Environmental Research of the
Federal Ministry for the
Environment, Nature Conservation,
and Nuclear Safety (BMU), Germany

Project number: FKZ 3715 67 422 0, FKZ 3716 67 422 0

Report number: [entered by the UBA library]

REACH Compliance:
Data availability in REACH registrations
Part 2: Evaluation of data waiving and adaptations for chemicals ≥ 1000 tpa

by

Angelika Oertel

Katrin Maul

Jakob Menz

Anna Lena Kronsbein

Dana Sittner

Andrea Springer

Anne-Katrin Müller

Uta Herbst

Kerstin Schlegel

Agnes Schulte

German Federal Institute for Risk Assessment (BfR)
Max-Dohrn-Str. 8-10, 10589 Berlin

On behalf of the German Environment Agency (UBA)

August, 2017

Abstract

In the European Union, chemicals manufactured or imported in quantities above one tonne per year (tpa) have to be registered at the European Chemicals Agency (ECHA). Standard information requirements and rules for data waiving and adaptation are set out in Regulation No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

The aim of the project was to evaluate toxicological and ecotoxicological information on selected endpoints in registration dossiers of high tonnage chemicals (≥ 1000 tpa). In total, 1814 lead and individual dossiers of phase-in substances submitted to ECHA until March 2014 were examined. The methodology included screening, formal and refined approaches.

Screening of registration dossiers suggested on the one hand shortcomings in data quality or data gaps, respectively, and on the other hand that data waiving and adaptation were frequently used (Springer et al., 2015). Subsequently, these data waiving and adaptations were evaluated with formal and refined approaches and constitute the main focus of this report.

The overall outcome of the screening, the formal and refined checking of dossiers was that for 19 to 56 % of the evaluated data for a specific endpoint either fulfils standard information requirements or data waiving/adaptation were of adequate quality. In contrast to this, 12 to 61 % of the evaluated datasets for an endpoint were characterised by a lack of essential information (data) or a need for amendment was identified. Regarding the remaining 12 to 61 % of datasets for the endpoints, the quality of the dossier could not be concluded on because either the assessment of the available information was timewise too extensive (*e.g.* non-guideline studies) or outside the scope of the project.

The sameness of substance identity amongst joint submissions was assessed in lead and respective member registrations submitted to ECHA by July 2015. Additionally, test material used in key studies was compared to the registered substance in lead and individual registrations.

Kurzbeschreibung

In der Europäischen Union müssen Chemikalien, die in Mengen über einer Tonne pro Jahr (tpa) hergestellt oder eingeführt werden, bei der Europäischen Chemikalienagentur (ECHA) registriert werden. In der Verordnung Nr. 1907/2006 zur Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH) sind unter anderem Standarddatenanforderungen zu toxikologischen und ökotoxikologischen Endpunkten und Regeln für den Datenverzicht und die Anpassung festgelegt.

Ziel des Projektes war es, toxikologische und ökotoxikologische Daten zu ausgewählten Endpunkten sowie für die Umweltexpositionsbewertung in Registrierungsdossiers von hochtonnagigen Chemikalien (≥ 1000 tpa) zu bewerten. Insgesamt wurden 1814 federführende und individuelle Registrierungsdossiers von Phase-in-Stoffen, die der ECHA bis März 2014 vorgelegt wurden, untersucht. Die Methodik umfasste Screening, formale und verfeinerte Prüfungen.

Das Screening von Registrierungsdossiers wies einerseits auf Mängel in der Datenqualität bzw. Datenlücken und andererseits das häufige Nutzen von Datenverzicht und Anpassung hin (Springer et al., 2015). Anschließend wurden der begründete Datenverzicht und die Datenanpassungen mit formalen und verfeinerten Prüfungen bewertet, was den Schwerpunkt dieses Berichts ausmacht.

Das Gesamtergebnis des Screenings, der formalen und der verfeinerten Prüfung von Registrierungsdossiers war, dass für 19 bis 56 % der ausgewerteten Daten für einen bestimmten Endpunkt entweder die Standarddatenanforderungen erfüllt waren oder ein begründeter Ansatz für Datenverzicht/ Anpassung in angemessener Qualität vorgelegen hat. Im Gegensatz dazu waren 12 bis 61 % der ausgewerteten Datensätze der Endpunkte durch fehlende Daten gekennzeichnet oder ein Überarbeitungsbedarf wurde identifiziert. Hinsichtlich der verbleibenden 12 bis 61 % der Datensätze der End-punkte konnte die Qualität des Dossiers nicht abschließend beurteilt werden, weil entweder

die Bewertung der verfügbaren Daten zeitlich zu umfangreich war (z. B. Studien, die nach anderen Richtlinien durchgeführt wurden) oder diese lagen außerhalb des Leistungsumfangs der Projekte.

Die Gleichheit der Stoffidentität unter den gemeinsamen Einreichungen wurde in federführenden Registrierungen und den entsprechenden Mitregistrierungen bewertet, die der ECHA bis Juli 2015 vorgelegt wurden. Darüber hinaus wurde das Testmaterial, das in Schlüsselstudien verwendet wurde, mit dem registrierten Stoff sowohl in Datensätzen der federführenden als auch in individuellen Registrierungen verglichen.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

AF	Assessment factor
AbioDeg	Abiotic degradation (endpoint)
BCF	Bioconcentration factor
Bioaccu	Bioaccumulation (endpoint)
BioDeg	Biotic degradation (endpoint)
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)
DevTox	Developmental toxicity (endpoint of TRep)
DNEL	Derived no-effect level
DOC	Dissolved organic carbon
EC	European Community
EC50	Effect concentration causing 50 % effect
ECHA	European Chemicals Agency
Ecotox	Ecotoxicity (endpoint)
ENV	Environment
EOGRTS	Extended One-Generation Reproductive Toxicity Study
ERC	Environmental release category
ESR	Endpoint study record
EU	European Union
Expo	Environmental exposure (endpoint)
Germvivo	Germ cell test *in vivo* (study type)
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GLP	Good Laboratory Practice
GMbact	Bacterial gene mutation test (study type)
GMvitro	Gene mutation test *in vitro* (study type)
GMvivo	Gene mutation test *in vivo* (study type)
HBM	Hydrocarbon Block Method
HC5	Hazardous Concentration affecting 5 % of the species
HH	Human health

IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	Partition coefficient between Organic Carbon and Water
K_{ps}	Solubility product constant
log K_{ow}	10-base logarithm of n-octanol/water partition coefficient
Muta	Mutagenicity (endpoint); includes genotoxicity as well (within the scope of this project)
n	Number (of)
NO(A)EL	No observed (adverse) effect level
NOEC	No observed effect concentration
OECD	Organisation for Economic Co-operation and Development
PBT/vPvB	Persistent, bioaccumulative, toxic/very persistent, very bioaccumulative
PEC	Predicted environmental concentration
PNDT	Prenatal developmental toxicity
PNEC	Predicted no effect concentration
PROC	Process category
QMRF	(Q)SAR Model Reporting Format
QPRF	(Q)SAR Prediction Reporting Format
(Q)SAR	Quantitative Structure-Activity Relationship
RDT	Repeated dose toxicity (endpoint)
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)
ReproTox	Reproductive toxicity (endpoint of TRep)
SID	Substance identity
SIEF	Substance Information Exchange Forum
SIP	Substance Identity Profile
spERCs	Specific Environmental Release Categories
SSD	Species sensitivity distribution
STOT RE	Specific target organ toxicity – repeated exposure
S_w	Water solubility
TG	Test guideline
$ThCO_2$	Theoretical carbon dioxide production
tpa	Tonne(s) per annum (year)
T/D	Transformation/Dissolution
TRep	Toxicity of reproduction (developmental and reproductive toxicity; endpoint)

UVCB	Substances of Unknown or Variable composition, Complex reaction products or Biological materials
WAF	Water Accommodated Fraction
WoE	Weight of evidence
w/w	Mass fraction (weight/weight)

Summary

Introduction

The European chemicals legislation ensures the protection of human health and the environment. Therefore, the safe use of chemicals should be demonstrated according to Regulation No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). REACH Article 5 "no data no market" forms the legal basis for the obligation to register chemicals with the European Chemicals Agency (ECHA). Chemicals manufactured or imported in quantities over one tonne per year (tpa) have to be registered.

In our previous report entitled "REACH Compliance: Data availability of REACH registrations - part 1: screening of chemicals > 1000 tpa" (Springer et al., 2015) toxicological and ecotoxicological information on phase-in chemicals as well as their environmental exposure were evaluated. Overall, 1814 lead and individual registration dossiers submitted to ECHA until March 2014 were examined.

The following endpoints relevant to human health were selected: mutagenicity, developmental and reproductive toxicity and repeated dose toxicity. Selected endpoints relevant to the environment were: biotic and abiotic degradation, bioaccumulation and ecotoxicity. Additionally, the environmental exposure assessment was evaluated. The screening approach was based on a decision tree for each endpoint and the environmental exposure assessment and reflects the information requirements of the REACH Regulation.

The screening of registration dossiers identified shortcomings in data quality or even data gaps and the fact that data waiving and adaptations were frequently used. However, most of these data waiving and adaptations were not concluded on in the previous project due to time restrains.

Subsequently, these data waiving and adaptations were evaluated in two follow-up projects. Formal and refined approaches were performed according to specific and general rules set out in the REACH regulation for data waiving and adaptations. The results of these evaluations are presented in this report.

A substance under REACH is defined by its substance identity. Substances with the same substance identity can submit a joint submission of data sets under REACH. In order to examine the sameness of substance identity in joint submissions, the substance identity was compared in the lead registration dossier and in member registration dossiers. In addition, the test material used in key studies should be suitable for the registered substance. These questions were examined in representative samples of registration dossiers submitted to ECHA by July 2015.

Remark: The methodologies applied within the scope of the REACH Compliance projects are not comparable with the official compliance check by ECHA according to REACH Article 41.

Methodology

The "International Uniform Chemical Information Database" (IUCLID, version 5.6.0.1 and 6) hosted by ECHA was used to evaluate registration dossiers.

Evaluation of data waiving and adaptations

Formal check (project II)

The applied approach considered both "specific rules" set out for each endpoint in REACH Annexes VII to X and "general rules" in Annex XI for data waiving and adaptations of the standard information requirements. The acceptance criteria used for the "formal check" are to a great extend based on the REACH Annexes VII to XI but as well on the endpoint specific guidance documents (*e.g.* ECHA (2016a)). For that reason this procedure is defined within the project as "formal check".

Endpoints that had not been finalised during the time course of project I were subjected to the formal check. The main focus of the formal check was to evaluate justifications for endpoint specific data waiving as well as for read-across and grouping approaches. Consequently, endpoints that contained toxicological data based on a weight of evidence approach or on (quantitative) structure-activity relationship ((Q)SAR) models were excluded from the formal check; an exception being the endpoint "ecotoxicology". Applying those criteria, 850 dossiers were identified for a detailed examination of the data supporting the endpoint repeated dose toxicity, 1133 and 917dossiers, respectively for the endpoint reproductive and developmental toxicity and 653 for the endpoint genotoxicity. Additionally, amongst the selected dossiers for evaluating the data of the environmental endpoints 533 dossiers covered the endpoint biodegradation, 1029 were related to abiotic degradation, 315 to bioaccumulation and 1493 dossiers contained relevant data on the endpoint ecotoxicology.

For instance, information on grouping of substances and read across approaches were checked against the following REACH-criteria: Is a key study with an appropriate reliability and exposure duration/scenario available and are similarities based on "(1) a common functional group; (2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or (3) a constant pattern in the changing of the potency of the properties across the category"? It should be noted that the analogue or category approach was not assessed, because this would require an in-depth scientific analysis to confirm that the REACH requirements are fulfilled.

One example for the evaluation of waiving justifications is the check whether specific rules of column 2 were correctly applied and addressed in the justification. If the waiving was referenced for instance to Annex VIII 8.4.2. column 2 first bullet point, adequate data from an *in vivo* cytogenicity test should be available. Consequently, during the formal check it was examined whether the registrant fulfilled this obligation by providing an appropriate key study or an adaptation such as read-across.

Often, more than one data waiving/adaptation was presented in the dossier to either omit or fulfil a certain standard information requirement. In these cases each data waiving/adaptation was assessed and concluded on individually. If possible, a final conclusion was drawn reflecting information requirements for the endpoint.

Refined check (part of project III)

To evaluate weight of evidence approaches, refined approaches for the human health endpoints mutagenicity, developmental and reproductive toxicity and the environmental endpoint ecotoxicity were developed. Main evaluation criteria were that at least two pieces of information were provided, all pieces of information were documented appropriately and that the line of evidence was conclusive. These refined check of weight of evidence approaches assessed cases remaining without conclusion within the previous screening and/or formal check.

Concerning human health endpoints, case groups of similar constellations were identified and analysed in-depth whenever feasible. For example, studies with non-standard administration route for reproductive and developmental toxicity as well as waiving justifications without conclusion after the formal check were evaluated.

Additionally, a refined approach was developed to evaluate whether aquatic long-term toxicity testing is triggered by the result of the chemical safety assessment, *e.g.* if the quantitative risk assessment indicates a risk or the substance is poorly water soluble.

A tiered approach was applied to evaluate the environmental exposure assessment as part of an iterative chemical safety assessment. In general, an appropriate chemical safety assessment incorporates diverse endpoints (*e.g.* abiotic/biotic degradation, ecotoxicity). Therefore, a refined check on exposure assessment was only conducted for a small case-group of dossiers that fulfilled the respective standard

information requirements on abiotic/biotic degradation and ecotoxicity. The stepwise approach assessed i) the quality of physicochemical/fate input parameters, ii) the availability of required exposure scenarios, iii) the availability of environmental release factors, and iv) the plausibility of exposure scenarios.

Substance sameness in lead and member dossiers of joint submissions

The sameness of the substance identity between lead and member dossiers according to REACH Article 11(3) was evaluated. This is the requirement for a joint submission of the same substance. Therefore, a random sample of lead and member registration dossiers submitted to ECHA until July 2015 was selected.

This was examined separately for the three substance types: mono-constituents, multi-constituents and UVCB substances. Mono-constituents and multi-constituents substance were judged to have the same substance identity if the main constituents were identical and the 80 %- and 80/10 %-rule respectively has been followed.

Equivalency of test materials used in key studies with the registered substance

Another objective of the project was to verify that the demands on test material identity were met by lead and individual registrants in their registration dossiers. The chemical identity of the test material used in key studies was compared to the chemical identity of the registered substance and its equivalence was established. For this purpose lead and individual registration dossiers were selected at random from dossiers submitted to ECHA by July 2015.

Results and discussion

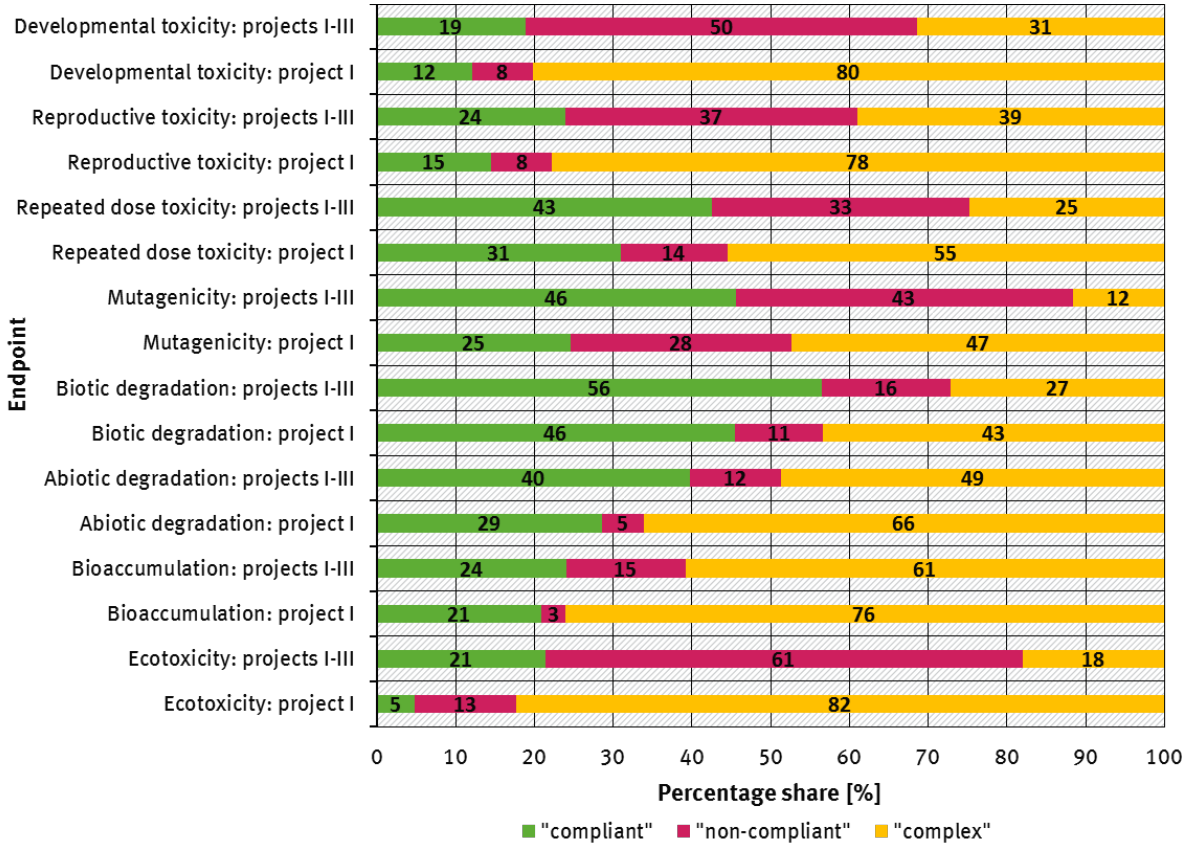
Results from the previous screening (project I, (Springer et al., 2015)) and an update including the formal and refined checks (project II and III) are presented in Figure 1. The datasets of endpoints categorised as “compliant” fulfilled either the standard information requirement or were based on an appropriate justification for data waiving or adaptations in line with the REACH Annexes. Percentages of “non-compliant” endpoints are indicative of shortcomings in data quality or even data gaps. To cover these endpoints the submitted datasets require either submission of additional study data, a testing proposal or data waiving justification or adaptations and/or an improvement in data quality. The category “complex” denotes endpoints pending a conclusion.

Screening results (project I) supposed two main crosscutting reasons for “non-compliant” either the mismatch between test substance and the registered substance without indicating grouping of substances and read-across approaches or study entries without reference to valid test guidelines (Springer et al., 2015).

Results of the formal check showed that, frequently, read-across/grouping, weight of evidence and (Q)SARs were formally not adequately justified and/or documented. In addition, justifications for data waiving based on endpoint specific or exposure-based rules were insufficient in numerous dossiers. Moreover, justifications for waiving or adaptation of mandatory studies were often not available or did not consider specific or general rules of REACH Regulation.

Still, endpoints remained without conclusion because they require a case-by-case review or they were not included in the formal and refined check.

Figure 1: Screening of data availability for human health and environmental endpoints in dossiers of phase-in-substances (≥ 1000 tonnes per year) – project I – and updated results after formal and refined check of data – project I-III (total number for each endpoint: 1814)



Environmental exposure

Screening of the environmental exposure assessment already demonstrated that environmental exposure scenarios were not provided in several chemical safety reports although this is mandatory for classified substances or persistent, bioaccumulative and toxic (PBT) substances or very persistent and very bioaccumulative (vPvB) substances (266 of 1814 dossiers) (Springer et al., 2015). Thus, the safe use of chemicals was not sufficiently demonstrated.

The refined check of environmental exposure was applied to a limited number of 26 dossiers. These were selected because they provided data of sufficient quality for the endpoints abiotic/biotic degradation and ecotoxicity. Seven dossiers were regarded as “non-compliant” because neither environmental exposure scenarios relevant to humans via environment nor a respective justification for their omission were provided. For the remaining 19 dossiers no conclusions could be drawn because either an adaptation for the physico-chemical/fate input parameters was applied or a justification that exposure scenarios for man via environment are not required was available.

Substance sameness in lead and member dossiers of joint submissions

The sameness of substance identity amongst joint submissions was fulfilled for all members of a Substance Information Exchange Forum (SIEF) in 89 % of cases for mono-constituent substance and in 50 % of the cases for multi-constituent substances. Thus, the requirement of the sameness of the registered substance was fulfilled within the majority of the SIEFs. Out of the total numbers of member dossiers evaluated, 98 % of the member dossiers for mono-constituent substances and 57 % of the member dossiers for multi-constituent substances registered their substance correctly in their SIEF.

It appears that 24 % of the member dossiers of multi-constituent substances were either not registered within the correct SIEF or the substance identity was not adequately demonstrated. In 19 % of the member dossiers of multi-constituent substances a conclusion could not be drawn whether the substance identity was the same as in the lead dossier.

Equivalency of test materials used in key studies with the registered substance

The analysis of the available key studies over all considered endpoints (without those using read-across/grouping) revealed that the test material was equal to the registered substance in 66 % of the evaluated key studies. In contrast, in 28 % of key studies the test material was not considered equal to the registered substance and in 6 % of key studies the equivalency could not be deduced. For the two latter cases, it could not be determined whether a grouping/read-across approach was intended but maybe not properly indicated.

Conclusions and Outlook

The overall results of the three projects suggest that significant data gaps and/or inadequate waiving/adaptations were identified in ≥ 1000 tpa registration dossiers. The examined dossiers were concluded "non-compliant" in the range of 12 to 61 %, depending on the evaluated endpoint. These require either the submission of an appropriate study (or data) or a testing proposal or the submission of a justification (or of an improved and appropriate justification) for waiving or adaptation. In general, data gaps may impede a comprehensive risk assessment for the human health and the environment and call into question whether a safe use of chemicals can be warranted.

However, 12 to 61 % of the examined endpoints still remain without a conclusion. Potentially, these provided data for the endpoints could be either in line with the information requirements or provide additional data gaps, unjustified data waiving or invalid surrogate data and/or insufficient data quality.

Nevertheless, based on the outcome of the evaluation on data availability and quality in REACH registrations it is recommended that registrants scrutinise the need of an update of their registration dossier in order to meet the information requirements – either with respect to the standard testing or by justified data waiving and/or surrogate data. Recommendations to registrants have been developed to address frequently identified problems and will be published separately (Oertel et al., 2017).

Currently, a follow-up project evaluating the data availability and quality of dossiers covering the range of 100-1000 tpa is ongoing.

Zusammenfassung

Einleitung

Die europäische Chemikaliengesetzgebung soll den Schutz der menschlichen Gesundheit und der Umwelt gewährleisten. Hierbei sollte die sichere Verwendung von Chemikalien nach der Verordnung Nr. 1907/2006 zur Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH) nachgewiesen werden. REACH Artikel 5 „ohne Daten kein Markt" bildet die Rechtsgrundlage für die Verpflichtung zur Registrierung von Chemikalien bei der Europäischen Chemikalienagentur (ECHA). Chemikalien, die in Mengen über einer Tonne pro Jahr (tpa) hergestellt oder importiert werden, müssen registriert werden.

In dem vorherigen Bericht „REACH Compliance: Datenverfügbarkeit in REACH-Registrierungen – Teil 1: Screening von Chemikalien > 1000 tpa" (Springer et al., 2015) wurden toxikologische und ökotoxikologische Daten von Phase-in-Chemikalien sowie die Umweltexpositionsbewertung evaluiert. Insgesamt wurden 1814 federführende und individuelle Registrierungsdossiers, die der ECHA bis März 2014 vorgelegt wurden, untersucht.

Die Daten der folgenden für die menschliche Gesundheit relevanten Endpunkte wurden untersucht: Mutagenität, Entwicklungs- und Reproduktionstoxizität und Toxizität bei wiederholter Aufnahme. Ausgewählte Endpunkte, die für die Umwelt bedeutsam sind, waren: abiotische/biologische Abbaubarkeit, Bioakkumulation und Ökotoxizität. Darüber hinaus wurde die Umweltexpositionsbewertung beurteilt. Der Screening-Ansatz basierte auf Entscheidungsbäumen für jeden Endpunkt sowie für die Umweltexpositionsbewertung und spiegelt die Informationsanforderungen der REACH-Verordnung wider.

Das Screening von Registrierungsdossiers zeigte Mängel in der Datenqualität oder sogar Datenlücken und dass begründete Ansätze für Datenverzicht/Anpassung häufig verwendet wurden. Allerdings wurden die meisten der Begründungen für Datenverzicht/Anpassung aufgrund zeitlicher Beschränkungen im vorangegangenen Projekt nicht abschließend bewertet.

Die angeführten Begründungen für Datenverzicht/Anpassung wurden anschließend in zwei Nachfolgeprojekten untersucht. Formale und verfeinerte Prüfansätze wurden entsprechend der endpunktspezifischen und allgemeinen Regeln, die in der REACH Verordnung für den begründeten Datenverzicht und die Datenanpassungen festgelegt sind, angewendet. Die Ergebnisse dieser Prüfungen werden in diesem Bericht vorgestellt.

Ein Stoff unter REACH ist durch seine Stoffidentität definiert. Stoffe mit der gleichen Stoffidentität können unter REACH eine gemeinsame Einreichung des Stoffdatensatzes vornehmen. Um die Gleichheit der Stoffidentität in gemeinsamen Einreichungen zu untersuchen, wurde die Stoffidentität im federführenden Registrierungsdossier und in denen der Mitregistranten miteinander verglichen. Darüber hinaus sollte das in Schlüsselstudien verwendete Testmaterial für den registrierten Stoff geeignet sein. Diese Fragen wurden in repräsentativen Stichproben von Registrierungsdossiers, die bis Juli 2015 bei der ECHA eingereicht wurden, untersucht.

Anmerkung: Die im Rahmen der REACH-Compliance-Projekte angewandten Methoden sind nicht mit der „Prüfung der Registrierungsdossiers auf Erfüllung der Anforderungen" nach REACH Artikel 41 durch die ECHA vergleichbar.

Methodik

Die „internationale einheitliche chemische Informationsdatenbank“ (IUCLID, Version 5.6.0.1 und 6), die von der ECHA gestellt wird, wurde zur Bewertung der Registrierungsdossiers verwendet.

Evaluierung begründeter Ansätze für Datenverzicht/Anpassung

Formale Prüfung (Projekt II)

Der verwendete Ansatz betrachtete sowohl „spezifische Regeln“, die für jeden Endpunkt in den REACH Anhängen VII bis X beschrieben sind, als auch „allgemeine Regeln“ des Anhang XI für begründete Abweichungen von den Standarddatenanforderungen. Die verwendeten Akzeptanzkriterien der „formalen Prüfung“ basieren zum größten Teil auf den REACH Anhängen VII bis XI und den endpunktspezifischen Leitfäden der ECHA (z.B. ECHA (2016a)). Aus diesem Grund wird diese Prozedur innerhalb des Projekts als „formale Prüfung“ definiert.

Die Bewertung der Verfügbarkeit und Qualität der Datensätze für die Endpunkte, die während des ersten Projektes nicht abschließend bewertet wurden, wurden der formalen Prüfung unterzogen. Der Schwerpunkt der formalen Prüfung lag darin, die Begründungen für einen endpunktspezifischen Datenverzicht sowie für die Stoffgruppen- und Analogiekonzepte zu bewerten. Nachfolgend wurden Endpunkte, deren toxikologische Ersatzdaten auf einem „Beweiskraft der Daten“-Ansatz oder auf Modellen für (quantitative) Struktur-Wirkungs-Beziehungen ((Q)SAR) basierten, von der formalen Prüfung ausgeschlossen. Eine Ausnahme bildet der Endpunkt „Ökotoxikologie“. Bei der Anwendung dieser Kriterien wurden 850 Dossiers für eine detaillierte Untersuchung der Daten für den Endpunkt Toxizität bei wiederholter Aufnahme, 1133 und 917 Dossiers für die Endpunkte Reproduktions- und Entwicklungstoxizität und 653 für den Endpunkt Mutagenität ausgewählt. Darüber hinaus wurden für die Umweltendpunkte 533 Dossiers zur biologischen Abbaubarkeit, 1029 zur abiotischen Abbaubarkeit, 315 zur Bioakkumulation und 1493 Dossiers zur Ökotoxikologie ausgewählt.

So wurden beispielsweise Informationen zu Stoffgruppen- und Analogiekonzepten anhand folgender REACH-Kriterien überprüft: Ist eine Schlüsselstudie mit einer/-m angemessenen Zuverlässigkeit und Expositionsdauer/-szenario verfügbar und sind Ähnlichkeiten basierend auf „ 1) einer gemeinsamen funktionellen Gruppe, 2) gemeinsamen Ausgangsstoffen und/oder strukturell ähnlichen Produkten des physikalischen und biologischen Abbaus, 3) oder einem festen Muster, nach dem sich die Wirkungsstärke der Eigenschaften über die Stoffgruppe hinweg ändert“ beschrieben? An dieser Stelle ist anzumerken, dass die inhaltliche Richtigkeit der REACH Anforderungen an Stoffgruppen- und Analogiekonzepte selbst nicht beurteilt wurde, da dies eine eingehende wissenschaftliche Analyse erfordert hätte.

Ein Beispiel für die Bewertung von Datenverzichtsbegründungen ist die Prüfung, ob die endpunktspezifischen Regeln der Spalte 2 korrekt angewendet und adressiert wurden. Wurde der Datenverzicht zum Beispiel auf Anhang VIII 8.4.2. Spalte 2 erster Aufzählungspunkt bezogen, sollten ausreichend Daten aus einer zytogenetischen Untersuchung *in vivo* vorliegen. Somit wurde während der formalen Prüfung untersucht, ob der Registrant diese Pflicht durch die Angabe einer angemessenen Schlüsselstudie oder einer Datenanpassung, wie z.B. dem Stoffgruppen- und Analogiekonzept, erfüllt.

Oftmals wurde im Dossier mehr als eine Begründung für Datenverzicht/Anpassung vorgelegt, um entweder auf eine bestimmte Standarddatenanforderung zu verzichten oder diese dadurch zu erfüllen. In diesen Fällen wurde jeder Ansatz individuell beurteilt. Wenn möglich, wurde eine Schlussfolgerung insgesamt für den Endpunkt gezogen, um die Datenanforderungen zu bewerten.

Verfeinerte Prüfung (Teil von Projekt III)

Zur verfeinerten Prüfung der „Beweiskraft der Daten"-Ansätze wurde eine Methodik zur Prüfung für die Gesundheitsendpunkte Mutagenität, Entwicklungs- und Reproduktionstoxizität und für den Umweltendpunkt Ökotoxizität entwickelt. Wesentliche Bewertungskriterien waren, dass mindestens zwei unabhängige Informationen vorgelegt wurden, alle Informationen entsprechend dokumentiert wurden und der geführte Beweis eindeutig nachvollziehbar war. Diese verfeinerte Prüfung der „Beweiskraft der Daten"-Ansätze wurde für Fälle angewendet, die innerhalb des vorherigen Screening und/oder formalen Prüfung nicht entschieden werden konnten.

In Bezug auf die Gesundheitsendpunkte wurden Fallgruppen ähnlicher Konstellationen identifiziert und, wenn möglich, eingehend analysiert. Zum Beispiel wurden Studien, die mit nicht standardisierten Methoden für die Reproduktions- und Entwicklungstoxizität durchgeführt wurden, sowie Fälle, die auf begründetem Datenverzicht beruhten und nicht im Rahmen der formalen Prüfung bewertet wurden, einbezogen.

Zusätzlich wurde ein verfeinerter Ansatz zur Beurteilung entwickelt, ob die aquatischen chronischen Toxizitätstests aufgrund der Stoffsicherheitsbeurteilung erforderlich wurden, z.B. wenn die quantitative Risikobewertung ein Risiko anzeigt oder der Stoff sehr schwer wasserlöslich ist.

Es wurde ein abgestuftes Konzept angewandt, um die Umweltexpositionsbewertung im Rahmen einer iterativen Stoffsicherheitsbeurteilung zu bewerten. Im Allgemeinen gehen in die Stoffsicherheitsbeurteilung die Ergebnisse verschiedener Endpunkte (z.B. abiotische/biologische Abbaubarkeit, Ökotoxizität) ein. Daher wurde nur für eine kleine Anzahl von Dossiers eine verfeinerte Prüfung der Umweltexpositionsbewertung durchgeführt, die die jeweiligen Standarddatenanforderungen für den abiotischen/biologische Abbaubarkeit und die Ökotoxizität erfüllten. Der schrittweise Ansatz umfasste i) die Qualität der physikalisch-chemischen Eingangsparameter sowie das Verhalten und den Verbleib in der Umwelt, ii) die Verfügbarkeit der erforderlichen Expositionsszenarien, iii) die Verfügbarkeit von Freisetzungskategorien zur Beschreibung der Umweltexposition und iv) die Plausibilität der Expositionsszenarien.

Gleichheit der Stoffidentität bei gemeinsamer Einreichung eines Stoffdatensatzes

Es wurde die Gleichheit der Stoffidentität zwischen dem federführenden Registrierungsdossier und den Mitregistrierungsdossiers nach REACH Art. 11 (3) bewertet. Dies ist die Voraussetzung für eine gemeinsame Einreichung des gleichen Stoffes. Daher wurden repräsentative Stichproben von federführenden Dossiers und denen der Mitregistranten, die bei der ECHA bis Juli 2015 vorgelegt wurden, ausgewählt.

Dies wurde unterteilt nach drei Stofftypen untersucht: einkomponentige Stoffe, mehrkomponentige Stoffe und UVCB-Stoffe. Die Stoffgleichheit von einkomponentigen und mehrkomponentigen Stoffen wurde hinsichtlich der Identität der Hauptbestandteile bewertetet und wenn die 80 %- bzw. 80/10 %-Regel befolgt wurde.

Übereinstimmung des Testmaterials in Schlüsselstudien mit dem registrierten Stoff

Ein weiteres Ziel des Projektes war es, zu überprüfen, ob die Anforderungen an die Identität des Testmaterials in federführenden und individuellen Registrierungsdossiers erfüllt wurden. Die chemische Identität des in Schlüsselstudien verwendeten Testmaterials wurde mit der Stoffidentität des registrierten Stoffes verglichen und seine Äquivalenz festgestellt. Zu diesem Zweck wurden repräsentative Stichproben von federführenden und individuellen Registrierungsdossiers, die bei der ECHA bis Juli 2015 vorgelegt wurden, ausgewählt.

Ergebnisse und Diskussion

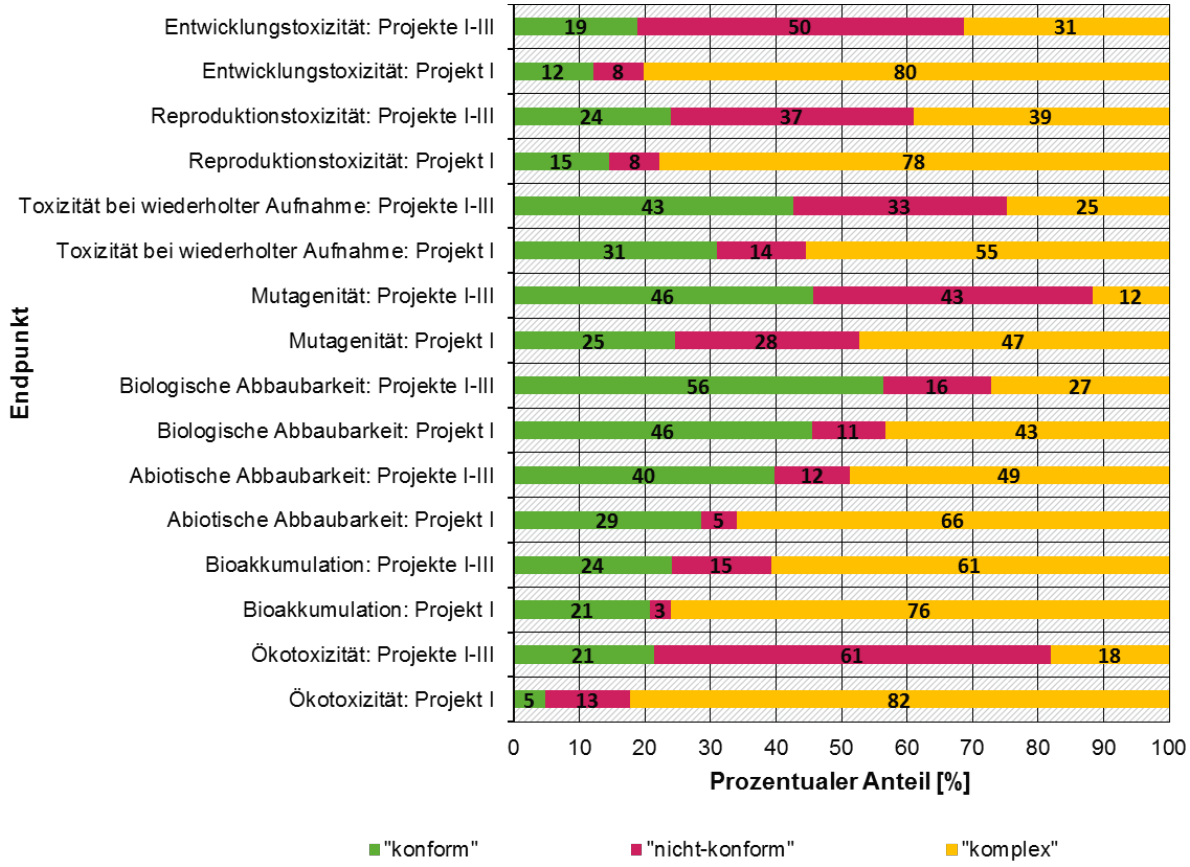
Die Ergebnisse aus dem vorangegangen Screening (Projekt I, (Springer et al., 2015)) und eine Aktualisierung mit den Ergebnissen aus der formalen und verfeinerten Prüfung (Projekt II und III) sind in Abbildung 1 dargestellt. Die Datensätze von Endpunkten, die als „konform“ bewertet wurden, erfüllten entweder die Standarddatenanforderung oder basierten auf einer angemessenen Begründung für den Datenverzicht/die Anpassung nach den Regeln der REACH Anhänge. Der prozentuale Anteil der einzelnen Endpunkte, die mit „nicht-konform“ bewertet wurden, deutet auf Mängel in der Datenqualität oder sogar auf Datenlücken hin. Um die Datenanforderungen für diese Endpunkte zu erfüllen, sind entweder zusätzliche Daten, das Einreichen von Versuchsvorschlägen oder ein den Regeln entsprechender Ansatz für Datenverzicht/Anpassung und/oder eine Verbesserung der Datenqualität erforderlich. Die Kategorie „komplex“ bezeichnet Endpunkte, bei denen eine Schlussfolgerung aussteht.

Die Ergebnisse des Screening (Projekt I) zeigten, dass die zwei Hauptursachen für eine Bewertung als „nicht-konform“ waren, dass das Testmaterial nicht mit dem registrierten Stoff übereinstimmte ohne ein Stoffgruppen- und Analogiekonzept und, dass die Studien nach nicht anerkannten Richtlinien oder Testmethoden durchgeführt worden sind (Springer et al., 2015).

Die Ergebnisse der formalen und verfeinerten Prüfung zeigten, dass die verwendeten Stoffgruppen- und Analogiekonzepte, (Q)SARs und „Beweiskraft der Daten“-Ansätze nicht korrekt begründet und/oder dokumentiert wurden. Außerdem wurde ein Datenverzicht, der entweder auf endpunktspezifischen oder expositionsbasierten Regeln begründet wurde, in zahlreichen Dossiers unzureichend dokumentiert. Zudem waren Begründungen für den Datenverzicht/die Anpassung von erforderlichen Studien oft nicht verfügbar oder es wurden nicht die endpunktspezifischen oder allgemeinen Regeln der REACH-Verordnung berücksichtigt.

Dennoch blieben immer noch Endpunkte ohne Schlussfolgerung, da diese entweder eine Einzelfallprüfung erfordern oder nicht in die formale und/oder verfeinerte Prüfung einbezogen worden sind.

Abbildung 1: Screening der Datenverfügbarkeit der Gesundheits- und Umweltendpunkte in Dossiers von Phase-in-Stoffen (≥ 1000 Tonnen pro Jahr) – Projekt I – und aktualisierte Ergebnisse nach der formalen und verfeinerten Prüfung der Daten – Projekt I-III (Gesamtanzahl für jeden Endpunkt: 1814)



Umweltexpositionsbewertung

Das Screening der Umweltexpositionsbewertung zeigte bereits, dass in zahlreichen Stoffsicherheitsberichten keine Expositionsszenarien für die Umwelt vorlagen, obwohl dies für eingestufte Stoffe oder für persistente, bioakkumulierbare und toxische (PBT-)Stoffe sowie sehr persistente und sehr bioakkumulierbare (vPvB-)Stoffe (266 von 1814 Dossiers) vorgeschrieben ist (Springer et al. 2015). So wurde die sichere Verwendung von Chemikalien nicht hinreichend nachgewiesen.

Die verfeinerte Prüfung der Expositionsbewertung für die Umwelt wurde mit einer begrenzten Anzahl von 26 Dossiers durchgeführt. Diese wurden ausgewählt, da sie Daten in ausreichender Qualität für die Endpunkte abiotische/biologische Abbaubarkeit und Ökotoxizität lieferten. Sieben Dossiers wurden als „nicht konform“ bewertet, da weder Szenarien für die Exposition des Menschen über die Umwelt noch eine entsprechende Begründung für deren Weglassen gegeben wurden. Für die verbleibenden 19 Dossiers konnte keine Schlussfolgerung gezogen werden, da entweder für die physikalisch-chemischen Parameter oder das Verhalten und den Verbleib der Stoffe in der Umwelt Datenanpassungen oder eine Begründung, dass Expositionsszenarien für den Menschen über die Umwelt nicht erforderlich sind, vorlagen.

Gleichheit der Stoffidentität bei gemeinsamer Einreichung eines Stoffdatensatzes

Die Gleichheit der Stoffidentität unter den gemeinsamen Einreichungen eines Stoffdatensatzes wurde für alle Mitglieder eines Forums zum Austausch von Stoffinformationen (SIEF) in 89 % der Fälle für einkomponentige Stoffe und in 50 % der Fälle für mehrkomponentige Stoffe erfüllt. Bezogen auf die Gesamtzahl der Mitregistrierungsdossiers haben 98 % der Mitregistrierungsdossiers der einkomponentigen Stoffe und 57 % der Mitregistrierungsdossiers der mehrkomponentigen Stoffe ihren Stoff im richtigen SIEF registriert.

Hingegen wurden 24 % der Mitgliedsdossiers von mehrkomponentigen Stoffen entweder nicht im SIEF desgleichen Stoffes registriert oder die Stoffidentität wurde nicht ausreichend beschrieben. In 19 % der Mitgliedsdossiers von mehrkomponentigen Stoffen konnte nicht geklärt werden, ob die Stoffidentität die gleiche war wie die im federführenden Dossier.

Übereinstimmung des Testmaterials in Schlüsselstudien mit dem registrierten Stoff

Die Analyse der verfügbaren Schlüsselstudien über alle betrachteten Endpunkte (ohne solche, die Stoffgruppen- und Analogiekonzepte verwendeten) ergab, dass das Testmaterial dem registrierten Stoff in 66 % der ausgewerteten Schlüsselstudien entspricht. Im Gegensatz dazu war bei 28 % der Schlüsselstudien das Testmaterial nicht gleich dem registrierten Stoff und in 6 % der Schlüsselstudien konnte keine eindeutige Entscheidung abgeleitet werden. Für die beiden letztgenannten Gruppen konnte nicht überprüft werden, ob ein Stoffgruppen- oder Analogiekonzept beabsichtigt war und dieses möglicherweise nur nicht richtig ausgewiesen wurde.

Schlussfolgerungen und Ausblick

Die Gesamtergebnisse der drei Projekte zeigen, dass in den Registrierungsdossiers der ≥ 1000 tpa Stoffe signifikante Datenlücken und/oder unzureichend begründete Fälle von Datenverzicht/Anpassung vorlagen. Die untersuchten Dossiers wurden je nach ausgewertetem Endpunkt zu Anteilen zwischen 12 und 61 % als „nicht konform“ beurteilt. Hier ist entweder die Einreichung von geeigneten Studien/Daten oder eines Versuchsvorschlags oder eine Begründung bzw. eine verbesserte und geeignete Begründung für Datenverzicht/Anpassung notwendig. Im Allgemeinen können Datenlücken eine umfassende Risikobewertung für die menschliche Gesundheit und die Umwelt unmöglich machen und stellen daher in Frage, ob die sichere Verwendung von Chemikalien garantiert werden kann.

Allerdings bleiben 12 bis 61 % der Datensätze zu den untersuchten Endpunkten ohne Schlussfolgerung. Potenziell könnten diese Fälle entweder die Datenanforderungen erfüllen oder es handelt sich um weitere Datenlücken, unzureichend begründete Ansätze für Datenverzicht/Anpassung und/oder Fälle mit unzureichender Datenqualität.

Auf Grundlage der Bewertungsergebnisse zur Datenverfügbarkeit und -qualität in REACH-Registrierungen wird empfohlen, dass Registranten die Notwendigkeit einer Aktualisierung ihres Registrierungsdossiers prüfen, um die Datenanforderungen zu erfüllen – entweder durch die Bereitstellung von Standarddaten oder durch begründete Ansätze für Datenverzicht/Anpassung. Empfehlungen für Registranten wurden entwickelt, um häufig identifizierte Probleme zu lösen (Oertel et al., 2017). Diese werden separat veröffentlicht.

Derzeit befindet sich ein Folgeprojekt zur Bewertung der Datenverfügbarkeit und -qualität in REACH-Registrierungsdossiers für 100-1000 tpa Stoffe in Bearbeitung.

1 Introduction

1.1 REACH registration dossiers of high tonnage chemicals

The chemical regulation 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) was adopted to improve the protection of human health and the environment by increasing the knowledge about chemicals that are manufactured, imported, marketed and used in the European Union (EU) (EC, 2006). Companies are obliged to register chemicals manufactured or imported in quantities of more than one tonne per year (tpa) with the European Chemicals Agency (ECHA) in order to provide sufficient information for hazard and risk assessment of chemicals as well as for their safety of use. The information requirements and possible adaptations for chemicals produced or imported at a level of 1000 tpa or more ("high tonnage band") are set out in REACH Annexes VII to XI.

In line with the envisaged high level of protection of human health and the environment and the central paradigm of REACH Article 5 ("no data, no market"), valid and complete safety data are a pre-requisite for responsible risk management of chemical substances on the EU market as well as for identifying priority substances for further regulatory action.

Information requirements under REACH vary according to the manufactured or imported tonnage. To this end, four manufacturing or importing thresholds (equal or greater than one, ten, 100 and 1000 tpa, respectively) have been identified, to which the REACH Annexes VII to X apply successively. For the registration of chemicals manufactured or imported above 1000 tpa the full set of information according to REACH Annexes VII to X has to be submitted.

Registrants are obliged to consider all existing data and alternatives on the testing of animals to fulfil the requirements. In this context, also read-across and grouping approaches or (Quantitative) Structure-Activity Relationships ((Q)SAR) are appropriate. Other reasons for waiving animal tests are possible. However, a sufficient justification with respect to the criteria laid out in REACH Annexes VII to X column 2 or Annex XI is necessary. If, as a last resort to close a data gap, testing in vertebrates is considered, first a testing proposal must be provided by the registrants. When ECHA approved the proposal animal testing is permitted.

Finally, manufacturer or importers are obliged to register the same substances under the umbrella of consortia to facilitate data sharing (Substance Information Exchange Forum (SIEF)).

To assure data quality, a comprehensive guidance framework on information requirements and the registration procedure is available. The responsibility for presenting data compliant with the information requirements lies with the registrants. Nevertheless, compliance checks according to REACH Article 41 on no less than 5 % of the dossiers of each tonnage band are carried out by ECHA. Although the proportion of all dossiers formally checked for compliance is rather small, it covers a large number of high tonnage registrations, since ECHA is systematically focusing its compliance checks on lead and individual registration dossiers with regard to substance identity and long-term toxicity endpoints (ECHA, 2017c). In addition, both ECHA and member states take other measures, including a check of the data availability, *e.g.* in their annual screening activities.

1.2 Project I – Screening (2014/2015)

Whether the registration dossiers of high tonnage chemicals (1000 tpa or more) registered by 2010 were in "compliance" with the information requirements set out in the REACH Regulation was a subject of the previous project "REACH Compliance: Data Availability of REACH Registrations", conducted from March 2014 to March 2015 (Springer et al., 2015). Herein, it was screened for each individual lead dossier whether the required toxicological and ecotoxicological information was available. The high tonnage chemicals were prioritised in this project due to their wide spread use and high relevance for the human health and the environment.

A systematic screening approach was developed based on the information requirements in the REACH Annexes and their interpretation as outlined by the REACH guidance documents to evaluate the huge amount of data.

The priority was laid on the following endpoints[1]:

Human health (HH):
- developmental and reproductive toxicity (DevTox and ReproTox – together toxicity of reproduction (TRep)),
- mutagenicity[2] (Muta),
- repeated dose toxicity (RDT),

Environment (ENV):
- biotic and abiotic degradation (BioDeg and AbioDeg),
- bioaccumulation (Bioaccu),
- ecotoxicity (Ecotox).

Additionally, the assessment of environmental exposure (Expo) was analysed in the chemical safety report (CSR).

In total, 1814 dossiers of phase-in substances, including lead and individual registration dossiers, were screened. The screening process was based on a systematic and standardised scheme (decision trees). The registration dossiers were evaluated regarding each endpoint listed above and assigned to one of the following conclusion categories:

- "compliant", *i.e.* in "compliance" with the REACH standard information requirements according to the screening criteria of this project,
- "non-compliant", *i.e.* in "non-compliance" with the REACH standard information requirements according to the screening criteria of this project,
- "complex", *i.e.* no conclusion regarding "compliance" or "non-compliance" could be made as a result of the screening,
- "testing proposal", *i.e.* a testing proposal is provided by the registrant in order to comply with the REACH information requirements.

It is important to note that the terms "compliant" and "non-compliant" were used to address fulfilling or does not the criteria within the scope of the project and not for legal (non) compliance; they reflect the general availability of the information required in terms of REACH and the developed screening scheme for a standardised check.

[1] In the following, for reasons of convenience the term "endpoint" describes data of human health or environmental endpoints.

[2] In the following, for reasons of convenience the term "mutagenicity" describes information requirements related to genotoxicity and mutagenicity.

For defined circumstances a conclusion on conformity or non-conformity could not be made and these cases were assigned to the category "complex". This mostly applied when a waiving justification or surrogate data were presented instead of the standard tests. These data could not be assessed within the limited time frame of the screening. Additionally, some endpoint-related particularities also resulted in the conclusion "complex".

In addition to the endpoint results, each dossier itself was classified as follows:

- "compliant" – cases for which all endpoints of a dossier were assigned to be "compliant",
- "non-compliant" – cases for which at least one of the endpoints was regarded as "non-compliant",
- "complex" – cases for which none of the endpoints was categorised as "non-compliant" and at least one endpoint was allocated to "complex" or "testing proposal".

One of the main results of the previous project was that, at the endpoint level, a remarkable high rate of the dossiers included waiving or adaptations for the standard information requirements. Those were mainly not concluded and, therefore, categorised as "complex". The highest percentages of "complex" cases were observed for the endpoints TRep, Bioaccu and Ecotox (73 to 82 %), whereas the other endpoints had proportions of 43 to 66 %. Thereby, the read-across approach played an important role, in particular regarding HH endpoints (Springer et al., 2015).

At the dossier level, 42 % of all checked dossiers were assigned to the conclusion category "complex", whereat in the majority of these cases five or six endpoints remained undecided (Springer et al., 2015).

Thus, a considerable part of the endpoint data of the registered high tonnage chemicals has not been examined in more detail regarding their conformity with the REACH Regulation. However, additional information was recorded during the examination of dossiers giving some first indications for further investigations.

1.3 Project II – Formal check (2015/2016)

The project "Availability of human health and environmental data for high tonnage chemicals under REACH – project II: more detailed compliance check", carried out between April 2015 and July 2016, was initiated to gain more detailed information on data availability and quality in REACH registrations of high tonnage chemicals. It is connected to the outcome and conclusions of the previous project I regarding a more in-depth analysis of endpoints without conclusion ("complex") which made up the majority previously. In addition, the aspects of substance sameness within SIEFs and of equivalency of test material used in key studies with the registered substance in lead and individual registration dossiers were included as new topics.

Accordingly, the project had the following tasks:

- checking the substance sameness in lead and the related member dossiers (lead and member dossiers),
- checking the equivalency of the test material used in key studies with the registered substance as implemented by the registrant (lead and individual registration dossiers),
- checking formal conformity of data waiving and the use of surrogate data with the respective requirements of the REACH Regulation for endpoints which remained without conclusion in the previous project ("complex") (lead and individual registration dossiers).

The concepts regarding these tasks are briefly summarised in the subsequent paragraphs and described in more detail in the respective method chapters. Checking of substance sameness between and within registration dossiers was conducted because the description of substance identity (SID) and the determination of sameness of substances are some of the most challenging aspects of the registration process under REACH. ECHA observed that many registration dossiers have shortcomings

regarding adequate information on that issue (ECHA, 2015a). Within the scope of this project, a comprehensive assessment of the provided information on SID as needed according to REACH Article 10 and as specified in Annex VI 2. was not feasible. Therefore, the investigations focused on two selected aspects.

The first objective was to examine whether the same substance was used in lead and member dossiers of joint registrations. For mono-constituent and multi-constituent substances, this was done in a brief and standardised manner according to criteria of Article 11(3) REACH.

The second objective was to check in the International Uniform Chemical Information Database (IUCLID) whether the test materials used in key studies corresponded to the registered substance. This was done for lead and individual registrations in a brief and standardised manner. Important to note is that the information as given by the registrant in IUCLID was used and not assessed with regards to the scientific appropriateness.

The main focus of project II was to further clarify the high number of unresolved "complex" endpoint cases of the previous project. These decisions mainly based on data waiving and the use of surrogate data instead of the standard tests. The investigation comprised one standardised check whether these approaches fulfilled the formal criteria for waiving and adaptation set out in Annexes VII to XI of the REACH Regulation. It was not aimed at verifying waiving and adaptation approaches with respect to the scientific aspects, *e.g.* by assessing the appropriateness of the read-across/grouping based on structural, physico-chemical and toxicological properties. This can only be done in a case-by-case assessment and was not feasible within this project.

1.4 Project III – Refined check (2016/2017)

The first part of project III "Availability of human health and environmental data for high tonnage chemicals under REACH – Finalisation of phase 2 and examination of registration dossiers of chemicals 100-1000 tpa" still concerned chemicals manufactured or imported in quantities 1000 tpa or more and was carried out between August 2016 and January 2017. It was connected to the outcome and conclusions of the previous project I and project II regarding a more in-depth analysis of endpoints without conclusion ("complex") to obtain more detailed information on data availability and quality in REACH registrations of high tonnage chemicals. In addition, an estimate of new animal studies for TRep, that is DevTox and ReproTox, followed.

Thus, the first part of the project III had the following tasks for the selected HH endpoints Muta, ReproTox and DevTox, and the ENV endpoints Ecotox and Expo:

- developing concepts and checking the remained "complex" endpoints from the screening (project I),
- developing concepts and checking the remained "complex" endpoints from the formal check (project II) as far as possible,
- estimating the number of dossiers with potential data gaps for developmental and reproductive toxicity.

Since very different case groups from the different endpoints have been left unresolved in the previous projects, different approaches to the solution had to be developed accordingly. These concepts are described in detail in the respective method chapters and involve as a first step a systematic approach with the aim to provide a content-related analysis for the now remaining endpoints without conclusion ("complex"). The refined approach was applied on a selection of dossiers as this procedure required case-by-case conclusions.

2 Methods

2.1 Overview

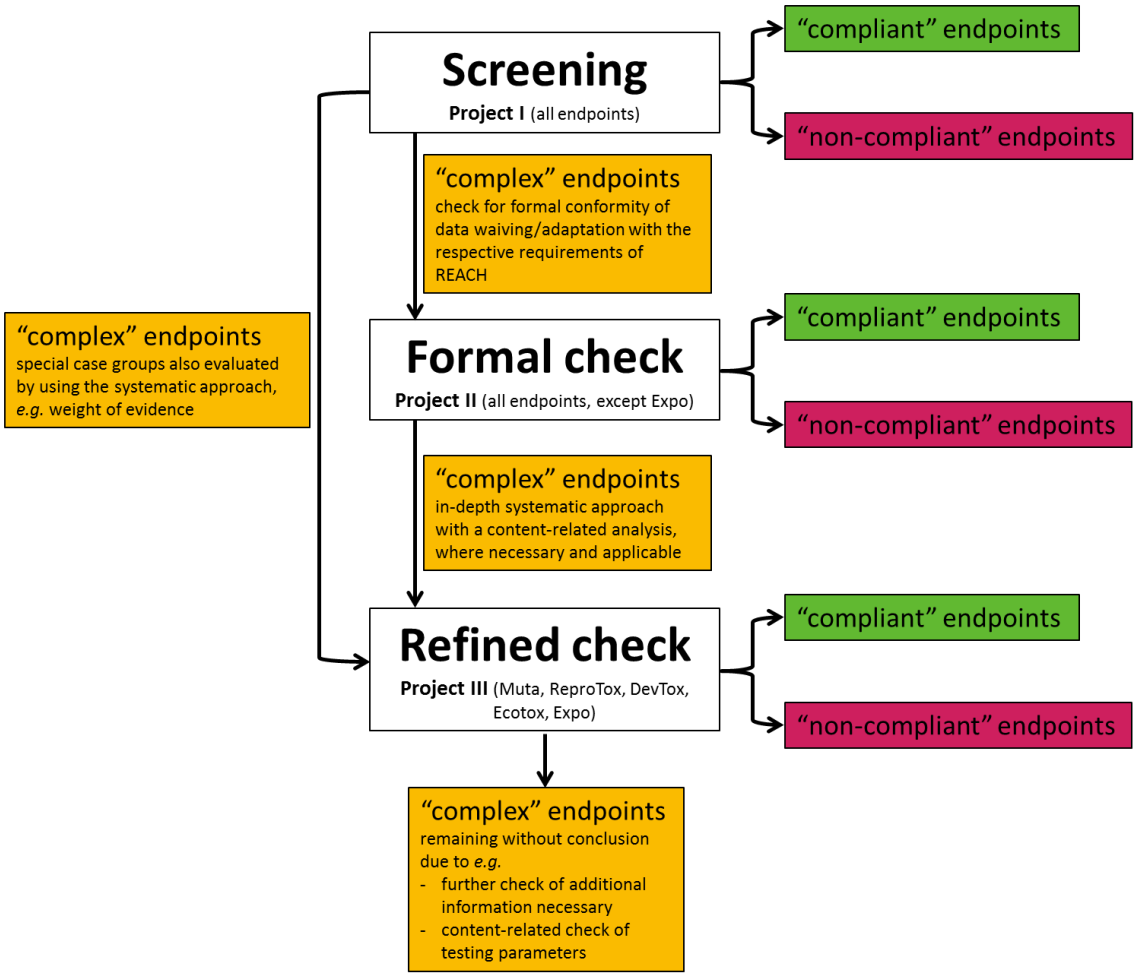
The stepwise approach which was used for the evaluation of the data availability in REACH registration of chemicals equal or above 1000 tpa consists of the screening (project I), the formal check (project II) and the refined check (project III). An overview is given in Figure 2-1.

Within the scope of screening the availability of standard information requirements according to REACH Regulation (Annexes VII to X column 1) was assessed by using a systematic screening approach with decision trees (Springer et al., 2015).

During the second project the formal conformity of data waiving and adaptations according to REACH requirements (Annexes VII to X column 2 or Annex XI), *e.g.* read across/grouping approaches and (Q)SAR models was evaluated.

The refined check consists of an in-depth analysis of waiving justifications and adaptations with general and endpoint specific formal criteria specified in REACH Annexes (including content-related aspects, where necessary and applicable) and an analysis of special case groups without conclusion after the screening.

Figure 2-1: Overview of the stepwise approach in project I to III



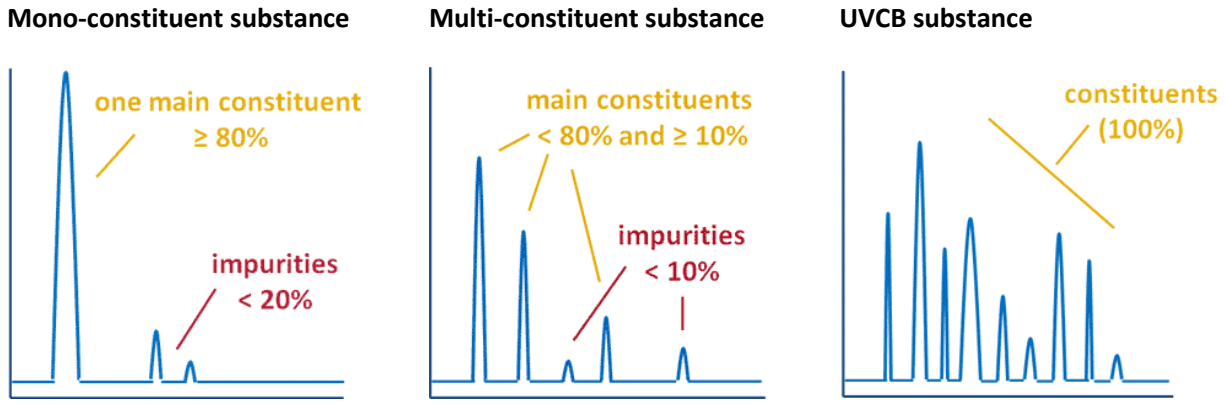
2.2 Substance sameness in lead and member dossiers of joint submissions

Manufacturers/importers are obliged to register the same substances within a joint submission according to the REACH Regulation. One registrant has the role as "lead registrant" submitting the lead dossier. The other registrants are "member registrants" of the joint submission and responsible for submitting their member dossiers. Both members and lead registrants have to provide information on their own substance identity.

