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REACH Compliance: Data Availability of REACH Registrations

Part 1: Screening of chemicals > 1000 tpa

For our Environment

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REACH Compliance: Data Availibility of REACH Registration

Part 1: Screening of chemicals › 1000 tpa

by

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Kurzbeschreibung

Der Bericht stellt im Rahmen des Projektes „REACH Compliance: Auswertung der Datenverfügbarkeit aus den REACH Registrierungen“ Erkenntnisse und Ergebnisse aus einem Screening von 1932 Dossiers federführender und individueller Registranten von sogenannten ‚Phase-in‘-Stoffen mit einer Jahresproduktion ab 1000 Tonnen vor. Hierbei wurde die Verfügbarkeit von Registrierungsdaten zu ausgewählten Endpunkten vergleichend zu den Standardinformationsanforderungen und ihrer möglichen Abweichungen gemäß den Anhängen VII bis XI der REACH Verordnung (EC) Nr. 1907/2006 mit einem web-basierten standardisierten Verfahren geprüft. Untersucht wurden die Gesundheitsendpunkte Toxizität nach wiederholter Applikation, Reproduktions- und Entwicklungstoxizität und Mutagenität sowie die umweltrelevanten Endpunkte Abbaubarkeit (biotisch, abiotisch), Bioakkumulation, Ökotoxizität und Umweltexposition. Als Ergebnis des Screenings wurden die zu den jeweiligen Endpunkten eingereichten Informationen den vier Kategorien „konform“, „nicht konform“, „Testvorschlag“ oder „komplex“ – keine Zuordnung zu einer der anderen Kategorien möglich - zugeordnet. Aus den Endpunktentscheidungen wurde die Zuordnung „konform“, „nicht konform“ oder „komplex“ für das gesamte Dossier abgeleitet. Von den 1932 vorliegenden Dossiers konnten 1814 in diesem Projekt bewertet werden. Im Ergebnis wiesen 58% der Dossiers entsprechend des Screenings Mängel hinsichtlich der Erfüllung der Standardanforderungen auf („nicht konform“). In der Mehrheit dieser Dossiers lagen für einen oder zwei Endpunkte keine ausreichenden Informationen vor. Häufige Mängel in „nicht konformen“ Dossiers waren Angaben zu Testsubstanzen, die nicht mit denen der registrierten Substanz übereinstimmten und Studien, die nicht entsprechend den Prüfrichtlinien durchgeführt waren. Als „konform“ wurde nur ein Dossier klassifiziert, d.h. alle geprüften Endpunkte entsprachen im Screening den Anforderungen der REACH Anhänge. 42% der Dossiers wurden als „komplex“ bewertet. Hier konnte für mindestens einen Endpunkt im Rahmen des Screenings keine Zuordung zu „konform“ oder „nicht konform“ getroffen werden. In diesen Fällen lagen zumeist Ersatzdaten zu einem anderen Stoff (häufig nach dem sogenannten „Grouping/Read-Across“-Ansatz) oder Begründungen für einen Datenverzicht vor. Diese Fälle bedürfen einer weitergehenden Analyse. Die Ergebnisse zeigen, dass eine Verbesserung der Daten in den Registrierungsdossier erforderlich ist.

Abstract

The report on the project “REACH Compliance: Data Availability of REACH Registrations” presents findings and results from the screening of 1932 dossiers of lead and individual registrants covering phase-in substances with a production volume of equal or above 1000 tpa. The standard information requirements necessary for the registration and their adaptation options for high tonnage substances are specified in the REACH Regulation (EC) No 1907/2006, Annexes VII to XI. Within this project, the availability of data to fulfil these requirements was screened with a standardised web-based approach. The endpoints considered were repeated dose toxicity, developmental and reproductive toxicity, and genetic toxicity as human health-related endpoints and degradation (biotic, abiotic), bioaccumulation, ecotoxicity and exposure as environment-related endpoints. As a result of the screening, the endpoints were assigned to one of the categories “compliant”, “non-compliant”, “testing proposal” or “complex” – an allocation to one of the other categories was not possible in this project. Based on the endpoint conclusions, the dossiers were assigned to one of the categories “compliant”, “non-compliant” or “complex”. 1814 of the 1932 included dossiers could be evaluated in the project. According to the screening, 58% of the investigated dossiers showed deficiencies in terms of REACH information requirements (“non-compliant”). For the majority of these dossiers, information on one or two endpoints was not available or not sufficient. Two frequently observed reasons for the conclusion “non-compliant” were that the used test material did not correspond to the registered substance and that studies were not conducted according to the appropriate guidelines. Only one dossier was

regarded as “compliant”, i.e. the REACH requirements were fulfilled for all endpoints according to the screening. 42% of the dossiers remained without firm conclusion (“complex”), i.e. an assignment to the categories “compliant” or “non-compliant” could not be made for at least one endpoint. Thereby, registrants frequently applied surrogate data (e.g. a grouping/read-across approach) or presented a justification for data waiving. A more detailed analysis is required to conclude on “complex” dossiers. The results demonstrate that an improvement of data in registration dossiers is required.

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List of Abbreviations and Terms

AbioDeg	abiotic degradation (endpoint)
adaptation	adjustment of REACH Regulation Annexes VII to X, Column 1 standard information requirements in accordance with REACH Annexes VII to X, Column 2 or Annex XI
AoC	areas of concern; kind of data selection in ECHA CCH
BCF	bioconcentration factor
Bioaccu	bioaccumulation (endpoint)
BioDeg	biotic degradation (endpoint)
BOD	biochemical oxygen demand
CCH	official compliance check by ECHA according to REACH Regulation Article 41
CLH	harmonised classification and labelling according to CLP Regulation (EC) No. 1272/2008, Annex VI
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
C&L	Classification & Labelling information on notified and registered substances received from manufacturers and importers; C&L inventory is a database of ECHA published on web, which also includes the list of harmonised classifications according to CLP Regulation (EC) No. 1272/2008, Annex VI.
CMR	carcinogenic, mutagenic or toxic to reproduction
CoRAP	Community Rolling Action Plan; ECHA list of substances which are or will be evaluated by member states
CSA	chemical safety assessment
CSR	chemical safety report
CT	“compliant”, i.e. in compliance with the REACH standard information requirements according to the screening criteria of this project
CX	“complex”, i.e. no conclusion on “compliant” or “non-compliant” regarding to the screening applied in the project
Cytvitro	Cytogenicity/micronucleus test in mammalian cells (study type)
Cytvivo	Cytogenicity/micronucleus test in vivo (study type)
DevTox	Developmental toxicity (study type)
DOC	dissolved organic carbon
EC	European Commission
EC_{50}	median effective concentration

ECHA	European Chemicals Agency
Ecotox	ecotoxicity (endpoint)
ENV	environment
ESR	endpoint study record
ESS	endpoint study summary
Expo	environmental exposure (endpoint)
EU	European Union
Germvivo	germ cell test in vivo (study type)
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GMbact	bacterial gene mutation test (study type)
GMvivo	gene mutation test in vivo (study type)
HH	human health
IUCLID	International Uniform Chemical Information Database
kH	Henry's law constant
KnowSEC	Managing Knowledge of Substances of Ecological Concern
LC_{50}	median lethal concentration
log K_{ow}	n-octanol/water partition coefficient
Muta	genetic toxicity (endpoint)
NC	"non-compliant", i.e. in non-compliance with the REACH standard information requirements according to the screening criteria of this project
NO(A)EL	no observed (adverse) effect level
OECD	Organisation for Economic Co-operation and Development
OCSPP	Office of Chemical Safety and Pollution Prevention
OPPTS	Office of Prevention, Pesticides and Toxic Substances
PBT/vPvB	persistent, bioaccumulative, toxic/very persistent, very bioaccumulative
PEC	predicted environmental concentration
Petrorisk-Model	calculation tool for environmental risk assessment of petroleum substances
phase-in substances	Substances which, under certain conditions, were already manufactured or placed on the market before REACH's entry into force. Substances fulfilling at least one of the following criteria may be considered as phase-in substances in accordance with REACH (Article 3(20)): a) Substances listed in the European Inventory of Existing Commercial Chemical Substances (EINECS) b) Substances that have been manufac-

	tured in the EU (including the countries that joined on 1 January 2007) but have not been placed on the EU market after 1 June 1992 c) Substances that qualify as "no-longer polymer''
pK_a	acid dissociation constant
PNEC	predicted no effect concentration
QMRF	(Q)SAR Model Reporting Format
QPRF	(Q)SAR Prediction Reporting Format
(Q)SAR	Quantitative Structure–Activity Relationship
RA	grouping/read-across
RDT	repeated dose toxicity (endpoint)
ReproTox	Reproductive toxicity (study type)
REACH	Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH)
RSS	robust study summary
SIEF	Substance Information Exchange Fora
STOT RE	Specific target organ toxicity — repeated exposure
SVHC	substances of very high concern
S_w	water solubility
TG	test guideline
ThOD	theoretical oxygen demand
$ThCO_2$	theoretical CO_2 production
TRep	toxicity to reproduction (endpoint)
TP	testing proposal
tpa	tonnes per annum
US EPA	United States Environmental Protection Agency
UVCB	substance of Unknown or Variable composition, Complex reaction products or Biological materials
waiving	REACH Regulation Annexes VII to X, Column 1 standard testing regime/standard information requirements are deliberately not fulfilled by the registrant
WoE	weight of evidence

Zusammenfassung

Einleitung

In der Europäischen Union müssen Hersteller und Importeure von Chemikalien diese bei der Europäischen Chemikalien Agentur (ECHA) registrieren. Ziel ist es, genügend Informationen sowohl zur Gefahren- und Risikocharakterisierung von Chemikalien als auch für das Risikomanagement zu erhalten. Für Chemikalien mit einer Jahresproduktion von 1000 Tonnen und mehr sind die Informationsanforderungen und deren mögliche Anpassungen in den Anhängen VII bis XI der REACH Verordnung (EG) Nr. 1907/2006 festgelegt. Im Rahmen des Projekts haben das Bundesinstitut für Risikobewertung (BfR) und das Umweltbundesamt (UBA) ein systematisches webbasiertes Screening-Werkzeug zur Überprüfung der Datenverfügbarkeit gemäß REACH entwickelt. Damit wurden am BfR ausgewählte Umwelt- und Gesundheitsendpunkte in 1814 Dossiers hochtonnagiger Chemikalien standardisiert auf Übereinstimmung mit den Anforderungen der REACH Anhänge überprüft.

Die Standardanforderungen für dieses höchste Tonnageband beinhalten aufwendige Untersuchungen zu zahlreichen Endpunkten. Jedoch gilt das vorrangige Gebot, auf Tierversuche weitgehend zu verzichten. Daher ist es vorgeschrieben, dass Firmen grundsätzlich die Stoffregistrierung zusammen mit anderen Firmen durchführen und dabei die Daten zu Chemikalien gemeinsam nutzen sollen. Des Weiteren sollen die bisher verfügbaren Daten sowie Daten aus Alternativen zu Tierversuchen, soweit möglich, verwendet werden. Darüber hinaus ist es möglich, auf Tierversuche aufgrund von Informationen zur Exposition zu verzichten, vorausgesetzt geeignete Risikomanagementmaßnahmen wurden getroffen. Zu tatsächlich identifizierten Datenlücken werden von Registranten zunächst Testvorschläge eingereicht. Sofern ECHA diese Vorschläge billigt, dürfen Tierversuche durchgeführt werden.

Das Projekt hatte zum Ziel zu überprüfen, welche Daten in den Registrierungsdossiers der seit dem Inkrafttreten von REACH bis 2010 registrierten hochtonnagigen Stoffe verfügbar sind. Das entwickelte Screening wurde an einer hohen Anzahl an Dossiers durchgeführt, ist jedoch nicht mit dem „Compliance Check“ gemäß REACH Art. 41 der ECHA vergleichbar.

Methodik

Zu einem Stichtag im März 2014 wurden 1932 Dossiers von federführenden und nach REACH Art. 11 (3) individuell einreichenden Registranten von sogenannten „Phase-in“ Chemikalien festgestellt. Geprüft wurden die gesundheitsrelevanten Endpunkte Toxizität nach wiederholter Applikation, Reproduktions- und Entwicklungstoxizität und Mutagenität, und die Umweltendpunkte Abbaubarkeit (biotisch und abiotisch), Bioakkumulation, Ökotoxizität und Umweltexposition. Um die hohe Anzahl an Dossiers hinsichtlich dieser Endpunkte zu überprüfen, musste ein Verfahren entwickelt werden, mit dem auf einfache, schnelle und reproduzierbare Weise eine Bewertung der Daten möglich war. Es wurde daher auf Basis der REACH Anforderungen ein standardisiertes Schema von aufeinanderfolgenden Fragen in Form von Entscheidungsbäumen entwickelt. Zur Arbeitserleichterung bei der Prüfung und Speicherung der Abfrageergebnisse wurden diese Entscheidungsbäume in ein webbasiertes Wissensmanagementsystem (KnowSEC) eingepflegt. Mit diesem Werkzeug wurde die Prüfung durchgeführt und die in Excel exportierten Ergebnisse wurden später einer beschreibenden statistischen Aufbereitung unterzogen.

Die Ergebnisse der untersuchten Endpunkte wurden einer der vier Kategorien zugeordnet:

- „konform“ mit den Anforderungen im Rahmen des Screenings,
- „nicht konform“ mit den Anforderungen im Rahmen des Screenings,
- „komplex“ – eine Zuordnung zu „konform“ oder „nicht konform“ konnte nicht vorgenommen werden und

- „Testvorschlag“, soweit mindestens ein Testvorschlag des Registranten vorgefunden wurde.

Ein Gesamturteil für jedes Dossier wurde auf Basis der Ergebnisse für die Endpunkte bestimmt:

- „konform“, soweit alle Endpunkte mit den Anforderungen im Rahmen des Screenings voll übereinstimmten,
- „nicht konform“, wenn mindestens ein Endpunkt des Dossiers die Bewertung als „nicht konform“ im Rahmen des Screenings erhalten hatte und
- „komplex“, wenn kein Endpunkt „nicht konform“ war, jedoch mindestens ein Endpunkt die Bewertung „komplex“ oder „Testvorschlag“ erhalten hatte.

Die Kategorie „komplex“ wurde für Ergebnisse genutzt, die mit der hier entwickelten Screening-Methode nicht den Kategorien „konform“ oder „nicht konform“ zugeordnet werden konnten, da sie eine genauere Evaluierung der eingereichten Daten erfordern. Dies trifft z.B. auf Fälle zu, bei denen Testmethoden verwendet wurden, die nicht den Standardanforderungen entsprechen und bei denen stattdessen Ersatzdaten eingereicht wurden oder ein begründeter Datenverzicht vorlag.

Folgende weitere Untersuchungen wurden an ausgewählten Dossiers durchgeführt:

Erstens wurde für eine bessere Interpretation und Einordnung der Ergebnisse dieses Screenings ein Vergleich mit den Ergebnissen des regulären Compliance Checks durchgeführt. Dieser wird nach Artikel 41 der REACH Verordnung durch die Europäische Chemikalien Agentur (ECHA) vollzogen und umfasst mindestens 5 % der Dossiers. Basis der Untersuchung waren die verfügbaren Einzelentscheidungen der ECHA, die auf einer umfangreichen Überprüfung aller Daten einer Registrierung beruhen. Diesen wurden die Screening-Ergebnisse der vorliegenden Studie gegenübergestellt.

In einer weiteren Untersuchung wurde eine kleine Stichprobe von Dossiers und Endpunkten, für die keine Entscheidung getroffen werden konnte („komplex“), näher untersucht. Das Ziel war es, beispielhaft einen Eindruck zur Datenverfügbarkeit in diesen Dossiers zu erhalten. Nach vertiefter Prüfung sollte möglichst eine Entscheidung über „konform“ und „nicht konform“ getroffen werden. Weiterhin wurden die zugrunde liegenden Gründe gemäß der REACH Datenanforderungen nach den Anhängen VII bis XI und weitere, gruppiert.

Ergebnisse

Von 1932 Dossiers wurden 118 Dossiers von der weiteren Analyse ausgeschlossen, weil 115 einem Kategorieansatz folgten und drei Dossiers aus technischen Gründen nicht bewertet werden konnten. Insgesamt wurden1814 Dossiers in diesem Projekt geprüft. 58 % der geprüften Dossiers erhielten die Zuordnung „nicht konform“, weil sie in mindestens einem der Endpunkte nicht den Anforderungen im Rahmen des Screenings entsprachen. In der Mehrheit dieser Dossiers lagen für einen oder zwei Endpunkte keine ausreichenden Informationen vor. 42 % der geprüften Dossiers wurden als „komplex“ beurteilt; d. h. mindestens ein Endpunkt, am häufigsten jedoch fünf bis sechs Endpunkte, konnten nicht abschließend bewertet werden. Ein Dossier (0,1 %) erwies sich als vollständig „konform“, d. h. entsprach in allen geprüften Endpunkten den Anforderungen des Screenings.

Betrachtet man die Endpunktergebnisse, ergibt sich eine etwas andere Verteilung der Zuordnung der Kategorien. Abgesehen vom Endpunkt biotische Abbaubarkeit war die häufigste Zuordnung die Kategorie „komplex“. Dabei fielen besonders die drei Endpunkte Entwicklungs-/Reproduktionstoxizität, Bioakkumulation und Ökotoxizität mit den höchsten Anteilen auf (73 bis 82 %). Die übrigen Endpunkte besaßen nur einen Anteil von 43 bis 66 % „komplexe“ Fälle. Dagegen erhielten die Zuordnung „konform“ 45 % der Dossiers für den Endpunkt biotische Abbaubarkeit und 21 bis 30 % der Dossiers für Mutagenität, wiederholte Applikation, abiotische Abbaubarkeit, Bioakkumulation und Umweltexposition. Nur geringe Anteile an der Zuordnung „konform“ wiesen die Endpunkte Entwicklungs-/Reproduktionstoxizität (5 %) und Ökotoxizität (4 %) auf. Hierbei handelt es sich auch

um diejenigen Endpunkte, die die aufwändigsten Studien erfordern. Weiterhin wies der Endpunkt Mutagenität mit 28 % den höchsten Anteil „nicht konformer“ Entscheidungen auf. Bei den übrigen Endpunkten betraf dies 3 bis 15 % der Dossiers.

Die Zuordnung „komplex“ beruhte häufig darauf, dass auf die Erfüllung der Standardanforderungen begründet verzichtet wurde („waiving“) oder Ersatzdaten verwendet wurden („adaptation“). Bei fehlendem Test gemäß Standardanforderungen wurde häufig ersatzweise ein Testergebnis mit einem anderem Stoff vorgelegt (Gruppenansatz („Grouping“) oder „Read-Across“ gemäß REACH Anhang XI). Im Prüfbereich Gesundheit betraf dies ca. die Hälfte der Endpunktentscheidungen mit Datenverzicht. Im Umweltbereich war der Anteil deutlich geringer, mit ca. einem Drittel lag Grouping/Read-Across beim Endpunkt Ökotoxizität an erster Stelle der Kategorien zum Datenverzicht. Bei den übrigen Endpunkten hatte dies untergeordnete Bedeutung (≤ 5 %). Diese Fälle erfordern eine genauere Untersuchung, ob der Bezug zu einer anderen Substanz oder der Gruppenansatz angemessen ist.

Endpunkte wurden als „konform“ betrachtet, wenn alle Standardinformationen gemäß den REACH Anhängen VII bis X, Spalte 1 vorlagen und abschließend beurteilt werden konnten. Ein weiterer Grund für diese Zuordnung war für die Endpunkte Mutagenität und Reproduktionstoxizität zudem eine bestimmte harmonisierte Einstufung nach CLP. Für Reproduktionstoxizität betraf dies 80 % der „konformen“ Fälle. Für den Bereich Umwelt bildeten den Großteil der Kategorie „konform“ Fälle, die einen gültigen Datenverzicht nach einem Spalte 2 Kriterium der REACH Anhänge aufwiesen. Des Weiteren wurde der Endpunkt Umweltexposition als „konform“ eingestuft, wenn keine harmonisierte Einstufung nach Anhang I der CLP-Verordnung vorlag und die Substanz keine PBT/vPvB-Eigenschaften besaß.

Zwei endpunktübergreifende Gründe waren im Wesentlichen dafür verantwortlich, dass die Entscheidung „nicht konform“ zugeordnet wurde. Der erste Grund war, dass die Angaben zur Testsubstanz nicht mit denen der registrierten Substanz übereinstimmten und für die Abweichung eine Begründung fehlte. Für den Gesundheitsbereich betrug der diesbezügliche Anteil 26 bis 33%. Im Hinblick auf den Umweltbereich betraf dies 7 bis 79 %. Der zweite Grund war der fehlende Bezug zu einer akzeptierten Prüfrichtlinie. Der Anteil für diesen Grund betrug zwischen 19 und 27 % für den Bereich Gesundheit und 7 bis 38 % für den Umweltbereich.

Testvorschläge gab es im Prüfbereich Umwelt nur sehr selten, im Prüfbereich Gesundheit jedoch häufig bei den Endpunkten Wiederholte Applikation und Entwicklungs-/Reproduktionstoxizität (in 120 bzw. 196 Dossiers). Vermutlich waren die Dossiers seit der Registrierung noch nicht aktualisiert worden, weil die entsprechenden Studien, insbesondere die Zwei-Generationen-Studie für die Reproduktionstoxizität, bis zum Stichtag des Projekts noch nicht durchgeführt oder abgeschlossen waren.

Im Folgenden werden endpunktspezifische Ergebnisse dargestellt.

Mutagenität: Für diesen Endpunkt waren in etwa 47 % der Dossiers entsprechend dem Screening die Daten nicht abschließend beurteilbar („komplexe“ Fälle). Der vergleichsweise hohe Anteil (28 %) der Zuordnung als „nicht konform“ hängt damit zusammen, dass ein Datenverzicht nicht begründet wurde. Dies könnte auf die Komplexität der Anforderungen in diesem Bereich zurückzuführen sein, die sich daraus ergibt, dass bestimmte Tests in Abhängigkeit von den Ergebnissen zuvor durchgeführter Studien erfolgen müssen. Hier bestehen seitens der Registranten möglicherweise Unklarheiten in der Interpretation der REACH Anhänge bzw. der entsprechenden Leitfäden.

Entwicklungs-/Reproduktionstoxizität: Der auffällig hohe Anteil (73 %) an der Zuordnung „komplex“ im Hinblick auf diesen Endpunkt beruhte auf dem allgemein höheren Anteil an Dossiers ohne Standarddaten, für die aber eine Begründung des Datenverzichts oder Ersatzdaten angegeben waren. Hierbei lagen in 74,1 % der „komplexen“ Fälle gar keine Studienergebnisse gemäß den Standardanforderungen vor. In 15,4 % waren zumindest Ergebnisse zur Entwicklungstoxizität an einer oder zwei Tierarten vorhanden. Am häufigsten fehlte eine Zwei-Generationen-Studie. Ein vergleichsweise ge-

ringer Anteil von 5 % der Dossiers entsprach entsprechend des Screenings den REACH Anforderungen.

Wiederholte Applikation: Hier lagen in 56 % der Dossiers nicht abschließend beurteilbare Daten zur subchronischen Toxizität vor. Bei 24 % der Dossiers war eine valide (sub)chronische Studie für diesen Endpunkt vorhanden, während sie bei 14 % der Dossiers fehlte oder nicht den Anforderungen entsprach. Es wurde häufig beobachtet, dass eine subchronische Studie oder Ersatzdaten bzw. begründeter Datenverzicht fehlten, wenn eine subakute Studie vorhanden war.

Biotische Abbaubarkeit: Der Anteil der Dossiers, der im Hinblick auf diesen Endpunkt als „komplex" eingestuft wurde (43 %), war im Vergleich zu allen anderen Endpunkten am geringsten. Der Anteil derer, die als „konform" eingestuft wurden, war mit 45 % am höchsten. Letztere Zuordnung war im Wesentlichen auf zwei Gründe zurückzuführen. Zum einen wurden für diesen Endpunkt häufig die vorgeschriebenen Standardmethoden zur Bestimmung der leichten biologischen Abbaubarkeit eingesetzt. Zum anderen lagen oft anorganische Substanzen vor, für die ein Datenverzicht laut REACH Verordnung zulässig ist. Bei Endpunkten der Kategorie „nicht konform" (11 %) fehlten dagegen in der Regel Angaben zum Screening-Test auf leichte biologische Abbaubarkeit.

Abiotische Abbaubarkeit: Der sehr geringen Zahl von Endpunkten, die als „nicht konform" eingestuft wurden (5 %), standen 29 % Endpunkte der Kategorie „konform" und zwei Drittel der Kategorie „komplex" gegenüber. Hauptursache für die Zuordnung „nicht konform" war das Fehlen von Daten aus dem Hydrolyse-Test. Die Hauptgründe für die Zuordnung von Endpunkten zur Kategorie „komplex" waren die Verwendung von Ersatzdaten oder Datenverzicht. Bei der Mehrzahl der Endpunkte, die als „konform" eingestuft wurden, lag Datenverzicht mit Bezug auf Anhang VIII, Spalte 2 der REACH Verordnung vor (Substanz biologisch leicht abbaubar oder Wasserlöslichkeit < 1 mg/L).

Bioakkumulation: Etwa drei Viertel der Dossiers wurden im Hinblick auf den Endpunkt Bioakkumulation als „komplex" bewertet. Hierfür lagen im Wesentlichen drei Gründe vor. In jeweils etwa einem Viertel dieser Fälle waren die Substanzen anorganisch und/oder ionisch dissoziierbar. Da für diese Substanzen derzeit keine geeigneten Methoden zur Bestimmung der Bioakkumulation vorhanden sind, ist eine Einzelfallentscheidung notwendig. Die übrigen als „komplex" bewerteten Endpunkte basierten im Wesentlichen auf verschiedene Kategorien des begründeten Datenverzichts. Weiterhin lag für den überwiegenden Anteil der 21 % als „konform" eingestuften Endpunkte ein Datenverzicht mit Bezug zum Anhang IX, Spalte 2 der REACH Verordnung zu Grunde (log $K_{ow} \leq 3$).

Ökotoxizität: Dieser Endpunkt wies im Vergleich mit den übrigen Endpunkten mit 82 % den höchsten Anteil in der Zuordnung „komplex" auf. Ausschlaggebend hierfür war zu einem Drittel die Verwendung des Grouping/Read-Across Konzeptes. Ein weiterer Punkt war die Angabe von Begründungen für den Verzicht auf experimentelle Daten für die vorgeschriebenen akuten und chronischen Studien. 13 % der Dossiers wurden hinsichtlich des Endpunktes Ökotoxizität als „nicht konform" beurteilt. Die häufigste Ursache hierfür war die Verwendung einer Testsubstanz, die nicht mit der registrierten Substanz übereinstimmte. Lediglich 4 % der Dossier erfüllten bzgl. dieses Endpunktes die Kriterien des Screenings („konform").

Exposition in die Umwelt: Mehr als die Hälfte der Dossiers wurde im Hinblick auf diesen Endpunkt als „komplex" bewertet, da die vorhandenen Expositionsszenarien bzw. die qualitative Expositionsbewertung eine zeitaufwändige Detailprüfung erfordern würde. In knapp einem Drittel der Fälle wurden die vorhandenen Daten als „konform" mit den Informationsanforderungen betrachtet, da diese Substanzen weder als PBT/vPvB eingestuft noch eine Klassifizierung nach CLP-Verordnung vorhanden waren und somit eine Expositionsbewertung nach REACH Art. 14(4) nicht erforderlich ist. Hingegen lagen für 15 % der Substanzen harmonisierte Einstufungen nach der CLP-Verordnung vor; jedoch fehlte eine Expositionsbewertung für den Umweltbereich, so dass diese Endpunkte als „nicht konform" bewertet wurden.

Vergleich mit Ergebnissen des ECHA Compliance Checks

Im Prüfbereich Gesundheit war der Vergleich mit den Entscheidungen aus dem offiziellen Compliance Check (CCH) für 31 Stoffe bzw. Dossiers möglich. In den Entscheidungen der ECHA wurden insbesondere Daten zur Entwicklungstoxizität an einer zweiten Spezies und Daten zur subchronischen Toxizität gefordert. Berücksichtigt man zeitliche Verschiebungen in der Prüfung der Dossiers und die Tatsache, dass für dieses Projekt Ersatzdaten und Begründungen für den Testverzicht in der Regel nicht näher untersucht wurden, deckten sich die Forderungen für diese Endpunkte in etwa mit den Screening Ergebnissen im vorliegenden Projekt.

Exemplarische Analyse von „komplex“ Fällen

Die vertiefend angelegte Analyse von ausgewählten, durch das Screening als “komplex” eingestuften Endpunkten bzw. Dossiers zeigte einige Tendenzen auf. Jedoch ist eine breitere Untersuchung notwendig, um auf Basis der jeweils individuellen Fälle Rückschlüsse auf das Gesamtspektrum der Dossiers ziehen zu können. Hierbei konnten Fälle, die sich ausschließlich auf einen Grouping/Read-Across Ansatz stützen, nicht näher betrachtet werden. Insgesamt konnten für viele der ausgewählten „komplexen“ Endpunkte bzw. Dossiers Entscheidungen getroffen werden. Diese resultierten sowohl in der Zuordnung „konform“ als auch „nicht konform“ für die betreffenden Endpunkte. Die Entscheidung „nicht konform“ beruhte insbesondere auf einer nicht ausreichenden Begründung für den Testverzicht.

Weiterhin zeigten sich bei der Analyse der „komplexen Fälle“ wiederholt bestimmte Sachverhalte bei den Endpunkten. Für den Prüfbereich Gesundheit fehlte in den exemplarisch untersuchten Beispielfällen z. B. häufig ohne hinreichende Begründung oder Ersatzdaten der Test zur Entwicklungstoxizität an einer zweiten Tierart. Auf die Zwei-Generationen-Studie wurde oftmals mit dem unzureichenden Hinweis auf die festgestellte geringe Toxizität in anderen Endpunkten verzichtet. Dies kann eine akzeptable Argumentation sein, wenn zusätzlich auch auf expositionsbezogene Parameter eingegangen wird, was aber i.d.R. nicht der Fall war. Eine ähnliche Sachlage fand sich auch bei dem Endpunkt subchronische Toxizität, wenn auf Daten aus anderen Studien verwiesen wurde, die jedoch häufig die geforderte zeitliche Vorgabe der Testung über mindestens 90 Tage nicht erfüllen konnten.

Im Prüfbereich Umwelt konnten bei der Analyse der exemplarisch gewählten „komplex“ Fälle verschiedene endpunktübergreifende wie auch endpunktspezifische Problemfelder identifiziert werden. Hierzu zählten z.B. die ungenügende Dokumentation von Daten bei dem Einsatz von (Q)SAR-Methoden, die Verwendung sog. „Petrorisk“-Modelle für Petroleum-Produkte, die Angaben zu Stoffidentität und physikalisch-chemischen Eigenschaften für UVCB-Stoffe und die hohe Anzahl von Testmethoden, die nicht den Standardverfahren entsprachen. Letzteres trat insbesondere beim Endpunkt Ökotoxizität auf.

<u>Schlussfolgerungen</u>

Im Ergebnis des Screenings ist festzustellen, dass mehr als die Hälfte der untersuchten Dossiers in mindestens einem Endpunkt nicht den Datenanforderungen von REACH zu entsprechen scheint. Solche Datenlücken erschweren eine umfassende Risikobewertung für Mensch und Umwelt und stellen somit in Frage, ob eine sichere Verwendung von Chemikalien gewährleistet werden kann. Besonders kritisch zu bewerten sind Dossiers mit Datenmängeln zu mehreren Endpunkten.

Für die Mehrzahl der Endpunkte wurde festgestellt, dass in den Registrierungen ersatzweise Daten zu anderen Stoffen, Daten aus Nicht-Standard-Methoden oder Begründungen für den Datenverzicht gegeben wurden. Eine Bewertung dieser Fälle konnte im Rahmen dieses Projektes nicht erfolgen.

Verbleibende Unsicherheiten bei den komplexen Fällen sind mit Umsicht zu interpretieren und sind insbesondere auf die angewendete Screening-Methodik zurückzuführen. Eine weitere Auflösung der komplexen Fälle wird dazu beitragen, die Gesamtzahl der Entscheidungen „konform“ und „nicht

konform“ zu erhöhen. Exemplarisch gezeigt werden konnte dies auch in dem hier durchgeführten kleineren Teilprojekt der detaillierteren Untersuchung „komplexer Fälle“.

In dieser Screening Studie wurde ein Dossier als „nicht konform“ betrachtet, sobald ein Endpunkt die Zuordnung „nicht konform“ in Bezug auf die REACH Anforderungen erhalten hat. Dieser Ansatz kann als sehr konservativ angesehen werden. Da umfangreiche Informationen zu vielen Endpunkten für hochtonnagige Substanzen erforderlich sind, ist die Wahrscheinlichkeit hoch, dass einzelne Daten unzureichend sind. Betrachtet man jedoch, dass die REACH Anforderungen Standardinformationen für Substanzen mit einem Produktionsvolumen von mindestens 1000 Tonnen sind, und dass viele Substanzen höhere Produktionsvolumen von bis zu mehreren 100 000 Tonnen pro Jahr erreichen, und die untersuchten Endpunkte von besonderer Bedeutung für die menschliche Gesundheit und Umwelt sind, erscheint dies gerechtfertigt.

Darüber hinaus wurden im Verlauf des Projektes auch Probleme erkannt, die teils den komplexen Testanforderungen bzw. möglicherweise auch Unklarheiten in den Anhängen der REACH Verordnung oder den ECHA Leitfäden geschuldet waren.

Die Projektergebnisse sind eine gute Basis für die Auswahl und Priorisierung von Stoffen für Verfahren unter REACH und für weitere Auswertungen.

Summary

Introduction

In the European Union chemicals have to be registered with European Chemicals Agency (ECHA) by the respective manufacturers or importers. The aim is to provide sufficient information for the hazard and risk characterisation of chemicals as well as for risk management. The information requirements and their possible adaptations for chemicals produced at tonnages of 1000 tpa or more are set out in Annexes VII to XI of the REACH Regulation (EC) No. 1907/2006. Within the scope of this project the Federal Institute for Risk Assessment (BfR) and the Federal Environmental Agency (UBA) developed a systematic web-based screening tool to assess the availability of the required data according to REACH. In this regard, BfR screened in a standardised manner the data on selected environmental and human health endpoints in 1814 dossiers of high tonnage chemicals for accordance with the respective REACH Annexes.

On the one hand, the standard requirements for this tonnage level are extensive and challenging and these substances have to be evaluated with regard to numerous endpoints. Therefore, companies that intend to register the same substances should share data and cooperate in the registration process. On the other hand, animal testing should as far as possible be avoided and instead existing data and alternatives on the testing of animals should be used if available. Further, omission of animal tests is possible due to exposure considerations if appropriate risk management is provided. If actual information gaps are identified, testing proposals have to be provided by the registrant first. When ECHA approved these proposals testing on animals is permitted.

The aim of the project was to assess the data availability in registration dossiers of high tonnage substances which were registered since REACH came into force until 2010. The developed screening was applied on a high number of dossiers. However, this procedure was not comparable with the official compliance check by ECHA according to REACH Art. 41.

Methodology

At a due date in March 2014 altogether 1932 dossiers of phase-in substances from lead and individual registrants [acc. to REACH Art. 11 (3)] were established. For human health the selected endpoints covered repeated dose toxicity, developmental/reproductive toxicity and genetic toxicity, and for the environment degradation (biotic and abiotic), bioaccumulation, ecotoxicity and environmental exposure. To screen the high number of dossiers regarding these endpoints an approach had to be developed which allowed evaluation of the data in a simple, rapid and reproducible way. Therefore, a standardised screening method referring to the REACH requirements was developed. It was based on decision trees with a number of questions built on one another. To simplify the data screening and data storage, the decision trees were implemented into a web based knowledge management system (KnowSEC). After its application, the results of the screening were finally exported to Excel files for descriptive statistics.

The screening results for each endpoint were assigned to one out of four endpoint categories:

- “compliant” – if the information requirements within the scope of the screening were fulfilled
- “non-compliant” – if the information requirements within the scope of the screening were not fulfilled
- “complex” - an assignment to “compliant” or “non-compliant” was not applied
- “testing proposal” – if at least one testing proposal was available.

All endpoint conclusions of a dossier were combined into one single dossier conclusion:

- "compliant" –if the information requirements within the scope of the screening for all endpoints were fulfilled
- "non-compliant" – if the information requirements within the scope of the screening for at least one endpoint was not fulfilled
- "complex" – if at least one endpoint conclusion was "complex" or "testing proposal" and no endpoint conclusion was "non-compliant".

Thereby, the category "complex" was used for endpoints and dossiers that could not be clearly assigned to the categories "compliant" or "non-compliant" according to the applied screening methodology because they required a more detailed analysis. For example, if the conducted test method was not in accordance with the standard information required and instead an adaptation or waiving was available.

