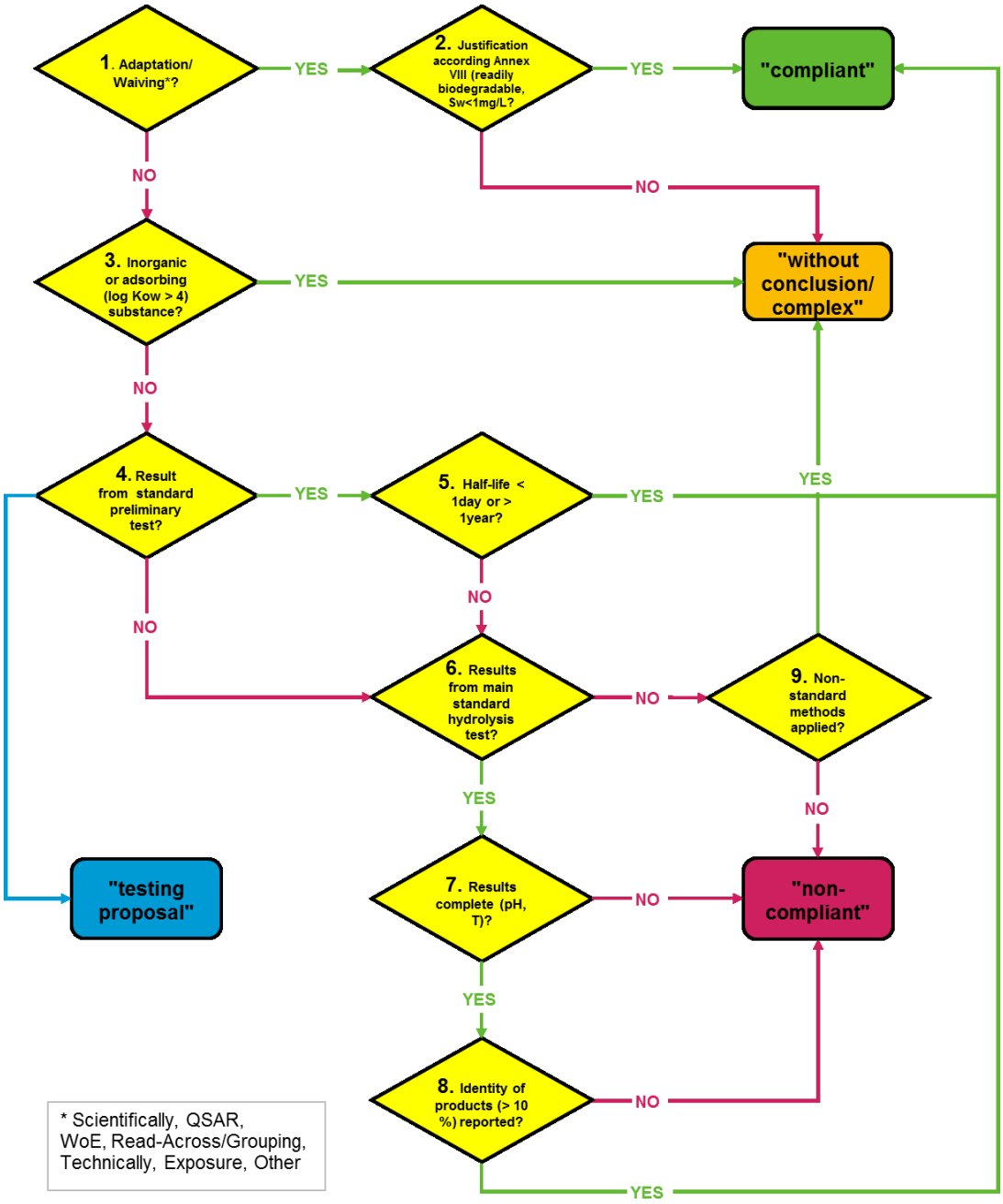
B.2.1 Screening

The screening of data availability for the endpoint abiotic degradation was based on the same decision tree that was developed within the first part of the REACH compliance Project for the screening of ≥ 1000 tpa substances (Figure A5). The exact queries of the decision tree are summarised in the text box beneath. A more detailed description of the screening methods can be found in the report on the first part of the REACH compliance Project (Springer et al., 2015).

Questions used in the decision tree of the endpoint abiotic degradation

Question 1: Is waiving/adaptation available?
Question 2: Is waiving justified with Sw < 1 mg/L or is the substance readily biodegradable according to Annex VIII 9.2.2.1. column 2?
Question 3: Is the substance highly adsorptive (log K_{OW} > 4) or inorganic?
Question 4: Is a result from a standard pre-test available (OECD TG 111)?
Question 5: Are the extrapolated half-lives derived from a hydrolysis pre-test < 1 day or > 1 year at all relevant pH values?
Question 6: Is a result from a standard main test available (OECD TG 111)?
Question 7: Are results available for all relevant pH values and temperatures?
Question 8: Are degradation products (> 10 %) identified?
Question 9: Was a non-standard method applied?

Figure A5: Decision tree of the endpoint abiotic degradation



adapted from Springer et al. (2015)

B.2.2 Formal check

The identified endpoint-specific approaches for data waiving were assessed with respect to the specific rules outlined in column 2 of REACH Annex VIII (Table A12). A more detailed description of the formal check approach is included in the second report on the REACH compliance Project (Oertel et al., 2018b).