In this part, the aim was to verify that the same substance has been registered in joint submissions of 1000 tpa or more substances. Therefore mono-constituent substances, multi-constituent substances and UVCB substance (Figure 2-2) were evaluated separately. These substance types are defined as:

- A substance is regarded as a mono-constituent substance if the mass fraction of the main constituent is at least 80 % (weight/weight (w/w)). Respectively, the mass fraction of impurities should be smaller than 20 % (w/w). This is the "80 %-rule". (ECHA, 2014a).
- Multi-constituent substances contain more than one main constituent. The mass fraction of each main constituent lies between 10 and 80 %. Impurities have a mass fraction of less than 10 % (ECHA, 2014a). In short, the "80/10 %-rule" should be followed.
- UVCB substances cannot be sufficiently characterised by its chemical composition. The reasons are that the number of different constituents is relatively large, of which a significant part is unknown. Additionally, the composition of UVCB substances can vary or is poorly predictable. Since main constituents cannot be easily identified the origin of the substance/s and the manufacturing process are important for substance identity (ECHA, 2014a).

Figure 2-2: Overview of the three main substance types



Source: European Chemicals Agency, http://echa.europa.eu/

2.2.1 Sampling

A list of lead and member dossiers and individual registrations compiled by ECHA on 1st July 2015 was used for this investigation. Important to note that this list is different to the list of lead and individual registrations provided by ECHA in March 2014 used in project I (Springer et al., 2015) and in chapter 2.5.1.

In total, the list of 1st July 2015 covered 2141 lead dossiers and individual registrations as well as 25265 member dossiers. All lead dossiers being part of a joint submission were chosen for further evaluation. These lead dossiers were evaluated separately dependent on the substance type as shown in Table 2-1. Representative sample sizes for each substance type were calculated with an online sample size calculator (Table 2-1). Subsequently, lead dossiers were randomly collected in SPSS software (IBM, Version 21).

The first step of checking the substance sameness of lead and member dossiers within a joint submission was the examination of up to ten randomly selected member dossiers. This was supposed to cover the entire number of member dossiers for the majority of joint submissions. If the number of member dossiers exceeded the number of ten, a further 10 % of the remaining member dossiers were randomly selected and checked. Thereby, the result of 10 % was rounded up from five upwards at the first decimal place. However, in sum a maximum of 30 member dossiers was checked for each joint submission.

Table 2-1: Representative sample size of lead dossiers for the three substance types calculated with an online sample size calculator* (95 % confidence level, 10 % confidence interval)

Substance type	Total lead dossiers	Sample size
Mono-constituent	886	87
Multi-constituent	88	46
UVCB	628	83
Total	**1602**	**216**

***** Global Market Insite Inc. (GMI): Solutions, Sample size calculator. http://www.gmi-mr.de/solutions/sample-size-calculator.php. Accessed July 2015.

2.2.2 Examination

The IUCLID Database is used for managing information on chemical substances registered in Europe by both registrants and authorities. A member state authority access for IUCLID version 5.6.0.1 (ECHA, 2014d) was used to evaluate data on substance identity. IUCLID sections listed in Table 2-2 were assessed to verify that the same substance was registered in lead and corresponding member dossiers. In both lead dossier and all member dossiers it was investigated whether identification and naming complied with the ECHA guidance on identification and naming of substances under REACH (ECHA, 2014a).

Information on the registration, substance type and sameness of main constituents was evaluated and documented in MS Excel. The MS Excel table used is shown in Annex 1. Additional information on special cases was documented with descriptors (Table 6-1 in Annex 1) or as free text.

Firstly, for all substance types, the entire entries covering different qualities/purity grades were assessed. At least one of these should fulfil the rules for acceptance specified for each substance type or according to the basic criteria (Table 2-3, Table 2-4 and Table 2-6). If at least one of the listed quality/purity grades showed deviations, this fact was documented (see descriptor list in Annex 1). Secondly, it was concluded whether the substance belongs to the selected substance type and that the rules described in the following subchapters for certain substance types were followed.
Finally, the sameness of the substance identity between lead and each member dossier was evaluated and concluded. From these results it was concluded whether it was a joint submission based on one (same) substance. If the sameness between lead and at least one member dossier was not given the lead dossier/joint submission was evaluated as “non-compliant”.

In the definition for the term “substance” according to REACH Article 3(1) it is stated that a substance is “a chemical element and from its compounds any solvent is excluded, which may be separated without affecting the stability of the substance or changing its composition” (EC, 2006). With respect to this, compounds which still included solvents in relevant concentrations were not accepted, except a justification was given which stated that otherwise the stability or composition of the substance would have been changed.

Alloys are regarded as special mixtures in the REACH Regulation and not as multi-constituent substances according to Annex I 0.11 of the REACH Regulation (EC, 2006). Therefore, single metals of an alloy have to be registered separately (BAuA, 2015). This circumstance was also considered here. The same applies for inorganic catalysts as set out in chapter 5 of the ECHA guidance (ECHA, 2014a).

Table 2-2: IUCLID sections used to assess substance identity and sameness of lead and member dossiers for mono-constituent, multi-constituent and UVCB substances

IUCLID Section	Information obtained
1.1 Identification: chemical name	General name
1.1 Identification: reference substance	EC and CAS number, CAS/IUPAC name if substance and reference are identical
1.1 Identification: reference substance and "Go to link target" >> Reference substance information	Description, of *e.g.* origin, process
1.1 Identification: type of substance	Mono- or multi-constituent substance or UVCB; for UVCBs: type of UVCB substance
1.2 Composition: constituents	Number of constituents and identifiers of the constituents (EC, CAS number, names); typical concentration, and/or concentration range of each constituent; different products/qualities etc.
3.1 Technological process: methods of manufacture of substance, methods of article production*	Description of origin and process

* This section was removed/migrated in IUCLID 6.
IUPAC: International Union of Pure and Applied Chemistry

Dossiers of mono-constituent substances

Dossiers of mono-constituent substances were assessed stepwise:

- It was verified in the lead dossier and all member dossiers that the main constituent and impurities were in line with the "80 %-rule" (see chapter 2.2) for mono-constituent substances. Since the 80 %-rule is regarded as guidance, deviations have to be justified (ECHA, 2014a).
- The substance identity of the main constituent was compared between lead and member dossiers to conclude the sameness.
- Basic criteria (Table 2-3) were considered for mono-constituent substances.

Table 2-3: Basic criteria to verify if two mono-constituent substances have the same substance identity (ECHA, 2014a)

Substance criteria for sameness or difference
Substances with identical CAS/EC number are the same
Hydrated and anhydrous form are regarded as the same for the purpose of registration
Acids and bases and their salts are different
Individual salts are different
Branched and linear alkyl chains are different
Saturated and unsaturated alkyl chains are different
Substances with different chiral centres are not the same
Different isomers are not the same

Dossiers of multi-constituent substances

Dossiers of multi-constituent substances were evaluated with the following steps:

- Based on the 80/10 %-rule (see chapter 2.2) it was verified that the mass fraction of each main constituent lies between ≥ 10 % and < 80 % (w/w).
- Sameness between lead and member dossiers was concluded if all recognised main constituents were the same.
- Additionally, basic criteria given in Table 2-4 were considered

Table 2-4: Basic criteria to verify if multi-constituent substances have the same substance identity (ECHA, 2014a)

Substance criteria for sameness or difference
Substances with identical CAS/EC number are the same
Substances with a more narrow or broader amount distribution of constituents in comparison to the questioned substance are different
Substances with only one, a subset of the constituents or more constituents in comparison to the questioned substance are different

Pre-analysis of Dossiers of UVCB Substances

For UVCB substances it is important to provide additional information on their origin and manufacturing process to be compared between lead and member dossiers due to their unknown composition and/or variable composition and/or large number of components.

As a conclusion on the sameness is not possible or intended for UVCB substances, the aim of this project was primarily to document the information given to characterise the UVCB and summarise the observed obstacles during the examination.

In this respect, the dossiers were checked in an explorative manner. The specific circumstances as well as the obstacles regarding the "sameness" (in a sense of that a joint registration is appropriate) between lead and member dossiers were documented for each joint submission. In comparison to mono- and multi-constituent substances, for UVCB additional parameters such as the origin and the manufacturing process or refinement were considered from the process description in IUCLID 5 section 3.1 as well to verify if two UVCB substances can be registered jointly (ECHA, 2014a). A significant change in origin or process might lead to a different substance which has to be registered separately.

A starting point for assessing UVCB substance sameness was their categorisation according to the ECHA guidance document (ECHA, 2014a), see Figure 2-3. This categorisation is not exhaustive. However, the table gives examples of concrete identifiers for sources and processes and, additionally, also examples for other types of identifiers.

A standard concept for checking whether two UVCB substances are the same cannot be deduced from the ECHA guidance on identification and naming of substances under REACH (ECHA, 2014a). However, specific types of UVCB substances have specific characteristics and properties which may allow for the application of specific criteria. They are described in more detail in the ECHA guidance document and for these substances a rough checking scheme could be compiled as set out in Table 2-5. Basic criteria to conclude whether UVCB substances could be registered jointly are provided in Table 2-6.

In addition, it was examined if specific identifiers of different categories of UVCB substances, which might have practical impact on the assessment, were indicated in the dossiers. A preliminary conclusion was made in each member dossier in comparison to the respective lead dossier, if possible.

Figure 2-3: Main identifiers for examples that represent various types of UVCB substances serving as a starting point for assessing the sameness of UVCB substances in lead and member dossiers (ECHA (2014a), p. 22)

IDENTIFICATION AND NAMING OF SUBSTANCES UNDER REACH AND CLP VERSION 1.3 – FEBRUARY 2014

Table 4.2 : Grouping of main identifiers for examples that represent various types of UVCB substances

Common features		Examples or representatives	Main identifiers		
			Source	*Process*	*Other Identifiers*
UVCB substances (Substances of Unknown or Variable composition, Complex reaction products or Biological materials) *[Chapter 4.3]*	Biological materials (B)	Extracts of biological materials e.g. natural fragrances, natural oils, natural dyes and pigments	• Plant or animal species and family • Part of plant/animal	• Extraction • Fractioning, concentrating, isolation, purification, etc. • Derivation*	• Known or generic composition • Chromatographic and other fingerprints • Reference to standards • Colour index
		Complex biological macromolecules e.g. enzymes, proteins, DNA or RNA-fragments, hormones, antibiotics			• Standard enzyme index • Genetic code • Stereo configuration • Physical properties • Function/activity • Structure • Amino acid sequence
		Fermentation products antibiotics, biopolymers, enzyme mixtures, vinasses (products of sugar fermentation) etc.	• Culture medium • Micro-organism applied	• Fermentation • Isolation of products • Purification steps	• Type of products: e.g. antibiotics, biopolymers, proteins etc • Known composition
	Chemical and mineral substances with poorly defined, complex or variable composition (UVC)	Reaction mixtures with poorly predictable and/or variable composition	• Starting materials	• Chemical reaction type, e.g. esterification, alkylation, hydrogenation	• Known composition • Chromatographic and other fingerprints • Reference to standards
		• Fractions or distillates, e.g. petroleum substances • Clay e.g. bentonite • Tars	• Crude oils • Coal/peat • Mineral gases • Minerals	• Fractionation, distillation • Conversion of fractions • Physical processing • Residues	• Cut off ranges • Range of chain length • Ratio aromatic/ aliphatic • Known composition • Standard index
		Concentrates or melts, e.g. metallic minerals, or residues of various melting or metallurgic processes, e.g. slags	• Ores	• Smelting • Heat treatment • Various metallurgic processes	• Known or generic composition • Concentration of metals

* Underlined processes indicate synthesis of new molecule

Table 2-5: Selected identifiers used for examination of the conformity of specific UVCB substances in lead and member dossiers according to ECHA (2014a)

UVCB group (example)	Chapter ECHA guidance	Criteria/identifiers
Substances with variation in the carbon-chain lengths, naturally with plant/animal origin or synthetic ("linear fatty acids C8-C16")	4.3.2.1	Substances with constituents which have a unique structural characteristic: they have at least a long chain alkyl group, often with a functional group. Constituents differ in at least one of the following alkyl chain group characteristics (defined in general by relation to a reference substance): carbon number, saturation, structure (linear or branched) **and/or** position of the functional group. Chemical identity is sufficiently described by the following three descriptors: ► alkyl descriptor: carbon chain length, even/uneven numbered, linear/branched, saturated/unsaturated; a narrow chain length does not cover a broader one (and vice versa) **and** ► functionality descriptor: *e.g.* carboxylic acid, ammonium, amine; position of group **and** ► salt descriptor: cation/anion of the salt where appropriate; source and/or process where appropriate; chain length has to correspond to chain length of origin, *e.g.* from a plant source only even numbered alkyl chains result. Composition is variable and should be within the ranges of the identifiers of the reference substance, if given. Otherwise only a qualitative comparison concerning the alkyl chain range given (*e.g.* C12-C14) is carried out. Check if reference of member is identical to lead reference.
Substances obtained from oil (petroleum substances) or oil like (*e.g.* coal) sources ("naphtha (petroleum), full-range alkylate, butane-containing")	4.3.2.2	Typical identifiers for this type of UVCB substances comprise the stream's source, refinery process, general composition, carbon number and chain length, boiling range, other physical characteristics, and predominant hydrocarbon type. Within the project the following parameters were checked to verify if substances of lead and member dossiers were the same: ► name ► source ► process ► composition: 1. number of main constituents (≥ 10 %) 2. kind of main constituents (often given as generic terms, sometimes specified with CAS/EC) 3. concentration ranges (concentrations sum up to 100 %; conformity with respect to the predominant hydrocarbon type(s)) 4. presence of hazardous constituents (GHS classification) in relevant concentrations*
Enzymes	4.3.2.3	These substances are characterized by ► the name of the active enzyme (activity is the identifier after IUBMB-classification) ► amounts of active enzymes, further proteins, carbohydrates , lipids and salts ► origin (plant or animal species), if given ► process (fermentation and purification phase) The following identifiers (name) have to be given (*e.g.* in the reference description) and should be identical for lead/member: ► IUBMB# name, *e.g.* amylase, a- ► enzyme class no., *e.g.* 3.2.1.1 ► reaction type, *e.g.* hydrolysis The composition will typically be within the following ranges. Water, if without change of composition separable, is not included: ► active enzyme protein 10 - 80 % ► other proteins/peptides/amino acids 5 - 55 %, ► carbohydrates 3 - 40 %,

UVCB group (example)	Chapter ECHA guidance	Criteria/identifiers
		► lipids 0 - 5 %, ► inorganic salts 1 - 45 %, total 100 % The composition is variable, but ranges should be similar to those of the lead with the main focus on the active enzyme. If not a chemical group but a concrete substance is given (for constituents ≥ 10 % or substances with relevant classification and/or PBT-assessment), this should be mentioned in all dossiers. Origin (plant or animal species), if given, has to be in accordance between lead and member. Process consists of fermentation phase and recovery (purification) phase. Organisms, medium, conditions and purification process characterises the total process. If details are given these should be in accordance.

* Hazardous substances found in petroleum products cover *e.g.* benzene, toluene and n-hexane. A more comprehensive list can be found in (Clark et al., 2013). The concentration limits triggering hazard classification are specified in Annexes I and VI of the CLP regulation (EC, 2008b). Substances of lead and member dossiers should have the same hazard classification based on their composition. GHS: Globally Harmonized System of Classification and Labelling of Chemicals

IUBMB name: International system of enzymes nomenclature by International Union of Biochemistry and Molecular Biology (IUBMB); http://www.chem.qmul.ac.uk/iubmb/enzyme

Table 2-6: Basic criteria within the project to verify whether UVCB substances can be considered the same (ECHA, 2014a)

Substance criteria for sameness or difference
Substances with identical CAS/EC number are considered the same*
Substances derived from different species/genus are not the same
Enzyme concentrates with the same IUBMB* number and the same production organism are regarded as the same
Purified extract/concentrate and the crude extract are different

* IUBMB = International system of enzymes nomenclature by International Union of Biochemistry and Molecular Biology

Substance sameness within joint submissions and registrants' role in the supply chain

An additional analysis addressed whether differences regarding substance sameness in joint submissions are present depending on the role of the registrant in the supply chain (manufacturer, importer or only representative). This was investigated for mono-constituent and multi-constituent substances and the results are presented in Annex 9.

2.3 Equivalency of test materials used in key studies and the registered substance

It was investigated whether test material of (eco-)toxicological studies had the same SID as the registered substance. The check was carried out for all relevant HH and ENV endpoints included in the previous project (RDT, ReproTox, DevTox, Muta, Bioaccu, BioDeg, AbioDeg, and Ecotox). If substance sameness was not given, a further investigation whether a read-across was intended, and accidentally not documented, instead of reporting a key study did not took place.

2.3.1 Sampling

The identical random sample of lead dossiers described in chapter 2.2.1 was selected again to evaluate test material identity used in key studies. Additionally, random samples of individual dossiers were selected for each substance type as described in chapter 2.2.1. Table 2-7 gives an overview on the sample size.

Table 2-7: Representative sample sizes of lead and individual dossiers for each substance type calculated with an online sample size calculator* (95 % confidence level, 10 % confidence interval)

Kind of dossier	Substance type	Total dossiers	Sample size
Lead dossiers as part of a joint submission	mono-constituent	886	87 (from chapter 2.2.1)
	multi-constituent	88	46 (from chapter 2.2.1)
	UVCB	628	83 (from chapter 2.2.1)
Individual dossiers[#]	mono-constituent	161	61
	multi-constituent	75	41
	UVCB	303	72
Sum of all lead dossiers and individual dossiers	*mono-constituent*	*1047*	*148*
	multi-constituent	*163*	*87*
	UVCB	*931*	*155*
Total		**2141**	**390**

* Global Market Insite Inc. (GMI): Solutions, Sample size calculator. http://www.gmi-mr.de/solutions/sample-size-calculator.php. Accessed July 2015

[#] Individual dossiers: 312 lead dossiers without member dossiers and 227 individual submissions

2.3.2 Examination

All available key studies in the specific IUCLID sections for a particular endpoint were assessed, irrespective of whether the information/study type was required or not according to the REACH Regulation. An overview on the relevant IUCLID sections for each endpoint is given in Table 2-8.

Table 2-8: Overview on the endpoint specific IUCLID sections for substance check in "key studies"

Endpoint	Checked IUCLID sections
Repeated dose toxicity	7.5.1 Repeated dose toxicity: oral 7.5.2 Repeated dose toxicity: inhalation 7.5.3 Repeated dose toxicity: dermal 7.5.4 Repeated dose toxicity: other routes
Toxicity to reproduction	7.8.1 Toxicity to reproduction
Developmental toxicity	7.8.2 Developmental toxicity/teratogenicity
Mutagenicity	7.6.1 Genetic toxicity *in vitro* 7.6.2 Genetic toxicity *in vivo*
All ENV endpoints	4.7 Partition coefficient 4.8 Water solubility
Biotic degradation	5.2.1 Biodegradation in water: screening tests 5.2.2 Biodegradation in water and sediment: simulation tests 5.2.3 Biodegradation in soil 5.4.2 Henry's Law constant
Abiotic degradation	5.1.2 Hydrolysis 5.2.1 Biodegradation in water: screening tests
Bioaccumulation	4.21 Dissociation constant 5.3.1 Bioaccumulation: aquatic/sediment
Ecotoxicity	6.1.1 Short-term toxicity to fish 6.1.2 Long-term toxicity to fish 6.1.3 Short-term toxicity to aquatic invertebrates 6.1.4 Long-term toxicity to aquatic invertebrates

It is important to note that it was not checked whether the study itself was appropriate as the aim was to elucidate if information of experimental studies with the same SID as the registered substance was available unless otherwise adapted.

Key studies using read-across approaches can also be identified and are typically based on the eco-/toxicological information from related substances. Their occurrence within an endpoint entry was documented and the study was not further assessed. The field "study result type" had to be flagged as read-across. "(Q)SAR" or "estimated per calculation" entries as well as "other" studies, which can also be flagged as key studies in IUCLID, had to be stated as having been carried out with the registered substance. Otherwise they had to be flagged as read-across.

For the purpose of this project, the test material identity was compared in IUCLID for each key study with the registered substance. This comprised the assessment of the following two fields in the IUCLID section "Test materials":

- "Test material equivalent to submission substance identity"/"Identity of test material same as for substance defined in section 1 (if not read-across)": The registrant had chosen "Yes" or "No" in this section; and/or
- "Test material identity": Registrants filled in identifiers such as the name and/or EC/Chemical Abstracts Service (CAS) number of the substance used in the study.

At least one of the two sections had to be filled out. The information on test material should have been a "Yes" **and/or** identifiers should have matched to those of the registered substance. Otherwise, it was concluded that the key study was not carried out with the registered substance. Inconsistent information on the test material also resulted in a rejection. With respect to this, for UVCB substances the same rules regarding naming applied as set out in (ECHA, 2014a) (*e.g.* substances with variation in the carbon chain lengths). It was not verified whether a read-across justification was available.

All documentation and analysis was performed in MS Excel. The structure of the MS Excel table for the documentation of information can be found in Annex 2.

2.4 Information from screening of dossiers (project I)

2.4.1 Information used for formal check

In project I (Springer et al., 2015) a standardised screening with decision trees was developed. The decision criteria based on the standard information requirements of the REACH Regulation as set out in Annexes VII to X. The following endpoints were evaluated in project I: RDT, TRep, Muta, AbioDeg, BioDeg, Bioaccu and Ecotox, and additionally, Expo. A conclusion on each endpoint was made as well as an overall conclusion for each dossier in project I. Endpoints remained without a conclusion (category "complex") if an experimental study required as standard information (REACH Annexes VII to X column 1) was either waived or adapted. But this was only accepted if a waiving justification or a respective adaptation according to Annexes VII to X column 2 or Annex XI was available. These "complex" endpoints would have required a detailed analysis to decide whether they comply with REACH Annexes VII to X column 2 or Annex XI.

Moreover, certain special cases of the human health endpoints remained without conclusion ("complex"), *e.g.* if a more detailed assessment of the appropriateness of the applied exposure route was necessary.

Additionally, the applied waiving and adaptation categories selected by the registrants in IUCLID were documented in MS Excel. The categories for **waiving/adaptation** in IUCLID 5 comprise:

- "study scientifically unjustified" or
- "study technically not feasible" or
- "exposure considerations" or
- "other justification" or
- "read-across based on grouping of substances (category approach)" or "read-across from supporting substance (structural analogue or surrogate)", documented as "read-cross/grouping" or
- "weight of evidence" (WoE) or
- "(Q)SAR".

Frequently, more than one waiving or adaptation category for a particular endpoint were used and, accordingly, all of them were documented within project I. On the one hand, for the endpoints TRep, Muta and Ecotox more than one standard testing regime should be available to fulfil the standard information requirements. On the other hand, multiple waiving/adaptation categories were chosen to omit a certain standard testing regime. Especially, the waiving category "study scientifically unjustified" was often given in addition to a read-across or WoE approach.

WoE approaches were excluded for the formal check when they were used as the sole approach – with exception for Ecotox. However, the exclusion of these adaptations was not always possible due to the kind of documentation in project I (Springer et al., 2015). Moreover, the given justification for the waiving or adaptation was not always in agreement with the option selected in IUCLID. Though, this could only be elucidated within formal check. Therefore, adaptation categories which were *per se* excluded from the check were additionally examined whenever this could not be avoided.

2.4.2 Information used for refined check

After the screening some special case groups left "complex" concerning human health endpoints, which were not examined in the second project phase. These special case groups are summarised in Annex 5, Table 6-12.

Furthermore, WoE approaches have been excluded from the formal check for all endpoints. These WoE were evaluated within the refined check (see chapter 2.6.2) for the HH endpoints ReproTox, DevTox and Muta (see chapter 2.6.3.6), and the ENV endpoint Ecotox (see chapter 2.6.4.2).

For the ENV endpoint Expo information from "complex" cases was available from project I (Springer et al., 2015) that either a quantitative (911 dossiers) or qualitative exposure assessment (101 dossiers) is available. Further information of project I from other endpoints was used for the evaluation of Expo as well (see chapter 2.6.5).

2.5 Formal check

In the preceding project I (Springer et al., 2015), a high number of endpoints was not concluded and was assigned to the conclusion category "complex". This based mainly on waiving or adapting standard information required. Regularly, this was justified with "column 2 specific rules" or "general rules" for adaptation from standard testing, REACH Annexes VII to X or Annex XI, respectively. Frequently, grouping of substances and read-across approaches were used to adapt for the required standard information (REACH Annex XI 1.5.). The formal check was applied to evaluate endpoints not concluded in the screening of project I.

Data waiving or adapting standard information has to be clearly stated in the registration dossiers (REACH Annexes VII to X introduction, 3rd bullet point). Moreover, citing the endpoint "specific rules" set out in column 2 of REACH Annexes VII to X or the "general rules" of REACH Annex XI is mandatory. If another reason than those mentioned in these rules applies, this fact has clearly to be stated as well as the reason (REACH Annexes VII to X introduction, last passage). Both, "specific rules" and "general rules" were taken for the formal check and named as REACH rules. The formal check comprised a stepwise proceeding:

- waiving/adaptations used for a particular endpoint case were documented to illustrate the case-specific situation,
- general formal criteria were evaluated,
- more endpoint- or waiving/adaptation-related specific aspects were checked.

Every waiving/adaptation option presented by the registrant or deduced by project staff from the justifications was evaluated and concluded. Finally, an overall conclusion was drawn on the accumulated information gained for each endpoint case. The concrete procedure is described in the following chapters.

The endpoint Expo was excluded because the formal criteria for this endpoint were already checked in project I (Springer et al., 2015). Furthermore, the examination was not intended to address other adaptations than read-across, such as WoE, (Q)SAR (except for the ENV endpoints), *in vitro* tests, studies not carried out according to standard methods or human data.

2.5.1 Sampling

The base for the formal check was the list of relevant endpoints without conclusion ("complex") derived from project I (Springer et al., 2015). The concerned dossiers in the list were compiled by ECHA by 7th March 2014.

Endpoints without conclusion ("complex") which did not rely on waiving or adaptation or were solely based on a WoE approach, (Q)SAR, *in vitro* tests, studies not carried out according to standard methods or human data according to the specification of the registrant in IUCLID were excluded. For Ecotox adaptations based on WoE and (Q)SAR were included in the sampling.

An overview on the total number of endpoints without conclusion ("complex") analysed is given in Table 2-9, the number of analysed dossiers are given in the right column.

Table 2-9: Sample size of endpoints without conclusion ("complex") for each human health and environmental endpoint

Endpoint	Endpoints concluded "complex" in project I	Endpoints without conclusion ("complex") based on waiving/read-across and without other single adaptation approaches
RDT	1006	850*
ReproTox	1321$	1133
DevTox		917
Muta	858	653
AbioDeg	1198	1029
BioDeg	786	533
Bioaccu	1380	315
Ecotox	1493	1493#
Total	**8042**	**6923**

* Four additional dossiers based on testing proposal and were excluded from the analysis.
$ Numbers of endpoints without conclusion ("complex") for TRep in the previous project; in the following projects the distinction was made between DevTox and ReproTox.
# 34 complex WoE cases from project I were included.

2.5.2 Formal criteria for evaluation

Is the reference justifying waiving or adaptation appropriate to the REACH Regulation?

Waiving and adaptations of standard information requirements can be applied according to specific rules set out in Annexes VII to XI of the REACH Regulation (EC, 2006). With respect to this it is important to be aware that only certain rules of the endpoint specific criteria (REACH Annexes VII to X column 2) are applicable for substances of 1000 tpa or more. At best, the registrant directly references to the specific part of the REACH Annexes VII to XI. If this is not the case, the justification should be ex-

plicit enough to allow for an unequivocal attribution to one of the rules specified in the REACH Annexes. During this examination it was documented whether the reference was given by the registrant or had been deduced within the project.

If no reference could be deduced from the justification of a particular waiving, the case was supposed to relate to REACH Annexes VII to X introduction, last passage (other reasons apply than those mentioned in Annexes VII to XI). These cases were only further evaluated if possible ("obviously non-compliant" cases).

Does the justification given for waiving or adaptation comply with the REACH Regulation?

For waiving justifications it was checked whether the registrants named and commented on the criteria they referenced to. That means it was not regarded as formally sufficient if the registrant simply mentioned the waiving according to a specific REACH Annex, as the registrant also has to justify this choice (further explain how and why this rule applies to its substance). A more detailed description of the criteria that were checked for each waiving option can be found below.

In certain cases, some criteria were accepted although they were not mentioned in the waiving justifications, because they were available in the endpoint study records (ESRs) and thus the criteria fulfilled the waiving justifications.

Are endpoint study records available for adapting standard information?

If the registrant used an adaptation approach (*e.g.* read-across or non-Good Laboratory Practice (GLP) studies) to replace the required data from standard tests, it was necessary to provide appropriate ESRs for the surrogate data. It was not accepted if the studies the registrant refers to in a waiving justification were only cited in the text or only references to secondary literature were given. Occasionally, the ESRs might also have been available in other IUCLID sections and were accepted if the registrant referred to the section or endpoint.

"Specific rules" and "general rules" as formal criteria

Besides the general formal criteria which apply to all waiving/adaptation categories, more specific criteria were checked. These were derived from the distinct rules that are defined in column 2 of the REACH Annexes VII to X (waiving options for each endpoint) and Annex XI (overall waiving/adaptation options that apply to all endpoints) of the REACH Regulation. Not all of the rules mentioned in the REACH Annexes could be included in the check because several aspects require an in-depth assessment of the dossiers which was not part of this project. The criteria which were addressed within this project are summarised for the overall waiving/adaptation options in Table 2-10.

For endpoint specific waiving options they are compiled in Table 2-11 for HH and in Table 2-12 for ENV. Besides, the tables also include a short comment how these criteria were assessed. It is important to note that it was not part of this check to verify whether the waiving justifications or adaptations were appropriate with regard to (scientific) content and it was also not assessed whether the statements and data presented by the registrants were correct. Exceptions with respect to interpretation of the content were only made for "obvious cases". Furthermore, due to the circumstances that the investigated dossier list dated from March 2014, criteria were derived from the version of the REACH Regulation that was in force at that time.

Table 2-10: Checked formal criteria for waiving or adapting standard information requirements according to Annex XI of the REACH regulation

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
Annex XI 1. Testing does not appear scientifically necessary*			
Annexes VII to X; Article 13(3) tests shall be conducted in accordance with methods laid down in a commission Regulation; Article 13(4) test shall be carried out with the principles of GLP	Annex XI 1.1.1. Use of existing data; Data on physico-chemical properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3)	► data are valid for the investigated endpoint and the study is performed using an acceptable level of quality assurance ► sufficient documentation is provided	► study as ESR available ► key study available ► reliability of 1 or 2
Annexes VII to X; Article 13(3); Article 13(4)	Annex XI 1.1.2. Use of existing data; Data on human health and environmental properties not carried out according to GLP or the test methods referred to in Article 13(3)	► exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) ► adequate and reliable documentation	► study as ESR available ► key study available ► reliability of 1 or 2 ► test duration comparable or longer
Annexes VII to X	Annex XI 1.1.3. Use of existing data; historical human data	Minimum requirement: registrant mentioned "human data"	► study as ESR available (alternatively also in IUCLID section 7.10) ► key study available ► reliability of 1 or 2
Annexes VII to X	Annex XI 1.2. WoE	not included in formal check	
Annexes VII to X	Annex XI 1.3. (Q)SAR	► (Q)SAR model is scientifically validated ► substance falls within the applicability domain of the (Q)SAR model ► adequate and reliable documentation of the method	► study as ESR available ► key study available ► reliability of 1 or 2 ► QMRF and QPRF available ► OECD criteria for validation: 1. defined endpoint 2. distinct algorithm 3. applicability domain 4. Goodness-of-fit, robustness and predictivity (internal and external validation) 5. mechanistic interpretation (in QMRF, ESR or endpoint summary) ► substance falls within the applicability domain of the model (in the QMRF, ESR or endpoint summary)

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
Annexes VII to X	Annex XI 1.4. *In vitro* methods	Test method indicates the presence of a dangerous property of the substance related to the respective endpoint **or** if the test method does not indicate the presence of a dangerous property: ► scientific validity of the test method has been established by a validation study according to internationally agreed validation principles ► adequate and reliable documentation of the method is provided	► study as ESR available ► key study available ► reliability of 1 or 2 non-hazardous substances: test is scientifically validated
Annexes VII to X	Annex XI 1.5. Grouping of substances and read-across approach	Structural similarities based on: ► a common functional group **or** ► the common precursor and/or likelihood of common breakdown products (physical and biological processes) or ► a constant pattern in the changing of the potency of the properties across the category General criteria: ► exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) ► adequate and reliable documentation	► structural similarities are explained[#] ► study as ESR available ► key study available ► reliability of 1 or 2 ► test duration comparable or longer
Annex XI 2. Testing is technically not possible			
Annexes VII to X	Annex XI 2.	Testing might technically not be 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**	criterion is explained in waiving justification

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
		► relevant concentrations are corrosive (according to Annexes VII to X, introduction, passage 4) **or** ► method has technical limitations that do not allow for testing	
Annex XI 3. Substance-tailored exposure-driven testing			
Annex VII 8.6. and 8.7. Annex IX and X	Annex XI 3.	Based on exposure scenario(s) in CSR. All conditions are fulfilled: ► absence or no significant exposure in exposure scenarios of the manufacture and all identified uses and ► a DNEL or a PNEC can be derived and ► exposures are always well below the DNEL or PNEC **or** substances not incorporated in an article: ► for all relevant scenarios throughout the life cycle strictly controlled conditions as set out in Article 18(4)(a) to (f) apply **or** for substances incorporated in an article in which it is permanently embedded all of the following conditions are fulfilled: ► the substance is not released during its lifecycle **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	► criteria are explained in waiving justification **and** ► exposure scenarios **or** qualitative exposure assessment are available in CSR

* Adaptations in italic type were only checked if they were present in addition to a waiving justification or read-across and could therefore not be excluded prior to the check.

[#] The explanation was usually given in particular assessment reports, in the CSR, in the endpoint summary or in the respective ESR. In rare cases if justifications were provided at other or unusual locations this might have not been considered/found within the standard procedures of this project.

Table 2-11: Checked formal criteria for waiving standard information requirements according to Annexes VII to X of the REACH regulation for each HH endpoint

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
Reproductive and developmental toxicity*			
Annex IX 8.7.2. DevTox, 1st species	Annex IX 8.7. column 2	same criteria as in Annex X for DevTox, 2nd species	same evaluation as for DevTox, 2nd species
Annex X 8.7.2. DevTox, 2nd species 8.7.3. ReproTox	Annex X 8.7. column 2, first passage, 1st bullet point	known genotoxic carcinogen	criterion is explained in waiving justification
	Annex X 8.7. column 2, first passage, 2nd bullet point	known germ cell mutagen	criterion is explained in waiving justification
	Annex X 8.7. column 2, first 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 ► 1st bullet point: ► study as ESR available ► key study available ► reliability of 1 or 2
Annex X 8.7.3. ReproTox	Annex X 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 X 8.7.3. DevTox, 2nd species	Annex X 8.7. column 2, 3rd passage	criteria for classification as toxic for development cat. 1A or 1B (H360D) are met	criterion is explained in waiving justification
Mutagenicity			
In vitro tests			
Annex VII 8.4.1. GMbact	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* chromosome aberration test are available	► study as ESR available ► key study available ► reliability of 1 or 2
	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
Annex VIII 8.4.3. GMvitro	Annex VIII 8.4.3. column 2	adequate data for *in vivo* mammalian gene mutation test are available	► study as ESR available ► key study available ► reliability of 1 or 2
In vivo soma cell tests (if *in vitro* tests were positive)			
Annex IX 8.4. column 2 *in vivo* tests	only options of Annex XI apply		
In vivo germ cell test (if *in vivo* soma cell tests were positive)			
Annex IX/X 8.4. column 2, second passage germ cell test	Annex IX/X 8.4. column 2, 2nd passage	potential for germ cell mutagenicity can be judged on the basis of all available data, including toxicokinetic evidence	criterion is explained in waiving justification

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
Repeated dose toxicity			
Annex IX 8.6.1. 28-day study	Annex IX 8.6.1. column 1	90-day study available	► study as ESR available ► key study available ► reliability of 1 or 2
Annex IX 8.6.2. 90-day study	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 STOT RE1 (H372) **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 1st bullet point: ► study as ESR available ► key study available ► reliability of 1 or 2
	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	1st bullet point: ► study as ESR available ► key study available ► reliability of 1 or 2
	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
	Annex IX 8.6.2. column 2, 1st passage, 4th bullet point	► substance is unreactive and 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 3rd bullet point: ► study as ESR available ► key study available ► reliability of 1 or 2

* The REACH standard information requirement for ReproTox in March 2014 was the two-generation study and not yet the extended one-generation study which is the current requirement.
STOT RE = specific target organ toxicity – repeated exposure

Table 2-12: Checked formal criteria for waiving standard information requirements according to Annexes VII to X of the REACH regulation for each ENV endpoint

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
Biotic and abiotic degradation			
Annex IX Biotic	Annex IX 9.2.1.2. column 2 Simulation testing on ultimate degradation in surface water	substance is highly insoluble in water or readily biodegradable	► S_w < 1 mg/L; IUCLID section 4.8 ► study as ESR available ► key study available ► reliability of 1 or 2 ► pass level for readily biodegradable (70 % removal of DOC and 60 % of ThOD or $ThCO_2$ production for respirometric methods, has to be reached in a 10-day window within the 28-d period of the test, 10-d window begins with when biodegradation has reached 10 % DOC, ThOD or $ThCO_2$)
	Annex IX 9.2.1.3. column 2 Soil simulation testing	substance is readily biodegradable or direct and indirect exposure of soil is unlikely	► study as ESR available ► key study available ► reliability of 1 or 2 ► pass level for readily biodegradable ► exposure scenario CSR
	Annex IX 9.2.1.4. column 2 Sediment simulation testing	substance is readily biodegradable or direct and indirect exposure of sediment is unlikely	► study as ESR available ► key study available ► reliability of 1 or 2 ► pass level for readily biodegradable ► exposure scenario CSR
Annex VIII Abiotic	Annex VIII 9.2.2.1. column 2 Hydrolysis as a function of pH	substance is highly insoluble in water or readily biodegradable	► study as ESR available ► key study available ► reliability of 1 or 2 ► S_w < 1 mg/L; IUCLID section 4.8 ► pass level for readily biodegradable
Annex IX	Annex IX 9.2.3. column 2 Identification of degradation products	unless substance is readily biodegradable	► ESR available ► key study available ► reliability of 1 or 2 ► pass level for readily biodegradable

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
► **Bioaccumulation**			
Annex IX Bioaccumulation	Annex IX 9.3.2. column 2	substance has a low potential for bioaccumulation (for instance a log K_{ow} ≤ 3) and/or a low potential to cross biological membranes **or** direct and indirect exposure of the aquatic compartment is unlikely	► study as ESR available ► key study available ► reliability of 1 or 2 ► K_{ow} ≤ 3 ► exposure scenario CSR
► **Ecotoxicity**			
Annex VII 9.1. Aquatic toxicity	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.	► study as ESR available ► key study available ► reliability of 1 or 2 ► S_w < 1 mg/L ► CSR
Annex VIII	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** ► 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.	► study as ESR available ► key study available ► reliability of 1 or 2 ► S_w < 1mg/L ► CSR

Waived/adapted standard information	Reference for waiving/adaptation	Criteria to be addressed in the justification	Evaluation
		► If the substance is poorly water soluble, the long-term aquatic toxicity study (Annex IX 9.1.6.) should be considered.	
Annex IX 9.1. Aquatic toxicity	Annex IX 9.1.5. column 2 Long-term toxicity testing on invertebrates (*Daphnia*)	Long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment.	CSA See refined check in 2.6.4.1
Annex IX	Annex IX 9.1.6. column 2 Long-term toxicity testing on fish *The information shall be provided for one of the sections below* 9.1.6.1. Fish early-live stage (FELS) toxicity test 9.1.6.2. Fish short term toxicity test on embryo and sac-fry stages 9.1.6.3. Fish, juvenile growth test	Long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment.	CSA See refined check in 2.6.4.1

$ThCO_2$: Theoretical carbon dioxide production, DOC: Dissolved organic carbon

2.5.3 Additional procedure and criteria

Repeated dose toxicity pre-check of route considerations

For testing RDT the oral administration route is the preferred exposure route (ECHA, 2015b). However, the dermal or inhalation route is relevant if the physico-chemical properties suggest testing and if these routes are important in relation to uses and human exposure. REACH Annex IX 8.6.2. column 2 gives the criteria under which circumstances dermal or inhalation testing is appropriate (trigger).

These trigger comprise for dermal testing the following aspects:

- ► skin contact in production and/or use is likely; and
- ► the physico-chemical properties suggest a significant rate of absorption through the skin; and
- ► toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test; or systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies; or *in vitro* tests indicate significant dermal absorption; or significant dermal toxicity or dermal penetration is recognised for structurally-related substances.

Inhalation administration has to be tested if the following is true: Exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.

Registrants have to consider these REACH criteria to determine whether testing of an administration route is appropriate and often include their argumentation into the waiving justification, sometimes along with other criteria important according to the general (REACH Annex XI) and endpoint specific criteria (REACH Annexes VII to X column 2) for waiving/adaptation of the 90-day study in general. Within the project it was decided to separate these two aspects or levels of argumentation.

Therefore, previous to the general check for RDT, see the chapter 2.5.2, an administration route related check was applied. Here, the presented data and the waiving argumentation were considered. The following aspects were checked in the indicated order:

An administration route was not further considered, irrespective of other argumentation included,

- if no data or no waiving justification was presented in IUCLID for the respective administration route;
- if the waiving justification indicated that dermal or inhalation testing was not appropriate/not necessary because of the expected uses/expected exposure (thus no exposure scenarios/no derived no-effect level (DNEL) calculation);
- if the waiving justification stated that the trigger for dermal or inhalation testing according to REACH were not true;
- if the waiving justification indicated that dermal or oral testing was not appropriate/not necessary because of the fact that the substance was very volatile or a gas (REACH Annex XI 2.).

In contrast, all the remaining routes with waiving justifications containing only points for general waiving of 90-day study in terms of REACH Annexes VII to X column 2 or Annex XI criteria were included in the below described check.

Evaluation of additional information

In addition to the general and waiving/adaptation-specific criteria, certain observations were documented via free texts or, if they repeatedly occurred, descriptors were introduced for use in the memo field. For example, it was noted if read-across studies were not performed according to the test methods in line with REACH Article 13(3) (*e.g.* draft guideline study). A full list of the descriptors can be found in Annex 3. This additional information was mainly used for documentation.

Concerning the ENV endpoint Bioaccu, testing results achieved with prior versions of the Organisation for Economic Co-operation and Development test guideline (OECD TG) 305 were accepted for the OECD TG 305 C (OECD, 1981e) and OECD TG 305 E (OECD, 1981a) but not for OECD TG 305 A (OECD, 1981c), OECD TG 305 B (OECD, 1981b) and OECD TG 305 D (OECD, 1981d).

Accepted guidelines for the endpoint Ecotox beside the standard testing methods according to test method regulation (EC, 2008a) are summarised in Annex 4. For these methods a memo “sim guide” was added and it was checked as well as whether test duration, reliability and species were appropriate.

Other standard methods or non-standards tests can be applied to fulfil the information requirements. This is possible if reference to REACH, Annex XI 1.1.2. is given and the conditions are met to consider the data as equivalent to data resulting from the test methods referred in REACH Article 13(3). Guidance for the evaluation of other test guidelines and non-standard test is given in Regulatory framework of REACH (ECHA, 2016a). When other guidelines were followed the memo “oth guide” was added and the ENV endpoint Ecotox was not concluded (“complex”). Also, non-standard tests were not concluded and the ENV endpoint Ecotox remained without a conclusion (“complex”).

The following standard methods were not accepted ("non-compliant") as long-term toxicity method, because these are considered as short-term toxicity tests for fish:

- OECD TG 204 (OECD, 1984)
- ISO 10229-1 (ISO, 1994a)
- ASTM 729-88a (ASTM, 1993a)
- EPA/600/4-90/027 (US EPA, 1991)

Furthermore, it was documented if waiving/adaptations were used to incriminate the registered substance regarding its toxic potential or to exonerate it. How this was specifically deduced from the IUCLID entries depended on the endpoint. Table 2-13 gives an overview on the sources and the interpretation of the information for each endpoint. RDT was not included in the analysis because the objective of this endpoint is to identify relevant concentration ranges of toxicity and to derive no observed (adverse) effect levels (NO(A)EL). If ambiguous or conflicting information on the incrimination or exoneration of the substance was given, no conclusion was made.

Table 2-13: Assessed source and interpretation of information to deduce if waiving/adaptations were used to incriminate or exonerate the toxic potential of the registered substance in formal check*

Endpoint	Source	Interpretation of information
Muta	► ESR of key study/studies (read-across/grouping)	► outcome of a particular test was interpreted as positive by the registrant – incrimination ► outcome of a particular test was interpreted as negative by the registrant – exoneration
	► ESR for data waiving ► summary of ESR	► registrant stated that substance is supposed to be mutagenic – incrimination ► registrant stated that substance is supposed to be not mutagenic – exoneration
DevTox	► ESR of key study/studies (read-across/grouping) ► ESR for data waiving ► summary of ESR	► registrant stated that substance is supposed to be developmental toxic – incrimination ► registrant stated that substance is supposed to be not developmental toxic – exoneration ► registrant stated that effects on the progeny independent of maternally toxic effects - incrimination ► registrant stated that effects on the progeny due to maternally toxic effects – exoneration ► registrant stated that effects on the progeny statistically significantly different in comparison to control – incrimination ► registrant stated that effects on the progeny not statistically significantly different in comparison to control – exoneration
ReproTox	► ESR of key study/studies (read-across/grouping) ► ESR for data waiving ► summary of ESR	► registrant stated that substance is supposed to be toxic to reproduction – incrimination ► registrant stated that substance is supposed to be not toxic to reproduction – exoneration ► registrant stated that effects on the progeny independent of maternally toxic effects – incrimination ► registrant stated that effects on the progeny due to maternally toxic effects – exoneration ► registrant stated that effects on the progeny statistically significantly different in comparison to control – incrimination ► registrant stated that effects on the progeny not statistically significantly different in comparison to control – exoneration

Endpoint	Source	Interpretation of information
Bioaccu	► CSR, Chapter 8 ► ESR of key study/studies (read-across/grouping) ► ESR for data waiving ► summary of ESR	► registrant stated that the substance is bioaccumulative – incrimination ► registrant stated that the substance is not bioaccumulative – exoneration
BioDeg	► CSR, Chapter 8 ► ESR of the key study/studies (read-across/grouping) ► ESR for data waiving ► summary of ESR	► registrant stated that the substance is persistent or very persistent – incrimination ► outcome of a particular test was interpreted as positive by the registrant – incrimination ► outcome of a particular test was interpreted as negative by the registrant – exoneration
AbioDeg	► CSR, Chapter 8 ► ESR of key study/studies (read-across/grouping) ► ESR for data waiving ► summary of ESR	► registrant stated that the substance is persistent or very persistent – incrimination ► registrant stated that the substance is not persistent – exoneration
Ecotox	► CSR, Chapter 8 ► ESR of key study/studies (read-across/grouping) ► ESR for data waiving ► summary of ESR	► registrant stated that the substance is toxic or classified – incrimination ► registrant stated that the substance is not toxic or not classified – exoneration

* Analysis was not done for RDT because the objective of this endpoint is to identify relevant concentration ranges of toxicity and to derive NO(A)ELs.

2.5.4 Conclusion categories

Sometimes it was possible to conclude cases immediately without a further formal check. These "obvious cases" were judged by content. Here, it was clearly discernible that waiving/adaptation was not required because appropriate data were available in accordance with the REACH Regulation, *e.g.* appropriate experimental studies or a relevant harmonised classification. These cases were concluded as "obviously compliant". "Obviously non-compliant" applied to waiving/adaptations for which it could clearly deduced that they are not in conformity with the REACH Regulation. Examples are given in Table 2-14.

First, a single conclusion was made for each waiving/adaptation option that occurred for a particular endpoint. If a particular case fulfilled the general as well as the respective waiving/adaptation-specific criteria set out in chapter 2.5.2 it was allocated to the conclusion category "formally compliant". If the criteria were not fully met, the case was assigned to the category "formally non-compliant". Here again, it is emphasised that conclusions were only drawn with respect to formal aspects and not regarding the content of waiving justifications or adaptation approaches.

A further category comprised cases which were no "obvious cases", but which could also not be evaluated with regard to formal criteria because no specifications were given in the REACH Regulation and/or the given justification/case-specific situation requires a more detailed analysis. This comprised especially WoE approaches and waiving according to REACH Annexes VII to X introduction, last passage. These cases remained in the conclusion category "complex".

In some of the dossiers more than one waiving or adaptation is provided to meet the information requirements of the REACH Regulation. This is the reason why each offered waiving/adaptation was evaluated. It was checked if at least one of the waiving/adaptations was appropriate to fulfil the information required. Finally, based on the conclusions of all waiving/adaptations used for a particular endpoint within a registration, an overall conclusion on the endpoint was derived. Here, the same five conclusion categories as mentioned above were applied. The waiving/adaptation option which was closest to the fulfilment of the criteria was the decisive factor for the overall endpoint conclusion.

The endpoints Muta, DevTox, BioDeg and Ecotox required a broader approach for the endpoint conclusion because information on different study types or species had to be present or depend on other results. Regarding different waiving/adaptations for a particular study type or species the same procedure as described above was applied. Subsequently, the study type or species that had the waiving/adaptation option which deviated most from the fulfilment of the formal criteria was the decisive factor for the overall conclusion.

Table 2-14: Conclusion categories for waiving/adaptations or endpoint conclusions in formal check

Conclusion category	Description
"Obviously compliant"	No further evaluation was required because the case is obviously in line with REACH Regulation, *e.g.*: ► ESR provides that standard testing regime is fulfilled ► substance is exempted from the obligation to register (REACH Annex IV and V) ► waiving/adaptation is not required
"Formally compliant"	criteria of formal check are fulfilled (see chapter 2.5.2)
"Complex"	waiving/adaptation cannot be concluded with the formal check, *e.g.*: ► WoE approaches ► CSA indicates that aquatic long-term toxicity testing is not required (REACH Annex IX 9.1. column 2)
"Obviously non-compliant"	No further evaluation was required because the case is obviously **not** in line with REACH Regulation, *e.g.*: ► justification is not related to the required test ► waiving/adaptation is not required ► justification is not related to all relevant components of the substance ► justification is not related to the registered substance ► waiving/adaptation is not available but required ► read-across approaches only rely on screening or short-term studies that showed no adverse effects or showed adverse effects but were not used for a relevant hazard classification and NOAEL extrapolation ► ESRs are not available for WoE studies to which the registrant refers to ► registrant only argues that minor studies showed no endpoint specific toxicity, *e.g.* screening studies for TRep or 28-day studies for RDT ► route-to-route extrapolation for RDT ► substance is corrosive or acidic at high concentration, but lower concentrations could be tested ► reference and justification do not match or no justification is available for the given reference ► use of the (Q)SAR model PETRORISK as only waiving justification for ENV endpoints Moreover, additional individual issues were also observed and documented during the assessment.
"Formally non-compliant"	criteria of formal check are **not** fulfilled (see chapter 2.5.2)

2.5.5 Data treatment and analysis

All data were documented in Excel single sheets for the general and waiving/adaptation-specific criteria as well as the overall conclusion for the endpoint. The analysis of the collected data was also carried out in Excel and was performed, on the one hand, in relation to the derived endpoint conclusions, and on the other hand, in relation to the investigated waiving/adaptations. The respective basis is given in each figure and table in chapter 3. Table 2-15 gives an overview on the descriptors which were used in figures, tables and texts in this report for all waiving/adaptation categories and situations found in the dossiers.

Table 2-15: Descriptors used in figures, tables and texts in formal check for all waiving/adaptation categories and situations found in the dossiers

Descriptor	Waiving/adaptation category or situation in the dossiers – description
REACH Annex IV and V	Waiving according to REACH Annex IV or V (exemptions from the obligation to register)
Calculation	IUCLID waiving category
Endpoint specific	Waiving according to endpoint specific criteria set out in REACH Annexes VII to X column 2
Exposure considerations	Waiving according to REACH Annex XI 3. (substance-tailored exposure-driven testing)
Incorrect REACH reference	Waiving justification refers to a REACH reference which is not appropriate
Meaningless justification	Justification without meaningful content
Non-standard methods	Non-standard methods were used for ENV endpoints
No reference	Registrant does not refer to the waiving/adaptation options set out in REACH Annexes VII to X column 2 or Annex XI; these cases are assigned to REACH Annexes VII to X introduction, last paragraph
Not available	Waiving/adaptation was not available, but required
Not required	Waiving/adaptation was not required
Other	Waiving option selected by registrant in IUCLID
(Q)SAR	(Q)SAR model
Read-across	Grouping/read-across approach
Scientifically unjustified	Waiving according to REACH Annex XI 1.1. (use of existing data), 1.4. (*in vitro* methods) **or** waiving option selected by registrant in IUCLID, depending on the context
Technically not feasible	Waiving according to REACH Annex XI 2. (technically not possible)
WoE	Weight of evidence approach

2.6 Refined check

Even after screening and formal check a number of "complex" cases remained without conclusions for their endpoints. On these remaining "complex" cases groups of similar cases were built and case-group specific approaches, including a content-related analysis if necessary, was developed for a refined check in project III. Case-by-case-analysis of small-scale case groups was also performed. For larger case groups only test samples could be assessed.

2.6.1 Sampling

The refined check was conducted based on the list of lead dossiers dating March 2014 (screened in the first project). All lead and individual dossiers which had remained "complex" in project I and II were included. The respective dossiers were checked using the software application IUCLID version 6 (ECHA, 2016b). It should be noted that a few weeks before the test was carried out, a migration from IUCLID version 5 to version 6 took place. For the examination it was assumed that the registrants had checked their own data with regard to a complete migration.

A complete overview of all endpoint cases without a conclusion ("complex") in the screening and a detailed description can be found in Annex 5.

These cases were supposed to be checked in the refined check with the following exceptions. The endpoints RDT (152 cases), AbioDeg/BioDeg (169/252 cases), and Bioaccu (1095 cases) were excluded in the third project phase, *i.e.* the "complex" cases finally remained without conclusion.

During the formal check several endpoint cases also remained without conclusion ("complex"), concerning a descriptive summary see Annex 5. The main part of these cases involved WoE approaches, alone or in combination with other waiving/adaptation justifications. The following endpoints have not been considered further in the third phase and remained finally without conclusion: RDT (121 cases), AbioDeg/BioDeg (132/234 cases), and Bioaccu (31 cases). Therein, "complex" endpoints based on grouping/read-across approaches alone have not been counted.

Endpoint cases with a conclusion based on the decisive waiving/adaptation category "grouping/read-across", only checked formally in the second phase, were not considered further – except if they appear again during the analysis of WoE approaches or in other case groups during the refined check.

Table 2-16 gives the total number of "complex" endpoint cases after screening and formal check. However, not all "complex" endpoint cases could be included into the refined check as the systematic concept was not applicable and/or due to a lack of time and personnel resources.

Table 2-16: Number of "complex" endpoints after screening and formal check

Endpoint	Number
Muta	285
ReproTox	514
DevTox	631
Ecotox	1078
Expo	1012

2.6.2 Weight of evidence concept for all endpoints

WoE approaches use a combination of information from several independent sources to give the evidence to fulfil the standard information requirements. One definition of WoE is "The process of considering the strengths and weaknesses of various pieces of information in reaching and supporting a conclusion concerning a property of the substance." (ECHA, 2010). Guidance is given in ECHA (2010) to (1) "Gather all relevant information…: published literature, read-across from chemical analogues/homologues, (Q)SAR predictions, data from existing studies, *in vitro* studies, epidemiological data/human experience, etc." and to (2) "Assess the overall package to conclude on an endpoint". This approach could be applied, *e.g.* when information from a single piece of information is not sufficient.

A WoE approach could be considered, if (ECHA, 2010)

- different studies show conflicting results,
- independent information that individually may be evaluated as insufficient,
- newly developed test methods are applied and additional information is available,
- other guideline studies or non-standard methods are applied and additional information is available.

The available evidence depends on factors such as the quality of the data, consistency of results, nature and severity of effects, and relevance of the information. It is essential to provide adequate and reliable documentation. For support of the justification the robustness and reliability of the different data sources should be taken into account.

Within the third project phase those endpoints presenting data based on a WoE approach were checked for the first time and described in detail in the following chapters regarding the HH and ENV endpoints.

First, the kind of implementation of the WoE approach in the IUCLID software was documented. Although a proper WoE approach includes, as a minimum, two separate study records flagged as "WoE", here the kind of implementation was not relevant for further checking. Also, usually one single value is not sufficient as a WoE. In particular, information from a secondary data source should be confirmed by other information (ECHA, 2017a). However, the intention was that provided data should not be downgraded by formalism, so that the requirement of at least two study records flagged as "WoE" was not considered here. Thus, the pure intention of the registrant to combine different pieces of information was regarded as WoE approach.

2.6.3 Human health endpoints

2.6.3.1 Reproductive toxicity – harmonised classification

Has the substance already been classified according to the Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (CLP) Annex VI (EC, 2008b) for effects on sexual function and fertility and developmental toxicity (reproductive toxicity category 1A or 1B/H360FD), no further testing may be necessary if the available data are adequate to support a robust risk assessment (REACH Annex X 8.7. column 2, second and third paragraph; (ECHA, 2015b)). However, the adequacy of the data has not been checked within the scope of the screening. As a result, the conclusion for the endpoint toxicity to reproduction was left open for seven dossiers because of a harmonised classification.

A robust risk assessment is in general supported if toxicity data are available from which quantitative effect levels may be derived to serve for dose-response effect assessment. Thus, for those "complex" toxicity to reproduction endpoints matching the above classification criteria established for the screening, the availability of respective data and the availability of no observed adverse effect levels (NOAELs) for developmental and reproductive toxicity data were required to be checked.

During the refined check the available study data of already classified substances were not checked from a content-related view, but it was checked whether in the respective IUCLID section data were provided and at least one effect level was given in the endpoint study summary. If this was indeed the case, it has been assumed that the registrant has made an assessment of the available data and that the data were sufficient for deriving the effect level. In particular, the derivation of a NOAEL was assumed to be important. However, to check whether the respective data were available, the screening according to project I for toxicity to reproduction was conducted on these endpoint cases.

2.6.3.2 Reproductive and developmental toxicity – non-standard administration route

According to REACH Annexes IX and X for testing TRep the most appropriate route of administration, having regard to the likely route of human exposure, should be used for the identification of the developmental/reproductive hazards. Therefore, a decision must be made on which route(s) is (are) most appropriate, considering the oral, inhalation and dermal route as humans may normally exposed to substances by one or more of these routes.

As the oral route is the default route for testing TRep except the inhalation route for gases, the screening assumed that the oral route (inhalation for gases) was to be applied. However, in cases where all the standard information was present, but a route other than the oral (inhalation for gases) was applied, then these cases have been assigned "complex" in the screening, *i.e.* were left open at this stage of examination. As a result of the screening, in total 15 such cases have been revealed. As part of the refined check, these 15 dossiers were reopened and, based on case-by-case analysis, each a decision on the correctness of this other route was taken.

According to OECD TG 416 the orally administration via diet, drinking water, or gavage is preferred and according to OECD TG 414 the test substance or vehicle is usually administered orally by intubation. If another route of administration is used, for both tests the tester should provide justification and reasoning for its selection. *E.g.* available information on route-specific toxicity or toxicokinetics may indicate that the use of oral administration of substance would not be relevant for assessing the human health hazards via inhalation, which would be the main route of exposure. From the ECHA guidance on robust study summaries (ECHA, 2012b; ECHA, 2012c) it is also recommended to additionally report on the test conditions and/or the exposure method in cases the dermal or inhalation administration route was selected. Additionally, further appropriate modifications of the tests may be necessary so that to exclude confounding factors such as *e.g.* additional stress to the pregnant animals (ECHA, 2015b).

To take the decision on the correctness of the inhalation or dermal route in principle the following information from the IUCLID dossiers were considered (overview):

- availability of a justification and content of the justification provided,
- physico-chemical properties (and classification),
- uses and thereof possible human exposure,
- if necessary, effects resulting from the selected route of administration,
- if necessary, toxicokinetic data and data from other available toxicity tests,
- availability of additional information on the test conditions and exposure method.

The Table 6-14 in Annex 6 gives an overview of IUCLID sections which were considered for retrieving the respective information.