Supplementary to the screening further investigations on selected dossiers were conducted:

First, in order to achieve a better interpretation of the screening results a comparison with results from the compliance check (CCH) of the European Chemicals Agency (ECHA) was performed. ECHA's CCH is conducted in accordance with Art. 41 REACH Regulation and covers at minimum 5% of all dossiers. The individual decisions of ECHA that based on a comprehensive evaluation of registration data was compared with the respective screening results of this project.

Second, a small number of dossiers and endpoints which were not concluded during the screening ("complex") were evaluated in more detail. The aim was to exemplary achieve deeper insight into their data availability. If possible "complex" conclusions were changed to the categories "compliant" or "non-compliant". Moreover, the underlying reasons were grouped according to the REACH information requirements in Annexes VII to XI and additional.

Results

118 of 1932 dossiers were excluded from further analysis, since a category approach was used (115 dossiers) or the dossiers could not be screened due to technical reasons (3 dossiers). Thus, 1814 dossiers were evaluated in this project. Altogether 58% of the dossiers were assigned to the conclusion category "non-compliant" because for at least one endpoint the required standard information was not available. For the majority of these dossiers, information on one or two endpoints was not available or not sufficient. Further, 42% of all dossier conclusions were "complex", whereby at least one endpoint, however, in the majority of these cases five or six endpoints, remained undecided. Only one dossier (0.1%) was, for all selected endpoints, in compliance with the requirements according to the screening.

The distribution of endpoint conclusion categories differed from those of the dossiers. Apart from biotic degradation the most frequent endpoint conclusion category was "complex". The highest percentages of "complex" conclusions were observed for the endpoints toxicity to reproduction, bioaccumulation and ecotoxicity (73 – 82%), whereas the other endpoints had proportions of 43 – 66%. Further, biotic degradation resulted in the highest percentage of "compliant" conclusions (45%). For the majority of the endpoints (genetic toxicity, repeated dose toxicity, abiotic degradation, bioaccumulation and environmental exposure) the range was 21 – 30%. Very few "compliant" conclusions were recorded for toxicity to reproduction (5%) and ecotoxicity (4%); both endpoints require the most elaborated studies. Moreover, the endpoint genetic toxicity had the highest percentage of "non-compliant" conclusions (28%). In contrast, for the other endpoints the range of "non-compliant" conclusions was 3 – 15%.

The main crosscutting reason why endpoints were considered "complex" was the justified waiving of standard information or the use of surrogate data ("adaptation"). Among this grouping/read-across approaches according to REACH, Annex XI 1.5 were a frequent reason for the endpoint conclusion

"complex". In these cases experimental data were provided by substitutes for the registered substance. For human health endpoint conclusions approximately half of all adaptation/waiving arguments based on grouping/read-across approaches. The percentage was in general much lower for environmental endpoints. However, the percentage was high for ecotoxicity with about one third grouping/read-across approaches, whereas it was of minor importance (< 5%) for the other endpoints. These cases require a case-by-case evaluation to verify the reference to other substances or the grouping approach.

Endpoints were assigned to the category "compliant" if all standard information requirements according to REACH Annexes VII to X, Column 1 were available and could be evaluated. An additional reason for the endpoints genetic toxicity and reproductive toxicity was a particular harmonised classification according to CLP. For reproductive toxicity this applied to 80% of all "compliant" cases. With respect to the environmental endpoints, the most frequent reason for the category "compliant" was valid data waiving according to Column 2 criteria of the REACH Annexes. Moreover, the endpoint environmental exposure was categorised as "compliant" if no classification according to Annex I of the CLP Regulation was available and the substance had no PBT/vPvB properties.

For the endpoint conclusion "non-compliant" two main crosscutting reasons were identified during the screening. First, the used test material was not in accordance with the registered substance, and for this deviation no reasonable justification was presented. For human health endpoints the percentages of these "non-compliant" conclusions were between 26 – 33% and for environmental endpoints within a range of 7 – 79%. The second reason was that study entries were without reference to acceptable test guidelines. The percentage of this reason was between 19 – 27% and 7 – 38% for human health and environmental endpoint conclusions, respectively.

Testing proposals occurred very rarely for environmental studies, whereas they were frequently provided for human health endpoints, e. g. in 120 and 196 dossiers for repeated dose toxicity and toxicity to reproduction, respectively. These dossiers had possibly not been updated since the registration. This was probably because the respective studies, particularly the two-generation study for toxicity to reproduction, had not been performed or concluded until the due date of this project.

Endpoint-specific results are presented in the following section.

Genetic Toxicity: For this endpoint in approximately 47% of all dossiers a conclusion on the acceptability of the data could not be made within this project ("complex"). The comparatively high percentage (28%) of "non-compliant" cases for genetic toxicity was caused by the fact that registrants did not justify data waiving. This might be due to the complexity of the requirements for this endpoint, i. e. particular tests have to be performed depending on the outcome of previous studies. Registrants might have misinterpreted the explanations given in the respective REACH Annexes or ECHA guidance documents.

Developmental and Reproductive Toxicity: The assignment "complex" occurred for a strikingly high percentage (73%) of all dossiers. It was observed that the required standard studies were frequently not available, but were substituted or the registrants provided justification for data waiving. For the majority of these cases (74.1%) neither appropriate experimental studies for developmental toxicity nor reproductive toxicity were provided. In 15.4% of the "complex" endpoint conclusions at least adequate data for developmental toxicity in one or two species were presented. In contrast, the current requirement for reproductive toxicity, the two-generation study, was most often not available. A comparatively low percentage of the dossiers (5%) fulfilled the REACH requirements according to the screening.

Repeated Dose Toxicity: 56% of all dossiers with respect to this endpoint remained undecided ("complex") because registrants adapted or waived the standard information. For 24% of all dossiers valid data on (sub)chronic toxicity were available, whereas these data were missing or inadequate in

14% of the dossiers. A common observation was that experimental data and an adaptation or waiving were not provided for the subchronic study when subacute testing had been performed.

Biotic Degradation: This environment endpoint had the lowest percentage of "complex" endpoint conclusions (43%) compared to all other endpoints. In accordance to this, 45% of the dossiers were regarded as "compliant" for this endpoint. Two reasons for the latter assignment were observed: First, the required standard methods were frequently used regarding ready biodegradability. A second reason was that substances were often anorganic and, thus, data waiving is permitted according to the REACH Regulation. Where the endpoint category was "non-compliant" (11%), the required data from screening studies for ready biodegradability were often not available.

Abiotic Degradation: The low number of "non-compliant" endpoint conclusions (5%) was accompanied by 29% "compliant" conclusions. Accordingly, about two third of dossiers for this endpoint were regarded as "complex". The main reason for the "complex" assignment was that adaptation/ waiving was used, whereas the dominant reason for the conclusion "compliant" was that waiving according to REACH Regulation Annex VIII, Column 2 was applied (substance is readily biodegradable or water solubility < 1 mg/L). The main reason for the category "non-compliant" was that data were not available for the hydrolysis test.

Bioaccumulation: About three quarters of the dossiers were allocated to the endpoint conclusion category "complex" for this endpoint. Three main reasons accounted for this assignment. First, for approximately one quarter of the "complex" endpoint conclusions substances were anorganic and/or ionisable. Methods to determine bioaccumulation of these substances are not yet available, thus, a case-by-case analysis is instead required. The other two reasons for "complex" generally based on different categories of justified data waiving. Furthermore, for most of the 21% "compliant" cases an acceptable data waiving according to Annex IX, Column 2 of the REACH Regulation was presented ($\log K_{ow} \leq 3$).

Ecotoxicity: With 82% "complex" endpoint conclusions, ecotoxicity was assigned to this category with the highest percentage compared to all endpoints. In one third of these cases a grouping/read-across approach accounted for this conclusion. Another reason was that the data waiving of the required acute and chronic studies was justified. Further, 13% of all dossiers were assigned to "non-compliant" regarding the endpoint ecotoxicity. Thereby, the main reason was that the test material used in a particular study did not correspond to the registered substance. Only 4% of the dossiers fulfilled the screening criteria for this endpoint ("compliant").

Environmental exposure: More than half of all dossiers were allocated to "complex" for this endpoint because the provided exposure scenarios and the qualitative exposure assessment, respectively, require an in-depth analysis. Almost one third of all endpoints were regarded as "compliant" because the substances were not classified as PBT/vPvB and also not classified according to the CLP Regulation. Accordingly, an exposure assessment in line with REACH Art. 14(4) is not required. In contrast, for 15% of the substances a classification according to the CLP Regulation was available. However, no environmental exposure assessment was conducted in these cases. Therefore, the respective endpoint conclusion was "non-compliant".

Comparison with ECHA Compliance Checks

With respect to human health a comparison with the decisions of the official ECHA compliance check (CCH) could be conducted for 31 dossiers (substances). Regarding these dossiers, ECHA especially requested data for developmental toxicity in a second species and for subchronic toxicity as a result of their CCH. The results from the screening phase of our project largely corresponded to the conclusions of ECHA. It was also taken into account that registrants might have updated their dossiers and that there might have been differences in the available registration data as well as the fact that adaptations and waiving justifications were not evaluated in this project.

Exemplary "complex" case analysis

A second minor part of the project covered the more detailed analysis of a selection of endpoints and dossiers that were assigned "complex" during the screening. Due to the small number the results of this analysis should not be regarded as representative for the entirety of dossiers. Further, grouping/read-across was not assessed. Overall, the previous conclusions could be revised for the majority of "complex" endpoints and dossiers. Accordingly, these cases were than allocated to the endpoint categories "compliant" or "non-compliant". The category "non-compliant", in particular, was assigned because data waiving was not sufficiently justified.

Certain issues were repeatedly observed for the human health endpoints. For example, with respect to toxicity to reproduction a justified data waiving or an adaptation for the developmental toxicity study in the second species was often not available. The two-generation study was frequently waived applying the justification that other studies showed no or low toxicity (for the developing and reproductive organs). This could be an acceptable argumentation if exposure-related aspects are addressed as well, but this was usually not the case. A similar, inadequate waiving argumentation was frequently used for the subchronic repeated dose toxicity study if a subacute test with no or low toxicity was available.

Endpoint-specific as well as overall endpoint issues could be identified for the environmental "complex" part of dossiers. Examples are the insufficient data documentation applying (Q)SAR models, the use of "Petrorisk" models for petroleum products, the problematic assessment of UVCB-substances with regard to substance identity and physicochemical properties, and the high number of test methods which deviated from the standard methods. The latter was particularly observed for the endpoint ecotoxicity.

Conclusions

According to the screening method of this project, more than half of the dossiers seemed not to fulfil the standard information requirements of the REACH Regulation for at least one endpoint. Such data gaps may impede a comprehensive risk assessment for the human health and the environment and question whether a safe use of chemicals can be warranted. Those dossiers that showed inadequate data for several endpoints are, thereby, of highest concern.

For the majority of endpoints surrogate data of other substances, non-standard data or justifications for data waiving were provided to substitute the experimental studies referred to in the REACH Annexes. A firm conclusion on these cases could not be made within this project.

The remaining uncertainties in these cases result from the screening approach applied in this project which did not allow to conclude "compliant" or "non-compliant" for a high number of endpoints and dossiers. The results need careful consideration. A detailed analysis of "complex" cases will certainly increase the overall number of "compliant" as well as "non-compliant" dossiers as indicated from the detailed analysis on a selection of "complex" cases.

In this screening study, a dossier was concluded as "non-compliant" if at least one endpoint was "non-compliant" with respect to the REACH requirements. This may be regarded as a conservative approach. Since a vast amount of information for many endpoints is requested for high tonnage chemicals, the probability is high that single datasets are inadequate. However, with regards to the fact that the information requirements are standard information for substances with a high production volume of at least 1000 tpa and that many of them are gaining much higher production levels (up to several 100 000 tpa), this conclusion is considered justified and reflects the particular importance of the considered endpoints with regards to their relevance for human health and the environment.

Besides the results on the data availability, this project identified several general issues and concerns in registration dossiers. These might have resulted from the comprehensiveness and the complexity of the testing requirements for substances at this tonnage level and some ambiguities in the Annexes of the REACH Regulation or ECHA guidance documents.

The project results are a good basis for further analysis of the quality of registration dossiers and a helpful tool for the prioritisation of substances for different procedures under REACH.

1 Introduction

1.1 REACH Registration Dossiers of High Tonnage Chemicals

The chemical legislation REACH was adopted to improve the protection of human health and the environment by increasing the knowledge about chemicals that are produced, marketed and used in the European Union. Companies are obliged to register chemicals at a production or import volume 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 management. The information requirements and possible adaptations for chemicals produced 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 Art. 5 (“no data, no market”), valid and complete safety data are a prerequisite 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 tonnage. To this end, four manufacturing 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 produced above 1000 tpa the full set of information according to Annexes VII to X has to be submitted. Requirements are high, in particular regarding developmental and reproductive toxicity, mutagenicity, repeated dose toxicity and ecotoxicity according to recognised test guidelines.

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 (Q)SARs are allowed, despite the fact that for some of these concepts criteria development is still on-going. Waiving of animal tests can also be justified based on exposure considerations according, when appropriate risk management measures are implemented. However, for omission of required standard tests a sufficient justification with respect to the criteria laid out in REACH Annexes VII to X, column 2 or Annex XI has to be given. If, as a last resort, testing in vertebrates has to be considered to close the data gap, a corresponding testing proposal must be provided by the registrants and is then evaluated by ECHA. When ECHA approved these proposals testing on animals is permitted.

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

To assure data quality a comprehensive guidance system 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 on no less than 5% of the dossiers of each tonnage band are carried out according to REACH Article 41 in order to control dossier quality. Thus, irrespective of some other processes under the REACH Regulation which include also a check of the data availability, the number of dossiers fully checked is low.

The registration of so-called phase-in substances is divided into phases. The first registration deadline concerning high tonnage chemicals (≥ 1000 tpa), CMR substances from 1 tpa and water toxicants from 100 tpa, ended in 2010. Toxicological data on chemicals produced from 1000 tpa are, therefore, now available. High and elaborate standards are applied at this highest tonnage level.

Thus, in light of the fact that only a minimum of 5% of dossiers per tonnage band is reviewed by ECHA in terms of compliance to the REACH Annexes, problems on data availability can be expected regarding fulfilment of the information requirements.

1.2 Objectives of the Project

In this regard and with the purpose to identify substances with urgent needs for further regulation under REACH a project was conducted. Thereby, the current study aimed at checking whether the high demands on registrants to fulfil information requirements were met and the according toxicological and ecotoxicological information is available. Due to their generally high relevance for human health and the environment and based on often wide-spread use, high priority was given to the high tonnage chemicals. The lead and individual registration dossiers of the phase-in substances that were to register by 2010 were checked. In the project a targeted but highly relevant part of the registration dossiers was addressed by a screening.

The study was carried out to gather information on data availability in the registration dossiers and compliance with the information requirements in the REACH Annexes and their interpretation as outlined by the REACH guidance documents. In contrast to the overall compliance check by ECHA that includes the whole dataset and all endpoints, this project gave priority to the so-called higher tier endpoints as these endpoints (such as chronic and reproductive toxicity or aquatic toxicity) are of high relevance for the human health and environment. This means that the additional requirements of REACH Annex IX and X (in comparison to those of Annex VII and VIII) were checked with priority. These higher-tier study requirements were, therefore, the preferred field of investigation to identify areas for further actions including the filling of identified data gaps.

The following toxicological endpoints have been regarded to be of high relevance in terms of human health and the environment:

Human health:

- developmental and reproductive toxicity,
- genetic toxicity,
- repeated dose toxicity.

Environment:

- biotic and abiotic degradation,
- bioaccumulation,
- ecotoxicity,
- environmental exposure.

In order to achieve access to the full (eco)toxicological data sets, only the dossier of the lead registrant within a SIEF was considered. In cases where data sharing was not comprehensively applied, also individual registrants not participating in a SIEF [“opt-out” according to REACH Art. 11 (3)] were considered.

A systematic approach was needed to assess the huge amount of data and to classify the results. Classification (in terms of a categorisation) should finally allow for separation of compliant and non-compliant data from data which could not be assessed in this project (not concluded) due to staff and time constraints.

Furthermore, to enable a reasonable interpretation of the result categories, a comparison to the outcome of the official compliance check (acc. to REACH Art. 41) was considered appropriate. A further analysis of not concluded cases (category “complex”) should give insights with respect to dossiers where e.g. standard information were adapted or waived.

2 Screening Procedure

2.1 Overall Approach

The scope of the current study was to check selected endpoints of all lead and individual registration dossiers of phase-in substances of the first registration deadline for compliance with the REACH Annexes VII to X. Non-phase-in substances, CMR[1] substances with a production volume < 1000 tpa and substances classified as acute/chronic toxic to the aquatic environment (H400/H410) with a production volume < 1000 tpa which have been also registered within the first registration phase, were exempted from this investigation. The check was carried out in a brief and standardised form (screening). For this purpose, decision trees for each endpoint that reflect the information requirements of the REACH Annexes were developed, tested and then applied. The concept was designed based on the REACH Annexes VII to XI, the information given in the respective ECHA guidance documents, ECHA data submission manual, the IUCLID 5 end-user manual and recommendations of experts in the BfR and UBA. The versions used from these documents were those which were in force in March 2014 when the screening concept for this project was developed.

A list of dossiers compiled by ECHA by 7th March 2014 was used as the basis for screening. Therefore, based on this list a total of 1932 registration dossiers were examined. The list was handled confidentially as it indicated the concrete dossiers to be examined.

As a result of the screening, each examined endpoint of a dossier was allocated to one of the following 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.

The term "compliant" with the REACH Regulation is not used here in a legal way, as this study was not conducted with the full scope of an official compliance check as laid out by REACH Art. 41. Rather the term should be seen as reflecting the general availability of the information required in terms of REACH. Also, the data in the registration dossiers have not been assessed in full detail, due to the limited time available. Therefore, standardisation of the procedure was of particular importance. The same regards to the term "non-compliant", which does not mean that actually additional data is required to fulfil the requirements of the REACH Regulation. In fact, the term means that the data checked were not in line with the requirements according to the screening scheme developed for this project.

A special feature of the screening was that for defined circumstances a conclusion on conformity or non-conformity was not carried out and a conclusion "complex" was taken. This was most often the case when an adaptation/waiving of a standard test was indicated in the dossier. Registrants are obliged to provide a justification and/or to refer to possibly already existing data which can be used for adaptation of the standard requirements. These justifications and/or surrogate data could not be

[1] Substances classified as carcinogenic, mutagenic and/or toxic for reproduction.

assessed in-depth within the limited time frame of the screening. Therefore, a firm conclusion was not possible. Additionally, some endpoint-related particularities also led to the conclusion "complex". Moreover, for cases for which a testing proposal for an endpoint or part of an endpoint was outlined by the registrant, the availability of appropriate endpoint data was not checked at all.

In addition to the endpoint results, each dossier 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".

The applied screening scheme was progressively developed by drafting a decision tree in a first step (drafting period), applying it in a second step to a number of dossiers (test period) and then finally refining it by adding additional questions and/or by changing the query (finalisation of the screening concept). The latter step was necessary because several cases were identified during the test period that had not been considered yet in the first draft. Additionally, simplifications were introduced in the final steps of concept development to keep the process as clear and understandable as possible. Although the different endpoints each required a different approach, standardisation of the endpoint decision trees was attempted as far as possible. The complete process was conducted in close collaboration with the experts of BfR and UBA experienced in the assessment of the individual endpoints and reflects their expertise and criteria for decision making within the constraints given by the circumstances of the screening (e.g. limited time and standardised procedure where possible).

In the following sections, for each endpoint the standard information as required in terms of the REACH Regulation and the decision trees that were built upon this basis are explained in detail. Prior to the presentation of the actual concept, the software used for screening is briefly introduced.

The software application used for managing the information about chemical substances registered in Europe is the International Uniform ChemicaL Information Database (IUCLID). It is mainly applied by the chemical industry and authorities and is maintained by ECHA. A member state authority access of the 2013/2014 updated version[2] was used to access the data provided by the registrants to fulfil REACH requirements. The IUCLID sections which were considered during the screening are presented in the text box on the next page.

For the hands-on screening and the collection and documentation of the required information the web-based application KnowSEC was used. KnowSEC is a knowledge management system based on a wiki software[3]. First, all decision trees were implemented into this software. The system was an appropriate help in terms of managing both, the queries in the decision trees and the storage of data. Answers and additional information were stored in relation to every question throughout the tree. The additional information was stored in so-called "memos". These memos were an integral part of the screening, because information that was not retrieved as part of the decision trees could be documented. Moreover, in KnowSEC multiple answers are allowed for a question. Export in the 'comma-separated values' format (csv) allowed for further analysis of the stored data. All information entered in the project can be used later on without re-entering the data itself.

[2] IUCLID, Version: 5.6.0.1 (European Commission, European Chemicals Agency. http://iuclid.eu/)

[3] KnowWE (Knowledge Wiki Environment). http://www.d3web.de/

A version of KnowSEC[4] was installed at the BfR and was used by applying a web browser. The substance list was implemented such that retrieval of substances, application of the decision tree and storage of the answers and memos was possible in connection with it. Confidential data were not entered into the software.

Examined IUCLID sections

1 General information
- 1.1 Identification

2 Classification & Labelling and PBT Assessment
- 2.1 GHS
- 2.3 PBT Assessment

4 Physical and chemical properties
- 4.7 Partition coefficient
- 4.8 Water solubility
- 4.21 Dissociation constant

5 Environmental fate and pathways
- 5.1.2 Hydrolysis
- 5.2.1 Biodegradation in water: screening test
- 5.2.2 Biodegradation in water and sediment: simulation test
- 5.2.3 Biodegradation in soil
- 5.3.1 Bioaccumulation: aquatic/sediment
- 5.4.2 Henry's Law constant

6 Ecotoxicological information
- 6.1.1 Short-term toxicity to fish
- 6.1.2 Long-term toxicity to fish
- 6.1.1 Short-term toxicity to aquatic invertebrates
- 6.1.2 Long-term toxicity to aquatic invertebrates

7 Toxicological information
- 7.5 Repeated dose toxicity:
- 7.5.1 oral,
- 7.5.2 inhalation,
- 7.5.3 dermal
- 7.6 Genetic toxicity:
- 7.6.1 in vitro,
- 7.6.2 in vivo
- 7.8 Toxicity to reproduction:
- 7.8.1 toxicity to reproduction,
- 7.8.2 developmental toxicity/teratogenicity

13 Assessments reports

[4] KnowSEC, Version: KnowWE 20140508_13:22 (denkbares GmbH, Würzburg, Germany. http://www.denkbares.com)

2.2 General Aspects of the Screening Procedure

Apart from the decision trees, which are outlined in the following chapters and are related to the endpoint-specific REACH information requirements, it was necessary to have a general definition of compliance in terms of which data could be accepted with respect to these requirements. This related to data quality in general but also to how the data are stored, categorised and presented within IUCLID. While in principle registrants should set up their dossiers according to the design of the IUCLID system and the specific rules outlined by ECHA within several guidance documents and webinars, it is up to the user to consider these rules and accordingly use the system in a way that the data is properly presented to risk assessors. At the start of the current study it was obvious that this might possibly result in a high diversity of dossier quality. Thus, decisions on how to manage this diversity were made in order to standardise the screening. Although IUCLID and registration manuals were considered, the following rules applied during the screening should not be regarded as universally applicable for the registration of chemicals. However, these rules based on the point of view that the registrant is responsible for data presentation. Thus, proper presentation was a pre-requisite, whereas data presented in a way difficult to understand could not be considered.

2.2.1 Suitability of Data Entries and Data Quality

Data entries in IUCLID: Only those endpoint study records (ESRs) were assessed which had to be completely filled out in IUCLID ("robust study summary"). They are designated as "key studies" or "weight of evidence" (WoE) approaches (both can be picked in the field "purpose flag"). Besides experimental data, key studies can also comprise grouping/read-across and (Q)SAR approaches. Within this screening, a minimum requirement for experimental studies was that they were flagged as key studies and based on "experimental results" (field "study result type") to accept them as standard information.

Reliability categories (acc. Klimisch, Andreae, & Tillmann, 1997) in IUCLID: For key studies which may include experimental studies as well as grouping/read-across or (Q)SAR approaches, only ESRs with reliability category 1 or 2 were considered for further analysis. For weight of evidence entries, the reliability category was not considered.

Study types and test guidelines in IUCLID: Studies intended to fulfil the standard information requirements have to be appropriate and scientifically as well as formally acceptable. Therefore, they have to be conducted according to or their design must be similar to the internationally accepted test guidelines, i.e. in general to OECD and/or EU standard test protocols. Compilations of test guidelines for every endpoint accepted within the screening can be found in the endpoint-specific concepts described below. It is to be noted that guidelines not mentioned in the endpoint-specific concept were not accepted. If a guideline was given without specification (e.g. an OECD guideline without number), at least the study type had to be in agreement with the requested study type. However, the information on the study type alone, possibly with a general remark that a guideline was considered, was not accepted. Usually, the test guideline is entered in the respective section under "materials and methods" in each ESR, but also entries in other fields were accepted as long as the guideline was clearly named. The fields "qualifier" and "deviations" to specify the extent of compliance with the indicated guideline entries were not assessed.

Quality management criteria: The compliance of studies with Good Laboratory Practice (GLP) criteria was not subject of the current project, because the reliability scores for individual ESRs as assigned by the registrants were not questioned.

Other sources: Simply referencing secondary literature such as books or reviews without "robust study summaries" was not accepted to fulfil the requirements within the scope of the screening.

2.2.2 Adaptation/waiving of Standard Information Requirements

If no experimental key study and no testing proposal are available, registrants have to provide a justification for adapting or waiving standard information requirements (REACH Regulation Annexes VII to X, Column 1) either according to Annexes VII to X, Column 2 or the general rules defined in Annex XI, no. 1 to 3.

With respect to the meaning of adaptation and waiving the definition given in ECHA practical guide no. 4 (ECHA, 2010) was used. Adaptation comprises the use of non-standard methods to fulfil the information requirements such as read-across or WoE approaches. Waiving is applied if the submission of standard information is not considered necessary by the registrant, e.g. due to physicochemical properties of the substance or exposure-related issues.

Annex VII to X, Column 2 sets out endpoint-specific adaptations based on physicochemical properties of substances, exposure-related issues and availability of information from other relevant studies.

Annex XI, no. 1 to 3 applies to all endpoints and includes an adaptation/waiving of testing due to:

- scientific reasons including use of existing data, weight of evidence (WoE), qualitative or quantitative structure-activity relationships ((Q)SARs), in vitro methods, grouping of substances and read-across,
- technical reasons,
- substance-tailored exposure-driven reasons.

During screening, adaptation/waiving events and categories were documented. In these cases, the respective endpoint was regarded as “complex”.

Usually, adaptation/waiving entries in IUCLID have the following structure:

- “purpose flag”: empty,
- “data waiving”: one of the following waiving categories has to be selected from a pick list (study technically not feasible, study scientifically unjustified, exposure considerations, other justification),
- “justification for data waiving”: has to be filled with a free text,
- “study result type”: empty,
- “reliability”: empty.

This was the basis for accepting adaptation/waiving of information during the screening of the project if standard information were not provided. A detailed assessment of these entries was not carried out. However, the field “justification for data waiving” was checked for the existence of a reasonable content.

Accordingly, WoE, (Q)SARs, grouping of substances and read-across were all accepted to result in the classification as “complex” during screening provided the following IUCLID configurations were given. Usually a “robust study summary” was available.

WoE:

- “purpose flag”: weight of evidence,
- “data waiving”: might have been filled, but this is no must,
- “justification for data waiving”: empty,
- “study result type”: had to be filled, depending on the study,
- “reliability”: had to be filled.

Qualitative or quantitative structure-activity relationships ((Q)SARs), grouping of substances or read-across:

- "purpose flag": key study,
- "data waiving": empty,
- "justification for data waiving": empty,
- "study result type": filled (grouping/read-across, (Q)SAR),
- "reliability": filled, category 1 or 2.

2.2.3 Testing Proposals

Testing proposals (TPs) can be found as ESRs in IUCLID instead of experimental studies and adaptation/waiving approaches. They are a notification that the registrant plans to conduct a study, because standard information requirements are not available. The necessity to perform these investigations will be checked by ECHA. Before carrying out a test, the proposal has to be approved. It was decided to accept a proposal to match the endpoint conclusion category "TP" within our screening if it carried "experimental study planned" in the field "study result type". Furthermore, information about the study period (e.g. regarding repeated dose toxicity, aquatic toxicity) and the applied study type had to be given.

During screening using the decision tree, TPs were considered by the option "TP" besides "Yes" and "No" for the respective questions. The selection of "TP" entailed that the user exits the decision tree at this point and did not continue the query because a decision was made. The proposals themselves were not assessed in this project as this has already been done by ECHA for substances which belong to the tonnage category ≥ 1000 tpa. However, at the time of checking the dossier, an update of the dossier by the registrant might not yet have been available.

2.2.4 Substance Used for Testing

An in-depth assessment of the substance identity was not part of the current study. However, it was checked whether the test material used in a particular experimental key study corresponded to the registered substance according to the list provided by ECHA for this project. The test material information was evaluated in the IUCLID section "test material" of the respective ESR:

- Usually in the field "test material equivalent to submission substance identity / identity of test material same as for substance defined in section 1 (if not read-across)" the answer "Yes" is selected;
- if the latter was not applied, the correct CAS and/or EC number had to be given in either the IUCLID field "test material identity" or the field "details on test material";
- if contradictory or incorrect information were given (e.g. the CAS and/or EC number was not correct or a "No" had been selected while CAS and/or EC number were correct), the ESR was not accepted and the memo "identity" was stored (refer to the memo list in Annexes 1, and 2).

This stringent proceeding was applied because a verification of the test material information could not be carried out within this project. Therefore, it was not possible to distinguish between formal mistakes or more serious concerns when another substance identity or ambiguous information were given.

2.3 Screening of Human Health Endpoints

2.3.1 General Aspects of Acceptance of Data Entries in IUCLID

In general, data entries were accepted if the respective studies were performed according or similar to the appropriate OECD, EU and/or current US EPA guidelines listed below in the respective screening concept for each endpoint. Additionally, guidelines of the FDA, ICH, NTP and Japan as well as 'old' US EPA guidelines were accepted, provided that the correct study type was given in the IUCLID endpoint study record (ESR). Entries based on data not carried out according to the standards mentioned above were not accepted. This also applied to studies based on guidelines from other authorities. Memos were applied in several cases (Annex 1).

Moreover, a special provision was made for human health with respect to the acceptance of adaptation/waiving of standard information. This was necessary due to the fact that ESRs for different study types and species have to be recorded under the same section in IUCLID for the human health endpoints. As specifications regarding the study type and animal species do not necessarily have to be provided when ESRs are flagged for "waiving" or the application of surrogate data ("read-across" or "WoE"), the criteria defined above in the general concept for the acceptance of study data (Chapter 2.2.2) had to be complemented to adequately allocate such ESRs to the required study categories for the three endpoints. Therefore, the following rules for the acceptance of adaptation/waiving were applied. However, in all cases described below a differentiation was necessary: for genetic toxicity according to the respective IUCLID sections in vivo and in vitro test data were considered separately; for reproductive toxicity a differentiation between developmental toxicity and toxicity to reproduction (two-generation study) was necessary and for repeated dose toxicity, different administration routes were considered separately.

If theoretically more than one adaptation/waiving was required, because more than one data entry/study type was missing, it was defined that the presence of one single ESR flagged with "waiving" was sufficient to result in the categorisation as "complex". The reasons are outlined as follows:

- "Exposure considerations" and "study technically not feasible" (Annex XI, no. 2 and 3) are substance-specific and should apply for all experimental studies.
- "Study scientifically unjustified" and "other justification"(Annex XI, no. 1 and adaptations according to Annex VII –X, Column 2) are without further specifications in the ESR except in the "justification for data waiving", which was not assessed during screening.

Additionally, ESRs flagged as WoE were accepted for more than one data requirement. For WoE usually more than one ESR is available and the respective entries were not further assessed during the screening (conclusion "complex"). Therefore, WoE possibly can apply for several study types.

Furthermore, endpoint-specific rules were applied in the case of ESRs flagged for "grouping/read-across":

- Genetic toxicity: the correct study type was necessary for the acceptance of data to match the category "complex". In other words, every required study type required its own grouping/read-across ESR.
- Developmental toxicity 2nd species: provided that data for developmental toxicity for one species was accepted, grouping/ read-across for a 2nd species could only be accepted if a different species was tested.
- Reproductive toxicity/developmental toxicity, one species: one grouping/read-cross per IUCLID section (7.8.1 Toxicity to reproduction, 7.8.2 Developmental toxicity/teratogenicity) independent of the species and the guidelines applied for the testing was accepted to result in categorisation

as “complex”. This was due to the possible complexity and connections between the results which could not be assessed during screening.

- Repeated dose toxicity: a subchronic study is the standard information requirement according to REACH Annex IX, but, of course, a valid chronic study would also be acceptable. Therefore grouping/read-across ESRs based on a subchronic or chronic study were both regarded as sufficient, whereas a grouping/read-across based on a subacute study alone was not accepted to be assigned to the category “complex”.

2.3.2 Genetic Toxicity

Information Requirements

Genetic toxicity refers to irreversible and transmissible changes of the DNA in cells. If germ cells are affected, these changes can be passed on to the next generation. Mutations can also result in carcinogenic and teratogenic effects.

The superordinate term genotoxicity refers to irreversible as wells as reversible (e.g. through repair mechanisms) changes of the DNA.

The purpose of testing for genotoxicity is to assess the potential of chemicals to cause changes of the genetic information which may lead to cancer or heritable damage and diseases in humans.

The endpoints which are considered for the assessment of the mutagenic potential of substances are:

1. Gene mutations and
2. Chromosome aberrations (numerical and structural changes of chromosomes).

Furthermore, there exist in vitro and in vivo studies for both endpoints.

Depending on the respective result of each study, which can be “positive” or “negative”, further studies may have to be conducted or not.

It is assumed that in case of a positive result for genetic toxicity in soma cells it is also likely that germ cells might be affected by the same substance and the respective studies have to be provided. Accordingly, when no mutagenic potential could be proven for soma cells, no studies in germ cells are required. A proven damage to germ cells always indicates that soma cells are affected by the same substance as well (refer to ECHA endpoint specific guidance, Chapter R.7a (ECHA, 2014c).

According to the aforementioned guidance the relevant information requirements for genetic toxicity comprise the test methods listed in Table 1.

Moreover, older studies based on the “Mouse spot assay” (OECD TG 484 (1986)) are accepted as in vivo studies for gene mutation (GMvivo).

For substances with a production volume of 1000 tonnes or more per year, Annexes VII to X of the REACH Regulation have to be taken into consideration. If there are no data and a harmonised classification according to the CLP Regulation is not available for a given substance, the registrant has to submit the following data (standard information requirements):

- Results from a bacterial gene mutation test (GMbact, Annex VII, 8.4.1., Column 1) are mandatory, since no adaptation according to Column 2 can be applied.
- Results from an in vitro chromosome aberration test with mammalian cells (Cytvitro, Annex VIII, 8.4.2., Column 1) have to be available.

The data for chromosome aberration can also be derived from an in vivo study with soma cells (Cytvivo). If GMbact is negative, while Cytvitro is positive and Cytvivo negative, the conclusion according to ECHA guidance R.7a (ECHA, 2014c p. 354) would be "not genotoxic".

If the results for gene mutation in bacteria and cytogenicity in mammalian cells are negative, an in vitro gene mutation test with mammalian cells (GMvitro, Annex VIII, 8.4.3., Column 1) is required. If this test is negative as well, no further testing is required.

Table 1: Overview on the accepted test methods for the assessment of Genetic Toxicity*

Category	Category[a]	OECD TG[b]	EU method[c]	Test method	US EPA analogue[d]
Gene mutation, bacteria, in vitro	GMbact	471 (1997a)	B.13/14	Bacterial reverse mutation test	
Chromosome aberration, mammalian cells, in vitro	Cytvitro	473 (1997c)	B.10	In vitro mammalian chromosome aberration test	OPPTS 870.5375 In vitro mammalian chromosome aberration test.
		476 (1997b)	B.17	In vitro mammalian cell gene mutation test - mouse lymphoma assay (NOT: hprt test)	OPPTS 870.5300 In vitro mammalian cell gene mutation test.
		487 (1997b)	nein	In vitro micronucleus test	
Gene mutation, mammalian cells, in vitro	GMvitro	476	B.17	In vitro mammalian cell gene mutation test - hprt test or mouse lymphoma assay	OPPTS 870.5300 In vitro mammalian cell gene mutation test.
Chromosome aberration, soma cells, in vivo	Cytvivo	474 (1997e)	B.12	In vivo mammalian erythrocyte micronucleus test	OPPTS 870.5395 Mammalian erythrocyte micronucleus test.
		475 (1997d)	B.11	In vivo mammalian bone marrow chromosome aberration test	OPPTS 870.5385 Mammalian bone marrow chromosome aberration test
Gene mutation, soma cells, in vivo	GMvivo	486 (1997h)	B.39	Unscheduled DNA synthesis test with mammalian liver cells in vivo	
		488	B.58	Transgenic rodent somatic and germ cell	

Category	Category[a]	OECD TG[b]	EU method[c]	Test method	US EPA analogue[d]
		(2013b)		gene mutation assays	
		489 (2014)	Not available	In vivo alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay) (Tice et al., 2000) (Hartmann et al., 2003)	
Germ cells	Germvivo	483 (1997f)	B.23	Mammalian spermatogonial aberration test	OPPTS 870.5380 Mammalian spermatogonial chromosome aberration test
		478 (1984b)	B.22	Rodent dominant lethal test	OPPTS 870.5450 Rodent dominant lethal assay
		488	B.58	Transgenic rodent somatic and germ cell gene mutation assays	
		489	Not available	Comet assay (refer to GMvivo)	

* Referring to ECHA guidance on information requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint specific guidance. Version 2.4 from February 2014. This was the current version when the concept for the screening was developed for this project.