Table A12: Abiotic degradation - Formal check of endpoint-specific justifications for data waiving

Standard information requirement (column 1)	REACH reference (column 2)	Required justification	Additional criteria
Annex VIII, 9.2.2.1. Hydrolysis as a function of pH	Annex VIII, 9.2.2.1. 1st bullet point	The substance is readily biodegradable	▪ Adequate documentation of ready biodegradability ▪ Key study with reliability 1 or 2 or WoE ▪ Pass level for ready biodegradability
	Annex VIII, 9.2.2.1. 2nd bullet point	The substance is highly insoluble in water	▪ Adequate documentation of water solubility ▪ Key study with reliability 1 or 2 or WoE ▪ Sw < 1 mg/L

B.2.3 Refined check

Waiving with reference to the chemical structure

This case group comprises all cases of data waiving that were justified with the absence of hydrolysable functional groups in the chemical structure of the registered substance.

The presence or absence of hydrolysable functional groups was assessed with the HYDROWIN v2.00 module of US EPA's EPI Suite (US EPA, 2012). The software identifies a variety of chemical structure classes that undergo hydrolysis and estimates acid- and base-catalysed hydrolysis rate constants or gives relevant experimental data. The CAS number of the registered substance was preferably used as input parameter for the *in silico* screening. If the CAS number was not recognized by the program's internal data base, another attempt was made by using the SMILES notation of the substance.

The endpoint conclusion was "compliant" if no hydrolysable functional groups were detected in the chemical structure(s) of the registered substance. In the opposite case, the endpoint was concluded "non-compliant". If the presence or absence of hydrolysable structures could not be unequivocally elucidated, the endpoint was concluded "complex".

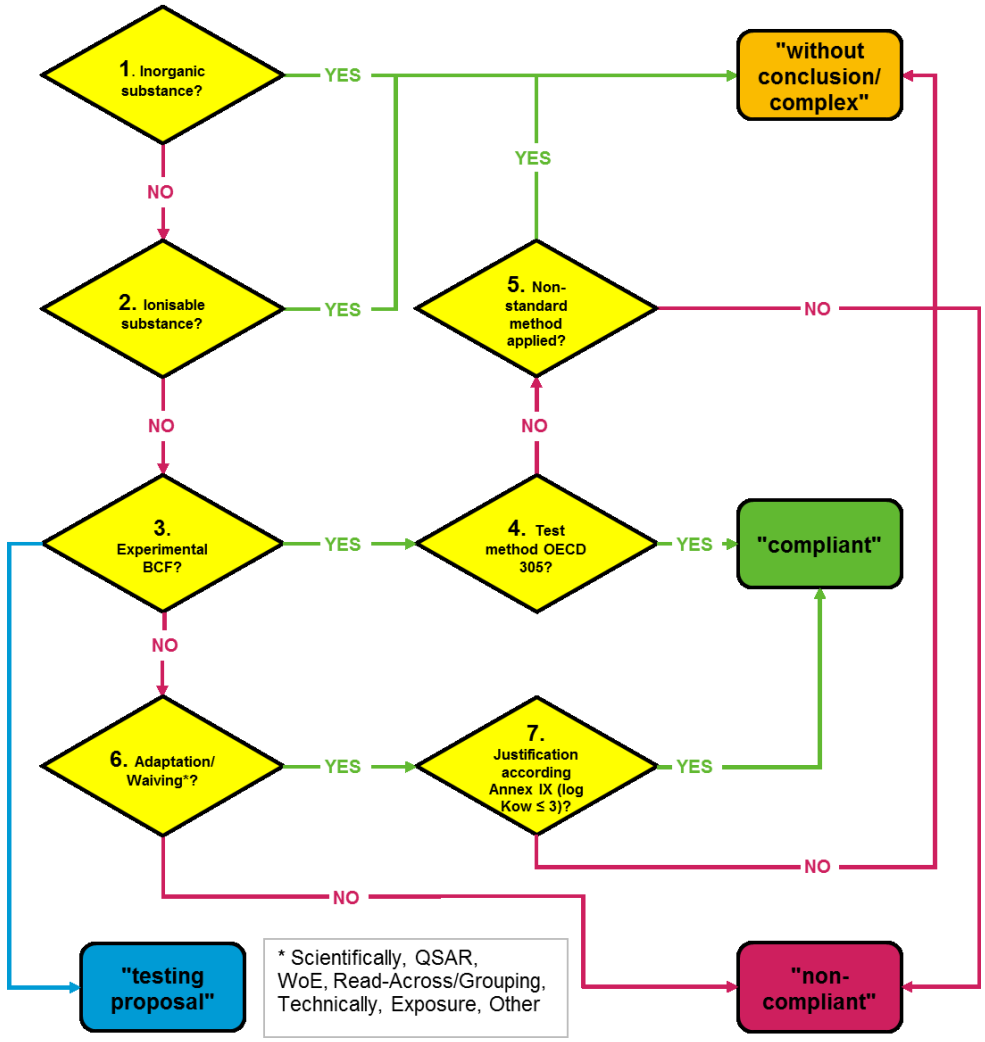
B.3 Bioaccumulation

B.3.1 Screening

The screening of data availability for the endpoint bioaccumulation was based on the same decision tree that was developed within the first part of the REACH compliance Project for the screening of ≥ 1000 tpa substances (Figure A6). The exact queries of the decision tree are summarised in the text box beneath. A more detailed description of the screening methods can be found in the report on the first part of the REACH compliance Project (Springer et al., 2015).

Questions used in the decision tree of the endpoint bioaccumulation
Question 1: Is the substance inorganic?
Question 2: Is the substance ionisable or hydrolytically unstable?
Question 3: Is an experimental BCF available?
Question 4: Is the test conducted according to OECD TG 305?
Question 5: Is another acceptable non-standard method applied?
Question 6: Is waiving/adaptation available?
Question 7: Is waiving justified with a log K_{OW} ≤ 3 according to Annex IX 9.3.2. column 2?