The ECHA guidance on the information requirements gives indications on the substance physical state or properties matching the respective routes for testing the reproductive and developmental toxicity (ECHA, 2015b): "In practice, testing via the oral route is usually performed with liquids and dusts and testing via inhalation route is usually performed with gases and liquids with very high vapour pressure. Testing via dermal route might be necessary under specific circumstances, for example for substances with high dermal penetration and indications for a specific toxicity following dermal absorption." Further, inhalation testing is required when the substance is mainly sprayed in its application or otherwise the use indicates mainly inhalation exposure to humans. Then, also substances with low vapour pressure may be predominantly tested by inhalation. Hereby, as an approximate comparative value in this study and based on the comparison between known substances, the range with less than about 100 hPa was assigned to a high/medium vapour pressure and the range with less than about 10 hPa was assigned to a low vapour pressure (at a temperature of 20 or 24°C).

2.6.3.3 Developmental toxicity – waiving justification for second species

In October 2014 ECHA confirmed that prenatal developmental toxicity (PNDT) on a second species is a standard information requirement for substances manufactured or imported of 1000 tpa or more (ECHA, 2014e). It was stated further that from 1 September 2015, ECHA will, where relevant, request in its dossier evaluation decisions information on two species to be provided in one run in a dossier (ECHA, 2015c).

Information on two species allows a more comprehensive evaluation of PNDT. Registrants are, therefore, responsible for performing the second-species study, unless such a study is unnecessary as a result of the adaptations according to REACH Annexes. However, a justification for data waiving is then needed. If the outcome of the first test and all other relevant available data is taken into account, an adaptation pursuant to REACH Annex X 8.7. column 2 or pursuant to REACH Annex XI might be justified. Here, also substance-specific aspects might be relevant (ECHA, 2015b).

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. However, if the rabbit is selected as a first species, and/or is already available, which may be done *e.g.* if the rabbit is considered to be the more sensitive species or when the two-generation-study was already applied with rats, a rodent species might be the second species. In any case, an adequate justification must be provided for other species than the rat and the rabbit (ECHA, 2015b).

The screening of project I was conducted in summer 2014. At this time it was already confirmed that a second species was a standard requirement for PNDT testing (ECHA, 2013). However, the actions applied by ECHA derived from this fact were still under progress. Therefore, in the screening of lead dossiers the lack of a waiving justification for second species PNDT testing was concluded as "complex". 252 dossiers presented PNDT testing data on only one species (Table 6-12 in Annex 5). As a consequence of the above described progress these dossiers have been finally concluded as "non-compliant" for the endpoint DevTox.

Within the group of cases presenting waiving/adaptation justifications for OECD TG 414/second species a further evaluation was conducted when the cases were reopened during the analysis of other aspects (*e.g.* WoE).

2.6.3.4 Mutagenicity – special cases

During the screening three cases remained "complex" for which minimum one positive *in vivo* soma cell test **and** a negative *in vivo* germ cell test (Germvivo) **and** *in vitro* bacteria test or waiving/adaptation of *in vitro* bacteria test were available.

The refined check was conducted as follows: Since a guideline study for the *in vitro* bacteria test stated as key study was available, all ESR were checked concerning completeness (standard information requirement) and outcome (genotoxicity: negative/positive/ambiguous) based on the REACH Annexes VII to X (Annex 7)Annex 7, and the Endpoint specific guidance, including the mutagenicity testing strategy (ECHA, 2015b).

If all requirements are fulfilled the dossier was classified as "compliant". If the ESRs do not include all study data which were sufficient to make a conclusion on the genotoxicity of the substance the decision was "non-compliant". One case of this group was checked concerning the *in vitro* bacteria test, but then the study data of the substance was additionally checked as described in the chapter 2.6.3.6 due to the WoE approach of one *in vitro* test.

2.6.3.5 Mutagenicity, developmental and reproductive toxicity – available waiving justifications

The formal check contained the evaluation of waiving/adaptation justification by using "general rules" and "specific rules" as described in chapter 2.5.2. Cases which were still without conclusion ("complex") after the formal check presented justifications of the following categories:

- data waiving/adaptation based on other justification than related to REACH,
- endpoint specific data waiving/adaptation,
- other cases.

For some dossiers two decisive waiving/adaptation categories were chosen (*e.g.* noref and WoE), so that both aspects of justification were evaluated at the same time. Concerning the HH endpoints 144 cases for DevTox, 240 cases for ReproTox, and 45 cases for Muta remained "complex" (Annex 5).

Table 2-17 describes the evaluation of waiving/adaptation justifications for all three endpoints. In a first step the justification, presented in the endpoint summary and/or the waiving section of the ESRs, was evaluated. During the formal check only the waiving justification of the ESRs were considered. The main reasons were analysed if they fitted to the named reference and if they were sufficient for data waiving. The decisive criteria for "non-compliant" and cases without conclusion ("complex") are also summarised in Table 2-17.

Table 2-17: Waiving justification check for endpoints DevTox, ReproTox and Muta in refined check

Main category and aspects:		
Reference and/or main facts of the waiving justification (waiving justification and/or endpoint summary):		
REACH Annex and section(s) classification of substance free text (main arguments)		
Available key study/studies (if necessary):		
OECD test guideline or no guideline grouping/read-across approach	Documentation of deviations, *e.g.* inhalation dermal reliability 3 or 4 no guide (Ames) other guide no route available no species available bacterial strains metabolic activation number of dose groups sex controls specified, valid?	<u>For Muta:</u> result of testing (negative/positive/ambiguous)
Decisive criterion for conclusion:		
<u>ReproTox and DevTox:</u> grouping/read-across justification missing waiving/study second species missing only no guide studies, not reliable no guide studies, WoE sufficient? (key parameters?) standard information requirements – data not sufficient exposure requirements of (Q)SAR not fulfilled further check of waiving justification (mentioned studies) or key parameters		<u>Muta:</u> grouping/read-across justification missing standard information requirements – data not sufficient exposure requirements of (Q)SAR not fulfilled
Conclusion:		
"compliant" "non-compliant" no conclusion ("complex")	if further check (*e.g.* of additional studies and/or information, content-related) is necessary	

2.6.3.6 Evaluation of weight of evidence

First of all, some general aspects, listed in Table 2-18, were documented and checked in the same way for every endpoint. However, where irrespective of the presented study records flagged as "WoE" other criteria for waiving was used, *e.g.* based on REACH Annexes VII to X column 2, the endpoint of the dossier was not further checked for the WoE approach. Rather another check, such as the formal check of waiving justifications, was applied. Caution: Waiving was actually not applied if "WoE" study records flagged additionally as "waiving" aiming at presenting information which could not fulfil the requirements for the technical compliance checks.

Further, a WoE approach requires a summary considering the diverse study data for the endpoint and presenting the kind of approach applied concerning the presented information. Thus, a summary was regarded as prerequisite for further checking.

Table 2-18: Weight of evidence: Common documentation and checking aspects for all human health endpoints in refined check

Questions	Answers	Consequences
General		
How is WoE implemented in IUCLID?	► one ESR with the flag WoE ► a minimum of 2 ESRs each with the flag WoE ► ESRs with the flag WoE plus additional information (except the summary) ► only ESR-key studies available ► only other information than WoE-flagged ESRs available (supporting studies, justification text, …) except the summary ► at least one ESR with flag WoE includes "Data Waiving" aiming at documenting a study with some basic fields not filled ► no WoE available because available ESRs aim at data waiving according to REACH Annexes VII to X column 2 ► no WoE available due to other reasons than waiving according to REACH Annexes VII to X column 2	If no WoE is available the check is stopped and another check is conducted. No other consequences followed (question is for documentation only).
Is a WoE summary available?	Yes No ("Yes" means that several studies are considered in the endpoint study summary, the CSR, an extra document, or in another text.)	Answer "No" induces stop of checking and the endpoint conclusion "non-compliant". Answer "Yes" induces endpoint specific checking.

Further aspects of the study data were checked according to endpoint specific requirements. In particular, the degree of information checked according to a screening, a formal check and/or a content-related check in relation to the total checking effort was dependent on the endpoint.

The WoE approach for HH endpoints has been reviewed analogously to the screening, with the difference that the information for each required type of study (two-generation-study, bacterial gene mutation test (GMbact), cytogenicity/micronucleus test in mammalian cells *in vitro* (Cytvitro) etc.) could have been distributed over several studies.

In addition to the general concept (see above), the relevance criteria (endpoint, guideline, species, administration route, etc.) were analysed in a first step (step 1), which corresponded to a minimum requirement per study type and per study and across the studies. In this way, a number of dossiers could already be sorted out as "non-compliant". If the minimum requirements were met or at least the requirements regarding in particular the most critical aspects, the question was asked which criteria of relevance per type of study and per study and across the studies were to be applied in addition (step 2), so that the studies can be accepted in the sense of a screening for the refined check.

It was therefore important to examine the particularly critical criteria in order to identify non-relevant data. A complete content-related check has not been carried out. There was also no formal check of the WoE summary of the registrant.

Since a more in-depth analysis of grouping/read-across approaches was not planned within the project, the grouping/read-across approaches within the WoE approach were checked according to the previous formal check. *I.e.* it was not checked if this approach was acceptable concerning the content but only with regard to formal criteria.

The test material of studies included in the WoE approach had to be the same as the registered substance.

If it was not possible to prove that the data was unacceptable in an endpoint, based on the basic/critical criteria, further checking was left without conclusion ("complex"). Further relevance criteria should then be examined (step 2).

Developmental and reproductive toxicity

Within the scope of the above described step 1 the following Table 2-19 gives the criteria for the check concerning the endpoints DevTox and ReproTox. The procedure was conducted similar to applying a decision tree.

If the endpoint conclusion was "complex" because all relevance criteria according to step 1 have been fulfilled, further relevance criteria should be examined. The reason was that other parameters/relevance criteria might be limited. However, read-across/grouping was not considered further. Therefore, the following additional relevance criteria (step 2) should be checked according to OECD TG 414 and 416, respectively:

- sex,
- frequency and period of administration,
- number of animals per dose level,
- number of dose levels,
- Is a control group available?,
- Is the result given: toxicity yes or no (ESR)?,
- Are effect levels (NOAELs) available (endpoint study summary)?.

Table 2-19: Weight of evidence check for developmental toxicity and reproductive toxicity in refined check: Relevance criteria step 1

Questions		Answers	Consequences
If grouping/read-across data is available for **all** ESRs related to the WoE approach, a one-step examination is possible:			
Are the requirements of the formal check fulfilled?		Yes No No, but read-across justification available Yes = following parameters are fulfilled: **DevTox:** ► for at least **two studies**: ► study type/endpoint: developmental toxicity ► reliability: 1 or 2 ► guideline: OECD TG 414* ► two species tested across the two studies: rodent (rat, mouse, hamster), non-rodent (rabbit, dog) ► administration route: standard (oral; inhalation for gases) **ReproTox:** for at least one study: ► study type/endpoint: reproductive toxicity/two-generation study ► reliability: 1 or 2 ► guideline: OECD TG 416# ► species tested: rodent ► administration route: standard (oral; inhalation for gases) **and** a grouping/read-across justification is available.	Both answers induce stop of checking. If the answer is "No" the endpoint conclusion is "non-compliant" (according to the formal check). If the answer is "Yes" the endpoint conclusion "complex" follows because other parameters might be limited (and actually further relevance criteria should be examined). However, grouping/read-across is not considered further.
If grouping/read-across data is not available or only for **at least one but not all** of the ESRs related to the WoE approach, diverse aspects were to be assessed subsequently			
1	**DevTox:** Were at least two guideline-studies (rodent and non-rodent) and at least one guideline-study according to screening available (grouping/read-across ESRs included)? **ReproTox:** Is at least one guideline-study according to screening available (grouping/read-across ESRs included)?	Yes No Yes = following parameters are fulfilled: **DevTox:** for at least **two studies**: ► study type/endpoint: developmental toxicity ► reliability: 1 or 2 ► guideline: OECD TG 414* ► two species tested across the two studies: rodent (usually rat), non-rodent (usually rabbit) ► administration route: standard (oral; inhalation for gases) or a justification if a non-standard route was tested **ReproTox:** for at least one study: ► study type/endpoint: reproductive toxicity/two-generation study ► reliability: 1 or 2 ► guideline: OECD TG 416+ ► species tested: rodent or a justification if a non-rodent species was tested	If the answer is "No" the check is stopped and the endpoint conclusion "non-compliant" follows. The following questions should be answered for documentation. If the answer is "Yes" the endpoint conclusion is dependent on the other requirements. Go to question 4 (if grouping/read-across data is available) and 5.

Questions		Answers	Consequences
		► administration route: standard (oral; inhalation for gases) a justification if a non-standard route was tested	
2	Which are the deviations from the above criteria in those studies, which are most close to these criteria and/or are most reliable?	Documentation of deviations by descriptors, *e.g.* dermal inhal second species lacking (DevTox) non-rodent available (ReproTox) reliability 3 reliability 4 no guide screening other guide no route available no species available other endpoint	For answer "second species lacking" question No. 3 should be answered in addition. Otherwise go to question 4 (if grouping/read-across data is available) and 5.
3	**DevTox:** If the second species is not available: Is a justification for the lacking of the second species available?	Yes No	If the answer is "No" the check is stopped and the endpoint conclusion "non-compliant" follows. The following questions should be answered for documentation. If the answer is "Yes" the endpoint conclusion is dependent on the other requirements. Go to question 4 and 5.
4	If grouping/read-across data is available: Is a grouping/read-across justification available?	Yes No	If the answer is "No" the check is stopped and the endpoint conclusion "non-compliant" follows. The following questions should be answered for documentation. If the answer is "Yes" the endpoint conclusion is dependent on the other requirements. Go to question 5.
5	Is the test material of all ESRs of the WoE approach (except grouping/read-across approaches) the same as the registered substance?	Yes No	If the answer is "No" the check is stopped and the endpoint conclusion "non-compliant" follows. If the answer is "Yes" for questions 1 to 5 if applicable, the provisionally endpoint conclusion "complex" follows. Further relevance criteria should be examined (step 2).

* DevTox: each a study with a rodent species (rat, mouse, hamster) and a non-rodent species (rabbit, dog), in sum two studies according to or similar or equivalent to guideline OECD 414

ReproTox: a study with a rodent species (rat, mouse) according to or similar or equivalent to guideline OECD 416

Mutagenicity

Within the scope of the above described general procedure the following Table 2-20 gives the criteria for the WoE check concerning Muta. The procedure was conducted similar to applying a decision tree. In contrast to the TRep endpoints during the evaluation of the Muta endpoint step 1 and 2 were combined, if necessary, due to the fact that the outcome (negative/positive/ambiguous) of the testing determined the need for further *in vitro* and *in vivo* tests. Therefore, in addition to the above introduced relevance criteria other information of the ESRs had to be checked parallel:

- waiving/adaptation reason/category during screening and formal check (*e.g.* waiving for GMbact or category "WoE", and if WoE is combined with a grouping/read-across approach),
- missing tests as key study if noted during screening,
- available key studies, inclusive the outcome, and decisive study type of formal check.

Table 2-20: Weight of evidence check for mutagenicity in refined check: Relevance criteria – decisive differences to toxicity of reproduction endpoints are underlined

Questions		Answers	Consequences
If grouping/Read-across data is available for **all** ESRs related to the WoE approach, a one-step examination is possible:			
Are the requirements of the formal check fulfilled?		Yes No No, but read-across justification available Yes = basic/critical endpoint specific parameters such as study type/endpoint "mutagenicity", reliability 1/2, relevant guidelines, species, administration route etc. which are sufficient to characterise basically the relevance of a study are "compliant" for a decisive number of ESRs **and** a grouping/read-across justification is available.	If the answer is "No" the endpoint conclusion is "non-compliant" (according to the formal check). If the answer is "Yes" other parameters might be limited and further relevance criteria should be examined.
If grouping/read-across data is not available or **at least one but not all** of the ESRs related to the WoE approach, diverse aspects were to be assessed subsequently			
1	Is at least one guideline-study according to screening available (grouping/read-across ESRs included)?	Yes No Yes means that the following parameters are fulfilled for at least one study: ► study type/endpoint: mutagenicity ► reliability: 1 or 2 ► OECD guideline	If the answer is "No" the check is normally stopped and the endpoint conclusion "non-compliant" follows. Concerning respective Muta cases the answer "No" results in another further check (*i.e.* formal check of grouping/read-across or of (Q)SAR). The following questions should be answered for documentation. If the answer is "Yes" the endpoint conclusion is dependent on the other requirements. Go to question 4 (if grouping/read-across data is available) and 5.
2	Which are the deviations from the above criteria in those studies, which are most	Documentation of deviations by descriptors, *e.g.* inhal reliability 3/4	For Muta this check already involves step 2 criteria.

Questions		Answers	Consequences
	close to these criteria and/or are most reliable?	no guide (Ames) other guide no route available no species available bacterial strains metabolic activation number of dose groups sex controls specified, valid?	Go to question 4 (if grouping/read-across data is available) and 5.
4	If grouping/read-across data is available: Is a grouping/read-across justification available?	Yes No	If the answer is “No” the check is stopped and the endpoint conclusion “non-compliant” follows. The following questions should be answered for documentation. If the answer is “Yes” the endpoint conclusion is dependent on the other requirements. Go to question 5.
5	Is the test material of all ESRs of the WoE approach (except grouping/read-across approaches) the same as the registered substance?	Yes No	If the answer is “No” the check is stopped and the endpoint conclusion “non-compliant” follows. If the answer is “Yes” the endpoint conclusion is further depending on the overall data base including the outcome of the testing.

If necessary all ESRs were checked concerning completeness (standard information requirement) and outcome (mutagenicity[3]: negative/positive/ambiguous) based on the REACH Annexes VII to X and the Endpoint specific guidance, including the mutagenicity testing strategy (ECHA, 2015b), and supported by a summary of information requirements of the screening in project I with regard to Muta waiving/adaptation (Annex 7, (Springer et al., 2015)).

Depending on the available information (key studies and ESRs flagged as WoE, the step 1 and 2 criteria, and the results) all elements of the mutagenicity testing (gene and cytogenetic mutation and genotoxic hazard to germ cells), if necessary, had to be included in the endpoint.

[3] In the following, for reasons of convenience the term “mutagenicity” describes information requirements related to genotoxicity and mutagenicity.

2.6.4 Environmental endpoint ecotoxicity

2.6.4.1 Evaluation of chemical safety assessment

An evaluation of dossiers where the endpoint Ecotox could not be concluded in project II because the registrant justifies data waiving with REACH Annex IX column 2 - Chemical Safety Assessment (CSA) indicates no risks – is required. Therefore an evaluation of the CSA is needed.

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.

Results of the CSA indicate if testing is not required. This is the case, when

- aquatic toxicity is unlikely to occur because of mitigation factors,
- other toxicity information is adequate,
- substance is neither classified, persistent, bioaccumulative, toxic (PBT) nor very persistent, very bioaccumulative (vPvB),
- exposure assessment and risk characterisation identify no risk,
- other long-term toxicity information on both species is available,
- one species is substantially more sensitive, subsequently long-term testing with the most sensitive species is sufficient,
- long-term testing on fish is not required if predicted environmental concentration (PEC)/predicted no effect concentration (PNEC) < 1 based on long-term daphnia result and an assessment factor (AF) 50.

According to ECHA guidance on information requirements (ECHA, 2016a) long-term testing of aquatic toxicity may be triggered by, *e.g.:*

- quantitative risk assessment indicates that PEC/PNEC > 1,
- substance is poorly water soluble,
- information on a specific mode of action,
- unexpected sensitivity of a group of organisms,
- monitoring data confirm that the substance occurs in the aquatic environment.

An appropriate PNEC derivation is an important step in the CSA. Cases where the PNEC derivation was not appropriate could be decided as “formally non-compliant”. An adaptation of PNEC with the PETRORISK model is considered as “obviously non-compliant”.

Results from screening and formal check could be used to identify “compliant” or “non-compliant” cases and as well identifying cases for evaluation: It can be concluded that the results of the CSA are “obviously non-compliant” when the endpoint Expo is either “non-compliant” or “formally non-compliant”. Consequently, dossiers of project I where the endpoint Ecotox is “non-compliant” are assigned to the conclusion category “obviously non-compliant”.

Data for CSA were not evaluated when a non-standard method was applied for one of the experimental studies required. The reason is that it was not possible to conclude experimental study applying non-guideline methods within this project. Thus, the endpoint could not be concluded if at least for one experimental study non-standard method were used.

Table 2-21: Refined check of the chemical safety assessment for the endpoint ecotoxicity

Criteria/trigger	Long-term testing required	Evaluation
Risk is indicated ► PEC/PNEC > 1	► unless other reliable and adequate long-term toxicity information is available ► for both species, starting with *Daphnia*, long-term toxicity testing with fish is not required if PEC/PNEC < 1 based on results of long-term testing with *Daphnia* and AF 50	screening of the dossiers
No toxicity in short-term tests ► if with log K_{ow} > 3 (or BCF > 100) **and** ► if PEC_{local} **or** $PEC_{regional}$ > 1/100th of water solubility	► unless other reliable and adequate long-term toxicity information is available ► for both species, starting with *Daphnia*, long-term toxicity testing with fish is not required if PEC/PNEC < 1 based on results of long-term testing with *Daphnia* and AF 50	► if log_{Kow} > 3 ► all PEC should be smaller < 1/100th water solubility
No toxicity due to poor water solubility	► unless other reliable and adequate long-term toxicity information is available ► for both species, starting with *Daphnia*; long-term toxicity testing with fish is not required if PEC/PNEC < 1 based on results of long-term testing with *Daphnia* and AF 50	► other long-term test from two trophic levels should be available ► PEC/PNEC < 1 for all exposure scenarios
Information is available that one species is substantially more sensitive	► testing with the more sensitive species ► *e.g.* if a HC5 was estimated it should be analysed whether NOEC values below 5 % of the SSD belong always to one trophic level	R.7b, Figure R.7.8-4 R.10, page 23, further recommendations
Information on a specific mode of action	► long-term toxicity testing if indications on a specific mode of action are available (*e.g.* OECD TG 234 (OECD, 2011) Fish Sexual Development Test for endocrine disruptors)	

2.6.4.2 Evaluation of weight of evidence

WoE approaches for the ENV endpoint Ecotox were evaluated with respect to factors for evaluation provided by ECHA (Table 2-22). The approach for the ENV endpoints differed compared to the HH endpoints. It should be recognised that more than one piece of information is required for WoE and that the line of evidence has to be documented in a transparent way. Requirements on sources or documentation are not defined in the REACH regulation for the different pieces of information. Therefore, the overall information deduced from different sources has to be evaluated for decision making on hazardous properties of the substance. For instance, the other information could also be provided from other standard information already documented in another IUCLID section or from peer reviewed sources. The evaluation of WoE was processed in Excel datasheets addressing the criteria of Table 2-23 and Table 2-24.

Table 2-22: Evaluation factors in weight of evidence approaches in refined check (ECHA, 2010)

Factor	Criteria	Evaluation
Reliability	► reliable without restrictions (1) ► reliable with restriction (2) ► not reliable (3) ► not assignable (4)	No evaluation required, because ► for WoE approaches a reliability of 3 or 4 is also accepted. ► It is technically not possible to submit an ESR without declaring reliability ► reliability should be adequate for the decision to be taken
Relevance	Test material should be equivalent to submitted substance	To be verified
	Test method and conditions should not be too different from internationally approved test guidelines	Generally, the study should be adequate for the decision to be drawn. Sufficient documentation to verify that the study is fit for purpose on its own or with the complementary information.
	Invested effects for the endpoint should be clearly related to toxicity of the substance	Criteria of OECD 23 should be excluded, *e.g.*: ► Adsorption effects ► volatilisation ► no toxic impurities ► pH ► high viscosity ► masked by complexation
	It should be verified that alternative methods are applicable for the substance	Description that method/model is validated for the substance
Adequacy	Data should be appropriate for ► for classification ► PNEC derivation	A decision tree would be required for decision making. These cases remain not concluded (“complex”).
Quantity	► Overall WoE refers to more than one study/piece of information ► Assessing the strength of evidence: more than one study/piece of information the more the better	If only one ESR is available it should be verified whether additional information is available or reference weighing of information. Case where no other information and no reasoning is apparent are concluded to be “formally non-compliant”. But it should be proved if another approach potentially complies with REACH regulation.

Table 2-23: Refined check of weight of evidence approaches for the environmental endpoint ecotoxicity – Table part A

Factor				Evaluation	
REACH Annex XI 1.2 1st clause		REACH Annex XI 1.2. 2nd clause 1st part	REACH Annex XI 1.2. 2nd clause 2nd part	REACH Annex XI 1.2. not appropriate	REACH Annex XI 1.2 not appropriate
Several independent sources of information leading to the conclusion that a substance has/has not a particular dangerous property	Overall WoE refers to more than one study/piece of information	Newly developed test method leading to the conclusion that a substance has/has not a particular dangerous property	International test method recognised by the Commission or Agency as equivalent leading to the conclusion that a substance has/has not a particular dangerous property	One clear adequate study with reliability 1/2 available	Data waiving is proposed
1 (yes, criterion is explained) 2 (only reference to Annex is given) 3 (no respective explanation is given)	1 (yes, criterion is given) 2 (criterion is not given)	1 (yes, criterion is explained) 2 (only reference to Annex is given) 3 (no respective explanation is given)	1 (yes, criterion is explained) 2 (only reference to Annex is given) 3 (no respective explanation is given) 4 (only no guideline studies)	1 (WoE not appropriate)	1 (WoE not appropriate)

Table 2-24: Refined check of weight of evidence approaches for the environmental endpoint ecotoxicity – Table part B

Factor									Conclusion
Relevance					Adequacy		Documentation		
Test material should be equivalent to submitted substance	Investigated effects for the endpoint should be clearly related to toxicity of the substance	It should be verified that alternative methods are applicable for the substance	REACH Annex XI 1.3. 2nd paragraph - only if one or more studies based on (Q)SAR (criteria of formal check)	REACH Annex XI 1.5. 2nd paragraph - only if one or more studies based on read-across (criteria of formal check)	Data should be appropriate for classification	Data should be appropriate for PNEC derivation	ESR for experimental study, read-across or (Q)SAR	WoE justification for using this evidence instead of standard testing; judgement documented and reported	
1 (given for each study/ piece of information) 2 (not given) 3 (read-across included)	1 (given for each study/ piece of information) 2 (not given)	1 (given for each study/ piece of information) 2 (not given)	1 (yes, criteria are met) 2 (no, criteria are not met)	1 (yes, criteria are met) 2 (no, criteria are not met)	1 (yes, criterion is given) 2 (not given)	1 (yes, criterion is given) 2 (not given)	1 (yes) 2 (no)	1 (yes) 2 (no)	1 (“formally compliant”) 2 (“formally non-compliant”) 3 (no conclusion) (no entry - not applicable)

2.6.5 Environmental exposure

Exposure assessment was already evaluated with a decision tree (Springer et al., 2015) in the preceding project I. In project I, Expo was not concluded ("complex" cases) either due to the availability of exposure scenarios (911 dossiers) or qualitative exposure assessments (101 dossiers). These require an in-depth analysis with respect to

- REACH Annex I 5. exposure scenarios and
- REACH Annex I 5. and 6. qualitative exposure assessment.

Since the evaluation of qualitative exposure assessments cannot be realised with a standardised approach, these cases were not further addressed within this project.

In the current project, a stepwise approach is applied for the evaluation of exposure assessment in CSA (Table 2-25). An appropriate exposure assessment incorporates diverse input parameters from standard information required in REACH Annexes VII to X (*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 ENV endpoints AbioDeg and BioDeg. In the current evaluation only registration dossiers were evaluated if the ENV endpoints AbioDeg and BioDeg were evaluated as "compliant" either in project I and/or in project II as "formally compliant" or "obviously compliant".

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 in "compliance" with the information requirements for the endpoint Ecotox. Accordingly, only registration dossiers were chosen for evaluation if the endpoint Ecotox was evaluated as "compliant" in screening and formal check either as "formally compliant" or "obviously compliant". Also, cases where the PNEC was calculated with the PETRORISK model are assessed as "obviously non-compliant", because the risks are underestimated with this model (Rorije et al., 2012). Since for the ENV endpoint Ecotox only aquatic testing was evaluated within project I and II evaluation of PNEC focusses in this project on the freshwater compartment.

In some cases, there may be also different fate/hazard profiles relevant over the life cycle of a substance due to changes of the substance composition. These cases would also require a more detailed analysis and were also not further addressed for this reason.

If more than 5 exposure scenarios were presented in the CSR, a random sample of 5 scenarios was chosen for steps 3 (Completeness screening of elements) and 4 (Exposure estimation) considering manufacture and different uses of the substance.

Table 2-25: Refined check of environmental exposure assessment in the chemical safety report

Parameter	Criteria	Action
Step 1 : Selection of registration dossiers for further evaluation		
Exposure assessment	Is a quantitative exposure assessment available?	Yes = further evaluation
AbioDeg and BioDeg	Are AbioDeg and BioDeg both "compliant"*?	Yes = further evaluation
Ecotox	Is Ecotox "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" adaptation/waiving = "complex"
Step 3: Completeness screening of elements		
Exposure scenarios	Is an exposure scenario available for manufacture and each identified use?	Yes = further evaluation No = "non-compliant"
Exposure of workers	Is the exposure of workers available?	Yes = further evaluation No, without justification = "non-compliant" No, with justification = "complex"
Environmental exposure	Is the environmental exposure available for each exposure scenario?	yes = further evaluation No, without justification = "non-compliant" No, with justification = "complex"
Human exposure via environment	Is the exposure of humans via environment available for each exposure scenario?	Yes = further evaluation No, without justification = "non-compliant" No, with justification = "complex"
Exposure/risk for aggregated sources	Is the exposure/risk for aggregated sources available?	Yes = further evaluation No, without justification = "non-compliant" No, with justification = "complex"
Step 4: 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 5: 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 registrations dossiers: "compliant" of project I and "formally-compliant" and "obviously-compliant" endpoint of project II.

[#] 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

2.7 Estimated number of dossiers with potential data gaps for developmental and reproductive toxicity

Although a high effort has already been made to develop alternative test methods, toxicity testing on reproduction and development including teratogenicity as required under REACH still relies on animal studies. The assumed data gaps in dossiers concerning the endpoints DevTox and ReproTox due to lacking animal studies or due to missing or inappropriate justifications were summed up over the projects I, II and III. Hence, the considered cases consisted of:

- "non-compliant" dossiers within the scope of the screening (project I)
- "non-compliant" dossiers within the scope of the formal check (project II)
- "non-compliant" dossiers within the scope of the refined check (project III) including dossiers, for which the waiving of the second species for PNDT is lacking

A certain percentage of dossiers was left open for conclusion ("complex") because the evaluation during the refined check did not include all "complex" cases or a further check of content-related information (WoE analysis) was needed. These cases were not taken into account for the estimate of the potential data gaps.

3 Results and discussion

3.1 Substance sameness in lead and member dossiers of joint submissions

In this part, results on sameness of substance identity in lead and member dossiers are presented. The assessed random sample comprised in total 216 lead dossiers and 1272 member dossiers. Since the number of member dossiers varied between 1 and 448 within a joint submission a maximum number of 30 member dossiers was analysed (see details on sampling in chapter 2.2.1). According to the concept in chapter 2.2, in 72 % of the investigated joint submissions the entire member dossiers were checked as the number of member dossiers was equal or below ten. 28 % of the joint submissions exceeded the number of ten member dossiers therefore the maximum of 30 member dossiers was checked. An overview is given in Table 3-1.

Table 3-1: Overview on the random samples of joint submissions and member dossiers for different substance types

Substance type	Joint submissions		Joint submissions with members ≤ 10		Joint submissions with members > 10		Range of members	
	n	%	n	%	n	%	n	n checked
Mono-constituent substances	87	40	60	69	27	31	1-448	1-30
Multi-constituent substances	46	21	41	89	5	11	1-82	1-16
UVCB substances	83	38	54	65	29	35	1-182	1-29
Total	**216**	**100**	**155**	**72**	**61**	**28**	**1-448**	**1-30**

The overall results for the three substance types are summarised in Table 3-2. The SIDs in lead and member dossiers appeared to be the same in the majority of joint submissions for **mono-constituent substances**, but only in half of the joint submissions for **multi-constituent substances**. 35 % of the multi-constituent's joint submissions and 9 % of the mono-constituent's joint submissions showed that the SID were not the same in lead and member dossiers according to the applied approach. This comprised the evaluation of the 80 %- and 80/10 %-rule and the check whether the SID of registered substances are the same within joint submissions (see chapter 2.2). 2 % of the multi-constituent's joint submissions and 15 % of the mono-constituent's joint submissions were not concluded because either information was not available in IUCLID section 1.1 or 1.2 or expert judgement would have been required.

For **UVCB substances**, conclusions were drawn if possible, primarily for the purpose of illustration of tendencies and identification of general issues. The concluded submissions amounted to 36 % with the same substances in lead and member dossiers (Table 3-2). For 64 % (n = 53) of the UVCB joint submissions a conclusion could not be drawn. These joint submissions would require case-by-case analysis using additional information from the registrant.

Table 3-2: Overview on the conclusions for the investigated joint submissions for all substance types*

Substance type	Submissions with sameness concerning SIDs		Submissions without sameness concerning SIDs		Submissions without conclusion	
	n	%	n	%	n	%
Mono-constituent substances	77	89	8	9	2	2
Multi-constituent substances	23	50	16	35	7	15
UVCB substances[#]	30	36			53	64

* Reference to the number of investigated joint submissions according to Table 3-1.
[#] For UVCB substances conclusions were only drawn if possible.

3.1.1 Mono-constituent substances

In 89 % (n = 77) of the investigated joint submissions of mono-constituent substances the 80 %-rule was fulfilled and the SIDs of all members and the lead dossiers were the same (Table 3-2).

In 9 % (n = 8) of joint submissions SID between lead and at least one member dossier were not the same. Of these, seven joint submissions with more than ten member dossiers have been checked. Here, for only one or two member dossiers the substance was not the same as in the lead dossier.

Comparing the total number of member dossiers' SIDs to the lead dossiers' SIDs, 98 % of the member dossiers provide the same SID. Thus, it could be concluded for the "well-defined" mono-constituent substances that the REACH requirement of substance sameness is well implemented between member and lead dossiers ≥ 1000 tpa, submitted to ECHA until 1st of July 2015.

Mono-constituent substance registrations in which the SID deviated between lead and member dossiers were mainly related to submissions in which water was regarded as a main constituent. This concerns mainly an inappropriate SID rather than the sameness of SIDs within the joint submission.

Water was partly described to be present in significant quantities in the substance of one dossier of the joint submission while it was not declared or was only declared as impurity in another dossier (six submissions, documented by the descriptor "SOL", see Annex 1). Solvents should be excluded according to REACH Article 3(1) except they are necessary for stability or belong to the composition (EC, 2006). Therefore, the presence of relevant amounts of solvents has to be justified. This was not done for the examples identified here. Apart from that, it could be deduced that water was not required for stability or did belong to the composition as the lead/and or (other) members were capable of excluding it or minimising its amount. It was observed, that eleven (mainly member) dossiers included more than one quality/purity grade for which either at least one of these did not comply with the 80 %-rule, or at least one main constituent of the member dossier was not the same as the main constituent of the lead dossier (documented by the descriptor "DEVPRO", Annex 1). Only 2 % (n = 2) of joint submission remained without conclusion. In these two submissions the typical concentrations and the concentration ranges of the substances registered by the lead dossiers were below 80 % and a justification was given. At the same time, several of the member dossiers of these submissions indicated deviating or much broader concentration ranges for their registered substances. Here, identical justifications within joint submissions were present whenever the typical concentration was below 80 %. Since the in-depth analysis of these joint submissions was not possible in the scope of the project, a conclusion was not drawn.

Moreover, the following minor problems were observed, each only in relation to one or two member dossiers of joint submissions:

- In one member dossier the information on constituents and their concentrations for the starting material in the production process was given instead of the information for the registered substance.
- Deviation from the 80 %-rule without justification was present in two of 14 member dossiers.
- The substance registered by the lead included several salts, while one member dossier covered only one of those salts.

In one joint submission, two of the above mentioned inconsistencies were observed.

As a general issue it was observed, that eleven (mainly member) dossiers included more than one quality/purity grade for which either at least one of these did not comply with the 80 %-rule, or for at least one the main constituent of the member dossier was not the same as the main constituent of the lead dossier (documented by the descriptor "DEVPRO", Annex 1).

3.1.2 Multi-constituent substances

50 % (n = 23) of all joint submissions investigated for multi-constituent substances fulfilled the 80/10 %-rule and the identity and number of main constituents was equal between lead and member dossiers. In contrast, in 35 % (n = 16) of the submissions SIDs in lead and member dossiers were not the same according to the approach applied here (Table 3-2). 15 % (n = 7) of the submissions were not concluded. One submission had no member dossiers in the provided ECHA list, although it was designated as joint submission. Thus, no comparison could be made.

As already mentioned, SIDs were regarded as the same for half of the joint submissions for multi-constituent substances. However, in three of these submissions deviations from the 80/10 %-rule were observed for the lead and all member dossiers because the concentration for at least one of the main constituents was below 10 % (documented by the descriptor "< 10", Annex 1). Since this equally occurred in all lead and member dossiers of these joint submissions, these submissions were nevertheless regarded to comprise the same substance in the dossiers because the constituent lists in lead and member dossiers have already detected to be the same.

Regarding sameness of the substances in lead and member dossiers, approximately one third of all investigated joint submissions for multi-constituent substances showed the following deviating issues. In some submissions, several of these issues were observed.

- The number as well as the kind of main constituents differed between lead and member dossiers. In contrast, the 80/10 %-rule was mostly fulfilled for both, lead and member dossiers. If certain cases did not comply with that rule, the reason was mainly that the concentration range laid completely below 10 % for at least one constituent (in total 54 dossiers and 16 submissions, documented by the descriptor "< 10", Annex 1).
- Components were not equally stated to be "constituent" or "impurity" (16 member dossiers, documented by the descriptor "CONIMP", Annex 1).
- Constituents of the lead dossier were missing in member dossiers.
- Constituents listed in the member dossiers could not be compared to those of the lead dossier because required identifiers of the constituents were not available (five member dossiers, documented by the descriptor "NEI", Annex 1).
- The presence of significant amounts of solvent in the constituents list of one party while it was not declared by the other party (two joint submissions, see also Figure 6-2).

Joint submissions that remained without conclusion comprised seven of the examined joint submissions. Reasons were as follows:

- Registrants did not specify the single constituents and instead only the registered substance was given in the constituents section (15 member dossiers, documented by the descriptor "REGSUB", Annex 1), so that a comparison between substances of lead and member dossiers was not possible. Especially, this occurred if the registered substance was composed of different isomers.
- The specific isomers of one constituent were declared by one party while the other missed it.
- A stabiliser was required for the substance and made up approximately 40 to 50 % of the whole composition. All member dossiers used significant amounts of completely or partly other stabilisers than the lead dossier.

Furthermore, in 12 member dossiers the concentration range of at least one constituent differed significantly compared to the lead dossier (documented by the descriptor "DEVRA", Annex 1). However, the conclusion was not affected by this aspect as long as the number and the kind of main constituents were the same. This illustrates that, despite the fact that multi-constituent substances are well-defined by definition, concentration ranges of substance are often not the same or not similar in lead and member dossiers.

In some member dossiers several qualities/purity grades were registered. Here, quantitative differences in identical components are possible. However, it should be justified within the joint submission that the test materials used for testing cover different concentrations of main components. The check conducted here regarding sameness criteria in lead and member dossiers comprised the quality/purity grades which appeared to comply most with the substance in the lead dossier. For seven member dossiers of multi-constituent substances at least one of the qualities/purity grades considerably differed in comparison to the lead dossier (documented by the descriptor "DEVPRO", Annex 1). However, this fact influenced not the result as long as one of the qualities/purity grades was the same in comparison to the substance of the lead.

3.1.3 Substances of Unknown or Variable Composition, Complex Reaction Products or Biological Materials

The number of member dossiers in the 83 selected joint submissions for UVCB varied between 1 and 182. In 65 % (n = 54) of the evaluated joint submissions the entire member dossiers could be assessed; in 35 % (n = 29) of the joint submissions the number of member dossiers exceeded ten.

Table 3-4 gives an overview on the preliminary conclusions where UVCB substance could be registered jointly.

For comparison of the distribution of substance types the use of respective categories in IUCLID were counted for all 628 lead dossiers of UVCB submissions with member dossiers, including the random sample of 83 joint submissions taken for the actual investigation, and for the random sample alone. These categories comprised the IUCLID categories selected by the registrants. The result is listed in Table 3-3. As shown in the table the random sample is fairly representative for the distribution of the types of UVCB substances in all lead dossiers.

Table 3-3: Different IUCLID types of UVCB substances: Distributions as specified by the registrants

Type of UVCB substance	Related to all 628 relevant lead dossiers		Related to the 83 randomly selected lead dossiers	
	n	%	n	%
Organic	296	47	38	46
Petroleum product	210	33	32	39
Inorganic	72	12	9	11
Other (*e.g.* kerogens, enzymes)	40	6	3 (kerogens: 2, enzymes: 1)	4
Not specified	6	1	0	0
Organometallics	4	1	1	1

Table 3-4: Preliminary conclusions for investigated UVCB joint submissions

Type of UVCB substance	Subtype	Number	Submissions within appropriate joint submissions	Submissions without conclusion
Organic	Substance with variation in the carbon chain	18	10	8
	Reaction product	18	8	10
	Fermentation product	1	1	0
	Other	1	0	1
Petroleum product		32	4	28
Inorganic	Metallic concentrate/melt and reaction product/mixture	9	5	4
Other	Kerogen	2	1	1
	Enzyme	1	1	0
	Organometallic	1	0	1
Total		**83**	**30**	**53**

In general, information on the substance identity provided in the IUCLID sections 1.1 and 1.2 should be sufficient to conclude whether a joint registration of UVCB substances is appropriate. However, the results of Table 3-4 show that the information from IUCLID section 1.1 and 1.2 is often insufficient to allow a conclusion. The following information should enable a conclusion on the SID for UVCB substances:

- Name of substance,
- numerical substance identifiers (CAS, EC number),
- substance type,
- further information, *e.g.* origin or manufacturing processes,
- composition.

It is generally difficult to conclude on the substance sameness for UVCB substances at a screening level and without substantial knowledge on the manufacturing processes. Overall, two things proved to be important regarding the description of UVCB substances in registration dossiers:

- Test materials used for the standard testing regime should represent the boundaries in composition of the joint submission. Quantitative differences for identical constituents are possible. But if the differences are significant, test materials used for testing should cover either the observed concentration ranges or a joint submission is not possible.
- Since EINECS entries are often described in general terms, in a first approximation, substances are regarded as the same if the European Community (EC) numbers match. It is possible that despite of matching EC numbers, the manufacturing processes are different so that the resulting compositions must be considered as different substances.

3.2 Equivalency of test materials used in key studies with the registered substance

3.2.1 Dossier-related overall results

The evaluated sample comprised 390 dossiers using the same selection of lead dossiers of joint submissions (n = 216) as for the evaluation of substance sameness (see chapter 2.2). Additionally, a random sample was drawn from individual submissions (n = 174).

It was investigated whether test materials in key studies (if not read-across) have been correctly declared as matching with the registered substance by the registrant.

Over all endpoints (on average), 59 % of the evaluated dossiers contained only key studies with test materials that were correctly stated to be either the same as the registered substances and/or read-across from other substances. In 13 % of the dossiers (on average), the test material did not match the registered substance or a conclusion was not possible due to conflicting information. In the remaining 28 % of the dossiers (on average), a key study was not provided for the particular endpoint (*e.g.* due to justified data waiving, or if only supporting studies were provided) or key studies were generally not available for all evaluated endpoints.

Figure 3-1 illustrates the detailed results for the investigated endpoints. For 19 to 44 % of dossiers ("physico-chemical properties" excluded), test materials of all available key studies for an endpoint were in accordance with the respective registered substances (light green). Overall, a slight difference was demonstrated between HH and ENV endpoints, as for HH endpoints 19 to 37 % (average: 29 %) and for ENV endpoints 24 to 44 % (average: 37 %) of dossiers showed key studies with consistency of the test material to the registered substance.

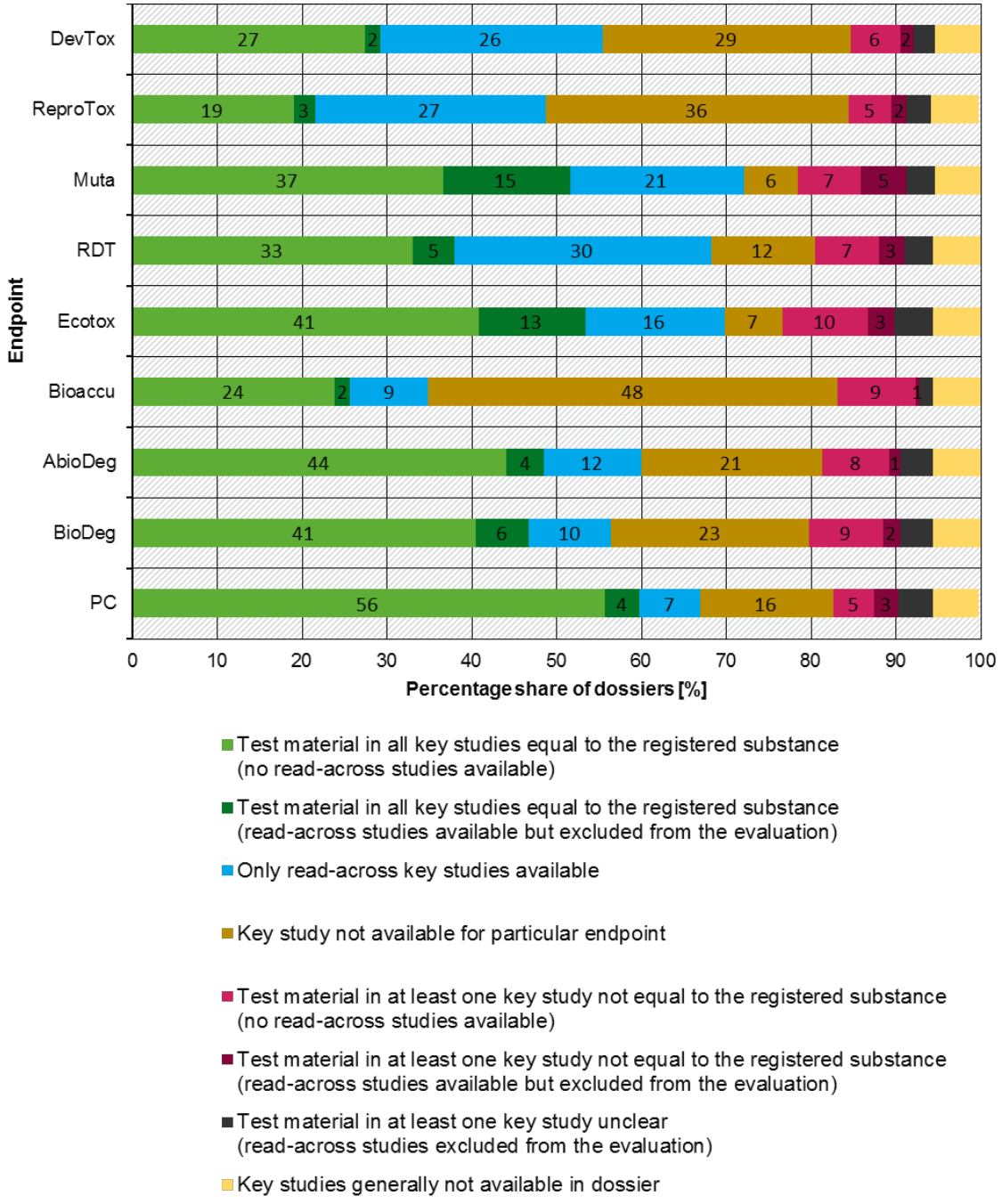
Read-across approaches have been applied frequently for several endpoints. The assessment of equivalency among the registered substance and the used test material in key studies is not expedient in these cases. Hence, dossiers containing read-across studies were itemised separately ("read-across studies available") and the respective key studies were excluded from the evaluation (Figure 3-1).

The average percentage of dossiers containing only read-across key studies (blue bars) was higher for HH endpoints (26 %) in comparison to ENV endpoints (12 %).

Due to waiving of the required animal tests or providing supporting studies only, a high percentage of dossiers for some endpoints did not contain any key study (light brown bars). The endpoints DevTox and ReproTox as well as the endpoint Bioaccu showed rather high percentages (29 %, 36 % and 48 %, respectively). In contrast, low percentages were observed for Muta (6 %), Ecotox (7 %) and RDT (12 %).

Further, also the amount of dossiers per endpoint where test materials in key studies were not consistent with registered substances was divided into two aspects (light and dark magenta, *i.e.* not consistent; and black colour, *i.e.* unclear, in Figure 3-1). In sum, in 10 to 18 % of the dossier sample (n = 390) the test material in at least one key study per endpoint did not match the registered substance or it was not possible to determine whether it does (unclear). A detailed listing of absolute numbers is given in Table 6-4 in Annex 2.

Figure 3-1: Dossier-related equivalency of the registered substance with the test materials used in key studies*



* Based on 390 examined dossiers. The absolute numbers for each endpoint are presented in Table 6-4 in Annex 2.
PC = physico-chemical properties (log K_{ow}, water solubility)

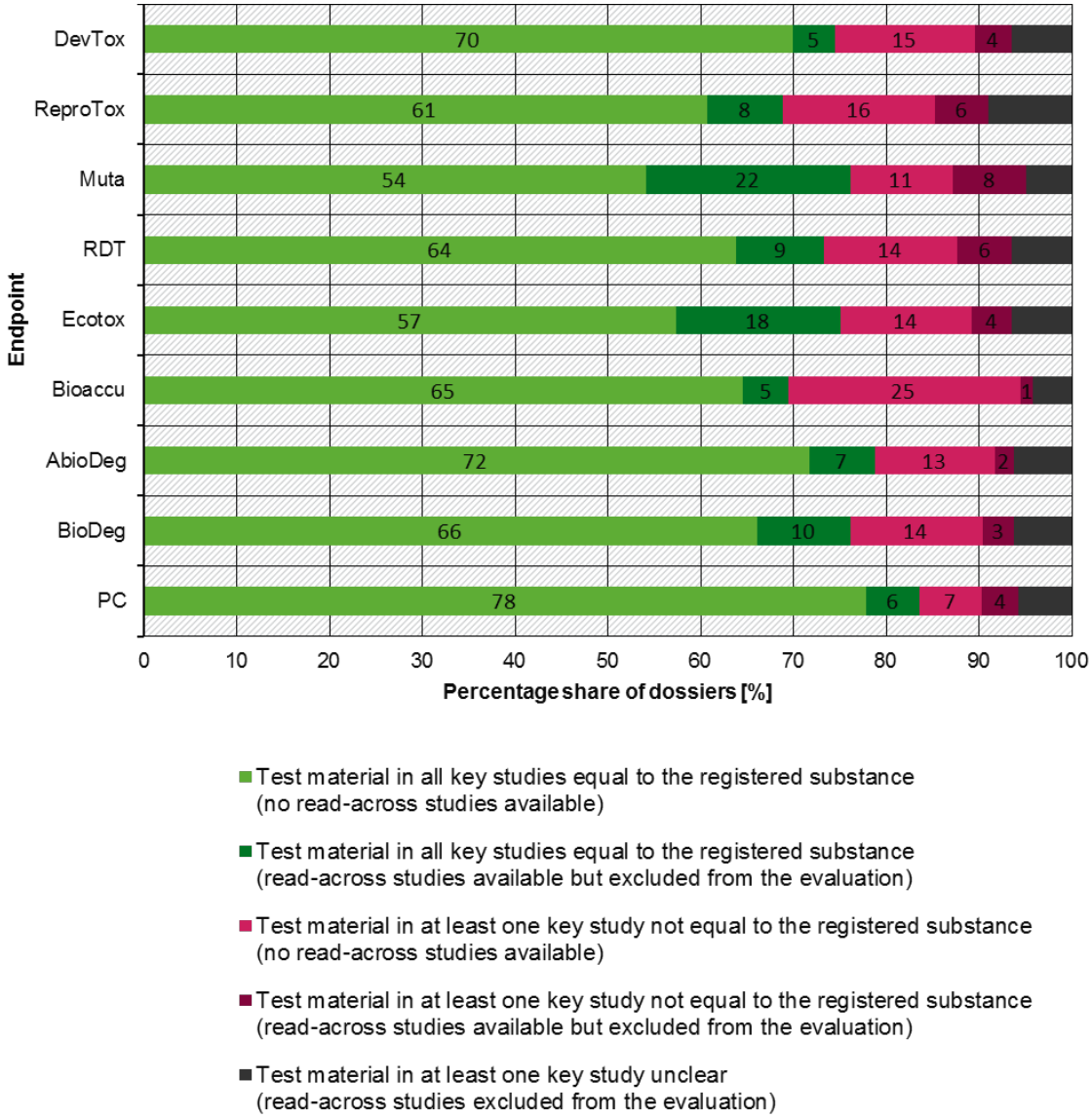
3.2.2 Dossier-related overall results – dossiers without key studies excluded

Figure 3-2 shows the dossier-related overall results excluding dossiers without key studies and dossiers that contained only read-across key studies for the respective endpoint. In 69 to 79 % of this adjusted set of dossiers, depending on the endpoint, the test material in the according key study was stated to be the registered substance.

ReproTox and Bioaccu had with more than 30 % the highest percentage of dossiers with at least one key study showing inconsistencies regarding the test material. The minimum in this regard comprised 21 % for AbioDeg ("physico-chemical properties" excluded).

A detailed listing of absolute numbers is given in Table 6-4 in Annex 2 also being basis for chapter 3.2.

Figure 3-2: Dossier-related equivalency of the registered substance with the test materials used in key studies – dossiers without key studies excluded*



* For this analysis, dossiers without key studies or with read-across key studies only were subtracted from the total of 390 dossiers. The absolute numbers for each endpoint are presented in Table 6-4 in Annex 2. PC = physico-chemical properties (log K_{ow}, water solubility)

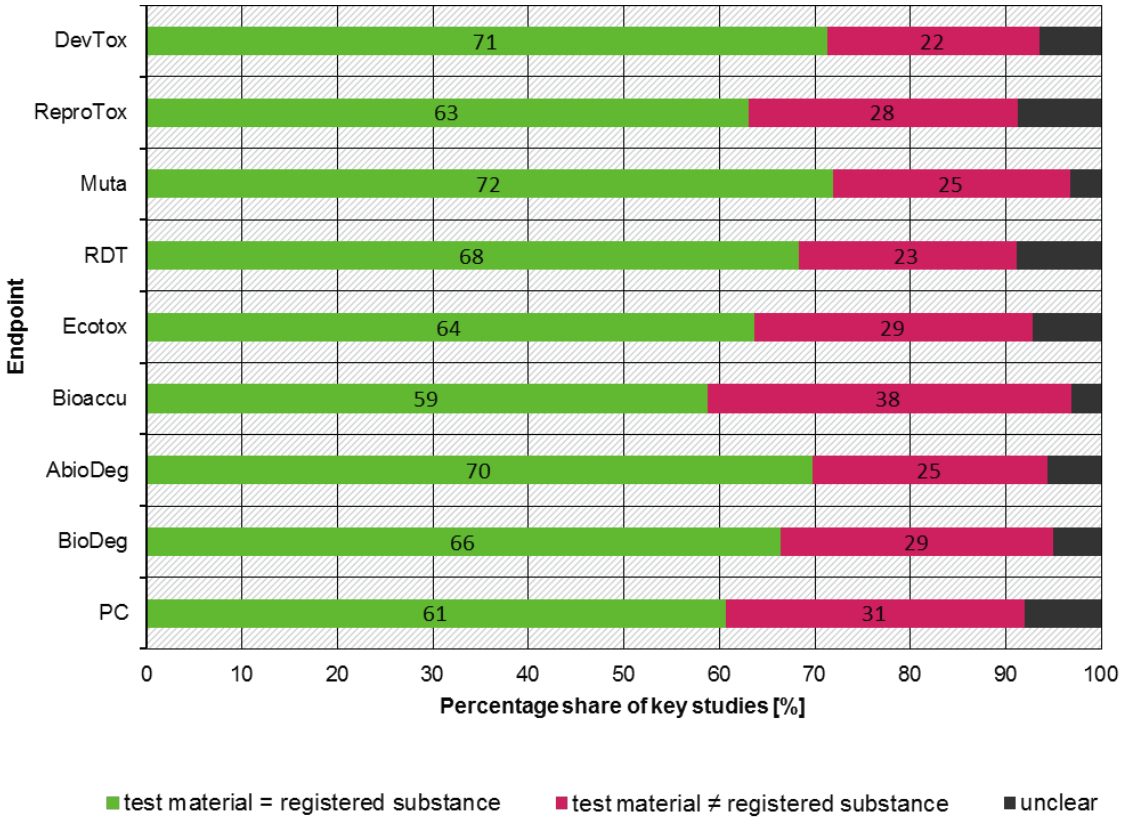
3.2.3 Results in relation to key studies

In sum, 7436 key studies were counted in the assessed registration dossiers. 2971 of these study records were flagged as read-across key studies. Thus, information on test materials in 4465 ESRs for key studies were compared to the respective registered substances.

Overall, it was found that the information on test material was equal to the respective registered substance for 2958 (66 % of total) key studies. In 1236 (28 % of total) key studies the test material was not equal to the registered substance and for 271 (6 % of total) key studies it remained unclear which material was tested.

Figure 3-3 illustrates the results for the endpoints excluding all read-across key studies. Differences were observed between endpoints: For 59 to 72 % of key studies the test material was in accordance with the registered substance (as declared by the registrant). The lowest percentage of key studies with consistent information on test materials were observed for physico-chemical properties (log K_{ow} and water solubility) endpoints (61 %) and for Bioaccu (59 %), whereas the highest percentages with more than 70 % were related to the endpoints AbioDeg, Muta, DevTox. Regarding key studies for which the test material was not equal to the registered substance, the highest percentage was observed for Bioaccu (38 %). This deviates the most from the average of all endpoints, which was 28 %. Absolute numbers can be found in Table 6-5 in Annex 2.

Figure 3-3: Equivalency of the test material used in key studies with the registered substance*



* Based on available key studies in 390 examined dossiers (read-across studies were excluded from the evaluation). The absolute numbers of available key studies for each endpoint are presented in Table 6-5 in Annex 2. PC = physico-chemical properties (log K_{ow}, water solubility)

Further information was gained on the average number of available key studies per endpoint and dossier (including read-across studies). This number was compared to the required number of studies. Overall, the average number of available key studies matched or exceeded the number of required

studies for almost all endpoints. However, in case of DevTox, the average number of available key studies (1.2) was remarkably lower than the number of required studies (2). DevTox usually requires the testing on two different animal species. According to project I, the reason for the low number of key studies is that data on the second species were often not provided, for example due to data waiving.

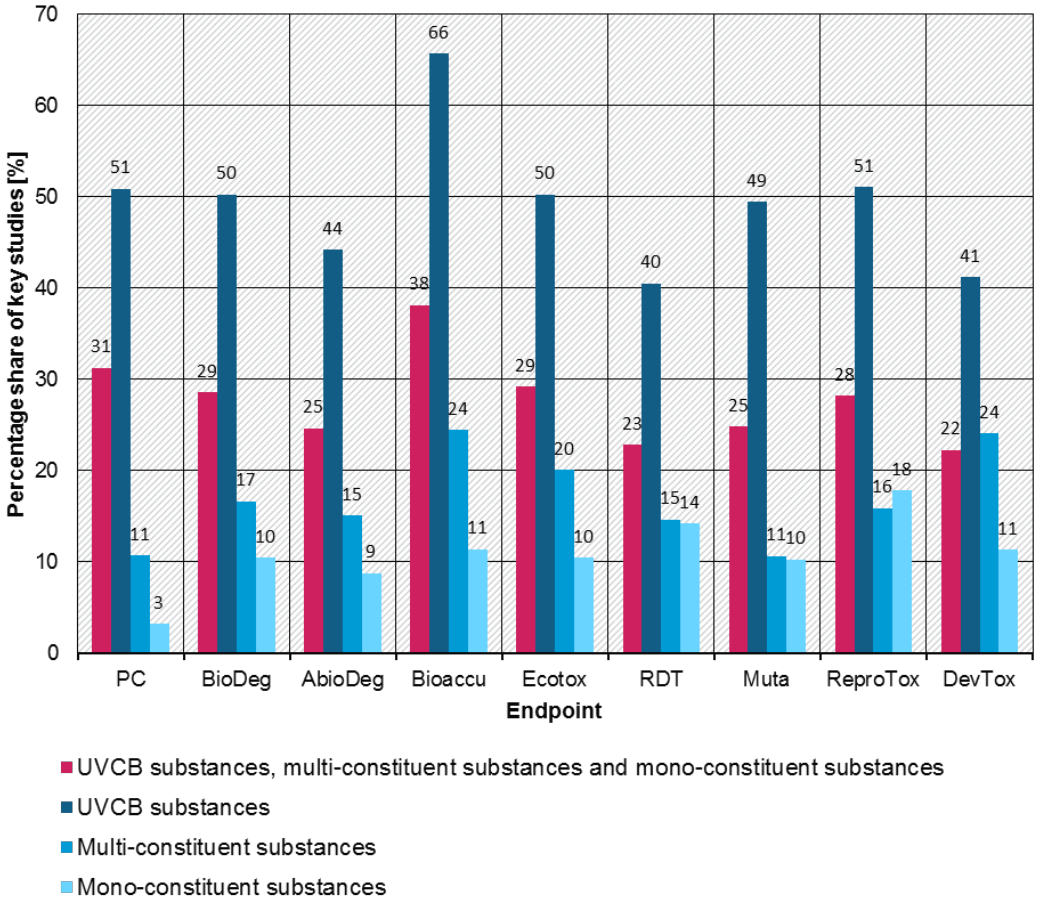
3.2.4 Inconsistencies in key studies in relation to substance type

The dossiers checked consisted in total of 155 dossiers for UVCB substances, 88 dossiers for multi-constituent substances and 147 dossiers for mono-constituent substances. The percentage of key studies where the information on test material was found not to comply with the registered substance (on average 28 %, chapter 3.2.3) was further analysed with respect to the different substance types.