[a] According to ECHA guidance on information requirements, R.7a endpoint specific guidance (ECHA, 2014c); [b] OECD guidelines for the Testing of Chemicals, Section 4 (OECD, 2015); [c] REACH Test Methods Regulation (EC) No 440/2008; [d] Office of Chemical Pollution Prevention (OCSPP) harmonised test guidelines, series 870 – Health effects test guidelines (OCSPP, 2015).

If one of the in vitro tests is positive, a corresponding in vivo test has to be performed including the analysis of soma cells (Annexes VIII to X, 8.4., Column 2). That means a GMvivo has to be conducted if GMbact and/or GMvitro were positive, a Cytvivo test is required if Cytvitro was positive. Hence, it might happen that in vivo tests with the analysis of soma cells have to be provided for the two endpoints, gene mutation as well as chromosome aberration (Annex X, 8.4., Column 2).

If a positive result was obtained from an in vivo study with soma cells, the risk for genetic toxicity in germ cells has to be evaluated. If the available data and the toxicokinetic analysis are not sufficient for risk assessment, an appropriate genetic toxicity test for germ cells has to be conducted (Germvivo, Annexes IX and X, 8.4., Column 2). ECHA and EU member states currently debate if this test has to be for the same endpoint as the positive in vivo test using soma cells for analysis. If the germ cell test is positive, a second in vivo test with soma cells, covering the other endpoint, is dispensable.

Standard information requirements according to Annexes VII to X of the REACH Regulation do not have to be addressed if the substance has a harmonised classification according to the CLP Regulation as carcinogenic category 1A or 1B (H350, may cause cancer) or as (germ cell) mutagen category

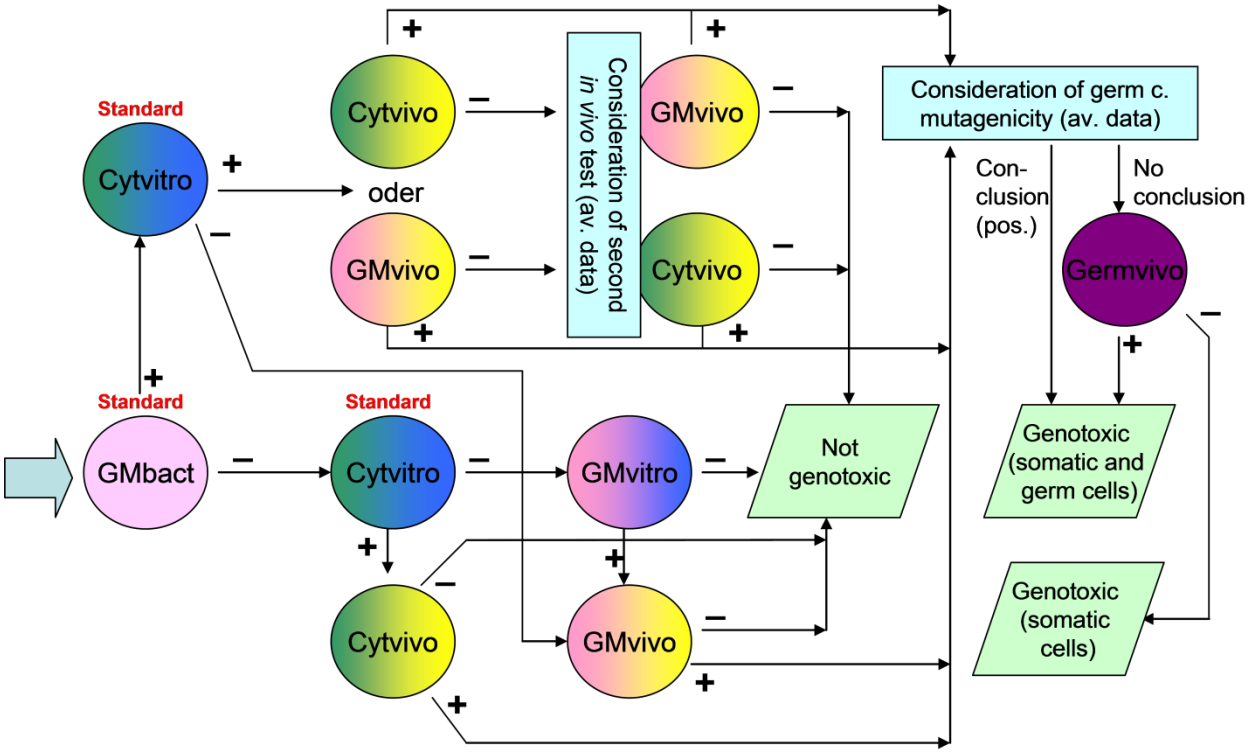
1A or 1B (H340, may cause genetic defects). Annex VI of the CLP Regulation includes a list of substances with harmonised classification.

If a substance possesses a harmonised classification as mutagen category 2 (H341, suspected of causing genetic defects), which generally results from genotoxicity studies with soma cells, germ cell genetic toxicity has to be considered according to Annexes IX and X of the REACH Regulation. In vitro studies with mammalian cells are not required in that case (adaptation for Cytvitro according to Annex VIII, 8.4.2., Column 2).

During the screening, the in vivo studies were not checked for the route of administration and the experimental species used, as these parameters require a more detailed analysis.

Positive as well as negative results for one study type might be available for certain substances. In this case, studies were not accepted but a memo was included in KnowSEC carrying the keyword "Widerspruch" (inconsistency).

Figure 1: Genetic Toxicity Testing Scheme According to REACH Information Requirements



The scheme was adapted from ECHA guidance R.7a (ECHA, 2014c p. 351-357)

Decision Tree

A detailed explanation for every step in the decision tree is given, each following the appropriate textbox containing a question. Figure 2 shows the decision tree as a whole.

Question No.1

Is the substance listed in Annex VI of the CLP Regulation as a carcinogen category 1A or 1B or a germ cell mutagen category 1A or 1B?

The harmonised classification had to be checked in Annex VI of the CLP Regulation or in the C&L inventory on ECHA website. If the substance held the harmonised classification no further data were required.

Answer YES: Continuation with question 2.B

Answer NO: Continuation with question 2

Remark when the answer was YES: Formally, the registrant had to include an adaptation/waiving for the standard information requirements. However, in such cases "compliance" was confirmed, since this is solely a formal question and the studies might have been available. If the substance was classified as carcinogen or mutagen category 1A or 1B, no further requirements had to be fulfilled, e.g. availability of sufficient data for risk assessment.

Question No. 2

Is an in vivo test for germ cells (Germvivo) available?

Note to IUCLID entries: If the field "tissues and cell types examined" did not give sufficient information on the nature of the cell type examined, the ESR was screened for keywords like "germ cell", "egg cell", "ovum", "ovule", "sperm (cell)" or "spermatozoa". Relevant sections to find out if germ cells were examined comprised the title of the ESR, the title of the study, the result part or the study summary.

Answer YES: Continuation with question 2.A

Answer NO: Continuation with question 3

Remark when the answer was YES: If the germ cell test was positive, it is supposed that the substance also affects soma cells. No additional testing was required then. However, formally, there had to be an adaptation/waiver for the standard information. Again, in such cases "compliance" was confirmed, since this is solely a formal question and the studies might have been available.

An accurate approach for information retrieval would include the question if the germ cell genetic toxicity test corresponds to the positive soma cell test (chromosome aberration or gene mutation). This information would have no relevance if the germ cell test is positive, but matters if the test is negative. In the latter case the screening continued to ask for the available soma cell tests (question 3), if they were positive (question 3.A) and if germ cell genetic toxicity was assessed (question 3.A.2; it was already known from question 2 that this was investigated), but did not evaluate if the positive soma cell tests corresponded to the negative germ cell test. However, two arguments spoke against the consideration of this issue in the decision tree: 1. Based on the experience made in the test run, it was supposed that this case very rarely, if at all, occurs. At the same time, its integration would have required a complex extension of the decision tree. 2. There exists no international agreement on how to treat these cases. Therefore, it was not possible for us to classify dossiers as "compliant"/"non-compliant" based on the presence of corresponding in vivo tests for germ and soma cells. These cases were classified as "complex", provided that all other requirements were fulfilled.

Question No. 2.A

Is the Germvivo positive?

Answer YES: Continuation with question 2.B

Answer NO: Continuation with question 3

Remark if the answer was NO: A negative germ cell test does not exclude that soma cells are affected by the substance. At least the standard information requirements had to be fulfilled.

Question No. 2.B

Is a bacterial genetic toxicity test (GMbact) available?

Answer YES: Classification as "compliant"

Answer NO: Continuation with question 2.C

Remark: Waiving was only possible according to Annex XI; Column 2 of Annexes VII to X does not contain waiving possibilities for GMbact.

Question No. 2.C

Is an adaptation/waiver available for GMbact?

Answer YES: Classification as "complex"

The adaptation/waiving category had to be specified in KnowSEC. If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If "No" and "Yes – adaptation/waiving category" were selected simultaneously the conclusion was "non-compliant".

Answer NO: Classification as "non-compliant"

Question No. 3

Is an in vivo genetic toxicity test for soma cells (Cytvivo, GMvivo) available?

Answer YES: Continuation with question 3.A

Answer NO: Continuation with question 4

Question No. 3.A

If in vivo tests for soma cells are available, are they all negative?

Answer YES: Continuation with question 3.B

Answer NO: Continuation with question 3.A-2

Question No. 3.A-2

Is a Germvivo available?

Answer YES: Continuation with question 3.A-3

Genetic toxicity has been proved for soma cells, but not for germ cells. Data for the mandatory GMbact or an adaptation/waiving for GMbact still had to be provided.

Answer NO: Continuation with question 5 (adaptation/waiving)

Adaptation/waiving options if the answer was no (question 5):

Table 2: Genetic toxicity adaptation/waiving 1

Question	Answer	Adaptation/waiving required for...
3.A-2	No	Germvivo

Question No. 3.A-3

Is a GMbact or an adaptation/waiver for GMbact available?

Answer YES: Classification as "complex"

Even if a GMbact was available, the classification was "complex", as it was not assessed if the Germ-vivo and the positive soma cell test, both present, corresponded to each other with respect to the study type. If an adaptation/waiver existed, the category had to be specified simultaneously in KnowSEC. If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If "No" and "Yes – adaptation/waiving category" were selected simultaneously the conclusion was "non-compliant".

Answer NO: Classification as "non-compliant"

Question No. 3.B

Are results for both in vivo tests for soma cells (Cytvivo, GMvivo) available?

Answer YES: Continuation with question 2.B

Answer NO: Continuation with question 3.C

Remark when the answer was YES: Formally, the registrant had to include adaptations/waivers for the in vitro standard information. In such cases "compliance" was confirmed, since this is solely a formal question. However, results for GMbact are mandatory.

Question No. 3.C

Only one in vivo test for soma cells is available. Which one is it: Cyt (Cytvivo) or GM (GMvivo)?

One had to select the available study type (Cytvivo or GMvivo). The decision tree split at this point.

Cytvivo: Continuation with question 3.C-2

GMvivo: Continuation with question 3.D a)

Question No. 3.C-2

Are results for Cytvitro available and are they positive?

Answer YES: Continuation with question 3.C-3

GMbact was still required.

Answer NO: Continuation with question 3.D b)

Question No. 3.C-3

Is a GMbact available?

Answer YES: Continuation with question 3.C-4 (result)

Answer NO: Continuation with question 2.C (adaptation/waiving)

Question No. 3.C-4

Is the GMbact negative?

Answer YES: Classification as “compliant”

Answer NO: Continuation with question 3.C-5 (adaptation/waiving for GMvivo)

Question No. 3.C-5

Is an adaptation/waiver for GMvivo available?

Answer YES: Classification as “complex”

The adaptation/waiving category had to be specified in KnowSEC. If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If “No” and “Yes – adaptation/waiving category” were selected simultaneously the conclusion was “non-compliant”.

Answer NO: Classification as “non-compliant”

A second in vivo test for soma cells has only to be performed if required. Therefore, the decision tree continued with the information retrieval for the in vitro tests.

Question No. 3.D-a

Results for GMvivo are present. Are results for Cytvitro and GMbact available?

Results for gene mutation in vivo were present. Results for chromosome aberration in vivo were not present. Therefore, the respective in vitro test (Cytvitro) had to be available. GMbact is mandatory, even if an in vivo gene mutation test exists.

Answer YES: Continuation with question 3.E (result)

Answer NO: Continuation with question 5 (adaptation/waiving)

Adaptation/waiving options when the answer was “No”:

Table 3: Genetic toxicity adaptation/waiving 2

Question	Answer	...was available	Adaptation/waiving required for...
3.D a)	No	Cytvitro	GMbact
3.D a)	No	GMbact	Cytvitro
3.D a)	No	No in vitro test	Cytvitro and GMbact

Question No. 3.D-b

Results for Cytvivo are present. Are results for GMvitro and GMbact available?

Results for chromosome aberration were present, while results for gene mutation were not available. GMbact is mandatory under all circumstances. Results for GMvitro have to be given if GMbact is negative as well as Cytvivo and Cytvitro, if available (at this point of the decision tree, results for chromosome aberration tests could have only been negative, positive results would not have led to this question).

Answer YES: Continuation with question 3.E (result)

Answer NO: Continuation with question 5 (adaptation/waiving)

Adaptation/waiving options when the answer was "No" (one had to keep in mind that Cytvivo (and eventually Cytvitro) were present and negative):

Table 4: Genetic toxicity adaptation/waiving 3

Available test	Result	Adaptation/waiving required for...	Reason
GMbact	Negative	GMvitro	A negative result was present for gene mutation and chromosome aberration, respectively
GMvitro	Negative	GMbact	GMbact, which is mandatory, was not available
No in vitro test	No result for gene mutation	GMbact	GMbact, which is mandatory, was not available; adaptation/waiving for GMvitro could not be demanded, because no result for gene mutation was given
GMbact	Positive	GMvivo	GMvitro was not required, but GMvivo
GMvitro	Positive	GMbact and GMvivo	GMvivo was required; GMbact, which is mandatory, was not available

Question No. 3.E

The required in vitro tests are present. Are the results negative for Cytvitro (from 3.D-a) or GMbact and GMvitro (from 3.D-b)?

Answer YES: Classification as "compliant"

Answer NO: Continuation with question 5 (adaptation/waiving)

Adaptation/waiving options when the answer was "No":

Table 5: Genetic toxicity adaptation/waiving 4

Question	Answer	Adaptation/waiving required for...
3.E	No	In vivo gene mutation or chromosome aberration, depending on the positive in vitro test

Question No. 4

Are all three in vitro tests available (GMbact and Cytvitro and GMvitro)?

No in vivo studies were available. Therefore, GMbact and Cytvitro had to be present and negative, which entailed the requirement of a GMvitro. From this point on, compliance could only be reached when all in vitro tests were negative.

Answer YES: Continuation with question 4.A (result)

Answer NO: Continuation with question 5 (adaptation/waiving)

One or more in vitro and/or in vivo tests were not available, depending on the available in vitro tests and their results. Therefore, the ESRs for in vitro tests had to be checked for the study types and also for the result of the respective study type. Moreover, the existence of an adaptation/waiver had to be checked for in vitro as well as in vivo studies.

Adaptation/waiving options when the answer was "No":

Table 6: Genetic toxicity adaptation/waiving 5

Available test(s)	Result	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

Question No. 4.A

All three in vitro tests are available. Are they all negative?

Answer YES: Classification as "compliant"

Answer NO: Continuation with question 5 (adaptation/waiving)

One or more in vivo tests were not available, depending on which in vitro tests were positive.

Adaptation/waiving options when the answer was no:

Table 7: Genetic toxicity adaptation/waiving 6

Question	Answer	Adaptation/waiving required for…
4.A	No	In vivo gene mutation or chromosome aberration, depending on the positive in vitro test

Question No. 5

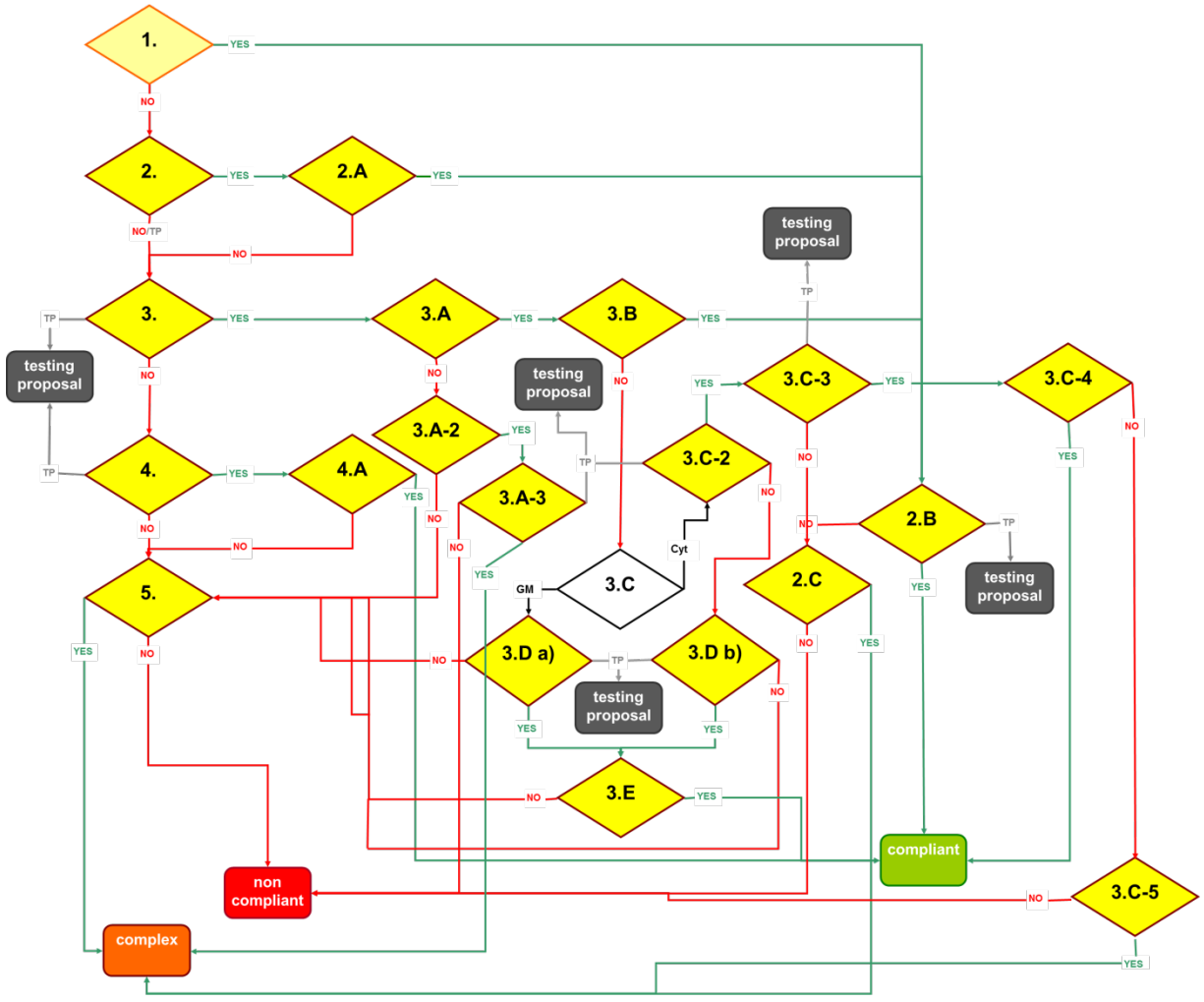
Is an adaptation/waiver available? (Depending on the previous question and the respective results of the tests)

Answer YES: Classification as “complex”

The adaptation/waiving category had to be specified in KnowSEC for one or more adaptations/waivers (5.A and 5.B). If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If “No” and “Yes” had been selected simultaneously the conclusion was “non-compliant”.

Answer NO: Classification as “non-compliant” if at least one adaptation/waiver is missing

Figure 2: Genetic Toxicity Decision Tree[5]



[5] The decision tree only contains the number of each question. Full questions are documented in the description of the decision tree in the text above.

2.3.3 Repeated Dose Toxicity

Information Requirements

The aim of repeated dose toxicity studies is the general characterisation of the toxicological profile of a given test substance after repeated application and the deduction of doses which enable threshold definition with respect to human exposure. These studies, among other things, comprise the examination of physiological, morphological and behavioural parameters, the identification of specific target organs, the analysis of dose-response relationships and investigations with respect to the reversibility of toxic effects. Depending on the required information, studies can be conducted over several weeks (subacute), months (subchronic), for one year or for the whole lifespan of the experimental animal (both chronic). Screening studies, which cover an exposure period of 14 to 28 days, are intended to give preliminary data on relevant doses and targets. Both 28-day studies and 90-day studies provide information on test substance toxicity at target organs, organ systems or tissues, the dose-response relationship of the observed effects and the determination of a no observed (adverse) effect level (NO(A)EL). The 90-day study is of higher predictivity with regards to the chronic health. Chronic studies are designed for substances to which humans may be exposed for a prolonged time, e.g. at their working place or through their food consumption. All studies have to be performed using an appropriate route of administration taking into account the most likely route of human exposure. Additionally, repeated dose studies may also provide information on more specific toxicity, e.g. reproductive toxicity.

Testing for repeated dose toxicity comprises a tiered approach which includes the following endpoints:

- Screening studies (14 to 28 days)
- Subacute toxicity (regularly the so-called 28-day study is applied)
- Subchronic toxicity (regularly the so-called 90-day study is applied)
- Chronic toxicity (studies which cover at least 12 months)

Furthermore, the appropriate route of administration has to be chosen taking into account what is the most likely route of human exposure. The oral route is usually the preferred one in repeated dose toxicity studies. Under certain conditions, depending on the substance and the relevant human exposure route, administration by the dermal route or by inhalation might be appropriate. Dermal exposure may be appropriate if the physicochemical properties of the substance support a penetration through the skin and if skin contact is likely. Testing by the inhalation route will be applied if the vapour pressure allows an absorption by inhalation and/or if aerosols, particles or droplets of the substance are of an inhalable size. Of course, it has to be a likely route of human exposure as well.

Table 8 lists the OECD and EU guidelines for repeated dose toxicity studies accepted under REACH, as well as the respective US EPA analogues to the OECD guidelines. The OECD TG 407 and 408 (1995a, 1998b), which cover oral administration, are regularly applied for 28-day and 90-day studies, respectively. Separate, but, with regard to the content, similar guidelines are available for the dermal and inhalation exposure routes (OECD, 1981f, 1981g, 2009e, 2009f). With regard to the chronic toxicity, the guidance in OECD TG 453 (combined carcinogenicity and chronic toxicity test) is essentially the same as in OECD TG 452 (chronic toxicity) (2009c, 2009d). Therefore, the latter is an accepted guideline for the assessment of chronic toxicity. In contrast, dedicated carcinogenicity studies according to OECD TG 451 (2009b) are not sufficient for this purpose. OECD TG 422 (1996) covers the screening test for repeated dose toxicity and is acceptable as replacement for a 28-day study. In OECD TG 419 and 424 (1997g, 2004c), specific organ toxicity (neurotoxicity) is addressed.

Table 8: Overview on the accepted test methods for the assessment of repeated dose toxicity*

Study Type	OECD TG[a]	EU method[b]	Route	Species	US EPA analogue[c]
Repeated dose 28-day oral toxicity study in rodents	407	B.07	oral	rat	OPPTS 870.3050 Repeated Dose 28-day oral toxicity study in rodents
Repeated dose dermal toxicity: 21/28-day study	410	B.09	dermal	rat, rabbit or guinea pig	OPPTS 870.3200 21/28-day dermal toxicity
Repeated dose inhalation toxicity: 28-day or 14-day study	412	B.08	inhalation	rat	
Repeated dose 90-day oral toxicity study in rodents	408	B.26	oral	rat	OPPTS 870.3100 90day oral toxicity in rodents
Repeated dose 90-day oral toxicity study in non-rodents	409	B.27	oral	dog	OPPTS 870.3150 90.day oral toxicity in non-rodents
Subchronic dermal toxicity: 90-day study	411	B.28	dermal	rat, rabbit or guinea pig	OPPTS 870.3250 90-day dermal toxicity
Subchronic inhalation toxicity: 90-day study	413	B.29	inhalation	rat	OPPTS 870.3465 90-day inhalation toxicity
Chronic toxicity study (12 months)	452	B.30		rodent: rat, non-rodent: dog	OPPTS 870.4100 chronic toxicity
Combined chronic toxicity/carcinogenicity studies	453	B.33		rat	OPPTS 870.4300 Combined chronic toxicity/carcinogenicity
Combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test (Remark: accepted as	422				OPPTS 870.3650 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test

Study Type	OECD TG[a]	EU method[b]	Route	Species	US EPA analogue[c]
28-day study)					
Neurotoxicity study in rodents	424	B.43		rat	
Delayed neurotoxicity of organophosphorus substances: 28-day repeated dose study	419	B.38		hen	

* Referring to ECHA guidance on information requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint specific guidance. Version 2.4 from February 2014. This was the current version when the concept for the screening was developed for this project.

[a] OECD Guidelines for the Testing of Chemicals, section 4 (OECD, 2015), [b] REACH Test Methods Regulation (EC) No 440/2008, [c] Office of Chemical Pollution Prevention (OCSPP) harmonised test guidelines, series 870 – Health effects test guidelines (OCSPP, 2015).

Table 9 lists guidelines which provide information on repeated dose toxicity, but are not accepted as a full replacement.

Table 9: Further OECD test guidelines, which provide information on repeated dose toxicity*

Test method	OECD TG[a]	US EPA analogue[b]
Two-generation reproduction toxicity study	416	OPPTS 870.3800 Reproduction and fertility effects
One-generation reproduction toxicity study	415	
Prenatal developmental toxicity study	414	OPPTS 870.3700 Prenatal developmental toxicity study
Reproduction/developmental toxicity screening test	421	OPPTS 870.3550 Reproduction/developmental toxicity screening test
Developmental neurotoxicity study	426	
Carcinogenicity study	451	OPPTS 870.4200 Chronic Toxicity

* Referring to ECHA guidance on information requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint specific guidance. Version 2.4 from February 2014. This was the current version when the concept for the screening was developed for this project.

[a] OECD Guidelines for the Testing of Chemicals, section 4 (OECD, 2015), [b] Office of Chemical Pollution Prevention (OCSPP) harmonised test guidelines, series 870 –Health effects test guidelines (OCSPP, 2015).

For substances with a yearly production volume of 1000 tonnes or more, basically the same standard information requirements apply as for substances with a production volume of 100 tpa (Annex IX, 8.6.1./2., Column 1).

The additional requirements in Annex X, 8.6.3./4., Column 2, which cover long term and special studies, only apply for cases which require an in-depth analysis of certain issues. Adaptation/waiving does not need to be conducted, because standard information requirements according to Column 1 do not exist. Hence, these requirements will not be checked during the screening of the presented project, but could be a subject for the planned in-depth analysis at the end of the project.

A 90-day study is mandatory for substances with production volumes of 100 tonnes or more per year (Annex IX, 8.6.2., Column 1). Rodents are the preferred species and the most appropriate route of exposure has to be applied. This study is dispensable if a suitable chronic study is available (Annex IX, 8.6.2., Column 2, second bullet point). Moreover, the 90-day study can be waived when the substance undergoes immediate disintegration and there are sufficient data on the cleavage products (Annex IX, 8.6.2., Column 2, third bullet point).

Finally, a 90-day repeated dose toxicity study also does not have to be conducted if a 28-day study is available which causes a classification of the substance as STOT RE1 (H372) and enables an extrapolation of the derived NOAEL towards the NOAEL for the 90-day study (Annex IX, 8.6.2., Column 2, first bullet point). Furthermore, a negative 28-day study, also as limit test, is sufficient if the substance is unreactive, insoluble, not inhalable and there is no evidence of absorption, particularly when human exposure is limited (Annex IX, 8.6.2., Column 2, fourth bullet point).

There are no entries in Column 2 of Annex IX, 8.6.1. Therefore, the 28-day study can only be waived according to Annex XI criteria, with the exception of the exposure-related waiving (Annex XI, no. 3), which is not accepted in this case according to Annex IX, 8.6.1., Column 1. The 28-day study, however, is not required if a valid 90-day study (or a suitable chronic test) has been conducted (Annex IX, 8.6.2., Column 1).

In vitro or screening studies do not comply with the requirements, with the exception of screening studies according to OECD TG 422 (1996), which are accepted as 28-day study. Nevertheless, for substances marketed at 100 tpa or more, a 90-day study is also mandatory in that case.

Criteria for the selection of dermal application or inhalation as routes of exposure are defined in Annex IX, 8.6.2., Column 2.

Decision Tree

Checking the appropriate route of administration was not a part of the screening of the project. Therefore, studies were accepted if they fulfilled all criteria defined in this endpoint-specific concept section and the ESR concept (chapter 4.3), but independent of the route of exposure.

Rodents are the default experimental species for repeated dose toxicity testing, but, depending on the substance, other animal models might be more suitable. As this requires a more detailed assessment, the endpoint classification “compliant” was only assigned, if valid studies with rodents were available, while non-rodent studies led to the classification “complex”.

Two standard information requirements (28-day and 90-day study) had to be provided for repeated dose toxicity according to Annex IX, Column 1, and, consequently, two adaptations/waivers if the respective studies were not available. However, only one adaptation/waiver was requested in this project (refer to chapter 4.1 for justification), which had to be valid as adaptation/waiver for a 90-day study.

A 28-day study or the corresponding adaptation/waiver did not have to be provided if a 90-day study was available. In contrast, a 90-day study or the respective adaptation/waiver was required even if a 28-day study had been conducted.

A detailed explanation for every step in the decision tree is given, each following the appropriate textbox containing a question. Figure 3 shows the decision tree on the whole.

Question No. 1

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

Answer YES: Continuation with question 1.A (species)

A 90-day study is not required according to Annex IX, 8.6.2., Column 2.

Answer NO: Continuation with question 2

Remark if the answer was YES: Formally, the registrant had to include an adaptation/waiving for the standard information (90-day and 28-day study). However, in such cases "compliance" was confirmed, since this is solely a formal question and the studies might have been available.

Question No. 1.A

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

Answer RODENT: Classification as "compliant"

Answer NON-RODENT: Classification as "complex"

Question No. 2

Is a subchronic toxicity study (≥ 90 days) available?

Answer YES: Continuation with question 1.A (species)

A 28-day study is not required according to Annex IX, 8.6.1., Column 1.

Answer NO: Continuation with question 3

Question No. 3

Is a subacute toxicity study (28 days) available?

Answer YES: Continuation with question 3.A

An adaptation/waiver for the 90-day study still had to be provided.

Answer NO: Continuation with question 4

Remark if the answer was YES: A 28-day study was only accepted if the route of exposure was the same as for the adaptation/waiver of the 90-day study.

Question No. 3.A

Is an adaptation/waiver available (for the subchronic study)?

Answer YES: Classification as "complex"

The adaptation/waiving category had to be specified in KnowSEC. If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If "No" and "Yes – adaptation/waiving category" were selected simultaneously the conclusion was "non-compliant".

Answer NO: Classification as "non-compliant"

Remark if the answer was YES: The route of exposure had to be identical for the 28-day study and the adaptation/waiver of the 90-day study.

Question No. 4

Is an adaptation/waiver available (for the subacute toxicity study) according to Annex XI, no. 3 (exposure-related)?

Answer YES: Classification as “non-compliant”

If more than one adaptation/waiver was available and study types were not stated, the adaptation/waiver which was not according to Annex XI, no. 3 was allocated to the 28-day study. If only one adaptation/waiver was available and the study type was not stated, the adaptation/waiver applied, at least in parts, for the 28-day study.

Answer NO: Continuation with question 5

Question No. 5

Is an adaptation/waiver available (for the subchronic study)?

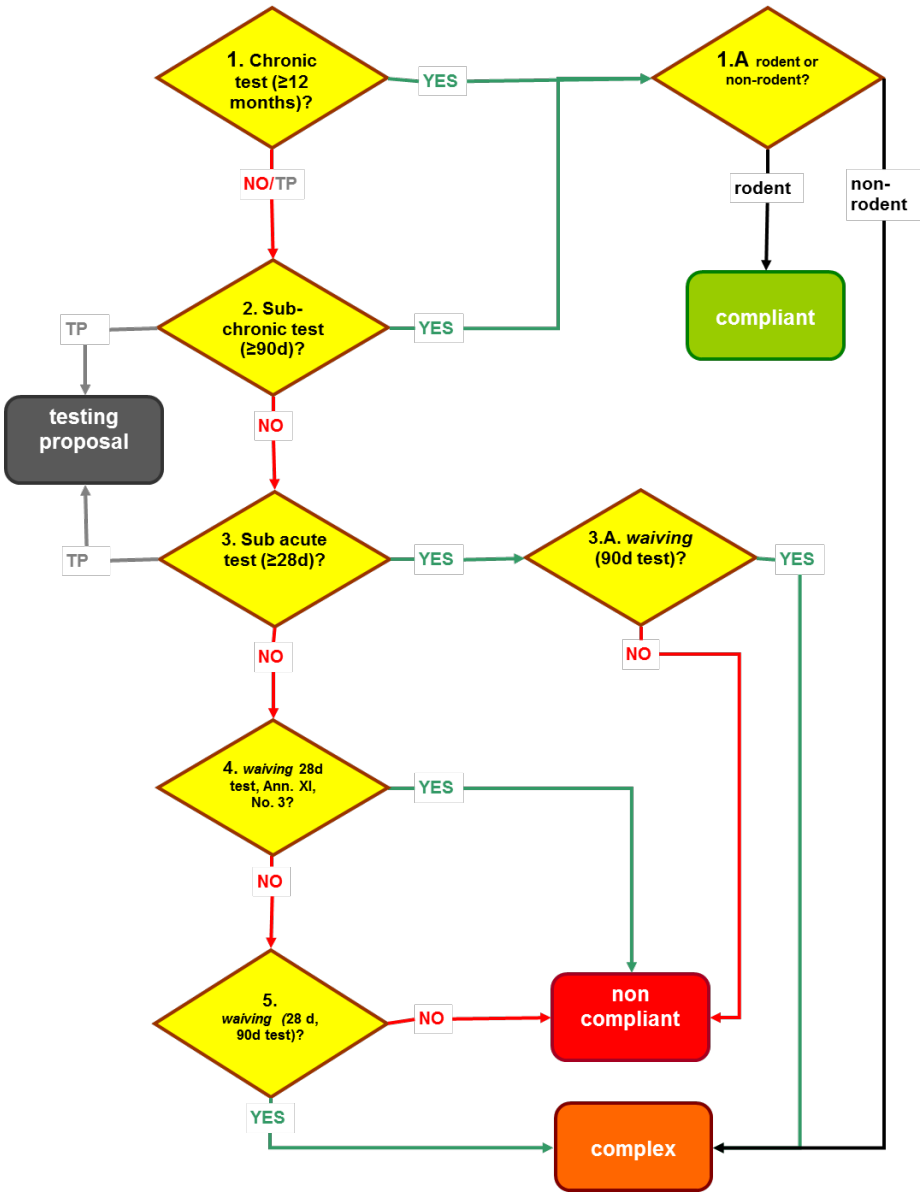
Answer YES: Classification as “complex”

The adaptation/waiving category had to be specified in KnowSEC (5.A). If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If “No” and “Yes” were selected simultaneously the conclusion was “non-compliant”.

Answer NO: Classification as “non-compliant”

Remark if the answer was YES: A read-across had to be available for the 90-day or a chronic study in order to be accepted as adaptation for subchronic toxicity.

Figure 3: Repeated Dose Toxicity Decision Tree



2.3.4 Toxicity to Reproduction

Information Requirements

Reproductive toxicity comprises adverse effects of substances on the fertility and reproduction performance of the parental generation and the development of the offspring during pregnancy (prenatal) and the lactation period (postnatal). In developmental toxicity studies, pregnant female animals are exposed to a test substance in order to assess embryonic and foetal development of the progeny until birth (prenatal). Subsequently, the offspring is thoroughly examined for morphological and physiological variations and anomalies. In reproductive toxicity studies, both sexes are exposed to the chemical well before and during the mating period. Treatment of the females continues until nursing of the offspring is completed. This approach so far constitutes the exposure scenario for a one-generation study. A continuation of substance treatment with the progeny will be the basis for a two-generation study. In these studies, effects on reproductive as well as developmental parameters

are the subject of examination. Moreover, NOAELs for reproduction and development can be derived from reproductive toxicity studies.