Figure A6: Decision tree of the endpoint bioaccumulation



adapted from Springer et al. (2015)

B.3.2 Formal check

The identified endpoint-specific approaches for data waiving were assessed with respect to the specific rules outlined in column 2 of REACH Annex IX (Table A13). A more detailed description of the formal check approach is included in the second report on the REACH compliance Project (Oertel et al., 2018b).

Table A13: Bioaccumulation – formal check of endpoint-specific justifications for data waiving

Waived/adapted standard information (column 1)	Reference for waiving/adaptation (column 2)	Required justification for waiving/adaptation	Assessment criteria
Annex IX, 9.3.2. Bioaccumulation in aquatic species, preferably fish	Annex IX 9.3.2. 1st bullet point	*The substance has a low potential for bioaccumulation (for instance a log K_{OW} ≤ 3) and/or a low potential to cross biological membranes*	▪ Adequate and reliable documentation of log Kow ▪ Key study with reliability 1 or 2 or WoE ▪ log K_{OW} ≤ 3
	Annex IX 9.3.2. 2nd bullet point	*Direct and indirect exposure of the aquatic compartment is unlikely*	▪ Exposure scenarios or qualitative exposure assessment available

B.3.3 Refined check

The endpoint-specific refined check was not conducted for bioaccumulation since most inconclusive screening evaluations were attributed to intrinsic substance properties (*i.e.* inorganic or ionisable substances). These cases would require extensive analysis of physico-chemical substance properties and experimental conditions that could not be realised within the timeframe of the project.

B.4 Ecotoxicity

B.4.1 Screening

The approach for screening the standard information requirements for the endpoint ecotoxicity was adapted from (Springer et al., 2015) and the general approach is described there.

The specific questions for the screening in the case of ecotoxicity are summarised in the text box beneath and presented as decision tree in Figure A7.

Questions used in the decision tree of ecotoxicity

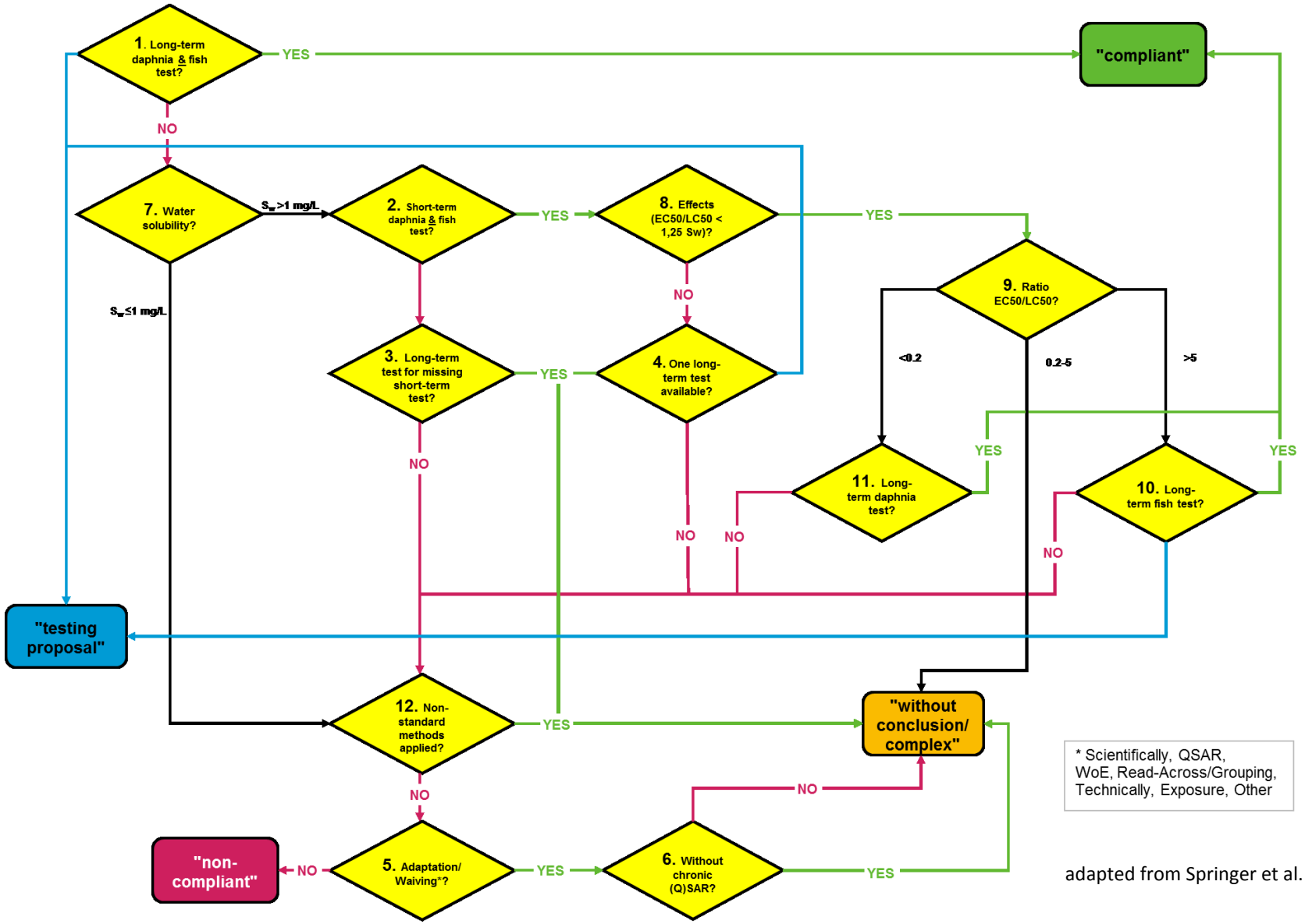
Question 1: Are long-term studies for fish and invertebrates available?
Question 2: Are short-term studies for fish and invertebrates available?
Question 3: Is a long-term test available in place of a missing short-term test?
Question 4: Is a long-term study available?
Question 5: Is a waiving/adaptation available?
Question 6: Is waiving/adaptation exclusively justified by (Q)SAR for long-term studies?
Question 7: What is the water solubility of the substance (mg/L)?
Question 8: Are any effects measured (ratio EC_{50}/LC50 < 1.25 fold water solubility)?
Question 9: What is the toxicity ratio (EC_{50}/LC_{50}) in the short-term tests?
Question 10: Is a long-term fish study available?
Question 11: Is a long-term invertebrates study available?
Question 12: Is a non-standard method applied?