Figure 3-4 shows the percentage of key studies with test material not in accordance to the registered substance per endpoint and substance type. The red bar represents for each endpoint the percentage of key studies with inconsistent test materials in relation to the total number of key studies per endpoint, regardless of the substance type (22 to 38 %, as calculated already in chapter 3.2.3). In comparison to this, the percentage of key studies with inconsistent test material is clearly higher for UVCB substances (41 to 66 %).

In contrast, in dossiers for multi-constituent substances and in particular mono-constituent substances much lower percentages for key studies with inconsistent test material were observed. 11 to 24 % of the available key studies for multi-constituent substances and 3 to 18 % of the available key studies for mono-constituent substances were affected.

Figure 3-4: Percentage share of key studies with test material not considered equal to the registered substance in relation to the total number of key studies per endpoint and type of substance*



* Based on available key studies in 390 examined dossiers (read-across studies were excluded from the evaluation). The absolute numbers of available key studies for each endpoint are presented in Table 6-5 and Table 6-6 in Annex 2.
PC = physico-chemical properties (log K_{ow}, water solubility)

Over all endpoints, on average 49 % of UVCB key studies showed that the test material was not in accordance with the registered substance. In contrast, for mono-constituent substances and multi-constituent substances the percentages were considerably lower with 17 % and 11 %, respectively.

The frequent inconsistencies observed for UVCB substances might be due to the fact that they are by definition complex in composition and not clearly defined. Therefore, it is difficult to provide the identical test material. Hence, often only one constituent of the registered substance was used to meet the REACH standard information requirements.

In terms of three aspects data of UVCB substances used to meet the REACH standard information requirements is subject to uncertainties for the registrant as well as in terms of the check conducted here:

1. For a decision on using available data for REACH registration, a verification of substance sameness or similarity cannot be carried out in a standardised way for UVCB substances, see the previous chapter on assessing the substance sameness between lead and member in a joint submission. On the other hand, the check of key studies was conducted in a simple but reliable way on the information given in an ESR (CAS/EC number; substance name; yes/no specification by the registrant), and therefore relies on the information given by the registrant. A declaration on how the registrant

has assessed the substance sameness between each test material and the registered substance might be useful.

2. The accordance with the REACH requirements for cases of testing with one or a few constituents of an UVCB substance is given for certain cases. However, the criteria are yet unclear based on ECHA guidance and a justification by the registrant might be useful but is yet not explicitly required by ECHA.
3. Also overall "compliance" of the key studies to the REACH standard information requirements and how registrants have presented their data in IUCLID play a role to finally conclude on the appropriateness of the data in terms of REACH. However, these aspects have not been evaluated during the check.

Thus, the results achieved here reflect a situation with particular high uncertainty regarding UVCB substances for registrants and authorities assessing the presented data in the REACH registration. Therefore, the guidance should be improved to overcome this situation. Also, a case-by-case analysis is required to evaluate the test material for UVCB substances.

3.2.5 Number of read-across key studies (Excursus)

As stated above key studies for which "read-across" was indicated as study result type in IUCLID were counted during the investigation. Their proportion in relation to the totally counted key studies is depicted in Table 3-5. The percentage of read-across key studies is high for HH endpoints and Ecotox (42 to 59 % of all key studies). The percentage is considerably lower for the remaining endpoints (20 to 25 %).

Table 3-5: Number of key studies and relation to the read-across approaches per endpoint*

Endpoint	Total number of key studies	Number of read-across key studies	Percentage read-across key studies of total key studies [%]
PC	918	182	19,8
BioDeg	686	168	24,5
AbioDeg	583	136	23,3
Bioaccu	295	72	24,4
Ecotox	1568	664	42,3
RDT	906	534	58,9
Muta	1682	768	45,7
ReproTox	362	214	59,1
DevTox	436	234	53,7

* Based on available key studies in 390 examined dossiers. PC = physico-chemical properties (log K_{ow}, water solubility)

Moreover, the fraction of read-across key studies depends on the substance type. In all examined dossiers for UVCB substances, 49 % of key studies accounted for read-across whereas for multi-constituent substances only 29 % and for mono-constituent substances only 25 % were related to this approach. Because of this difference, the fraction of read-across key studies were further analysed for each substance type and endpoint.

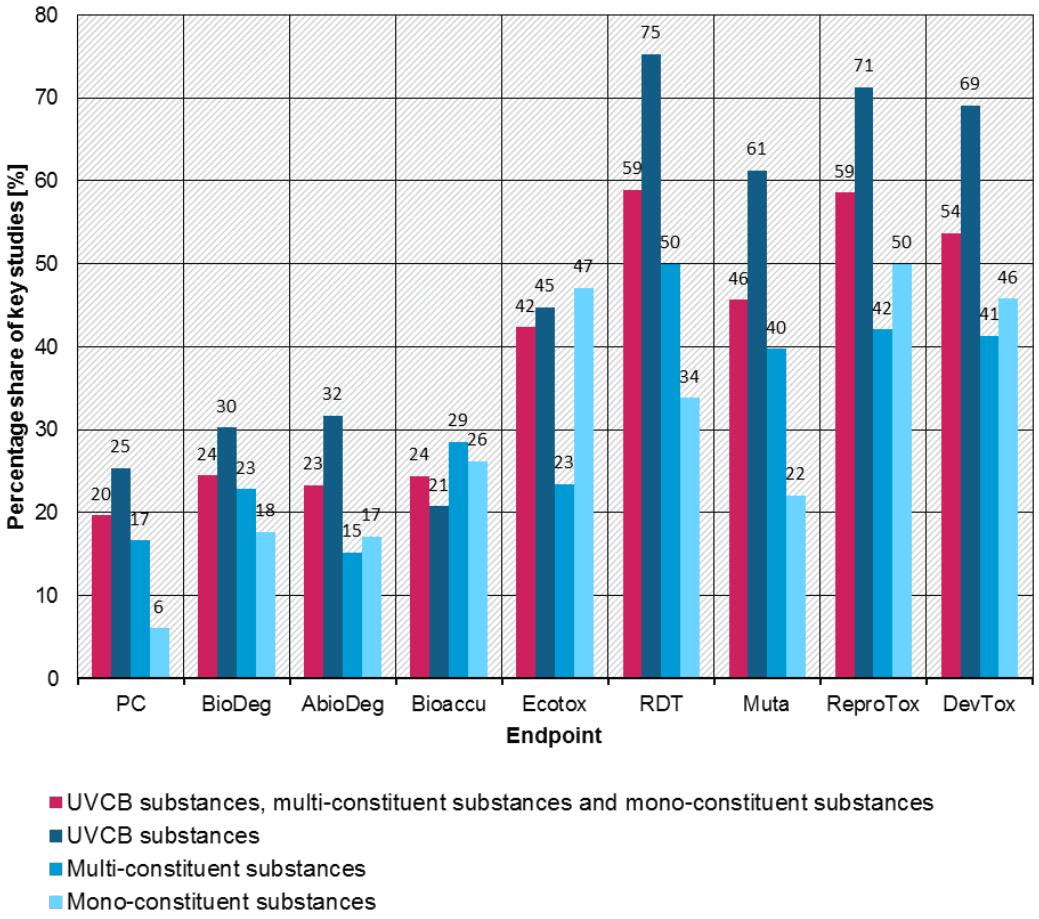
The results illustrated in Figure 3-5 additionally show – for each substance type – the fraction of all read-across key studies in relation to the total number of key studies per endpoint (Table 3-5). The

percentage of read-across key studies in dossiers of UVCB substances was considerably higher compared to dossiers of multi- and mono-constituent substances for all examined endpoints. Only for Bioaccu similar percentages of read-across key studies were found for the different substance types. For AbioDeg and Ecotox, the percentages of read-across key studies in dossiers of UVCB substances is even twice of the percentage of at least one of the other substance types.

According to the generally high amount of read-across key studies for HH endpoints and also Ecotox, the most striking result is that the percentage of read-across key studies in dossiers for UVCB substances is with 61 to 75 % for HH endpoints the highest.

In contrast, in dossiers for mono-constituent substances RDT and Muta show the lowest percentage of read-across key studies among all substance types and the HH endpoints (34 % and 22 %, respectively).

Figure 3-5: Percentage share of read-across key studies in relation to the total number of key studies per endpoint and type of substance*



* Based on available key studies in 390 examined dossiers. The absolute numbers of available key studies for each endpoint are presented in Table 6-5 and Table 6-6 in Annex 2. PC = physico-chemical properties (log K_{ow}, water solubility)

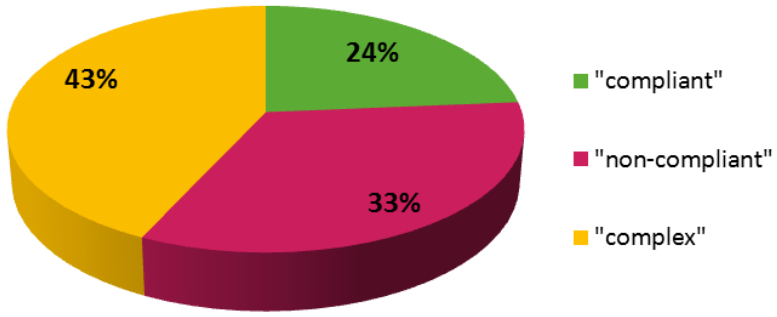
3.3 Formal check

Within project II all endpoint cases without conclusion ("complex") from project I due to data waiving or grouping/read-across approaches were checked regarding the fulfilment of the formal criteria developed according to the REACH Regulation. The waiving/adaptation options provided by the registrants were investigated. As the result of the examination, the endpoint cases were assigned to one of the following endpoint conclusion categories: "obviously compliant", "formally compliant", "obviously non-compliant", "formally non-compliant" or remained "complex". For an initial overview, results of all HH and ENV endpoints were compiled and conclusion categories were simplified to "compliant" ("obviously compliant" and "formally compliant"), "non-compliant" ("obviously non-compliant" and "formally non-compliant") and "complex". The outcome is depicted in the subsequent chapter 3.3.1, detailed results with the categorisation into five endpoint conclusion categories for individual HH and ENV endpoints are following.

3.3.1 Overall results of all endpoints

In total, 6923 previous endpoint cases without conclusion ("complex") were assessed, and the summarised results regarding the endpoint conclusions for all HH and ENV endpoints are shown in Figure 3-6. 57 % of the former endpoint cases without conclusion ("complex") could be concluded. 24 % of the endpoint cases were regarded as "compliant", *i.e.* they fulfilled the selected formal REACH criteria for data waiving or the use of adaptations or there were obvious reasons that data provided by the registrants were sufficient regarding the REACH requirements. 33 % of the investigated endpoint cases were assigned to "non-compliant" because the formal REACH criteria for waiving/adaptations were not fulfilled or there were obvious reasons that the given information or justifications were insufficient. 43 % of all endpoint conclusions could not be resolved within the scope of the developed concept and remained "complex".

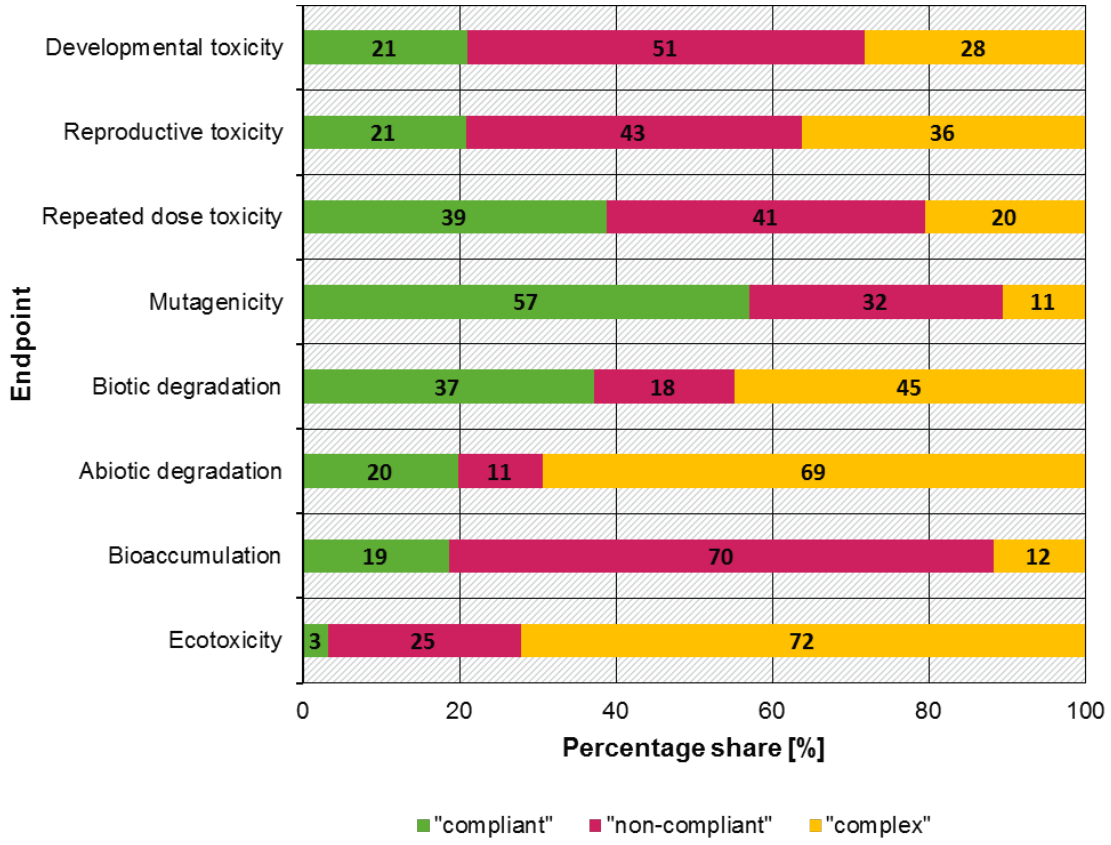
Figure 3-6: Conclusions over all endpoint decisions in formal check (total number: 6923)



An overview on the endpoint conclusions for each endpoint is given in Figure 3-7. It be can deduced from the figure that a higher rate of conclusions could be derived for HH endpoints with percentages ranging from 64 % for ReproTox to 89 % for Muta in comparison to ENV endpoints. For ENV endpoints a stronger variation between the endpoints was observed. The lowest percentages of concluded endpoints were present for Ecotox and AbioDeg with percentages of 28 % and 31 %, respectively, while 88 % could be concluded for Bioaccu and 55 % for BioDeg. That means, depending on the endpoint, 11 to 72 % of all endpoint cases remained without conclusion. With respect to the concluded cases, all endpoints, except Muta, BioDeg and AbioDeg, had in common that the number of "non-compliant" endpoint cases exceeded those of "compliant" endpoint cases. Of all endpoints, Muta had by far

the highest percentage of "compliant" endpoint conclusions with 57 %, while "non-compliant" endpoint cases were predominantly observed for Bioaccu with 70 %. In contrast, the lowest number of "compliant" endpoint cases was present for Ecotox with 3 %, while AbioDeg had only 11 % "non-compliant" endpoint cases. This is due to the fact that for most dossiers on both endpoints no conclusion could be derived within this investigation.

Figure 3-7: Endpoint conclusions for human health and environment in formal check*



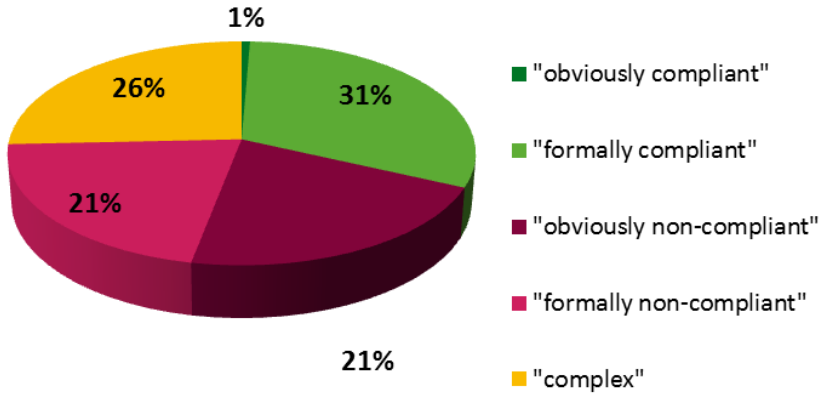
* Total number of checked dossiers: 917 DevTox, 1133 Reprotox, 850 RDT, 653 Muta, 533 BioDeg, 1029 AbioDeg, 315 Bioaccu, 1493 Ecotox.

3.3.2 Overall results of human health endpoints

The total number of dossiers for the investigated endpoints was: 917 for DevTox, 1133 for ReproTox, 653 for Muta, and 850 for RDT. For RDT, four additional dossiers were excluded from the check because a testing proposal was available. Apparently, these dossiers have incorrectly been allocated to the "complex" category in the screening of project I.

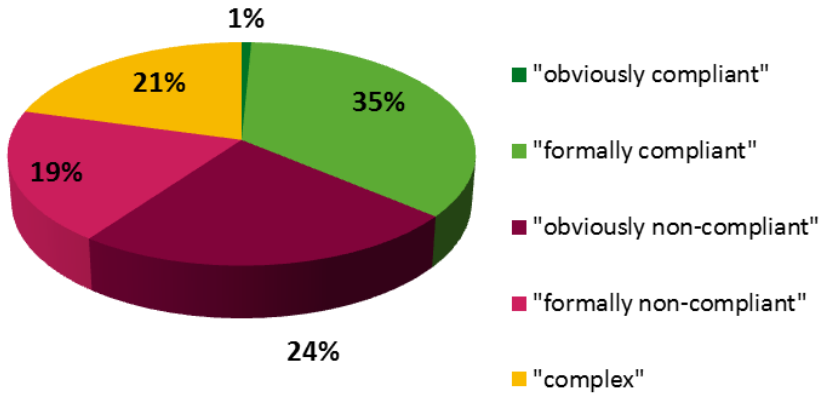
Figure 3-8 illustrates the distribution if the conclusions of all HH endpoints are summarised. Almost one third of all cases were allocated to the endpoint conclusion category "formally compliant", which means that the waiving/adaptations fulfilled the formal criteria of the REACH Regulation according to the approach applied here. The categories "obviously non-compliant", "formally non-compliant" and "complex" contributed more or less equally to the remaining two third with percentages between 21 to 26 %. "Obviously compliant" cases rarely occurred which is reflected by a low percentage of 1 %.

Figure 3-8: Human health: Conclusions over all endpoint decisions in formal check (total number: 3553)



Often more than one waiving or adaptation was presented to meet the information requirements for a particular HH endpoint. Hence, the distribution of endpoint conclusions differed from the conclusions on individual cases of data waiving/adaptation (Figure 3-9). Slightly more than one third of all waiving/adaptations fulfilled the formal criteria, while the conclusion categories “obviously non-compliant” and “formally non-compliant” contributed with 24 % and 19 %, respectively. Percentages for the category “complex” were slightly lower with 21 % compared the endpoint conclusions. Again, “obviously compliant” cases were of minor importance with 1 %.

Figure 3-9: Human health: Conclusions over all waiving/adaptations in formal check (total number: 6309)



An overview on the total number of available and missing waiving/adaptations for each endpoint is given in Table 3-6. For all endpoints, the number of available waiving/adaptations is higher than the number of total dossiers checked, indicating that often more than one waiving/adaptation was applied by registrants. For ReproTox, DevTox and RDT, on average 1.5 to 1.7 waiving/adaptations were identified per dossier. Not surprisingly, for Muta the ratio was higher with 2.2. This is due to the necessity that data for at least three different study types have to be presented. For 71 cases of this endpoint, a (probably) required waiving/adaptation was not available. The number was even higher for DevTox with 176 cases and that instance also applied to RDT with 13 cases.

Table 3-6: Human health: Number of available and missing waiving/adaptations for each endpoint in formal check

HH endpoint	Available waiving/ adaptations	Waiving/adaptation missing, but required (or probably required)	Total
DevTox	1371	174 (2)	1547
ReproTox	1791	0	1791
Muta	1407	51 (20)	1478
RDT	1480	10 (3)	1493

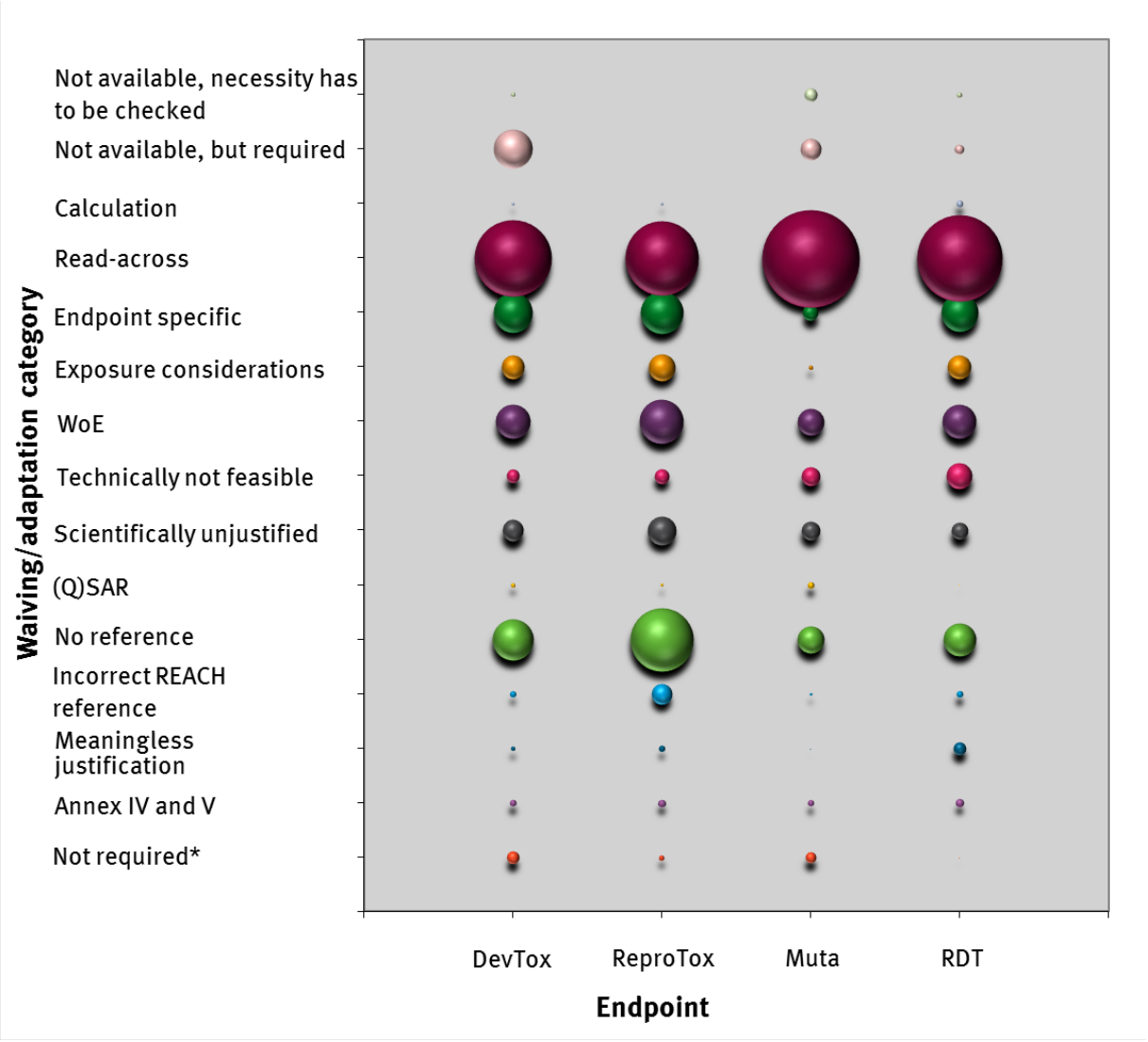
It was documented whether the specific REACH reference for each waiving/adaptation was clearly stated by the registrant or had to be deduced from justification or endpoint summary during the assessment. Over all HH endpoints, in 51 % of waiving/adaptations the registrant sufficiently indicated according to which option he intended to waive/adapt the required standard information (Table 3-7). In 49 % of waiving/adaptations, this was not clearly mentioned and had to be derived from the content of the justification or endpoint summary.

Table 3-7: Human health: Overview whether REACH reference was given by the registrant or deduced within the examination for each endpoint in formal check – excluding read-across approaches and cases with a missing waiving/adaptation

HH endpoint	Reference given by registrant		Reference deduced within examination	
	n	[%]	n	[%]
DevTox	360	54	301	46
ReproTox	572	50	581	50
Muta	185	65	101	35
RDT	274	44	346	56
Total/Mean	**1391**	**51**	**1329**	**49**

Figure 3-10 summarises waiving/adaptation categories applied by the registrants for the HH endpoints. Waiving/adaptations, either clearly stated by the registrants or deduced within the formal check, were included in Figure 3-10. In general, DevTox, ReproTox and RDT had a higher diversity regarding the application of different waiving/adaptation options in comparison to Muta. However, read-across was by far the most frequent option chosen among all endpoints. In accordance with the lower diversity, it was especially dominant for Muta. For DevTox, ReproTox and Muta, justifications without a relation to the options described in Annex XI or Annexes VII to X column 2 of the REACH Regulation ("no reference" – those were allocated to REACH Annexes VII to X introduction, last passage) ranked second regarding the frequency of use. This waiving option was also important for RDT. Moreover, WoE approaches were observed frequently in addition to other waiving/adaptations for all endpoints. Endpoint specific reasons according to column 2 criteria and exposure-based waiving of data according to REACH Annex XI 3. were especially applied for DevTox, ReproTox and RDT. Conspicuous observations regarding the individual endpoints comprised that waiving due to technical reasons ("technically not feasible") was particularly observed for RDT, while the categories "scientifically unjustified" and "incorrect REACH reference" were preferably used for ReproTox. As already mentioned above, DevTox and Muta were the only endpoints for which waiving/adaptations were not available in several cases due to the fact that studies for different study types or species have to be presented and a waiving/adaptation was missing for at least one. Other categories were of minor importance. The concrete numbers and percentages of waiving/adaptations for all HH endpoints can be found in Table 6-9 (Annex 3).

Figure 3-10: Human health: Frequency of waiving/adaptation categories in formal check (total number: 6309)



* "not required": acceptable study available or read-across (acceptable study) available for hydrated form or anhydride or relevant harmonised classification.

In addition to the analysis if applied waiving/adaptations fulfilled the formal criteria according to the REACH Regulation, it was also investigated whether data waiving or surrogate data were used to incriminate or exonerate the registered substance with respect to its endpoint specific toxic potential. An overview on the obtained results is given in for the HH endpoints DevTox, ReproTox and Muta. For the vast majority of cases, 78 to 90 % depending on the endpoint, waiving/adaptations were used to exonerate the substance regarding its toxic potential. Thus waiving/adaptations were mainly used to demonstrate that no endpoint specific hazard is expected to occur. In contrast, 6 % or less of the waiving/adaptations were applied to incriminate the compound with respect to its toxic potential, *i.e.* to conclude that a hazard is supposed to exist. For 7 to 18 % no waiving/adaptation was available, although (probably) required, or a tendency regarding this issue could not be deduced from the given justification.

Table 3-8: Human health: Overview whether waiving/adaptations were used to incriminate or exonerate the toxic potential of the registered substance in formal check*

HH endpoint	Waiving/adaptation used to incriminate		Waiving/adaptation used to exonerate		No waiving/adaptation available or tendency not deducible	
	n	[%]	n	[%]	n	[%]
DevTox	61	4	1207	78	279	18
ReproTox	50	3	1612	90	129	7
Muta	88	6	1262	85	128	9
Total/Mean	**199**	**4**	**4081**	**85**	**535**	**11**

*Analysis was not done for RDT because the objective of this endpoint is to identify relevant concentration ranges of toxicity and to derive NO(A)ELs.

3.3.3 Repeated dose toxicity

From the total of 854 RDT "complex" dossiers (without WoE solely applied), four dossiers were excluded from the check because for each a testing proposal was available (*i.e.* 850 checked dossiers). In total 1493 waiving justifications and read-across (Table 3-6) were detected for RDT and its different exposure routes. Thus, on average 1.8 waiving/adaptations were applied per dossier.

However, for 59 dossiers a waiving/adaptation was not available for the oral route, although testing the oral route is the standard information requirement according to REACH Annex IX. This fact was documented but did not contribute to the endpoint conclusion if a waiving/adaptation for the dermal and/or inhalation route was available.

Route considerations

For the 1493 examined waiving/adaptations and grouping/read-across the distribution between the three different routes was as follows:

- 803 oral route,
- 455 inhalation route,
- 235 dermal route.

Here, 49 dossiers with a waiving justification for omitting the oral route have been documented and included in the descriptive statistical analysis because the oral route is the preferred or standard route for testing RDT. This included also waiving based on technical considerations explaining that the substance is gaseous (in these cases the waiving justification was not categorised as "technically not feasible"). These dossiers remained without conclusion ("complex") as it was not the aim to evaluate its correctness. The respective waiving/adaptation presented for dermal and/or inhalation route was checked and thus contributed to the endpoint conclusion.

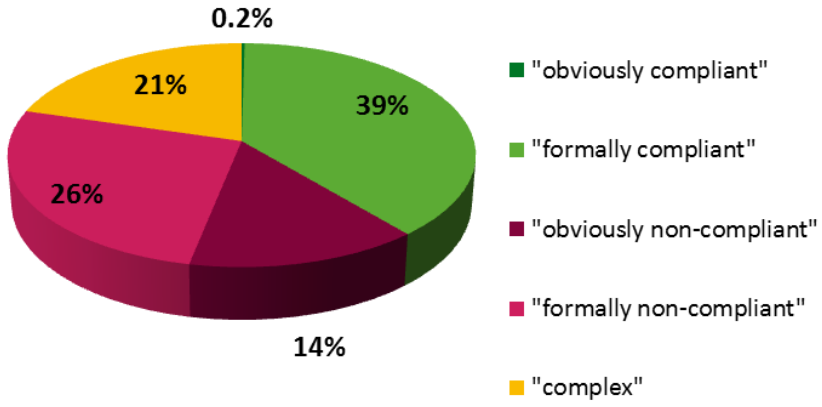
Two justifications for waiving each the dermal and inhalation route (in sum four waiving) have been included in the analysis of the examined waiving/adaptations because these presented each a justification based on route-to-route extrapolation but at the same time actually the data for the indicated oral route was missed.

In 94 cases of waiving, mostly applied for waiving the testing of dermal or inhalation route, it was stated that oral data (or data for another route) was available and/or a route-to-route extrapolation was indicated. The triggers for testing dermal or inhalation route were not mentioned. These cases were documented but their correctness was not evaluated.

Overall results

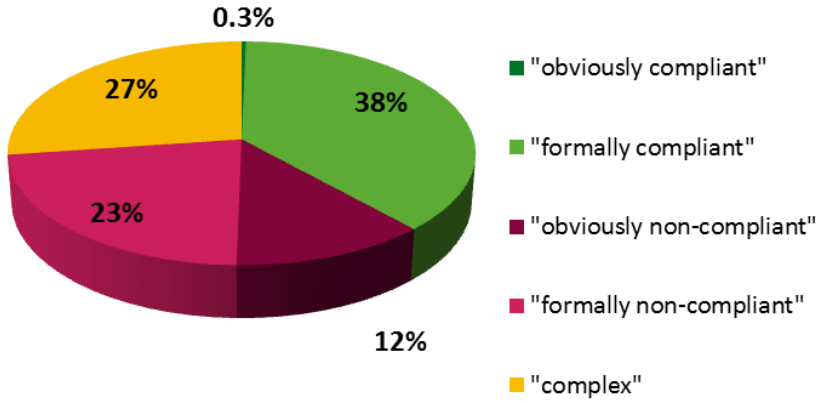
39 % of the dossiers examined regarding RDT fulfilled the formal requirements and, therefore, were allocated to the category "formally compliant" (Figure 3-11). In contrast, in sum 40 % of the dossiers were "non-compliant", while 21 % remained without conclusion. Two "obviously compliant" cases were observed (0.2 %). In comparison to the endpoint conclusions over all HH endpoints (Figure 3-8), RDT showed with 39 % more dossiers which were regarded as "compliant".

Figure 3-11: Repeated dose toxicity: Endpoint conclusions in formal check (total number: 850)



Moreover, analysis of waiving/adaptations resulted in a similar distribution compared to the endpoint conclusions (Figure 3-12). 38 % of all waiving/adaptations fulfilled the formal criteria ("formally compliant"), while the conclusion categories "obviously non-compliant" and "formally non-compliant" contributed in sum with 35 % and "complex" contributed with 27 %. Five "obviously compliant" cases occurred (0.3 %).

Figure 3-12: Repeated dose toxicity: Conclusions over waiving/adaptations in formal check (total number: 1493)



Waiving categories regarding different routes of exposure

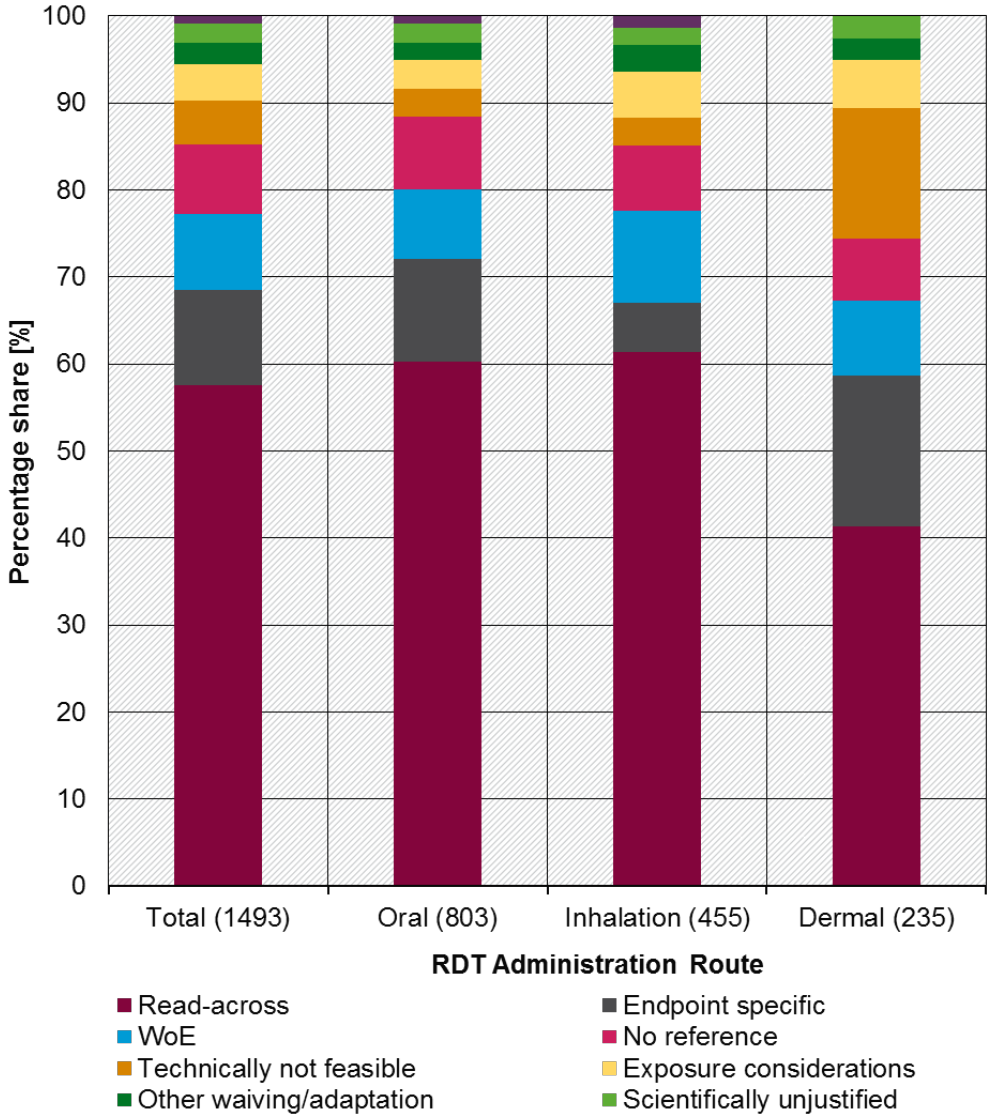
Figure 3-13 gives an overview on the distribution of the waiving/adaptation categories that were derived from the justifications for waiving and the presented adaptations. The left bar illustrates the distribution of waiving/adaptation categories in total for RDT as it was already shown by Figure 3-10 in comparison to the other HH endpoints (in relation to 1493 total waiving/adaptations). The read-across approach was predominantly applied (57 %) followed by waiving based on REACH Annexes VII to X column 2 ("endpoint specific", 11 %), WoE approach (9 %) and in principle plausible justifications without reference to the REACH criteria for waiving ("no reference", 8 %). According to the introductions of the REACH Annexes VII to X another justification criteria is acceptable where appropriate. Other waiving/adaptations show a proportion of 5 % ("technically not feasible") or less.

The other bars illustrate each the distribution in relation to a separate route of administration. Waiving related to the oral and inhalation route (in relation to 803 and 455 waiving, respectively) are similarly distributed in comparison to the total waiving/adaptations.

Despite this, the distribution of waiving/adaptation categories for the dermal route (in relation to 235 waiving/adaptations) differs from the oral and inhalation route because the percentage of read-across approach was only 41 % (in contrast around 60 % for oral and inhalation route). This might be due to the fact that in general RDT testing is less frequently applied administrating the substance to the skin. Absorption of the substance through the skin is a precondition for testing systemic effects.

In contrast, endpoint specific waiving and waiving based on substance-related reasons ("technically not feasible") show higher proportions for the dermal route in comparison to the other routes and the total distribution (17 % and 15 %, respectively). Endpoint specific reasons might be higher due to frequent route-to-route extrapolation for dermal testing based on an existent 28-day study applied to a different route of administration. Substance-related reasons comprised *e.g.* cases of high reactive substances which were not tested at all but test results of a similar substance were related to the oral or inhalation route. Thus, the read-across approach was applied for oral/inhalation route and a justification based on the REACH criteria "technically not feasible" was stated for dermal route.

Figure 3-13: Repeated dose toxicity: Waiving/adaptation categories of routes in formal check (percentage per route)*



* Total number per administration route in brackets.

Decisive waiving for endpoint conclusion

In the following Figure 3-14 a combination of two analysed aspects is shown:

- distribution of decisive waiving/adaptations for the endpoint (partly more than waiving category per dossier), and
- their contribution to the different possible endpoint conclusions.

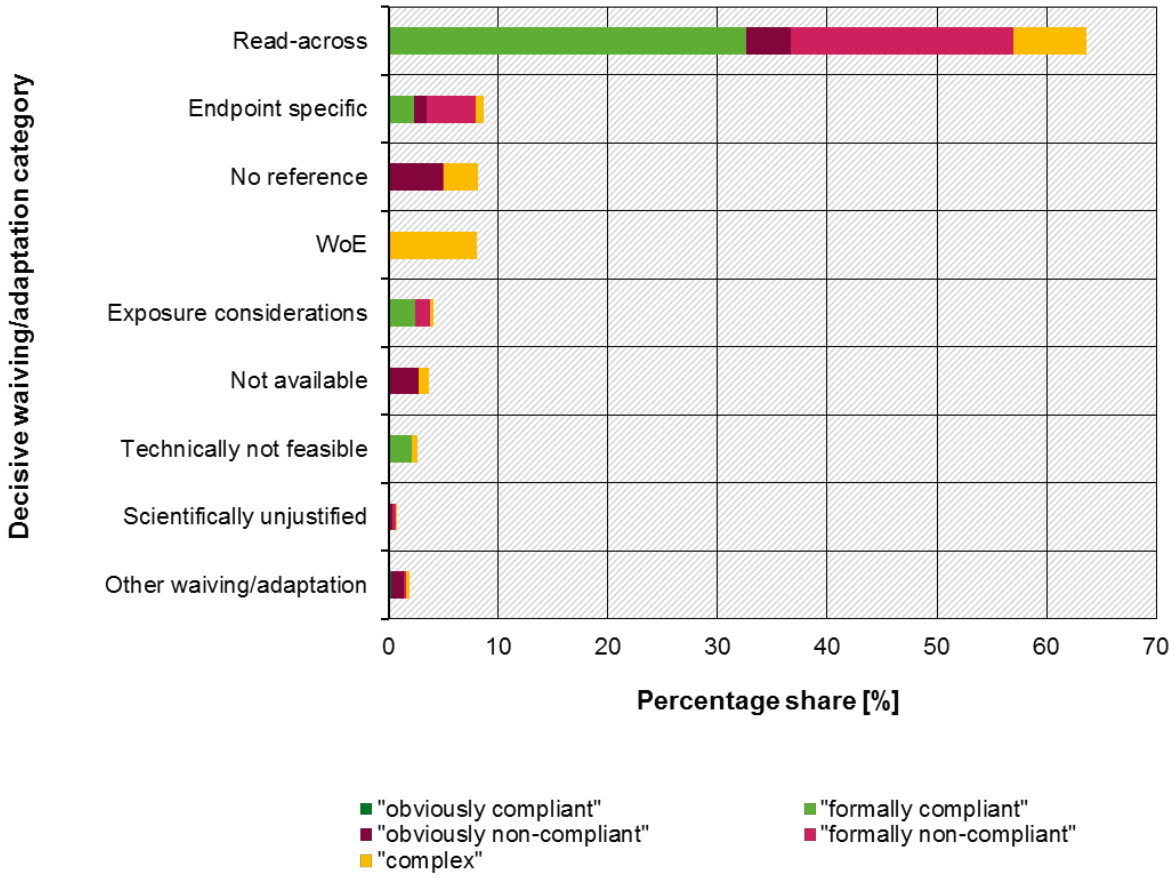
In accordance with the observation that read-across was the predominant waiving/adaptation category for RDT (Figure 3-10 and Figure 3-13), read-across was also in 63 % of all decisive waiving the critical factor for the endpoint conclusions (Figure 3-14). Read-across contributed in half of the cases to the conclusion "formally compliant" (51 %). 38 % of the dossiers in which read-across was decisive for the endpoint conclusion were assigned to the conclusion categories "obviously non-compliant" or "formally non-compliant". Here, mostly the respective similarity/grouping explanation, which is mandatory for read-across, was not given. Further reasons for "non-compliance" are explained below. About 11 % of the read-across remained "complex" (no conclusion).

Furthermore, "endpoint specific" reasons were decisive for the endpoint conclusion in 9 % of all decisive waiving. A contribution to the endpoint conclusions "obviously non-compliant" or "formally non-compliant" is predominant (49 of 75 cases, 65 %). The main reasons for "non-compliance" are explained below.

Similarly, the waiving/adaptation categories "no reference" and "WoE" contributed with each 8 % of all decisive waiving to the endpoint conclusions. However, more than half of the "no reference" cases were "obviously non-compliant" (43 of 71 cases, 61 %). One of the main reasons for "non-compliance" is explained below. Since WoE will be evaluated in a later stage of the project, all respective dossiers remained "complex" for RDT so far if not another waiving/adaptation was available being in "compliance" with the REACH criteria. The latter cases contributed in contrast to the conclusion "formally compliant".

The remaining waiving/adaptation categories contributed less to the endpoint conclusions (each < 5 % of all dossiers): This comprised the waiving/adaptation categories "exposure considerations", "technically not feasible" and "scientifically unjustified" (11 cases of non-GLP data or human data) as well as the fact that other waiving/adaptations were appropriate (wrong direct reference to REACH, meaningless justification, the IUCLID waiving flag "calculation" or reference to REACH Annex IV/V) or that a waiving justification was not available at all.

Figure 3-14: Repeated dose toxicity: Decisive waiving/adaptation categories and their contribution to the endpoint conclusions in formal check



To sum up, formal criteria were mostly fulfilled if the registrant applied a read-across approach. However, a considerable number of read-across cases were still not in conformity with the formal aspects. Further, the formal criteria developed here according to REACH Annexes VII to X column 2 were in most cases not fulfilled. More details are explained in the following.

Reasons for "non-compliance"

Information on why dossiers were allocated to the conclusion categories "formally non-compliant" and "obviously non-compliant" was documented during the check. From Figure 3-14 it could be revealed that this was specifically observed for certain waiving/adaptation categories. Table 3-9 gives an overview on the underlying reasons for the specific conclusions for the most important waiving/adaptations.

An inadequate **read-across approach** was most often the reason for "non-compliance". 860 waiving/adaptations from the total of 1493 accounted for read-across. Due to route-to-route extrapolation (48 cases based on read-across and were excluded), 812 read-across cases were actually examined. 50 cases of the examined read-across studies provided to fulfil the requirement of a 90-day study were referring to screening or short-term testing. These cases were categorised as "obviously non-compliant" (Table 3-9). Within the 860 read-across cases 233 were concluded as „formally non-compliant". Surprisingly often, the document or explanation on the read-across justification (category/similarity approach explanation) was not available. The explanation was usually given in particular assessment reports, in the CSR, in the endpoint summary or in the respective ESR. Another important fact was that the testing guideline could not be deduced or the exposure duration was not comparable.

Regarding read-across approaches for the 90-day study it was documented whether the study was conducted "according to" the respective OECD TG. In about half of all investigated read-across approaches the studies were flagged as "similar to" guideline, had no guideline entry or another guideline was specified (Annex 3 Table 6-1). Even if the read-across was "formally compliant", the latter two cases could potentially lead to more cases of "non-compliance". This would require a more detailed analysis which was not within the scope of the project (*e.g.* to determine whether all key parameters of the OECD TG were covered).

In total, 162 waiving cases accounted for REACH Annexes VII to X column 2 criteria ("**endpoint specific"**). In 16 datasets of investigated waiving/adaptations a chronic study was not available (although the column 2 justification was appropriate). Moreover, often the justification does not fully cover the criterions given in the REACH Annexes VII to X column 2 (43 cases).

An important argument which does not comply with REACH criteria for waiving the 90-day study was that minor studies (a screening or 28-day study which was not used for classification) showed no endpoint specific toxicity ("obviously non-compliant"). Here, 35 cases occurred and were allocated to the waiving category "**no reference**".

Table 3-9: Repeated dose toxicity: Main reasons for the allocation of particular waiving/adaptations to the conclusion categories "obviously non-compliant" and "formally non-compliant" in formal check

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number of waiving/ adaptations	Percentage [%] of all RDT waiving/ adaptations*
"Obviously non-compliant"	Read-across	read-across studies only based on screening (OECD TG 421 or 422) or short-term tests (*e.g.* 28-day study), those showed no adverse effects or showed adverse effects which were not used for a relevant classification and NOAEL extrapolation	50	3
	No reference	argumentation that minor studies (*e.g.* screening or 28-day studies) showed no endpoint specific toxicity	35	2
"Formally non-compliant"	Read-across	► similarity justification not available (220 cases)# ► key study not available (29 cases)# ► exposure duration in the key study was not comparable or guideline could not be deduced (55 cases)#	233	16
	Endpoint specific	► waiving according to REACH Annex IX 8.6.2. column 2, 2nd bullet point: chronic study (key study) is not available (but an appropriate justification) (16 cases) ► waiving according to REACH Annex IX 8.6.2. column 2, 3rd or 4th bullet point: not all criteria are addressed (27 cases)x	43	3

* Reference to 1493 investigated/missing waiving/adaptations.

More than one reason might apply for a particular case.

x Bullet point 3: Criterion 1: Substance undergoes immediate disintegration.
Criterion 2: There are sufficient data on the cleavage products.
Bullet point 4: Criterion 1: Substance is unreactive, insoluble and not inhalable.
Criterion 2: There is no evidence of absorption.
Criterion 3: There is no evidence of toxicity in a 28-day study.
It frequently occurred that only one criterion was addressed.

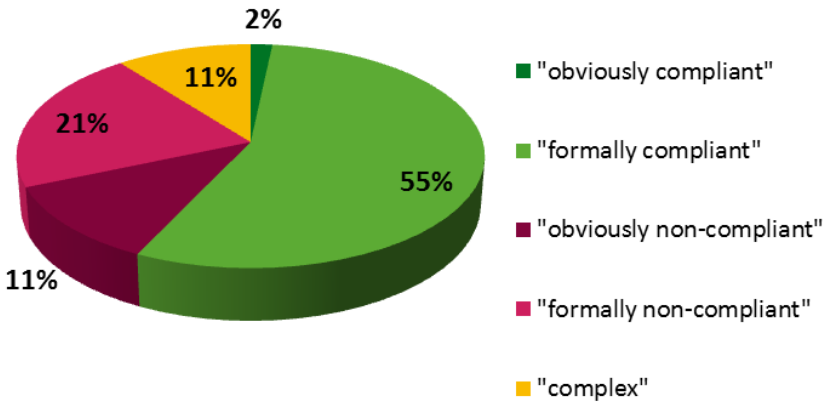
3.3.4 Mutagenicity

Muta requires standard information for different study types and testing has to be performed in a tiered approach depending on the respective outcome. Not all aspects that result from this rather comprehensive testing structure were verified and checked during the screening applied in project I. Therefore, simplifications and generalisations were introduced in the decision tree and the documentation of the checked data. One example might illustrate this: It was documented if read-across was available for the minimally required *in vitro* tests (GMbact and Cytvitro). However, the results of the surrogate studies were not evaluated in project I. Accordingly, the information obtained from project I was: an endpoint is "complex" because an adaptation is available for GMbact and Cytvitro. The formal check performed in this project included a more detailed analysis of the specific case, *e.g.* it could be deduced that read-across studies for both *in vitro* tests were negative and, as a consequence, a gene mutation test *in vitro* (GMvitro) had to be included as well.

Overall results

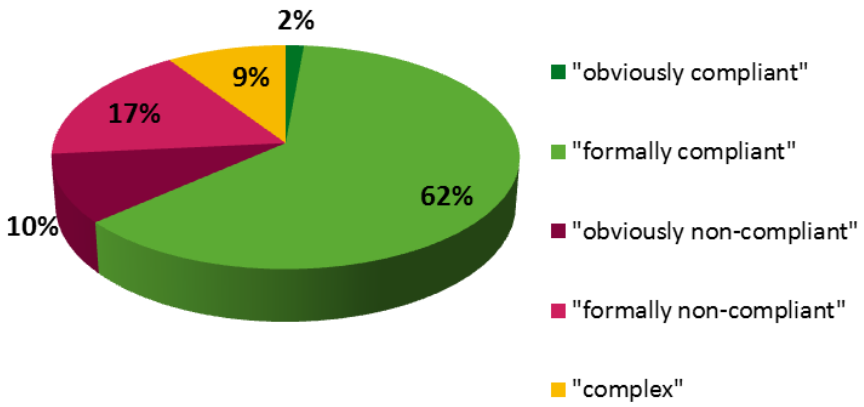
For Muta 653 dossiers with 1478 waiving/adaptations (Table 3-6) were analysed. 55 % of the dossiers fulfilled the formal requirements ("formally compliant") according to the approach applied in this project (Figure 3-15). 21 % of the dossiers were "formally non-compliant" and 11 % were regarded as "obviously non-compliant", which sums up to a total of 32 % of "non-compliant" cases. 11 % remained "complex" and 2 % were regarded as "obviously compliant". In comparison to the endpoint conclusions over all HH endpoints (Figure 3-8), Muta was the endpoint with the highest number of "formally compliant" and "obviously compliant" dossiers. Therefore, it contributed less to the conclusion categories "complex" and "obviously non-compliant" than the other HH endpoints.

Figure 3-15: Mutagenicity: Endpoint conclusions in formal check (total number: 653)



Related to the total number of waiving/adaptations, the number of "formally compliant" cases was even higher with 62 % of all waiving/adaptation conclusions (Figure 3-16). The percentage of "obviously non-compliant" cases was similar to those observed for the analysis of endpoint conclusions. Percentages of "formally non-compliant" and "complex" cases were slightly lower. Regarding the circumstances that usually a waiving/adaptation is applied for several required study types, these data indicate that for the majority of them formally acceptable waiving/adaptation approaches were available. However, as soon as one of the waiving/adaptations of a particular dossier did not fulfil the requirements or a conclusion could not be made, the whole endpoint for this dossier was regarded as "non-compliant" or "complex", respectively. This might explain the higher percentages of "obviously non-compliant", "formally non-compliant" and "complex" cases regarding the endpoint conclusion.

Figure 3-16: Mutagenicity: Conclusions over waiving/adaptations in formal check (total number: 1478)



Decisive waiving/adaptation categories for the endpoint conclusions

The next graph (Figure 3-17) intended to visualise two issues:

- Which waiving/adaptation categories were decisive for the endpoint conclusions?
- What was the distribution of the endpoint conclusions for a particular waiving/adaptation category?

Muta was the HH endpoint for which almost exclusively read-across was used as adaptation (Figure 3-10). Accordingly, this was also the predominant decisive category for the endpoint conclusions with 73 % (Figure 3-17). Second ranked the category "not available" with 8 %, which applied to the dossiers for which a waiving/adaptation was not available, but usually required for at least one of the study types. The waiving category "no reference" was decisive for 6 % of all checked dossiers, and "WoE" for 4 %. The contribution of other categories or combinations of categories was marginal with less than 2 % each.

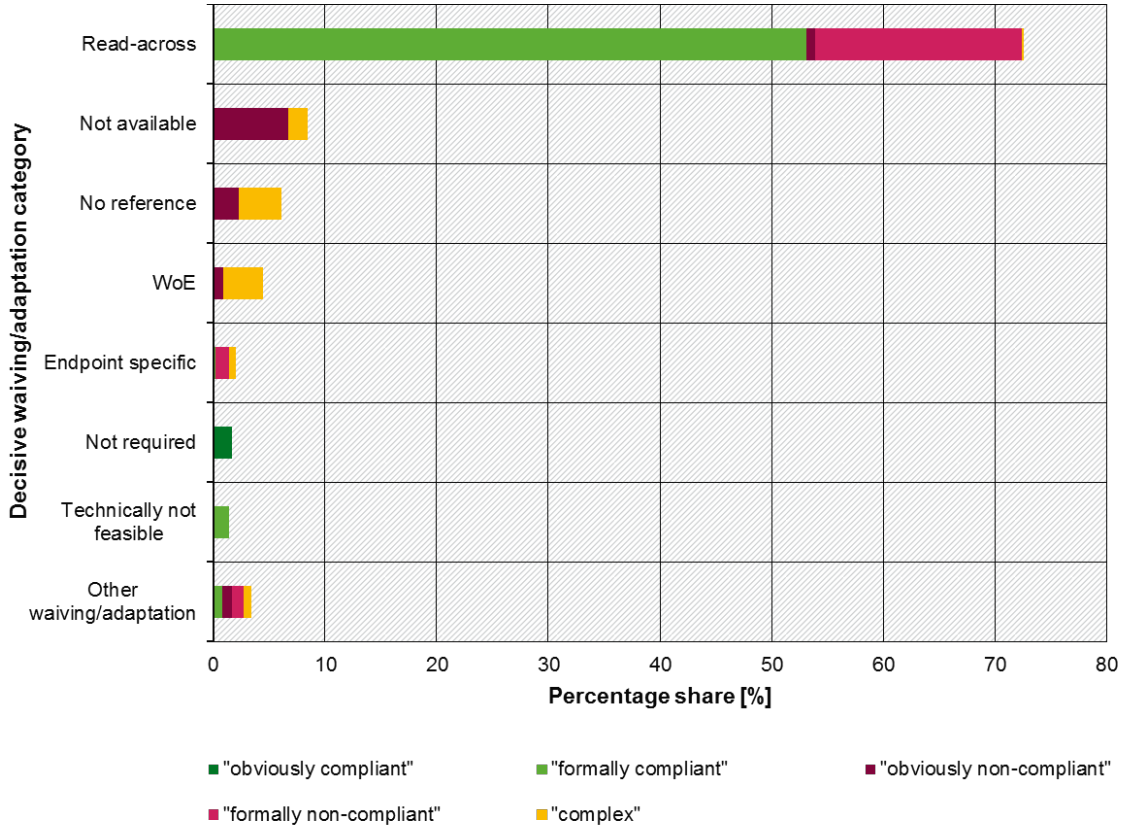
Eleven dossiers were observed for which waiving/adaptation was not required because adequate experimental studies were available. In four of these dossiers the study was performed with the anhydride of the substance and according to the ECHA guidance on identification and naming of substances, hydrated and anhydrous forms of a compound can be regarded as the same (ECHA, 2014a). Other registrants marked their key studies as read-across, although the registered substance was used. These dossiers were responsible for the presence of "obviously compliant" cases (contributing with 2 %) in Muta endpoint conclusions. Muta showed a conspicuously lower diversity of applied waiving/adaptation categories than *i.e.* DevTox and ReproTox.

The vast majority of read-across was concluded to be "formally compliant" (53 %). The remaining dossiers did mostly not fulfil the formal criteria for read-across (19 %). Obviously, most of the dossiers for which at least one waiving/adaptation was missing, were allocated to the category "obviously non-compliant". Eleven of these dossiers remained "complex" because expert judgement on the interpretation of ambiguous results in the presented experimental studies and on the necessity to perform, as a consequence, further *in vivo* studies would have been required. Approximately one third of the dossiers which used a waiving without reference to REACH Annexes were regarded as "obviously non-com-

pliant", while for two third no conclusion could be made. Most dossiers which based on WoE as the decisive adaptation category remained "complex". Minor decisive waiving/adaptation categories contributed to all endpoint conclusion categories.

In summary, read-across was the predominant adaptation category used by the registrants for Muta and formal criteria were fulfilled in most cases. However, read-across also essentially contributed to the number of "formally non-compliant" cases. In several dossiers, required waiving/adaptations were not available and this was the main reason for the conclusion "obviously non-compliant". Dossiers with justifications not referring to the options set out in the REACH Regulation also contributed to this category. Nevertheless, the bigger part of these cases requires a more detailed analysis of the given justification and remained "complex". Muta was the HH endpoint with highest number of dossiers for which waiving/adaptation was not required because appropriate standard studies were available. These were regarded as "obviously compliant".

Figure 3-17: Mutagenicity: Decisive waiving/adaptation categories and their contribution to the endpoint conclusions in formal check



Reasons for "non-compliance"

Similar to the other evaluated endpoints, for Muta the reasons why dossiers were allocated to the conclusions categories "formally non-compliant" and "obviously non-compliant" were analysed as well. From Figure 3-17 it could be revealed that this was specifically observed for certain waiving/adaptation categories. Table 3-10 gives an overview on the underlying reasons for the specific conclusions for these waiving/adaptations.

The **read-across approach** was in 224 adaptations from the total of 1109 waiving/adaptations "formally non-compliant" concerning the endpoint Muta. The predominant reason was that the explanation of (structural) similarity was missing. However, in a considerable number the exposure duration

in the key study was shorter than in the corresponding test method or not given. This especially applied to read-across approaches for GMbact. Also, no key study with a reliability of 1 or 2 was available in some dossiers.

Regarding the documentation whether read-across approaches for the required tests were conducted according to the respective OECD TG, it was observed that one third of all read-across were flagged as "similar to" the OECD TG, had no guideline entry or another guideline was specified (Annex 3 Table 6-1). Even if the read-across was "formally compliant", the latter two cases could potentially lead to more cases of "non-compliance". This would require a more detailed analysis which was not within the scope of the project (*e.g.* to determine whether all key parameters of the OECD TG were covered).

The main contributor to the conclusion category "obviously non-compliant" for Muta was that **waiving/adaptations were not available**, although required. This accounted for 51 cases. In several dossiers, registrants applied different free justifications that were obviously not in "compliance" with the REACH Regulation (28 cases), *e.g.* GMvitro was waived with the justification that GMbact and chromosomal aberration studies (Cytvitro or cytogenicity/micronucleus test *in vivo* (Cytvivo)) had negative results or it was just stated that the substance is not mutagenic or toxic without references. In 22 waiving/adaptations registrants referred to specific studies in the context of an (assumed) WoE approach, but the respective ESRs were not available. An additional reason for the conclusion category "obviously non-compliant" was that the given reference and justification did not match or no justification was available for the reference (23 cases).

A minor contributor to the conclusion "formally non-compliant" was the use of an "**endpoint specific**" waiving for *in vitro* studies using the argumentation that appropriate *in vivo* studies are available. However, acceptable key studies for the *in vivo* tests could not be identified.