Screening tests do not provide the complete information, because the duration of exposure is shorter, the number of animals is limited and not all required parameters are assessed.

Studies for reproductive and developmental toxicity under REACH are required for substances with a production volume of 10 tpa or more (Annex VIII). The following two endpoints are distinguished:

- Toxicity to reproduction / fertility (ReproTox),
- Toxicity to development / teratogenicity (DevTox).

A separate IUCLID subsection exists for each endpoint, while discrimination under the CLP Regulation is only possible with the help of attached specifications in the hazard statements (F for fertility and D for development).

Table 10 lists the OECD and EU guidelines which address reproductive and developmental toxicity. Studies according to OECD TG 414 and 416 (2001a, 2001b) or equivalent guidelines are mandatory for substances with a production volume of ≥ 1000 tpa and are the only studies which give full information on all relevant aspects of reproduction and development. OECD TG 414 comprises the assessment of developmental and teratogenic effects in the offspring until birth as well as toxic effects in dams/does. Postnatal development of the litter is usually not monitored. At the Annex IX level (100-1000 tpa), one species is tested, the involvement of a second species might be indicated, depending on the outcome of the first study and all other relevant available data. For substances marketed at 1000 tpa or more, testing in two species (rodent and non-rodent, usually rabbits) is mandatory. Reproductive capacities of males and females and pre- as well as postnatal development are the main subjects of OECD TG 416. This study extends over two generations and rodents (usually rats) are the preferred species for testing.

Screening for reproductive / developmental toxicity according to OECD TG 421 or 422 (1995b, 1996) is especially relevant for substances with a yearly production volume of ≥10 up to 999 tonnes, but insufficient for tonnage groups which require complete information on all aspects of reproduction and development. Moreover, the one-generation reproduction toxicity study (OECD TG 415 (1983)) cannot replace the two-generation reproduction toxicity study under REACH. The proposed extended one-generation reproduction toxicity study (OECD TG 443 (2012c)) has, at the time of development of this concept, not yet been implemented into the REACH Annexes. Repeated dose toxicity studies (e.g. OECD TG 407 or 408 (1995a, 1998b)) might give hints on potential interferences of a substance with the reproductive system, but the information is incomplete. OECD TG 426 (2007) only addresses toxicity to the developing nerve system.

A multitude of in vitro methods is available to assess adverse effects on reproduction and development, e.g. the Embryonic Stem Cell Test (Seiler & Spielmann, 2011), the limb bud micromass culture (Spielmann et al., 2004), the whole embryo culture (Piersma et al., 2004) and numerous tests addressing different aspects of fertility (Schenk et al., 2010). Though several of these methods are scientifically validated, they are not yet accepted by regulatory organs and none of them has been included in the OECD testing guidelines inventory until now. However, in vitro tests can have a supporting function and can be used as triggers, e.g. a positive result in a validated in vitro test could provide a justification for further testing.

Table 10: Overview on the accepted test methods for the assessment of reproductive and developmental toxicity*

Study Type	OECD TG[a]	EU method[b]	US EPA analogue[c]	Production volume (t/a)	Repro-Tox	DevTox
Reproduction/developmental toxicity screening test	421			≥10	Screening	Screening
Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test	422			≥10	Screening	Screening
Repeated dose 28-day or 90-day oral toxicity study in rodents	407/408	B.07/B.26		≥100	Screening	
Prenatal developmental toxicity study	414	B.31	OPPTS 870.3700-Prenatal developmental toxicity	≥100, ≥1000 (2. species)		Test (incl. teratogenicity, pregnant females)
Two-generation reproduction toxicity study	416	B.35	OPPTS 870.3800-Reproduction and fertility effects	≥100	Test	Test
One-generation reproduction toxicity study	415	B.34		Non-standard	Test	
Extended one-generation reproductive toxicity study	443			Non-standard	Test	Test
Developmental neurotoxicity study	426			Non-standard		Test

* Referring to ECHA guidance on information requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint specific guidance. Version 2.4 from February 2014. This was the current version when the concept for the screening was developed for this project.

[a] OECD Guidelines for the Testing of Chemicals, section 4 (OECD, 2015), [b] REACH Test Methods Regulation (EC) No 440/2008, [c] Office of Chemical Pollution Prevention (OCSPP) harmonised test guidelines, series 870 – Health effects test guidelines (OCSPP, 2015).

If the substance is classified according to the CLP Regulation as a genotoxic carcinogen (carcinogen category 1A or 1B and mutagen category 2) or germ cell mutagen (mutagen category 1A or 1B), no

testing is required. However, data should be robust enough for risk management (Annexes VIII to X, Column 2).

Moreover, if a classification as reproductive toxicant (category 1A or 1B, H360) damaging fertility and the unborn child (H360FD) exists, no further studies have to be conducted. If only one specification of the hazard statement applies (H360D or H360F) the respective other study has to be provided (DevTox if classification is H360F, ReproTox if classification is H360D) according to Annexes VIII to X, Column 2. In all cases, data should enable a robust risk assessment (Annexes VIII to X, Column 2).

Studies assessing ReproTox (OECD TG 416 (2001b), one species, generally rat) and DevTox (OECD TG 414 (OECD, 2001a), two species, rodent and non-rodent) are mandatory for substances with a production/import volume of ≥1000 tpa (Annex X, 8.7.2 and 8.7.3, Column 1; Annex IX, 8.7.2 and 8.7.3, Column 2). Consequently, screening studies can be omitted. In vitro studies are not accepted, but can be part of an adaptation approach.

ReproTox and DevTox studies can be waived if the substance is of low toxicological activity, if there is no or no significant human exposure and if toxicokinetic data prove that no systemic absorption occurs via relevant routes of exposure (Annex IX, 8.7, Column 2). Moreover, adaptation and waiving options according to Annex XI apply.

The appropriate route of administration has to be chosen taking into account what is the most likely route of human exposure (Annex X, .7.2 and 8.7.3, Column 1). Oral administration is the standard to assure information retrieval about systemic toxicity in reproductive toxicity studies.

Decision Tree

As a first step, it was checked if the substance has a harmonised classification according to the CLP Regulation, because no further studies are needed in this case and the endpoint classification was “compliant”.

Furthermore, the endpoint was classified as “compliant” if all standard information were provided and the oral route of exposure was chosen, except for gases, which require administration by inhalation. If another route of exposure was applied the conclusion was “complex”, because this case needs a more detailed analysis. The conclusion “non-compliant” was only assigned if valid standard information and adaptations/waivers were not available for ReproTox and/or DevTox. All other cases were classified as “complex”. Two exceptions from these rules exist:

1. DevTox: If no study or adaptation/waiver was available for the second species, the conclusion was “complex”, because the need to perform this study requires a more detailed analysis.
2. ReproTox: If the study was performed in non-rodents, the conclusion was “complex”, because this issue requires a more detailed analysis.

Although it is mentioned in Annex IX, 8.7.3, Column 2, a two-generation study in a second species is usually not conducted in practice. Therefore, this requirement was not included in the decision tree. A one-generation study (OECD TG 415 (1983)) cannot replace a two-generation study (OECD TG 416 (2001b)).

The species (rodent or non-rodent) were considered in the decision tree where possible. Though, it was not be documented what kind of rodent or non-rodent was used (e.g. mouse, rat, rabbit etc.). The preferred species for OECD TG 416 (2001b) are rodents (usually rat), while two studies, with a rodent and a non-rodent model, are required for OECD TG 414 (2001a). Either a rodent or a non-rodent study has to be available when only a single OECD TG 414 is present. Studies using other species were not accepted.

The appropriate route of exposure is usually the oral administration, with the exception of gases, for which an exposure via inhalation is necessary. However, application routes were only checked if all standard information was available and the conclusion "compliant" was possible. The latter occurred if oral administration was chosen for liquids and solids or inhalation for gases. All other combinations were assigned to the endpoint conclusion "complex", as it needs a more detailed analysis to verify if they are appropriate. The check of the route of exposure was not relevant for the subsequent steps in the decision tree, because the endpoint could not be classified as "compliant" anymore.

A detailed explanation for every step in the decision tree is given, each following the appropriate textbox containing a question. Figure 4 shows the decision tree on the whole.

Question No. 1

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

This question relates to Annex X, 8.7, Column 2, first section, first and second bullet point. The harmonised classification had to be checked in Annex VI of the CLP Regulation or in the C&L inventory on ECHA website. If the substance held the harmonised classification no further data were required.

Answer YES: Classification as "compliant"

Answer NO: Continuation with question 2

Remark when the answer was YES: Formally, the registrant had to include an adaptation/waiving for the standard information requirements. However, in such cases "compliance" was confirmed, because this is solely a formal question and studies might have been available. Therefore the decision tree stopped at this point. Furthermore, also a check whether sufficient risk management measures were in place was not included in the screening scheme (Annex X, 8.7, Column 2, first section, second bullet point).

Question No. 2

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

The question relates to Annex X, 8.7, Column 2, second and third section. The harmonised classification had to be checked in Annex VI of the CLP Regulation or in the C&L inventory on ECHA website.

Answer YES: Classification as "complex"

It still has to be proven that the available data are sufficient to support a robust risk assessment (Annex X, 8.7, Column 2, second and third section).

Answer NO: Continuation with question 3

Question No. 3

Are all standard information requirements (ReproTox [OECD TG 416], rodent and DevTox [OECD TG 414], two studies, rodent and non-rodent) available?

Answer YES: Continuation with question 3.A (route of exposure)

Answer NO: Continuation with question 3.B

Remark: A harmonised classification as H360F or H360D might exist.

Question No. 3.A

Was the route of exposure by inhalation for gases and oral for liquids and solids for the available ReproTox (OECD TG 416, rodent) and DevTox (OECD TG 414, two species) studies?

Answer YES: Classification as "compliant"

Answer NO: Classification as "complex"

A more detailed analysis was required whether the applied administration is an appropriate route of exposure.

Question No. 3.B

Are DevTox studies (OECD TG 414) for two species, rodent and non-rodent, available, while a ReproTox study (OECD TG 416) in rodents is missing?

Answer YES: Continuation with question 3.C

Answer NO: Continuation with question 4

Question No. 3.C

Is the substance classified as a reproductive toxicant (category 1A or 1B, H360) according to the CLP Regulation affecting fertility (H360F)?

The question relates to Annex X, 8.7, Column 2, second section. The answer had no impact on subsequent questions or the conclusion, as an adaptation/waiving was required in any case, including – in case the answer was "Yes" – a proof that a robust risk management is possible.

Answer YES: Continuation with question 3.C-2

Answer NO: Continuation with question 3.C-2

Question No. 3.C-2

Is an adaptation/waiver for the ReproTox study in rodents (OECD TG 416) or a non-rodent study for ReproTox (OECD TG 416) available?

Answer YES: Classification as "complex"

A more detailed analysis was required of whether the applied adaptation/waiving or the non-rodent study (non-standard species) was appropriate.

It had to be specified in KnowSEC if the ReproTox study was conducted in non-rodents and, in case of adaptation/waiving, what kind of adaptation/waiving category was used. If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If "No" and "Yes – adaptation/waiving category" were selected simultaneously the conclusion was "non-compliant".

Answer NO: Classification as "non-compliant"

Question No. 4

Are a DevTox study (OECD TG 414) in one species and a ReproTox study (OECD TG 416) in rodents available?

Answer YES: Continuation with question 4.A

Answer NO: Continuation with question 5

Remark: A harmonised classification as H360F or H360D might exist.

Question No. 4.A

Is an adaptation/waiver for the DevTox study (OECD TG 414) in the second species available?

The question was only for information. The answer had no impact on subsequent questions or the endpoint conclusion.

Answer YES: Classification as “complex”

It had to be specified in KnowSEC what kind of adaptation/waiving category was used. If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If “No” and “Yes” were selected simultaneously the conclusion was “non-compliant”.

Answer NO: Classification as “complex”

This exception in the conclusion rules applied because the need to perform a study in a second species required a more detailed analysis (see chapter 4.1.3.4).

It was not checked if an appropriate route of exposure was chosen for both tests, ReproTox and DevTox, and if a suitable animal model was used in the DevTox study.

Question No. 5

Is only a study on DevTox (OECD TG 414, one species), only a study on ReproTox (OECD TG 416, rodent) or no study according to standard information requirements available?

One had to select the available study type (414, 416 or no study). The decision tree split at this point.

414: Continuation with question 5.A

416: Continuation with question 5.B

No study: Continuation with question 6

Question No. 5.A

Is the substance classified as a reproductive toxicant (category 1A or 1B, H360) according to the CLP Regulation affecting fertility (H360F)?

The question was purely information on Annex X, 8.7, Column 2, second section. The answer had no impact on subsequent questions or the conclusion.

Answer YES: Continuation with question 5.A-1

Answer NO: Continuation with question 5.A-1

Question No. 5.A-1

Is an adaptation/waiver for the DevTox study (OECD TG 414) in the second species available?

The question was only for information. The answer had no impact on subsequent questions or the endpoint conclusion.

Answer YES: Continuation with question 5.A-2

It had to be specified in KnowSEC what kind of adaptation/waiving category was used. If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If “No” and “Yes” were selected simultaneously the conclusion was “non-compliant”.

Answer NO: Continuation with question 5.A-2

Question No. 5.A-2

Is an adaptation/waiver for the ReproTox study in rodents (OECD TG 416) or a non-rodent study for ReproTox (OECD TG 416) available?

Answer YES: Classification as “complex”

A more detailed analysis was required whether the applied adaptation/waiving or the non-rodent study (non-standard) was appropriate.

It had to be specified in KnowSEC if the ReproTox study was conducted in non-rodents and, in case of an adaptation/waiving, what kind of adaptation/waiving category was used (5.A-2 a)). If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If “No” and “Yes” were selected simultaneously the conclusion was “non-compliant”.

Answer NO: Classification as “non-compliant”

It was not checked if an appropriate route of exposure was chosen for both tests, ReproTox and DevTox.

Question No. 5.B

Is the substance classified as a reproductive toxicant (category 1A or 1B, H360) according to the CLP Regulation affecting the unborn child (H360D)?

The question was purely information on Annex X, 8.7, Column 2, third section. The answer had no impact on subsequent questions or the conclusion.

Answer YES: Continuation with question 5.B-2

Answer NO: Continuation with question 5.B-2

Question No. 5.B-2

Is an adaptation/waiver for the DevTox study (OECD TG 414) available?

Answer YES: Classification as “complex”

It had to be specified in KnowSEC what kind of adaptation/waiving category was used (5.B-2 a)). If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If “No” and “Yes” were selected simultaneously the conclusion was “non-compliant”.

Answer NO: Classification as “non-compliant”

Question No. 6

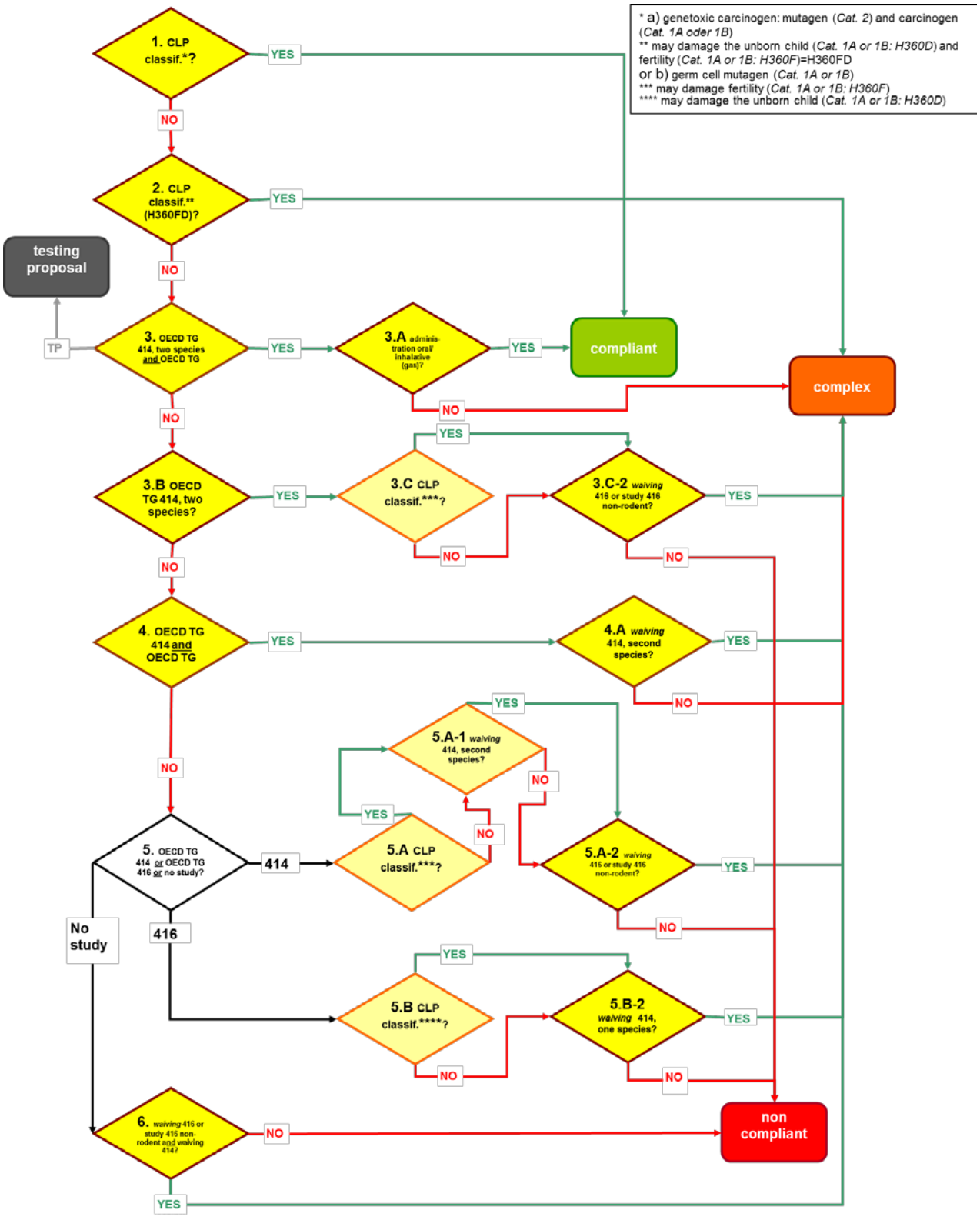
Are an adaptation/waiver for the ReproTox study (OECD TG 416) or a non-rodent study for ReproTox (OECD TG 416) and an adaptation/waiver for the DevTox study (OECD TG 414) available?

Answer YES: Classification as “complex”

It had to be specified in KnowSEC what kind of adaptation/waiving category was used (6.A for DevTox, 6.B for ReproTox). If more than one adaptation/waiving category was given, two or more categories were selected in KnowSEC. If “No” and “Yes” were selected simultaneously the conclusion was “non-compliant”.

Answer NO: Classification as “non-compliant”

Figure 4: Toxicity to Reproduction Decision Tree



2.4 Screening of Environmental Endpoints

Four endpoints are part of the environmental assessment area; degradation, bioaccumulation, ecotoxicity, and environmental exposure. The endpoint degradation is subdivided into biotic and abiotic degradation (BioDeg and AbioDeg, respectively), and for both subitems a separate assessment has been performed. Below, the concept for the screening of environmental endpoints is described. Beside a brief general description of the information requirements the decision trees with the underlying questions are explained in detail for each endpoint. The questions with the endpoint-specific abbreviation are summarised at the end of each section, and the memos specifying environmental information during the screening are listed in Annex 2.

2.4.1 Degradation

Substances that cannot be degraded either biologically or through physicochemical processes remain in the environment for long periods of time. When these substances continue to enter the environment, they accumulate there. The evaluation of the degradation of a substance plays an important part in hazard assessment (e.g. classification and labelling, C&L), risk assessment (chemical safety assessment, CSA), and the identification of PBT (persistent, bioaccumulative, toxic) and vPvB (very persistent, very bioaccumulative) substances, e.g. for the identification of substances of very high concern under REACH. If a registration dossier is not compliant or lacks information on degradation, this can lead to an underestimation of the hazard/risk posed by the respective substance to the environment.

2.4.1.1 Biotic Degradation

Information requirements

According to the REACH Regulation, Annex VII, 9.2.1.1, a test for ready biodegradability must be conducted for substances which are produced or imported in quantities of more than 1 tpa. This test can only be omitted according to Annex VII, Column 2, 9.2.1.1 – in the subsection of the dossier dealt with here – if the substance is inorganic (ECHA, 2012a, p. 162f.). The test method is selected depending on the volatility, water solubility and adsorptive characteristics of a substance. If an incorrect test method was selected and the results on biodegradation are therefore distorted, this case will not be considered further in this process and assigned to the category “complex”.

If a substance is not readily biodegradable, additional simulation tests must be carried out in a suitable medium from a production or import quantity of 100 tpa, REACH Regulation Annex IX, 9.2 and ECHA (2012a, p. 164f.). In the case of non-adsorptive substances, a simulation test of ultimate degradation in surface water should be used (Annex IX, 9.2.1.2), unless the substance is highly insoluble in water (Annex IX, Column 2, 9.2.1.2). For adsorptive substances, a distinction is made between degradation simulation tests in soil (Annex IX, 9.2.1.3) and in sediment (Annex IX, 9.2.1.4). However, if no direct exposure of soil or sediment is to be expected, these tests can be omitted (Annex IX, Column 2, 9.2.1.3 and 9.2.1.4). If a simulation test is conducted, the degradation products have to be identified according to Annex IX, 9.2.3.

If no simulation test was conducted in the case of a production/import quantity of more than 100 tpa, and no justifications according to Annex IX, Column 2, 9.2.1.2 – 9.2.1.4, or other explanations were provided (waiving/read-across to similar substances), the conclusion was “non-compliant”. If adaptation/waiving was performed, this case was not be considered further, because it was too complex for this project, unless the justification was in line with Annex IX, Column 2, 9.2.1.2.

Decision tree

The specific questions for the screening in the case of biotic degradation are summarised in the text box beneath and presented as decision tree in Figure 5.

Questions used in the decision tree of the endpoint biotic degradation

Question 1: "Is the substance inorganic?"

Question 2: "Is information available regarding ready biodegradability?"

Question 3: "Is the substance not readily biodegradable?"

Question 4: "Is an adequate standard method and no waiving applied?"

Question 5: "Is the substance highly adsorptive (log Kow › 4)?"

Question 6: "Is a simulation test in surface water available?"

Question 7: "Is adaptation/waiving available?"

Question 8: "Is waiving justified with S_w ‹ 1 mg/L according to Annex IX, Column 2, 9.2.1.2"

Question 9: "Is a simulation test in sediment or soil available?"

Question 10: "Is a standard-method applied?"

Question 11: "Are degradation products identified?"

The first test item queried whether the substance is inorganic (question 1). If this question was answered with “Yes”, no biotic degradation tests were necessary (Annex VII, Column 2, 9.2.1.1). The conclusion was thus “compliant” with respect to this endpoint. If the answer was negative, the decision tree was continued with question 2.

The second step (question 2) checked whether screening information on ready biodegradability was available (standard information requirement with production/import quantities > 1 tpa). This information can be found in IUCLID section 5.2.1 or in the chemical safety report (CSR) in section 4.1.2.1.2. If no information on ready biodegradability was available despite a standard information requirement, the conclusion was “non-compliant”, unless a testing proposal was provided. “Non-compliant” conclusions based on inconsistent test material identity were also documented via memos.

If information on ready biodegradability was available (next to standard screening tests also information based on adaptation/waiving or non-standard test was accepted here), it was checked whether the substance is readily biodegradable or not (question 3). Depending on the test method, a substance is considered not readily biodegradable when the proportion of dissolved organic carbon (DOC) is < 70% or the theoretical carbon dioxide development or theoretical oxygen consumption is < 60%. For details see Table 11 or the OECD test guidelines for ready biodegradability (OECD, 1992b, 2006) or the respective REACH Test Methods Regulation (EC) No 440/2008.

In the case of a readily biodegradable substance (question 3: “No”), the fourth step (question 4) checked whether the correct test method was used. As reported in OECD TG 301 and 310 (1992b, 2006), not all test methods are suitable for poorly water soluble (water solubility, S_w < 100 mg/L), volatile (Henry’s law constant, k_H > 10 Pa m³/mol) or adsorptive substances (partition coefficient n-octanol-water, log K_{ow} > 4). Table 11 shows which methods are suitable for which substances. If the suitability of the test method was unclear according to recommendation in the OECD guidelines, the recommendations from ECHA guidance are adopted (ECHA, 2012a, p. 181f.). If the correct test method according to ECHA guidance was used, the conclusion was “compliant” for this endpoint. If it was the case that the test method was not suitable due to the substance properties, further consideration was too complex for this project and a memo was added. The information on substance prop-

erties can be found in IUCLID under section 4.7 (log K_{ow}), 4.8 (S_w) and 5.4.2 (k_H). The CSR contains the information on water solubility and partition coefficient in section 1.3 and on volatility in section 4.2.2. Information with respect to biodegradability based on adaptation/waiving or non-standard tests was also considered "complex". The conclusion was accompanied by a respective memo to differentiate the cases.

If a substance is not readily biodegradable, the adsorption potential (question 5) determines which simulation test must be available in accordance with the information requirement for production/import quantities > 100 tpa. In the case of a non-adsorptive substance (log $K_{ow} \leq 4$), a simulation test in surface water according to OECD TG 309 (2004a) must be conducted (question 6; IUCLID section 5.2.2; CSR section 4.1.2.1.3); in the case of an adsorptive substance, a simulation test in sediment according to OECD TG 308 (2002a) and soil according to OECD TG 307 (2002b) is carried out (question 9; IUCLID section 5.2.2; CSR section 4.1.2.1.3 and IUCLID section 5.2.3; CSR section 4.1.2.2, respectively). If the simulation test was carried out according to one of these standard methods (question 10), it was checked whether the degradation products were identified (question 11). If this is the case, the conclusion was considered "compliant"; otherwise, it was "non-compliant". If other test methods were used, the conclusion was "complex".

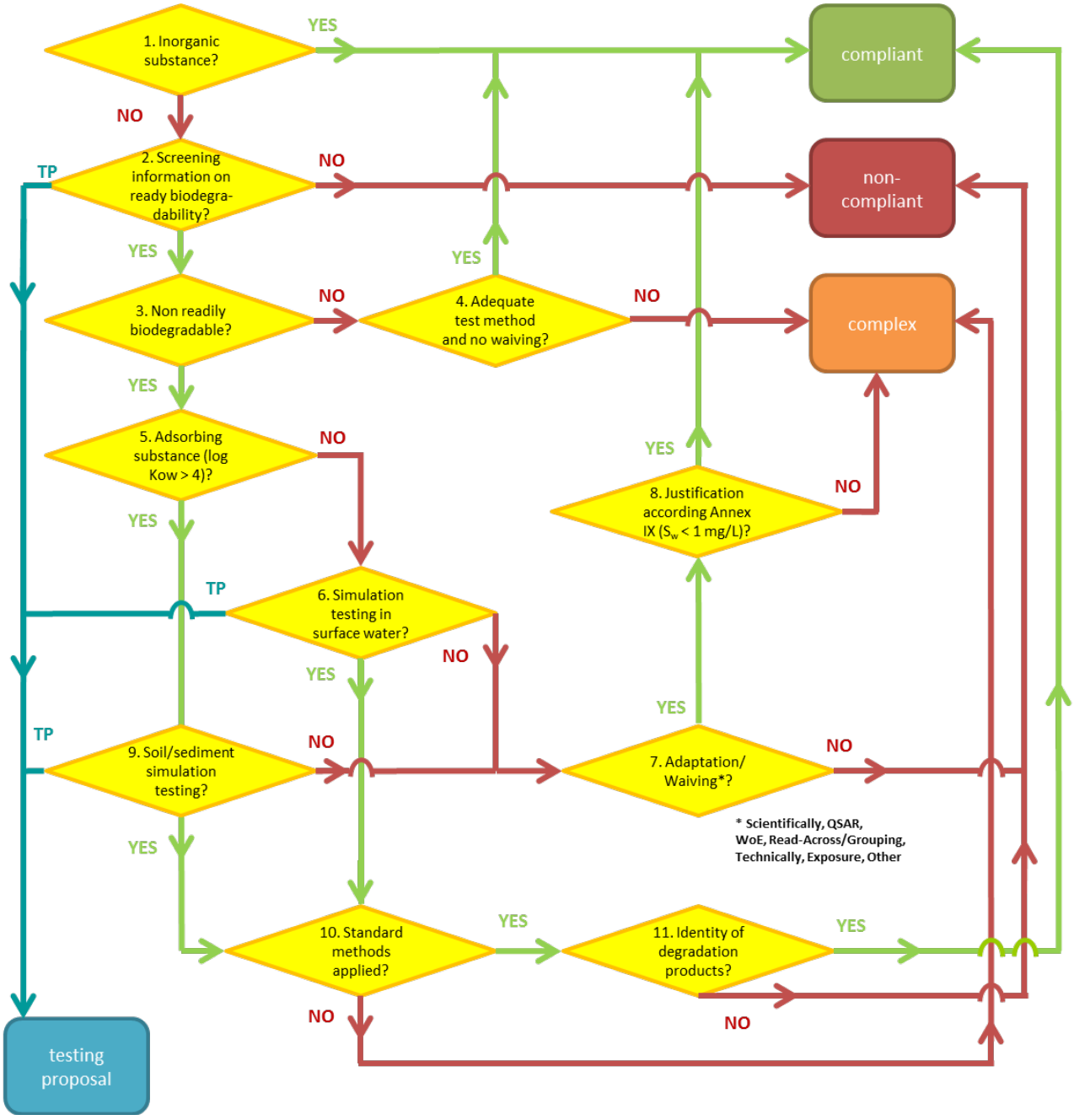
If no simulation test was carried out despite production/import quantities of more than 100 tpa, and this was not justified by waiving (question 7), e.g. with respect to Annex IX, Column 2, 9.2.1.2 – 9.2.1.4, or read-across to similar substances, the conclusion was "non-compliant", unless a testing proposal was given. If adaptation/waiving were documented, it was investigated whether it took place for the simulation test on surface water with reference to low water solubility in accordance with Annex IX, Column 2, 9.2.1.2 (question 8). Waiving with this justification was considered "compliant"; other adaptations/waiving were considered "complex", unless the waiving was not justified with respect to the right compartment, surface water on the one hand, sediment and soil on the other. Then this endpoint conclusion was considered "non-compliant" and was accompanied by a memo.

Table 11: Test methods, threshold conditions and suitability for standard tests on ready biodegradability according to OECD TG and EU test methods

Test method		Substance is not readily biodegradable if...	Suitability with respect to substance-specific physico-chemical properties		
OECD TG	EU		Poorly soluble (S_w < 100 mg/L)	Volatile (k_H > 10 Pa*m³/mol)	Adsorptive (log K_{ow} > 4)
301 A	C.4 A	DOC < 70%	-	-	+/- (-)
301 B	C.4 C	$ThCO_2$ < 60%	+	-	+
301 C	C.4 F	ThOD < 60%	+	+/- (+)	+
301 D	C.4 E	ThOD < 60%	+/- (+)	+	+
301 E	C.4 B	DOC < 70%	-	-	+/- (-)
301 F	C.4 D	ThOD < 60%	+	+/- (+)	+
310	C.29	$ThCO_2$ < 60%	+	+	+/- (+)

If the suitability of the test method is unclear "+/-" according to the labelling in OECD TG 301 and 310 (1992b, 2006), the characters in brackets ( ) specify the appropriateness according to ECHA guidance R.7b (2012a p. 181f.). EU test methods according to REACH Test Methods Regulation (EC) No 440/2008.
S_w – Water solubility; k_H – Henry's law constant; K_{ow} –Partition coefficient, n-octanol-water; DOC – Dissolved Organic Carbon; ThOD – Theoretical Oxygen Demand; $ThCO_2$ – Theoretical CO_2 production.

Figure 5: Biotic Degradation Decision Tree



2.4.1.2 Abiotic Degradation

Information requirements

If a substance is produced or imported in quantities greater than 10 tpa, a hydrolysis test as a function of the pH value must be conducted according to Annex VIII, 9.2.2.1. However, if the substance is readily biodegradable or highly insoluble in water, it is possible to omit this test in accordance with Annex VIII, Column 2, 9.2.2.1 (ECHA, 2012a, p. 163.).

If no test of hydrolytic degradation was conducted in the case of a production/import quantity of more than 10 tpa and no waiving justifications according to Annex VIII, Column 2 or other explanations were provided (waiving of the test due to chemical structure), the conclusion was "non-compliant". If adaptation/waiving was performed because the substance is highly adsorptive (log K_{ow} > 4) this case did not need to be considered further, as it was too complex for this project. The same applies to inorganic substances.

Decision tree

The specific questions for the screening in the case of abiotic degradation are summarised in the text box beneath and presented as decision tree in Figure 6.

Questions used in the decision tree of the endpoint abiotic degradation

Question 1: "Is adaptation/waiving available?"

Question 2: "Is waiving justified with S_w ‹ 1 mg/L or is the substance readily biodegradable according to Annex VIII, Column 2, 9.2.2.1?"

Question 3: "Is the substance highly adsorptive (log K_{ow} › 4) or inorganic?"

Question 4: "Is a result from a standard pre-test available?"

Question 5: "Are the extrapolated half-lives derived from a hydrolysis pre-test ‹ 1 day or › 1 year at all relevant pH values?"

Question 6: "Is a result from a standard main test available?"

Question 7: "Are results available for all relevant pH values and temperatures?"

Question 8: "Are degradation products (› 10%) identified?"

Question 9: "Was a non-standard method applied?"

Question 1 checked whether it was possible to omit the test with the justification "waiving". If this was the case, it was checked whether the test on hydrolysis was waived in accordance with Annex VIII, Column 2, 9.2.2.1 (question 2), either because the substance is readily biodegradable or highly insoluble in water. The data to be checked for this purpose can be found in IUCLID section 5.2.1 or CSR section 4.1.2.1, and in IUCLID section 4.8 or CSR section 1.3, respectively. Substances with a water solubility of less than 1 mg/L are considered highly insoluble in water. If one of these justifications was present, the conclusion was "compliant" for this endpoint; otherwise, it was "complex". A further reason for waiving the test on degradation through hydrolysis can be the chemical structure of the substance, as certain chemical functional groups resist degradation through hydrolysis or as the substance is stated as inorganic. Both types of justification resulted in the categorisation as "complex" because they have to be considered in more detail (see also Chapter 5.3). If the substance was considered readily biodegradable by the registrant in the ESR for biotic degradation, but that conclusion was based on waiving, a non-standard method or an inconsistent test material identity, the respective conclusion for abiotic degradation needed further evaluation. To generate information about the quantity of these adaptation/waiving justifications memos were added (Annex 2).

If no adaptation/waiving was given the results of the tests on degradation through hydrolysis needed to be evaluated. First, it was checked whether it is an "experimentally difficult substance", i.e. whether it displays a strong tendency towards adsorption, which can be assumed if the log K_{ow} > 4.0 (IUCLID section 4.7; CSR section 1.3) or the substance is inorganic (question 3). For both substance groups the conclusion represented a "complex" case, however, if an OECD TG 111 (2004c) study was available, a memo was added. If this point did not apply, the decision tree was continued with question 4.

The test guidelines to be used for evaluating hydrolysis, "OECD 111 – Hydrolysis as a Function of pH" (OECD, 2004c) and EU test guideline "C.7: Degradation – Abiotic Degradation Hydrolysis as a function of pH" (according to REACH Test Methods Regulation (EC) No 440/2008) are intended to determine the degradation of a substance through hydrolysis at the pH values 4, 7 and 9. For this purpose, a preliminary test (question 4) first needs to be conducted for the three pH values listed at 50 °C over a period of 5 days (IUCLID section 5.1.2; CSR section 4.1.1.1). In principle, however, it is also possible to omit the preliminary test and carry out a main test directly – in this case, question 6 follows. Hydrolysis tests that were not conducted according to or based on the methods listed above were considered "non-compliant".

If this preliminary test shows one of the following results at one or more of the relevant pH values (question 5):

a) less than 10% of the test substance was degraded through hydrolysis after 5 days; or

b) more than 50% of the test substance was degraded through hydrolysis after 2.4 hours,

it can be assumed in case a) that the half-life period in the environment at 25 °C will amount to more than one year and in case b) that the half-life period in the environment at 25 °C will be less than one day. If one of the two cases given above applied at one pH value, no further hydrolysis test was necessary for this pH value. If one of the results listed above applied at all three relevant pH values, no further studies were necessary and the test was considered "compliant". If no further test was carried out for the relevant pH values that did not meet either criterion a) or b) from question 4, the entire test was to be assessed as "non-compliant", unless a testing proposal was given. If the result of the preliminary test did not meet criterion a) or b) for one pH value, a comprehensive test was required for this pH value (question 6). If values from the literature indicating that a hydrolysis test was not necessary were given in place of the preliminary test, this case was classified as "complex" (via question 6 and question 9).