Accepted test methods fulfilling the standard information requirements are summarised in Table A15. Test methods not mentioned in ECHA (2017b) were considered "complex" as described below, unless they were insufficient. Memos were accompanied for short-term tests with a deviation of the standard exposure duration, 48 h instead of 96 h for fish tests, and 24 h instead of 48 h for *Daphnia* tests. Aquatic toxicity tests were evaluated as "non-compliant" when, *e.g.* test duration for Daphnia magna was only 24 h and no other information was provided;

For substances with a water solubility $S_w \leq 1$ mg/L the decision tree was adapted because long-term toxicity testing for daphnia and fish is a standard information requirement for poorly water soluble substances according to REACH Annexes VII and VII, respectively. Accordingly, in these cases testing cannot be omitted by REACH Annex IX, 9.1. column 2 justification and testing, a testing proposal or an appropriate waiving or adaptation should be available. If the substance is highly insoluble registrants should justify that aquatic toxicity is unlikely to occur at the limit of the water solubility. This requires further information such as transformation/dissolution studies or identifying the components of the water accommodated fraction or a limit test.

For substances with a water solubility > 1 mg/L the detailed procedure is described in (Springer et al., 2015).

Figure A7: Decision tree of the endpoint ecotoxicity



adapted from Springer et al. (2015)

B.4.2 Formal check

The applied method for the formal check were adapted from (Oertel et al., 2018b). In contrast to the preceding project on ≥ 1000 tpa substance waiving according to Annex IX 9.1.5. column 2 – Long-term toxicity testing on invertebrates (Daphnia) – and Annex IX 9.1.6. column 2 – Long-term toxicity testing on fish – were not included in the formal check. Instead, the waiving justifications with reference to the chemical assessment were directly evaluated in the refined check (see chapter B.4.3).

Table A14: Endpoint ecotoxicity: checked formal criteria for waiving standard information requirements according to Annexes VII to VIII of the REACH Regulation for short term toxicity testing (remark: REACH Annex IX long-term toxicity testing is part of the refined check)

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
► **Ecotoxicity**			
REACH Annex IX			► Refined check
REACH Annex VII 9.1. Aquatic toxicity	REACH Annex VII 9.1.1. column 2 Short-term toxicity testing on invertebrates (preferred species *Daphnia*)	*The registrant may consider long-term toxicity testing instead of short-term* ► there are mitigating factor indicating that aquatic toxicity is unlikely to occur (highly insoluble in water, unlikely to cross biological membranes) **or** ► a long-term aquatic toxicity study on invertebrates is available or ► adequate information for environmental classification + labelling is available ► If the substance is poorly water soluble, the long-term aquatic toxicity study (Annex IX 9.1.5.) should be considered.	► ESR available ► key study with a ► reliability of 1 or 2 ► S_w ► CSR
REACH Annex VIII	REACH Annex VIII 9.1.3. column 2 Short-term toxicity testing on fish	*The registrant may consider long-term toxicity testing instead of short-term* ► there are mitigating factor indicating that aquatic toxicity is unlikely to occur (highly insoluble in water, unlikely to cross biological membranes) **or**	► ESR available ► key study with a reliability of 1 or 2 ► S_w ► CSR

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
		► a long-term aquatic toxicity study on fish is available **or** ► Long-term aquatic toxicity testing shall be considered if the CSA indicates the need for further effects. ► If the substance is poorly water soluble, the long-term aquatic toxicity study (Annex IX 9.1.6.) should be considered.	

B.4.3 Refined check

Evaluation of chemical safety assessment

Long-term toxicity testing on invertebrates and fish is triggered by the results of the CSA. Waiving of long-term toxicity testing on fish referring to REACH Annex IX column 2 was used frequently to justify omitting testing. The evaluation of the chemical safety assessment for that purpose is the aim of the refined check for the endpoint Ecotox. The method applied is described in (Oertel et al., 2018b).