Table 3-10: Mutagenicity: Main reasons for the allocation of particular waiving/adaptations to the conclusion categories "obviously non-compliant" and "formally non-compliant" in formal check

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number of waiving/ adaptations	Percentage [%] of all Muta waiving/ adaptations*
"Obviously non-compliant"	Not available	waiving/adaptation not available, but required	51	3
	Diverse	different free justification texts	28	2
	WoE, no reference	ESRs not available for studies which registrant refers to – (assumed) WoE approach	22	1
	Scientifically un- justified, endpoint specific	given reference and justification do not match or no justification given for reference	23	2
"Formally non-compliant"	Read-across	► similarity justification not available (116 cases)# ► key study not available (36 cases)# ► exposure duration in the key study was not comparable or not given (92 cases)#, especially observed for GMbact	224	15
	Endpoint specific	key study for respective *in vivo* test not available	14	1

* Reference to 1478 investigated/missing waiving/adaptations.

[#] More than one reason might apply for a particular case.

Decisive study types for the endpoint conclusions

The endpoint Muta requires experimental data for at least three study types. The *in vitro* tests for bacterial gene mutation (GMbact) and chromosomal aberration (Cytvitro) have to be conducted. If the results of both are negative, a gene mutation test in mammalian cells (GMvitro) has to be performed. If one of the *in vitro* tests is positive, data for the respective *in vivo* test have to be presented. This comprises a gene mutation test *in vivo* (GMvivo) and/or a study analysing chromosomal aberrations (Cytvivo). Depending on all available data, it might be necessary to perform an *in vivo* test with germ cells (also see Annex 7).

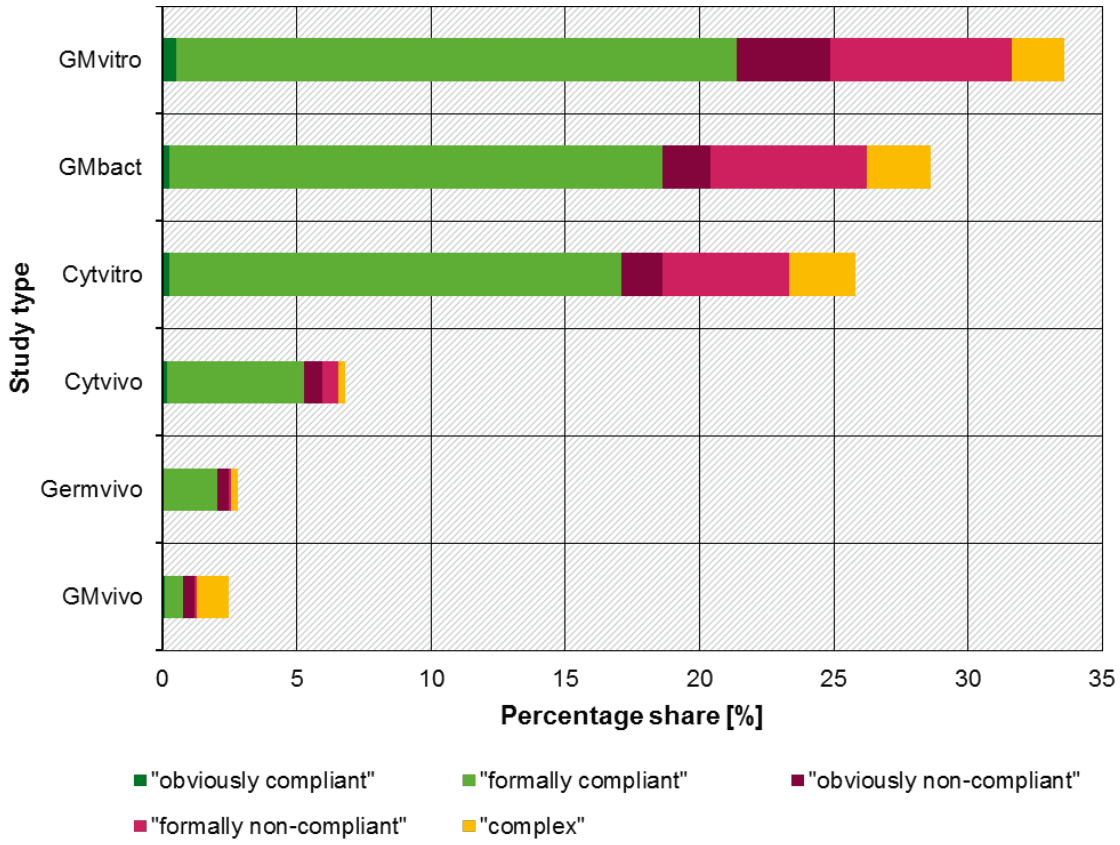
Therefore, it was of interest to analyse which study types were decisive for the endpoint conclusions and which distribution of conclusions could be observed for the study types. This was done for each single study type in relation to all decisive tests over all dossiers (Figure 3-18). In total, 1182 of the 1478 waiving/adaptations were decisive. An additional analysis addressed the decisive combinations of study types in relation to all 653 investigated dossiers (Figure 3-19).

One can see that GMvitro was the predominant study type for which experimental studies were not available and instead a waiving/adaptation was/had to be presented (Figure 3-18). It contributed with 34 % to the analysis of all decisive tests for the endpoint conclusions. Either it was the only waived study type or it was waived in combination with one or both of the other *in vitro* tests (Figure 3-19). In total, it contributed to 61 % of all endpoint conclusions.

Regarding the decisive single study types, GMbact and Cytvitro ranked second and third with 29 % and 26 %, respectively (Figure 3-18). Alone and in combination with other study types, each of them contributed to approximately half of all endpoint conclusions (Figure 3-19). All three *in vivo* tests were of minor importance with respect to the analysis of the contribution of single study types (Figure 3-18). The percentages were 7 % for Cytvivo, 3 % for Germvivo and 3 % for GMvivo. Nevertheless, Cytvivo, alone or in combination with other study types, was also a decisive factor for the endpoint conclusions in 12 % of all dossiers (Figure 3-19). Germvivo and GMvivo contributed with 5 % and 4 %, respectively.

If waiving/adaptations of *in vitro* tests were decisive for the endpoint conclusion, they were mostly “formally compliant” (Figure 3-18). However, several cases did not fulfil the formal criteria. This applied to approximately 5 % of decisive waiving/adaptations for each of the *in vitro* test. Notably, decisive waiving/adaptations for GMvitro had the highest percentage of “obviously non-compliant” cases (4 %) among all study types. Cytvitro and GMbact also contributed to this conclusion category, although only with a few cases (2 %, respectively). A minority of decisive waiving/adaptations remained “complex” for all *in vitro* tests and could not be finally concluded (2 to 3 %). “Obviously compliant” cases were rarely observed with percentages of 0.5 % or below. Decisive waiving/adaptations for Cytvivo and Germvivo predominantly contributed to “formally compliant” conclusions. If GMvivo comprised a decisive waiving/adaptation, which rarely occurred, these cases mostly remained “complex” or were concluded as “formally compliant”.

Figure 3-18: Mutagenicity: Contribution of single study types to the endpoint conclusions in formal check*



* given as percentage of 1182 waiving/adaptations for the different study types which is the sum of all waiving/adaptations which were decisive over all dossiers

In most dossiers, experimental studies for GMbact, Cytvitro and GMvitro were not available and waiving/adaptation was provided for all three *in vitro* tests. Therefore, a combination of these three tests was frequently decisive for the endpoint conclusion (Figure 3-19). The majority (20 % of all analysed dossiers) was “formally compliant”, but some (3 % of all analysed dossiers) were allocated to the conclusion category “formally non-compliant”.

Second ranked the situation that only the waiving/adaptation for GMvitro was decisive. That does not imply that there was no waiving/adaptation for another test, but this might have been not decisive regarding the endpoint conclusion. In accordance with the observation that GMvitro had the highest percentage of “obviously non-compliant” cases among all study types (Figure 3-18), it was the most important reason that the entire endpoint Muta was allocated to “obviously non-compliant” (6 % of all analysed dossiers) (Figure 3-19). Moreover, GMvitro also strongly contributed to the endpoint conclusion “formally non-compliant” with 5 % of all analysed dossiers. Summing up both conclusion categories, more than half of the dossiers for which GMvitro was decisive, were not in “compliance” with the REACH Regulation. This corresponds 11 % of all checked dossiers. The other half comprised all other conclusion categories, with “formally compliant” being the most prominent (6 % of all analysed dossiers).

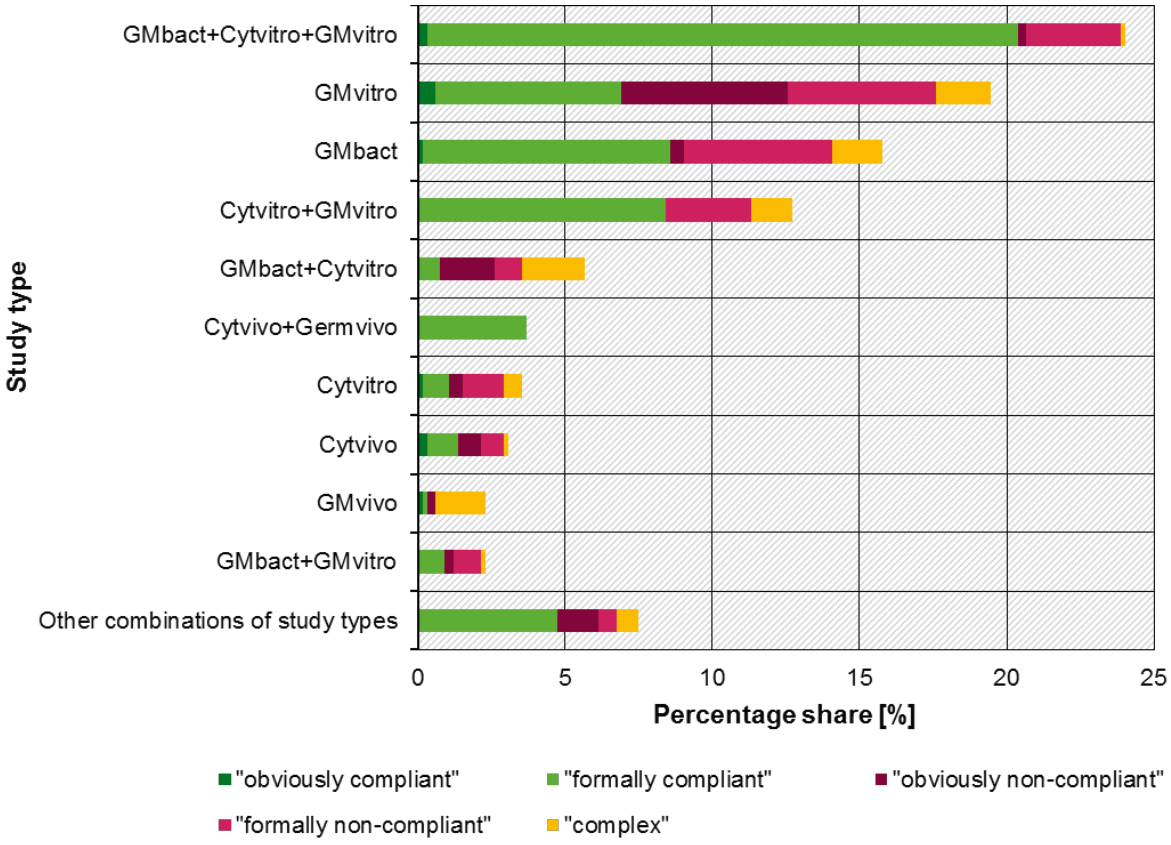
GMbact was the decisive study type in 16 % of all analysed dossiers. Half of the cases were concluded as “formally compliant”. However, GMbact also strongly contributed to “formally non-compliant” endpoint conclusions which might be explained by the high number of read-across approaches for which the exposure duration was not given (Table 3-10).

The combination Cytvitro+GMvitro was also frequently decisive (13 % of all analysed dossiers) and formal criteria were fulfilled in the majority of these dossiers (8 %, Figure 3-19). In contrast, the combination GMbact+Cytvitro strongly contributed to the conclusion categories “obviously non-compliant” and “complex” (2 % of all analysed dossiers, respectively). Interestingly, a combination of Cytvivo+Germvivo was responsible for the endpoint conclusion in 4 % of all dossiers and was always in “formal compliance” with the REACH criteria. Dossiers for which GMvivo was the only decisive study type mostly remained “complex” (2 % of all analysed dossiers). The remaining single study types or combinations contributed to all conclusion categories.

In general, Muta had the highest number of dossiers which were regarded as “formally compliant”. This might be due to the frequent application of read-across (Figure 3-17).

The presented results indicate that missing information on GMvitro was one of the main reasons for “formal non-compliance” of this endpoint. In addition, other reasons for “formal non-compliance” according to the REACH criteria were observed concerning read-across approaches which were applied for the three *in vitro* tests.

Figure 3-19: Mutagenicity: Decisive (combination of) study types for the endpoint conclusions in formal check*



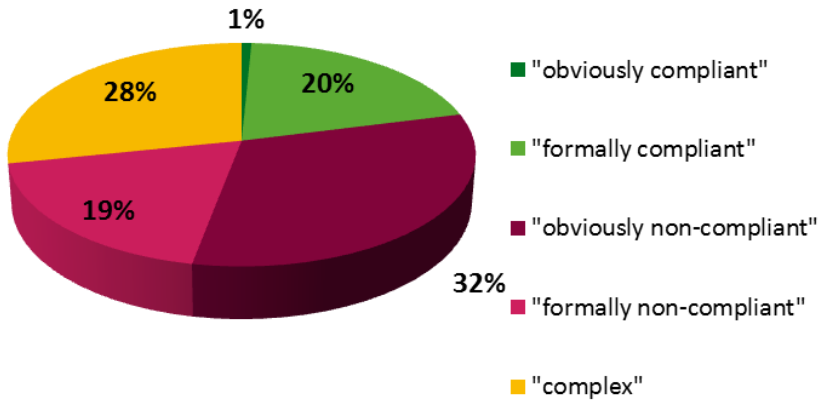
* given as percentage of all 653 analysed dossiers

3.3.5 Developmental toxicity

Overall results

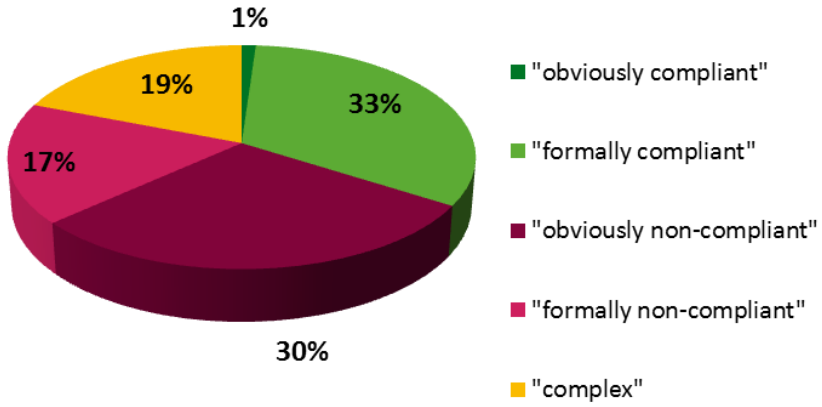
For DevTox 917 dossiers with 1547 waiving/adaptations (Table 3-6) were analysed. With respect to the endpoint conclusions, approximately half of the dossiers (51 %) did not fulfil the formal requirements according to REACH due to formal or, more frequently, due to obvious reasons (Figure 3-20). 20 % of the dossiers were regarded as "formally compliant", while 1 % was allocated to the conclusion category "obviously compliant". Less than one third remained without a conclusion ("complex"). In comparison to the endpoint conclusions over all HH endpoints (Figure 3-8), DevTox had considerably more endpoint cases which were regarded as "obviously non-compliant" and contributed less to the conclusion category "formally compliant".

Figure 3-20: Developmental toxicity: Endpoint conclusions in formal check (total number: 917)



A closer look on the total number of conclusions derived for each waiving/adaptation reveals that here the number of "formally compliant" cases was higher with 33 % at the expense of "complex" cases with 19 % (Figure 3-21). That indicates that in certain dossiers, the endpoint conclusion "non-compliant" was drawn, although a formally acceptable waiving/adaptation was available. DevTox requires studies or waiving/adaptations for two species. Therefore, this observation might be due to missing information for the second species, which was frequently noted and will be described in more detail in the following sections.

Figure 3-21: Developmental toxicity: Conclusions over waiving/adaptations in formal check (total number: 1547)



Decisive waiving/adaptation categories for the endpoint conclusions

The next graph (Figure 3-22) illustrates two issues:

- Which waiving/adaptation categories were decisive for the endpoint conclusions?
- What was the distribution of the endpoint conclusions for a particular waiving/adaptation category?

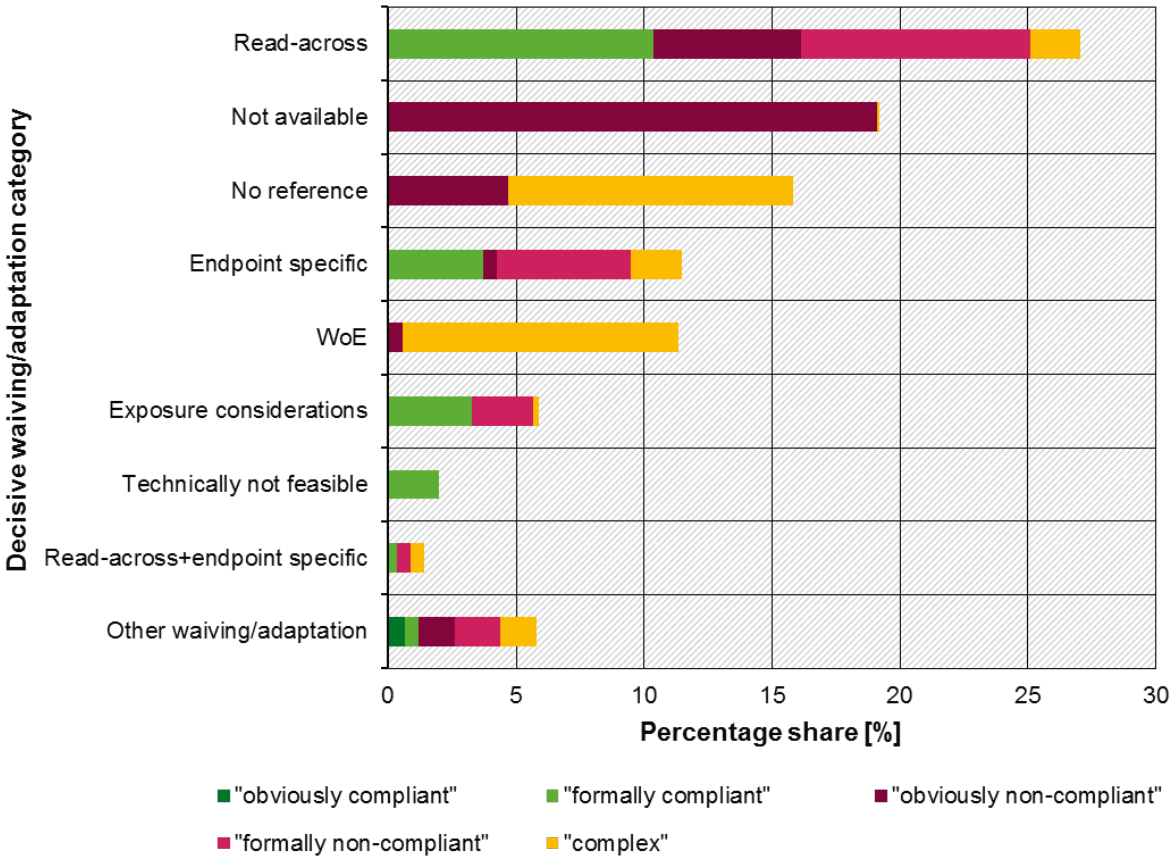
In accordance with the observation that read-across was the predominant waiving/adaptation category for DevTox (Figure 3-10), it also contributed most to the endpoint conclusions with 27 % (Figure 3-22). The categories “not available” and “no reference” ranked as second and third with 19 and 16 %, respectively. An “endpoint specific” argumentation as well as WoE approaches, applied by the registrants besides another waiving/adaptation, also considerably contributed with 12 % and 11 %, respectively. “Exposure considerations” with 6 %, “technically not feasible” with 2 % and the parallel approach of “read-across and endpoint specific” with 1.5 % were less frequently observed. The remaining categories or combinations of categories were of minor importance with a percentage of less than 1 % each (in sum 6 %).

The majority of the read-across approaches were concluded to be “non-compliant” due to formal (9 % of all waiving/adaptations) or obvious reasons (6 % of all waiving/adaptations). However, one third of all read-across cases fulfilled the formal criteria (10 % of all waiving/adaptations). Obviously, if required waiving/adaptations were not available, these endpoint cases were concluded as “obviously non-compliant” and they contributed most to this category. WoE approaches and “no reference” were the predominant waiving/adaptation categories which contributed to the conclusion category “complex”, but several cases were also regarded as “obviously non-compliant”. The categories “endpoint specific” and “exposure considerations” were frequently “formally compliant” or “formally non-compliant”. In contrast, “technically not feasible” only contributed to “formally compliant” cases. No conclusion category dominated for the remaining waiving/adaptation categories.

To sum up, formal criteria were often fulfilled if the registrant applied a read-across approach, argued according to an endpoint specific criterion of column 2, if exposure considerations were present or studies were waived due to technical reasons. However, a considerable number of cases of these waiving/adaptation categories, except “technically not feasible”, were not in conformity with formal requirements. Additionally, a smaller number of read-across approaches was “obviously non-compliant”.

The conclusion category "obviously non-compliant" represented the majority, if required waiving/adaptations were not available. Moreover, cases with "no reference" contributed as "obviously non-compliant" to the decisive waiving/adaptation category. Here, registrants used a "free" justification for waiving, *i.e.* they did not refer to the concrete options set out in Annex XI or Annexes VII to X column 2 of the REACH Regulation. Approximately 30 % of these dossiers remained without conclusion. This applied to waiving/adaptation categories for which no formal criteria could be derived from the REACH Regulation, *e.g.* if a WoE approach was presented in addition to another waiving/adaptation or the registrant gave a "free" justification (category "no reference") which appeared reasonable and was not allocated to "non-compliant" due to an obvious weakness in the argumentation.

Figure 3-22: Developmental toxicity: Decisive waiving/adaptation categories and their contribution to the endpoint conclusions in formal check



Reasons for "non-compliance"

It was of interest to obtain more information on why dossiers were allocated to the conclusion categories "formally non-compliant" and "obviously non-compliant". From Figure 3-22 it could be revealed that this was specifically observed for certain waiving/adaptation categories. Table 3-11 gives an overview on the underlying reasons for the specific conclusions for these waiving/adaptations.

The **read-across approach** was most frequently affected. Half of those based on screening or short-term tests and were allocated to the category "obviously non-compliant" (Table 3-11). The other half was regarded as "formally non-compliant", mostly due to missing similarity justifications or key studies.

During the analysis it was additionally documented whether read-across studies for OECD TG 414 were (fully) conducted according to this testing guideline, *i.e.* it was noted if registrants stated that the study was performed similar to the OECD TG (descriptor "sim guide"), according to another guideline

(descriptor "oth guide") or without specification of a guideline (descriptor "no guide") (Annex 3 Table 6-1). For DevTox, the three options applied to 51 % (273 cases) of all read-across approaches for OECD TG 414. Even if the read-across was "formally compliant", the latter two cases could potentially lead to more cases of "non-compliance". This would require a more detailed analysis which was not within the scope of the project (*e.g.* to determine whether all key parameters of the OECD TG were covered).

The most frequent reason for concluding that waiving/adaptation cases were "obviously non-compliant" was that **testing in a second species was not addressed** (174 cases). From 201 waiving for which registrants used "**no reference**", 55 were allocated to this conclusion category, because the insufficient argumentation was presented that minor studies showed no toxicity. An additional reason for the conclusion category "obviously non-compliant" was that the **given reference and justification did not match or no justification was available for the reference** (32 cases). In several dossiers, registrants applied different free justifications that were obviously not in "compliance" with the REACH Regulation (12 cases), *e.g.* that the substance is similar to rock and, therefore, not developmentally toxic.

With respect to the conclusion category "formally non-compliant", the waiving categories "**endpoint specific**" and "**exposure considerations**" were notable contributors in addition to read-across. For 84 cases in which registrants intended to waive data according to REACH Annex X 8.7. column 2, 3rd bullet point, not all relevant criteria were properly addressed in the justification. Especially criterion 3 (there is no significant human exposure) was rarely discussed. Also, almost one third of all waiving with "exposure considerations" had formal deficiencies (19 cases), mostly because only criterion 1 was addressed, while an explanation of the other criteria was not available.

Table 3-11: Developmental toxicity: Main reasons for the allocation of particular waiving/adaptations to the conclusion categories "obviously non-compliant" and "formally non-compliant" in formal check

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number of waiving/ adaptations	Percentage [%] of all DevTox waiving/adaptations*
"Obviously non-compliant"	Not available	Waiving/adaptation not available for test in a second species	174	11
	Read-across	Read-across are studies only based on screening (OECD TG 421 or 422) or short-term tests (*e.g.* 90-day study), those showed no adverse effects or adverse effects which were not used for a relevant classification and NOAEL extrapolation	121	8
	No reference	Argumentation that minor studies (*e.g.* screening or 90-day studies) showed no endpoint specific toxicity	55	4
	Scientifically un-justified, endpoint specific	Given reference and justification do not match or no justification given for reference	32	2
	Diverse	Different free justification texts	12	1
"Formally non-compliant"	Read-across	► similarity justification not available (81 cases)# ► key study not available (51 cases)# ► exposure duration in the key study was not comparable or not given (11 cases)#	125	8
	Endpoint specific	Waiving according to REACH Annex X 8.7. column 2, 3rd bullet point ► at least one of the three criteria described there was not addressed in the justification[x]	84	5
	Exposure considerations	Waiving according to REACH Annex XI 3.2.(a) ► none or not all criteria listed (XI 3.2. (a)) were addressed in the justification[§] (this mostly applied to criteria 2 and 3), for 16 cases exposure scenarios were given	19	1

* Reference to 1547 investigated/missing waiving/adaptations.

More than one reason might apply for a particular case.

[x] Criterion 1: Substance is of low toxicological activity (regarding all endpoints).
Criterion 2: No systemic absorption occurs via relevant routes of exposure.
Criterion 3: There is no significant human exposure.
It frequently occurred that only one criterion was addressed. In most cases a description/discussion for criterion 3 was not available.

[§] Criterion 1: Absence of or no significant exposure.
Criterion 2: DNEL or PNEC can be derived from results of available test data.
Criterion 3: Exposures are always well below DNEL/PNEC.

Decisive study types for the endpoint conclusions

Usually, DevTox requires experimental data for two species, a rodent and a non-rodent species. In most "complex" dossiers neither of these studies was available (Springer et al., 2015).

In this regard, one frequent observation was that registrants used a more "general" justification for data waiving which was independent of the species. This applies to waiving categories such as "technically not feasible", "endpoint specific", "exposure considerations" or justifications with "no reference". In the context of this examination, this kind of "general" waiving/adaptation was regarded to count as waiving/adaptation for both species. It was the predominant contributor to the endpoint conclusion with approximately 46 %, as can be revealed from Figure 3-23.

The first species was the decisive study type if only an insufficient or non-assignable read-across approach for one species was presented by the registrant. This comprised 14 % of the investigated dossiers. At the same time, a waiving/adaptation for the second species was missing as well in these dossiers. However, this was not regarded as decisive because the performance of a study in a second species depends on the outcome in the first species.

In 13 % of all investigated "complex" dossiers, a waiving/adaptation was declared for each species and, at the same time, both contributed to the endpoint conclusion, *e.g.* both were formally acceptable or both were formally not in "compliance" with the REACH requirements.

In 28 % of the dossiers, the second species alone was decisive for the endpoint conclusion. This comprised dossiers in which an adequate study was available for one species and testing in the second species was waived/adapted **or** the waiving/adaptation for the first species was formally acceptable but the waiving/adaptation for the second species was not sufficient or not available. The latter was the predominant observation.

From these data, one can deduce that in approximately 20 % of all investigated dossiers registrants specifically waived/adapted studies for two species, while in the remaining 80 % this was not observed.

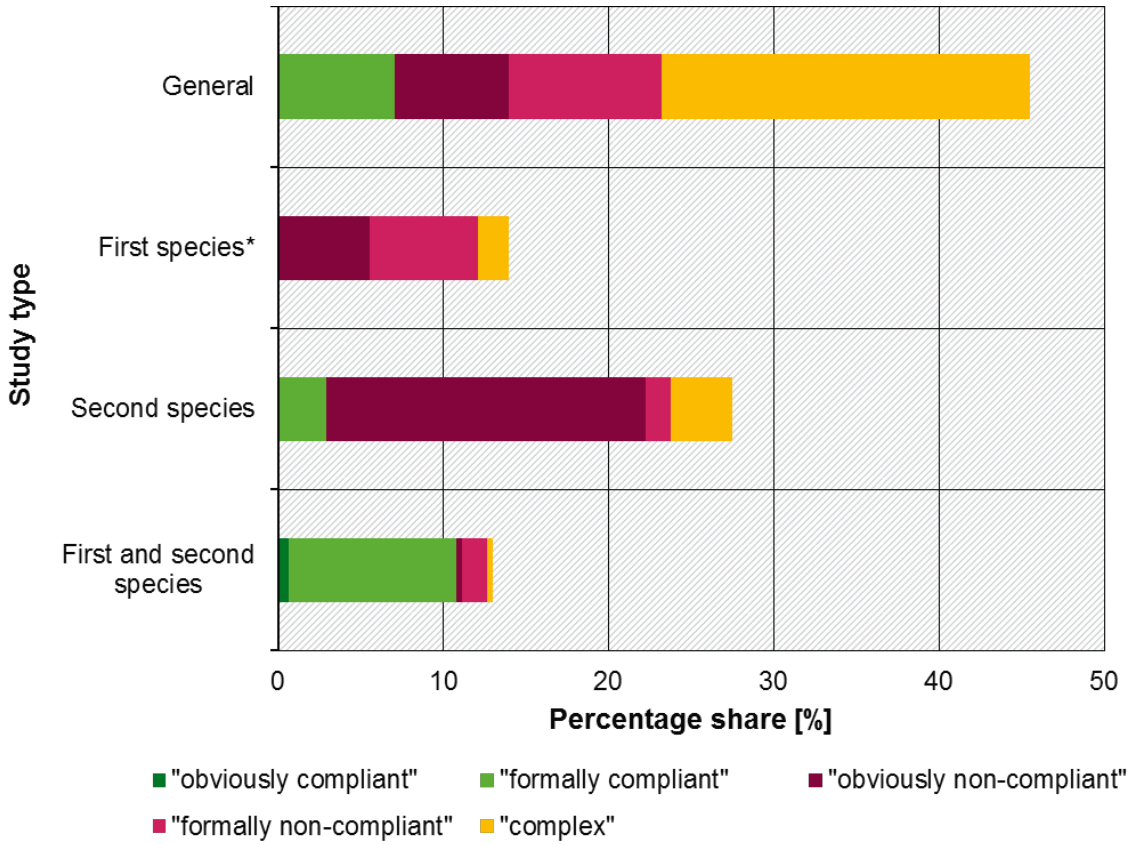
With respect to the endpoint conclusions, approximately half of the dossiers with a "general" waiving/adaptation were allocated to "complex" and were, therefore, the major contributors to this conclusion category. This is due to the frequent application of "WoE" and justifications with "no reference". The other half comprised more or less in equal parts the conclusion categories "formally compliant", "formally non-compliant" or "obviously non-compliant". The reasons for "non-compliance" were already described in the preceding chapter and in Table 3-11.

As already mentioned earlier, an insufficient or non-assignable read-across approach for one species was present if the first species was concluded to be the decisive study type. The reasons for "non-compliance" can be found in in the preceding chapter and in Table 3-11. For the vast majority of the dossiers for which the second species was the decisive study type, waiving/adaptation of a study on the second species was not available and the dossiers were allocated to the conclusion category "obviously non-compliant" (19 % of all endpoint conclusions). Interestingly, for dossiers with a specific waiving/adaptation for two species, the highest number of "formally compliant" cases was observed (10 % of all endpoint conclusions). This was for almost all dossiers due to formally acceptable read-across approaches.

In summary, one can say that mainly a "general" waiving/adaptation was applied for DevTox and that this often requires a more in-depth analysis of the justification. Specifically two species are rarely addressed in dossiers. However, due to the application of appropriate read-across approaches, these dossiers are usually in "formal compliance" with REACH. Although the applied approach did not allow for the examination of more complex waiving/adaptation approaches in detail, it was sufficient to prove

that in a high number of dossiers (especially those applying read-across), a specific waiving/adaptation for the second species was not available.

Figure 3-23: Developmental toxicity: Decisive study types for the endpoint conclusions in formal check*



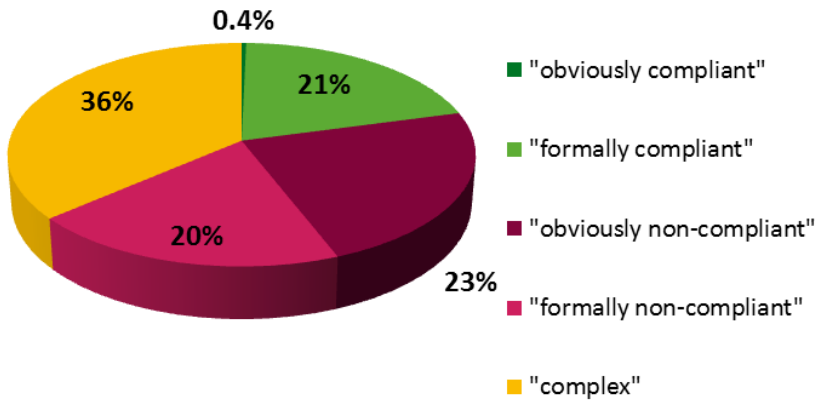
* Waiving/adaptation for the study on the second species is also not available, however, performance of a study in a second species depends on the outcome in the first species. Therefore, the study on the first species was regarded as the decisive study type.

3.3.6 Reproductive toxicity

Overall results

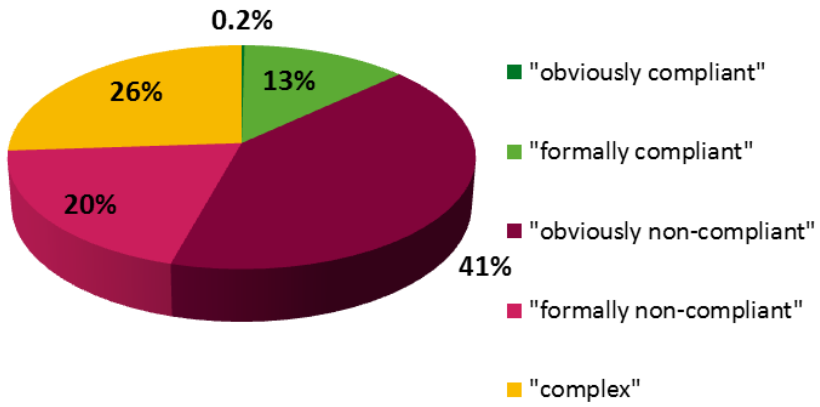
For ReproTox 1133 dossiers with 1791 waiving/adaptations were analysed. With respect to the endpoint conclusions, only 21 % of the dossiers fulfilled the formal requirements ("formally compliant") according to the approach applied in this project (Figure 3-24). 20 % of the dossiers were "formally non-compliant" and 23 % were regarded as "obviously non-compliant", which sums up to a total of 43 % of "non-compliant" cases. 36 % remained without conclusion and four "obviously compliant" cases were observed (results in 0.4 %). In comparison to the endpoint conclusions over all HH endpoints (Figure 3-8), ReproTox had essentially less endpoint cases which were regarded as "formally compliant" and especially contributed to "complex" cases.

Figure 3-24: Reproductive toxicity: Endpoint conclusions in formal check (total number: 1133)



Related to the total number of waiving/adaptations, the number of "obviously non-compliant" cases almost doubles and together with "formally non-compliant" cases sums up to 61 % of all waiving/adaptation conclusions (Figure 3-25). This occurred at the expenses of "formally compliant" and "complex" cases and indicates that in several dossiers, a "compliant" or "complex" and a "non-compliant" waiving/adaptation were available at the same time. The endpoint conclusion was then derived from the "compliant" or "complex" waiving/adaptation.

Figure 3-25: Reproductive toxicity: Conclusions over waiving/adaptations in formal check (total number: 1791)



Decisive waiving/adaptation categories for the endpoint conclusions

In the next graph (Figure 3-26) the following two issues are addressed:

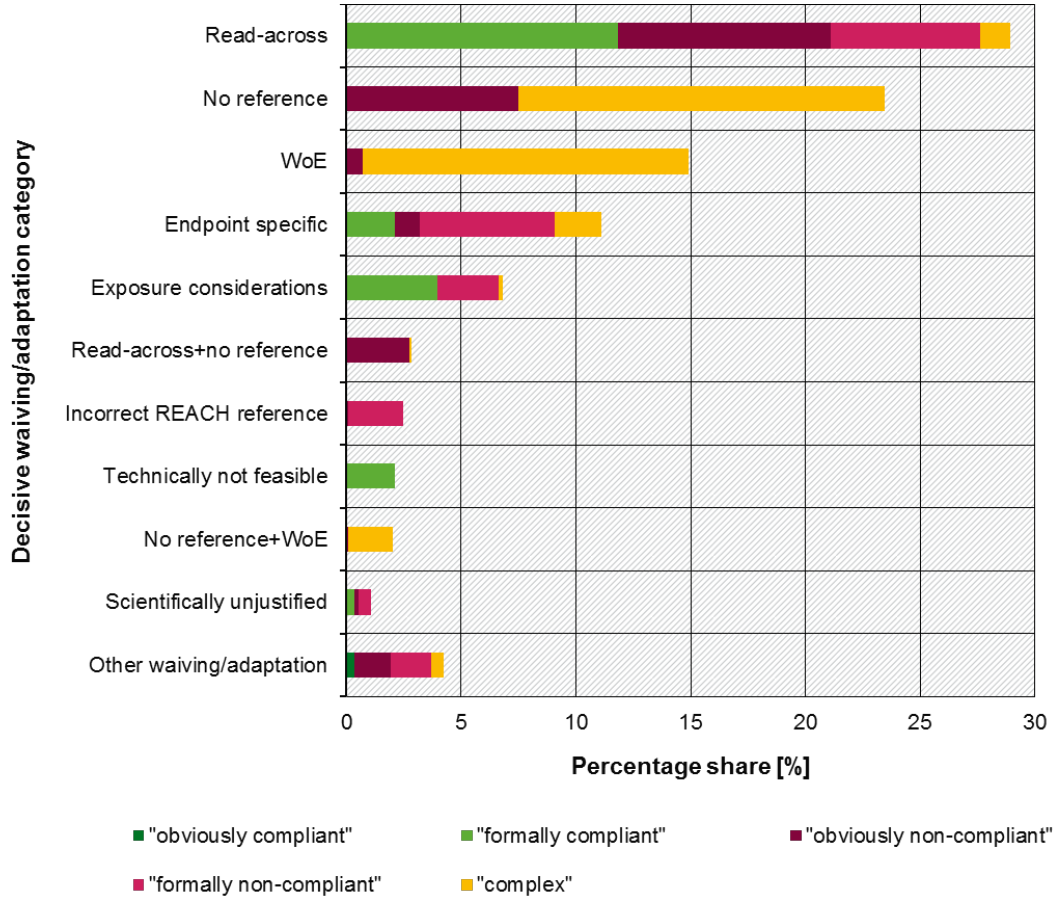
- Which waiving/adaptation categories were decisive for the endpoint conclusions?
- What was the distribution of the endpoint conclusions for a particular waiving/adaptation category?

In accordance with the observation that read-across was the most frequent waiving/adaptation category for ReproTox (Figure 3-10), it also contributed most to the endpoint conclusions (Figure 3-26) with 29 %. The category "no reference" ranked as second with 23 %. WoE approaches which were applied in addition to other waiving/adaptations were decisive for the endpoint conclusion in 15 % of all dossiers. "Endpoint specific" reasons contributed with 11 % and "exposure considerations" with 7 %. Other categories or combinations of categories contributed with less than 3 % which corresponds to a number of approximately 30 dossiers and less.

Read-across was frequently concluded to be "formally compliant" (12 %). However, most waiving/adaptations of this category did not fulfil the formal criteria (7 %) or were "non-compliant" due to obvious reasons (9 %). One third of all dossiers which belong to the category "no reference" were allocated to the conclusion "obviously non-compliant", while two third remained "complex". The vast majority of dossiers with a WoE approach could also not be concluded, except eight cases which were "non-compliant" due to obvious reasons. "No reference" and "WoE" were the waiving/adaptation categories which contributed most to the conclusion category "complex". Almost two third of the dossiers with "endpoint specific" reasons for waiving of experimental studies were "non-compliant", especially due to formal reasons. In contrast, dossiers with "exposure considerations" predominantly had "formally compliant" waiving, although several cases were observed which were not in accordance with the REACH Regulation. Among the minor waiving/adaptation categories particular endpoint conclusions contributed specifically to certain waiving/adaptation categories. "Read-across+no reference" were almost always concluded as "obviously non-compliant", "incorrect REACH references" as "formally non-compliant", "technically not feasible" as "formally compliant" and "no reference+WoE" as "complex".

To sum up, formal criteria were frequently fulfilled if registrants applied a read-across approach for ReproTox. This was also observed for "exposure considerations" and for all dossiers with the justification "technically not feasible". However, read-across also essentially contributed to the number of "obviously non-compliant" cases. As already observed for DevTox, one of the waiving/adaptation categories with the highest number of "obviously non-compliant" cases was "no reference". This waiving/adaptation, together with WoE approaches, also made up the majority of cases which could not be concluded. The conformity with formal criteria for ReproTox was often not given if registrants justified waiving according to criteria set out in REACH Annexes VII to X column 2. Several cases with "read-across" and "exposure considerations" were also not formally in "compliance".

Figure 3-26: Reproductive toxicity: Decisive waiving/adaptation categories and their contribution to the endpoint conclusions in formal check



Reasons for "non-compliance"

In order to obtain more detailed insights into why dossiers were allocated to the conclusion categories "formally non-compliant" and "obviously non-compliant" the main reasons were gathered (Table 3-12). The relevant waiving/adaptation categories and corresponding reasons were in most parts the same as for DevTox (Table 3-11).

The **read-across approach** was most often affected. 635 waiving/adaptations from the total of 1791 accounted for read-across. From those 355 cases only based on screening or short-term tests instead of a two-generation study and were, therefore, allocated to the category "obviously non-compliant" (Table 3-12). 105 cases were regarded as "formally non-compliant", mostly due to missing similarity justifications and key studies.

Regarding the documentation whether read-across approaches for OECD TG 416 were conducted according to this guideline, in 41 % the studies were flagged as "similar to" guideline, had no guideline entry or another guideline was specified (Annex 3 Table 6-1). Even if the read-across was "formally compliant", the latter two cases could potentially lead to more cases of "non-compliance". This would require a more detailed analysis which was not within the scope of the project (*e.g.* to determine whether all key parameters of the OECD TG were covered).

From 465 waiving for which registrants used "**no reference**", 203 cases were concluded as "obviously non-compliant" because of the insufficient argumentation that minor studies showed no toxicity. An additional reason for the conclusion category "obviously non-compliant" was that the given reference and justification did not match or no justification was available for the reference (67 cases). In several dossiers, registrants applied different free justifications that were obviously not in "compliance" with the REACH Regulation (32 cases). Some of these justifications were repeatedly observed, *e.g.* that the substance is similar to rock and, therefore, not toxic to reproduction. Another example was that the registrant used a read-across and referred to a study with n-hexane (harmonised classification as reproductive toxin category 2 for fertility) which showed no toxic effects to reproduction and, therefore, no classification was proposed.

119 cases of the "**endpoint specific**" waiving were concluded as "formally non-compliant", because not all relevant criteria of REACH Annex X 8.7. column 2, 3rd bullet point were properly addressed in the justification. Especially criterion 3 (there is no significant human exposure) was rarely discussed. In 44 cases, registrants incorrectly referred to REACH Annex IX 8.7.3., although Annex X 8.7.3. applies to substances manufactured or imported in quantities of ≥ 1000 tpa. Here, a two-generation study had to be conducted (please keep in mind that the dossier list was compiled in March 2014), even if the results of RDT studies did not trigger it. Almost one third all waiving with "**exposure considerations**" had formal deficiencies (26 cases), mostly because only criterion 1 was addressed, while an explanation of the other criteria was not given.

Table 3-12: Reproductive toxicity: Main reasons for the allocation of particular waiving/adaptations to the conclusion categories "obviously non-compliant" and "formally non-compliant" in formal check

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number of waiving/ adaptations	Percentage [%] of all ReproTox waiving/adaptations*
"Obviously non-compliant"	Read-across	Read-across are studies only based on screening (OECD TG 421 or 422) or short-term tests (*e.g.* 90-day study), those showed no adverse effects or showed adverse effects which were not used for a relevant classification and NOAEL extrapolation	355	20
	No reference	Argumentation that minor studies (*e.g.* screening or 90-day studies) showed no endpoint specific toxicity	203	11
	Scientifically un-justified, endpoint specific	Given reference and justification do not match or no justification given for reference	67	4
	Diverse	Different free justification texts	32	2
"Formally non-compliant"	Endpoint specific	Waiving according to REACH Annex X 8.7. column 2, 3rd bullet point ► at least one of the three criteria described there was not addressed in the justification[x]	119	6
	Read-across	► similarity justification not available (65 cases)[#] ► key study not available (53 cases)[#] ► exposure duration was not comparable/not given or guideline could not be deduced (12 cases)[#]	105	6
	Incorrect REACH reference	Waiving according to REACH Annex IX 8.7.3. (two-generation study required if RDT studies indicate adverse effects on reproductive organs or tissues)	44	2
	Exposure considerations	Waiving according to REACH Annex XI 3.2.(a) ► none or not all criteria listed (XI 3.2. (a)) were addressed in the justification[§] (this mostly applied to criteria 2 and 3), for 22 cases exposure scenarios were available	26	1

* Reference to 1791 investigated waiving/adaptations.

[#] More than one reason might apply for a particular case.

[x] Criterion 1: Substance is of low toxicological activity (regarding all endpoints).
Criterion 2: No systemic absorption occurs via relevant routes of exposure.
Criterion 3: There is no significant human exposure.
It frequently occurred that only one criterion was addressed. In most cases a description/discussion for criterion 3 was not available.

[§] Criterion 1: Absence of or no significant exposure.
Criterion 2: DNEL or PNEC can be derived from results of available test data.

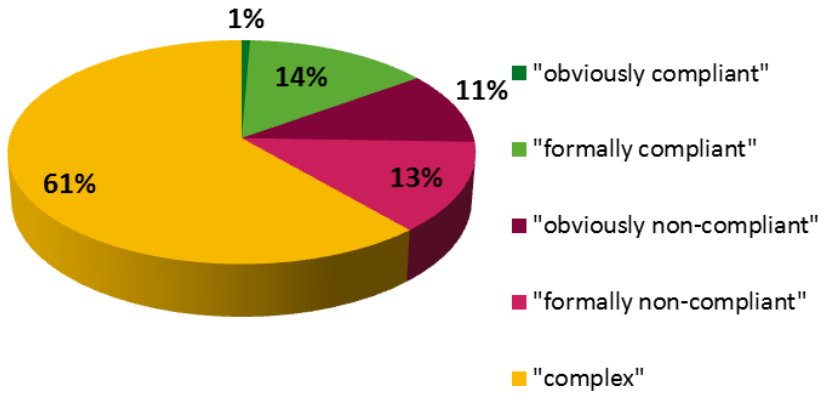
Criterion 3: Exposures are always well below DNEL/PNEC.

3.3.7 Overall results of environmental endpoints

The endpoint conclusion was often based on several waiving justifications or adaptations for different tests. If more than one test was required to fulfil the information requirements of an ENV endpoint, as it is the case for BioDeg, AbioDeg and Ecotox, an overall conclusion was made. In total, the formal check of the ENV endpoint sample comprised 3370 endpoint conclusions: 533 for BioDeg, 1029 for AbioDeg, 315 for Bioaccu and 1493 for Ecotox.

An overview of all ENV endpoint conclusions is shown in Figure 3-27. Here, 14 % of all ENV endpoint conclusions were classified as "formally compliant" and 1 % as "obviously compliant", whereas 11 % were assigned to "obviously non-compliant" and 13 % to "formally non-compliant", respectively. However, 61 % were not concluded and remained without conclusion ("complex") (Figure 3-27). The reasons behind the high rate of "complex" endpoint conclusions are described in more detail in the following chapters (chapter 3.3.8, 3.3.9 and 3.3.10).

Figure 3-27: Environment: Conclusions over all endpoint decisions in formal check (total number: 3370)



The results for all checked ENV waiving/adaptations (8032 cases) are summarised in Figure 3-28. First, more than half of the ENV waiving/adaptations (53 %) remained in the "complex" category. Second, the "obviously non-compliant" (7 %) and formally non-compliant" (19 %) ENV waiving/adaptations summate to 26 %. Third, 21 % of all ENV waiving/adaptations were concluded to be "formally compliant".

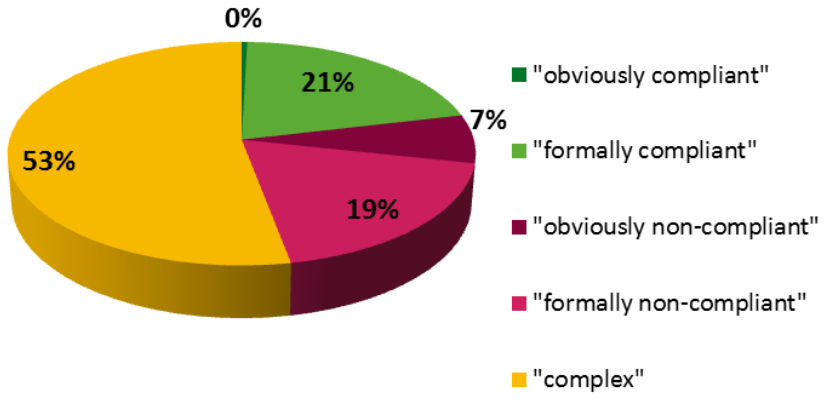
The percentage of "complex" waiving/adaptations is 7 % lower (53 %) than the "complex" ENV endpoint decisions with 61 % (Figure 3-28). The slightly higher percentage of "complex" ENV endpoint conclusions arose from the fact that at least one "complex" waiving/adaptation for the tests required occurred, assuming that the other tests complied with the developed formal criteria according to REACH or were not obligatory.

In comparison, the percentage of the "formally compliant" ENV waiving/adaptations with 21% was higher than in comparison to the "formally compliant" ENV endpoints with 14 %. However, this rather slight difference is apparent because all tests and/or ENV waiving/adaptations have to comply with the developed formal criteria according to REACH for being concluded as "formally compliant" regarding the ENV endpoint, finally.

Despite this, the differences in the percentages of "obviously non-compliant" and "formally non-compliant" conclusions between waiving/adaptations (7 % and 19 %) and ENV endpoints (11 % and

13 %) cannot be explained in one way. On the one hand, when alternatively another ENV waiving/adaptation for the same test was offered by the registrant (or this was deduced during the examination), which resulted in "formally compliant", "obviously compliant" or "complex" in itself, the overall ENV endpoint conclusion could also depend on the alternative waiving/adaptation. Accordingly, on the other hand when an alternative approach was not available or was concluded to be "obviously non-compliant" or "formally non-compliant", the ENV endpoint conclusion was either "obviously non-compliant" or "formally non-compliant".

Figure 3-28: Environment: Conclusions over all waiving/adaptations in formal check (total number: 8032)



Indication of the waiving/adaptation categories applied by the registrant should be clearly stated. Considering all ENV endpoints, the waiving or adaptation approach was clearly stated in 64 % of the available waiving/adaptations. Accordingly, the followed approach had to be deduced during the assessment in 36 % of the overall available waiving/adaptations. The proportion of proposed and deduced waiving/adaptation is given in Table 3-13 for all ENV endpoints.

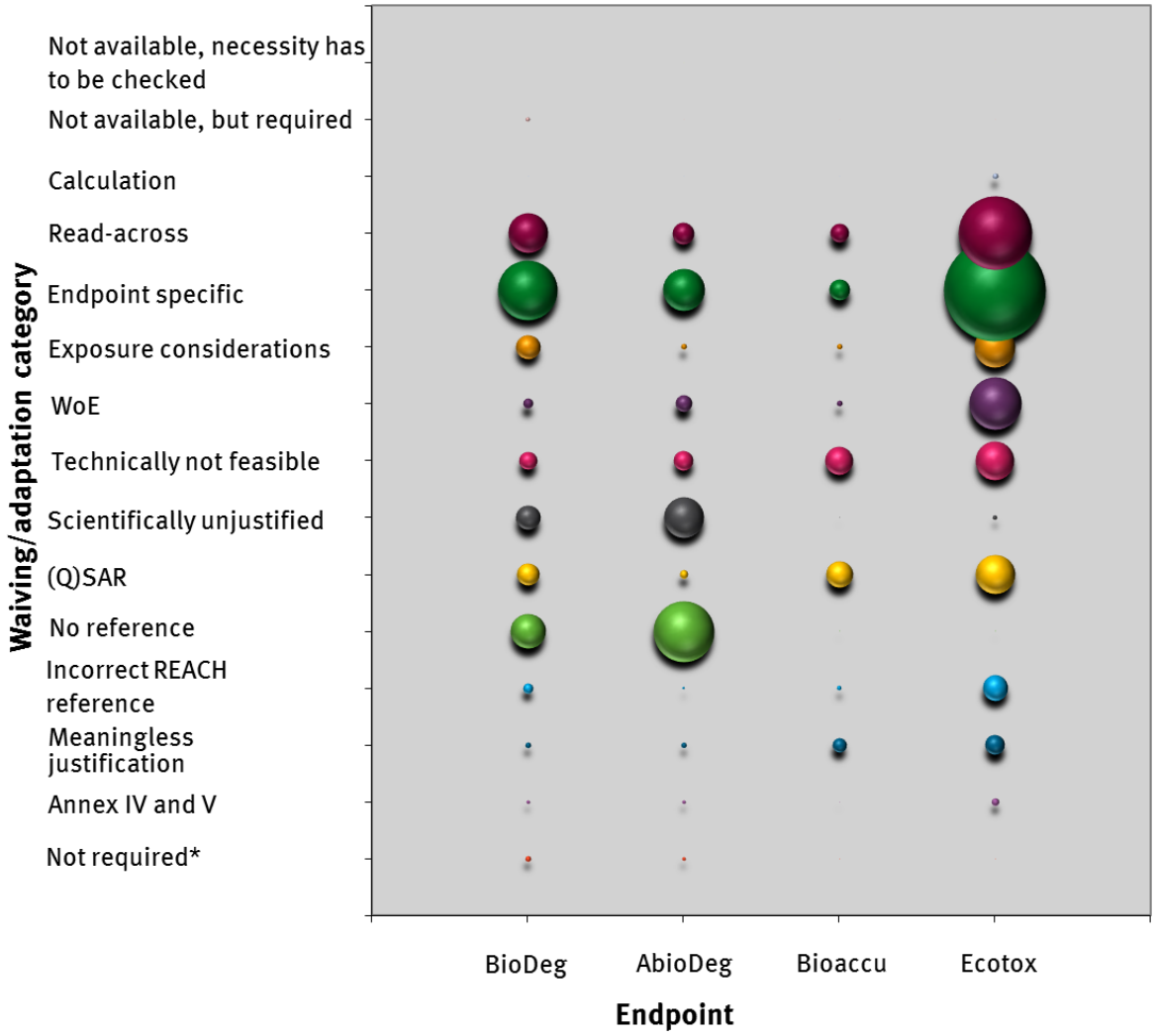
Table 3-13: Environment: Overview whether REACH reference was given by the registrant or deduced within the examination for each endpoint in formal check - excluding read-across approaches and cases with a missing waiving/adaptation

ENV endpoint	Reference given by registrant		Reference deduced within examination	
	n	[%]	n	[%]
BioDeg	447	31	1010	69
AbioDeg	699	50	709	50
Bioaccu	149	35	273	65
Ecotox	3504	84	683	16
Total/Mean	**4799**	**64**	**2675**	**36**

The frequency of waiving/adaptation categories applied by registrants for all ENV endpoints is presented in Figure 3-29. This figure includes all waiving/adaptations either directly proposed by the registrants or finally deduced during the examination. For the endpoint BioDeg and Ecotox the most frequently applied approach were endpoint specific criteria. The highest amount of waiving justifications

was neither related to certain criteria of REACH Annex VIII 9.2.2. column 2, nor to Annex XI for the endpoint AbioDeg. In general, these non-referenced cases usually had to be deduced during the investigation and were summarised in the category "no reference". Here, in-depth analysis is required whether the justification to omit testing might comply with the last paragraph of the introduction into REACH Annex VIII. The main waiving/adaptation categories for the endpoint Bioaccu based either on REACH Annex XI 2. – testing is technically not feasible (128 cases) or on REACH Annex XI. 1.3. – Qualitative or Quantitative structure-activity relationship (Q)SAR (116 cases). Read-across approaches were frequently used to adapt standard information required. Also (Q)SAR methods were applied frequently except for the endpoint AbioDeg. The frequencies and percentages of waiving/adaptations for all ENV endpoints are provided in Table 6-10 in Annex 3.

Figure 3-29: Environment: Frequency of waiving/adaptation categories in formal check (total: 7418)



Additionally, it was evaluated if the registered substance was incriminated or exonerated by data waiving or surrogate data concerning biotic and abiotic degradability, bioaccumulative and ecotoxicological properties. An incrimination of the substance was considered if, for instance, the registrant stated that:

- the substance is toxic because toxicity criterion of REACH Annex XIII is fulfilled or is classified as aquatic chronic 1 or aquatic acute 1, aquatic chronic 1, N, R50/53;
- the substance is persistent or very persistent because it fulfilled the persistence criterion or the very persistence criterion of REACH Annex XIII;

- the substance is bioaccumulative or very bioaccumulative because the bioconcentration factor (BCF) is higher than 2000 or 5000, respectively.

In contrast, exoneration was apparently given if *e.g.* the registrant stated that:

- the substance is readily biodegradable or hydrolysable;
- the substance is not bioaccumulative or the BCF is smaller than 2000;
- long-term toxicity testing is not required because the substance is not toxic in short-term test or the PEC/PNEC is smaller than 1.

The approach to assign waiving or surrogate data into the categories "waiving/adaptation used to incriminate", "waiving/adaptation used to exonerate" or "no waiving/adaptation available or tendency not deducible" has some constraints for the ENV endpoints.

Data waiving or surrogate data could also apply at the same time to both the categories "waiving/adaptation used to incriminate" and "waiving/adaptation used to exonerate". *E.g.* assuming a registrant who concluded from the surrogate data that BCF was greater than 2000, this implied that the substance fulfilled the bioaccumulative criterion. As a result, this could lead to the conclusion that "waiving/adaptation (was) used to incriminate". However, at the same time, the surrogate data supported the view that "waiving/adaptation (was) used to exonerate" because the substance was not very bioaccumulative. This is also one reason that 42 % of all suggested waiving/adaptations were allocated to the category "no waiving/adaptation available or tendency not deducible".

The results of the estimates whether waiving/adaptations were used to incriminate or exonerate the persistent, bioaccumulative or ecotoxicological potential of the registered substance are given in Table 3-14. The highest percentage of 37 % "waiving/adaptation (was) used to incriminate" the registered substance was apparent for the ENV endpoint AbioDeg. Frequently, the registrant stated that the substance is hydrolytically stable because of the chemical structure. Accordingly, only 18 % of the "waiving/adaptation(s were) used to exonerate" the registered substance for the ENV endpoint AbioDeg.

"Waiving/adaptation used to exonerate" the registered substance was estimated in 62 % and 58 % for the ENV endpoints Bioaccu and Ecotox and in 30 % for ENV endpoint BioDeg. In contrast, "waiving/adaptation used to incriminate" was considered in 2 %, 12 % and 13 % of the data waiving or surrogate data provided for the ENV endpoints Ecotox, Bioaccu and BioDeg, respectively.

Table 3-14: Environment: Overview whether waiving/adaptations were used to incriminate or exonerate the ecotoxicological potential of the registered substance

ENV endpoint	Waiving/adaptation used to incriminate		Waiving/adaptation used to exonerate		No waiving/adaptation available or tendency not deducible	
	n	[%]	n	[%]	n	[%]
BioDeg	191	13	432	30	834	57
AbioDeg	523	37	260	18	625	44
Bioaccu	52	12	261	62	109	26
Ecotox	72	2	2784	58	1912	40
Total	**838**	**16**	**3737**	**42**	**3480**	**42**

3.3.8 Biotic and abiotic degradation

Determinations of biotic and abiotic degradation of chemicals are of great importance and are key parameters for assessing the risk of long-term effects on biota. The degradability of a substance is dependent on its physico-chemical properties, its chemical structure and as well as on the environmental conditions. It is determined from laboratory based degradation tests, *e.g.* the OECD TG 301 "ready biodegradability test" and the OECD TG 111 "hydrolysis as a function of pH test". The results and discussion for both endpoints BioDeg and AbioDeg are presented separately.