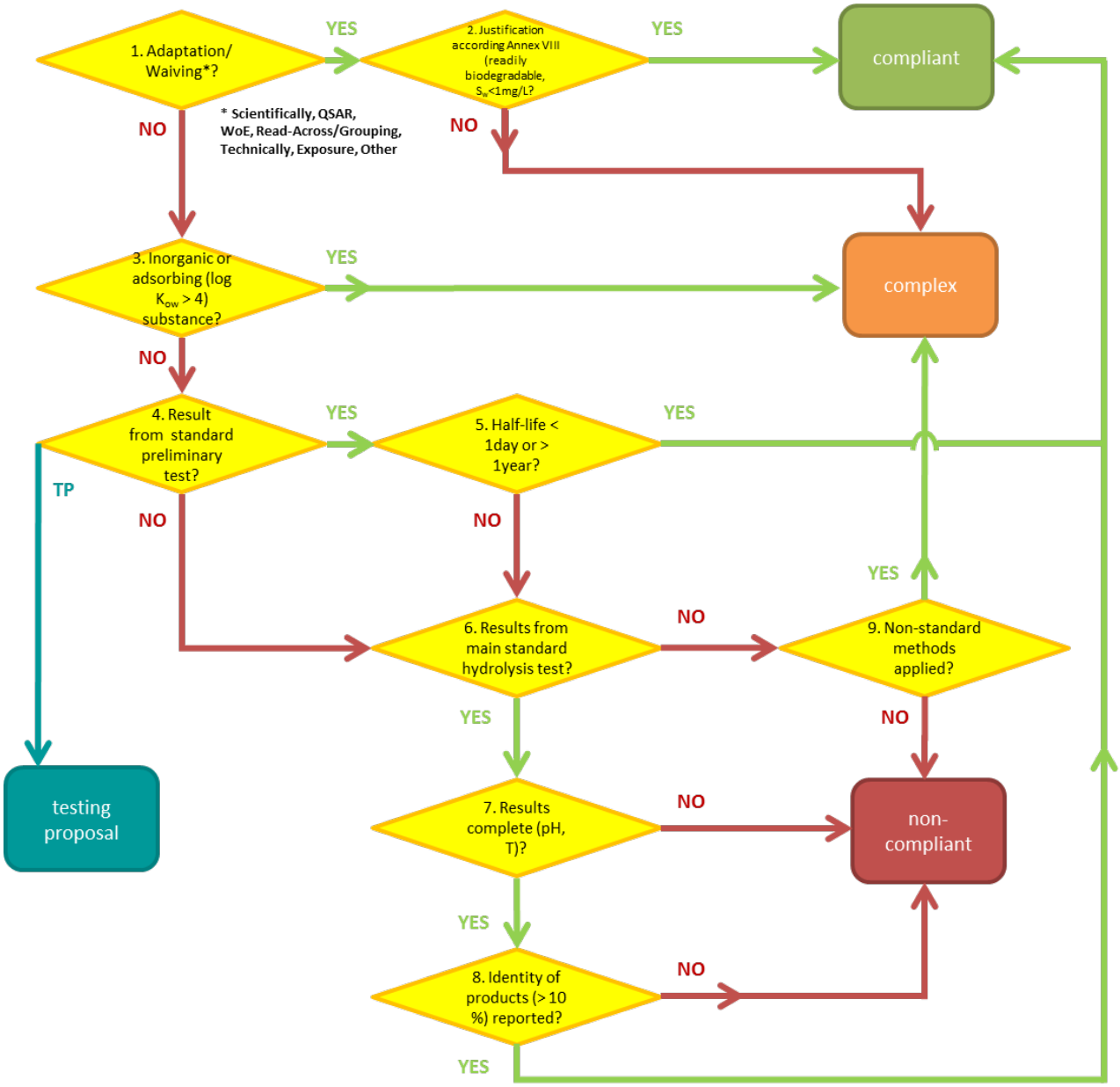
For the relevant pH values that required a comprehensive test (question 6), the temperatures must lie in the range between 10-70 °C and the hydrolysis rate must be extrapolated to a temperature of 25 °C from these results. For this purpose, the hydrolysis rate must be measured at three temperatures from the aforementioned temperature range over a period of 30 days or until 90% hydrolysis is reached (question 7).

In this context, it was checked whether hydrolysis had produced significant quantities of degradation products which had been contained in a concentration of more than 10% in a test medium and had to be identified (question 8). If the previously mentioned criteria were not met, the test was assessed as "non-compliant". If the relevant degradation products had been identified, the endpoint was considered "compliant".

If a method other than the standard test method specified above was used to determine the hydrolysis rate (question 9), the endpoint conclusion was "complex". Results without reference to a guideline were regarded as "non-compliant".

The decision tree in visualises the specific questions for the screening of abiotic degradation; it is supported by a text box with the questions on which the survey based.

Figure 6: Abiotic Degradation Decision Tree



2.4.2 Bioaccumulation

Information requirements

The estimation of the bioaccumulation potential plays an important role in understanding the behaviour of a substance in the environment. Substances that accumulate in organisms can reach higher internal concentrations and remain in the organism longer than substances with a lower bioaccumulation potential. This means a higher potential to cause toxic effects, also with a low external concentration and over a longer period of time, even when the external concentration in the environment has already decreased. In addition, bioaccumulative substances can spread throughout the food network and accumulate there. The information on the bioaccumulation potential of the substance is used for hazard assessment according to the CLP Regulation on classification and labelling, and may determine the necessity for conducting a long-term test on ecotoxicity and the assessment of the risk

of secondary poisoning. Bioaccumulation potential plays an important role in the identification of PBT substances and thus in the identification of substances of very high concern (SVHC) for the environment. The experimental concept of bioaccumulation testing which is currently applied only works without limitations for organic, non-ionic substances.

From an imported or produced volume of 100 tpa, the REACH Regulation, Annex IX, 9.3.2 stipulates a bioaccumulation test, preferably with fish, as a mandatory test requirement. Column 2 lists the particular conditions under which a bioaccumulation test can be waived (see also ECHA, 2012b, p. 13f.). Based on the questions specified below, a conclusion was made on whether the mandatory test requirements were met.

Decision tree

The specific questions for the screening in the case of bioaccumulation are summarised in the text box beneath and presented as decision tree in Figure 7.

Questions used in the decision tree of the endpoint bioaccumulation

Question 1: "Is the substance inorganic?"

Question 2: "Is the substance ionisable or hydrolytically unstable?"

Question 3: "Is an experimental BCF available?"

Question 4: "Is the test conducted according to OECD TG 305?"

Question 5: "Is another acceptable non-standard method applied?"

Question 6: "Is adaptation/waiving available?"

Question 7: "Is waiving justified with a log Kow ≤ 3 according to Annex IX, Column 2, 9.3.2?"

It was checked whether the standard requirement specified in Annex IX, 9.3.2 had been met, i.e. whether bioaccumulation had been determined through experiments (preferably in fish).

Due to the experiment-related problems with inorganic substances, these were to be classified to “complex” (question 1). The same applied to ionisable substances, i.e. substances that dissolve heterolytically into anions and cations in polar solvents, and hydrolytically unstable substances (question 2). Indications for ionisable substances are provided by certain chemical functional groups (carboxyl, sulfonic, phosphate group, phenols or amino group) and the acid dissociation constant (pK_a) which can be found in IUCLID section 4.21. If the pK_a is between 4 and 10, the substance was considered ionisable, neutral and ionic form exist side by side (“complex”). For pK_a values which are lower or higher than this range a look to the chemical structure would have been necessary, however, due to the limited time in the screening this was not possible.

If the substance was neither inorganic nor ionic or hydrolytically unstable, it was necessary to check for an experimental bioconcentration factor (BCF, question 3). A memo was added if the test material identity in the ESR was not the same as the registered one and these cases were concluded as “non-compliant” (via question 4 and 5). If an experimental BCF on the registered substance was derived according to OECD TG 305 (2012a), it was assumed that the dossier probably conforms to the standard requirements with respect to this point (question 4). In question 5 it was checked if a non-standard method had been applied. Studies which were conducted according to the outdated guidelines OECD TG 305 A, B or D (1981b, 1981c, 1981d) and those without reference to guidelines were considered “non-compliant” and a memo was added. Difficulties for the evaluation were posed by bioaccumulation tests that were carried out according to some test protocols, including OECD TG 305 C (1981e), whose validity is disputed. Therefore, studies according to the outdated guidelines

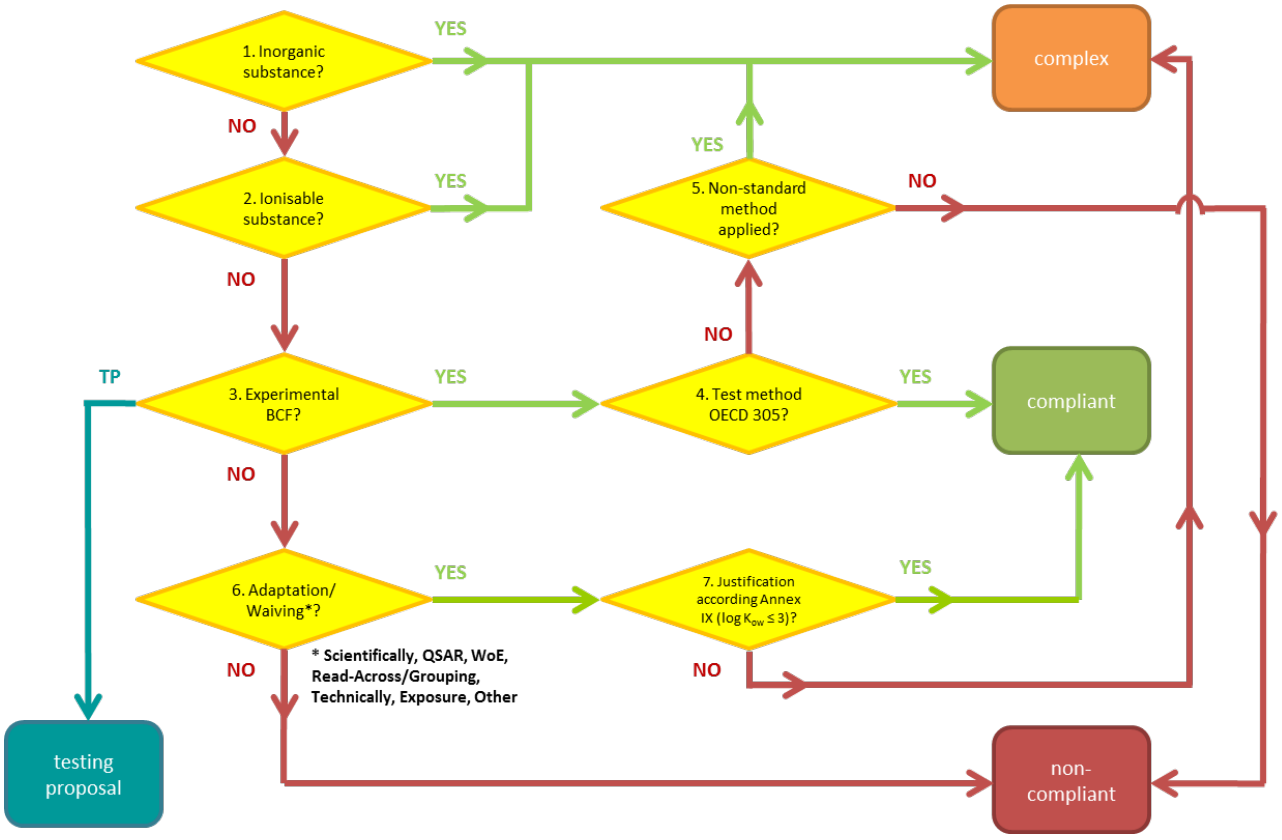
OECD TG 305 C and 305 E (1981a, 1981e) and to other guidelines were categorised as “complex” in the screening and a respective memo was recorded.

If no test data was available in general and no testing proposal was given either, it was checked whether reasons had been provided as to why the standard requirement had not been met (question 6). If this adaptation/waiving information was missing, it was clear that the dossier does not meet the standard requirement and the conclusion was thus considered “non-compliant”. If, however, reasons for adaptation/waiving were given, a more precise differentiation was required in the following verification steps.

Column 2 of Annex IX, 9.3.2 lists the specific conditions for deviation from Column 1. The bioaccumulation test can be waived, if the substance has a low bioaccumulation potential due to its properties. A log K_{ow} value of ≤ 3 and/or a molecule size with low potential to cross biological membranes are given as examples here. If a low log K_{ow} ≤ 3 was given as justification for not conducting the test, the endpoint conclusion was considered “compliant” (question 7). In certain cases, the specified log K_{ow} value may be incorrect, not plausible, or unsuitable for the substance, for example by reason of the surfactant properties of the substance. To maintain a reasonable i.e. manageable scope of verification, a check of the specified log K_{ow} value was not conducted under the screening scheme. However, if a log K_{ow} used for waiving justification had been derived via (Q)SAR, a memo was added. If the log K_{ow} is > 3 the conclusion was classified as “complex” for this endpoint.

Currently, the question of whether and in which way molecule size plays a part in bioaccumulation is a topic of international discussion. To maintain a reasonable scope of verification, this justification for omitting the bioaccumulation test resulted in the assignment “complex”. In addition, for all other adaptation/waiving justifications with respect to the bioaccumulation test the conclusion in the screening was “complex”, too.

Figure 7: Bioaccumulation Decision Tree



2.4.3 Ecotoxicity

Information requirements

The evaluation of the aquatic toxicity of a substance plays a key role in hazard and risk assessment (e.g. C&L and CSA), as well as in the identification of PBT/vPvB substances under the REACH Regulation. If required information is not available for this endpoint, hazard/risk to the environment can be underestimated. Information on aquatic toxicity is used to estimate the risk posed by substances and the hazard to freshwater and saltwater organisms. Aquatic toxicity is related to the intrinsic properties of a substance that can have an adverse effect on organisms after short-term or long-term exposure. In general, aquatic toxicity is specified by the concentration of the substance in the test water (ECHA, 2012a, p. 9.), apart from sediment toxicity which is not part of the screening. To maintain a reasonable scope of verification, the investigation in this project was limited to aquatic life or, more precisely, the pelagic zone, and here only fish and invertebrates (mainly *Daphnia*).

For substances with a tonnage of ≥ 100 tpa, the short-term tests on invertebrates and fish and the long-term tests on invertebrates and fish are standard requirements according to Annex VII, 9.1, Annex VIII, 9.1.3 and Annex IX, 9.1, respectively. However, there are exceptions. For example, when the long-term test is available, the corresponding short-term test (at the same trophic level) does not need to be carried out (e.g. a long-term test with fish is available, so a short-term test with fish does not need to be conducted). Other exceptions and their implementation into the decision trees are described below.

Decision tree

The specific questions for the screening in the case of ecotoxicity are summarised in the text box beneath and presented as decision tree in Figure 8.

Questions used in the decision tree of the endpoint ecotoxicity

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

In the first question it was evaluated whether acceptable long-term studies for fish and invertebrates were available. Long-term fish tests are covered in section 6.1.2 in IUCLID, while long-term invertebrate tests are covered in IUCLID section 6.1.4. This refers to tests which were ideally carried out according to OECD TG 211 (2012b) (long-term *Daphnia* test), OECD TG 210 (2013a) or higher – i.e. OECD TG 229, 230, 234 (2009a, 2011, 2012d). In addition, the OECD TG 212 (1998a) and OECD TG 215 (2000) long-term fish tests are acceptable; however, they are less sensitive than tests according

to OECD TG 210 (2013a) and restricted to specific log K_{ow} ranges (ECHA, 2012a p.26f.). Therefore, these methods were marked by a memo. Further acceptable guidelines that were used in this screening are summarised in Annex 3.

If the required information for long-term testing was present, it could be assumed that the dossier meets the standard requirements and was considered "compliant". The conclusion was independent of the availability of one or both short-term tests for invertebrates and fish. Annex VII, Column 2, 9.1.1: The short-term invertebrates test does not need to be conducted if a long-term invertebrates test is available. Annex VIII, Column 2, 9.1.3: The short-term fish test does not need to be conducted if a long-term fish test is available.

Test methods not mentioned on the list were considered "complex" as described below, unless they were insufficient. For example, the extended fish test (14 days) according to OECD TG 204 (1984a) cannot be considered suitable for long-term testing (ECHA, 2012a, p.26.). These cases were documented by memos. Further memos were added for long-term fish tests (e.g. OECD TG 210) and for long-term *Daphnia* tests (e.g. OECD TG 211) with reduced exposure duration.

ESRs based on experimental data without any reference to a guideline or ESRs in which the test material identity was not in accordance with that of the registered substance were considered "non-compliant" and were marked by memos.

"Testing proposals" were recorded as a separate conclusion. However, in cases where the conclusion did not clearly depend on the "testing proposal", further questions of the decision tree were examined and a memo was added.

For all entries that were missing one of the required long-term tests and were not classified as "testing proposal" it was important to differentiate between poorly water soluble and water soluble substances for experimental data based on the water solubility (S_w) of substances (question 7) which is listed in IUCLID section 4.8.

1) $S_w \leq 1$ mg/L

For poorly water soluble substances it was checked if both short-term tests on fish and invertebrates were available (question 2). Entries can be found under IUCLID 6.1.1 and 6.1.3. Short-term fish tests and short-term invertebrates tests were ideally carried out according to OECD TG 203 (1992a) and OECD TG 202 (2004b), respectively. A summary of other acceptable short-term tests as used in this screening is provided in Annex 3 of this report.

Test methods not mentioned in Annex 3 were considered "complex" as described below, unless they were insufficient. Memos were accompanied for short-term tests with a deviation of the standard exposure duration, 48 h instead of 96 h for fish tests, and 24 h instead of 48 h for *Daphnia* tests.

According to Annex VII, 9.1.1, long-term toxicity testing can be considered in place of short-term toxicity for invertebrates, and according to Annex VIII, 9.1.3, long-term toxicity testing can be considered in place of the short-term toxicity for fish. Therefore, if one of the short-term tests was missing and instead of that a long-term study for the same trophic level was presented (question 3) the endpoint conclusion was "complex". Important to note: for all long-term tests which were used in place of short-term tests the same test methods can be applied as those mentioned in the description of question 1.

The conclusion was also considered "complex" if both short-term tests were present and in addition one long-term test (question 4), either on fish or invertebrates, was available (Annex IX, 9.1.5 and 9.1.6).

On the other hand, if no long-term study was reported (question 4) or the present long-term study could not replace the missing short-term test (question 3) further test items followed.

First, it had to be investigated whether a non-standard guideline was conducted in place of the missing standard method(s) (question 12). Cases where a non-standard guideline was used are assessed as "complex".

Second, the availability of adaptation/waiving justifications was examined (question 5). In contrast to the other environmental endpoints this waiving question allowed for multiple answers, i.e. different justifications could have been provided in parallel. If a justification for adaptation/waiving was present, the endpoint was allocated to the category "complex". In addition, to differentiate adaptations via (Q)SAR between long-term and short-term studies question 6 was implemented. Cases of (Q)SAR adaptation for long-term studies were recorded separately from other reasons to get an overview of its quantity used in the registrations.

However, if neither a non-standard guideline (question 12) was available nor a justification for adaptation/waiving was present (question 5), the endpoint was considered "non-compliant".

2) S_w > 1 mg/L

At first, the availability of short-term tests for water soluble substances was examined (question 2), as described in the previous section.

If one of the short-term tests for fish and invertebrates were missing and instead of the missing short-term test a long-term study for the same trophic level was presented (question 3) the endpoint was assigned to the category "complex". If a long-term test instead of the missing short-term test was not available or even if both short-term studies were missing, question 12 and the aforementioned decision-making process followed with a conclusion either as "complex" or "non-compliant".

The short-term tests for fish and invertebrates were both available; question 2 was answered with "Yes". Subsequently question 8 asked whether the short-term tests showed effects or not. The effect was defined in terms of the EC_{50} and the LC_{50} values of the short-term tests being lower than 1.25 times the water solubility.

If no effects were detected it was checked if one long-term study was available (question 4). The following procedure was the same as described for this question in the previous section.

In case effects were observed, the question 9 evaluated the ratio between EC_{50} and LC_{50}. This ratio was used to differentiate further the need of long-term testing with respect to fish or invertebrates (ECHA, 2012a, p. 51.). The threshold limits of the ratio EC_{50}/LC_{50} reported in ECHA guidance were adapted due to results of the study "Comparison of Species Sensitivity of *Daphnia* and Fish in Acute and Chronic Testing" commissioned by the UBA (report is under preparation). Three cases could be differentiated and were assessed as follows:

a) EC_{50}/LC_{50} 0.2 - 5

EC_{50}/LC_{50} from 0.2 to 5 means that one organism is less than five times more sensitive than the other. If long-term studies for fish and invertebrates were not both available, this resulted in a "complex" conclusion.

b) EC_{50}/LC_{50} > 5 (question 10)

EC_{50}/LC_{50} > 5 means that the effect value of the short-term invertebrates test (EC_{50}) is five times higher than the effect value of the short-term fish test (LC_{50}, with 50% mortality in each case), i.e. the fish are five times more sensitive than the invertebrates. For this reason, it is sufficient if the long-term fish test is available. If the respective study was present the endpoint conclusion was considered "compliant".

If the required long-term test was missing and no testing proposal was reported, the decision-making process was continued with question 12 as described before. The subsequent conclusion was either “complex” or “compliant”.

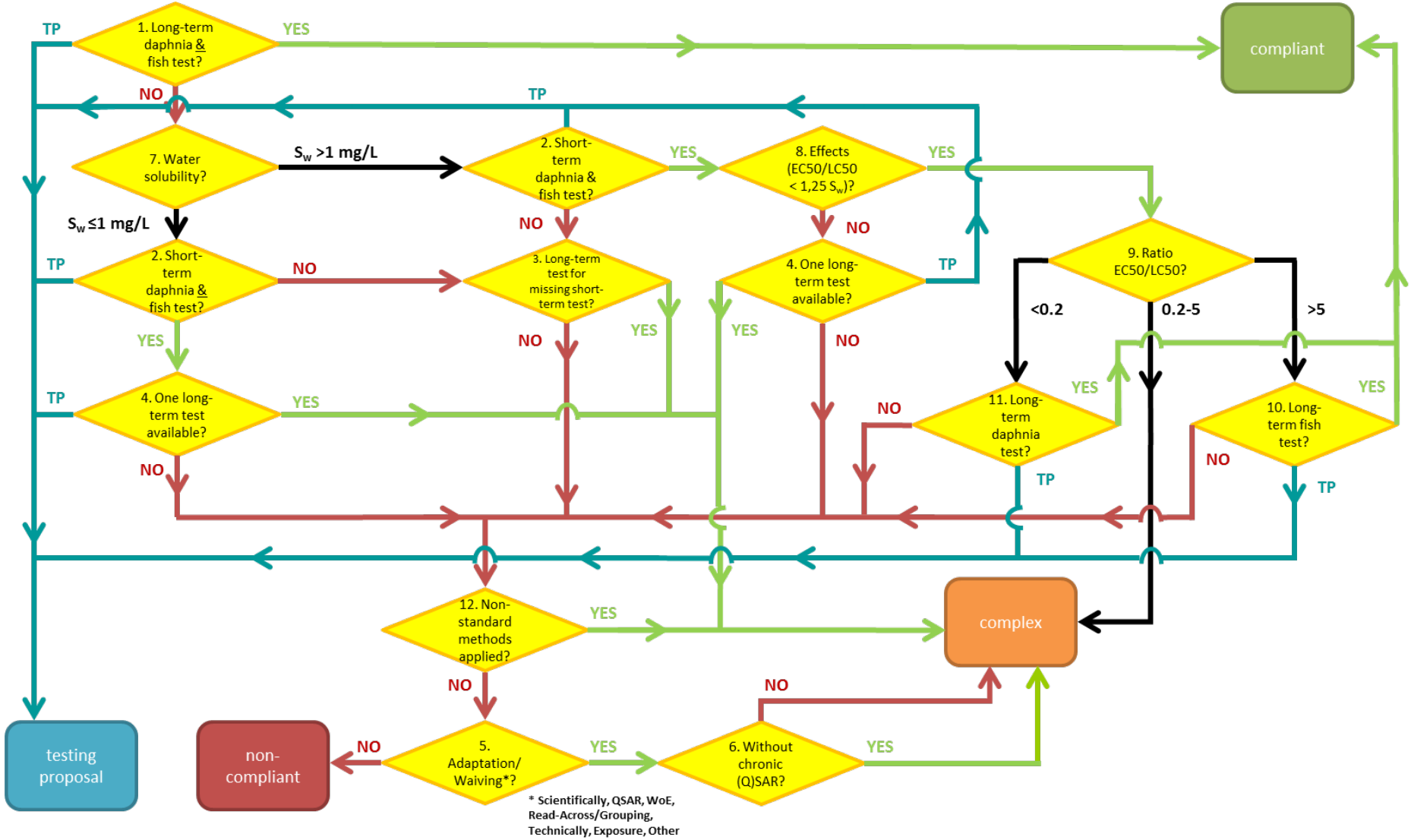
c) $EC_{50}/LC_{50} < 0.2$ (question 11)

$EC_{50}/LC_{50} < 0.2$ means that the effect value of the short-term fish test is five times higher than the effect value of the short-term invertebrates test (with 50% mortality in each case). This means that the invertebrates are five times more sensitive than the fish in this case. For this reason, it is sufficient if the long-term invertebrates test is available. If the respective study was present the endpoint was considered “compliant”.

If the required long-term test was missing and no “testing proposal” was reported, the decision-making process was continued with question 12 as described before. The subsequent conclusion was either “complex” or “compliant”.

If no experimental data were given in the ESRs in accordance with the information requirements of the REACH Regulation the reasons for this absence had to be evaluated. If a justification for adaptation/waiving was specified, the endpoint was allocated to “complex” because these cases could not be resolved within the scope of the screening project. Otherwise, if no reason was given, the endpoint conclusion was considered “non-compliant”.

Figure 8: Ecotoxicity Decision Tree



2.4.4 Exposure of the environment

Information requirements

The assessment of environmental exposure is an important component of chemical safety assessment under REACH. The aim of the exposure assessment is to investigate how chemicals spread in the environment and the extent to which people and the environment could be exposed to chemicals.

Exposure scenarios represent the basis for assessing exposure. They have to be prepared for every use supported by the producer or importer and for every stage in the life cycle of the chemicals, and they include a description of usage conditions. Based on these scenarios, an exposure assessment is conducted whereby the concentration of the substance to be expected in the various parts of the environment (Predicted Environmental Concentration – PEC) is determined. During the subsequent risk assessment, this value is compared to the estimated concentration at which no negative effects are to be expected (Predicted No-Effect Concentration – PNEC). The exposure scenarios are passed on in the supply chain in an extended safety data sheet. They are therefore an important basic condition for the safe use of chemicals, in particular with respect to the entire life cycle of the chemicals.

For capacity reasons, it could only be checked within the scope of this project whether the registrant had acknowledged the obligation for an exposure assessment at all. Other important questions relating to exposure assessment with respect to REACH conformity, such as whether all uses supported by the registrant were covered in the assessment, all life cycle phases were considered, the tonnages used were plausible, the conditions of use were realistic, or all relevant protected resources were taken into account could not be checked here.

ECHA guidance on information requirements and chemical safety assessment describes in section eight of "Part B: Hazard assessment" the conditions and scope of exposure assessment (ECHA, 2011a, p. 43ff.). According to Article 14(1) and (4) of the REACH Regulation, an exposure assessment and subsequent risk assessment is necessary for substances that are produced or imported in quantities of 10 tpa or greater, if they meet the criteria for one of the following hazard classes or categories outlined in Annex 1 of the CLP Regulation (1272/2008):

a) Hazard classes 2.1 to 2.4, 2.6 and 2.7, 2.8 Types A and B, 2.9, 2.10, 2.12, 2.13 Categories 1 and 2, 2.14 Categories 1 and 2, 2.15 Types A to F

b) Hazard classes 3.1 to 3.6, 3.7 Impairment of sexual function and fertility as well as development, 3.8 excluding narcotic effects, 3.9 and 3.10

c) Hazard class 4.1

d) Hazard class 5.1

or can be identified as PBT or vPvB substances (see list of hazard classes/categories in Annex 4 of this report).

Any of the above classifications as hazardous according to the CLP Regulation generally also makes carrying out exposure and risk assessment for the environment a mandatory requirement. If an exposure assessment is necessary as a consequence of this, the assessment must cover all adverse effects that have been investigated according to sections 1-4 of Annex I of the REACH Regulation (identification of adverse effects on human health, through physicochemical properties, and on the environment, as well as the identification of PBT and vPvB properties).

The following types of adverse effects were identified:

- Adverse effects that result in assignment to a hazard class/category

- Adverse effects for which categorisation criteria exist and information is available that the substance can cause these adverse effects, but the severity of the effects is below the categorisation criteria
- Adverse effects for which no categorisation criteria currently exist, but for which information is available that the substance can cause these effects.

According to this, the exposure assessment of a substance that meets at least one criterion as per Article 14(4) of the REACH Regulation must also consider adverse effects (either environmental or health related endpoints) for which no categorisation is in place. If the substance does not meet any criteria of Article 14(4) of the REACH Regulation, exposure assessment is not necessary. In this case, the absence of exposure scenarios is compliant with REACH Regulation (ECHA, 2011a, p. 43ff).

Some actors assume that the environmental exposure assessment merely needs to consider the environmental categorisations and risks which affect organisms in the aquatic compartment. However, the environmental categorisation does not cover all possible risks. For example, it does not include the compartments sediment, soil and air, or microbiological activity in sewage treatment plants. Moreover, toxicological effects in humans could also occur in other organisms. For this reason, the grounds for an environmental exposure assessment were also checked in this project. A differentiation in terms of categorisation between the environment and other endpoints was thus made in the decision tree.

Harmonised classification

The “harmonised classification and labelling for certain hazardous substances” (CLH) is listed in Annex VI of the CLP Regulation and is legally binding. Harmonised entries must be specified accordingly in the registration dossier. The substances with harmonised classification in Annex 1 of Directive 67/548/EEC on the “approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances” were adopted in Annex VI of the CLP Regulation.

Self-classification

According to Article 4 (1) and (3) of the CLP Regulation, producers, importers and downstream users of the CLP Regulation need to classify substances according to Title II of the CLP Regulation before placing them on the market if it is known that these substances fall under one or more hazard classes or differentiations which are not covered by the entry in Annex VI. This autonomous classification by the registrant is referred to as self-classification.

Regardless of whether CLH or self-classification is present, an exposure assessment must be carried out.

PBT/vPvB substances

Due to their long-lasting and bioaccumulative (as well as toxic) properties, a qualitative exposure assessment is necessary for PBT and vPvB substances, as no PNEC can be derived. This means that a quantitative exposure assessment or risk assessment cannot be performed. However, it is necessary to describe the way in which the substances can enter the environment, whether and how people and the environment can be exposed to the substances, and what use conditions need to be in place in order to keep exposure of people and the environment as low as possible. Since it is not possible to review such qualitative assessment of environmental exposure in a standardised manner, a more in-depth analysis would be required here.

For capacity reasons, it was not possible in the project to perform a comprehensive conformity check in the area of environmental exposure. For this reason, it was merely checked whether an environmental exposure assessment was requested according to the REACH Regulation and whether the registrant had recognised this obligation. Even if a positive result (“compliant”) was determined for this

sub-area, it is nevertheless possible that a dossier may not be “compliant” with respect to other environmental exposure aspects or endpoints that have not been checked.

Decision tree

The specific questions for the screening in the case of environmental exposure are summarised in the text box beneath and presented as decision tree in Figure 9.

Questions used in the decision tree of the endpoint environmental exposure

Question 1: "Does the substance have a harmonised classification for aquatic toxicity (H400, H410, H411 or H412)?"

Question 2: "Is the substance self-classified for aquatic toxicity (hazard statements H400, H410, H411 or H412)?"

Question 3: "Does the substance have a harmonised classification for aquatic toxicity (H413)?"

Question 4: "Is the substance self-classified for aquatic toxicity (H413)?"

Question 5: "Is any other harmonised classification available?"

Question 6: "Is any other self-classification available?"

Question 7a/7b: "Is the substance assessed as PBT or vPvB?"

Question 8: "Are environmental exposure scenarios available?"

Question 9: "Is a qualitative exposure assessment available?"

Before a check took place as to whether exposure scenarios for the environment had been prepared, it was first reviewed whether an environmental exposure assessment was necessary in principle. The criteria according to which this assessment was required are listed below.

The six combined questions (questions 1 - 6) for the test item “Classification in place?” were dealt with in parallel (Figure 9). First, the questions 1, 3, and 5 were checked with the help of the “C&L Inventory” database [6] in order to establish whether harmonised classification was in place. If there was a harmonised entry, it was necessary to check whether a corresponding entry was specified in section 3.1 “Classification and Labelling according to CLP/GHS” of the chemical substance report (CSR) or section 2.1 “Classification & Labelling according to GHS” and section 2.3 “PBT assessment” in IUCLID. If this was not the case, the conclusion was “non-compliant” and the result was documented via a memo for the respective question.

Reference to the aforementioned CSR or IUCLID sections could also be made to determine whether and how a registrant had self-classified the substance. The self-classification was checked in questions 2, 4 and 6.

The hazard categories were differentiated in three groups, which were used to assess both harmonised and self-classification in the same way. Substances, which were classified as H413, were recorded separately from the other categories related to aquatic toxicity, as a qualitative exposure assessment can be performed in this case.

Question 1 & 2

- H400: Very toxic to aquatic life
- H410: Very toxic to aquatic life with long lasting effects

[6] http://echa.europa.eu/de/information-on-chemicals/cl-inventory-database

- H411: Toxic to aquatic life with long lasting effects
- H412: Harmful to aquatic life with long lasting effects

Question 3 & 4

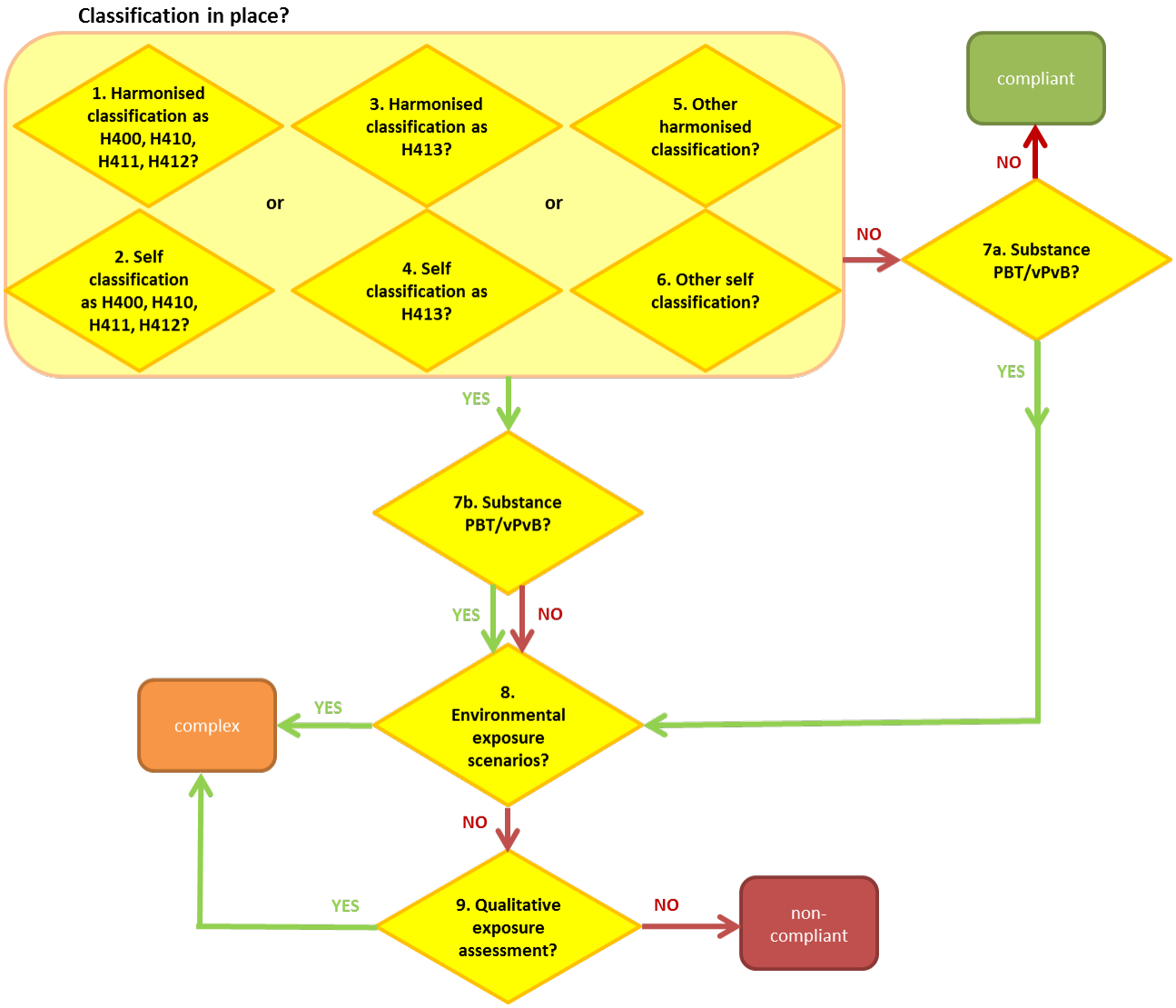
- H413: May cause long lasting harmful effects to aquatic life

Question 5 & 6

- Additional hazard class(es) listed in Article 14(4) of the REACH Regulation

If all questions 1- 6 were answered with "No", question 7a followed and it was checked whether the substance was PBT or vPvB. The related information can be found in section 8 of the CSR and in IUCLID section 2.3. The scope of this check did not include determining whether the assessment of the registrant was correct with respect to PBT properties. If the substance does not have PBT or vPvB properties, it is not necessary to prepare exposure scenarios based on these properties and the endpoint was considered "compliant". Otherwise, an environmental exposure assessment needed to be carried out (question 8).