Table A15: Extended list of accepted standard guidelines in the screening for long-term and short-term testing of aquatic toxicity for fish and invertebrates (starting with list of (Springer et al., 2015))

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
Long-term toxicity to fish			
EU C.14	Fish Juvenile Growth Test (replicate of the OECD TG 215)	EC (2008a)	Council Regulation (EC) No 440/2008
EU C.15	Fish Short-term Toxicity Test on Embryo and Sac-Fry Stages (replicate of OECD TG 2012)	EC (2008a)	Council Regulation (EC) No 440/2008
OECD TG 210	Fish, Early-life Stage Toxicity (FELS) Test	OECD (2013a)	R.7b, p. 31 (ECHA, 2017b)
OECD TG 212	Fish Short-term Toxicity Test on Embryo and Sac-Fry Stages	OECD (1998)	Council Regulation (EC) No 440/2008
OECD TG 215	Fish Juvenile Growth Test	OECD (2000b)	R.7b, p. 31 (ECHA, 2017b)
OECD TG 229	Fish Short-term Reproduction Assay	OECD (2012b)	
OECD TG 230	21-day Fish Assay	OECD (2009a)	
OECD TG 234	Fish Sexual Development Test	OECD (2011)	
40 CFR 797.1600	Fish, Early-life Stage Toxicity (FELS) Test	CFR (2001)	R.7b, p. 103 (ECHA, 2017b)
ASTM E1241-05(2013)	Standard Guide for Conducting Early Life-Stage Toxicity Tests with Fishes	ASTM (2013a)	
ASTM E-1241-92	Standard Guide for Conducting Early Life-Stage Toxicity Tests with Fishes - replaced by ASTM E1241-05(2013)		R.7b, p. 103 (ECHA, 2017b)
CAN EPS 1/RM/28	Toxicity tests using early life stages of salmonid fish (rainbow trout, coho salmon, or Atlantic salmon)	Environment Canada (1998)	R.7b, p. 103 (ECHA, 2017b)
EPA OPP 72-4	Fish Early Life-Stage and Aquatic Invertebrate Life-Cycle Studies	US EPA (1982)	ECHA Webinar (ECHA, 2013)
EPA OPP 72-5	Fish Life Cycle Toxicity		ECHA Webinar (ECHA, 2013)
EPA OPPTS 850.1400	Fish, Early-life Stage Toxicity (FELS) Test	US EPA (1996d)	ECHA Webinar (ECHA, 2013)
EPA OPPTS 850.1500	Fish Life Cycle Toxicity	US EPA (1996e)	ECHA Webinar (ECHA, 2013)

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
EPA OTS 797.1000	Fish, Early-life Stage Toxicity (FELS) Test		ECHA Webinar (ECHA, 2013)
FIFRA (§72-4 a)			R.7b, p. 103 (ECHA, 2017b)
NS (4763)	Determination Of Embryo-larval Toxicity To Freshwater Fish - Semistatic Procedure		R.7b, p. 103 (ECHA, 2017b)
SFS (5501)	Determination of embryo-larval toxicity to freshwater fish - Semistatic method		R.7b, p. 103 (ECHA, 2017b)
SS (SS028193)			R.7b, p. 103 (ECHA, 2017b)
Long-term toxicity to invertebrates			
EU C.20	*Daphnia magna* Reproduction Test (replicate of the OECD TG 211)	EC (2008a)	Council Regulation (EC) No 440/2008
OECD TG 211	*Daphnia magna* Reproduction Test	OECD (2012a)	R.7b, p. 56 (ECHA, 2017b)
OECD TG 202	21-d Reproduction Test, Part 2, performed before 1998 (replaced by OECD TG 211)		ECHA Webinar (ECHA, 2013)
40 CFR 797.1330	Daphnid Chronic Toxicity Test	CFR (2002a)	R.7b, p. 99 (ECHA, 2017b)
40 CFR 797.1350	Daphnid Chronic Toxicity Test (equivalent OECD TG 202, part 2)		R.7b, p. 99 (ECHA, 2017b)
40 CFR 797.1950	Mysid Chronic Toxicity Test	CFR (2004)	R.7b, p. 99 (ECHA, 2017b)
ASTM (E-1193-87)	Renewal life-cycle toxicity tests with saltwater mysids	ASTM (1993b)	R.7b, p. 99 (ECHA, 2017b)
ASTM E 1295	Three-Brood, Renewal Toxicity Tests with *Ceriodaphnia dubia* (Test duration of 7 d should be given)	ASTM (2013b)	R.7b, p. 29: (ECHA, 2017b)
EPA OPP 72-4	Fish Early Life-Stage and Aquatic Invertebrate Life-Cycle Studies	US EPA (1982)	ECHA Webinar (ECHA, 2013)
EPA OPPTS 850.1300	Daphnid Chronic Toxicity Test	US EPA (1996)	ECHA Webinar (ECHA, 2013)
EPA OPPTS 850.1350	Mysid Chronic Toxicity Test	US EPA (1996c)	ECHA Webinar (ECHA, 2013)
EPA OTS 797.1330	Daphnid Chronic Toxicity Test		ECHA Webinar (ECHA, 2013)
EPA OTS 797.1950	Mysid Chronic Toxicity Test		ECHA Webinar (ECHA, 2013)
Short-term toxicity to fish			