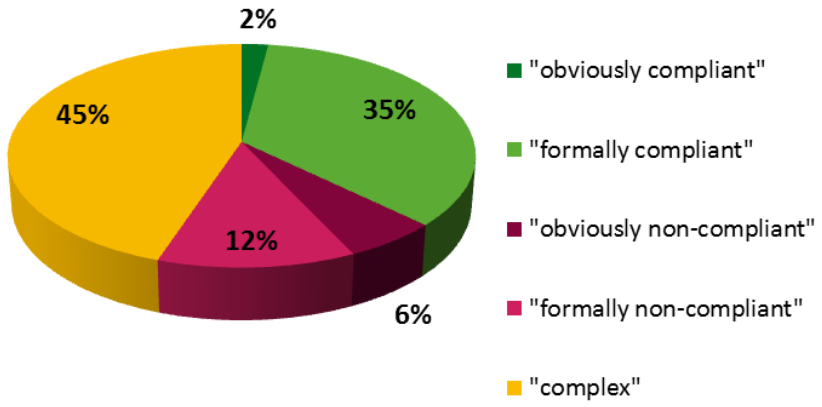
3.3.8.1 Biotic degradation

Regulatory decision making for hazard classification and screening of persistent properties is mostly based on the data obtained in the OECD TG 301 "ready biodegradability test". Information of higher-tier simulation testing – the biodegradation in water, sediment and soil – is triggered by the CSA (REACH Annex IX 9.2.) and shall be considered for the assessment of persistent properties (REACH Annex XIII 3.2.1.). The results of simulation testing provide further evidence on persistence, on degradation products and would refine the environmental risk assessment.

Overall results

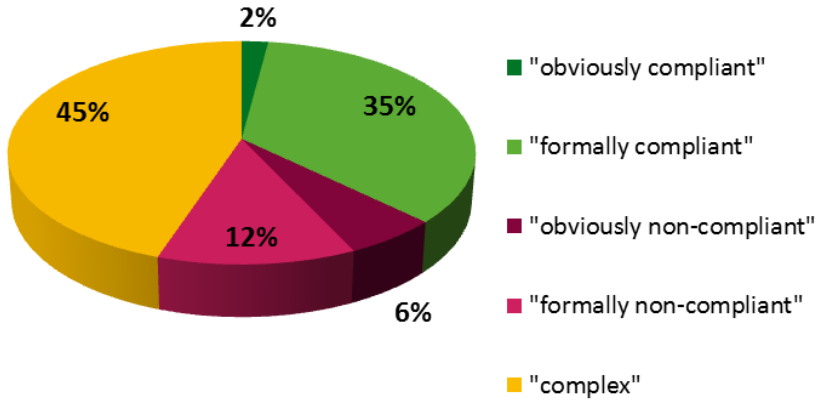
The endpoint BioDeg was evaluated in 533 dossiers. In 45 % (n = 239) of the dossiers the ENV endpoint BioDeg remained in the conclusion category "complex" (Figure 3-30). One third (35 %, n = 187) of all evaluated dossiers for this endpoint were classified as "formally compliant" and 2 % (n = 11) as "obviously compliant". The remaining dossiers were concluded either as "formally non-compliant" (12 %, n = 65) or as "obviously non-compliant" (6 %, n = 31).

Figure 3-30: Biotic degradation: Endpoint conclusions in formal check (total number: 533)



The distribution of all waiving/adaptation justifications (Figure 3-31, 1434 cases) shows the same distribution as for the endpoint conclusions (Figure 3-30). At this point, it has to be emphasised that eventually waiving/adaptation justifications were not counted for every kind of simulation testing – the number of waiving justification might be higher. This might be also probably a reason that both distributions shown in Figure 3-30 and Figure 3-31 are identical.

Figure 3-31: Biotic degradation: Conclusions over waiving/adaptations in formal check (total number: 1434)



Decisive waiving/adaptation categories for the endpoint conclusions

In total, 1434 waiving justifications are underlying for the overall ENV endpoint BioDeg conclusion of 533 dossiers. All decisive waiving/adaptation categories are summarised in Figure 3-32. Endpoint specific waiving/adaptation justifications were most frequently decisive for BioDeg (37 %) besides read-across approaches (29 %) and waiving arguments other than according to REACH column 2 of Annex VIII 9.2.1.1. and Annex IX 9.2.1.2., 9.2.1.3., 9.2.1.4., 9.2.3. or REACH Annex XI. The latter leads to the last paragraph of the introductions of the REACH Annexes VII and IX – no reference (15 %). For the remaining dossiers the decisive categories were allocated as follows: exposure considerations 8 % (n = 43), the application of (Q)SAR models 6 %, waiving not required 2 %, waiving according to REACH Annex XI 2. "technically not feasible" 1 %, WoE 1 %, incorrect REACH references 1 %, waiving according to Annex IV and V 0.4 % and "scientifically unjustified" 0.4%.

The majority of decisive waiving/adaptations for the ENV endpoint BioDeg based on endpoint specific conclusions (37 %). With respect to **column 2 waiving justifications (REACH Annex VII 9.2. and Annex IX 9.2.)**, 29 % of all dossiers remained "complex", whereas, 6 % were concluded as "formally compliant" and 2 % as "formally non-compliant". These conclusions based only on evaluated waiving justifications regarding the higher-tier tests of substances which were not readily biodegradable.

Considering waiving/adaptations based on **endpoint specific reasoning according to REACH Annex VII and IX 9.2. column 2**, 22 % of them were classified as "formally compliant", whereas only 8 % were evaluated as "formally non-compliant", 70 % remained "complex". All waiving justifications were related to surface water simulation testing and/or soil/sediment simulation testing.

The as "formally compliant" assigned waiving justifications were in accordance with the criteria listed in REACH Annex IX 9.2.1. to 9.2.3. column 2, Annex IX 9.2.1.3. and 9.2.1.4. column 2 – "The study need not be conducted if direct and indirect exposure of the soil/sediment is unlikely" – were most often quoted (n = 61 and 51) compared to all other column 2 criteria.

In contrast, "complex" waiving arguments referred to Annex IX 9.2. of the REACH Regulation (n = 414). According to REACH Annex IX 9.2. the registrant shall propose whether the higher-tier studies are required based on the results of the CSA: "Further biotic degradation testing shall be proposed by the registrant if the chemical safety assessment according to REACH Annex I indicates the need to investigate further the degradation of the substance and its degradation products". Based on this requirement, simulation testing on ultimate degradation in surface water as well as soil and sediment were

frequently omitted. Although this justification is in line with REACH, it was assigned to the conclusion category "complex", because a case by case evaluation of the CSA and ecotoxicity data is required.

Read-across approaches were for 29 % of the dossiers decisive for the ENV endpoint conclusion. With respect to read-across approaches 25 % of all dossiers were "formally compliant", 4 % "formally non-compliant" and 0.4 % "complex", respectively. In comparison to other waiving/adaptation categories read-across approaches had the highest percentage of "formally compliant" dossiers for this endpoint.

The results indicated that adaptations of the ready biodegradability test as required according to REACH Annex VII 9.2.1.1. were almost exclusively based on **read-across** approaches. The majority (80 %) of all read-across based adaptations was classified as "formally compliant" since the read-across justification indicated similarities listed in REACH Annex XI 1.5., paragraph 2 and a key study with sufficient exposure duration for the required information was available. Classified as "formally compliant", these read-across approaches contained studies conducted to other guidelines or non-standard TG. Whether these studies complied with the key parameters of the standard TG *e.g.* pass levels, validity, replicates etc. as demanded in REACH Annex XI 1.5., 2nd bullet point, was not evaluated and remains uncertain. In total, 160 of the 254 read-across approaches indicated readily biodegradability and, therefore, the absence of an adverse property for this endpoint. The "formally non-compliant" cases are presented under the header "Reasons for "non-compliance"".

Moreover, most waiving justifications according to the last paragraph of REACH Annexes VII to X (waiving category "no reference") were assigned to the conclusion category "complex" (87 %). A frequently used waiving justification (38 %) for the water, soil and sediment was that no or just minor degradation rates were observed in the test for readily biodegradation and similar results are expected for the simulation tests. This waiving justification has to be evaluated in the broader context of risk characterisation which could not be done in the scope of this formal check.

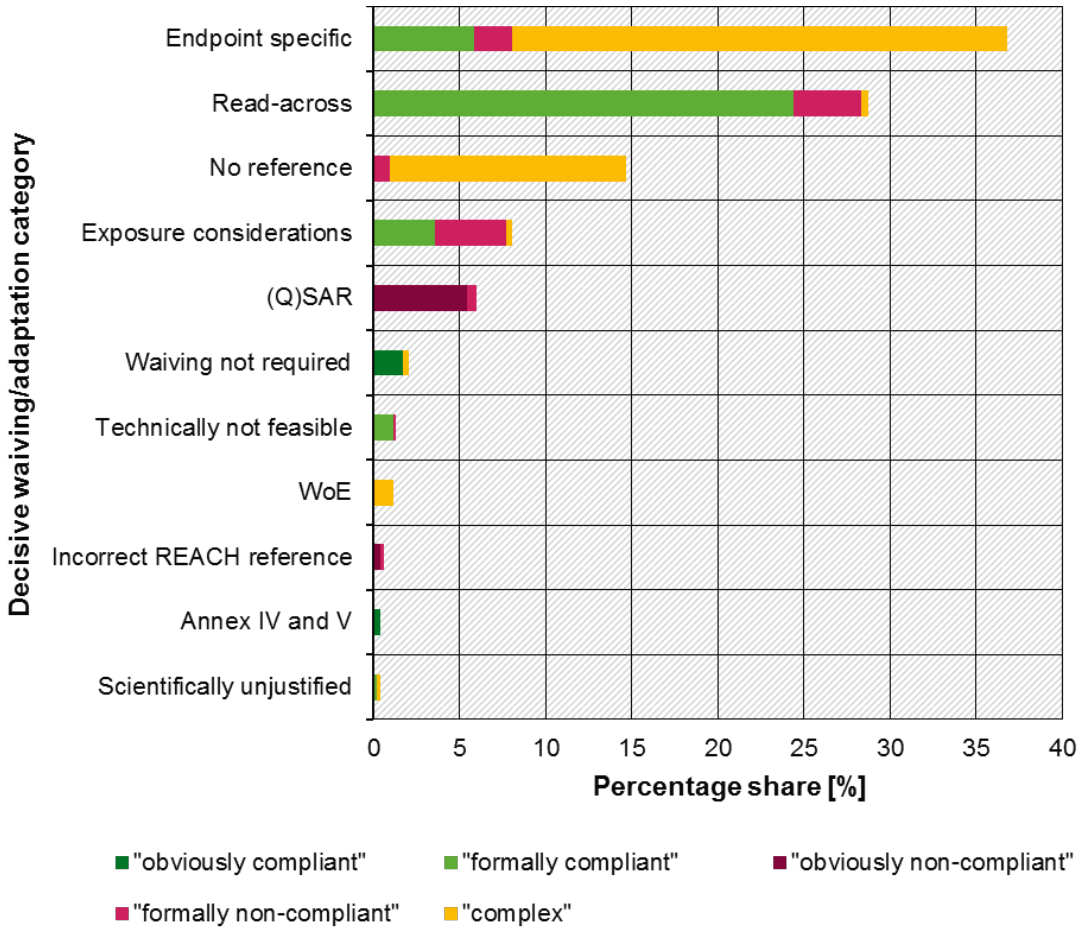
Furthermore, simulation testing on ultimate degradation in surface water as well as soil or sediment simulation testing was waived based on REACH Annex XI 3. (substance-tailored exposure-driven testing) (n = 95). However, more than half of these waiving justifications for this endpoint were assigned to the conclusion category "formally non-compliant" (n = 58), either because no exposure scenario was available in the CSR or no adequate justification and documentation was provided. Justifications as "Exposure based waiving" or "In accordance with Annex XI sediment simulation testing does not need to be conducted as exposure of sediment is unlikely" did not provide adequate documentation demonstrating that the criteria set out in REACH Annex XI 3.2.(a) to (c) were fulfilled. "Formally compliant" (n = 34) justifications fulfilled the criteria set out in REACH Annex 3.2.(a), (i) to (iii), or (b) and provided an exposure scenario in the CSR.

In seven dossiers (1 %) the waiving/adaptation with reference to REACH Annex XI 2. (testing technically not feasible), was also decisive (six dossiers "formally compliant", one dossier "formally non-compliant"). Nearly all justifications omitting the simulation testing were well-grounded according to REACH Annex XI 2. (testing technically not feasible) and were classified as "formally compliant" and referred at the same time to simulation testing (n = 51 "formally compliant" from n = 52 total).

In the current project (Q)SAR models were excluded for Bioaccu from the assessment (see chapter 2.5.1) but when there were present an evaluation was conducted. Predominately, the (Q)SAR tool PETRORISK (69 cases) was applied for the risk assessment of hydrocarbon UVCB substances (mainly petroleum products). Unfortunately, the underlying models, Hydrocarbon block method (HBM) and PETROTOX, require improvements to meet the validity criteria (Rorije et al., 2012). Therefore, these adaptations were considered to be "obviously non-compliant" – further explanation is given under the header "Reasons for "non-compliance"". But besides the PETRORISK tool, the application of (Q)SAR models (twelve cases) were most often evaluated as "formally non-compliant" (ten cases). Only two (Q)SAR model predictions were assigned to the category "formally compliant". In 6 % of the dossiers,

the (Q)SAR tool PETRORISK was also decisive for the ENV endpoint conclusion: 5.4 % „obviously non-compliant“ and 0.6 % “formally non-compliant”.

Figure 3-32: Biotic degradation: Decisive waiving/adaptation categories and their contributions to the endpoint conclusions in formal check (total number: 533 dossiers)



Reasons for “non-compliance”

An overview of reasons for “non-compliance” is given for the ENV endpoint BioDeg in Table 3-15. In the current project (Q)SAR models were as far as possible excluded in the assessment. But still, for 6 % of all waiving/adaptations a (Q)SAR model was present. Predominately, the (Q)SAR model PETRORISK (69 cases) was applied to estimate the BioDeg in water, soil and sediment for hydrocarbon UVCB substances (mainly petroleum products). PETRORISK is a (Q)SAR tool based on the target lipid model predicting, *e.g.* the toxicity of mainly petroleum products to aquatic organisms. However, the PETRORISK model was found to potentially underestimate the environmental risk related to the production and use of petroleum products. Further, the target lipid model upon which the tool is based, has not been sufficiently established and need modifications to meet scientific validity (Rorije et al., 2012). Thus, all (Q)SAR approaches based on the PETRKORISK tool were assigned to the conclusion category “obviously non-compliant”.

The categorisation of read-across approaches as “formally non-compliant” based mainly on the fact that the similarity justification was not available (33 cases) and/or the absence of a key study (eleven cases) and/or shorter exposure duration of the provided test (seven cases).

Exposure based waiving according to REACH Annex XI 3. (substance-tailored exposure-driven testing) was not appropriate in 35 cases although exposure scenarios were available in 25 cases. This conclusion was made because the formal reasoning was insufficient. Another reason for "formally non-compliant" cases was that the waiving justification cannot be assigned to the specific REACH Annex XI 3.2. (a) to (c) criteria (six cases) or that exposure scenarios were not available (17 cases).

Table 3-15: Biotic degradation: Main reasons for the allocation of particular waiving/adaptations to the conclusion categories "obviously non-compliant" and "formally non-compliant" in formal check

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number of waiving/adaptations	Percentage [%] of all BioDeg waiving/adaptations*
"Obviously non-compliant" (74 cases)	(Q)SAR	PETRORISK model was used to predict the biodegradation test	69	5
	Incorrect REACH reference	incorrect REACH reference	2	0.1
	Meaningless justification	no CSR	3	0.2
"Formally non-compliant" (n = 296)	Scientifically unjustified	wrong direct REACH reference with a respective wrong justification	98	7
	Exposure considerations	► Annex XI 3. (substance-tailored exposure-driven testing) (35 cases[x])[#] ► waiving justification cannot be assigned to the specific Annex XI 3.2.(a) to (c) criteria (6 cases)[#] ► exposure scenarios were not available in the CSR (17 cases)[#]	53	4
	Endpoint specific	Justification does not comply with ► REACH Annex IX 9.2.1.2. column 2, 1st bullet point (4 cases) ► REACH Annex IX 9.2.1.2. column 2, 2nd bullet point (6 cases) ► REACH Annex IX 9.2.1.3. column 2, 1st bullet point (3 cases) ► REACH Annex IX 9.2.1.3. column 2, 2nd bullet point (19 cases) ► REACH Annex IX 9.2.1.4. column 2, 1st bullet point (2 cases) ► REACH Annex IX 9.2.1.4. column 2, 2nd bullet point (12 cases) ► justification not related to the required test (1 case)	47	3
	Read-across	► similarity justification not available (33 cases)[#] ► key study not available (11 cases)[#] ► exposure duration was not comparable/not given or guideline could not be deduced (7 cases)[#]	49	3

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number of waiving/adaptations	Percentage [%] of all BioDeg waiving/adaptations*
	No reference	different free text	19	1
	Incorrect REACH reference	incorrect REACH reference	16	1
	(Q)SAR	► no ESR (5 cases)# ► no QMRF (10 cases)# ► no QPRF (7 cases)#	11	1
	Meaningless justification	different free text	2	0.1
	Technically not feasible	justification does not comply with REACH Annex XI 2., last sentence	1	0.1

* Reference to 1434 investigated/missing waiving. Waiving/adaptation justifications were not counted for each kind of simulation test and the overall number might be higher.
x For 25 cases exposure scenarios are available.
More than one reason might apply for a particular case.

3.3.8.2 Abiotic degradation

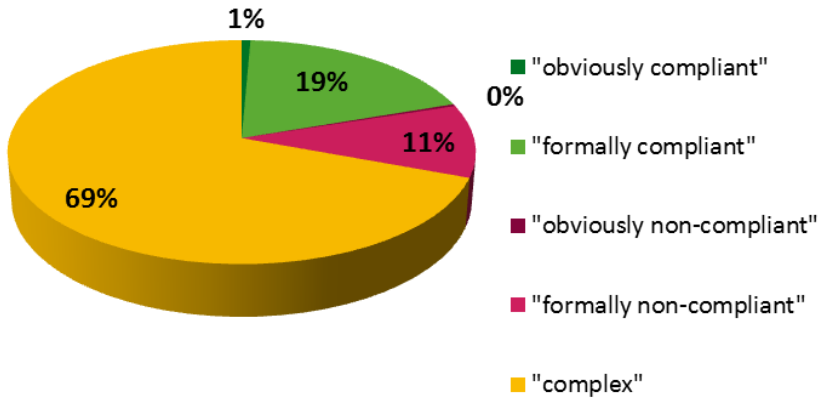
Chemicals can be altered under environmental conditions by biotic processes as well as abiotic processes such as photolysis, hydrolysis, oxidation and reduction reactions, nucleophilic substitution and elimination. Hydrolysis can greatly influence the fate and behaviour of substances in aquatic environments, sediments and soils. Hydrolysis is a standard information requirement for substances manufactured or imported in quantities of 10 tpa or more (REACH Annex VIII 9.2.2.1.). It is defined as "Decomposition or degradation of a chemical by reaction with water" (ECHA, 2016a) and as "Hydrolysis refers to a reaction of a test substance RX with water, with the net exchange of the group X with OH at the reaction centre: RX + HOH → ROH + HX" . Therefore, the test methods regulation as part of REACH (EC, 2008a) and the technical guideline OECD TG 111 (OECD, 2004b) specifies "a laboratory test method to assess abiotic hydrolytic transformations of chemicals in aquatic systems at pH values normally found in the environment (pH 4-9)". Also, according to OECD TG 111 a preliminary test (tier 1) is foreseen to investigate whether the substance is potentially stable or unstable against hydrolysis.

In environmental risk assessment the parameter hydrolysis rate or half-life is important to assess the persistence of a substance. The identification of major hydrolysis products and their environmental fate and behaviour should be addressed if indicated.

Overall results

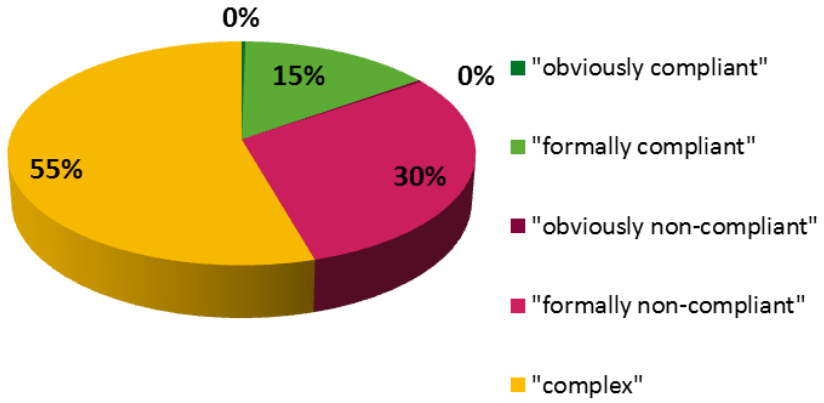
In total, 1029 dossiers were evaluated for the ENV endpoint AbioDeg. The main part (69 %) of the assessed dossiers remained without conclusion ("complex"). For 19 % of the dossiers, the endpoint AbioDeg was assigned to the category "formally compliant" and for 0.7 % to the category "obviously compliant". 11 % of the dossiers were identified as "formally non-compliant" and 0.3 % as "obviously non-compliant". Figure 3-33 shows the distribution for the endpoint conclusions of the evaluated dossiers.

Figure 3-33: Abiotic degradation: Endpoint conclusions in formal check (total number: 1029)



Altogether, 1408 waiving/justifications were recognised in 1029 dossiers for AbioDeg. In some cases more than one waiving/adaptation was either suggested or concluded from the justification text. Half (50.4 %) of the given waiving/adaptation justifications were without a specific reference to the respective section of REACH and had to be deduced by the project staff. The distribution of conclusion categories for the waiving/adaptation justifications is given in Figure 3-34. The cases without conclusion ("complex") share the main part with 55 %. However, the percentage of 30 % "formally non-compliant" cases is clearly higher and the percentage of 15 %"formally compliant" cases is slightly smaller compared to the figures of the dossiers (Figure 3-33).

Figure 3-34: Abiotic degradation: Conclusions over waiving/adaptations in formal check (total number: 1408)



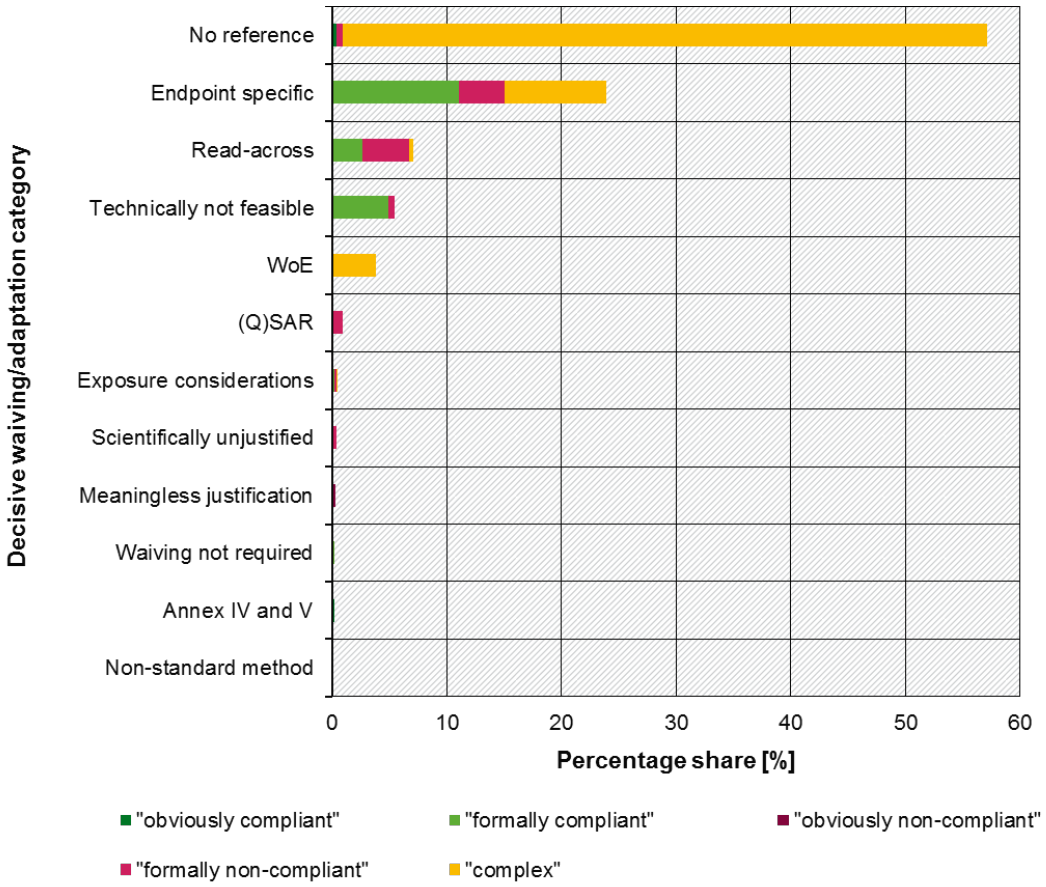
Decisive waiving/adaptation categories for the endpoint conclusions

In this chapter the analyses follows about which waiving/adaptation category was decisive concluding the ENV endpoint AbioDeg of the dossiers. The distribution is shown in Figure 3-35. Taking all waiving/adaptation justifications for the endpoint into account, cases for which none of the possibilities of REACH Annex VIII 9.2.2.1. column 2 or Annex XI were considered, were most abundant (57 %,

588 dossiers). Waiving in these cases could be justified – but have to be proofed in detail – with the last introductory paragraph of REACH Annex VIII.

The reference to REACH Annex VIII 9.2.2.1. column 2 – substance is readily biodegradable or highly insoluble – was the decisive category for 24 % of the dossiers. Further, in 5 % of the cases the omitting of testing was justified with regard to REACH Annex XI 2. ("technically not feasible"). Standard information required for AbioDeg were also adapted by read-across approaches (6 %), WoE (3 %) and (Q)SAR models (1 %). The remaining decisive waiving/adaptation categories were of minor relevance for this endpoint and can be seen as individual cases (exposure considerations 0.5 %, meaningless justification 0.3 %, waiving not required 0.2 %, waiving according to REACH Annex IV and V 0.2 % and use of a non-standard method 0.1 %).

Figure 3-35: Abiotic degradation: Decisive waiving/adaptation categories and their contribution to the endpoint conclusions in formal check (total number: 1029 dossiers)



One reason for the high percentage of "complex" cases was that the rationale behind the waiving justification could neither be allocated to an argument referring to REACH Annex VIII 9.2.2.1. column 2 nor referring to Annex XI (56 %, 578 dossiers). Therefore, a case by case conclusion is required to proof whether waiving is justified according to the last paragraph of the introduction into REACH Annex VIII "When for certain endpoint, information is not provided for other reasons than those mentioned in column 2 of this or in Annex XI, this fact and the reasons shall also be clearly stated". Conclusion making in these cases would require cut-off criteria and/or a case by case expert judgement conclusion. On the one hand, it should be worked out in detail how a waiving justification complies formally with the option of REACH Annex VIII introduction. On the other hand, it is necessary to verify whether the chemical structure of the substances is stable against hydrolysis. Thus, all provided justifications stated that the required hydrolysis test was not conducted based on the structural properties of the

substance, *e.g.* because of the absence of hydrolysable functional groups or because the substance is known to be stable against hydrolysis. These endpoint cases were therefore classified as "complex".

A number of substance families are known to be hydrolytically unstable, but certain functional groups characterising alkanes, alkenes, benzenes, biphenyls and polycyclic aromatics, alcohols, esters or ketones are often inert to hydrolysis (ECHA, 2012b; Sijm et al., 2007). This inertness criterion is not part of the criteria for waiving listed in REACH Annex VIII column 2. However, due to its wide application a modification with respect to the adaptation criteria for this endpoint may be considered. Hence, it is necessary to distinguish between functional hydrolysable and non-hydrolysable structures based on defined criteria.

Endpoint specific waiving justifications referring to REACH Annex VIII 9.2.2.1. column 2 comprised 21 % (297 cases) of all applied waiving justifications (1408 cases) for the ENV endpoint AbioDeg. Considering all waiving/adaptation justifications, 9 % (122 cases) of endpoint specific waivers were classified as "formally compliant", whereas 6 % (81 cases) as "formally non-compliant" and 7 % as "complex" (93 cases).

Reference to REACH Annex VIII 9.2.2.1. column 2 – "The study does not need to be conducted if the substance is readily biodegradable" – was given in 207 cases. This argument was reasonable in 97 cases and was accordingly allocated to the category "formally compliant". In 72 cases of the latter "formally compliant" cases the ready biodegradability studies based on properly applied read-across approaches. Other cases where the same waiving argument was reasonable could not be concluded because the endpoint "ready biodegradability" based either on WoE or a full test result according to a non-standard test method was provided. A detailed analysis will be necessary to investigate whether provided WoE data adequately covered this endpoint.

The second possibility to refrain from testing according REACH Annex VIII 9.2.2.1. column 2, is that the substance is highly insoluble in water. Although in REACH guidance documents no numeric value is given as cut-off criteria, water solubility (S_w) < 1 mg/L was chosen in the present project. This was considered to be "formally compliant" in 24 cases. Whereas, Scholten (2012) suggests 0.1 mg/L at 25°C to specify the official waiving argument (Scholten, 2012).

In total, 121 cases were "formally compliant" because the column 2 criteria (REACH Annex VIII 9.2.2.1.) were met adequately. In 114 dossiers the column 2 criteria was even decisive. In the preceding project, 441 of 1814 dossiers were "compliant" with reference to REACH Annex VIII 9.2.2.1. column 2 (Springer et al., 2015). Thereby, both amounts of "compliant" dossiers with respect to the column 2 criteria were summarised resulting in 558 dossiers. In conclusion, 31 % of the 1814 dossiers are formally in line with the column 2 criteria for the ENV endpoint AbioDeg. In project II, the percentage of "formally non-compliant" dossiers comprises 4 % (41 dossiers) with reference to REACH Annex VIII 9.2.2.1. column 2, whereas no dossier was assigned as "obviously compliant" or "obviously non-compliant". The category "complex" was allocated to 9 % of the investigated dossiers (n = 91) referring to REACH Annex VIII 9.2.2.1. column 2. Number and reasons of "formally non-compliant" waiving justifications referring to REACH Annex VIII 9.2.2.1. column 2 are presented below under the header "Reasons for "non-compliance"".

Adaptations of information requirements for AbioDeg with read-across approaches were present in 77 waiving/adaptations and were in most cases also decisive for the endpoint (7 %, 73 dossiers). The read-across approaches were assigned to the category "formally compliant" in 3 % (43 cases), whereas 2 % (30 cases) were classified as "formally non-compliant" based on the absence of adequate documentation and justification for the appropriateness of the read-across approach (23 cases) and/or for a shorter or not given duration of the test (20 cases).

Altogether, 4 % (63 cases) of all waiving/adaptation justifications referred to REACH Annex XI 2. – this waiving justification was for 5.4 % of the dossiers decisive (56 dossiers). The major part (51 dossiers)

was classified as "formally compliant" leading to a decisive conclusion for 5 % of the dossiers, accordingly. The reasons given for waiving were either in line with the first sentence of REACH Annex XI 2. considering that it was not possible to conduct the test as a consequence of the substance properties (30 cases), or they complied with the second sentence that the study could not be conducted as a consequence of the technical limitations of the test method (28 cases). The remaining eight "formally non-compliant" cases omitted the test for the same reasons but did neither fulfil the criteria of the above mentioned first sentence (five cases) nor the second sentence (three cases).

Reasons for "non-compliance"

For the ENV endpoint AbioDeg Table 3-16 summarises the main reasons for "non-compliance". This analysis is based on all waiving/adaptation justifications either directly proposed by the registrant or deduced from the waiving justification. "Obviously non-compliant" cases occurred rarely across the endpoint AbioDeg. In one read-across case an obviously not appropriate key study of the endpoint water solubility was cited, namely a study conducted according to the technical guideline OECD TG 105 (OECD, 1995). In other three cases a meaningless justification was given and resulted in the conclusion "obviously non-compliant".

The main cause of "formally non-compliant" cases was the selection of an inappropriate REACH waiving/adaptation criteria by the registrant (19 %, 271 cases). In these cases a scientific reason to omit testing was explained, *e.g.* the absence of hydrolysable functional groups. However, in conclusion, a wrong reference to REACH Annex XI "Testing does not appear scientifically necessary" was given, probably as a consequence of misinterpreting the requirements of this Annex. Accordingly, these cases were assigned to the conclusion category "formally non-compliant". The same conclusion resulted where it could be deduced from the justification that the reasoning seems to be appropriate, *i.e.* complies possibly with the last paragraph of the introduction of REACH Annex VIII. This result indicates general misinterpretation regarding the application of REACH Annex XI for waiving. It might appear that the caption of the section 1 "Testing does not appear scientifically necessary" is misleading and is used by the registrants as area for a general scientific justification. Despite this, REACH Annex XI 1. specifies only certain approaches to adapt information requirements and, in particular, offers not the possibility to completely omit delivering experimental study data. *E.g.,* frequently, the registrants indicated briefly that the substance is stable against hydrolysis because of the structure or because the substance does not contain hydrolysable functional groups. Indeed, the fact that a substance is stable against hydrolysis would, from a scientific point of view, verify to omit the test. Unfortunately, this waiving argument does not fit into the rules settled by REACH, unless it would be referred and documented in a formally correct way, *e.g.* as validated (Q)SAR study (REACH Annex XI, 1.3) or grouping/read-across approach (REACH Annex XI, 1.5). According to the ECHA, (Q)SAR and read-across approaches have been used to argue against hydrolysis testing due to lack of hydrolysable substructures (ECHA, 2008). Here, it appears that the registrant is not aware of the existing opportunities to demonstrate in a formally correct way that the substance is stable against hydrolysis.

A justification to omit testing on abiotic degradation according to REACH Annex VIII 9.2.2.1. column 2 was considered to be "formally non-compliant" in 81 cases for different reasons. First, the waiving justification "the substance is readily biodegradable" was present in 29 cases. Thereby, the criterion could not be confirmed with data but only the reference to REACH Annex VIII column 2 was given (six cases). In other twelve cases data were indeed given, but there was no key study with a reliability of 1 or 2 documented. Also, read-across approaches applied for the test on readily biodegradability were found to be "formally non-compliant" (14 cases), mainly because the test duration was too short or could not be deduced (nine cases) or the read-across approach was not properly applied (five cases). Second, in 15 cases the waiving criteria that $S_w < 1$ mg/L (REACH Annex VIII 9.2.2.1. column 2, 2nd bullet point) had not been confirmed by data presented in the registration dossier. Third, reference to

REACH Annexes VII to X column 2 was given (37 cases), but this did not relate to the hydrolysis test, *e.g.* because the substance was inorganic.

(Q)SAR models were classified as "formally non-compliant" (ten cases) due to the absence of the (Q)SAR model reporting format (QMRF) and/or (Q)SAR Prediction Reporting Format (QPRF), and/or another adaptation approach was not used in an appropriate way (two cases). Both, QMRF and QPRF are demanded in REACH Annex XI 1.3. to ensure the adequate documentation of the applicability, algorithm, endpoint, goodness of fit and robustness of the (Q)SAR model (ECHA, 2012d): "(Q)SAR prediction should be described in a detailed and transparent way such as the (Q)SAR model reporting format and the (Q)SAR prediction reporting format".

Table 3-16: Abiotic degradation: Main reasons for the allocation of particular waiving/adaptations to the conclusion categories "obviously non-compliant" and "formally non-compliant" in formal check

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number of waiving/ adaptations	Percentage [%] of all AbioDeg waiving/adaptation*
"Obviously non-compliant" (n = 4)	Meaningless justification	diverse justifications	3	0.2
	Read-across	key study of another endpoint (OECD TG 105)	1	0.1
"Formally non-compliant" (n = 423)	Scientifically unjustified	► wrong direct REACH reference with a respective wrong justification (271 cases) ► non-GLP study does not comply with the requirements (1 case)	272	19
	Endpoint specific	► justification does not comply with 1. REACH Annex VIII 9.2.2.1. column 2, 1st bullet point (29 cases) 2. REACH Annex VIII 9.2.2.1. column 2, 2nd bullet point (15 cases) ► direct reference to column 2 of REACH Annexes VII to X but the justification is not related to the required test (37 cases)	81	6
	Read-across	► similarity justification not available (23 cases)# ► key study not available (1 case)# ► exposure duration was not comparable/not given or guideline could not be deduced (20 cases)#	43	3
	(Q)SAR	► no ESR (6 cases)# ► no QMRF (3 cases)# ► no QPRF (6 cases)# ► study based on another adaptation (2 cases)#	10	0.7
	Technically not feasible	► justification does not comply with REACH Annex XI 2., 1st sentence (5 cases) ► REACH Annex XI 2., 2nd sentence (3 cases)	8	0.6

* Reference to 1408 investigated/missing waiving.

More than one reason might apply for a particular case.

3.3.9 Bioaccumulation

Depending on the properties of substances, *e.g.* lipophilicity, they may bioaccumulate in biota and biomagnify up in the food web, leading to potentially toxic concentrations in top-predators including fish and fish eating wildlife (Evers et al., 1998; Wyn et al., 2009). Thus, it is crucial to consider bioaccumulation, especially in the aquatic compartment, when assessing the risk of a chemical. Bioaccumulation under REACH is mostly estimated for aquatic systems using fish as indicator species (OECD, 2012a).

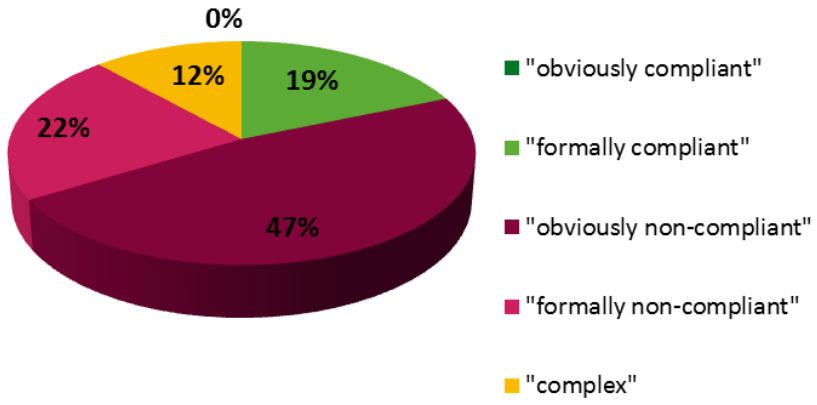
Information on aquatic bioaccumulation is used for hazard classification, PBT and vPvB assessment and is as well used for exposure modelling for the CSA. Results of bioaccumulation testing can also trigger long-term toxicity testing on invertebrates and on fish.

Bioaccumulation includes processes of uptake, distribution within the organism, metabolism and elimination/depuration. The bioconcentration of chemicals in the environment refer to the accumulation of a substance in an organism from the surrounding media *e.g.* water. Thereby, the BCF is the ratio of the concentration of a substance in an organism in relation to the concentration in the water. The BCF for fish is experimentally determined in laboratory exposure experiments as a flow-through fish test according to the technical guideline OECD TG 305. The test comprises the standard information required for chemicals of 1000 tpa or more according to REACH Annex IX 9.3.2. and the test method regulation as part of REACH (EC, 2008a), respectively. Predictions and non-testing data might be sufficient as part of a WoE approach since, according to REACH, animal testing should be carried out only as a last resort (ECHA, 2012b; ECHA, 2012c).

Overall results

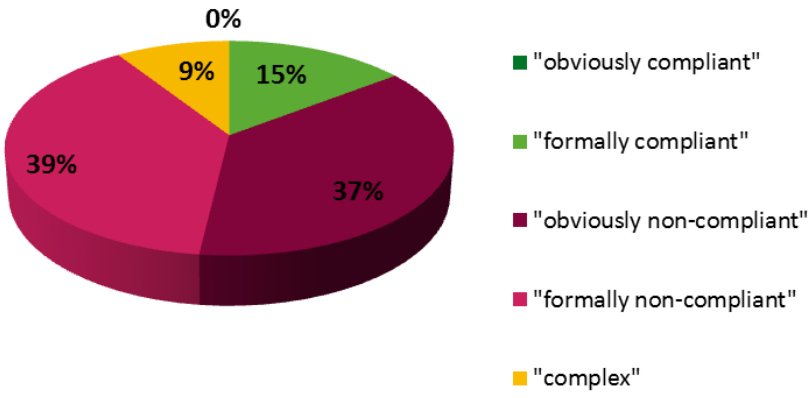
For the ENV endpoint Bioaccu 315 dossiers were evaluated. As a result, 19 % of all dossiers were assigned to the conclusion category “formally compliant”. None of the dossiers was found to be “obviously compliant”. Further, 47 % of all dossiers were categorised as “obviously non-compliant” and 22 % as “formally non-compliant”. In total, 12 % remained without conclusion (“complex”) requiring an in-depth analysis for evaluation. The distributions of endpoint conclusions as percentage of all conclusions are shown in Figure 3-36.

Figure 3-36: Bioaccumulation: Endpoint conclusions in formal check (total number: 315)



In total 422 waiving/adaptations were recognised for the endpoint Bioaccu. In some cases more than one waiving/adaptation was either proposed by the registrant or deduced from the waiving justification. Figure 3-37 presents the distribution of conclusions for waiving/adaptations given as percentage of all waiving/adaptations.

Figure 3-37: Bioaccumulation: Conclusions over waiving/adaptations in formal check (total number: 422)



Decisive waiving/adaptation categories for the endpoint conclusions

315 dossiers were evaluated for the endpoint Bioaccu. This included 422 waiving/adaptation justifications (Figure 3-37). Figure 3-38 shows the distribution among the different waiving/adaptation categories used for waiving the required bioaccumulation test. Most frequently, the overall conclusion "formally compliant" (19 %, 59 dossiers) was related to REACH Annex XI 2. "technically not feasible" (9 %, 29 dossiers), an endpoint specific waiving justification (5 %, 16 dossiers) or a read-across approach (4 %, eleven dossiers) and exposure considerations (1 %, three dossiers).

In total, 47 % (150 dossiers) of all dossiers were categorised as "obviously non-compliant" mainly based on (Q)SAR models (33 %, 103 dossiers), a meaningless justification (10 %, 31 dossiers) or a read-across approach without an ESR (3 %, ten dossiers) or endpoint specific waiving justification (1 %, four dossiers).

"Formally non-compliant" conclusions (22 %, 69 dossiers) mostly based on read-across approaches (10 %, 32 dossiers), endpoint specific Column 2 waiving justifications (8 %, 25 dossiers) and (Q)SAR models (2 %, six dossiers).

Either, substance specific reasons or exposure based considerations given as endpoint specific waiving justifications could not be concluded in 16 and in three dossiers, respectively. Another reason to omit the bioaccumulation test was that an analytical method (six dossiers) was not available, subsequently the bioaccumulation test was "technically not feasible". As well, six dossiers referred to another guideline or to a field study and four dossiers followed a WoE approach. Finally, one dossier included a testing proposal for Bioaccu.

The underlying waiving/adaptations according to REACH Annex XI 2. (30 %) and (Q)SAR models (28 %) were the two major justifications besides endpoint specific waiving justifications and read-across approaches (18 % and 14 %, respectively). A meaningless justification was given for 8 % of all waiving justifications and was accordingly concluded as "obviously non-compliant" endpoint case. The

remaining three percentages are almost evenly distributed among the decisive waiving/adaptation criteria "WoE", "exposure based adaptations" (REACH Annex XI 3.) or an "incorrect REACH reference".

Read-across approaches were also used to adapt the bioaccumulation test for fish required for this endpoint (14 %, 60 cases). Only 3 % (twelve cases) of the read-across approaches were in line with the REACH requirements justifying their allocation to the "formally compliant" group. Some endpoints with read-across approaches remained in the decisive waiving/adaptation category "complex" (four cases) because field studies or study data according to other guidelines than the currently valid TG were presented and thus require a detailed review.

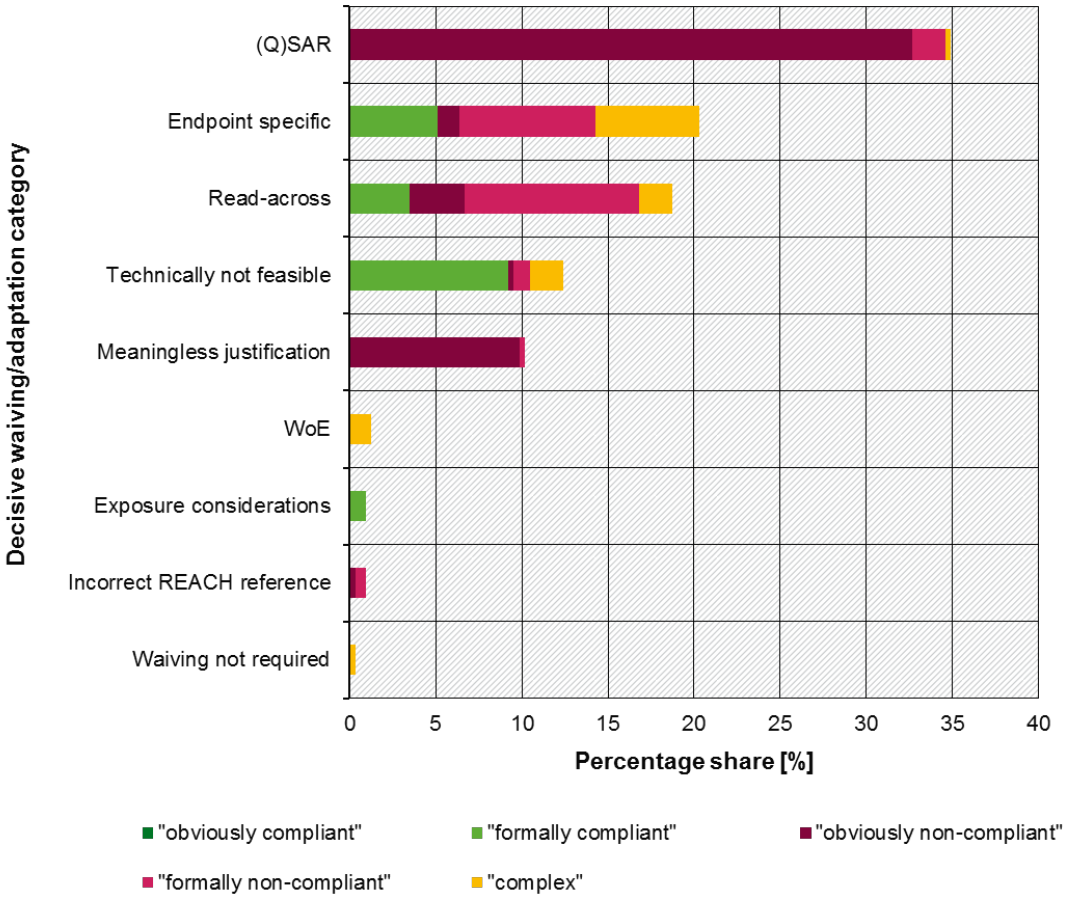
The waiving/adaptations evaluated and resulted as being "formally compliant" for this endpoint most often referred to REACH Annex XI 2. (7 %, 31 cases), and to REACH Annex IX 9.3. column 2 (endpoint specific; 4 %, 17 cases). The majority of justifications cited REACH Annex IX 9.3.2. column 2 – "The study need not be conducted if the substance has a low potential for bioaccumulation (10-base logarithm of n-octanol/water partition coefficient (log K_{ow}) ≤ 3) and/or a low potential to cross biological membranes" – (twelve cases) and/or referred to "direct and indirect exposure of the aquatic compartment is unlikely" (eight cases).

The potential of a substance to cross biological membranes is subject of a broader scientific discussion. Molecular size and weight are herein used as indicators. If the molecular length exceeds 4.3 nm, it is assumed that the substance does not accumulate of a significant amount in the organism. Several cut-off values indicating negligible absorption across fish tissue are suggested based on the molecular weight by the European Commission (700 g/mol) or the US EPA (1100 g/mol) (ECHA, 2012c; Leeuwen, 2007). However, the ECHA guidance document on PBT assessment only suggests the use of both arguments in a WoE approach together with other information (ECHA, 2012c). Thus, waiving according to REACH Annex IX 9.3.2. column 2, 1st bullet point, 2nd sentence, – "low potential to cross biological membranes" – might be formally in line with REACH. However, an in-depth evaluation of the parameter (molecular weight or size) is needed. It might be necessary to further define waiving due to this column 2-criterion based on the thresholds mentioned above.

All in all, 31 waiving justifications referring to REACH Annex XI 2. were concluded to be "formally compliant". From these, in 26 cases it was not be possible that the substance remains in the test solution because of volatile properties of the substance. Consequently, it was properly justified that the "Study cannot be conducted as a consequence of the technical limitations of a test method referred to in Article 13(3)" (REACH Annex XI 2., last sentence). The left five "formally compliant" cases were well-founded concluding that the "Study cannot be conducted as a consequence of the properties of the substance." (REACH Annex XI 2., first sentence).

Exposure based waiving adaptations according to REACH, Annex XI 3. was of less relevance within the waiving/adaptation justifications. Here, entirely four cases based on exposure consideration. Strictly controlled conditions were found to be "formally compliant" in one case. In contrast, two cases were "formally non-compliant" because neither environmental release categories (ERC) nor process categories (PROC) were compatible with strictly controlled conditions.

Figure 3-38: Bioaccumulation: Decisive waiving/adaptation categories and their contribution to the endpoint conclusions in formal check (total number: 315 dossiers)



Reasons for "non-compliance"

Reasons for "non-compliance" of certain waiving/adaptations for the endpoint Bioaccu are explained in Table 3-17. The application of (Q)SAR models were either assigned to the category "obviously non-compliant" (108 cases) or were classified as "formally non-compliant" (eight cases). A (Q)SAR-adaptation for hydrocarbon UVCB (petroleum products) was often combined with the argument "the test on bioaccumulation in fish is not technically feasible based on the complexity of the substance and instead the potential for bioaccumulation is estimated via (Q)SAR". This approach is recommended for UVCB petroleum substances by the ECHA (ECHA, 2012c). However, (Q)SAR models of the evaluated dossiers regarding UVCB petroleum substances were all based on estimations made with the PETRORISK model, PETROTOX or the HBM model, which fail to meet scientific validity (Rorije et al., 2012). This explains the high rate of dossiers allocated as "obviously non-compliant" regarding this endpoint, on the one hand. The high rate of "obviously non-compliant" dossiers is as well related to the sampling of dossiers for evaluation. This is due to the fact that for the endpoint Bioaccu those dossiers offering only an adaptation based on a (Q)SAR model were allocated in the first project to the "(Q)SAR" group. However, these were excluded within this project for further evaluation.

The other (Q)SAR models were all assigned to the conclusion category "formally non-compliant" (eight cases), because, on the one hand, adequate documentation of the applicability domain and validity criteria of the model itself was missed for all of them, and, on the other hand, also in terms of the used standard reporting formats, QMRF and QPRF.

Altogether, 34 endpoints with read-across approaches were "formally non-compliant" for different reasons. Here, the reasons for non-compliancy were mainly related to the testing requirements, but rather not related to the read-across approach itself. From all endpoints with read-across approaches, in 24 cases either the exposure duration was not comparable or not given, or the guideline could not be deduced. Consequently, the requirements of OECD TG 305 were not met (OECD, 2012a). The remaining reasons were related to the justification of the read-across approach itself (14 cases) or a key study was not available (four cases). In some cases also more than one reason was decisive for the conclusion "formally non-compliant". Finally, "obviously non-compliant" cases did not include appropriate study data (four cases).

The high number of "formally non-compliant" conclusions regarding waiving/adaptation (89 cases) originated mainly from the UVCB class of substances (85 cases). Meeting the requirements of REACH a "case-by-case consideration of the approach to define the appropriate information and methods (is) necessary" (ECHA, 2014b). However, a statement that the substance belongs to the UVCBs does not seem to be appropriate on its own for this purpose.

In 8 % of the cases (33 cases) a "meaningless justification" was given and, consequently, these were classified as "obviously non-compliant". Frequently, the registrants concluded with the partition coefficient log K_{ow} ≥ 10 (15 cases) that the substance does not expect to bioaccumulate and/or direct and indirect exposure of the aquatic compartment is unlikely and/or testing is not feasible. In these waiving justifications the calculated log K_{ow} of 10 or above was used as the only indicator for the reduced potential of a substance to bioaccumulate. The aquatic BCF of a substance is probably lower than 2000 if the calculated log K_{ow} is higher than 10 as stated in the ECHA guidance document R.11.4.1.2 (ECHA, 2012c). However, as further mentioned in the ECHA endpoint specific guidance document R.7c (ECHA, 2012d) regarding other indications of bioaccumulation potential (R.7.10.3.4), as well as mentioned in the ECHA guidance R.11 on PBT assessment regarding the endpoint bioaccumulation (R.11.1.3.2) (ECHA, 2014c), a log K_{ow} value of 10 or above should be used in a WoE approach. This should be based on expert judgment in combination with other indicators such as the molecular weight, maximum molecular length and a measured octanol solubility (ECHA, 2012b; ECHA, 2012c). Furthermore, in the information of the updated document from November 2014 it is clarified that, "if log K_{ow} > 6, the quantitative relationships between BCF and K_{ow} are uncertain. A preliminary BCF of 25000 (corresponding to a log K_{ow} of 6) should be assumed in the absence of better information."(ECHA, 2014c).

Table 3-17: Bioaccumulation: Main reasons for the allocation of particular waiving/adaptations to the conclusion categories "obviously non-compliant" and "formally non-compliant" in formal check

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number of waiving/ adaptations	Percentage [%] of all Bioaccu waiving/adaptations*
"Obviously non-compliant" (37 %, 157 cases)	(Q)SAR	► PETRORISK model or another model (PETROTOX or HBM) was used (85 cases) ► ESR not provided (23 cases)	108	26
	Meaningless justification	► Log K_{ow} ≥ 10 (15 cases)# ► reference and justification do not match or no/not sufficient justification given for reference (28 cases)# ► justification not related to all relevant components of the substance (2 cases)	33	8

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number of waiving/ adaptations	Percentage [%] of all Bioaccu waiving/adaptations*
		► justification not related to required test (1 case)		
	Read-across	ESR not available	10	2
	Endpoint specific	registrants refers to a BCF, but no ESR is available	5	2
	Incorrect REACH reference	incorrect REACH reference	1	0.2
"Formally non-compliant" (39 %, 164 cases)	Technically not feasible	► substance is a UVCB (85 cases) ► different reasons (3 cases) ► not specified (1 case)	89	21
	Read-across	► similarity justification not available (14 cases)# ► key study not available (4 cases)# ► exposure duration was not comparable/not given or guideline could not be deduced (24 cases)#	34	8
	Endpoint specific	► REACH Annex IX 9.3.2. column 2, 1st bullet point (20 cases)# ► REACH Annex IX 9.3.2. column 2, 2nd bullet point (8 cases)# ► key study not available (12 cases)#	30	7
	(Q)SAR	► QMRF is not available (8 cases)# ► QPRF is not available (8 cases)# ► model is not validated (7 cases)# ► no statement that substance is included in the applicability domain of the model (8 cases)#	8	2
	Incorrect REACH reference	incorrect REACH reference (2 cases)	2	0.5
	Exposure considerations	waiving justification cannot be assigned to the specific REACH Annex XI No 3.2.(a) - (c) criteria (1 case)	1	0.2

* Reference to 422 investigated waiving.

More than one reason might apply for a particular case.

3.3.10 Ecotoxicity

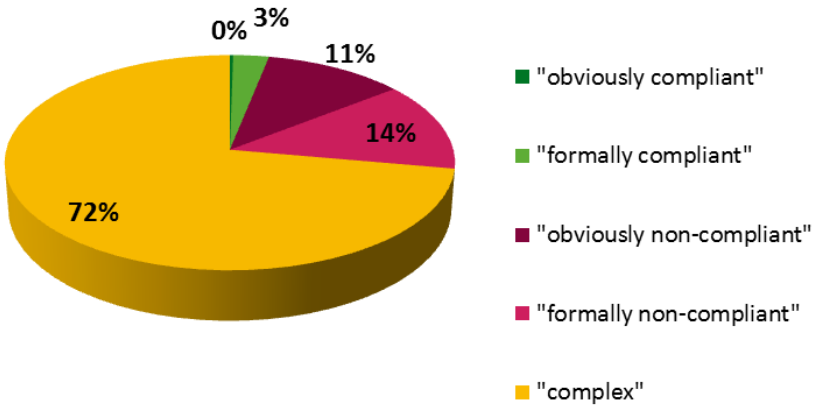
Information on aquatic toxicity as part of the endpoint Ecotox is required to assess the hazard and risks of a chemical to freshwater systems. Aquatic toxicity is described as the property of a substance to be detrimental to an organism in short-term and/or long-term exposure to that substance (ECHA, 2012a). Thus, the determination of aquatic toxicity is mainly based on data on short- and long-term toxicity regarding invertebrates (preferably *Daphnia*) as well as fish and algae. This information is most important for the environmental hazard assessment, *i.e.* classification and derivation of the PNEC and the identification of toxicity in the PBT and vPvB assessment. In addition, information on aquatic toxicity may influence to which extend data for other endpoints, *e.g.* Bioaccu, are required (ECHA, 2012c). Therefore, short-term tests with invertebrates and fish are required for a produced or imported quantity of at least 1 tpa and 10 tpa, respectively (REACH Annex VII 9.1.1. and Annex VIII 9.1.3.). Long-term testing should be considered if the substance is poorly water soluble. For produced or imported 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 to investigate long-term effects (REACH Annex IX 9.1.).

Overall results

In 1493 dossiers, the available information on short-term and long-term toxicity testing for invertebrates and fish was evaluated. These selected endpoints in dossiers remained without conclusion ("complex") in the preceding project and required further evaluation (Springer et al., 2015).

In the present project, the majority of the dossiers regarding this endpoint still remained without conclusion ("complex") (72 %, Figure 3-39). In total, 25 % of the dossiers were "non-compliant" (14 % "formally non-compliant" and 11 % "obviously non-compliant", see Figure 3-39). At least 3 % and 0.3 % of the dossiers were "formally compliant" and "obviously compliant", respectively, with regard to the information requirements.

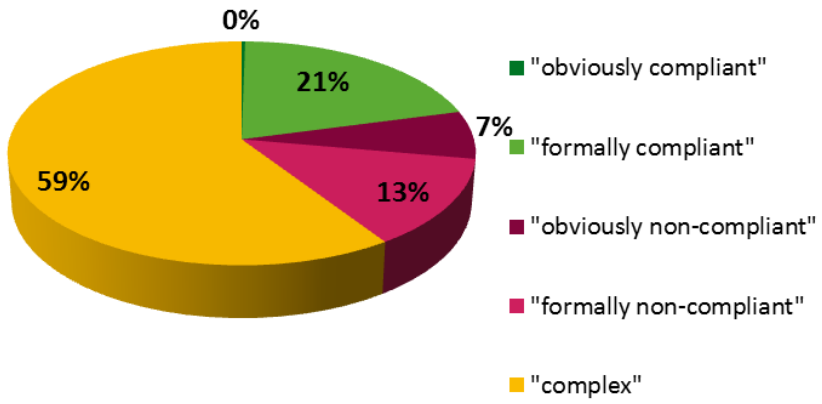
Figure 3-39: Ecotoxicity: Endpoint conclusions in formal check (total number: 1493)



The distribution of conclusions differs if endpoint specific waiving or adaptations for the required short- and long-term tests with invertebrates and fish were assessed. Results are shown in Figure 3-40. In total, 4768 waiving justifications were evaluated for the ENV endpoint Ecotox. Still, 59 % endpoint cases remained without conclusion ("complex") and are to be resolved in the follow-up project. The "formally non-compliant" and "obviously non-compliant" cases comprise 13 % and 7 %, respectively. Further, 21 % and in 0 % of all waiving and adaptations were assigned as "formally compliant" and "obviously compliant", correspondingly.

In order to fulfil the information requirements in the present project for Ecotox ("formally compliant" or "obviously compliant") either short- and long-term toxicity testing for each with two species is mandatory or is replaced by a reasonable waiving/adaptation approach. The difference in distribution between Figure 3-39 and Figure 3-40 can be explained with the independent evaluation of multiple waiving or adaptation approaches for different tests (short-term fish, long-term fish, short-term invertebrate and long-term fish) within the same dossier.

Figure 3-40: Ecotoxicity: Conclusions over waiving/adaptations in formal check (total number: 4768)



Ecotox decisive waiving/adaptation categories for the endpoint conclusions

In contrast to the other ENV endpoints, frequently, more than one waiving/adaptation category was decisive for the endpoint conclusion. Especially, this applies if more than one aquatic toxicity test remains without conclusion ("complex"). This is the reason why Figure 3-41 shows all decisive waiving/adaptation categories and not the endpoint conclusion.

Basically, inappropriate (Q)SAR models, *e.g.* PETROTOX, were responsible for the "non-compliant" conclusions but also read-across approaches or miscellaneous reasons contributed. The underlying reasons are analysed in detail below (header Ecotox reasons for "non-compliance"). Most of the "formally compliant" cases based on read-across approaches (28 dossiers). In the remaining cases, waiving or testing adaptations were successfully applied using different justifications, *e.g.* based on exposure considerations or reasoning that testing with the substance was technically not feasible.

Reasons for the high percentage of dossiers without conclusion ("complex") are related mainly to endpoint specific waiving arguments, regarding long-term toxicity testing on invertebrates (*Daphnia*) and fish according to REACH Annex IX 9.1.5./6. Another main reason was the use of a non-standard guideline. In these cases, either another or no official regulatory guideline was followed in testing.