Figure 9: Environmental Exposure Decision Tree



If at least one of the questions 1 - 6 was answered with “Yes”, it was first checked if the substance was PBT or vPvB (question 7b). This answer was for documentation purposes, and for both cases an environmental exposure assessment had to be available (question 8).

Question 8 could be answered using the information in section 9 “Exposure Assessment” of the CSR. It was also possible to obtain information here on why exposure scenarios were or were not prepared. If exposure scenarios were prepared, the dossier could be in compliance with the REACH Regulation. However, this could only be established by means of a detailed evaluation, which could not be performed in this project.

If the exposure scenarios were absent, question 9 checked whether a qualitative exposure assessment with regard to the environment was performed (CSR section 9). A qualitative exposure assessment was permitted, for example, in the case of categorisation in H413 or for PBT/vPvB substances. This qualitative assessment represented a “complex” case which has always been subjected to a detailed assessment that could not take place in the scope of this project. If the qualitative description of environmental exposure was absent in this step, this was an indication that the dossier was “non-compliant”.

In the decision tree of the endpoint environmental exposure is shown. The respective questions are recorded in the text box below.

3 Results and Discussion of the Screening Procedure

3.1 Overall

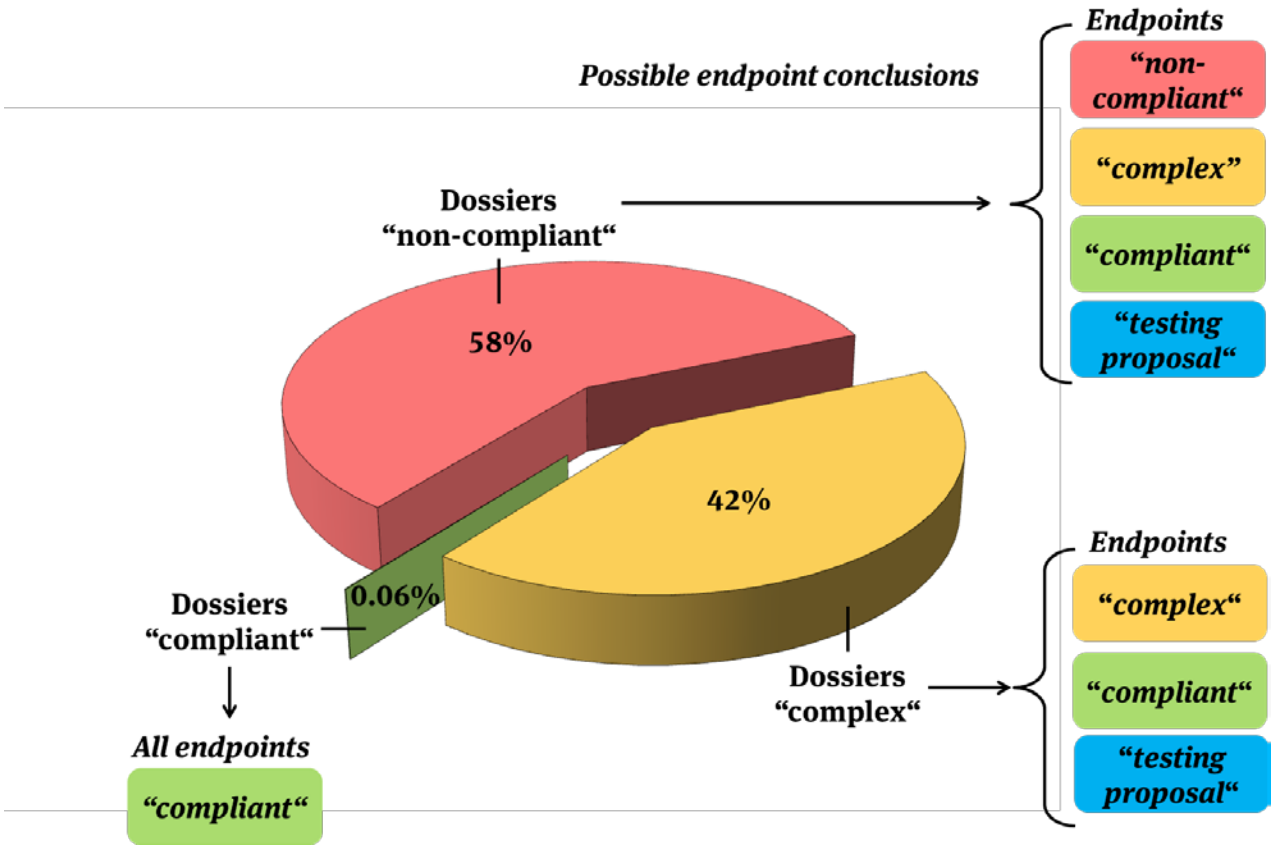
The screening resulted in the assignment of a conclusion category to each endpoint. On this basis the dossier achieved an overall categorisation as “compliant”, “non-compliant” or “complex”. In the following section the distribution over these categories resulting from the applied screening are illustrated for both the individual endpoints and the dossiers.

Dossier conclusions

The screening was applied to 1814 dossiers, checking the available information of the appropriate endpoints. Additionally, 118 dossiers were opened but did not contain toxicological or ecotoxicological information for single substances. Therefore, the screening was not carried out on these cases and the dossiers were postponed. Since 115 of these dossiers were part of different category approaches, common dossier entries were not directly accessible. Due to the limited time a detailed evaluation was not possible. For three out of 118 dossiers the provided UUID did not allow for the assessment of the correct dossier. For these reasons, the 118 dossiers are not part of the screening results documented in the following chapter.

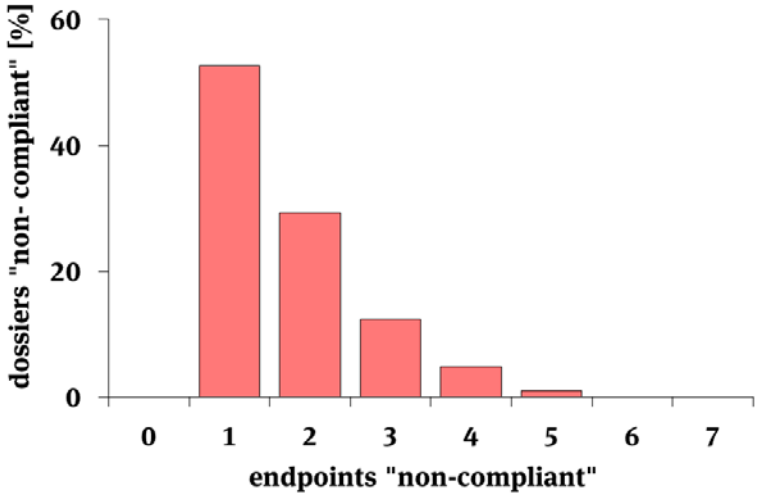
Figure 10 shows the distribution over the dossier conclusion categories for the 1814 checked dossiers based on the screening concept. Overall a single dossier (0.06%) resulted in the category “compliant” meaning that all endpoints were in accordance with the REACH information requirements as implemented in the screening.

Figure 10: Dossier conclusion categories - Distribution as percentage of completely checked dossiers (total number: 1814)



In contrast, 1043 of the 1814 dossiers (58%) were assigned to the category “non-compliant”. This implies that at least one of the eight checked endpoints was categorised as “non-compliant” with the REACH information requirements. The distribution regarding the actual number of “non-compliant” endpoints within the “non-compliant” dossiers is indicated in Figure 11. Half of these dossiers contained only one endpoint belonging to the “non-compliant” category, and one third of the dossiers contained two “non-compliant” endpoints. The remaining endpoints were categorised as “compliant”, “complex” or “testing proposal”.

Figure 11: Dossier conclusion category “non-compliant” - Frequency of “non-compliant” endpoints in all dossiers assigned as “non-compliant” (total number: 1043). See also Figures 12 and 13 for information on distribution of “complex” and “compliant” endpoints.



The category “complex” was assigned to 770 of the 1814 evaluated dossiers (42%, Figure 10). None of the considered endpoints of these dossiers was assigned to the category “non-compliant” whereas at least one of the endpoints was found to be “complex”. Therefore, at this time it remains unknown for 42% of the examined dossiers whether they are in accordance with the REACH information requirements. The distribution on how many endpoints were rated “complex” within the “complex” and “non-compliant” dossiers, which comprised almost all dossiers, is shown in Figure 12. In approximately 70% of the dossiers four to six endpoints were assigned to “complex”. For 125 dossiers (7%) only one or two endpoint had the allocation “complex” while all other endpoints were in compliance with REACH requirements according to the screening.

Figure 12: Dossier conclusion categories “complex” and “non-compliant” - Frequency of “complex” endpoints in dossiers assigned as “complex” or “non-compliant” (total number: 1813)

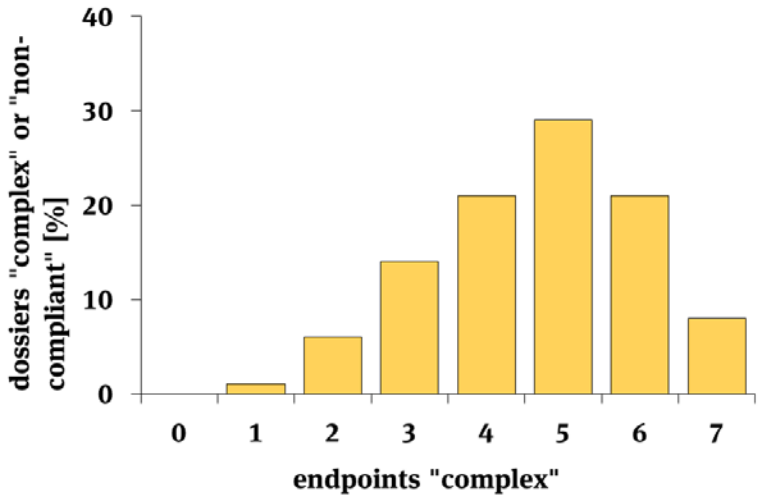
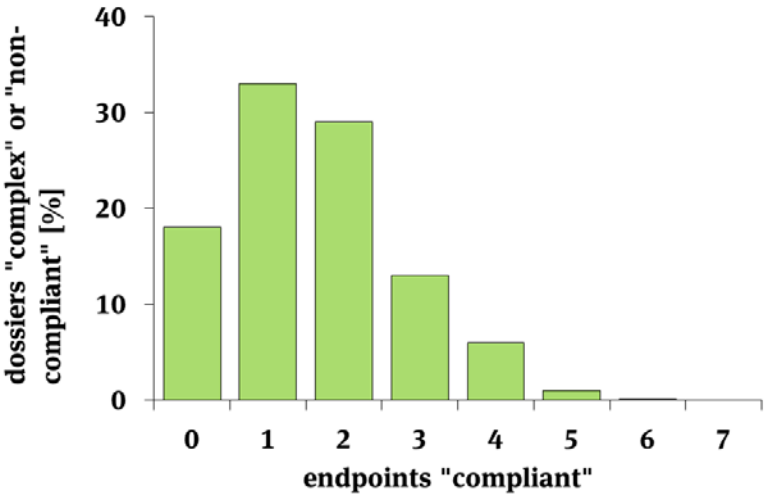


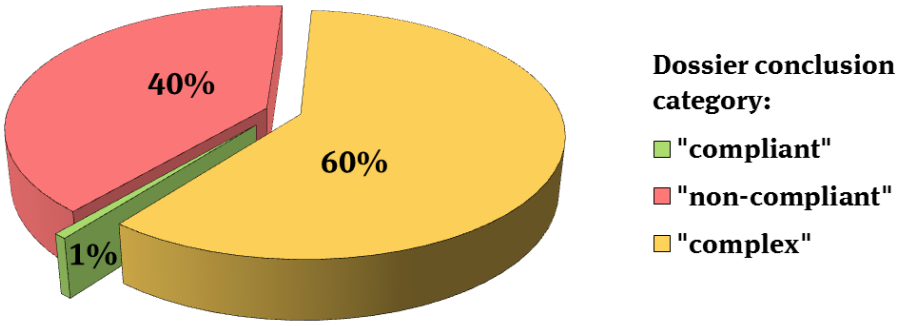
Figure 13 illustrates how many endpoints were rated “compliant” within the “complex” and “non-compliant” dossiers. The distribution shows a converse trend in comparison to the “complex” endpoints (Figure 12). In approximately 60% of the dossiers one to two endpoints were in compliance with REACH requirements according to the screening, while the remaining endpoints were allocated to “non-compliant”, “complex” or “TP”. 18% of all dossiers had no “compliant” endpoint, while more than three “compliant” endpoints were noted in approximately 7% of the dossiers.

Figure 13: Dossier conclusion categories “complex” and “non-compliant” - Frequency of “compliant” endpoints in dossiers assigned as “complex” and “non-compliant” (total number: 1813)



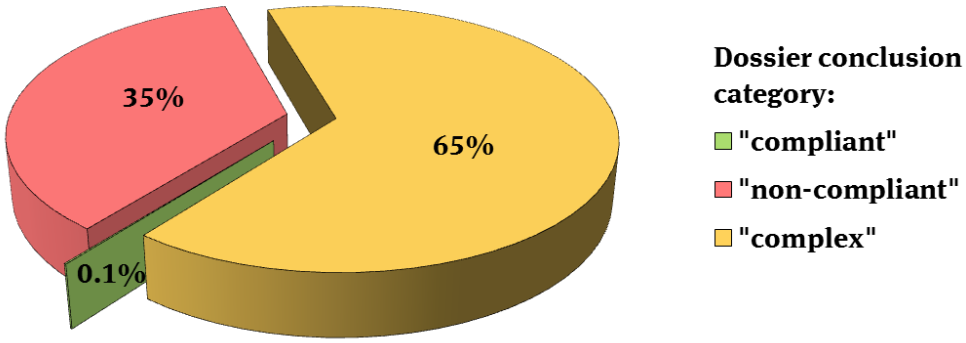
However, the results on a dossier level differ depending on whether either only HH or ENV endpoints were considered. With respect to the HH endpoints (Figure 14), the number of assignments to the dossier category “compliant” increased to 12 dossiers (1%) whereas the allocation to the “non-compliant” category decreased to 40%. Accordingly, the percentage of “complex” dossiers was higher with 60%.

Figure 14: Dossier conclusion categories for HH endpoints only - Distribution as percentage of completely checked dossiers (total number: 1814)



Considering only ENV endpoints (Figure 15), in accordance with the overall result one dossier (0.1%) was regarded as being “compliant”. The percentage of “non-compliant” dossiers was 5% lower in comparison to HH endpoints and 23% compared to the overall results. Accordingly, the number of “complex” dossier conclusions increased to 65%.

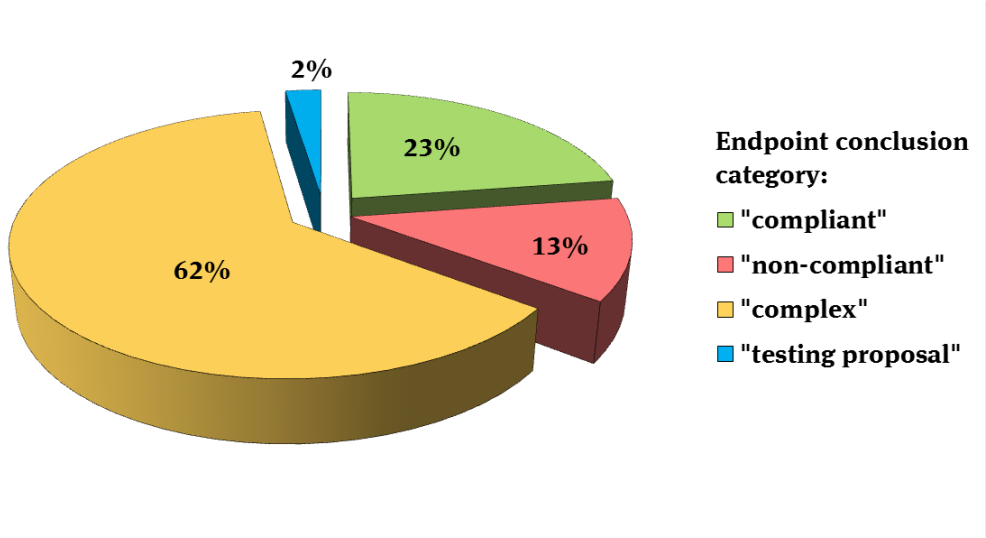
Figure 15: Dossier conclusion categories for ENV endpoints only - Distribution as percentage of completely checked dossiers (total number: 1814)



Endpoint conclusions

According to the screening scheme, already one “non-compliant” endpoint generated a “non-compliant” dossier. Therefore, the overall distribution of the endpoint conclusion categories “compliant”, “non-compliant“ and “complex” (Figure 16) was different from those of the dossier conclusion categories (Figure 10). Additionally, the inclusion of “TP” as an endpoint conclusion contributed to this difference. The most frequent endpoint conclusion category was “complex” (62%), followed by “compliant” and “non-compliant” conclusions with 23% and 13%, respectively. Testing proposals were used in 2% of all endpoints.

Figure 16: Endpoint conclusion categories - Distribution as percentage of completely checked HH and ENV endpoints (total number: 14512)



The actual distribution of endpoint conclusion categories differs considerably among the endpoints (Table 12 and Figure 17). The most frequent case assigned to individual endpoints was the category "complex" (43-82% of all dossiers depending on the endpoint). For developmental/reproductive toxicity, bioaccumulation and ecotoxicity the number of "complex" endpoint conclusions was particularly high (about 73 to 82% of all dossiers) whereas the remaining endpoints were in the range of 43 to 66%.

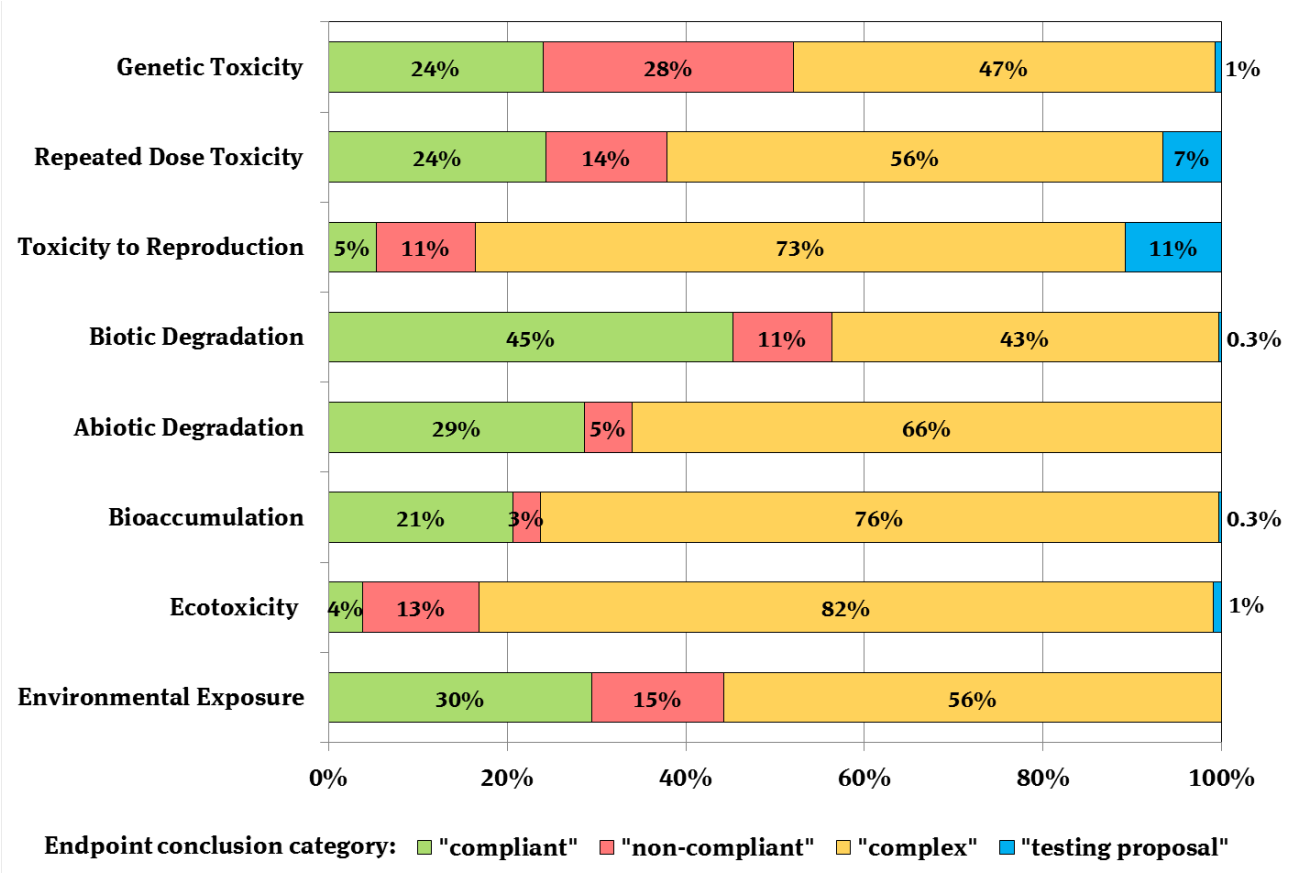
The endpoint category "non-compliant" was usually in the range of 3 to 15% of total dossiers per endpoint, but was strikingly higher for the endpoint genetic toxicity with 28%. Furthermore, dossiers that contained "compliant" endpoints were most often in the range between 20 to 30%. One exception was the endpoint biotic degradation which showed the highest number of "compliant" cases with 45%. In contrast, for the endpoints ecotoxicity and developmental/reproductive toxicity the conclusion "compliant" was drawn in only 4 and 5% of the cases, respectively.

During the screening, testing proposals were rarely found within the ecotoxicological part of dossiers. They were more frequently observed for human health endpoints. Repeated dose toxicity and developmental/reproductive toxicity contained the highest number of testing proposals (120 and 196, respectively).

Table 12: Endpoint conclusion categories - Distribution as number per each endpoint

Endpoint conclusion	Muta	RDT	TRep	BioDeg	AbioDeg	Bioaccu	Ecotox	Expo
"Compliant"	435	442	95	820	518	373	69	536
"Non-compliant"	509	246	202	202	98	56	235	266
"Complex"	858	1006	1321	786	1198	1380	1493	1012
"Testing proposal"	12	120	196	6	0	5	17	0
Total	1814	1814	1814	1814	1814	1814	1814	1814

Figure 17: Endpoint conclusion categories - Distribution as percentage per each endpoint in relation to total dossiers (total number: 1814)



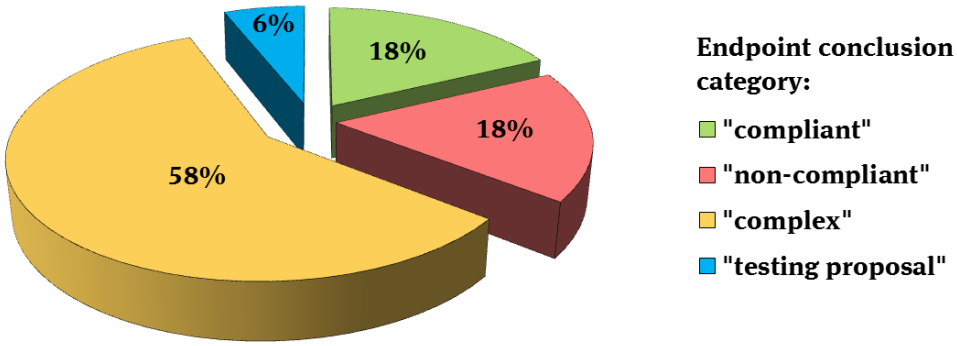
Given that the REACH standard information requirements are highly endpoint-specific resulting in differences in the nature and structure of the respective decision trees used in this project, the observed differences among endpoints are explained separately for each endpoint in the chapters below.

3.2 Human Health

3.2.1 Overall Results for Human Health Endpoints

Figure 18 illustrates the distribution if the conclusions of all HH endpoints are summated. For most cases no conclusion could be made – this includes the endpoint conclusion categories “complex” and “TP”, while approximately 1/3 of all cases could be allocated to “compliant” or “non-compliant”, which both contributed equally.

Figure 18: HH endpoint conclusion categories - Distribution as percentage of completely checked HH endpoints (total number: 5442)

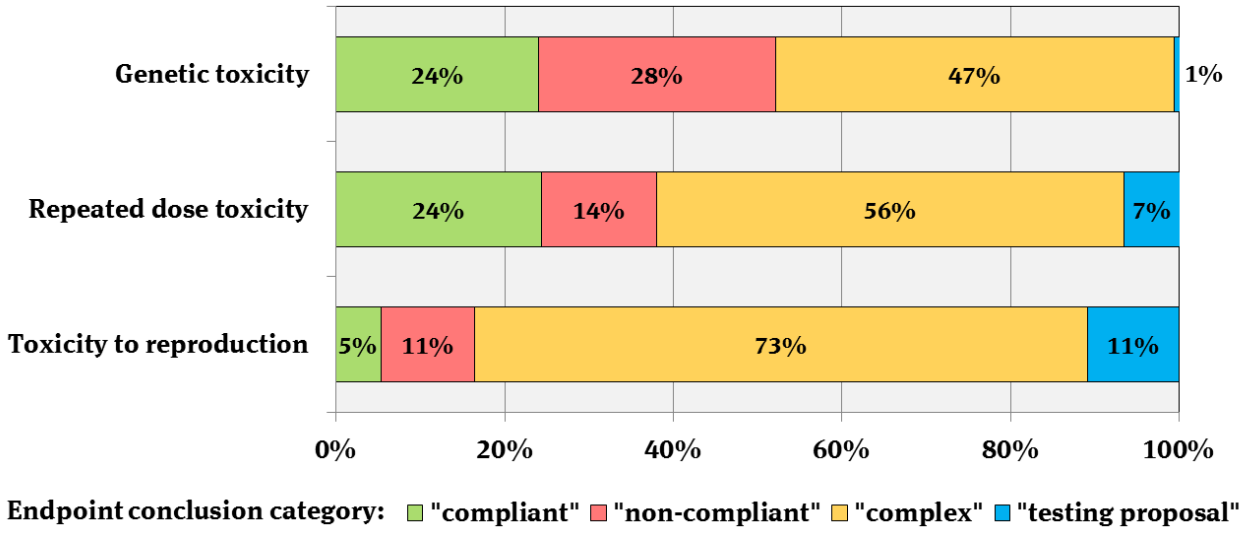


Results varied considerably, when the HH endpoints were regarded individually (Figure 19). Depending on which HH endpoint was considered, the rate of dossiers classified as

- “complex“ ranged from 47 to 73% of all dossiers,
- “non-compliant” ranged from 11 to 28%,
- “TP” ranged from 1 to 11%,
- “compliant” ranged from 5 to 24%.

Genetic toxicity (Muta) was the only endpoint for which a conclusion could be made in most of the dossiers (52%). However, it is also the endpoint with the highest percentage for the category “non-compliant” (28%) among all HH and ENV endpoints. For repeated dose toxicity (RDT), in 1/3 of all cases a conclusion could be made with “compliant” cases (24%) being more frequently observed than “non-compliant” cases (14%). Toxicity to Reproduction (TRep) contributed most of the cases without conclusion because this endpoint had the highest percentages for the categories “complex” and “TP” (73% and 11%, respectively) among the HH endpoints. Especially the number of “compliant” cases is with 5% very low in comparison to the other endpoints.

Figure 19: HH endpoint conclusion categories - Distribution as percentage per each HH endpoint in relation to total dossiers (total number: 1814)

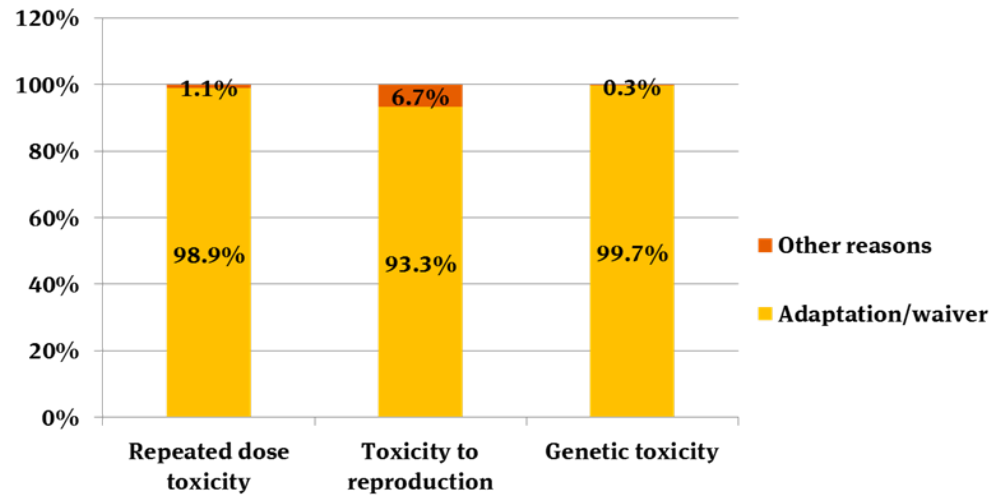


3.2.1.1 Human Health "Complex" Endpoints

The above results show that for 47 to 73% of the dossiers ("complex" cases) a conclusion on the "compliance" with the REACH information requirements was not achieved regarding HH endpoints. Nevertheless, data in dossiers sometimes partly fulfilled the information requirements regarding an endpoint because more than one study type was usually required. These cases are explained in the chapters below in relation to the single endpoints.

The overall cause in almost all (93 to 100% depending on the endpoint) of the "complex" endpoint conclusions was that for the missing information a waiving justification or adaptation of the standard information was presented (Figure 20).

Figure 20: Causes for the endpoint conclusion category "complex" for all HH endpoints



The distribution of the waiving/adaptation categories which have been documented within the screening is presented Figure 21 for each of the HH endpoints.

Taking all three endpoints together and based on the flag set by the registrant in the respective IUCLID endpoint study records (ESRs), grouping/read-across approaches (RA) accounted for 2449 cases or 48% of the total number of adaptations/waivers (5457 cases). Furthermore, 21% of the ad-

aptations/waivers referred to a rule set out in Annex XI No. 1 of the REACH Regulation("scientifically" in Figure 21). 17% were related to weight of evidence (WoE) approaches.

For the endpoint TRep the percentage of RA cases was considerable lower than the overall rate (36%), whereas "scientifically" was slightly higher (31%). For Muta the percentage of RA was 58%, followed by WoE (25%) and "scientifically" (8%). Regarding RDT, RA is close to the overall value (50%) and the other two important adaptation categories, WoE and "scientifically", appeared to be of equal relevance (both around 16%).

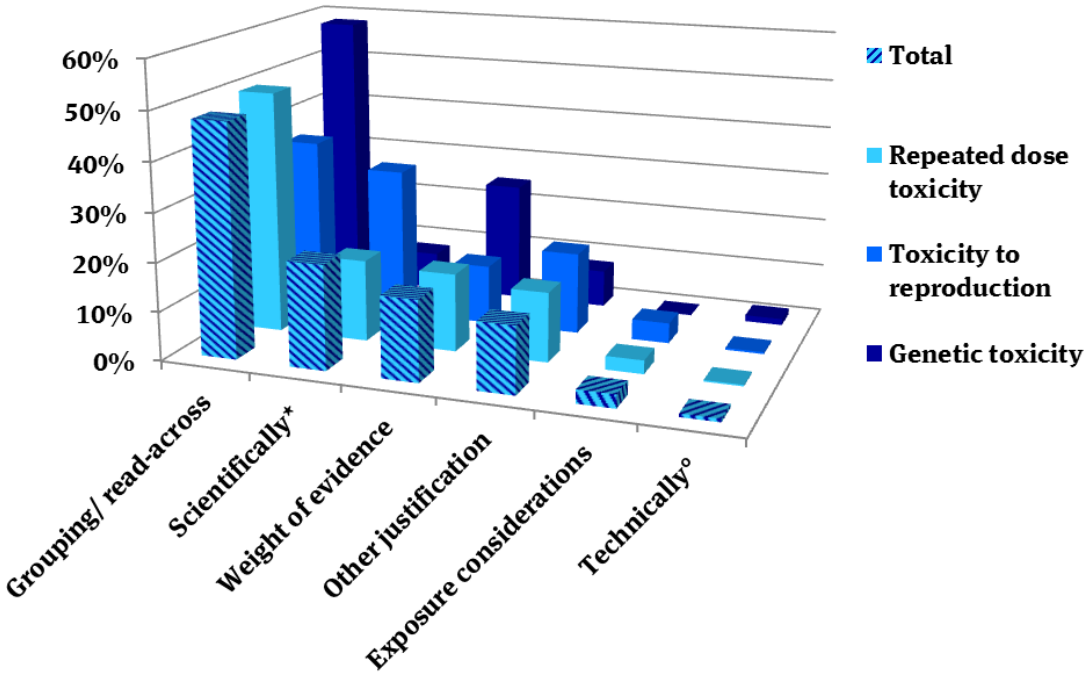
According to REACH Annex XI No. 1.2 and 1.5, WoE and RA belong to the adaptation option "testing does not appear scientifically necessary" which is flagged as "scientifically" in IUCLID. Moreover, if a WoE was indicated, RA might also have been applied because a WoE consists of one or several endpoint study records (ESR) with diverse experimental data. The adaptation category "scientifically" potentially also includes other surrogate data according to Annex XI No. 1 such as *in vitro* data or (Q)SAR. In conclusion, a clear separation between the adaptation categories RA, WoE and "scientifically" is not warranted. As a consequence, the aggregation of these three categories seems suitable. The sum of these categories accounts for 4523 or 86% of all adaptations/waivers (91% for Muta, 79% for TRep and 83% for RDT). As RA and WoE constitute the major part, it can be assumed, that mainly surrogate data, most often based on a grouping/read-across approaches, were presented for the HH endpoints if the standard tests were not carried out and waiving was flagged.

The waiving category "other justification" accounted for 14% of all waiving/adaptation cases (Figure 21). This category includes e.g. waiving of the standard information according to Annexes VII to X, Column 2. This category appears to be of minor importance for the HH endpoints. However, the waiving options set out in Column 2 have partly been implemented into the decision trees and were therefore considered to the extent that yes/no type answer could be retrieved within the screening procedure. Further details on this are included in the respective endpoint chapters.

Standard testing was rarely waived because a test was declared technically not feasible ("technically" in Figure 21) according to REACH Regulation Annex XI, 2 or because of "exposure considerations" according to Annex XI, 3 (in total 187 cases or 3.5%).

A frequent observation was that registrants selected multiple adaptation/waiving options for one endpoint entry. This might be due to the circumstance that two or more study types are required for Muta and different reasons were responsible that experimental data were not available. However, it was also observed that several options were selected for one study type.

Figure 21: Frequency of adaptation/waiving categories among the total number of adaptations/waivers as selected by the registrants in IUCLID for each endpoint and for all HH endpoints together (total)



* "scientifically" refers to the adaptation category "scientifically not justified" in IUCLID
° "technically" refers to the waiving category "technically not feasible" in IUCLID

3.2.1.2 Human Health "Non-compliant" Endpoints

For 11 to 28% of the dossiers depending on the HH endpoint the conclusion based on the screening resulted in "non-compliant" because adequate data according to the evaluation scheme were not present. Moreover, a waiving justification or surrogate data were not provided.

One of the predominant reasons for the endpoint conclusion category "non-compliant" was the fact that tests have not been carried out with the registered substance. Between 26 to 33% of the "non-compliant" assignments were related to this finding (Table 13). This accounted for "non-compliant" cases for which at least one of the required study was not accepted because the test material used did not correspond to the registered substance or the information was inconsistent. The remaining data in the same ESR could appear sufficient with respect to the standard testing requirements. As a result, the category "non-compliant" was assigned to the endpoint. This applied to less than 10% of total dossiers, but to about one third of the "non-compliant" cases. It was therefore a major cause for the conclusion "non-compliant".