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
EU C.1	Acute Toxicity for Fish	EC (2008a)	Council Regulation (EC) No 440/2008
EU 79/831/EEC, Annex V, C.1*	Acute Toxicity for Fish		
EU 84/449/EE, Annex, C.1*	Acute Toxicity for Fish		
EU 92/69/EEC, Annex, C.1*	Acute Toxicity for Fish		
ISO 10229-1	Determination of the Prolonged Toxicity of Substances to Freshwater Fish	ISO (1994)	ECHA Webinar (ECHA, 2013)
ISO 7346-1 EN ISO 7346-1	Determination of the acute lethal toxicity of substances to a freshwater fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)] - Part 1: Static method	ISO (1996a)	R.7b, p. 100 (ECHA, 2017b)
ISO 7346-2 EN ISO 7346-2	Determination of the acute lethal toxicity of substances to a freshwater fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)] - Part 2: Semi-static method	ISO (1996b)	R.7b, p. 100 (ECHA, 2017b)
ISO 7346-3 EN ISO 7346-3	Determination of the acute lethal toxicity of substances to a freshwater fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)] - Part 3: Flow-through method	ISO (1996c)	R.7b, p. 100 (ECHA, 2017b)
OECD TG 203	Fish, Acute Toxicity Test	OECD (1992a)	R.7b, p. 30 (ECHA, 2017b)
OECD TG 204	Fish Prolonged Toxicity Test: 14-day Study	OECD (1984)	R.7b, p. 30 (ECHA, 2017b)
40 CFR 797.1400	Fish acute toxicity test	CFR (2011)	
ASTM 729-88a	Standard Guide for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates and Amphibians	ASTM (1993a)	R.7b, p. 100 (ECHA, 2017b)
ASTM E 729-80:192		ASTM (1980)	
BS 6068-5-5.2:1985	Replaced by EN ISO 7346-1		R.7b, p. 100 (ECHA, 2017b)
BS 6068-5-5.3:1985	Replaced by EN ISO 7346-2		R.7b, p. 100 (ECHA, 2017b)
BS 6068-5-5.4:1985	Replaced by EN ISO 7346-3		R.7b, p. 100 (ECHA, 2017b)
CAN EPS 1/RM/9		Environment Canada (1990)	R.7b, p. 100 (ECHA, 2017b)
DIN 38412-15 (L)*	Determination of the Effect of Substances in Water on Fish (withdrawn)	DIN (1982b)	
DIN 38412-20	Determination of the Effect of Waste Water and Industrial Effluences on Fish	DIN (1980)	

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
	(withdrawn)		
EPA /600/4-90/027*	Methods for Measuring the Acute Toxicity of Effluents to Freshwater and Marine Organisms	US EPA (1991)	R.7b, p. 100 (ECHA, 2017b)
EPA 660/3-75-009	Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians	US EPA (1975a)	
EPA OPPTS 850.1075	Fish acute toxicity test, freshwater and marine	US EPA (1996b)	
EPA OTS 797.1400	Fish acute toxicity test, freshwater and marine		
FIFRA (§ 72-1)			R.7b, p. 100 (ECHA, 2017b)
NF T90-303-1	Equivalent to EN ISO 7346-1		R.7b, p. 100 (ECHA, 2017b)
NF T90-303-2	Equivalent to EN ISO 7346-2		R.7b, p. 100 (ECHA, 2017b)
NF T90-303-3	Equivalent to EN ISO 7346-3		R.7b, p. 100 (ECHA, 2017b)
NF T90-305	Determination of the acute toxicity of a substance to Salmo gairdneri. Static and flow through methods		R.7b, p. 100 (ECHA, 2017b)
SFS (3035+5073)			R.7b, p. 100 (ECHA, 2017b)
Short-term toxicity to invertebrates			
EU C.2	*Daphnia* sp. Acute Immobilisation Test (equivalent to OECD TG 202 (2004))	EC (2008a)	Council Regulation (EC) No 440/2008
EU 79/831/EEC, Annex V, C.2	*Daphnia* sp. Acute Immobilisation Test		
EU 84/449/EEC, Annex, C.2	*Daphnia* sp. Acute Immobilisation Test		
EU 92/69/EEC, Annex, C.2	*Daphnia* sp. Acute Immobilisation Test		
EU (L 384 A vol. 35 C.2)			R.7b, p. 98 (ECHA, 2017b)
ISO 6341 EN ISO 6341	Determination of the inhibition of the mobility of *Daphnia magna* Straus (Cladocera, Crustacea) - Acute toxicity test	ISO (2012)	R.7b, p. 98 (ECHA, 2017b)
OECD TG 202	*Daphnia* sp. Acute Immobilisation Test (48 h), Part 1, performed from 1998	OECD (2004a)	Council Regulation (EC) No 440/2008, ECHA Webinar (ECHA, 2013)
40 CFR 795.120	Gammarid acute toxicity test	CFR (2002b)	R.7b, p. 98 (ECHA, 2017b)

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
40 CFR 797.1300	Daphnid acute toxicity test	CFR (2015)	R.7b, p. 98 (ECHA, 2017b)
40 CFR 797.1330	Daphnid chronic toxicity test	CFR (2002a)	R.7b, p. 99 (ECHA, 2017b)
ASTM E 1295-89	Standard guide for conducting Three-Brood, renewal toxicity tests with *Ceriodaphnia dubia*	ASTM (1989)	R.7b, p. 98 (ECHA, 2017b)
ASTM E 729-88a	Standard Guide for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates and Amphibians	ASTM (1993a)	R.7b, p. 98 (ECHA, 2017b)
BS 6068-5-5.1:1990	Determination of the inhibition of the mobility of *Daphnia magna* Straus (Cladocera, Crustacea), Replaced by EN ISO 6341:1996		R.7b, p. 98 (ECHA, 2017b)
CAN EPS 1/RM/11	Reference Method for Determining Acute Lethality of Effluents to *Daphnia magna*	Environment Canada (2000)	R.7b, p. 98 (ECHA, 2017b)
DIN 38412-11 (L)*	Determination of the effect on microcrustacea of substances contained in water (daphnia short-time test) (withdrawn)	DIN (1982a)	R.7b, p. 98 (ECHA, 2017b)
EPA 600/4-89/001	Short-term methods for estimating the chronic toxicity of effluents and receiving waters to freshwater organisms	US EPA (1989)	R.7b, p. 98 (ECHA, 2017b)
EPA 600/4-90/027*	Methods for Measuring the Acute Toxicity of Effluents to Freshwater and marine organisms	US EPA (1991)	R.7b, p. 98 (ECHA, 2017b)
EPA 660/3-75-009	Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians	US EPA (1975b)	
EPA OPP 72-2			
EPA OPPTS 850.1010	Aquatic Invertebrate Acute Toxicity Test, Freshwater Daphnids	US EPA (1996a)	
EPA OTS 797.1300	Daphnid acute toxicity test		
FIFRA (§72-2)			R.7b, p. 98 (ECHA, 2017b)
NEN 6501	Determination of acute toxicity using *Daphnia magna* (Dutch Standard, withdrawn)		R.7b, p. 98 (ECHA, 2017b)
NEN 6502	Determination of chronic toxicity with *Daphnia magna* (Dutch Standard, withdrawn)		R.7b, p. 98 (ECHA, 2017b)
NF T90-301	Determination of inhibition of *Daphnia magna* mobility (French standard, replaced by EN ISO 6341)		R.7b, p. 98 (ECHA, 2017b)