Only four dossiers were "obviously compliant" – two of them because a registration of the substance was according to REACH Annex IV or V not necessary and for the others a read-across approach was not required.

Both short-term studies on either invertebrates or fish are obligatory with the exceptions mentioned in **column 2** as laid down in **Annex VII 9.1.1. and Annex VIII 9.1.3.** of the REACH Regulation. Whereas long-term toxicity testing must be considered if the substance is poorly water soluble or shall be proposed by the registrant if the CSA indicates the need to further investigate the effects on aquatic organisms.

The short-term tests can be replaced if a long-term study is available following the options in column 2 of REACH Annex VII 9.1.1. for the invertebrates or REACH Annex VIII 9.1.3. for fish. Registrants made "formally compliant" use from this option for the invertebrate toxicity testing in 26 dossiers but in only six dossiers for the fish toxicity testing.

The waiving of short-term aquatic testing on invertebrates or fish is "formally compliant" if there are indications that aquatic toxicity is unlikely to occur (*e.g.* the substance is unlikely to cross biological membranes). This reasoning was found in 27 dossiers for the invertebrate test and in 20 dossiers for the fish test to be "formally compliant". The "formally non-compliant" cases were 19 for the invertebrate test and 22 for the fish test.

The endpoint specific adaptation justification referring to REACH **Annex IX 9.1. column 2** "long-term toxicity testing shall be proposed by the registrant if the CSA indicates the need to investigate further the effects on aquatic organisms" was not concluded and, therefore, remained as "complex". Thus, all endpoint waiving classified as "complex" referred to REACH Annex IX 9.1. column 2 to omit long-term testing on either invertebrates (*Daphnia*) (648 cases) or fish (957 cases).

Almost all cases classified as "formally compliant" referred to REACH Annex VII 9.1.1. column 2 or Annex VIII 9.1.1. column 2 to refrain from short-term testing on invertebrates (*Daphnia*) (51 cases) or fish (27 cases), respectively.

An adaptation of long-term toxicity of fish and invertebrates was justified by referring to REACH Annex IX 9.1. column 2 "long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment indicates the need". This waiving justification was assigned to the conclusion category "complex" because an in-depth evaluation is needed to analyse whether the data presented in the CSA support this justification. Several aspects are important to be considered when evaluating the potential risk of chronic toxicity to aquatic species such as the potential to bioaccumulate, the route of exposure and input of the chemical in the aquatic environment. The ECHA guidance R.7b emphasises that a risk from the CSA is indicated by (ECHA, 2012a; ECHA, 2016a):

- a ratio of PEC/PNEC > 1 or
- for substances with a log K_{ow} > 3 (BCF > 100) and
- a PEClocal or PECregional > 1/100th of the water solubility

Other arguments used in registration dossiers were referring to substance properties such as low water solubility, ready biodegradability, low acute toxicity to either fish or invertebrates and species sensitivity. However, ECHA also states in its guidance document R.11 on PBT assessment that the toxicity criterion for PBT assessment cannot be decided on the basis of acute studies alone ECHA (2012c). When the checking criterion of the effect concentration causing 50 % effect (EC50) less than 0.1 mg/L is met, chronic studies are required (ECHA, 2012c). It was not possible to decide if long-term testing is necessary based on a sole formal evaluation. Further research is needed to evaluate whether the CSA indicates the absence of a risk to the aquatic environment or the presented data is sufficient for classification and risk assessment purposes.

Altogether 1182 **read-across approaches** were counted. A standard method was used in 934 cases and these were included in the further evaluation of the read-across approaches. The other 248 cases remained in the category "read-across+non-standard method" and were concluded as "complex" in 245 cases and three cases were "obviously non-compliant" because of the inappropriate usage of an OECD TG 204 study for the long-term fish test.

The majority of read-across approaches (72 %, 691 cases) was classified as "formally compliant". Read-across approaches were used predominantly in a "formally compliant" way either for the short-term toxicity testing on invertebrates (*Daphnia*) (221 cases) or fish (221 cases). Long-term toxicity testing on invertebrates comprised 185 cases and long-term toxicity testing for fish included 60 cases

of read-across classified as "formally compliant". An adaptation was not required in five cases and these cases were "obviously compliant".

The remaining 14 % of the read-across approaches were classified either as "formally non-compliant" (207 cases) or "obviously non-compliant" (30 cases) and are discussed below under the header "Ecotox reasons for "non-compliance"".

WoE approaches were identified in 468 cases. These were mainly allocated to the "complex" conclusion category including also 34 "complex" cases of project I which were not excluded for technical reasons in this project. Three of the WoE cases were "obviously non-compliant" due to missing ESRs.

In the further evaluation, **(Q)SAR** adaptations were classified either as "formally compliant" (26 cases) or as "obviously non-compliant" (131 cases) "formally non-compliant" (101 cases). More information on (Q)SAR methods is presented under the header "Ecotox reasons for "non-compliance"".

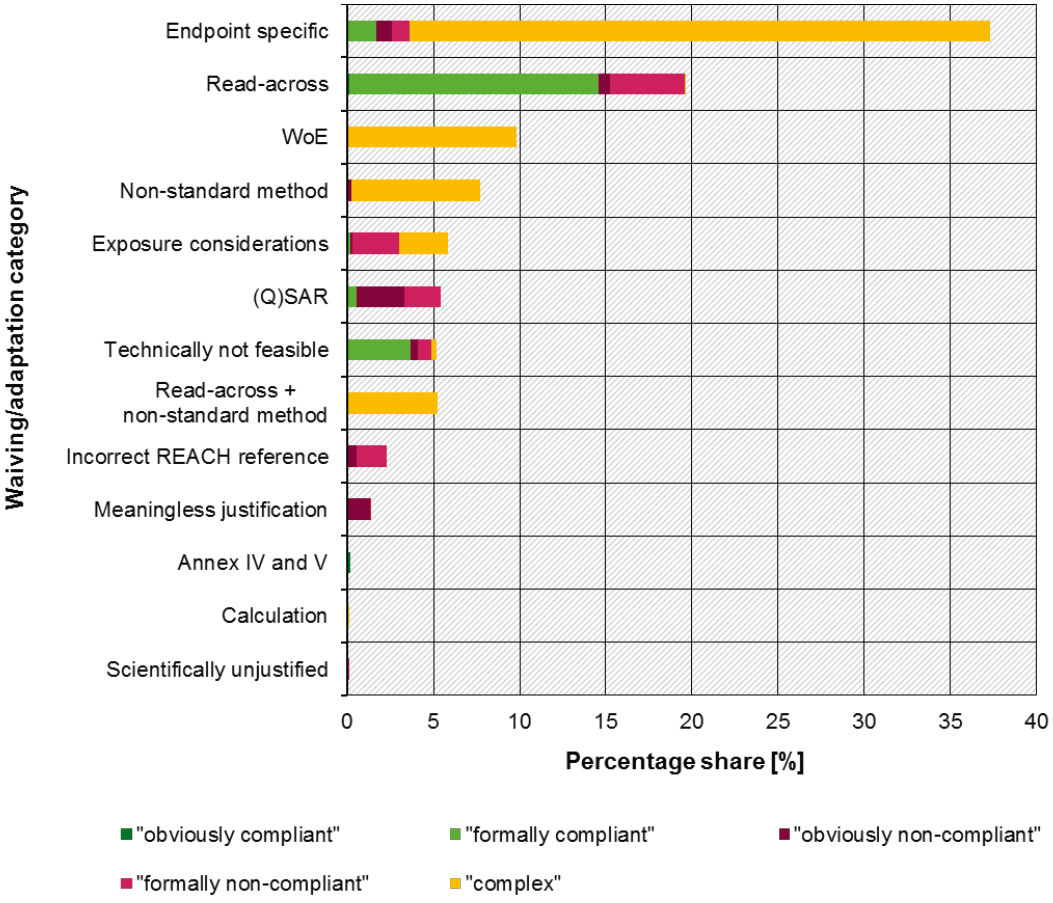
The waiving justification according to REACH **Annex XI 2. "Study cannot be conducted as a consequence of the properties of the substance"** was in 31 cases considered as "formally compliant" (*e.g.* substance reacts violently with water, reaction product with water is a flammable gas). In 191 cases, waiving of the test was justified based on **"Study cannot be conducted as a consequence of the technical limitations of a test method referred to in Article 13(3)"** and 142 of these cases were considered to be "formally compliant", whereas 35 were "formally non-compliant" and 14 remained without conclusion ("complex").

On the one hand long-term toxicity testing should be considered if the substance is poorly water soluble (< 1 mg/L) (Annex VII, 9.1.1 and Annex VIII, 9.1.3), on the other hand, Annex XI, 2, gives the opportunity that a "Study cannot be conducted as a consequence of the technical limitations of a test method referred to in Article 13(3)". This gives somehow a predicament. Although appendix R.7.8-1 describes how to deal with "Critical parameters for aquatic toxicity testing" including the water solubility as parameter, it does not specify the criteria when it is reasonable to waive aquatic testing. But finally, the registrant has to verify that aquatic toxicity is unlikely to occur and to demonstrate the safe use of the substance and that proper risk management measures are implemented. For this purpose, a waiving/adaptation of the standard testing regime should be justified or testing methods like the use of the transformation/dissolution (T/D) protocol for inorganic substances or the Water Accommodated Fraction (WAF) technique for organic substances could support waiving/adaptation of the standard information requirements.

Exposure-based waiving may be considered when environmental exposure is absent or not significant. Under these circumstances a refinement of the risk management would not be required.

In comparison, exposure based triggering of long-term aquatic testing according to REACH Annex IX is the case when a PEC/PNEC > 1 is given. It should be kept in mind that the reverse conclusion PEC/PNEC < 1 does not imply not to conduct the long-term testing because the risk of a chemical could also be triggered by other means in the CSA (*e.g.* for substances with a log K_{ow} > 3 (BCF > 100), a PEC_{local} or $PEC_{regional}$ > $1/100^{th}$ of the water solubility). In this connection, it was concluded that exposure based waiving according to REACH Annex XI 3.2.(a) (i) remained "complex" because this requires a more detailed assessment of the CSAs.

Figure 3-41: Ecotoxicity: Decisive waiving/adaptation categories and their contribution to the end-point conclusions in formal check (total number of waiving/adaptations: 4921 – including other standard and non-standard methods)



Reasons for "non-compliance"

An overview on reasons for "non-compliance" of waiving/adaptation justifications is given in Table 3-18. One can see that the reasons were numerous for Ecotox. The application of (Q)SAR models and read-across approaches were of major concern and therefore, the subsequent description focuses on these two adaptation approaches.

(Q)SAR models were applied 258 times to replace the required aquatic toxicity testing. Since 128 of those adaptation approaches calculated the toxicological data with the PETROTOX or PETRORISK model, they were assigned to the conclusion category "obviously non-compliant". These conclusions based on the recommendations of Rorije et al. (2012), who reviewed the PETROTOX model and the HBM that are both integrated into the PETRORISK model. The critical review summarises essential shortcomings with respect to the effect assessment. The underlying target lipid model showed some weaknesses concerning the validation (Rorije et al. (2012)):

- normal distribution for log CTLBB (critical target lipid body burden) were not met
- independent parameters were not met for CTLBB and the universal slope for narcosis
- numerical values used for acute-to-chronic ratio, including chronic values instead of no observed effect concentrations (NOECs)

An example given by Rorije et al. (2012) for Poly Aromatic Hydrocarbons (PAHs) shows that the hazardous concentration for 5 % of the species (HC5) is even after chemical class correction in average factor 3 to 5 times higher than if they were derived from chronic toxicity data.

Furthermore, if the weaknesses of the target lipid model were erased, an additional AF should be chosen and applied to the final HC5 value according the REACH guidance to address remaining uncertainties (Rorije et al. (2012).

The remaining adaptations regarding (Q)SAR models were further evaluated except for three cases. These were "obviously non-compliant" because no ESR was available.

(Q)SAR methods regarded as "formally non-compliant" were given for 2.1 % of all waiving/adaptations. A missing QMRF (39 cases) or QPRF (39 cases), insufficient validation according to the OECD principles (81 cases) and/or the substance was not included in the applicability domain of the model (65 cases) were the reasons for the high number of "formally non-compliant" (Q)SAR adaptations. The available (Q)SAR models are mostly suitable for the prediction of the short-term toxicity. In contrast, the validation of the (Q)SAR models for long-term toxicity requires improvement (Warnecke et al., 2011).

The documentation of the applied (Q)SAR models requires improvements. Both reporting formats – QMRF and QPRF – intend to assure transparency in the applied approaches. For this purpose, it is necessary also to provide the required information requested by the reporting formats QMRF and QPRF – and not to solely refer to literature, CSR, QMRF, QPRF or *vice versa*.

22 % of the read-across approaches were classified as "formally non-compliant" (207 cases), mainly because of insufficient documentation and justification of the read-across approach.

Table 3-18: Ecotoxicity: Main reasons for the allocation of particular waiving/adaptations to the conclusion categories “obviously non-compliant“ and “formally non-compliant“ in formal check

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number	Percentage [%] of all Ecotox waiving/ Adaptations*
"Obviously non-compliant" (7 %, n = 330)	(Q)SAR	► the PETROTOX or PETRORISK model was used to predict the acute and/or chronic tests (128 cases) ► ESR not available (3 cases)	131	2.7
	Meaningless justification	► reference and justification do not match or no justification given for reference (35 cases) ► justification not related to the required test (15 cases) ► ESR not available (8 cases) ► waiving not available (2 cases) ► CSR not available (1 case)	61	1.3
	Endpoint specific	► ESR not available (19 cases) ► justification not related to the required test (15 cases) ► justification and reference do not match (5 cases) ► CSR not available (2 cases)	41	0.9
	Read-across	► ESR not available	30	0.6
	Incorrect REACH reference	► different incorrect REACH references	24	0.5
	Technically not feasible	► metabolites are not addressed (4 cases) ► justifications do not match with REACH Annex XI 2 (10 cases) ESR was not available for water solubility (6 cases)	20	
	Non-standard method	► OECD TG 204 with a test duration of 14 d ► test duration too short (1 case) ► bioaccumulation test (1 case)	13	0.3
	Exposure considerations	► justification and reference do not match **or** no justification given for reference	5	0.1
	WoE	ESR not available	3	0.1
	Scientific reasons	reliability 3/4	2	0.04
"Formally non-compliant" (13 %, n = 614)	Read-across	► similarity justification not available (203 cases)[#] ► key study not available (5 cases)[#] ► exposure duration was not comparable/not given or guideline could not be deduced (2 cases)[#]	207	4.3
	(Q)SAR	► QMRF not available (39 cases)[#] ► QPRF not available (39 cases)[#] ► model not validated (81 cases)[#] ► substance not included in the applicability domain of the model (65 cases)[#] ► key study not available (9 cases)[#]	101	2.1

Conclusion category	Waiving/ adaptation category	Main reason(s)	Number	Percentage [%] of all Ecotox waiving/ Adaptations*
	Endpoint specific	► REACH Annex VII 9.1.1. column 2, 1st bullet point (5 cases) # ► REACH Annex VII 9.1.1. column 2, 2nd bullet point (2 cases) # ► REACH Annex VII 9.1.1. column 2, 3rd bullet point (1 cases) # ► REACH Annex VIII 9.1.3. column 2, 1st bullet point (11 cases) # ► REACH Annex VIII 9.1.3. column 2, 2nd bullet point (13 cases) # ► key study with a reliability 1/2 not available (12 cases) # ► ESRs not available for studies which registrant refers to (6 cases) ► justification not related to the required test (3 cases)	51	1.1
	Exposure considerations	► waiving according to REACH Annex XI 3.2.(a) (19 cases) # ► waiving justification cannot be assigned to the specific REACH Annex XI 3.2.(a) - (c) criteria (112 cases) # ► exposure scenarios were not available in the CSR (52 cases) #	131	2.7
	Incorrect REACH reference	► different incorrect REACH references	84	1.8
	Technically not feasible	only reference to REACH Annex XI 2., last sentence was given and/or the explanation was not sufficient (35 cases)	37	0.8
	Meaningless justification	► justification not related to all relevant components of the substance (2 cases) ► justification not related to required test (1 case)	3	0.1

* Reference to 4768 investigated waiving.

More than one reason might apply for a particular case.

3.4 Refined Check

3.4.1 Overall results of human health endpoints

Remaining data of the project I (chapter 3.4.1.1 to 3.4.1.4) and project II (chapter 3.4.1.5), further data after the screening and formal check (chapter 3.4.1.6) were analysed further with regard to particular aspects of HH endpoints as *e.g.* non-standard administration routes, available waiving/adaptation justification which required an evaluation in detail, or the implementation of WoE approaches.

3.4.1.1 Reproductive Toxicity – harmonised classification

Seven dossiers were evaluated with regard to availability of standard information (or adaptation) and effect level assessment for the endpoint TRep. All seven dossiers were concluded as "compliant" because in the dossiers testing data have been evaluated and effect levels have been derived.

Data availability was concluded based on the conduction of the screening process developed in project I. According to the screening, standard information was available for two dossiers concerning DevTox and two dossiers concerning ReproTox. Table 3-19 gives the results of the screening from project I conducted on these endpoint cases. It is to be noted that the lack of a PNDT study in a second species or lack of an according waiving justification was concluded as "non-compliant" (despite the conclusion "complex" within project I), see also chapter 2.6.3.3. Actually, the lacking of the second species or a waiving in this regard for DevTox occurred several times. Also, presented studies were not conducted according to or similar to the OECD guidelines.

However, the presented data was not further assessed due to the fact that the substances have been already classified according to CLP (classification for effects on sexual function, fertility and developmental toxicity – Reproductive Toxicity Category 1A or 1B (H360FD)).

Table 3-19: Developmental/reproductive toxicity: Harmonised classification Repr.* 1 A/B (H360FD)

Data availability: Number of decisions according to screening and deviations from the standard information			Number of NOAEL availability	Number of decisions
TRep (combined tree) according to project I	DevTox	ReproTox		
5 "non-compliant" 2 "complex"	5 "non-compliant" waiving 2nd species lacking; non-guideline study, waiving lacking 2 "compliant"	5 "non-compliant" non-guideline study, waiving lacking; screening, waiving lacking 2 "compliant"	7 Yes	7 "compliant"

* Repr. = Reproductive Toxicity Category

3.4.1.2 Reproductive and developmental toxicity – non-standard administration route

Registrants are obliged to use all existing data. Animal experiments may only be carried out if data gaps are present. Therefore, it was investigated whether there are any properties of the substances that oppose the administration route under investigation. Otherwise the studies have been accepted.

Out of the 15 cases examined, one dossier was not evaluated, since obviously data for the two-generation study were missing. This dossier remained "complex" for both endpoints ReproTox and DevTox. The data might possibly not be properly migrated from IUCLID 5 to IUCLID 6.

Of the 14 cases, inhalation studies were reported in eleven cases. This was in one case a substance with very high vapour pressure (> 100 hPa) and, in five cases, substances with high vapour pressure (> 10 hPa). The inhalation route has therefore been regarded as "compliant" for these dossiers for ReproTox and DevTox. The remaining five cases were volatile substances with boiling points around 80-150 °C but low vapour pressure below 10hPa. However, all of these substances are used as binders/solvents in filling compositions or paints and are evaporating under the conditions of normal use. Human exposure is therefore, in general, the inhalation route ("compliant" for ReproTox and DevTox). However, a justification for the administration route was not available in some of these dossiers. In this regard, dossiers should be improved. In contrast, additional information on the test conditions and exposure method was always available.

Three dossiers were set "compliant" for ReproTox (standard information available according to screening) but a dermal developmental study conducted in rabbits was each presented. A justification for the administration was always not available. Due to the classification concerning skin contact and/or the described bioavailability of the substance during testing according to the OECD TG 414, the three dossiers were categorised as "compliant".

3.4.1.3 Developmental toxicity – waiving justification for second species

As already described in the concept, all 252 dossiers for the endpoint DevTox **lacking the waiving justification for the second species** were concluded as "non-compliant" in the refined check (Table 6-12 in Annex 5). These results contributed to the updated results for the endpoint DevTox.

Two cases for which the waiving/adaptation justification for OECD TG 414/second species was available and which remained "complex" were set as "non-compliant" because the waiving/adaptation for OECD TG 416 was not available.

Other cases of waiving/adaptation justifications are described in chapter 3.4.1.5.

3.4.1.4 Mutagenicity – special cases

During the screening of project I three cases remained "complex" for which minimum one positive *in vivo* soma cell test **and** a negative Germvivo **and** *in vitro* bacteria test or waiving/adaptation of *in vitro* bacteria test were available.

These open dossiers were analysed case-by-case: Since a guideline study for the *in vitro* bacteria test stated as key study was available, all ESR were checked concerning completeness (standard information requirement) and outcome (genotoxicity: negative/positive/ambiguous). If all requirements are fulfilled the dossier was classified as "compliant" (one case out of three). The second case was grouped as "non-compliant" because the ESRs did not include all study data which were needed to make a conclusion on the genotoxicity of the substance. The third case of this group was primarily checked concerning the *in vitro* bacteria test, but then the study data was checked concerning the WoE approach of the other *in vitro* and *in vivo* ESRs (see chapter 2.6.2 and 2.6.3.6).

3.4.1.5 Mutagenicity, developmental and reproductive toxicity – available waiving justifications

The remaining "complex" endpoints from the formal check of project II (see Table 6-13 in Annex 5) for Muta, DevTox and ReproTox belonged to the following categories:

- endpoint specific
- justification available, but not based on REACH criteria
- other justifications
- WoE (description see chapter 3.4.1.6)

For the grouping/read-across approaches the formal check was conducted during project II. Within the scope of the refined check formal criteria for this approach were evaluated if the mentioned category (see above) was combined with grouping/read-across. For Muta a conclusion could be made if

the standard information requirements, accordingly with regard to the results of the testing, were fulfilled and the grouping/read-across approach fulfilled the formal criteria.

If possible, conclusions concerning the "complex" endpoints were drawn, mainly due to formal and/or obvious reasons. In some cases the waiving/adaptation justification was so extensive and included different aspects so that the presented information and studies should be evaluated in detail to come to a conclusion. If such a further check (*e.g.* of additional studies and/or information, content-related) was necessary the endpoint had to remain without conclusion (still "complex"). Hence, the majority of cases would require case-by-case analysis and/or expert judgement.

Endpoint specific justifications

The waiving/adaptation justifications of this case group were mainly based on REACH Annex X 8.7. column 2 – on the one hand by giving the correct reference or on the other hand by describing that the substance is known to be a genotoxic carcinogen. Only a few registrants specified the classification within the waiving text and/or the endpoint summary. The highest proportion of these cases remained "complex" due to the necessary in-depth analysis if the substance is already classified and if the study data, if available, could lead to an alteration of the classification.

Concerning Muta all cases, just four, could be concluded – one case was set as "compliant", the other were "non-compliant" because of missing data. If the substance is known to be carcinogenic category 1A or 1B or germ cell mutagenic category 1A, 1B or 2 the availability of the *in vitro* bacteria test is formally necessary (accordingly to REACH Annex VII 8.4.1.). However, in one case the decision was "compliant" because independent of the result of the *in vitro* bacteria test the classification would not be altered. Concerning another case the result of the *in vitro* bacteria test could lead to additional requirements. With regard to the second criterion the ESRs were checked if adequate data for *in vivo* mammalian gene mutation test were available. When all standard information requirements were fulfilled the conclusion was set as "compliant".

Available justifications without REACH reference

The cases of this group were categorised due to justifications which were not based on REACH criteria, *i.e.* registrant does not refer to the waiving/adaptation options set out in REACH Annexes VII to X column 2 or Annex XI; these cases are assigned to REACH Annexes VII to X introduction, last paragraph. During the refined check not only the waiving text but also the endpoint summary was evaluated.

The waiving/adaptation justifications of this group often included the reference REACH Annex XI 1. "testing does not appear scientifically necessary" as well as in combination with other reasons or consisted of a free text. Case-by-case analysis led to a conclusion, without exception "non-compliant", or to further check of the presented information (cases remained "complex"). Reasons for "non-compliance" are mentioned in Table 2-17. The most frequently recurrent waiving/adaptation justifications were "natural materials/products" and "inert substance". One part of these cases remained without conclusion ("complex"), the other part had to be categorised as "non-compliant".

Other justifications

After the refined check the cases within the category "not available" (see Table 2-15) were set as "non-compliant" due to missing standard information or waiving/adaptation justification which were not fulfilled within the ESRs. The justifications referring to REACH Annex IV could be accepted, so that four cases of the endpoints Muta, DevTox and ReproTox were set as "compliant". Also, exposure scenarios (REACH Annex XI 3.) were mentioned in different justifications – these cases required a further more content-related check and remained, therefore, without conclusion ("complex").

3.4.1.6 Evaluation of weight of evidence

The remaining "complex" endpoints from the screening (see Table 6-13 in Annex 5) could be divided in the following subgroups for Muta:

- for adaptation of *in vitro* bacteria test
- for adaptation of two tests *in vitro* and/or *in vivo*
- for adaptation of one of the two waived tests *in vitro* and/or *in vivo* WoE

The cases without conclusion of the endpoints DevTox and ReproTox were subdivided with regard to the availability of the adaptation of the OECD TG 414/416 (see Table 6-13 in Annex 5). Furthermore, some cases without conclusion of the category "WoE" overlapped with the other justification categories, described in chapter 3.4.1.5 (see Table 6-13 in Annex 5), and were evaluated at the same time.

Mutagenicity

If a substance is known to be carcinogenic category 1A or 1B or germ cell mutagenic category 1A, 1B or 2 the availability of the *in vitro* bacteria test is formally necessary (REACH Annex VII 8.4.1.). Within the WoE approach of these cases the availability of reliable study data of the *in vitro* bacteria test was accepted and the endpoints were set as "compliant" (nine cases). One case remained without conclusion ("complex") because the mentioned second information source should be evaluated further.

The main part of WoE approaches with an adaptation for one or two *in vitro* and/or *in vivo* tests were evaluated to some extent for developing the evaluation concept and testing it. The available ESRs were screened for key studies and for studies categorised as WoE. On the one hand the completeness of the standard information requirements and on the other hand the results of the testing which can determine further studies were evaluated.

In order of frequency the "non-compliant" cases were caused by missing studies – mainly on the "side" of the gene mutation testing – or by positive study results which were not explained in detail and/or considered for the overall conclusion of the endpoint by the registrant. Moreover, in a few cases the grouping/read-across justification was lacking. The "complex" cases could not be concluded because the available study data should be evaluated further – *e.g.* additional no guideline-studies were presented, supporting studies had to be taken into account, and the not-considering of studies were explained. "Compliant" cases offered the necessary study data within the WoE approach and concerning the whole endpoint, and presented, if applicable, a formally "compliant" grouping/read-across justification.

Developmental and reproductive toxicity

Since the evaluation of the endpoints DevTox and ReproTox could strictly divided into two steps (see chapter 2.6.3.6), at first the deviations of the available studies from the standard (*i.e.* screening of project I), which are most close to standard or are most reliable were determined. All cases remained without conclusion ("complex") after the first step, unless *e.g.* the grouping/read-across justification or the justification for waiving the second species concerning DevTox was missing. Other reasons for "non-compliance" were the lack of decisive information, like route, species, or guideline, and if only no guideline-studies were available because these studies do not include the necessary aspects of TRep testing. The "non-compliant" conclusions were more than threefold predominate.

3.4.2 Ecotoxicity

In order to meet the information requirements within the project for the endpoint Ecotox it was necessary either to provide experimental data or a suitable adaptation or a waiving justification. This meant in detail to pass the criteria chosen for evaluation for the short-term toxicity testing and long-term toxicity testing for fish and invertebrates, respectively. Different combinations of experimental data or adaptations with read-across approaches, weight of evidence and (Q)SARs as well as waiving justifications for the respective endpoint following the special criteria (REACH Annexes VII to IX column 2) or the general criteria of REACH Annex XI were present in the dossiers.

The conclusion rate for the endpoint Ecotox increased from 28 % after formal check up to 78 % after the refined check. Figure 3-42 provides the percentages for the updated distribution after the refined check.

The endpoint Ecotox remained without a conclusion ("complex") if, *e.g.*

- a non-guideline study (*e.g.* scientific publication; memo: no guide), draft guideline (memo: no guide) or another guideline (memo: oth guide) was included for at least one of the four aquatic toxicity tests (memo: no guide);
- an adaptation of the assessment factor and a respective justification was present (memo: CSA, AF adapted);
- a testing proposal was present at least for one of the four aquatic toxicity tests
- if a WAF techniques was applied or T/D protocol was present.

Aquatic toxicity tests were evaluated as "non-compliant" when, *e.g.*

- the assessment factor was not concluded based on the delivered experimental data (*e.g.* experimental studies, read-across, WoE) and none explanation was given for adaptation;
- test duration for Daphnia magna was only 24h and no other information was provided;
- waiving of long-term aquatic toxicity testing with reference that the substance is highly insoluble but no further information providing that the substance showed no toxicity with the WAF or for inorganic substances no transformation/dissolution protocol is available (water solubility of the substance is smaller than 1 mg/L: memo: CSA, Sw < 1 mg/L).

The updated distribution for waiving/adaptation is shown in Figure 3-43. Still, 35 % of waiving/adaptations remained without a conclusion ("complex"). "Obviously non-compliant" waiving/adaptations contributed to 13 % and "formally non-compliant" waiving/adaptations to 24 %. Regularly, the "obviously non-compliant" waiving/adaptations were decisive for the overall endpoint conclusion. The percentages of "obviously compliant" and "formally compliant" waiving/adaptations were higher compared to endpoint conclusions.

Figure 3-42: Ecotoxicity: Updated conclusions after refined check (total number: 1493)

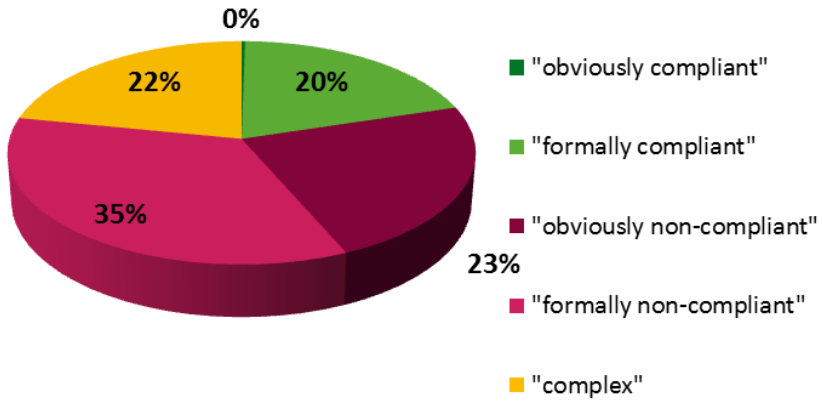
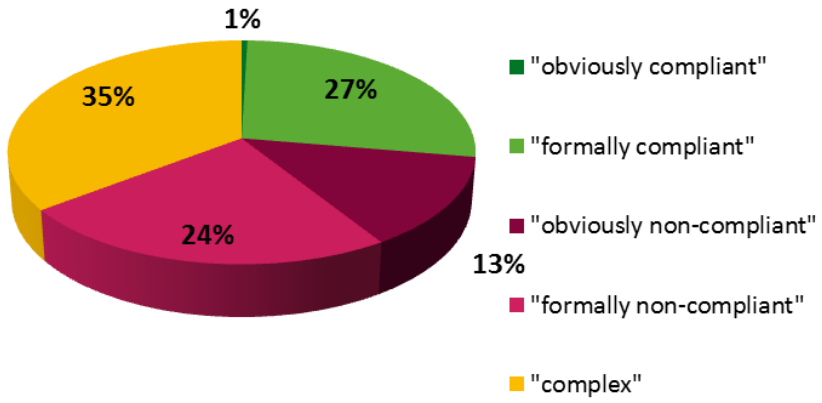


Figure 3-43: Ecotoxicity: Updated conclusions over waiving/adaptations after refined check (total number: 4949)



The updated distribution of conclusions for the individual waiving/adaptation categories after the refined check is given in Figure 3-41. An additional category “endpoint specific refined” is introduced as a waiving/adaptation category. Within this category waiving of long-term aquatic toxicity testing was justified according to REACH Annex IX column 2. Therefore, the CSA should not indicate a risk and/or no other information on a hazardous concern is available as already described in more detail in chapter 3.3.10.

In some cases, the conclusion of the formal check was withdrawn during the refined check. This was especially the case for the waiving/adaptation category “technically not feasible”, since the formal check only stated that waiving with reference to REACH Annex XI 2. was properly documented, but a content wise evaluation of the respective justification was not included.

In cases where the environmental exposure was assessed as “non-compliant” in project I it was concluded that the prerequisite was not available for the risk assessment (see chapter 2.6.4.1). In conclusion, these dossiers were evaluated as “obviously non-compliant” for the endpoint Ecotox (105 dossiers).

Frequently (in 236 dossiers), long-term aquatic testing was omitted providing that the substance is highly insoluble or the substance is poorly water soluble (water solubility smaller than 1 mg/L). As described in chapter 3.3.10 a water solubility < 1 mg/L triggers already long-term aquatic toxicity testing with daphnia and fish if a short-term aquatic test is required as standard data information according to REACH Annex VII or VIII. ECHA clarified in their questions & answers section that evidence is needed if it is stated that the substance is highly insoluble either by a T/D protocol for inorganic substances or aquatic toxicity testing should be conducted with the WAF technique (ECHA, 2017b).

The refined check provided for 224 dossiers that the justification was not sufficient for stating that aquatic toxicity is unlikely to occur at the limit of the water solubility. In two dossiers, it was justified to refrain from testing for a chronic fish test because experimental data for the chronic daphnia test were available and provided that PEC/PNEC is smaller than 1 with an AF of 50. A conclusion on the endpoint Ecotox was not made in ten dossiers because further evaluation is required either with respect to the T/D protocol or the WAF technique.

The REACH regulation requires using all experimental data available for the substances being registered. Therefore, guidance is given by ECHA (2016a) on how to evaluate and integrate experimental data in the chemical safety assessment. On the one hand ECHA (2016a) provides an overview of methods which could be assigned as equivalent to the methods according to Article 13(3), on the other hand, guidance is given on how to evaluate data from non-guideline studies and other guideline studies.

The endpoint Ecotox remained without a conclusion if a non-guideline study (*e.g.* scientific publication; memo: no guide), draft guideline (memo: no guide) or another guideline (memo: oth guide) was included for at least one of the four aquatic toxicity tests investigated.

WoE approaches were also analysed during the refined check and are described in detail the sub chapter 3.4.2.1. The results are already integrated in Figure 3-43 and Figure 3-44.

Exposure based waiving was evaluated during the formal check as well. Whenever reference to REACH Annex XI 3.(a) (substance-tailored exposure-driven testing) or PEC/PNEC < 1 was made these endpoints remained without a conclusion. A conclusion would have required an evaluation of the CSA whether a risk is indicated.

The refined check included the assessment whether an exposure based waiving was appropriate for the endpoint Ecotox. Therefore, both waiving/adaptation categories “exposure consideration” and “endpoint specific refined” were evaluated according to chapter 2.5.2 and 2.6.4.1. This was the case for 70 dossiers. Half of them remained without a conclusion for different reasons, *e.g.* the usage of non-guideline or other guideline studies for the other provided aquatic toxicity tests or the availability of a testing proposal and/or qualitative exposure assessment.

Overall, 24 dossiers met the criteria of the refined check and were evaluated as “formally compliant”. In five dossiers the ENV endpoint Ecotox was evaluated being “obviously non-compliant” because either the endpoint environmental exposure was “non-compliant” in project I or the PNEC integrated predictions from (Q)SAR models with non-available or insufficient or validation data. Another five dossiers were “formally non-compliant” for the endpoint Ecotox for different other reasons, *e.g.* if the applied AF was not appropriate.

Main reasons for “non-compliance” are given in Table 3-20.

Figure 3-44: Ecotoxicity: Updated decisive waiving/adaptation categories and their distribution to the endpoint conclusions after the refined check (total number of waiving/adaptations: 4949 – including other standard and non-standard methods)

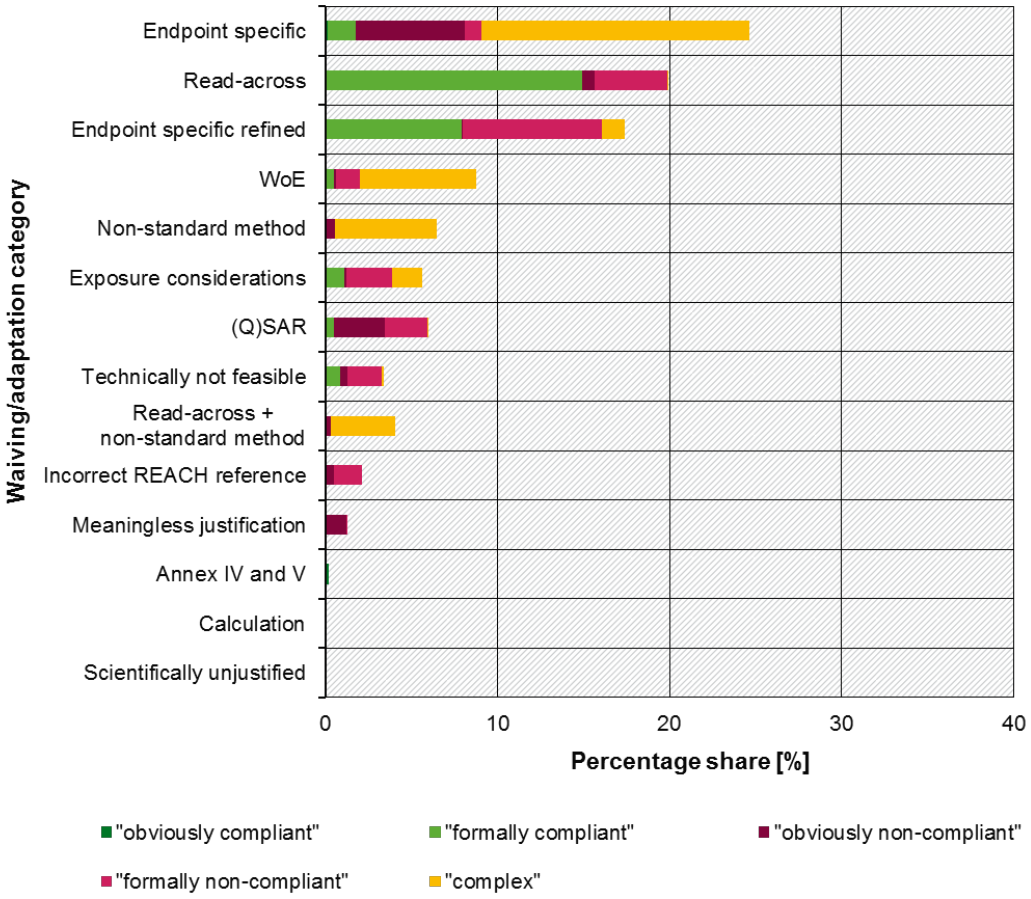


Table 3-20: Ecotoxicity – Chemical safety assessment: Main reasons for the allocation of particular waiving/adaptations to the conclusion categories “obviously non-compliant” and “formally non-compliant“

Conclusion category	Information	Main reason(s)	Number of waiving/adaptation
“Obviously non-compliant” (5 cases)	Non-standard method	► method not appropriate for the endpoint (short-term testing instead of long-term testing)	5
“Formally non-compliant“ (406 cases)	Water solubility	► substance is highly insoluble or poorly insoluble	224
	Assessment factor	► assessment factor not appropriate	73
	Expo	► environmental exposure assessment not available although required	38
	Risk is indicated	► PEC/PNEC > 1	22
	Mode of action	► a special mode of action	32
	Sensitivity	► one species is substantially more sensitive	18

3.4.2.1 Weight of evidence

A WoE approach was present for 435 waiving/adaptations. In total, 112 waiving/adaptations were evaluated more in detail. For 101 waiving/adaptations a WoE approach was suitable because more than one piece of information was provided and data waiving was not considered as well.

Overall, 25 WoE approaches were evaluated as "formally compliant", but in two cases, the provided WoE would not have been required.

In total, 334 WoE approaches remained without a conclusion, mainly due to the complexity of different additional waiving/adaptations for the ENV endpoint Ecotox. These cases would require case-specific judgements that would have exceeded the workload of the project.

In 27 dossiers, a WoE approach was applied to document the statistical extrapolation technique (*e.g.* species sensitivity distribution (SSD)/HC5) for PNEC derivation and usually each experimental study or read-across approach was flagged with WoE. Overall, these cases were not included in the further evaluation and remained without a conclusion ("complex") because an in-depth evaluation would be necessary.

(Q)SAR predictions were used in combination with a WoE approach in 28 adaptations of the standard information requirements for aquatic toxicity testing. These WoE approaches were entirely "formally non-compliant" because of documentation deficiencies regarding the (Q)SAR model and prediction for the respective endpoint. More precisely, QMRF and QPRF were not available.

The reasons for "non-compliance" were analysed in detail and the results are provided in

Table 3-21. This confirmed again that especially (Q)SAR and read-across approaches are both not justified and documented properly in several waiving/adaptations. This was in good agreement with the results provided in chapter 3.3.10 sub header "Reasons for "non-compliance"".

Table 3-21: Weight of evidence approaches: Main reasons for the allocation to the conclusion categories "obviously non-compliant" and "formally non-compliant"

Conclusion category	Information	Main reason(s)	Number
"Obviously non-compliant" (7 cases)	Method	► method not appropriate for the endpoint ► ESR not available for an experimental study, read-across or (Q)SAR	7
"Formally non-compliant" (71 cases)	Technically not feasible	► water solubility of the substance is < 1 mg/L	8
	Additional piece of information	► only one piece of information is available ► ESR not available for experimental study, read-across or (Q)SAR	6
	Read-across	At least one of the following criteria were not met: ► similarity justification not available# ► key study not available# ► exposure duration was not comparable/not given or guideline could not be deduced#	16
	(Q)SAR	At least one of the following criteria were not met: ► substance is not included in the applicability domain # ► QMRF and/or QPRF not provided# ► OECD validation criteria were not met	28
	Data were not appropriate for classification	► experimental study available, but a disregarded study shows an effect (1 case) ► insufficient documentation of additional information	10
	Data were not appropriate for PNEC derivation	► other information provides information that substance is hazardous	10
	WoE justification not available	Line of evidence was not provided	6

3.4.3 Environmental exposure

Step 1: Selection of dossiers for further evaluation

The "complex" cases of project I contained 911 dossiers with relevant classification and available quantitative exposure assessments (Springer et al., 2015). After selection of dossiers with the criteria of step 1, only 26 dossiers were regarded as suitable for further analysis with subsequent steps. The following observations of the refined check (Annex 8, Table 6-16) should therefore be interpreted in a qualitative manner, since the sample size of remaining dossiers with "compliant" input parameters was not sufficiently representative for a quantitative evaluation.

Step 2: Minimum information required

The selected dossiers were further analysed with regard to the quality of provided Tier 1 physico-chemical/fate properties, which resulted in zero "non-compliant" and 13 "complex" decisions due to adaptations of the standard information requirements. As example, the partition coefficient was frequently estimated from the individual solubility in n-octanol and water or calculated with (Q)SAR methods. However, it should be noted that in case of surfactants, the estimation of the partition coefficient from solubility was considered as sufficient, since the available standard methods are not applicable to surface active materials (ECHA, 2015b). The estimation of the vapour pressure by (Q)SAR and read-across was another frequently observed adaptation of physico-chemical standard information requirements. Read-across is usually not possible in case of vapour pressure (except for homologous series) and (Q)SAR may be used if determination by experiment is not feasible (ECHA, 2015b). Consequently, these cases would require a deeper assessment to clarify their "compliance".

Step 3: Completeness screening of elements

In ten out of the 13 remaining dossiers, the CSR provided more than five exposure scenarios, which led to a random selection of representative scenarios for the analysis. Hence, in these cases a "compliant" conclusion could only be referred to the selected scenarios and was not necessarily true for the exposure assessment as a whole. The availability of exposure scenarios resulted in one "non-compliant" conclusion in a case, where not all identified uses were covered by the provided exposure scenarios. The exposure of workers was always provided in the remaining ten dossiers. However, three dossiers were regarded as "non-compliant" as scenarios for the exposure of humans via the environment were not provided and a justification was missing. Moreover, four dossiers were concluded "complex", since the exposure of humans via the environment was not provided but a justification was presented. All the remaining dossiers provided scenarios for environmental exposure, but in three cases, the exposure/risk for aggregated sources was missing without justification.

Step 4: Exposure estimation

The provided quantities and emission days for manufacture and each identified use were available and plausible in the remaining two dossiers. However, both dossiers were finally concluded as "complex" due to the adaptation of ERC parameters with justification and the usage of specific environmental release categories (spERCs), respectively.

Step 5: Plausibility check

The correct assignment of PROCs and ERCs and the completeness of assessed life cycles may also represent important criteria for the "compliance" or "non-compliance" of exposure assessments. However, since all assessed dossiers were already concluded "complex" or "non-compliant" at previous stages of the evaluation process, a summary on these criteria could not be presented here.

Overall conclusion

The present results on exposure assessment emphasise that the required standard information according to REACH Annexes VII to X column 1 or the respective adaptations/waiving (REACH Annexes VII to X column 2 or Annex XI) are a prerequisite for the overall exposure and risk assessment. Explicitly, wrong input parameters could induce an error propagation underestimating potentially environmental risks. Hence, the frequently observed adaptations of the standard information requirements for the endpoints AbioDeg, BioDeg and Ecotox would require a case-specific decision on their "compliance", in order to increase the number of suitable dossiers for further evaluation. The same applies for the initial evaluation of Tier 1 physico-chemical/fate parameters (step 2), which should still be regarded as a reasonable starting point for a refined check.

The completeness screening (step 3) may represent a valuable criterion to verify the appropriateness of the exposure assessment. Although a limited number of dossiers were evaluated within this project it was already concluded in project I that environmental exposure scenarios were not available in several CSRs (266 of 1814 dossiers) although required (Springer et al., 2015).

The exposure estimation (step 4) represents a systematic approach to verify the usage of default ERCs on the one hand and on the other hand to identity adaptations of default ERC parameters and the usage of spERCs. Adaptations of default ERC would require an in-depth analysis in order to unequivocally identify "compliant" or "non-compliant" cases. Hence, a detailed analysis of environmental release parameters may only be reasonable for dossiers that fulfil the minimum information requirements confirming that the applied tiered approach of this project is adequate for its purpose.

3.5 Endpoint conclusions of screening, formal and refined check

The screening of project I investigated the availability of standard information required by the REACH Regulation in the 1814 examined dossiers of high tonnage chemicals. The main objective was to confirm that experimental studies were provided or that a waiving justification or an adaptation was present. Usually, if the required standard information was either waived with a respective justification or adapted with an appropriate approach a conclusion on the endpoint could not be drawn. Therefore, the endpoint remained without conclusion and was regarded as "complex". Subsequently, in a formal check in project II and a refined check in project III, the waiving/adaptations were evaluated in regard to their accordance with the rules of the REACH regulation. Finally, the assignments of the endpoints to "compliant", "non-compliant" and "complex" were updated with the newly derived results obtained in the formal and refined check (project II and III).

In Figure 3-45, results of project I are compared to the updated results after project II and III given for HH endpoints as well as for ENV endpoints. The update revealed an overall increase of the conclusion rate, *i.e.* dossiers which were considered as "compliant" or "non-compliant", compared to the decisions in project I.

It should be noted that the conclusion category for testing proposals was changed from "compliant" in project I to "complex" in the course of the update, since testing proposals were not subject to formal check and refined check and hence would still require further in-depth analysis to derive a final conclusion. DevTox and ReproTox have already been allocated to "complex" in project I if only for one of both endpoints a testing proposal was provided.

After screening, formal and refined check, the highest rate of "compliant" endpoint conclusions was observed for BioDeg (56 %), Muta (46 %) and RDT (43 %), whereas Ecotox (61 %), DevTox (50 %) and Muta (43 %) showed the highest rate of "non-compliant" conclusions.

The screening in project I resulted in 20 to 53 % endpoint cases within the HH endpoints that were concluded as "compliant" or "non-compliant" and in 47 to 80 % endpoint cases that were interpreted as "complex". Whereas after the screening, formal check and refined check (project I to III) of the HH endpoints 61 to 88 % were "compliant" or "non-compliant" and 12 to 39 % remained "complex". Depending on the respective endpoints, an increase by 31 to 49 %-points of the conclusion rate was observed for the HH endpoints after the formal and refined check. The strongest increase of the conclusion rate was observed for the HH endpoint DevTox. After the screening in project I, the conclusion rate was 20 % whereas in project I to III the conclusion rate increased to 69 %. Thus, an increase of 49 %-points was achieved.

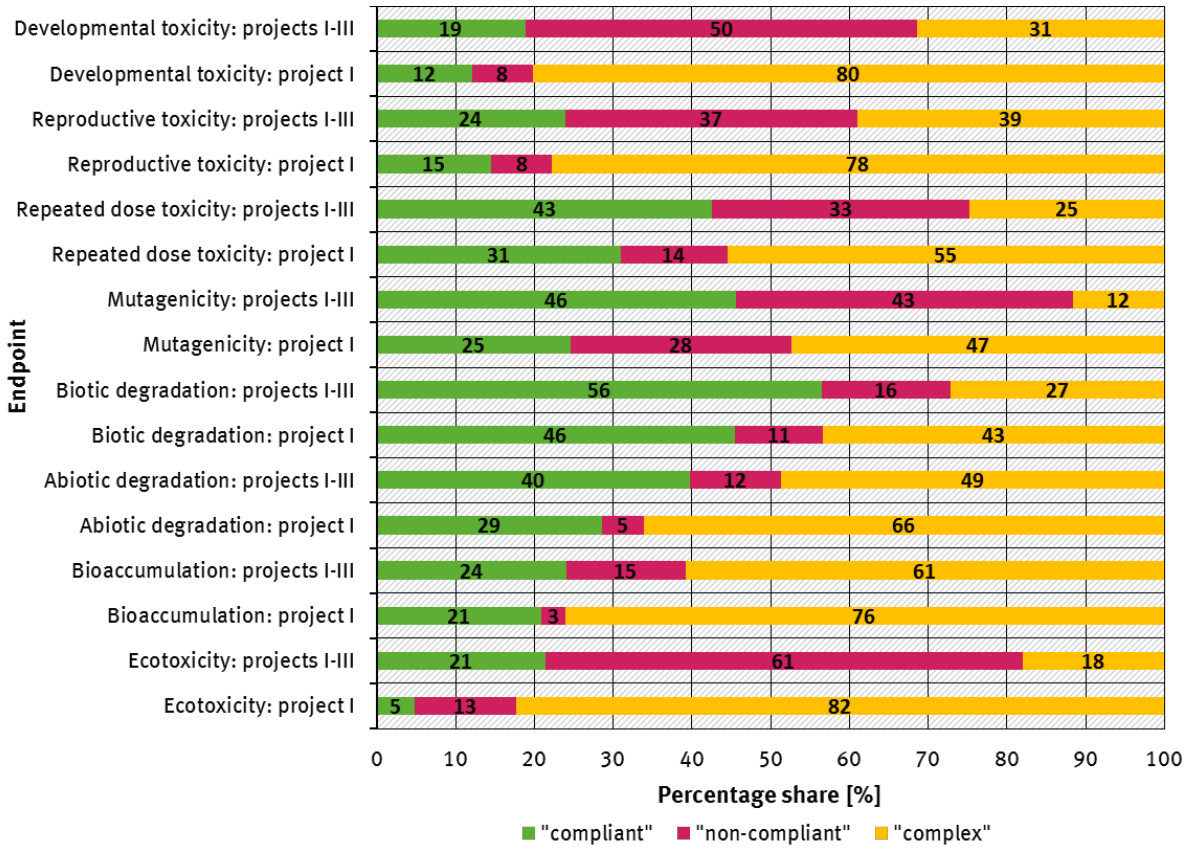
For the HH endpoints DevTox, ReproTox and RDT the percentage of "non-compliant" dossiers increased stronger than the one of the "compliant" dossiers. Only for the HH endpoint Muta the percentage of the "compliant" dossiers increased stronger than the one of the "non-compliant" dossiers. The majority of "non-compliant" endpoints after the screening, formal check and refined check was observed for DevTox due to a missing waiving justification for the second species (see chapter 3.4.1.3).

After the screening of ENV endpoints in project I, 18 to 57 % were considered as "compliant" or "non-compliant" and 43 to 82 % were regarded as "complex". Whereas after the screening, formal check and refined check (project I to III) of the ENV endpoints 39 to 82 % were concluded as "compliant" or "non-compliant" and 18 to 61 % remained "complex". Therefore an increase by 15 to 64 %-points of the conclusion rate was observed depending on the respective ENV endpoint after the formal and refined check. The strongest increase of the conclusion rate was observed for the ENV endpoint Ecotox after the formal and refined check. It increased by 64 %-points, from 18 (project I) to 82 % (project I to III).

For the ENV endpoints BioDeg and AbioDeg the percentage of "compliant" dossiers increased stronger than the one of the "non-compliant" dossiers. This is contrary to the ENV endpoints Bioaccu and Ecotox, where the percentage of "non-compliant" dossiers increased stronger.

In total, HH and ENV endpoints showed an increase of the conclusion rate after the formal and refined check (project II and III) compared to the results of the screening in project I. However, the increase was more pronounced for the HH endpoints than for the ENV endpoints, except for the endpoint Ecotox.

Figure 3-45: Screening of data availability for human health and environmental endpoints in dossiers of phase-in-substances (≥ 1000 tonnes per year) – project I – and updated results after formal and refined check of data – project I-III (total number for each endpoint: 1814)



3.6 Estimated number of dossiers with potential data gaps for developmental and reproductive toxicity

Toxicity testing on reproduction and development including teratogenicity as required under REACH is currently based on animal studies. For chemicals of the tonnage 1000 tpa and above the most comprehensive information is required for the endpoints DevTox and ReproTox. This standard information requirement is very often waived or adapted. If neither waiving nor adaptation is possible the registrant may have submitted a testing proposal.

The third project aimed at an estimate of the number of dossiers with a potential lack of animal studies for DevTox and ReproTox. This estimate considered the "non-compliant" cases of the three projects. Therefore, as a result of the screening, formal and refined check (project I, II and III) the identified data gaps regarding the endpoints DevTox and ReproTox were summed up (see Table 3-22). These data gaps included missing animal studies and cases without or insufficient justifications for waiving/adaptation. Additionally, the non-decided testing proposals (project I) could be taken into account.

Table 3-22: Developmental and reproductive toxicity: Summary of the "non-compliant" cases

Project phases	Developmental toxicity cases	Reproductive toxicity cases
Screening (project I)	140	136
Formal check (project II)*	294 ("obviously non-compliant") 172 ("formally non-compliant")	263 ("obviously non-compliant") 223 ("formally non-compliant")
Refined check (project III)#	294	48
Total sum after project III	**900**	**670**

* Within the scope of the formal check the conclusion "non-compliant" was divided into two subgroups, for description see Table 2-14.

The refined check included dossiers for which the waiving of the second species for prenatal developmental toxicity was lacking.

The summarised cases include obvious data gaps and dossiers which were "non-compliant" due to formal reasons, *e.g.* concerning the read-across approach. Therefore, not all of them will necessarily lead to the requirement of an animal test. In some cases the information requirements might be met by supplying (possibly already available) information, which addresses the according aspects in REACH Annex XI completely. Furthermore, "formally compliant" endpoints in the second project would still require an in-depth (scientific) analysis of justifications (*e.g.* on grouping/read-across) so that additional data gaps may appear.

At the end of project III, a number of dossiers finally remained without conclusion ("complex"). As not all cases could be included in the refined check (*e.g.* due to (Q)SAR). Additionally, a further check of content-related information from available studies without (full) compliance to TGs would be required, *e.g.* by a WoE analysis. These cases were not included in the estimate of potential data gaps. An approximation of data gaps for the remaining "complex" dossiers is supposed to be difficult due to the observed variation of reasons leading to the decision "complex".

Within the screening, testing proposals were categorised separately. In project I, 145 testing proposals were present for DevTox and 136 testing proposals were present for ReproTox (Springer et al., 2015). These numbers of tests might add to the total amount of "non-compliant" DevTox and ReproTox cases after project III (Table 3-22), which may function as an indicator for animal tests. Taking the testing proposals from project I into account, a total of 1045 cases/data gaps for DevTox and 806 for ReproTox were assumed.

Additionally, testing proposals for chemicals equal or above 1000 tpa submitted to ECHA and not yet decided could be taken into account. A dossier list with testing proposals under examination as at November 30th 2016 provided by ECHA was screened for phase-in substances with regard to the status of decisions. The following numbers of dossiers with testing proposals for the endpoints DevTox and/or ReproTox were identified:

- Developmental toxicity: 192 dossiers
- Reproductive toxicity: 193 dossiers.

These numbers of data gaps and not yet decided testing proposals cannot easily be summed up as additional testing proposals may have been submitted after March 2014 (date of dossier submission for this project) or testing proposals were already decided by ECHA (then they could be considered as "compliant"). For these additional testing proposals it cannot be concluded whether these were already accounted within the "non-compliant" cases or whether they belonged to the "complex" cases. The number of registrants who have sent testing proposals between March 2014 and November 2016 is unknown.

With Commission Regulation (EU) 2015/282 of February 20th 2015 the standard information requirement for ReproTox changed to an extended-one-generation reproductive toxicity study (EOGRTS, OECD TG 443) instead of a two-generation reproductive toxicity study (EC, 2015). Thus, the EOGRTS will be required where the two-generation study (OECD TG 416) was not available in 2014. Within the testing design of the EOGRTS some modules only need to be conducted if triggered (fulfilling the column 2 criteria).

All in all, 900 (DevTox) and 670 (ReproTox) dossiers with potential data gaps were estimated from the "non-compliant" cases after project III. Nevertheless, due to the above mentioned reasons, these numbers are only an indirect estimate for required animal tests and contain uncertainties.

4 Conclusions and outlook

(1) Substance sameness in lead and member dossiers of joint submissions

The evaluation of substance sameness in lead and member dossiers demonstrated that the same substance was registered in 89 % of the joint submissions for mono-constituent substances and in 50 % of the joint submissions for multi-constituent substances. The percentage of sameness is even higher if the total number of member dossiers over all evaluated joint submissions is contemplated. Thus, 98 % of member dossiers on mono-constituent substances and 57 % of member dossiers on multi-constituent substances indicated the same substance identity as the lead dossier.

The evaluation of substance sameness also revealed some obvious weaknesses regarding the description and definition of substance identity within joint submissions, particularly for multi-constituent and UVCB substances. Although multi-constituent substances should be clearly and coherently defined in the lead and in each of the member dossiers, half of the examined joint submissions did not provide the same substance identity in lead and member dossiers or a conclusion could not be derived within the scope this project. Further, for more than half (64 %) of the joint submissions for UVCB substances a conclusion was not possible. Information on the SID should be provided in the IUCLID sections 1.1 and 1.2 by lead and member registrants. This includes the name of substance, numerical substance identifiers (CAS, EC number), type of substance, (boundary) composition of the substance and information on the origin or manufacturing processes. The sameness of SID in lead and member dossiers can only be verified if the respective information is provided in IUCLID as intended. It is therefore recommended that registrants review the SIDs of their joint submission in order to scrutinise whether important information is missing, boundary composition(s) should be defined or the substance is probably registered in the wrong SIEF.

It is important to note, that sameness of the SID is a prerequisite for using the same data on physico-chemical properties, toxicity and ecotoxicity for the purpose of the hazard identification, classification and chemical safety assessment. Hence, member registrants are not able to demonstrate the safe use of their registered substance if the SID of the member dossier deviates significantly from the SID of the lead dossier.

The release of IUCLID version 6 in June 2016 could solve the observed difficulties by introducing a substance identity profile (SIP) for joint submissions (ECHA, 2016c). The registration dossiers have already been migrated from IUCLID 5 to IULID 6. Now, registrants should benefit from the opportunity to report more than one boundary composition. These boundary compositions form the SIP of the collectively registered substance and should reflect the provided hazard information and classification (ECHA, 2016c). Hence, the introduction of the SIP facilitates the comparison of substance identities within joint submissions and will be essential for assessing the relevance of existing data in the scope of REACH Annexes VII to XI.

(2) Equivalency of test materials used in key studies with the registered substance

The outcome of this evaluation revealed substance identity-related shortcomings in REACH dossiers. Regarding the total number of evaluated key studies over all endpoints, in 28 % of key studies the test material was not considered equal to the registered substance and in 6 % of key studies it remained unclear whether an appropriate material was tested. The percentage of dossiers in which the test material of at least one key study did not match the registered substance or did not allow a conclusion was only 10 to 18 % (depending on the endpoint), because often several key studies were affected for the same dossier and endpoint. It should be noted that it could not be determined whether a grouping or read-across approach was intended but maybe not properly indicated.

Further, regarding the type of substance, it was found that UVCB substances were more often affected by potential inconsistencies (41 to 66 % of key studies, depending on the endpoint) than mono-constituent or multi-constituent substances (3 to 18 % and 10 to 24 % of key studies, respectively). However, the respective dossiers of UVCB substances actually require a more detailed analysis to decide whether information on one or more constituent(s) of the UVCB substance is sufficient for the hazard assessment.