Table 13: Tests not carried out with registered substance: Number of "non-compliant" (NC) endpoints for which one of the required studies was not accepted because the test material did not correspond to the registered substance or information was inconsistent (NC + "Ident")[a]

Endpoint	NC	NC + "Ident"[b]	NC + "Ident"/NC [%]	NC + "Ident"/total dossiers [%]
TRep	202	65	32.2	3.4
RDT	246	63	25.6	3.3
Muta	509	170	33.4	8.8

[a] a) The substance used in a particular ESR was labelled with "No" in the field "testing material according to registered substance" or b) this field was not filled out and a wrong CAS/EC no./name was stated or c) "Yes" was entered and another CAS/EC no./name was given.
[b] Wrong or inconsistent test material identity was indicated at least once per endpoint by the memo "Ident" in connection to questions concerning toxicological endpoints answered with "no".

Another important reason for the endpoint conclusion category "non-compliant" within the screening was related to the fact that test data were only accepted if the registrant has stated that the studies were performed according or similar to the appropriate OECD guideline or comparable guidelines. Otherwise, the endpoint was assigned "non-compliant". For HH endpoints this applied to 19 to 27% of the "non-compliant" dossiers, depending on the endpoint evaluated (Table 14). To this end, cases were counted if at least for one question answered with "no" in the decision tree the memo "no guide" has been added during screening. This applied to less than about 5% of total dossiers, but to about one quarter of the "non-compliant" endpoint conclusions for all HH endpoints. Therefore, it is a second major cause for the endpoint conclusion category "non-compliant".

Table 14: Tests not carried out according to an appropriate guideline: Number of "non-compliant" (NC) endpoints for which at least one required study was not accepted because it was not conducted according to the respective OECD guideline or a comparable guideline (NC + memo "no guide").

endpoint	NC	NC + "no guide"	NC + "no guide"/NC [%]	NC + "no guide"/total dossiers [%]
TRep	202	55	27.2	3.0
RDT	246	56	22.8	3.1
Muta	509	94	18.5	5.2

3.2.2 Genetic Toxicity

The standard information required for Muta for high tonnage chemicals according to Annexes VII to X, Column 1, of the REACH Regulation are in vitro tests regarding gene mutation in bacteria (GMbact) and chromosome aberration in mammalian cells (Cytvitro). Additionally, gene mutation in mammalian cells (GMvitro) might be addressed if both studies had a negative result. Provided negative results in all three tests no further testing is required. Any positive in vitro test determines the need for in

vivo testing in soma cells (GMvivo, Cytvivo). Column 1 standard testing requirements are then adapted. Germ cell mutagenicity (Germvivo) might have to be tested if one of the in vivo tests was positive.

For the endpoint Muta 47% of all cases were assigned to the dossier conclusion category ”complex” and 28% to ”non-compliant” (Figure 19). For 24% of the cases the endpoint was allocated to “compliant”, while required tests were proposed through the declaration of a testing proposal (TP) in 1% of all cases.

With respect to the endpoint conclusion “compliant”, in slightly more than 50% of all dossiers information requirements were met by solely applying in vitro testing (Table 15, case 7). This comprised three study types, i.e. testing on gene mutation in bacteria and mammalian cells as well as chromosome aberration in mammalian cells. In 41.2% of all dossiers, at least one in vivo test had been performed (Table 15, cases 2 to 6). The most frequent in vivo study was testing for chromosome aberration (Table 15, case 3, 5 and 6), while gene mutation tests have rarely been performed in vivo (Table 15, case 4 and 6). Both endpoints tested in vivo were recorded in 6.4% of all dossiers, possibly as a follow-up because in vitro tests were positive or because toxicity studies had been performed before the applied in vitro tests were introduced. A positive germ cell test was recorded in only two dossiers (Table 15, case 2). Both dossiers were also checked for and actually had a valid GMbact which is formally still required. In 5.5% of all cases the conclusion was “compliant” due to an appropriate harmonised classification according to CLP (and the availability of a valid GMbact). The actual number of substances with a harmonised classification for Muta is higher (107 cases). Due to the formal requirement, dossiers without a study or an adaptation/waiver for GMbact were allocated to “non-compliant” or dossiers with an adaptation/waiving for this test to “complex”, though this information is not necessary for an adequate risk management when there is harmonised classification.

Table 15: Muta: Number and percentage of reasons for the endpoint conclusion “compliant” derived from the respective courses in the decision tree

Case	Decision tree course (question no.)	Number (Percentage [%])
1	1. - 2.B [a]	24 (5.5)
2	1. - 2. - … - 2.B [b]	2 (0.5)
3	1. - … - 3. - … - 3.C - … - 3.C-4 [c]	36 (8.3)
4	1. - … - 3. - … - 3.C - … - 3.D a) - 3.E [d]	1 (0.2)
5	1. - … - 3. - … - 3.C - … - 3.D b) - 3.E [e]	112 (25.8)
6	1. - 3. - … - 2.B [f]	28 (6.4)
7	1. - 4. - … - 4.A [g]	232 (53.3)
	Total	**435 (100)**

[a] Substance has a harmonised classification according to the CLP Regulation as carcinogen or mutagen and GMbact is available.
[b] A positive germ cell test and GMbact are available.
[c] Cytvitro was positive, while the result of Cytvivo is negative as well as the result of GMbact.
[d] GMvivo, GMbact and Cytvitro are available and have negative results.
[e] Cytvivo, GMbact and GMvitro are available and have negative results.
[f] GMvivo and Cytvivo are available and have negative results.
[g] GMvitro, GMbact and Cytvitro are available and have negative results.

As for most of the registered substances in vitro testing is sufficient to assess their genotoxic potency, new experimental studies performed in vivo were only proposed in 12 dossiers. In ten cases, regis-

trants proposed the performance of Cytvivo (5) or GMvivo (5). Both tests were suggested in one dossier and one registrant intended to conduct a non-standard test.

With 28% a rather high number of dossiers (in comparison to all other endpoints) was "non-compliant" for Muta. In all cases, missing standard information was not or not adequately substituted by an adaptation or waiver for at least one required study type (Muta-NC1 to 4 in Table 16).

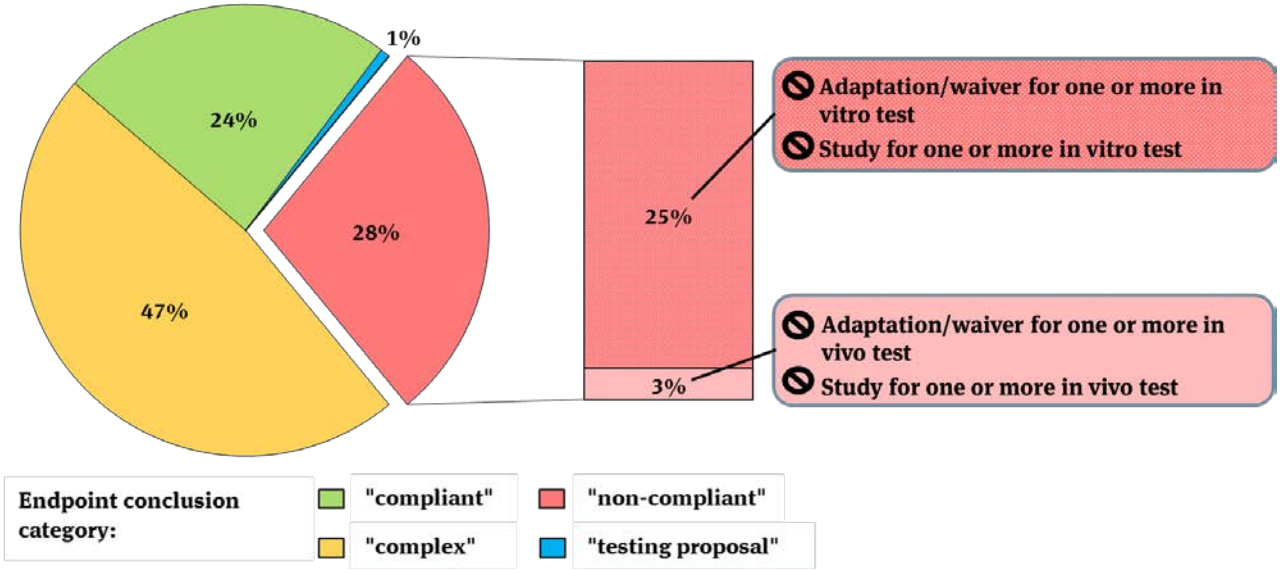
Table 16: Muta: Number and percentage of default reasons for the endpoint conclusion "non-compliant"

Reason	"Non-compliant"	"Non-compliant" Percentage [%]
Muta-NC1	30	5.9
Muta-NC2	477	93.7
Muta-NC3	2	0.4
Muta-NC4	0	0
Total	**509**	**100**

Muta-NC1: "Non-compliant", because a harmonised classification or in vivo test(s) are available, whereas an adaptation/waiving for GMbact is not available.
Muta-NC2: "Non-compliant", because an adaptation/waiving for one or two studies (in vitro and/or in vivo) is not available.
Muta-NC3: "Non-compliant", because an adaptation/waiving for GMvivo is not available.
Muta-NC4: "Non-compliant", because a negative Germvivo and at least one positive in vivo soma cell test are available, but a GMbact or an adaptation/waiving for GMbact is missing.

Figure 22 summarises how in vitro and in vivo studies contributed to the endpoint conclusion category "non-compliant". For approximately 90% of the cases an adequate study as well as an adaptation/ waiver were not available for at least one of the required in vitro tests. The lack of information on in vivo studies was less frequently observed in accordance with the fact that their requirement depends on the outcome of the in vitro testing.

Figure 22: Muta: Contribution of in vitro and in vivo studies to the endpoint conclusion category "non-compliant"



Due to the high amount of "non-compliant" cases for Muta, the conclusion "complex" was less frequent than for most of the other endpoints (Table 12 in Chapter 3.1). Nevertheless, almost 50% of the cases were allocated to "complex". The distribution of reasons for this endpoint conclusion is summarised in Table 17. Almost all cases (855, 99.6%) were assigned "complex" because an adaptation or waiver for one or two tests (in vitro or in vivo) was available (includes Muta-CX1, Muta-CX2, Muta-CX3). A minor reason (3 cases) was that the screening left open whether a reported negative germ cell test corresponded to the positive soma cell test (Muta-CX4 in Table 17).

Table 17: Muta: Number and percentage of default reasons for the endpoint conclusion "complex" (completely checked dossiers)

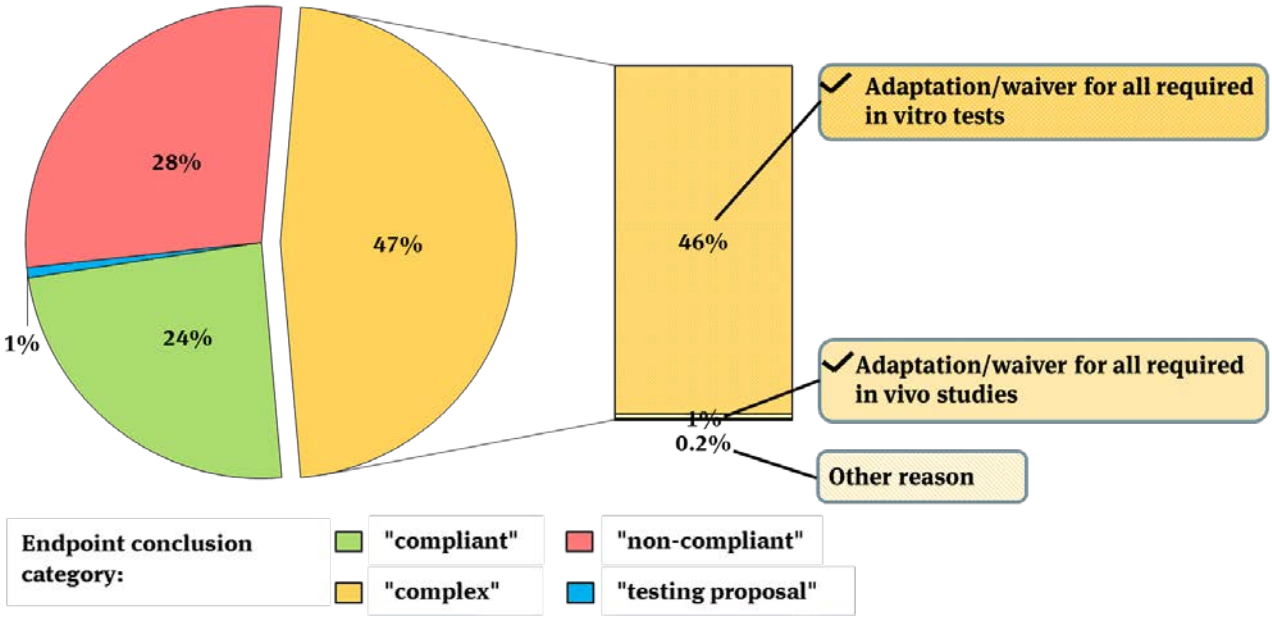
Reason	"Complex"	"Complex" Percentage [%]
Muta-CX1	68	7.9
Muta-CX2	787	91.7
Muta-CX3	0	0
Muta-CX4	3	0.4
Total	**858**	**100**

Muta-CX1: "Complex", because a harmonised classification or in vivo test(s) are available, but only an adaptation/waiving for GMbact.
Muta-CX2: "Complex", because an adaptation/waiving for one or two studies (in vitro and/or in vivo) is available.
Muta-CX3: "Complex", because an adaptation/waiving for GMvivo is available.
Muta-CX4: "Complex", because a negative Germvivo and at least one positive *in vivo* soma cell test are available as well as a GMbact or an adaptation/waiving for GMbact.

Figure 23 summarises how in vitro and in vivo studies contributed to the endpoint conclusion category "complex". An adaptation or waiver was required and provided predominantly for in vitro studies. Again, in vivo studies were required in the minority of dossiers and therefore their contribution is negligible.

With respect to the lower percentage of “non-compliant” endpoint conclusions (Figure 22), one can assume that for in vitro studies most of the registrants were aware of the requirement to substitute missing standard information by an adaptation or waiver. However, for most of the cases for which an in vivo study was required and no appropriate experimental data were available, an adaptation or waiver was not provided (11 “complex” endpoint conclusion vs. 47 “non-compliant” endpoint conclusions).

Figure 23: Muta: Contribution of in vitro and in vivo studies to the endpoint conclusion category “complex”

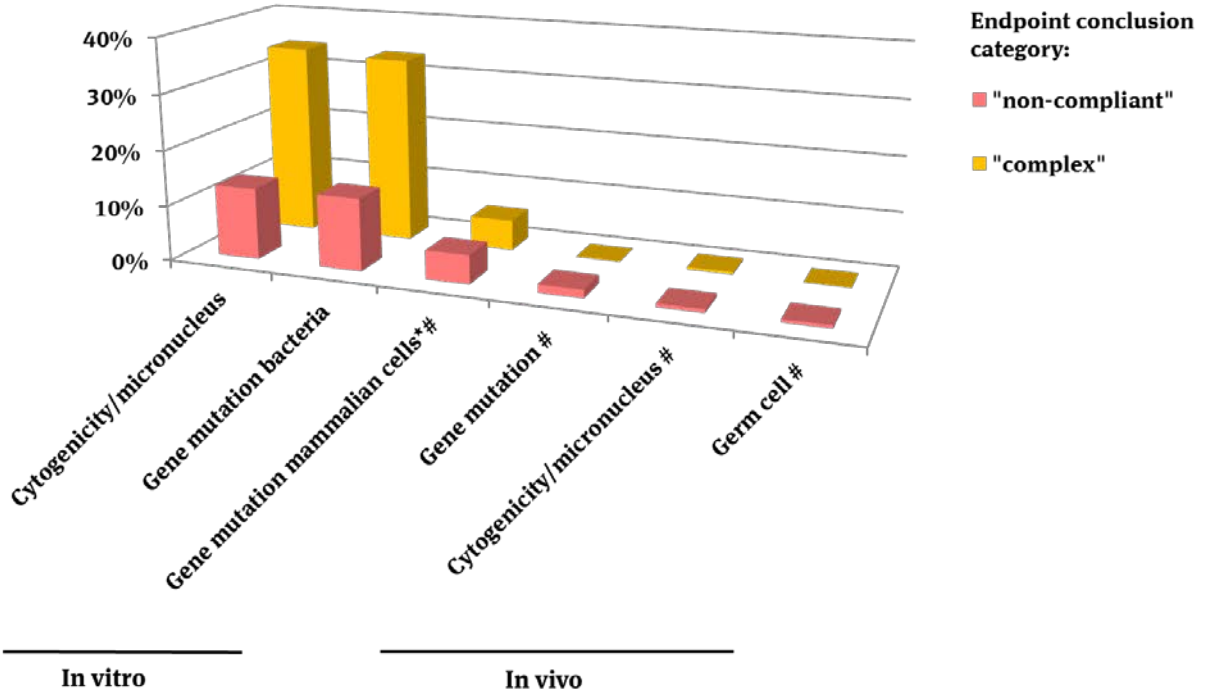


As mentioned above, in 855 of all “complex” endpoint conclusions an adaptation/waiving was applied. In the majority of these cases (756) a single adaptation/waiving category was applied by the registrant, while in 99 cases multiple adaptation/waiving categories were presented. This suggests a frequent use of one adaptation/waiving category for different study types in the same dossier. An adaptation of the standard information requirements was mainly based on the inclusion of existing (non-standard) data according to Annex XI, section 1of the REACH Regulation (90.7% of all adaptations/waivings). Grouping/read-across was the most frequent adaptation observed in all cases contributing with over 50% (Figure 21).

Figure 24 summarises to which extent the different study types for Muta were missing in “complex” and “non-compliant” endpoint conclusions or included inadequate data. The analysis was only done for each single study type and did not address the contribution of different combinations of study types. However, more than one test might be missing in a particular dossier. The result was that the in vitro tests on gene mutation in bacteria and on cytogenicity in mammalian cells contributed most with approximately 30% for “complex” and 10% for “non-compliant” endpoint conclusions each. Gene mutation in mammalian cells has to be addressed if the aforementioned in vitro tests were both negative. Since this study type was only in approximately 5% of the cases missing for each endpoint conclusion category, it could be concluded that gene mutation in mammalian cells was mostly provided if required. Third, the absence of the in vivo study types seemed to be of minor importance; the percentages were below 2% for all cases. However, the actual numbers for the in vivo study types and the gene mutation test in mammalian cells might be higher because results from the required in vitro studies were not yet available for a considerable percentage of the dossiers (“non-compliant” end-

point conclusions) and the adequacy of surrogate data was not evaluated in this project ("complex" endpoint conclusions).

Figure 24: Muta: Missing or inadequate study types in "complex" and "non-compliant" endpoint conclusions (given as percentage of total dossiers)



* Counted if the other in vitro tests were available.
# Counted if required based on the provided results.

3.2.3 Repeated Dose Toxicity

The standard information requirements for RDT for high tonnage chemicals according to REACH Regulation Annex IX are on toxicological effects occurring as a result of repeated dosing over a part of the lifespan, here subchronic testing (at least 90 days). Annex X, Column 1 indicates no further standard information requirements. In specific human exposure-triggered cases a long-term study such as chronic testing (at least one year) might be indicated (Annex X, Column 2). Specific adaptations of standard requirements are possible according to Annex IX. However, at least subacute test data have to be available.

For the endpoint RDT 56% of all dossiers were assigned to "complex" and 14% to "non-compliant" (Figure 19). For 24% of the dossiers the data presented in the dossiers were regarded as "compliant" and for 7% testing proposals (TP) were present.

Explaining the RDT decision tree in relation to the endpoint conclusions, it must be noted that dossiers were only assigned to "compliant", if a valid chronic test or subchronic test in rodents was available. However, if the study was performed in a non-rodent species, the endpoint was allocated to "complex" because the appropriateness of the species still has to be checked based on a case-by-case assessment that was not conducted during the screening. However, the main reason for the assignment "complex" was missing subchronic test data, while an adaptation/waiving was present. Partly, subacute test data were available. In total, three ways in the decision tree resulted in the assignment "complex". In contrast, the major reason for the endpoint conclusion category "non-compliant" was

that an adaptation/waiving was not available for the subchronic study. In these dossiers, a subacute test was partly available. Besides these two cases a third specific case, which is explained below, led to the endpoint conclusion category “non-compliant”.

When asking for the frequency of chronic in relation to subchronic data available in the dossiers (“compliant” cases), the result was that most frequently subchronic studies in rodents (80.5% of dossiers) were available. Only 19.5% of the data referred to chronic testing in rodents.

Regarding the 120 testing proposals found for RDT, there was one case noticeable because subacute testing was suggested. This was in contrast to the required subchronic testing. In all other cases a suchronic test was proposed.

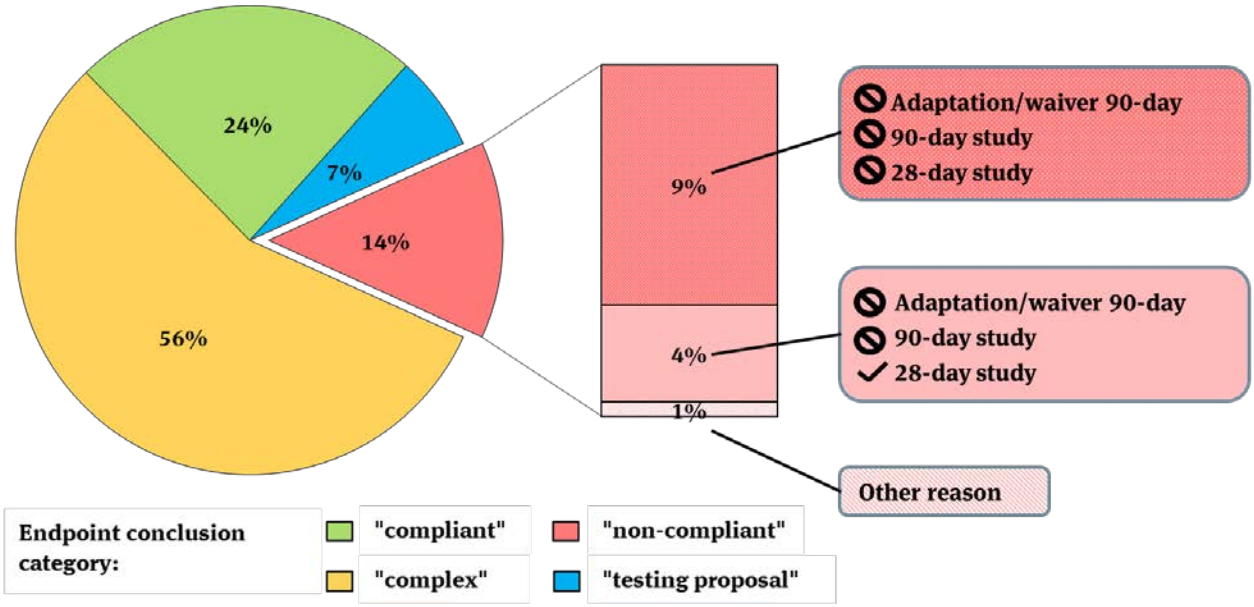
Further analysis of the cases concerning the endpoint conclusion category “non-compliant” indicated the following (Table 18 and Figure 25): The conclusion “non-compliant” applied to approximately 14% of all dossiers for the RDT (Figure 25). Thereof, 168 dossiers provided no acceptable information at all regarding this endpoint, neither an experimental study nor an adaptation/waiving. This applied to 68.3% of the “non-compliant” endpoint conclusions (RDT-NC3 in Table 18) and approximately 9% of all dossiers (Figure 25). 68 (or about a quarter) of the “non-compliant” endpoint conclusions, which accounted for 4% of the total dossiers, contained information on subacute testing (RDT-NC2 in Table 18 and Figure 25), while an adaptation/waiving for the required subchronic test was not available. Further, in a minority of 10 cases neither an appropriate subchronic nor an adequate subacute study were carried out. From these cases the only available waiver based on exposure considerations according to REACH Annex XI, No. 3 (RDT-NC1 in Table 18). Since this kind of waiving is not acceptable for subacute studies according to REACH Annex IX, 8.6.1., Column 1, these cases were assigned to “non-compliant”. However, the low number of cases reflects that this issue is of minor importance.

Table 18: RDT: Number and percentage of default reasons for the endpoint conclusion “non-compliant”

Reason	“Non-compliant”	“Non-compliant” Percentage [%]
RDT-NC1	10	4.1
RDT-NC2	68	27.6
RDT-NC3	168	68.3
Total	**246**	**100**

RDT-NC1: “Non-compliant”, because an adaptation/waiving according to Annex XI, no. 3 (exposure considerations) is the only available adaptation/waiving for the subacute test.
RDT-NC2: A subacute test is available. “Non-compliant”, because an adaptation/waiving for the subchronic test is not available.
RDT-NC3: “Non-compliant”, because an adaptation/waiving for the subacute and/or subchronic test is not available.

Figure 25: RDT: Overview of the distribution of endpoint conclusion categories and specification of "non-compliant" cases



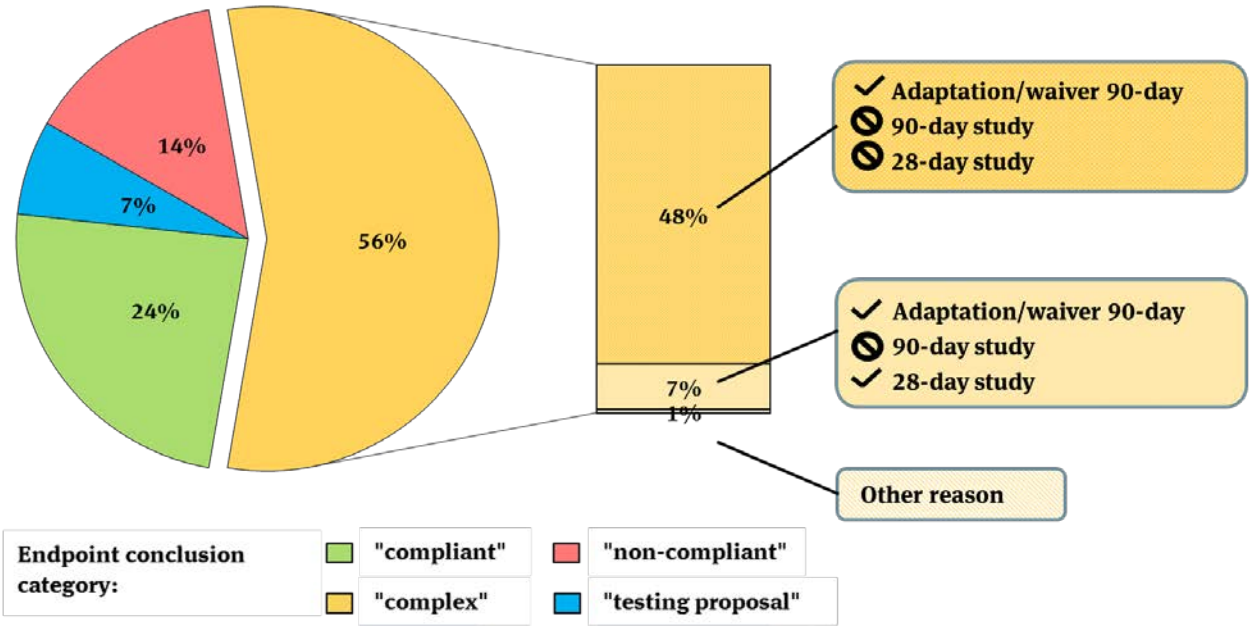
Further analysis of the cases concerning the endpoint conclusion category "complex" indicated the following (Table 19 and Figure 26): In 56% of all dossiers, information in terms of the standard requirements were not available or inadequate for RDT (Figure 26), but in almost all cases (98.9%, refer to RDT-CX2 and RDT-CX3 in Table 19) an adaptation/waiving was presented. At least subacute data were available for 133 dossiers (13.2% of total dossiers) whereas for 862 dossiers no appropriate experimental study was provided (85.7% of total dossiers). Additionally, 11 cases contained sufficient information in terms of RDT standard tests but were also assigned to be "complex" (RDT- CX1 in Table 19). This concerned those (sub)chronic studies that were carried out with a non-rodent species. However, according to REACH Annex IX, 8.6.2, Column 1 a rodent species has to be applied and further in-depth analysis of the appropriateness of a non-rodent model is required. As these cases represented only 1.1% of all "complex" endpoint conclusions, they were of minor importance.

Table 19: RDT: Number and percentage of default reasons for the endpoint conclusion "complex" (completely checked dossiers)

Reason	"Complex"	"Complex" Percentage [%]
RDT-CX1	11	1.1
RDT-CX2	133	13.2
RDT-CX3	862	85.7
Total	**1006**	**100**

RDT-CX1: "Complex", because a (sub)chronic test with non-rodents is available.
RDT-CX2: A subacute test is available. "Complex", because an adaptation/waiving for the subchronic test is available.
RDT-CX3: "Complex", because an adaptation/waiving is available for the subacute and subchronic (90-day study) tests.

Figure 26: RDT: Overview of the distribution of endpoint conclusion categories and specification of "complex" cases



Similar to the endpoints Muta and TRep, an adaptation of the standard information is mainly based on the inclusion of existing (non-standard) data according to Annex XI, section 1of the REACH Regulation (82.6% of all adaptations/waivers). Thereof, the grouping/read-across approach contributed, similar to the endpoint Muta, to almost half of the cases.

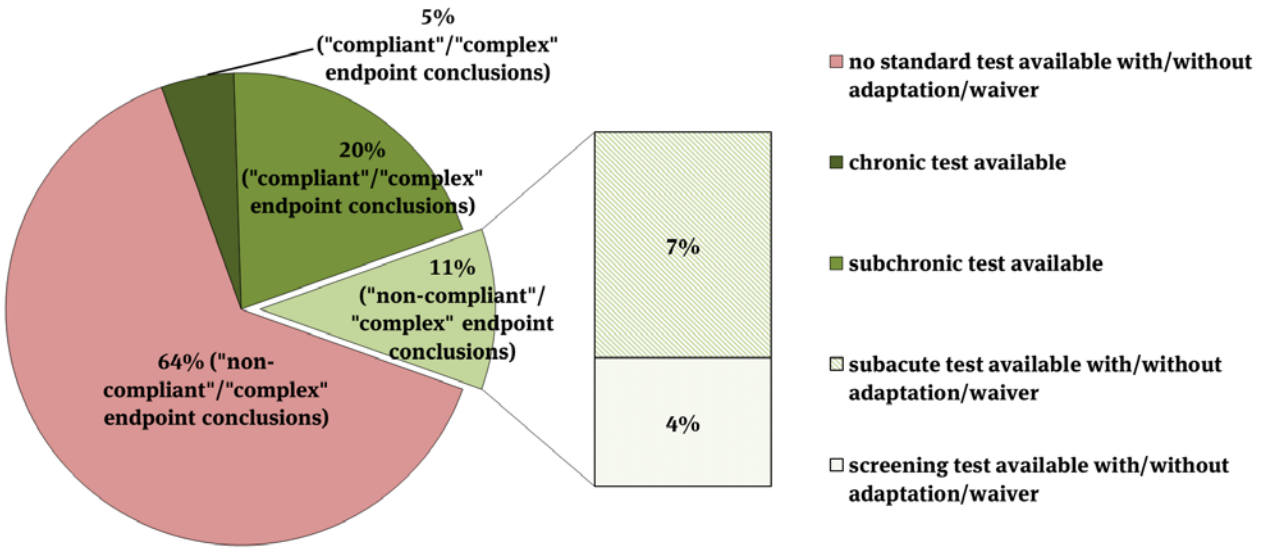
Most of the registrants adapted standard information or justified data waiving (56% of all dossiers). However, in 14% of all dossiers this was not addressed according to the screening approach applied here ("non-compliant"). This especially concerned dossiers in which a subacute test was provided, because the ratio of "complex" to "non-compliant" endpoint conclusion was lower with 2:1 (RDT-CX2: RDT-NC2) in comparison to those dossiers without a 28-day study (5:1, RDT-CX3: RDT-NC3) (Table 18 and Table 19).

In a different approach the availability of the different RDT study types in single dossiers was investigated (Figure 27). Dossiers with screening studies were also considered because they are regarded as an appropriate alternative for 28-day studies by ECHA (ECHA, 2014c). In total, for 36% of the dossiers data from screening, subacute, subchronic or chronic testing were available, independent of the presence or absence of adaptations/waivers. Most of these cases were "compliant" for RDT because adequate chronic or subchronic testing had been carried out (24% of the 25% referred to "compliant" endpoint conclusions). The remaining 1% related to studies in which testing was carried out in a non-rodent species and which were assigned "complex".

11% of total dossiers contained valid experimental data on subacute testing, while appropriate standard studies for the subchronic test were missing. For one third of these cases the lack of the subchronic test was not addressed (endpoint conclusion "non-compliant") and for two third an adapation/waiver was available (endpoint conclusion "complex"). This is shown in Table 18 (RDT-NC2) and Table 19 (RDT-CX2), respectively. Figure 27 indicates that in 7% of total dossiers subacute test data according to the respective OECD guideline were available whereas for 4% a screening study according to OECD TG 422 (1996) was provided. According to the screening scheme applied in this project, both study types are not regarded as sufficient to comply with the REACH requirements for

high tonnage chemicals. However, a case-by-case analysis could possibly reveal if they are adequate to fulfil the requirements.

Figure 27: RDT: Frequency of study types in single dossiers (given as percentage of total dossiers)



3.2.4 Reproductive Toxicity

The standard information requirements for TRep for high tonnage chemicals according to REACH Regulation Annex XII to X, Column 1, comprise developmental toxicity studies (DevTox) for two different species, commonly a rodent and a non-rodent species, and the two-generation toxicity study (ReproTox).

For the endpoint TRep 73% of all dossiers were allocated to the conclusion category “complex” and 11% to “non-compliant” (Figure 19). Only 5% of the cases were allocated to “compliant”, while required tests were proposed through the declaration of a testing proposal (TP) for a remarkable high percentage of 11% in comparison to all other endpoints.

There were two situations which supported the allocation to the conclusion “compliant”. The first was a harmonised classification of the substance as genotoxic carcinogen or germ cell mutagen which contributed 77 cases (81%). The implementation of reproductive and developmental toxicity studies is therefore not required. The second was that experimental studies for all standard information requirements were provided and an appropriate route of exposure with respect to the physico-chemical properties of the substance was chosen. This applied to a minority of 18 cases (19%). Therefore, in this screening study only 1% of the 1814 evaluated dossiers could provide appropriate testing to fulfil the standard information requirements for reproductive and developmental toxicity.

Besides the amount of the endpoint conclusions “complex” and “non-compliant”, the comparatively high percentage of testing proposals is another indicator for the lack of experimental standard studies regarding the endpoint TRep. Both study types, reproductive and developmental toxicity, similarly contributed to the proposal of new experimental studies (Table 20). For most cases only one study type was proposed. Nevertheless, 43.4% of the cases required testing for ReproTox as well as DevTox according to the registrants.

Table 20: TRep: Frequency of TPs for standard information requirements

Study type (corresponding OECD TG guideline)	Number	Percentage [%]
DevTox (414)	60 *	30.6
ReproTox (416)	51 §	26.0
DevTox (414) + ReproTox (416)	85	43.4
Total	**196**	**100**

* In two cases, DevTox studies with the first species were available and new testing was specifically proposed for the second species.

§ In four cases, the TP applied to other study types (OECD TG 422 [screening], 408 [90-day study] or 443 [extended one generation reproductive toxicity study]).

With respect to the endpoint conclusion "non-compliant", an adaptation or waiver was not available for at least one of the study types, ReproTox or DevTox, for all 202 cases (Table 21). The predominant situation was that experimental studies for both study types were missing (81.2%) which could be deduced from the fact that reason TRep-NC4 is solely connected with question 6 in the decision tree. For almost 20% of "non-compliant" endpoint conclusions acceptable data for one study type were available. For the latter, an adaptation/waiving for ReproTox was more often missing than for DevTox.

Additionally, the frequency of references to screening studies such as OECD TG 421 and 422 (1995b, 1996) was analysed in "non-compliant" endpoint conclusions. By counting the occurrence of the respective memo, 54 cases (26.7% of all "non-compliant" endpoint conclusions) could be identified for which this applied.

Table 21: TRep: Number and percentage of reasons for the endpoint conclusion "non-compliant" (completely checked dossiers)

Reason	"Non-compliant"	"Non-compliant" Percentage [%]
TRep-NC3	7	3.5
TRep-NC4	164	81.2
TRep-NC5	31	15.4
Total	**202**	**100**

TRep-NC3: "Non-compliant", because an adaptation/waiving for DevTox is not available.
TRep-NC4: "Non-compliant", because an adaptation/waiving for DevTox and/or ReproTox. A ReproTox study in non-rodents might be available, but is not accepted.
TRep-NC5: "Non-compliant", because an adaptation/waiving for ReproTox is not available.