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
ÖNORM M 6264	Determination of the acute toxicity of water content compared to *Daphnia magna* Straus (Cladocera, Crustacea), replaced by EN ISO 6341		R.7b, p. 98 (ECHA, 2017b)
SFS (5052)			R.7b, p. 98 (ECHA, 2017b)
SS (028180)			R.7b, p. 98 (ECHA, 2017b)

B.5 Environmental exposure assessment

The screening and refined check were adapted from the applied methods for the ≥ 1000 tpa substances (Oertel et al., 2018a; Springer et al., 2015). The check on completeness of the exposure assessment elements from the refined check was integrated into the screening to gain already more information on the quality of exposure assessment within the screening.

B.5.1 Screening

Screening of environmental exposure assessment is described in detail in (Springer et al., 2015). The adapted questions used in the decision trees are described in the text box below and in Figure A8. In contrast to (Springer et al., 2015) question 8 and 9 are in a reversed order. The question on the availability on exposure scenarios (former question 8, now 9) was extended to verify that the required elements of environmental exposure assessment were complete. Therefore, it was checked that the main elements of the exposure assessment were available (question 9a-e). These questions were integrated from the former refined check for ≥ 1000 tpa (Oertel et al., 2018b) into the screening.

For substances registered between 100-1000 tpa exposure assessment human via environment is only required if the substance is classified

- as specific target organ toxicity – repeated exposure – STOT RE 1; or
- as a carcinogen or mutagen (any category); or
- as toxic to reproduction (categories 1A or 1B).

Question 9 could be answered using the information in section 9 “Exposure Assessment” of the CSR. It was also possible to obtain information here on why exposure scenarios were or were not prepared.

Finally, within the screening it was concluded if there is an obligation for an exposure assessment and, if so, that either a qualitative exposure assessment or quantitative exposure assessment was provided. When the exposure scenarios were assessed as “complete” or “without conclusion” they could be further evaluated within the “refined check” (see below).

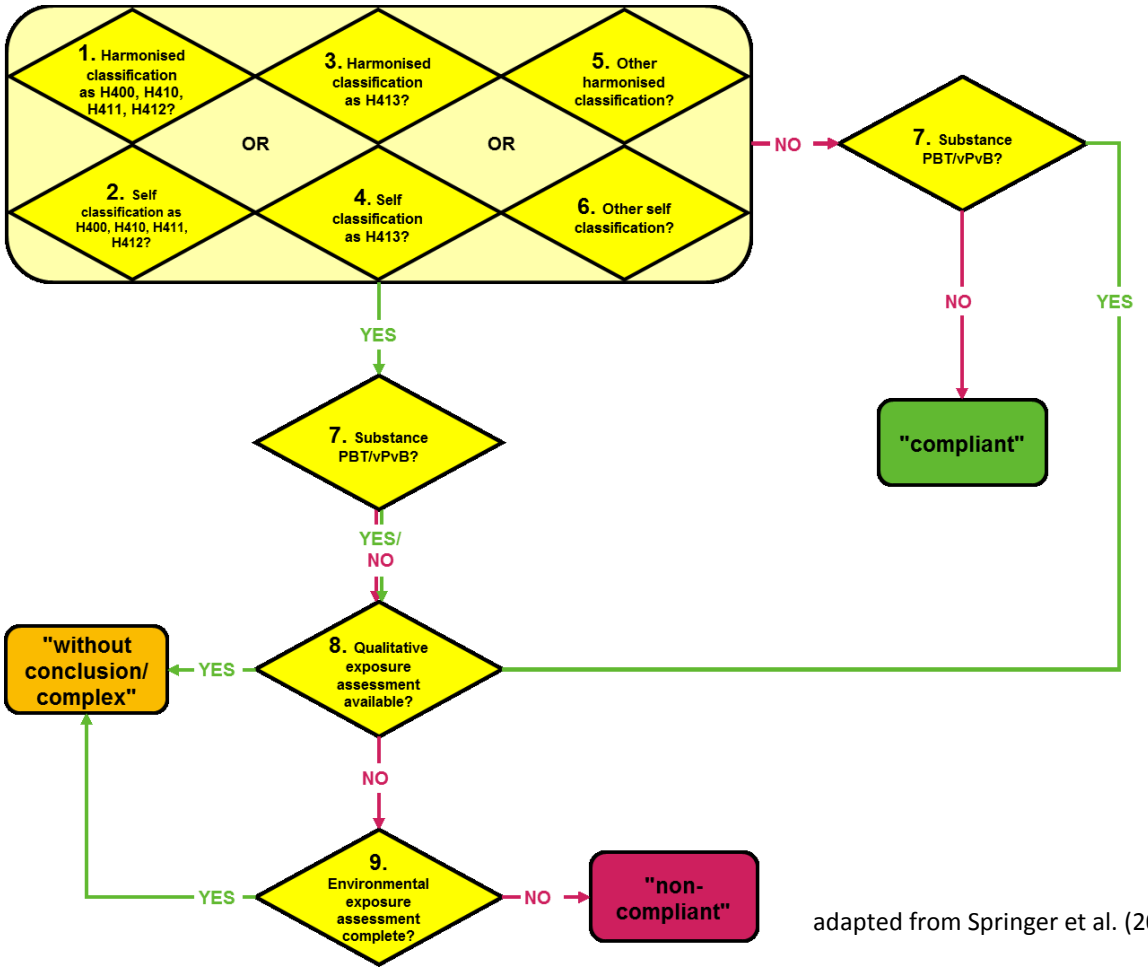
Further information on the environmental exposure assessment and the hazard categories can be found in (Springer et al., 2015).