The outcome of this investigation suggests that registrants often intended a read-across/grouping approach, but missed to declare their intention correctly in IUCLID. An additional issue is the use of similar but not identical substances (*e.g.* different salts of metals). Here, the guidance on identification and naming of substances under REACH (ECHA, 2014a) gives comprehensive support on substance sameness which should be strictly followed by registrants.

(3) Formal check of endpoints of dossiers without conclusion in project I due to justified data waiving or read-across/grouping approaches

After the screening of data availability in project I (2014/15), depending on the endpoint, 43 to 82 % of the evaluated dossiers of high tonnage chemicals have remained without conclusion ("complex"). This was mostly due to justified data waiving or adaptations (Springer et al., 2015).

Therefore, a new, extended approach of in-depth analysis (formal check) was developed to evaluate these unresolved endpoints. The second project (project II, 2015/16) comprises a more detailed analysis of 6923 endpoint decisions which remained without a conclusion ("complex") in project I. Within this new approach, the registrant's justification for data waiving and adaptation was evaluated with regard to formal criteria of REACH Annexes VII to XI. However, it could not be verified whether the presented data and the scientific interpretation of these data by the registrant were appropriate. Thus, a comprehensive analysis/final assessment solving all "complex" cases was not the intention of the project.

The new approach, although only addressing formal criteria, considerably contributed to further resolve endpoint cases that remained without a conclusion in project I. Over all endpoints, 57 % of the further evaluated cases in project II which remained without conclusion ("complex") after screening could be concluded by the extended approach (74 % of HH, 39 % of ENV endpoints), while 43 % still could not be concluded (11 to 72 %, depending on the endpoint). Of the formerly "complex" endpoint decisions, 24 % were in formal conformity with REACH according to the limited scope of the evaluation scheme. It should be noted that these cases still require a more detailed analysis with respect to the scientific validity of waiving justifications and read across/grouping approaches.

From the investigated endpoint cases in project II, 24 % were considered as "compliant" (32 % for HH, 15 % for ENV) and 33 % were assigned to "non-compliant" because formal criteria were not fulfilled or there were obvious reasons for insufficient information or justifications (42 % for HH, 24 % for ENV endpoints). Concerning the ENV endpoints, the main proportion (61 %) still remained without conclusion ("complex") after the formal check.

Overall, the updated results confirmed the observation of the previous project that data gaps and/or lack of data quality exist in registration dossiers of high tonnage substances. The extended evaluation approach differed considerably from the screening of the first project in which it was determined whether appropriate data with regard to study type, applied guideline, reliability, test material etc. was existent or not. In contrast, the main work in project II comprised the evaluation of the provided waiving justifications and adaptations and their content-related categorisation according to the respective formal REACH criteria.

As a consequence of the obtained results, it is recommended that registrants should more thoroughly consider the REACH criteria for waiving/adaptation of standard information that apply to the tonnage

band(s) of their substance(s). Moreover, the entire information required should be adequately presented in the registration dossiers. Possible starting points for improvement can be deduced from the "non-compliant" cases summarised below (Figure 4-1).

The evaluation of data waiving/adaptation was rather effective if the adopted REACH criteria were sufficiently precise. Consequently, it was easily possible to identify data gaps if these criteria were not fulfilled. In case of the environmental endpoints, this applies especially to the prerequisites and/or formal criteria for

- read-across/grouping approaches,
- endpoint specific waiving if column 2 criteria include precise cut-off criteria (*e.g.* substance is readily biodegradable, S_w < 1 mg/L),
- (Q)SAR,
- exposure based waiving because of strictly controlled conditions (REACH Annex XI 3.2. (b) and (c)).

When the selected REACH criteria resulted in more complex, multi-layered requirements, the applied approach for the evaluation of waiving/adaptation was often not conclusive. This was the case for

- information requirements depending on the outcome of the CSA provided in the CSR (BioDeg, Ecotox)
- exposure based waiving because of substance-tailored exposure-driven testing according to REACH Annex XI 3.,
- WoE.

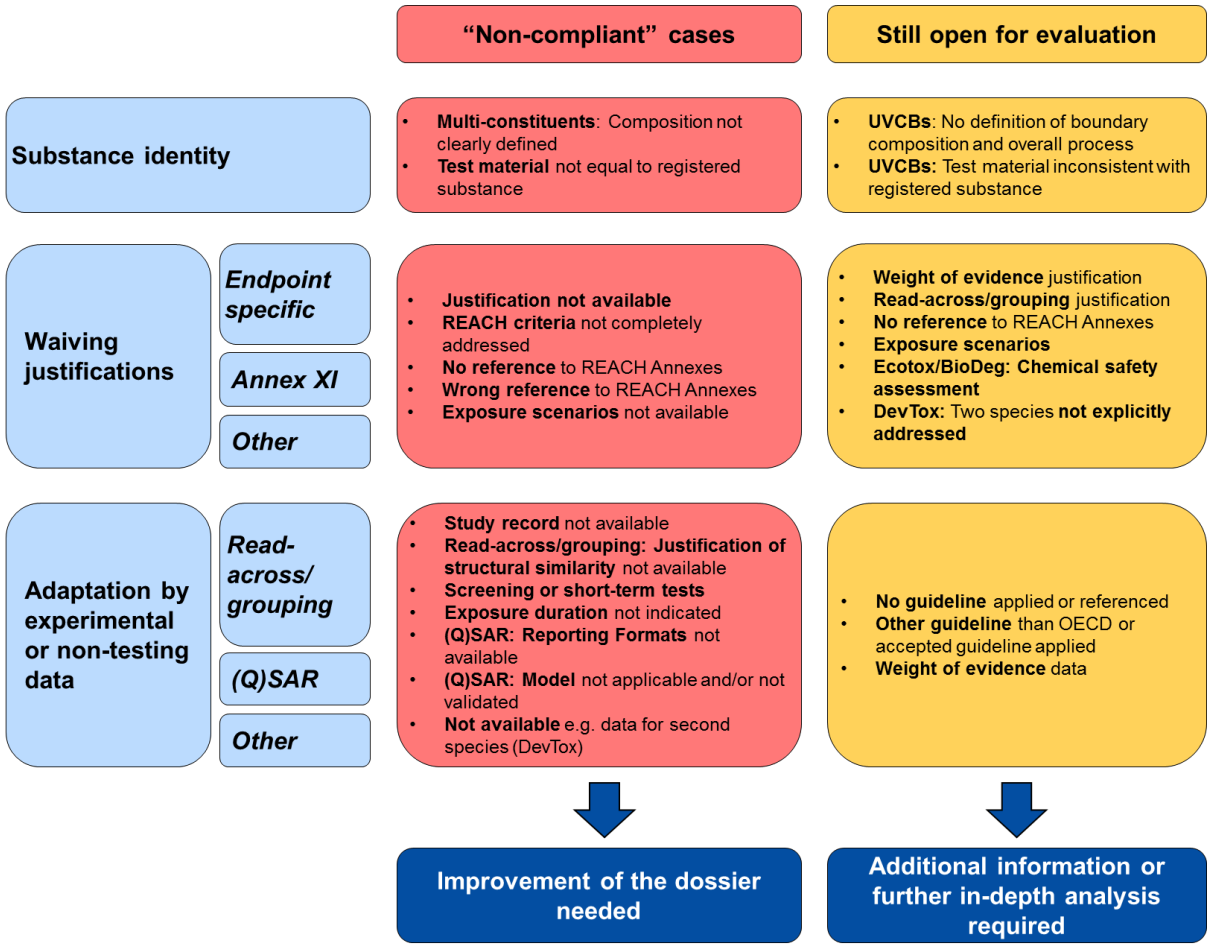
Although REACH offers different possibilities to omit or adapt standard information, the CSA is obligatory for high tonnage substances. Within this project it was not possible to determine whether the CSA adequately described the risks resulting from manufacture and use of the substance. Especially, in cases where waiving justifications complied with the selected REACH criteria, it remained unclear how risks and uncertainties were addressed.

In the second project, several issues concerning substance identity, data waiving and adaptation by use of surrogate data were identified in registration dossiers (Figure 4-1). The performed analysis provides an overview on issues and concerns that may require improvement of registration dossiers or further in-depth analysis.

The issue "no reference to REACH Annexes" was allocated to both categories ("non-compliant" and "still open for evaluation"), because it applied to data waiving with an obviously insufficient justification as well as data waiving with a possibly sufficient argumentation. The cross-cutting reasons for "non-compliant" and "complex" endpoint conclusions identified in the previous project are still valid (Figure 34 of the report; (Springer et al., 2015)).

The outlined reasons for "non-compliance" with regard to the evaluated formal requirements of REACH could be easily corrected or avoided. They in principle result from missing data and/or non-observance of data requirements (Figure 4-1).

Figure 4-1: Project II: Progress on checking data availability in REACH dossiers of high tonnage chemicals by analysis of substance identity-related issues and by formal check of data waiving/adaptation*



* in comparison to screening results on data availability (Springer et al., 2015)

(4) Refined check of endpoints of dossiers without conclusion of project I and II

The refined check confirmed the previously identified occurrence of data gaps and inappropriate approaches for data waiving/adaptation in registrations of chemicals of 1000 tpa or more. After integrating the results of project I, II and III, the examined dossiers were concluded "non-compliant" in the range of 12 to 61 %, depending on the evaluated endpoint. These percentages could be even higher since not all endpoint cases were conclusively assessed. Beyond, it is to be noted that the "compliant" endpoint cases of the formal check may still require a detailed scientific evaluation on the appropriateness of justifications for data waiving and adaptations, *e.g.* on grouping/read-across (which is in the responsibility of ECHA).

The refined evaluation of dossiers regarding Muta resulted in an increase of "formally compliant" cases. It should be noted that these cases may also require a detailed scientific evaluation just like the other "formally compliant" endpoint decisions in the formal check (project II).

After the refined check, however, the majority of the evaluated HH cases (Muta, DevTox, ReproTox) which were previously assessed as "complex" remained either without conclusion ("complex") or were set as "non-compliant" due to formal or obvious reasons. The main reasons for the category "complex" were that the examination of additional information would have been necessary or that the testing parameters would have needed a further content-related evaluation by an expert.

The evaluation of WoE approaches for HH endpoints – conducted in a small sample size – allowed only in some cases the conclusion "formally compliant" (only for Muta). The main proportion of WoE approaches remained without conclusion ("complex") for the same reasons as mentioned above. "Non-compliance" was predominantly based on formal reasons.

Recurrent waiving/adaptation justifications concerning the HH endpoints Muta, DevTox and ReproTox were gathered and categorised. The evaluation of these cases needs expert judgement as the defined groups could occur in future dossiers of chemicals at other tonnage levels.

Regarding the ENV endpoint Ecotox, the refined check provided as well "formally compliant" decisions. It should be kept in mind that this check does not replace the case by case evaluation done by ECHA. In general, a scientific sound evaluation could only be realised by an in-depth evaluation of the overall nested information provided in the dossiers. In contrast, the "obviously non-compliant" and "formally non-compliant" evaluated dossiers for the ENV endpoints are indicative either for a data gap or for not applying the specific and general rules in accordance with REACH Annexes VII to X column 2 or Annex XI.

The results on environmental exposure assessment show that the fulfilment of the standard information requirements according to REACH or the respective rules for data waiving/adaptation (REACH Annexes VII to X column 2 or Annex XI) provide the basis for an appropriate exposure and risk assessment. Due to the error propagation induced by wrong input parameters an underestimation of potential environmental risks might occur.

Results of project I, II and III

The conclusion rate increased with the progress of the projects due to the developed step-wise approach. This means that project II and III increased the conclusion rate in comparison to the screening results of project I (Figure 3-45). Thus, the number of endpoint decisions with the assignment "complex" decreased.

A stronger increase of the conclusion rate for the HH endpoints was observed than for the ENV endpoints. Finally, the results of the formal and refined check showed that a high proportion of former "complex" endpoints (project I) could be allocated to "compliant" or "non-compliant" decisions and that it is possible to solve many "complex" endpoints with the chosen approach.

(5) Estimated number of dossiers with potential data gaps for developmental and reproductive toxicity

A clear estimate of new animal studies needed, to bring the evaluated dossiers into compliance with the information requirements for DevTox and ReproTox, cannot be given. The estimate of data gaps for DevTox and ReproTox was based on the "non-compliant" results after the screening, formal check and refined check. These included cases with missing or inappropriate justifications for data waiving/adaptation. Not all of these cases, especially those that were "non-compliant" due to formal reasons (*e.g.* an insufficient justification for read-across/grouping), would necessarily lead to the requirement of an animal test. Nevertheless, a high number of data gaps was identified.

Outlook

In the first project, the screening of dossiers of chemicals ≥ 1000 tpa resulted in a high proportion of dossiers that could not be categorised as "compliant" or "non-compliant" for certain endpoints due to limited resources and capacity of the screening methodology. It is to note that the objective of the first project was to screen not only a small sample of registrations, but the total amount of lead and individual dossiers at 1000 tpa tonnage level. As previously outlined by Springer et al. (2015), the concept of gross examination ("screening") has a number of limitations and the results may bear uncertainties.

The second project aimed to refine the examinations, to reduce remaining uncertainties and to consolidate the screening results. Most of the dossiers with endpoints without conclusion ("complex") have been re-examined with respect to formal requirements and conclusions could be achieved on a higher rate of dossiers. However, conclusions on certain endpoints without conclusions ("complex") are still pending. In addition, certain endpoint cases without conclusion ("complex") in project I were not examined in project II, *e.g.* if a WoE approach was presented or because of reasons not due to the waiving of tests. These remaining issues were evaluated in the third project.

The refined check included Muta, ReproTox and DevTox concerning the HH endpoints as well as Ecotox and exposure as ENV endpoints. Although an in-depth systematic approach with a content-related analysis when necessary and applicable was conducted, up to 40 % dossiers (ReproTox) still remained without conclusion for different reasons.

Furthermore, beyond the scope of the previous projects, there are "compliant" endpoint cases from project II which still require a detailed scientific evaluation on the appropriateness of justifications for data waiving and adaptations (which is in the responsibility of ECHA).

Within the scope of all projects, significant data gaps and inappropriate waiving/adaptations were identified in registration dossiers of chemicals equal or above 1000 tpa. Thus, a need for improvement of registrations and further actions was confirmed.

It is planned to present summarised information and recommendations by communication media in English (Oertel et al., 2017) and German, giving interested registrants assistance for improving their registration dossiers and supporting the further development of regulatory guidance. Here, common errors and complex problems in the dossiers shall be published through the internet.

The current project aims to apply the developed concepts for checking registration dossiers on chemicals with ≥ 1000 tpa to the next tonnage level, the chemicals registered in quantities of 100 to 1000 tpa. Similar to the high total numbers of dossiers of chemicals ≥ 1000 tpa examined in the preceding projects, again about 2170 lead and individual registration dossiers will be evaluated.

The finalisation of the project III is planned for mid-2018.

5 References

ASTM (1980): E 729-80 - Standard Practice for Conducting Toxicity Tests with Fishes, Macroinvertebrates and Amphibians. American Society for Testing and Materials, Philadelphia, PA

ASTM (1989): E 1295-89 - Standard guide for conducting Three-Brood, renewal toxicity tests with Ceriodaphnia dubia. Annual Book of ASTM Standard, American Society for Testing and Materials 11 (01), 879-897

ASTM (1993a): E 729-88a - Standard guide for conducting acute toxicity tests with fishes, macroinvertebrates, and amphibians. Annual Book of ASTM Standards. American Society for Testing Materials, Philadelphia, PA

ASTM (1993b): E 1193-87 - Standard guide for conducting the renewal life-cycle toxicity tests with saltwater mysids. Annual Book of ASTM Standards. American Society for Testing Materials, Philadelphia, PA

ASTM (2013a): E1241-05 - Standard Guide for Conducting Early Life-Stage Toxicity Tests with Fishes. ASTM International, West Conshohocken, PA. DOI: 10.1520/E1241-05R13

ASTM (2013b): E1295-01 - Standard Guide for Conducting Three-Brood Renewal Toxicity Tests with Ceriodaphnia dubia, West Conshohocken, PA

BAuA (2015): REACH-CLP-Biozid Helpdesk, FAQ substance identity. http://www.reach-clp-biozid-helpdesk.de/de/FAQ/S-T/Stoffidentitaet/Stoffidentitaet-01.html (last accessed 20.01.2015)

CFR (2001): Code of federal regulations. Title 40 - Protection of Environment. Part 797 - Environmental Effects Testing Guidelines. Subpart B - Aquatic Guidelines. Section 797.1600 - Fish early life stage toxicity test.

CFR (2002a): Code of federal regulations. Title 40 - Protection of Environment. Part 797 - Environmental Effects Testing Guidelines. Subpart B - Aquatic Guidelines. 797.1330 - Daphnid chronic toxicity test

CFR (2002b): Code of federal regulations. Title 40 - Protection of Environment. Part 797 - Environmental Effects Testing Guidelines. Subpart B - Aquatic Guidelines. Section 795.120 - Gammarid acute toxicity test

CFR (2004): Code of federal regulations. Title 40 - Protection of Environment. Part 797 - Environmental Effects Testing Guidelines. Subpart B - Aquatic Guidelines. Section 797.1950 - Mysid shrimp chronic toxicity test.

CFR (2011): Code of federal regulations. Title 40 - Protection of Environment. Part 797 - Environmental Effects Testing Guidelines. Subpart B - Aquatic Guidelines. Section 797.1400 - Fish acute toxicity test

CFR (2015): Code of federal regulations. Title 40 - Protection of Environment. Part 797 - Environmental Effects Testing Guidelines. Subpart B - Aquatic Guidelines. Section 797.1300 - Daphnid acute toxicity test

Clark C.R., McKee R.H., Freeman J.J., Swick D., Mahagaokar S., Pigram G., Roberts L.G., Smulders C.J., and Beatty P.W. (2013): A GHS-consistent approach to health hazard classification of petroleum substances, a class of UVCB substances. Regulatory Toxicology and Pharmacology 67 (3), 409-420. https://doi.org/10.1016/j.yrtph.2013.08.020

DIN (1980): DIN 38412-20:1980-12 - German standard methods for the examination of water, waste water and sludge; bio-assays (group L), determination of the effect of waste water and industrial effluences on fish, fish-test (L 20) - withdrawn

DIN (1982a): DIN 38412-11:1982-10 - German standard methods for the examination of water, waste water and sludge; Test methods using water organisms (group L); Determination of the effect on microcrustacea of substances contained in water (Daphnia short-time test) (L 11) - withdrawn

DIN (1982b): DIN 38412-15:1982-06 - German standard methods for the examination of water, waste water and sludge; bio-assays (group L); determination of the effect of substances in water on fish, fish-test (L15) - withdrawn

EC (2006): 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), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. Official Journal of the European Union L 396/1, 30.12.2006

EC (2008a): Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Official Journal of the European Union L 142/1, 31.5.2008

EC (2008b): Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Official Journal of the European Union L 353/31, 31.12.2008

EC (2015): Commission Regulation (EU) 2015/282 of 20 February 2015 amending Annexes VIII, IX and X to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards the Extended One-Generation Reproductive Toxicity Study Text with EEA relevance. Official Journal of the European Union L 50/1, 21.2.2015

ECHA (2008): Guidance on information requirements and chemical safety assessment. Chapter R.6: QSARs and grouping of chemicals. May 2008, European Chemicals Agency, Helsinki.
https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

ECHA (2010): Practical guide 2: How to report weight of evidence. ECHA-10-B-05-EN. European Chemicals Agency, Helsinki. http://echa.europa.eu/documents/10162/13655/pg_report_weight_of_evidence_en.pdf

ECHA (2012a): Guidance on information requirements and chemical safety assessment. Chapter R.7b: Endpoint specific guidance. ECHA-12-G-22-EN, Version 1.2, November 2012, European Chemicals Agency, Helsinki. http://echa.europa.eu/documents/10162/13632/information_requirements_r7b_en.pdf

ECHA (2012b): Guidance on information requirements and chemical safety assessment. Chapter R.7c: Endpoint specific guidance. ECHA-12-G-23-EN, Version 1.1, November 2012, European Chemicals Agency, Helsinki. http://echa.europa.eu/documents/10162/13632/information_requirements_r7c_en.pdf

ECHA (2012c): Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT Assessment. ECHA-12-G-24-EN, Version 1.1, November 2012, European Chemicals Agency. http://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf

ECHA (2012d): Practical guide 5: How to report (Q)SARs. ECHA-10-B-10.1-EN. European Chemicals Agency, Helsinki

ECHA (2013): Long-term Aquatic Toxicity; ECHA Webinar: How to bring your registration dossier in compliance with REACH – Tips and Hints (Part 3), Helsinki. https://echa.europa.eu/documents/10162/22840246/04_webinar20130128_aquatox_tips_en.pdf/f65cb1ad-db6e-4356-a038-87790dcb806f

ECHA (2014a): Guidance for identification and naming of substances under REACH and CLP. ECHA-11-G-10.2-EN, Version 1.3, February 2014, European Chemicals Agency, Helsinki.

ECHA (2014b): Guidance on information requirements and chemical safety assessment. Chapter R.7c: Endpoint specific guidance. ECHA-14-G-06-EN, Version 2.0, November 2014, European Chemicals Agency, Helsinki. ISBN: 978-92-9244-762-5

ECHA (2014c): Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT/vPvB assessment. ECHA-14-G-07-EN, Version 2.0, November 2014, European Chemicals Agency, Helsinki.

ECHA (2014d): International Uniform Chemical Information Database (IUCLID), Version: 5.6.0.1. European Chemicals Agency, Helsinki. http://iuclid.eu

ECHA (2014e): Registrants: is your pre-natal toxicity information up-to-date? ECHA Newsletter, October 2014, Issue 5. https://newsletter.echa.europa.eu/home/-/newsletter/entry/5_14_registrants-is-your-prenatal-toxicity-information-uptodate (last accessed 17.01.2017)

ECHA (2015a): Evaluation under REACH. Progress Report 2014. European Chemicals Agency, Helsinki

ECHA (2015b): Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance. ECHA-15-G-04.1-EN. Version 4.1, October 2015, European Chemicals Agency, Helsinki

ECHA (2015c): How to address the information requirement on pre-natal developmental toxicity. ECHA/NA/15/15. https://echa.europa.eu/view-article/-/journal_content/title/how-to-address-the-information-requirement-on-pre-natal-developmental-toxicity (last accessed 17.01.2017)

ECHA (2016a): Guidance on information requirements and chemical safety assessment. Chapter R.7b: Endpoint specific guidance. ECHA-16-G-02-EN, Version 3.0, February 2016, European Chemicals Agency, Helsinki

ECHA (2016b): International Uniform Chemical Information Database (IUCLID), Version: 6. European Chemicals Agency, Helsinki. http://iuclid.eu

ECHA (2016c): Transition to the new IT tools - how to prepare. Technical information for existing registrants. ECHA-16-B-10-EN, March 2016, European Chemicals Agency, Helsinki. https://echa.europa.eu/documents/10162/13566/it_tools_transition_en.pdf

ECHA (2017a): Weight of evidence. https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/weight-of-evidence (last accessed 2017.01.17)

ECHA (2017b): What are the criteria for deciding if a substance is highly insoluble in water or poorly water soluble? Q&As, ID: 0836. https://echa.europa.eu/support/qas-support (last accessed 20.03.2017)

ECHA (2017c): Workshop on the implementation of ECHA's integrated regulatory strategy - proceedings 28 February – 1 March 2017, Helsinki [ECHA-17-R-10-EN]. https://echa.europa.eu/documents/10162/13628/regulatory_strategy_workshop_2017_report_en/2dafd9be-74ab-d154-a305-cb79113f8328

Environment Canada (1990): EPS 1/RM/9. Biological Test Method: Acute Lethality Test Using Rainbow Trout. Environment Canada, Ottawa, Ontario

Environment Canada (1998): EPS 1/RM/28-1E Second edition. Biological Test Method: Toxicity Tests Using Early Life Stages of Salmonid Fish (Rainbow Trout). Environment Canada, Ottawa, Ontario

Environment Canada (2000): EPS 1/RM/14, Second Edition. Biological Test Method: Reference Method for Determining Acute Lethality of Effluents to Daphnia magna. Environment Canada, Ottawa, Ontario

Evers D.C., Kaplan J.D., Meyer M.W., Reaman P.S., Braselton W.E., Major A., Burgess N., and Scheuhammer A.M. (1998): Geographic trend in mercury measured in common loon feathers and blood. Environmental Toxicology and Chemistry 17 (2), 173-183. http://dx.doi.org/10.1002/etc.5620170206

ISO (1994a): ISO 10229:1994 - Water quality - Determination of the prolonged toxicity of substances to freshwater fish - Method for evaluating the effects of substances on the growth rate of rainbow trout (*Oncorhynchus mykiss Walbaum* (Teleostei, Salmonidae))

ISO (1994b): ISO 10229:1994. Water quality - Determination of the prolonged toxicity of substances to freshwater fish - Method for evaluating the effects of substances on the growth rate of rainbow trout (Oncorhynchus mykiss Walbaum (Teleostei, Salmonidae))

ISO (1996a): ISO 7346-1:1996. Water quality - Determination of the acute lethal toxicity of substances to a freshwater fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)] - Part 1: Static method

ISO (1996b): ISO 7346-2:1996. Water quality - Determination of the acute lethal toxicity of substances to a freshwater fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)] - Part 2: Semi-static method

ISO (1996c): ISO 7346-3:1996. Water quality - Determination of the acute lethal toxicity of substances to a freshwater fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)] - Part 3: Flow-through method

ISO (2012): ISO 6341:2012. Water quality - Determination of the inhibition of the mobility of Daphnia magna Straus (Cladocera, Crustacea) - Acute toxicity test

Leeuwen C.J.V. (2007): General Introduction. In: Risk Assessment of Chemicals (Leeuwen C.J.v. and Vermeire T.G., eds.), chapter 1, pp. 1-36. Springer Netherlands. ISBN: 978-1-4020-6101-1. http://dx.doi.org/10.1007/978-1-4020-6102-8_1

OECD (1981a): Bioaccumulation: Flow-through Fish Test. OECD Guidelines for the Testing of Chemicals No. 305E. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (1981b): Bioaccumulation: Semi-Static Fish Test. OECD Guidelines for the Testing of Chemicals No. 305B. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (1981c): Bioaccumulation: Sequential Static Fish Test. OECD Guidelines for the Testing of Chemicals No. 305A. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (1981d): Bioaccumulation: Static Fish Test. OECD Guidelines for the Testing of Chemicals No. 305D. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (1981e): Bioaccumulation: Test for the Degree of Bioconcentration in Fish. OECD Guidelines for the Testing of Chemicals No. 305C. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (1984): Fish, Prolonged Toxicity Test: 14-day Study. OECD Guidelines for the Testing of Chemicals No. 204. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (1992): Fish, Acute Toxicity Test. OECD Guidelines for the Testing of Chemicals No. 203. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (1995): Water Solubility. OECD Guidelines for the Testing of Chemicals No. 105. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (1998): Fish, Short-term Toxicity Test on Embryo and Sac-fry Stages. OECD Guidelines for the Testing of Chemicals No. 212. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (2000): Fish, Juvenile Growth Test. OECD Guidelines for the Testing of Chemicals No. 215. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (2004a): Daphnia sp. Acute Immobilisation Test. OECD Guidelines for the testing of chemicals No. 202. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (2004b): Hydrolysis as a function of pH. OECD Guidelines for the Testing of Chemicals No. 111. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (2009): 21-day Fish Assay: A Short-Term Screening for Oestrogenic and Androgenic Activity, and Aromatase Inhibition. OECD Guidelines for the Testing of Chemicals No. 230. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (2011): Fish Sexual Development Test. OECD Guidelines for the Testing of Chemicals No. 234. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (2012a): Bioaccumulation in Fish: Aqueous and Dietary Exposure. OECD Guidelines for the Testing of Chemicals No. 305. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (2012b): *Daphnia magna* Reproduction Test. OECD Guidelines for the Testing of Chemicals No. 211. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (2012c): Fish Short Term Reproduction Assay. OECD Guidelines for the Testing of Chemicals No. 229. Organisation for Economic Cooperation and Developement (OECD), Paris

OECD (2013): Fish, Early-life Stage Toxicity Test. OECD Guidelines for the Testing of Chemicals No. 210. Organisation for Economic Cooperation and Developement (OECD), Paris

Oertel A., Maul K., Menz J., Kronsbein A.L., and Schulte A. (2017): Recommendations for registrants to improve data quality in registration dossiers for chemicals ≥ 1000 tpa. Report in preparation. German Federal Institute for Risk Assessment, Berlin, Germany, on behalf of the German Environment Agency, Dessau, Germany. http://www.umweltbundesamt.de/; http://www.bfr.bund.de/de/start.html

Rorije E., Verbruggen E.M.J., and de Knecht J.A. (2012): Service Request on a critical review of the environmental and physicochemical methodologies commonly employed in the environmental risk assessment of petroleum substances in the context of REACH registrations. National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands. http://echa.europa.eu/documents/10162/13628/review_environmental_physicochemical_methodol_en.pdf

Scholten E. (2012): Hydrolysis of chemicals as a function of structure and pH: Meeting the information requirements of REACH in a reliable way and opportunities for product innovation. http://www.fachoekotoxikologie.de/fileadmin/fachoekotoxikologie/abgeschlossene_Arbeiten/2012/PGS_OEkotoxikologie_wissenschaftliche_Abschlussarbeit_Scholten_Edzard.pdf

Sijm D.T.H.M., Rikken M.G.J., Rorije E., Traas T.P., McLachlan M.S., and Peijnenburg W.J.G.M. (2007): Transport, Accumulation and Transformation Processes. In: Risk Assessment of Chemicals (Leeuwen C.J.v. and Vermeire T.G., eds.), chapter 3, pp. 73-158. Springer Netherlands. ISBN: 978-1-4020-6101-1. http://dx.doi.org/10.1007/978-1-4020-6102-8_3

Springer A., Herrmann H., Sittner D., Herbst U., and Schulte A. (2015): REACH Compliance: Data Availability of REACH Registrations, Part 1: Screening of chemicals > 1000 tpa. Federal Institute for Risk Assessment, Berlin. Federal Environment Agency (Germany), Dessau. https://www.umweltbundesamt.de/publikationen/reach-compliance-data-availability-of-reach

US EPA (1975a): EPA-660/3-75-009. Methods for Acute Toxicity Tests with fish, invertebrates and amphibians

US EPA (1975b): Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians. Ecological Research Series EPA-660/3-75-009, April 1975

US EPA (1982): Pesticide Assessment Guidelines. Subdivision E. Hazard Evaluation: Wildlife and Aquatic Organisms. OPP 72–4. Fish Early Life-Stage and Aquatic Invertebrate Life-Cycle Studies

US EPA (1989): EPA/600/4-89/001 - Short-term methods for estimating the chronic toxicity of effluents and receiving waters to freshwater organisms. Cincinati, USA

US EPA (1991): EPA/600/4-90/027 - Methods for measuring the acute toxicity of effluents and receiving waters to freshwater and marine organisms. Cincinatti, USA

US EPA (1996a): Ecological Effects Test Guidelines. OPPTS 850.1010. Aquatic Invertebrate Acute Toxicity Test, Freshwater Daphnids

US EPA (1996b): Ecological Effects Test Guidelines. OPPTS 850.1075. Fish Acute Toxicity Test, Freshwater and Marine

US EPA (1996c): Ecological Effects Test Guidelines. OPPTS 850.1350. Mysid Chronic Toxicity Test

US EPA (1996d): Ecological Effects Test Guidelines. OPPTS 850.1400. Fish Early-Life Stage Toxicity Test

US EPA (1996e): Ecological Effects Test Guidelines. OPPTS 850.1500. Fish life cycle toxicity

US EPA (1996): Ecological Effects Test Guidelines. OPPTS 850.1300. Daphnid Chronic Toxicity Test

Warnecke D., Duis K., Knacker T., Schüürmann G., Kühne R., and Ost N. (2011): Review and Enhancement of New Risk Assessment Concepts under REACH. ECT Oekotoxikologie GmbH, Flörsheim, Helmholtz-Zentrum für Umweltforschung – UFZ, Leipzig. Federal Environment Agency (Germany), Dessau. https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/texte_48_2014_review_and_enhancement_of_new_risk_assessement_concepts_under_reach.pdf (last accessed 20140107)

Wyn B., Kidd K.A., Burgess N.M., and Curry R.A. (2009): Mercury biomagnification in the food webs of acidic lakes in Kejimkujik National Park and National Historic Site, Nova Scotia. Canadian Journal of Fisheries and Aquatic Sciences 66 (9), 1532-1545. http://dx.doi.org/10.1139/F09-097

6 List of Annexes

Annex 1

Table 6-1: List of descriptors used in the memory field of documentation

Descriptor	Application of descriptor
CONIMP	The allocation of at least one of the components to the categories “constituents” or “impurities” was inconsistent between lead and member dossiers.
SOL	Concentration was only given for the dissolved substance. It was not stated that the solvent is required as stabiliser.
DEVPRO	The registration applied to two or more products/qualities and while one of the products/qualities fulfilled the requirements at least one of the other products/qualities showed deviations.
REGSUB	The single constituents of a multi-constituent substance or UVCB substance were not specified. Instead, only identifiers for the registered substance itself were given.
NEI	Identification of substance is not possible due to missing information.
DEVRA	There is no overlap in the concentration range of at least one constituent in the member dossier in comparison to the range of the same constituent in the lead dossier.
< 10	80/10 %-rule not fulfilled because for one or more constituents the concentration range laid completely below 10 %.

Table 6-2: Table documentation style (Excel) with one example

BfR-No.	Joint submission name	Lead or member dossier?	Substance type	Total number of member dossiers	Number of member dossiers checked	Same number of main constituents as in lead dossier?	Same main constituents as in lead dossier?	Composition rules fulfilled? (≥ 80 %-rule for mono-constituents; < 80/≥ 10 %-rule for multi-constituents)	Case description	Case description summary	Conclusion (substance corresponds to those in lead dossier?)	Final conclusion	Memo
				only for lead	only for lead	only for member	only for member	lead and member	lead and member	only for lead	only for member	only for lead	
						only for multi		only for mono and multi	only for UVCB	only for UVCB			
		Lead Member	Mono-constituent Multi-constituent UVCB			1 (yes) 2 (no) 3 (cannot clearly be deduced)	1 (yes) 2 (no) 3 (cannot clearly be deduced)	1 (yes) 2 (no) 3 (cannot clearly be deduced)			1 (yes) 2 (no) 3 (cannot clearly be deduced)	1 (yes-100 %) 2 (no) 3 (cannot clearly be deduced)	
BfR99998	xxx	Lead	Multi	2	2			1				2	
BfR99997	xxx	Member	Multi			1	1	1			1		DEVRA
BfR99996	xxx	Member	Multi			2	2	1			2		

Annex 2

Table 6-3: Table documentation style (Excel) with one example

Substance name	BfR-No.	Endpoint	Key studies total	No. of key studies where test material = registered substance	No. of key studies where test material ≠ registered substance	No. of key studies with inconsistent information on test material	No. of key studies based on read-across	Result*	Memo#
B	C	D	E	F	G	H	I	J	K
Example1	BfR99999	PC	2	2				TRUE	
Example1	BfR99999	BioDeg	1	1				TRUE	
Example1	BfR99999	AbioDeg	2	1	1			FALSE	
Example1	BfR99999	Bioaccu	1				1	TRUE	
Example1	BfR99999	Ecotox	4	1		3		FALSE	
Example1	BfR99999	RDT	1			1		FALSE	
Example1	BfR99999	Muta	4	3			1	TRUE	
Example1	BfR99999	ReproTox	1		1			FALSE	
Example1	BfR99999	DevTox	1				1	TRUE	

* TRUE if F+I=E; FALSE if F+I≠E; ERROR if document not found.

free text

Table 6-4: Test material equivalency per endpoint with regard to examined dossiers

	TRUE				FALSE				
Endpoint	**Test material in all key studies equal to the registered substance (no read-across studies available)**	**Test material in all key studies equal to the registered substance (read-across studies available but excluded)**	**Only read-across key studies available**	**Key study not available for particular endpoint**	**Test material in at least one key study not equal to the registered substance (no read-across studies available)**	**Test material in at least one key study not equal to the registered substance (read-across studies available but excluded)**	**Test material in at least one key study unclear (read-across studies excluded)**	**Key studies generally not available in dossier**	**Error**
PC	217	16	28	61	19	11	16	21	1
BioDeg	158	24	38	91	34	8	15	22	
AbioDeg	172	17	45	83	31	5	15	22	
Bioaccu	93	7	36	188	36	2	6	22	
Ecotox	159	49	64	27	39	12	18	22	
RDT	129	19	118	48	29	12	13	22	
Muta	143	58	80	25	29	21	13	21	
ReproTox	74	10	106	139	20	7	11	22	1
DevTox	107	7	102	114	23	6	10	21	

PC: Physico-chemical properties (log K_{ow}, water solubility)

Table 6-5: Test material equivalency per endpoint with regard to examined key studies*

Endpoint	Total number of key studies	Key studies without read-across	Test material = registered substance (read-across studies excluded)	Test material ≠ registered substance (read-across studies excluded)	Unclear (read-across studies excluded)
PC	918	736	447	230	59
BioDeg	686	518	344	148	26
AbioDeg	583	447	312	110	25
Bioaccu	295	223	131	85	7
Ecotox	1568	904	575	264	65
RDT	906	372	254	85	33
Muta	1682	914	657	227	30
ReproTox	362	149	94	42	13
DevTox	436	202	144	45	13

* Based on available key studies in 390 examined dossiers. PC: Physico-chemical properties (log K_{ow}, water solubility)

Table 6-6: Key studies with test material not equal to the registered substance per endpoint and substance type (read-across studies excluded)*

Endpoint	UVCB: Total number of key studies	UVCB: Number of key studies with test material ≠ registered substance	Multi-constituent: Total number of key studies	Multi-constituent: Number of key studies with test material ≠ registered substance	Mono-constituent: Total number of key studies	Mono-constituent: Number of key studies with test material ≠ registered substance
PC	411	209	140	15	185	6
BioDeg	219	110	108	18	191	20
AbioDeg	181	80	106	16	160	14
Bioaccu	99	65	45	11	79	9
Ecotox	380	191	189	38	335	35
RDT	121	49	75	11	176	25
Muta	338	167	188	20	388	40
ReproTox	49	25	44	7	56	10
DevTox	51	21	54	13	97	11

* Based on available key studies in 390 examined dossiers. PC: Physico-chemical properties (log K_{ow}, water solubility)

Table 6-7: Key studies with read-across per endpoint and substance type*

Endpoint	Number of key studies	Number of read-across key studies	UVCB: number of key studies	UVCB: number of read-across key studies	Multi-con-stituent: number of key studies	Multi-con-stituent: number of read-across key studies	Mono-con-stituent: number of key studies	Mono-con-stituent: number of read-across key studies
PC	918	182	553	142	168	28	197	12
BioDeg	686	168	314	95	140	32	232	41
AbioDeg	583	136	265	84	125	19	193	33
Bioaccu	295	72	125	26	63	18	107	28
Ecotox	1568	664	688	308	247	58	633	298
RDT	906	534	490	369	150	75	266	90
Muta	1682	768	872	534	312	124	498	110
ReproTox	362	212	174	125	76	32	112	56
DevTox	436	234	165	114	92	38	179	82

* Based on available key studies in 390 examined dossiers. PC: Physico-chemical (log K_{ow}, water solubility)

Annex 3

Table 6-8: List of descriptors used in the memory field of documentation

Descriptor	Application of descriptor
Downgrade	Was assigned if it was suspected that data with relevance for the conclusion on the toxic potential of the substance were only reported as inferior data (*e.g.* relevant guideline studies with reliability 1 or 2 were marked as supporting studies); was only documented when obvious
No guide	Study was not conducted according to the required OECD guideline
Sim guide	Study was not conducted according to the required OECD guideline, but the registrant evaluated the study as similar or equivalent
Oth guide	Study was not conducted according to the required OECD guideline, but according to another guideline
Delet key	Deleted key study
Not 10d	Pass level for ready biodegradable is met within test duration, but not within the requested 10-day window
Incorrect ref expo	Incorrect direct REACH reference for waiving based on exposure considerations
Expert judg	Expert judgement as waiving justification
Corros	Technical waiving based on corrosivity of substance
Ra to TP (year)	Read-across to another substance for which testing is proposed, given with the year of the last update of the ESR

Table 6-9: Human health: Frequency of waiving/adaptations applied by the registrants for each endpoint

Waiving/adaptation category	DevTox		ReproTox		Muta		RDT	
	n	[%]	n	[%]	n	[%]	n	[%]
Read-across	694	45	635	35	1109	75	860	58
No reference	201	13	465	26	87	6	118	8
Endpoint specific	180	12	207	12	27	2	162	11
WoE	134	9	222	12	79	5	132	9
Exposure considerations	61	4	83	5	2	0	63	4
Incorrect REACH reference	4	0	47	3	1	0	5	0
Technically not feasible	19	1	25	1	41	3	76	5
Scientifically unjustified	52	3	92	5	39	3	33	2
(Q)SAR	2	0	1	0	5	0	0	0
Annex IV and V	5	0	6	0	4	0	7	0
Meaningless justification	2	0	4	0	0	0	19	1
Calculation	1	0	1	0	0	0	5	0
Not required*	16	1	3	0	13	1	0	0
Not available, but required	174	11	0	0	51	3	10	1
Not available, necessity has to be checked	2	0	0	0	20	1	3	0
Total	1547	100	1791	100	1478	100	1493	100

* Acceptable study available or read-across (acceptable study) available for hydrated form or anhydride or relevant harmonised classification.

Table 6-10: Environment: Frequency of waiving/adaptations applied by the registrants for each endpoint

Waiving/adaptation category	BioDeg		AbioDeg		Bioaccu		Ecotox	
	n	[%]	n	[%]	n	[%]	n	[%]
Read-across	257	18	77	5	60	14	934	20
No reference	201	14	628	45	0	0	0	0
Endpoint specific	602	42	297	21	73	17	1781	37
WoE	15	1	45	3	5	1	468	10
Exposure considerations	96	7	5	0	4	1	279	6
Incorrect REACH reference	16	1	1	0	3	1	107	2
Technically not feasible	52	4	63	4	128	30	247	5
Scientifically unjustified	98	7	274	19	0	0	3	0
(Q)SAR	82	6	11	1	116	27	258	5
Annex IV and V	2	0	2	0	0	0	8	0
Meaningless justification	5	0	4	0	33	8	64	1
Calculation	0	0			0	0	5	0
Not required*	5	0	2	0	0	0	0	0
Not available, but required	3	0	0	0	0	0	0	0
Not available, necessity has to be checked	0	0	0	0	0	0	0	0
Non-standard method					0	0	614[#]	13
Total	1434[$]		1408		422		4768	

* Acceptable study available or read-across (acceptable study) available for hydrated form or anhydride or relevant harmonised classification.

[#] 248 non-standard method included read-across

[$] waiving/adaptation justifications were not counted for each kind of simulation testing the number of waiving/adaptation justifications might be higher

Annex 4

Table 6-11: 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 (2013)	R.7b, p. 31 (ECHA, 2016a)
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 (2000)	R.7b, p. 31 (ECHA, 2016a)
OECD TG 229	Fish Short-term Reproduction Assay	OECD (2012c)	
OECD TG 230	21-day Fish Assay	OECD (2009)	
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, 2016a)
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, 2016a)
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, 2016a)
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)

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
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)
EPA OTS 797.1000	Fish, Early-life Stage Toxicity (FELS) Test		ECHA Webinar (ECHA, 2013)
FIFRA (§72-4 a)			R.7b, p. 103 (ECHA, 2016a)
NS (4763)	Determination Of Embryo-larval Toxicity To Freshwater Fish - Semistatic Procedure		R.7b, p. 103 (ECHA, 2016a)
SFS (5501)	Determination of embryo-larval toxicity to freshwater fish - Semistatic method		R.7b, p. 103 (ECHA, 2016a)
SS (SS028193)			R.7b, p. 103 (ECHA, 2016a)
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 (2012b)	R.7b, p. 56 (ECHA, 2016a)
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, 2016a)
40 CFR 797.1350	Daphnid Chronic Toxicity Test (equivalent OECD TG 202, part 2)		R.7b, p. 99 (ECHA, 2016a)
40 CFR 797.1950	Mysid Chronic Toxicity Test	CFR (2004)	R.7b, p. 99 (ECHA, 2016a)
ASTM (E-1193-87)	Renewal life-cycle toxicity tests with saltwater mysids	ASTM (1993b)	R.7b, p. 99 (ECHA, 2016a)
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, 2016a)
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)

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
EPA OTS 797.1950	Mysid Chronic Toxicity Test		ECHA Webinar (ECHA, 2013)
Short-term toxicity to fish			
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 (1994b)	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, 2016a)
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, 2016a)
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, 2016a)
OECD TG 203	Fish, Acute Toxicity Test	OECD (1992)	R.7b, p. 30 (ECHA, 2016a)
OECD TG 204	Fish Prolonged Toxicity Test: 14-day Study	OECD (1984)	R.7b, p. 30 (ECHA, 2016a)
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, 2016a)
ASTM E 729-80:192		ASTM (1980)	
BS 6068-5-5.2:1985	Replaced by EN ISO 7346-1		R.7b, p. 100 (ECHA, 2016a)
BS 6068-5-5.3:1985	Replaced by EN ISO 7346-2		R.7b, p. 100 (ECHA, 2016a)
BS 6068-5-5.4:1985	Replaced by EN ISO 7346-3		R.7b, p. 100 (ECHA, 2016a)

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
CAN EPS 1/RM/9		Environment Canada (1990)	R.7b, p. 100 (ECHA, 2016a)
DIN 38412-15 (L)*	Determination of the Effect of Substances in Water on Fish (with-drawn)	DIN (1982b)	
DIN 38412-20	Determination of the Effect of Waste Water and Industrial Effluences on Fish (withdrawn)	DIN (1980)	
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, 2016a)
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, 2016a)
NF T90-303-1	Equivalent to EN ISO 7346-1		R.7b, p. 100 (ECHA, 2016a)
NF T90-303-2	Equivalent to EN ISO 7346-2		R.7b, p. 100 (ECHA, 2016a)
NF T90-303-3	Equivalent to EN ISO 7346-3		R.7b, p. 100 (ECHA, 2016a)
NF T90-305	Determination of the acute toxicity of a substance to Salmo gairdneri. Static and flow through methods		R.7b, p. 100 (ECHA, 2016a)
SFS (3035+5073)			R.7b, p. 100 (ECHA, 2016a)
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, 2016a)

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
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, 2016a)
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, 2016a)
40 CFR 797.1300	Daphnid acute toxicity test	CFR (2015)	R.7b, p. 98 (ECHA, 2016a)
40 CFR 797.1330	Daphnid chronic toxicity test	CFR (2002a)	R.7b, p. 99 (ECHA, 2016a)
ASTM E 1295-89	Standard guide for conducting Three-Brood, renewal toxicity tests with *Ceriodaphnia dubia*	ASTM (1989)	R.7b, p. 98 (ECHA, 2016a)
ASTM E 729-88a	Standard Guide for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates and Amphibians	ASTM (1993a)	R.7b, p. 98 (ECHA, 2016a)
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, 2016a)
CAN EPS 1/RM/11	Reference Method for Determining Acute Lethality of Effluents to *Daphnia magna*	Environment Canada (2000)	R.7b, p. 98 (ECHA, 2016a)
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, 2016a)
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, 2016a)
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, 2016a)
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		

Guideline	Brief description/Comments	Guideline Reference	Reference for acceptance
FIFRA (§72-2)			R.7b, p. 98 (ECHA, 2016a)
NEN 6501	Determination of acute toxicity using *Daphnia magna* (Dutch Standard, withdrawn)		R.7b, p. 98 (ECHA, 2016a)
NEN 6502	Determination of chronic toxicity with *Daphnia magna* (Dutch Standard, withdrawn)		R.7b, p. 98 (ECHA, 2016a)
NF T90-301	Determination of inhibition of *Daphnia magna* mobility (French standard, replaced by EN ISO 6341)		R.7b, p. 98 (ECHA, 2016a)
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, 2016a)
SFS (5052)			R.7b, p. 98 (ECHA, 2016a)
SS (028180)			R.7b, p. 98 (ECHA, 2016a)

Annex 5

Table 6-12: Remaining "complex" endpoints from screening, not examined during formal check

Endpoint	Group of "complex" cases	Number
RDT	chronic or subchronic test was conducted with a non-rodent species	11
	subacute test with rodent was available; for adaptation of the subchronic test a WoE approach was available	8
	for adaptation of the subacute/subchronic test a WoE approach was available	133
Total		**152**
Muta	minimum of one positive *in vivo* soma cell test **and** a negative *in vivo* germ cell test **and** *in vitro* bacteria test or waiving/adaptation of *in vitro* bacteria test were available (1 also WoE)	3
	WoE: 10 WoE for adaptation of *in vitro* bacteria test 116 WoE for adaptation of two tests *in vitro* and/or *in vivo* 88 WoE for adaptation of one of the two waived tests *in vitro* and/or *in vivo*	214
Total		**217**
ReproTox	two-generation study (OECD TG 416) with a non-rodent species was conducted	0
ReproTox	WoE: 0 WoE for adaptation of OECD TG 416 (OECD TG 414/two species are available) 18 WoE for adaptation of OECD TG 416 (OECD TG 414/one species is available) 72 WoE for adaptation of OECD TG 416 (no other study available)	90
ReproTox/DevTox	substance classified Repr. 1A/1B: H360FD according to CLP Annex VI	7
ReproTox/DevTox	OECD TG 416 and OECD TG 414/two species are available, but at least one test was not conducted with the standard administration route (not oral and not inhalation for gases, respectively)	15
DevTox	Waiving/adaptation justification for OECD TG 414/second species **was not available**: 66 "complex" for TRep (OECD TG 416 and OECD TG 414/one species available) 20 "non-compliant" for TRep because waiving/adaptation for OECD TG 416 was not available (OECD TG 414/one species available) 166 "complex" for TRep because waiving/adaptation for OECD TG 416 was available (OECD TG 414/one species available)	252
DevTox	Waiving/adaptation justification for OECD TG 414/second species **was available** (at least OECD TG 414/one species available):	2 (+7 WoE)

Endpoint	Group of "complex" cases	Number
	2 "non-compliant" for TRep because waiving/adaptation for OECD TG 416 was not available (plus 7 WoE for DevTox, see below) (for 33 "complex", because waiving/adaptation for OECD TG 416 was available, a check regarding DevTox was already conducted in project II)	
DevTox	WoE: 1 WoE for adaptation of OECD TG 414/second species; (OECD TG 414/one species and OECD TG 416 available) 6 WoE for adaptation of OECD TG 414/second species; (OECD TG 414/one species available) 1 WoE for adaptation of OECD TG 414 (OECD TG 416 available) 104 WoE for adaptation of OECD TG 414 (no study available)	112
TRep total		**478**
AbioDeg		169
BioDeg		253
Bioaccu		1065
Ecotox		0
Expo		1012

Table 6-13: Remaining "complex" endpoints from project II (without grouping/read-across)

Endpoint	(Group description and) number of "complex" cases
RDT **total**	**121 dossiers**
Muta	26 WoE (1 also waiving not available, 2 also not based on REACH criteria) 4 Endpoint specific 27 Justification available, but not based on REACH criteria (2 also WoE) 14 Other justifications (1 also WoE)
Muta **total**	**68 dossiers, 71 waiving justifications**
ReproTox	185 WoE (1 also endpoint specific, 22 also not based on REACH criteria) 26 Endpoint specific (1 also WoE) 208 Justification available, but not based on REACH criteria (22 also WoE) 6 Other justifications
ReproTox **total**	**402 dossiers, 425 waiving justifications**
DevTox/general	87 WoE (1 also endpoint specific, 5 also not based on REACH criteria) 20 Endpoint specific (1 also WoE) 107 Justification available, but not based on REACH criteria (6 also WoE) 6 Other justifications
DevTox/second species	19 Weight of evidence (1 also not based on REACH criteria) 6 Endpoint specific 2 Justification available, but not based on REACH criteria 3 Other justifications
DevTox **total**	**243 dossiers, 250 waiving justifications**
AbioDeg	132
BioDeg	234
Bioaccu	31
Ecotox	1078
ENV Expo	0

Annex 6

Table 6-14: IUCLID sections

IUCLID section	Checked parts
2. Classification & labelling and PBT assessment	2.1 GHS
3. Manufacture, use and exposure	3.5 Use and exposure information 3.5.4 and 3.5.5 Widespread uses by professional workers, consumer uses (end uses)
4. Physico-chemical properties	4.3 Boiling point 4.6 Vapour pressure 4.7 Partition coefficient, n-octanol/water 4.8 Water solubility
7.1 Toxicokinetics, metabolism and distribution	dermal
7.2 Acute toxicity	7.2.3 Acute dermal toxicity
7.8 Toxicity to reproduction	endpoint study summary all available ESRs

GHS: Globally Harmonized System of Classification and Labelling of Chemicals

Annex 7

Table 6-15: Mutagenicity: Adaptation/waiving

Available test(s)	Result	Study data or adaptation/waiving required for…
GMbact	Negative	Cytvitro
GMvitro	Negative	GMbact, Cytvitro
Cytvitro	Negative	GMbact
No *in vitro* tests		GMbact, Cytvitro
GMbact	Positive	GMvivo, Cytvitro
GMvitro	Positive	GMbact, GMvivo, Cytvitro
Cytvitro	Positive	Cytvivo, GMbact
GMbact, GMvitro	Both negative	Cytvitro
GMbact, Cytvitro	Both negative	GMvitro
GMvitro, Cytvitro	Both negative	GMbact
GMbact, GMvitro	At least one positive	GMvivo and Cytvitro
GMbact, Cytvitro	At least one positive	GMvivo or Cytvivo
GMvitro, Cytvitro	At least one positive	GMbact; GMvivo or Cytvivo

Annex 8

Table 6-16: Refined check of the environmental exposure assessment

Step 1 : Selection of registration dossiers for further evaluation		
Further Evaluation	**“non-compliant” cases**	**“complex” cases**
26	-	-
Step 2: Minimum information required		
Further Evaluation	**“non-compliant” cases**	**“complex” cases**
13	0	13
Step 3: Completeness screening of elements		
Further Evaluation	**“non-compliant” cases**	**“complex” cases**
2	7	4
Step 4: Exposure estimation		
Further Evaluation	**“non-compliant” cases**	**“complex” cases**
0	0	2

Annex 9

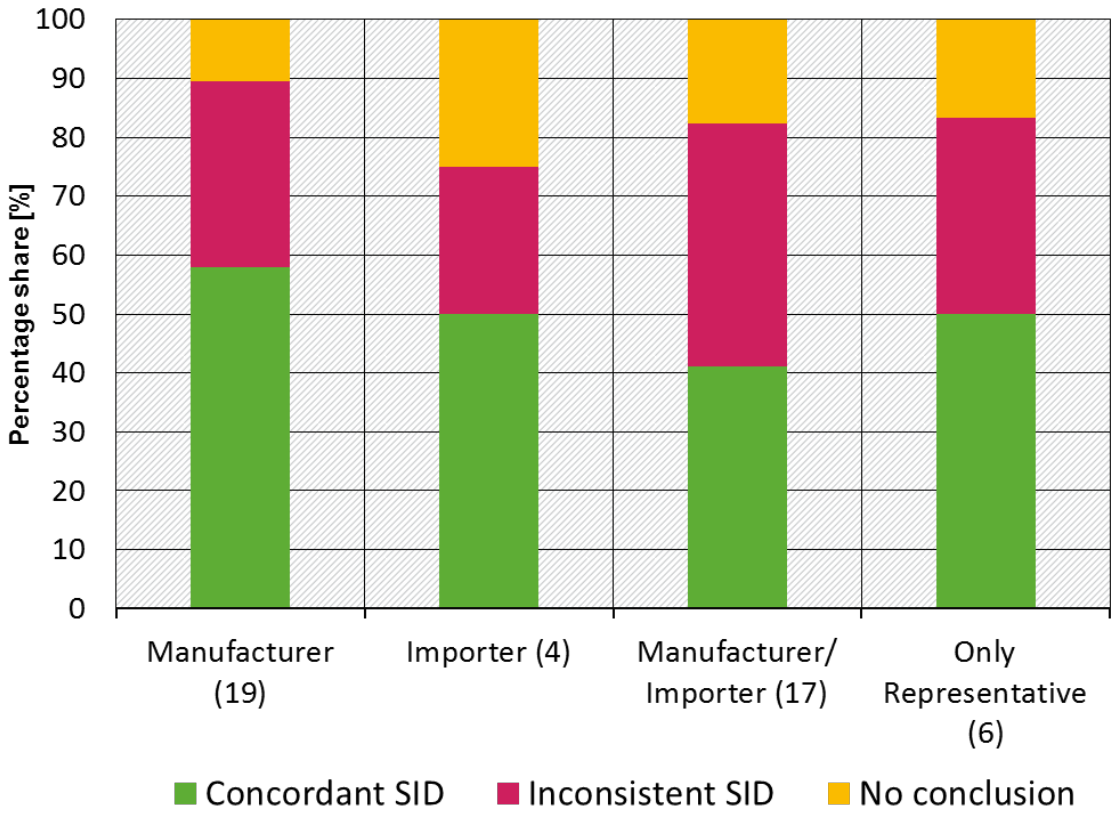
Substance sameness within joint submissions and registrants' role in the supply chain

In this Annex results on substance sameness in joint submissions in relation to lead registrant's role in the supply chain either as manufacturer or importer or both or as the only representative are presented. In addition, results on substance sameness between member dossiers compared to lead dossiers are presented for member registrants' role in the supply chain.

The results for mono-constituent substances on sameness in joint submissions showed no differences when presented with the lead registrants' role in the supply chain.

In Figure 6-1, the results on substance identity for multi-constituent substances within joint submission are presented with the information on the lead registrant's role in the supply chain. No statistical analysis was performed because of the small sample sizes of lead dossiers.

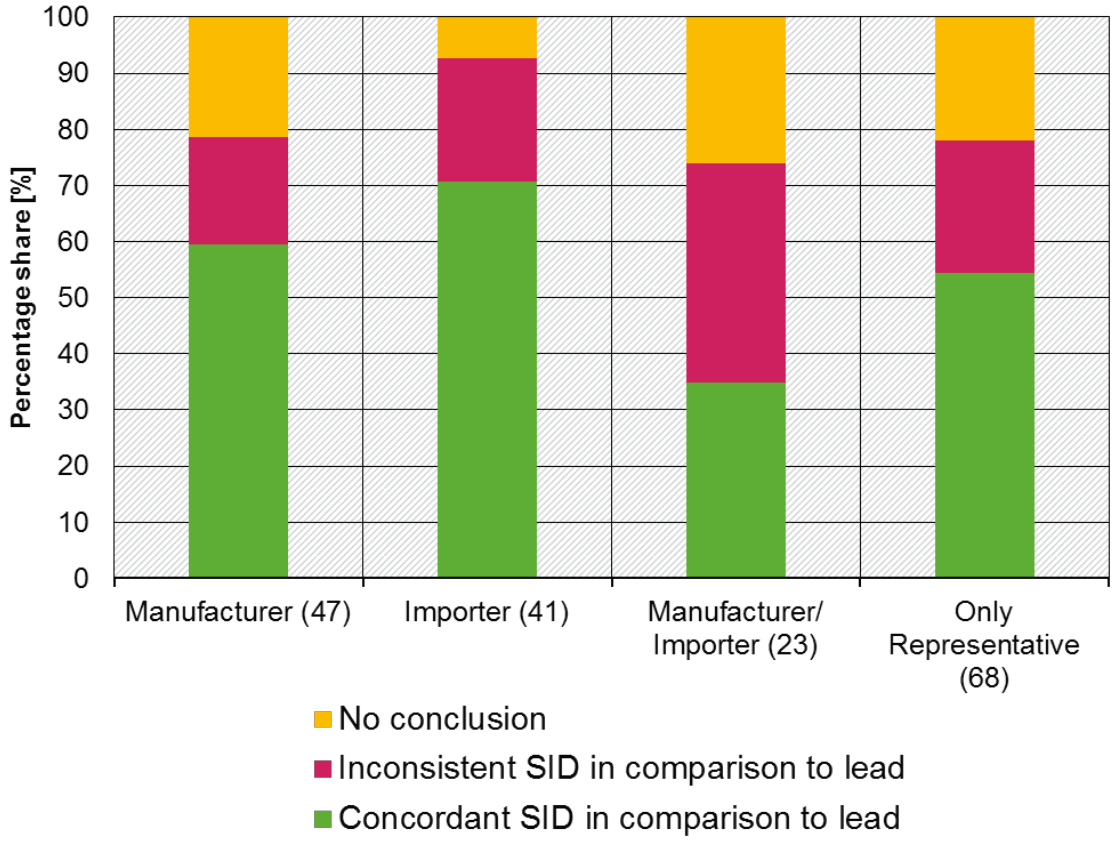
Figure 6-1: Substance identity of multi-constituent substances in joint submissions depending on lead registrant's role in the supply chain*



* Total number of investigated joint submissions: 46; number per supply chain in brackets.

The results on substance identity between member and lead dossier indicating member registrant' role in the supply chain are shown in Figure 6-2. No statistical analysis was performed because of the small sample sizes of member dossiers.

Figure 6-2: Conclusions for the investigated member dossiers of multi-constituent substances depending on the role of the member in the supply chain*



* Total number of investigated member dossiers: 179; number per supply chain in brackets.