Questions used in the decision tree of environmental exposure assessment

Question 1: Does the substance have a harmonised classification for aquatic toxicity (H400, H410, H411 or H412)?
Question 2: Is the substance self-classified for aquatic toxicity (hazard statements H400, H410, H411 or H412)?
Question 3: Does the substance have a harmonised classification for aquatic toxicity (H413)?
Question 4: Is the substance self-classified for aquatic toxicity (H413)?
Question 5: Is any other harmonised classification available?
Question 6: Is any other self-classification available?
Question 7a/7b: Is the substance assessed as PBT or vPvB?
Question 8: Is a qualitative exposure assessment available?
Question 9: Is the environmental exposure assessment complete?
Question 9a: Is an exposure scenario available for manufacture and each identified use?
Question 9b: Is the exposure of workers available?
Question 9c: Is the environmental exposure available for each exposure scenario?

Question 9d: Is the exposure of humans via environment available for each exposure scenario in the case it is required?
Question 9e: Is the exposure/risk for aggregated sources available?

Figure A8: Decision tree of the endpoint environmental exposure



adapted from Springer et al. (2015)

B.5.2 Formal check

The environmental exposure assessment was not included in the formal check like in the preceding project (Oertel et al., 2018b).

B.5.3 Refined check

Within the refined check only quantitative exposure assessment was evaluated in registration dossiers which provided "complete" environmental exposure scenarios or remained "without conclusion".

In the current project, a stepwise approach was applied for the evaluation of exposure assessment in CSA (Table A16). An appropriate exposure assessment incorporates diverse input parameters from standard information required in REACH Annexes VII to IX (e.g. physico-chemical properties, biodegradation). Therefore, fulfilling minimum information is the starting point for evaluation of exposure assessment.

The exposure estimation includes a characterisation of possible degradation, transformation, or reaction processes and an estimation of environmental distribution and fate (REACH Annex I 5.2.3.). For this purpose, input data are required from the endpoints AbioDeg and BioDeg.

If the initial exposure scenarios lead to a risk characterisation indicating that risks to human health and the environment are not adequately controlled, then it is necessary to carry out an iterative process to demonstrate adequate control (REACH Annex I 5.1.1.). Consequently, the final exposure scenario should provide that PEC/PNEC < 1. Hence, one requirement for an appropriate exposure assessment is that the input parameters for PNEC derivation are “compliant” with respect to information requirements for the endpoint Ecotox. Accordingly, only registration dossiers were chosen for evaluation if the endpoint Ecotox was evaluated as “compliant” either in screening, formal check or refined check.

If more than 5 exposure scenarios were presented in the CSR, a random sample of 5 scenarios was chosen for steps 3 considering manufacture and different uses of the substance.

Table A16: Refined check of environmental exposure assessment in the chemical safety report (adapted from (Oertel et al., 2018a))

Parameter	Criteria	Action
Step 1 : Selection of registration dossiers for further evaluation		
Exposure assessment	Is a quantitative exposure assessment available and it was assessed as complete in the screening?	Yes: further evaluation
Abiotic degradation and biotic degradation	Are abiotic degradation and biotic degradation both "compliant"*?	Yes: further evaluation
Ecotoxicity	Is Ecotoxicity "compliant" *?	Yes: further evaluation
Fate/hazard profiles	Is more than one fate/hazard profile relevant for the substance?	Yes: "complex"
Step 2: Minimum information required		
Physico-chemical/fate properties[#]	Are the required Tier 1 parameters of sufficient quality?	Yes: further evaluation No: "non-compliant" Waiving/adaptation: "complex"
Step 3: Exposure estimation		
Estimated quantities	Are the quantities for manufacture and each identified use available and plausible?	Yes: further evaluation No: "non-compliant"
Emission data	Are ERCs/spERCs and emission days available?	Yes: further evaluation No: "non-compliant" spERCs : "complex"
ERC parameters	Are the ERCs used with the default parameters?	Yes: further evaluation No, without justification: "non-compliant" No, with justification: "complex"
Step 4: Plausibility check		
PROCs and ERCs	Are there evident contradictions between PROCs and ERCs?	Yes: "non-compliant" No: further evaluation
Life cycle	Is the life cycle complete for each exposure scenario?	Yes: further evaluation No: "non-compliant"

* This includes the following registration dossiers: "Compliant" in the screening, formal or refined check.
[#] molecular weight, vapour pressure, water solubility, melting point, K_{ow} or partition coefficient between organic carbon and water (K_{oc}) or solubility product constant (K_{ps}), Biodegradation