Similar to the "non-compliant" endpoint conclusions, for most of the "complex" cases (74.1%; TRep-CX6) data on both study types, ReproTox and DevTox, were not available (Table 22). Second ranked the situation that DevTox studies in one or two species were available, while the ReproTox study was adapted/waived (TRep-CX4 and TRep-CX7 in Table 22). This is in accordance with the observation that data for ReproTox were also more frequently missing in cases with the conclusion "non-compliant" (Table 21). A third common issue with a percentage of 5% was that the DevTox study in a second species was not waived, while studies for DevTox in the first species and ReproTox were available (TRep-CX8 in Table 22). According to Annex IX, 8.7.2., Column 2 of the REACH Regulation the necessity to perform a DevTox in a second species is a standard requirement, but before testing all

available information including the outcome of the DevTox study in the first species has to be considered. This requires a more detailed analysis and was therefore allocated to "complex". An adaptation/ waiver for the DevTox study in the second species was only provided in 3 dossiers (TRep-CX3 in Table 22) and was therefore, in comparison to the 66 cases without adaptation/waiving, poorly addressed by the registrants. The remaining reasons (TRep-CX1, TRep-CX2 and TRep-CX5 in Table 22) only played a minor role.

Table 22: TRep: Number and percentage of reasons for endpoint conclusions (completely checked dossiers)

Reason	"Complex"	"Complex" Percentage [%]
TRep-CX1	7	0.5
TRep-CX2	15	1.1
TRep-CX3	3	0.2
TRep-CX4	204	15.4
TRep-CX5	8	0.6
TRep-CX6	979	74.1
TRep-CX7	39	3.0
TRep-CX8	66	5.0
Total	**1321**	**100**

TRep-CX1: "Complex", because the harmonised classification H360FD is available (Annex VI, CLP Regulation). Data was not further checked.
TRep-CX2: "Complex", because standard information requirements are full available, but no oral administration was applied in case of solids and liquids and no inhalative exposure in case of gases.
TRep-CX3: "Complex", because a ReproTox and a DevTox study (first species) are available and adaptation/waiving for a DevTox study in a second species is available (one adaptation/waiver).
TRep-CX4: "Complex", because in addition to a DevTox study (one species) an adaptation/waiving for ReproTox or a ReproTox study with a non-rodent is available (one adaptation/waiver or study).
TRep-CX5: "Complex", because a ReproTox study and one adaptation/waiving for DevTox is available (one adaptation/waiver).
TRep-CX6: "Complex", because standard requirements are not fulfilled and one adaptation/waiving for DevTox is available as well as an adaptation/waiving or a study with a non-rodent for ReproTox (two adaptations/waivers or one adaptation/waiving and one study).
TRep-CX7: "Complex", because in addition to two DevTox studies (two species) an adaptation/waiving for ReproTox or a ReproTox study with a non-rodent is available (one adaptation/waiver or study).
TRep-CX8: "Complex", because one study for DevTox (first species) and a study for ReproTox are available, whereas an adaptation/waiving for a DevTox test in a second species is not available.

Additionally, Table 23 gives an overview on the frequency of reasons in "complex" endpoint conclusions which were based on adaptation/waiving or on non-waiver. This clearly shows that with 93.3% the majority of the category "complex" resulted from an adaptation/waiving.

Table 23: TRep: Frequency of adaptation/waiving and non-waiver in complex dossiers with the endpoint conclusion "complex" for TRep

Adaptation/waiving / non-waiver	Reason category	Reason no.	Number	Percentage [%]
Adaptation/waiving	Adaptation/waiving	TRep-CX4 *, TRep-CX5, TRep-CX6 *, TRep-CX7 *,	1233	93.3

Adaptation/waiving / non-waiver	Reason category	Reason no.	Number	Percentage [%]
Non-waiver	Classification H360FD	TRep-CX1	7	0.5
	Route of exposure	TRep-CX2	15	1.1
	OECD TG 416 Non-rodent	TRep-CX4 *, TRep-CX6 *, TRep-CX7 *	0	0.0
	Adaptation/waiving for OECD TG 414, second species is not available	TRep-CX8	66	5.0
Total			**1321**	**100**

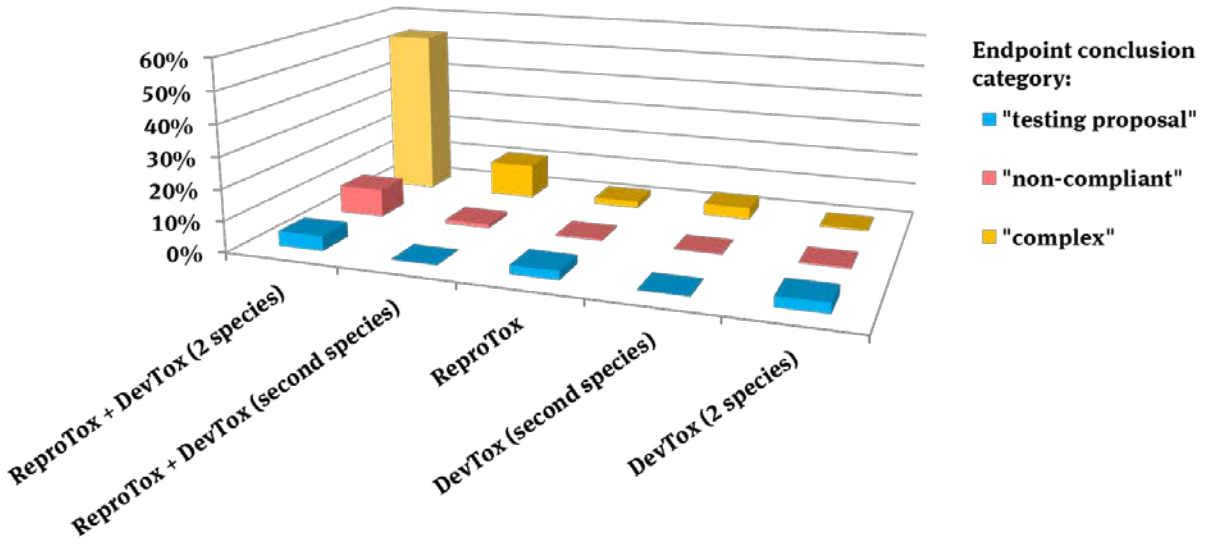
* Reasons include both, adaptation/waiving and non-waiver.

In the majority of these cases (732) a single adaptation/waiving category could be deduced, although, for 501 cases multiple adaptation/waiving categories were present. As already discussed in Chapter 3.2.1, grouping/read-across, “scientifically not justified” and “other justification” were the most frequent adaptations/waivers observed in all cases.

It was also analysed which study type was most often not provided or not adequate for TRep. Overall, in approximately 85% of all dossiers the ReproTox study was not available or data were not appropriate. DevTox was more frequently addressed because approximately 30% of all dossiers provided valid studies. However, for only 10% of all dossiers experimental data on testing in a second species were presented.

Figure 28 illustrates how the different combinations of study types contribute for each relevant endpoint conclusion category (“non-compliant”, “complex” and “TP”). The vast majority of dossiers neither presented an experimental study for ReproTox nor for DevTox. Second ranked the situation that testing for ReproTox and the DevTox study in the second species was not available. The absence of only one study type was less frequently observed.

Figure 28: TRep: Missing or inadequate study types in “complex”, “TP” and “non-compliant” endpoint conclusions (given as percentage of total dossiers)



Based on the observation described above that adaptation/waiving was poorly addressed for the DevTox study in the second species, the overall consideration of this test is of interest (Table 24). With respect to the performance of this study, only 4.4% of all dossiers provided acceptable experimental data. The test was even less considered regarding the application of adaptation/waiving approaches showing a percentage of 2.4%. These data show that a vast number of dossiers fail to consider this information requirement, which might be in part due to the actual formulation in Annex IX, 8.7.2., Column 2 that gives room for interpretation.

Table 24: TRep: Consideration of DevTox studies in a second species

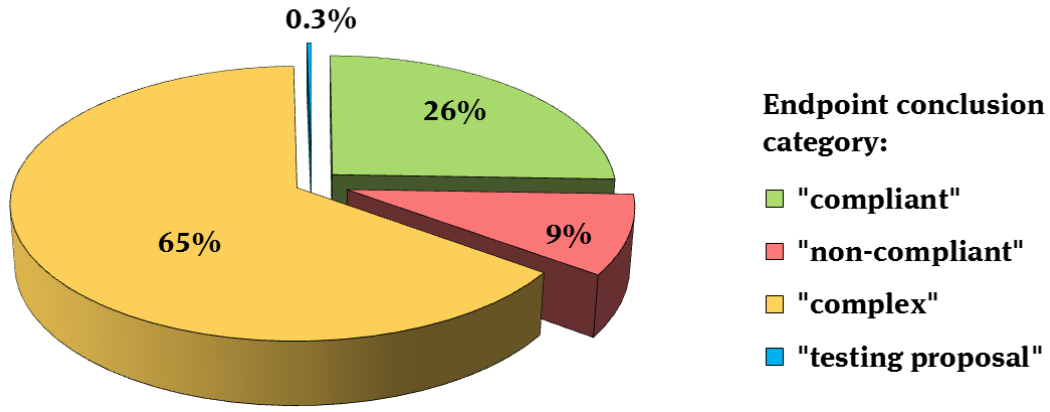
DevTox, 2-species has been...	Know SEC question no.	Other available studies	Number	Total (Percentage relating to completely checked dossiers [%])
performed	3.	414, 1.species + 416	33	**80 (4.4)**
	3.B	414, 1.species	47	
waived	4.A	414, 1.species + 416	3	**44 (2.4)**

3.3 Environment

3.3.1 Overall Results for Environmental Endpoints

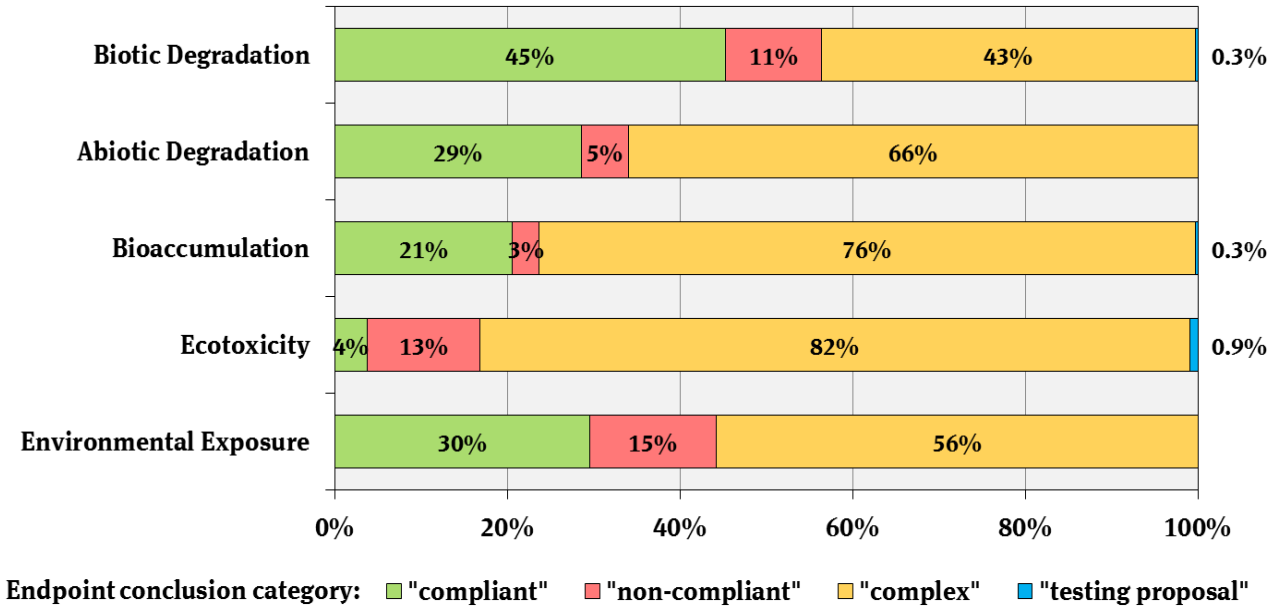
Figure 29 shows the overall distribution of all environmental endpoint conclusions (n = 9070) for 1814 dossiers subdivided into the four conclusion categories “compliant”, “non-compliant”, “complex” and “testing proposal”. 65% of the conclusions were “complex”, that means these cases remained undecided. About one quarter was assigned as “compliant” and about nine percent as “non-compliant”. “Testing proposals” were of minor importance for environmental endpoints with less than 1%.

Figure 29: ENV endpoint conclusions – Distribution as percentage of completely checked ENV endpoints (total number: 9070)



To gain a deeper insight the bar chart in Figure 30 illustrates the endpoint-specific distribution of the four conclusion categories. For four out of five endpoints more than half of the conclusions were assessed as “complex”, with Ecotox and Bioaccu displaying the highest percentages (82% and 76%, respectively). In contrast, BioDeg possessed the lowest number of “complex” endpoint conclusions (43%) and the highest amount of “compliant” cases (45%). About 20 – 30% of the conclusions for AbioDeg, Bioaccu and Expo were categorised as “compliant”, but only 4% for Ecotox. The percentages of “non-compliant” conclusions vary between approximately 3 – 15%, with Expo and Ecotox on the upper end of the scale and Bioaccu and AbioDeg at the lower one. Altogether, 28 testing proposals were recorded as an endpoint conclusion, which is less than 1% at all. Hereof, the majority of cases (17) were assigned to Ecotox.

Figure 30: ENV endpoint conclusion categories - Distribution as percentage per each ENV endpoint in relation to total dossiers (total number: 1814)



Seven adaptation/waiving categories were registered in KnowSEC by means of a single choice question for the endpoints BioDeg, AbioDeg and Bioaccu, and for Ecotox via a multiple choice question (Table 25). For the endpoint Expo these categories were irrelevant.

The highest number of waiving entries (1529) was noted for AbioDeg followed by Ecotox with 1424 entries, even though the latter was the result of a multiple choice question. In comparison to these endpoints, adaptation/waiving were observed considerably less frequent for Bioaccu and BioDeg (926 and 444 entries, respectively).

Justifications flagged as “scientifically” or “other” were the largest groups for AbioDeg, BioDeg and Bioaccu with a joint percentage between 61 – 85%. For Ecotox, by comparison, the percentage of these categories was 42%, and instead waiving justified by grouping/read-across (33%) was the dominating category. Grouping/read-across was of minor importance for the other endpoints (5% or below).

Some other endpoint-specific features are as follows: in approximately one fifth of the cases a (Q)SAR was applied as adaptation for the bioaccumulation test, exposure-related waiving was recorded in 13% with BioDeg and WoE approaches being used in 11% and 7% of the cases with Ecotox and Bioaccu, respectively.

The following sections describe the results for each endpoint in detail. This includes a compilation of the underlying reasons for the different conclusion categories as generated from KnowSEC, as well as text boxes where the reasons reported in full length. Beside this, information gathered from memos as reported in Annex 2 complement the findings.

Table 25: Adaptation/waiving categories for environmental endpoints itemised by frequency and percentage

Adaptation/waiving category	Degradation				Bioaccu		Ecotox	
	BioDeg		AbioDeg					
	n	[%]	n	[%]	n	[%]	n	[%]
Grouping/read-across	13	3	76	5	49	5	470	33
Weight of Evidence	15	3	26	2	67	7	150	11
(Q)SAR	4	1	32	2	192	21	128	9
Scientifically	109	25	685	45	231	25	200	14
Technically	17	4	98	6	40	4	24	2
Exposure	57	13	0	0	10	1	54	4
Other	229	52	612	40	337	36	398	28
Total	**444**	**100**	**1529**	**100**	**926**	**100**	**1424**	**100**

The question type for Biotic Degradation (BioDeg), Abiotic Degradation (AbioDeg) and Bioaccumulation (Bioaccu) was single choice and for Ecotoxicity (Ecotox) multiple choice.

3.3.2 Degradation

The results for the endpoint degradation are presented separately for BioDeg and AbioDeg.

3.3.2.1 Biotic Degradation

In 802 out of 1814 dossiers the endpoint conclusion for BioDeg was considered "compliant". Two main reasons, both accounting for approximately 50% of the cases, were responsible for this (Table 26). First, the respective substance was inorganic and therefore the test could be waived, and second, a standard method for the screening test on biodegradability was applied. Additionally, two other reasons for "compliant" were identified with a percentage below 1% each.

Three reasons can be differentiated with regard to the 202 dossiers for this endpoint which were considered "non-compliant". In nearly three quarters of these cases screening information on ready biodegradability was not available, and in about 20% of the cases information on adaptation/waiving for the missing simulation test was not presented. For both cases altogether 144 ESRs (Table 31) presented a test material identity which was not in accordance with the registered one and thereof, the vast majority was "non-compliant" with respect to the screening test.

For "complex" endpoint conclusions again two central reasons were responsible. On the one hand, the waiving justification for omitting the simulation test was not based on the Annex IX criterion (55.6%), and on the other hand, screening information on ready biodegradability was either determined with a non-standard method or a waiving justification was available (41.2%). Approximately 80% of the latter cases were "complex" due to waiving and the rest mainly due to non-standard tests. The additional information was compiled in memos during the screening (Annex 2). Furthermore, in 15 conclusions a method from the standard guideline OECD TG 301 (1992b) was chosen, which was not acceptable with regard to the physico-chemical properties of the substance (Table 11), primarily, because Henry's law constant exceeded the threshold value. These cases were initially considered "complex" to evaluate them in more detail. However, it is assumed that an in-depth analysis would classify these cases as "non-compliant".

Altogether, only a small number of dossiers (6) contained a "testing proposal" for a simulation test, either for surface water or for sediment/soil.

Table 26: Endpoint conclusions, their reasons, frequency and percentage for biotic degradation (BioDeg) of 1814 dossiers

Reason	"Compliant"		"Non-compliant"		"Complex"		"Testing proposal"	
	n	[%]	n	[%]	n	[%]	n	[%]
BioDeg-CT1	385	47.0						
BioDeg-CT2	424	51.7						
BioDeg-CT3	7	0.9						
BioDeg-CT4	4	0.5						
BioDeg-NC1			150	74.3				
BioDeg-NC2			46	22.8				
BioDeg-NC3			6	3.0				
BioDeg-CX1					324	41.2		
BioDeg-CX2					437	55.6		
BioDeg-CX3					25	3.2		
BioDeg-TP							6	100
Total	820	100	202	100	786	100	6	100

The reasons of the conclusions are categorised as "compliant" (CT), "non-compliant" (NC), "complex" (CX), and "testing proposal" (TP). Within a category they are differentiated according to the respective possibilities of the decision tree (see textbox below).

Endpoint conclusions and the underlying reasons for biotic degradation

BioDeg-CT1: "Compliant", because the substance is inorganic (Annex VII, Column 2, 9.2.1.1)

BioDeg-CT2: "Compliant", because a standard-method is available and no waiving is used

BioDeg-CT3: "Compliant", because waiving refers to Annex IX, Column 2, 9.2.1.2 (S_w < 1 mg/L)

BioDeg-CT4: "Compliant", because the degradation products are identified

BioDeg-NC1: "Non-compliant", because screening information on ready biodegradability is not available

BioDeg-NC2: "Non-compliant", because the waiving justifications for the simulation test are not available

BioDeg-NC3: "Non-compliant", because the degradation products are not identified

BioDeg-CX1: "Complex", because the screening test is conducted with a non-standard-method or a waiver is available

BioDeg-CX2: "Complex", because waiving with regard to a simulation test was not justified by reference to Annex IX, Column 2, 9.2.1.2 (S_w < 1 mg/L)

BioDeg-CX3: "Complex", because no standard simulation test is available

BioDeg-TP: A testing proposal is available.

3.3.2.2 Abiotic Degradation

Altogether, in 518 dossiers registration information for the endpoint AbioDeg was categorised as "compliant" (Table 27). The most frequent reason (85.1%) was waiving justified with reference to Annex VIII, i.e. the substance is considered either readily biodegradable or the water solubility is below 1 mg/L. Further, approx. 12.7% were assessed as "compliant", since the pre-test criteria had been fulfilled and no main test on degradation through hydrolysis had to be conducted.

The registration information assessed as "non-compliant" (98 dossiers) spread over three groups, all with regard to the hydrolysis test. In the majority of cases (68.4%), results from the main hydrolysis test were not available and no other method was applied. In addition, the results did not cover all relevant parameters (20.4%), and the degradation products were not determined (11.2%). The wrong test material identity and tests conducted not in accordance with any guideline are some of the grounds recorded by the means of the memos (Annex 2).

"Complex" cases are the largest endpoint conclusion category of AbioDeg. For about 90% of the endpoints a conclusion could not be derived, since an adaptation/waiving was used which was not related to the criteria described in Annex VIII. The evaluation of memos gives some deeper insight here: About one quarter of the ESR referred to adaptations based on the chemical structure, and more than 10% omitted the data because the substance was inorganic. In another approximately 10% of the endpoint conclusions the substance was considered as readily biodegradable in the ESR of BioDeg, but this evaluation was based on waiving, non-standard testing or on an inconsistent test material identity. Therefore, these waivers have to be checked in more detail. In 7.8% of the category "complex" the substance was inorganic or highly adsorptive, and no firm conclusion could be reached. Nevertheless, in about one third of these cases an OECD TG 111 test (2004c) was conducted.

Table 27: Endpoint conclusions, their reasons, frequency and percentage for abiotic degradation (AbioDeg) of 1814 dossiers

Reason	"Compliant"		"Non-compliant"		"Complex"	
	n	[%]	n	[%]	n	[%]
AbioDeg-CT1	441	85.1				
AbioDeg-CT2	66	12.7				
AbioDeg-CT3	11	2.1				
AbioDeg-NC1			20	20.4		
AbioDeg-NC2			11	11.2		
AbioDeg-NC3			67	68.4		
AbioDeg-CX1					93	7.8
AbioDeg-CX2					1088	90.8
AbioDeg-CX3					17	1.4
Total	518	100	98	100	1198	100

The reasons of the conclusions are categorised as "compliant" (CT), "non-compliant" (NC), and "complex" (CX). Within a category they are differentiated according to the respective possibilities of the decision tree (see textbox below).

Endpoint conclusions and the underlying reasons for abiotic degradation

AbioDeg-CT1: "Compliant", because waiving refers to Annex VIII, Column 2, 9.2.2.1 (substance is readily biodegradable or S_w ‹ 1mg/L)

AbioDeg-CT2: "Compliant", because the extrapolated half-lives from the hydrolysis pre-test are ‹ 1 day or › 1 year at all relevant pH-values

AbioDeg-CT3: "Compliant", because degradation products (› 10%) have been identified in standard hydrolysis main test

AbioDeg-NC1: "Non-compliant", because results from hydrolysis test do not cover the relevant pH values and temperatures

AbioDeg-NC2: "Non-compliant", because degradation products (› 10%) have not been identified in standard hydrolysis main test

AbioDeg-NC3: "Non-compliant", because results from standard hydrolysis main test are not available

AbioDeg-CX1: "Complex", because the substance is adsorptive (log K_{ow} › 4) or inorganic

AbioDeg-CX2: "Complex", because waiving does not refer to Annex VIII, Column 2, 9.2.2.1 (substance is readily biodegradable or S_w ‹ 1mg/L).

AbioDeg-CX3: "Complex", because a non-standard method was used for the hydrolysis test

3.3.3 Bioaccumulation

The results from the screening show that the great majority of the conclusions for Bioaccu were "complex" (1380). About one fifth of the cases (373) was assessed as "compliant", and 56 cases as "non-compliant" (Table 28).

The dominant explanation for "compliant" endpoint conclusions (93.8%) was waiving according to Annex IX, i.e. the log K_{ow} of the substance was equal to or below three. In 56 of these cases a (Q)SAR was applied to calculate the partition coefficient (Annex 2). The second reason, reliable information based on the experimental data from a study according to OECD TG 305 (2012a), occurred rarely.

In comparison, "non-compliant" endpoint conclusions show a more even distribution between the two reasons: first, ESRs which were classified due to a missing waiving justification possessed in most cases a test material identity inconsistent to the registered substance or the studies were conducted without any reference to a guideline.

Four different reasons could be distinguished among the category "complex". The most common reason was adaptation/waiving which was not in line with Annex IX (41.7%). "Complex" conclusions based either on the inorganic or ionisable and hydrolytically unstable nature of the substances each accounted for approximately one quarter of the cases. The smallest percentage being found for non-standard methods used to derive an experimental BCF. Most of these studies had been conducted according to OECD TG 305 C or E (1981a, 1981e) and therefore, have to be investigated in more detail.

Table 28: Endpoint conclusions, their reasons, frequency and percentage for bioaccumulation (Bioaccu) of 1814 dossiers

Reason	"Compliant"		"Non-compliant"		"Complex"		"Testing proposal"	
	n	[%]	n	[%]	n	[%]	n	[%]
Bioaccu-CT1	23	6.2						
Bioaccu-CT2	350	93.8						
Bioaccu-NC1			32	57.1				
Bioaccu-NC2			24	42.9				
Bioaccu-CX1					385	27.9		
Bioaccu-CX2					353	25.6		
Bioaccu-CX3					576	41.7		
Bioaccu-CX4					66	4.8		
Bioaccu-TP							5	100
Total	373	100	56	100	1380	100	5	100

The reasons of the conclusions are categorised as "compliant" (CT), "non-compliant" (NC), "complex" (CX), and "testing proposal" (TP). Within a category they are differentiated according to the respective possibilities of the decision tree (see textbox below).

Endpoint conclusions and the underlying reasons for bioaccumulation

Bioaccu-CT1: "Compliant", because the test is conducted according to OECD TG 305.

Bioaccu-CT2: "Compliant", because waiving refers to Annex IX, Column 2, 9.3.2 (log K_{ow} ≤ 3).

Bioaccu-NC1: "Non-compliant", because a waiving justification is not available.

Bioaccu-NC2: "Non-compliant", because the test is not performed according to OECD TG 305 or another accepted method

Bioaccu-CX1: "Complex", because the substance is inorganic

Bioaccu-CX2: "Complex", because the substance is ionisable at environmentally relevant pH values or hydrolytically unstable

Bioaccu-CX3: "Complex", because waiving does not refer to Annex IX, Column 2, 9.3.2 (log K_{ow} ≤ 3)

Bioaccu-CX4: "Complex", because a non-standard method is available

Bioaccu-TP: A testing proposal is available

3.3.4 Ecotoxicity

With regard to registration information for Ecotox 69 cases were assessed as "compliant", 235 as "non-compliant" and the major part (1493 "complex" endpoint conclusions) has to be examined in more detail (Table 29).

In the majority of cases the endpoint was considered "compliant" because both long-term studies were available (68.1%). Other "compliant" conclusions were related to cases in which one long-term study is sufficient to fulfil the information requirements, either the long-term fish or invertebrate study.

The only reason to classify this endpoint as "non-compliant" according to the decision tree is an absence of an adaption/waiving justification. In 185 of these cases memos were recorded since the test material identity was not the same as the identity of the registered substance and in 16 cases at least one of the key tests was not conducted in accordance with any guideline. However, other reasons could be responsible for the conclusions at the same time due to the complex structure of the decision tree.

Five different reasons for "complex" conclusions are pre-determined in the decision tree. In more than half of the cases adaptation/waiving was available (57.3%). The second most reason (23%) was a EC_{50}/LC_{50} ratio between 0.2 – 5. In almost 10% of the "complex" endpoint conclusions a non-standard method had been applied. Two further reasons represented a small percentage and referred to the availability of only one long-term study and an adaptation for long-term tests which was exclusively justified with a (Q)SAR.

The conclusion "testing proposal" was recorded in 17 cases; however, 31 additional testing proposals for long-term tests were available and were marked by memos (Annex 2). In these cases it was unclear if the endpoint conclusion category "testing proposal" would have been appropriate with respect to the structure of the decision tree and the endpoint conclusions were either considered "non-compliant" or "complex". The conclusion was "non-compliant", if the test material in one of the required tests was not in accordance with the identity of the registered substance; and the conclusion was considered "complex", for example, if adaptation/waiving for a relevant test was available. For these cases an in-depth analysis is required.

Table 29: Endpoint conclusions, their reasons, frequency and percentage for ecotoxicity (Ecotox) of 1814 dossiers

Reason	"Compliant"		"Non-compliant"		"Complex"		"Testing proposal"*	
	n	[%]	n	[%]	n	[%]	n	[%]
Ecotox-CT1	47	68.1						
Ecotox-CT2	4	5.8						
Ecotox-CT3	18	26.1						
Ecotox-NC1			235	100				
Ecotox-CX1					92	6.2		
Ecotox-CX2					142	9.5		
Ecotox-CX3					344	23.0		
Ecotox-CX4					855	57.3		
Ecotox-CX5					60	4.0		
Ecotox-TP							17	100
Total	69	100	235	100	1493	100	17	100

The reasons of the conclusions are categorised as "compliant" (CT), "non-compliant" (NC), "complex" (CX), and "testing proposal" (TP). Within a category they are differentiated according to the respective possibilities of the decision tree (see textbox below). *31 additional testing proposals for chronic studies were captured without a definite conclusion as testing proposal.

Supplementary information is provided by several memos (Annex 2): ten long-term studies for fish were conducted according to OECD TG 204 (1984a) and hence were not accepted. Studies according to OECD TG 212 and 215 (1998a, 2000), which have to be assessed in more detail, were documented

4 and 11 times, respectively. In 12 long-term studies, predominantly according to OECD TG 210 and 211 (2012b, 2013a), exposure duration was shorter than required. The same was observed in 37 short-term tests conducted mainly in accordance with OECD TG 203 and 202 (1992a, 2004b). An incorrect test material identity presented in the ESR for at least one of the long-term tests or short-term tests was recorded via memo. For all tests this was frequently observed (102 and 204 cases for long-term and short-term tests, respectively). Studies not referring to any guideline were numerous as well, i.e. 52 for long-term and 47 for short-term tests were recorded. However, the number of these cases could be larger, since memos have been combined for different ESRs in some cases.

Endpoint conclusions and the underlying reasons for ecotoxicity

Ecotox-CT1: "Compliant", because both long-term studies are available

Ecotox-CT2: "Compliant", because $EC_{50}/LC_{50} > 5$ and a long-term fish study is available

Ecotox-CT3: "Compliant", because $EC_{50}/LC_{50} < 0.2$ and a long-term invertebrate study is available

Ecotox-NC1: "Non-compliant", because a waiving justification is not available

Ecotox-CX1: "Complex", because only one long-term study is available

Ecotox-CX2: "Complex", because a non-standard method was submitted

Ecotox-CX3: "Complex", because the water solubility of the substance is larger than 1 mg/L and the ratio EC_{50}/LC_{50} was between 0.2 and 5

Ecotox-CX4: "Complex", because waiving is available

Ecotox-CX5: "Complex", because waiving for long-term study is exclusively justified by (Q)SAR

Ecotox-TP: A testing proposal is available

3.3.5 Exposure of the Environment

The endpoint Expo includes one reason for "compliant" and "non-compliant" conclusions each, and two for the category "complex" (Table 30). The endpoint conclusion was assessed as "compliant" in 536 dossiers, since the substance was neither classified according to the CLP Regulation nor was it a PBT/vPvB substance. In 266 dossiers no exposure assessment was available, although classifications with regard to Annex I, CLP Regulation were notified. Therefore, these endpoint conclusions were categorised as "non-compliant". More than 1000 dossiers were considered "complex" with respect to available environmental exposure scenarios and qualitative exposure assessments (90% and 10%, respectively).

Altogether, 138 harmonised classifications were recorded for environmental hazard categories of aquatic toxicity with the hazard statements H400, H410, H411 or H412, and in addition, 3 with the hazard statement H413. Another 517 dossiers contained other harmonised classifications. The number of self-classifications for these groups was 451, 30, and 998, respectively.

In 51 dossiers differences were observed between the harmonised classifications in the C&L Inventory and those inserted into IUCLID by the registrants (Annex 2). However, the endpoint conclusion was not influenced by these findings.

Three substances were classified as PBT/vPvB and another two "as if PBT/vPvB" by the registrants. For three out of five substances exposure scenarios and for the other two qualitative exposure assessments were conducted. In eight dossiers the information with respect to PBT properties was insufficient.

Table 30: Endpoint conclusions, their reasons, frequency and percentage for environmental exposure (Expo) of 1814 dossiers

Reason	"Compliant"		"Non-compliant"		"Complex"	
	n	[%]	n	[%]	n	[%]
Expo-CT1	536	100				
Expo-NC1			266	100		
Expo-CX1					911	90.0
Expo-CX2					101	10.0
Total	536	100	266	100	1012	100

The reasons of the conclusions are categorised as "compliant" (CT), "non-compliant" (NC), and "complex" (CX). Within a category they are differentiated according to the respective possibilities of the decision tree (see text-box below).

Endpoint conclusions and the underlying reasons for environmental exposure.

Expo-CT1: "Compliant", because the substance is not classified and is not PBT or vPvB

Expo-NC1: "Non-compliant", because no exposure assessment is available, although a classification according to Annex I, CLP Regulation is notified

Expo-CX1: "Complex", because environmental exposure scenarios are available

Expo-CX2: "Complex", because a qualitative environmental exposure assessment is available

3.4 Discussion of Results

3.4.1 Discussion of Overall Results

For each dossier all endpoint conclusions were combined into one single dossier conclusion according to the procedure described in Chapter 2.1. The outcome of the screening indicated on the one hand numerous data gaps in registration dossiers (58% "non-compliant") and on the other hand a huge number of cases that remained undecided (42% "complex") due to the limited time for evaluation (Figure 10).

The majority of dossier conclusions were "non-compliant" and the distribution of the endpoint conclusions demonstrated that in about 80% of these dossiers only one or two endpoints were "non-compliant" (Figure 11). Nevertheless, if at least for one endpoint the standard information required was not available the overall dossier had to be assigned as "non-compliant". This overall poor data availability is also reflected by the number of "compliant" endpoint conclusions. Only one dossier was in compliance with the information requirements for all evaluated endpoints and about 18% of all dossiers had no single "compliant" conclusion at all, whereas most dossiers had only one or two "compliant" conclusions (Figure 13). Though, independent from the dossier conclusion the predominant endpoint category was "complex" with 4 to 6 conclusions per dossier (Figure 12).

Supplementary to the distribution of the dossier conclusions it is essential to provide information about the distribution of endpoint conclusion categories and the underlying reasons for these conclusions. As shown in Figure 16 most endpoint conclusions remained undecided (62% of all checked endpoints) with large differences among the single endpoints (Figure 17). In general, this was mainly due to adaptation/waiving of the standard information which was predominantly based on grouping/read-across approaches. At HH endpoints these approaches accounted for nearly half of all adap-

tations (Figure 21), whereas at ENV endpoints only Ecotox had a relevant portion with approximately one third of all cases (Table 25). This distribution reflects the attempt to use existing data to avoid cost-intensive higher tier studies as well as to reduce animal testing with vertebrates. These latter tendencies, which are more relevant for HH than ENV endpoints, are supported by differences in the use of testing proposals between HH and ENV endpoints. With respect to this, relevant numbers of TPs were observed for the HH endpoints RDT and TRep (Figure 19). For ENV they only occurred for Ecotox and Bioaccu and only in a negligible number (Figure 30).

Of all endpoint conclusions, 13% were not in accordance with the required standard information (Figure 16). Two main crosscutting reasons were responsible for the "non-compliant" conclusions; first, the use of test material which was not in accordance with the identity of the registered substance. For HH the percentage was between 26 – 33% (Table 13) of the "non-compliant" conclusions of each endpoint, whereas the range for ENV endpoints was between 7 – 79% (Table 31). The second reason was the application of studies which were not referring to any acceptable standard-test guidelines for the respective endpoint. The proportion of this reason was between 19 – 27% and 7 – 38% for HH and ENV endpoint conclusions, respectively (Table 14 and Table 31). In the context of the screening only OECD/EU or comparable guidelines were accepted. In addition, for environmental endpoints the studies conducted according to other guidelines that may also be acceptable were assigned to the category "complex", since these have to be evaluated in more detail.

It is important to note that this screening study did not differentiate between endpoints which were "non-compliant" due to formal issues or due to reasons with regard to the content. The complexity of the REACH Regulation and of the dossier preparation certainly complicates a registration free of formal mistakes. However, the registrants are in charge to provide clear, accurate and unambiguous data that allow for a reliable risk assessment. In this context formal mistakes might lead to a lack of clarity regarding the content. The following example is supposed to illustrate this issue: as described above it was frequently observed that the test material used in a certain study did not correspond to the registered substance. A very likely reason might have been that the registrant intended to use a grouping/read-across approach but did not state it (through the selection of grouping/read-across in the respective IUCLID field). This might be regarded as a formal mistake. However, the registrant missed to clearly express its intention and consequently the provided study could not be accepted because it was not conducted with the registered substance. These mistakes can easily be prevented and a careful check of the fulfilment of formal criteria in registration dossiers by registrants will certainly help to lower the number of "non-compliant" endpoint conclusions.

Nearly one quarter of all endpoint conclusions (23%, Figure 16) were "compliant", for HH mainly because acceptable standard tests or harmonised classifications were available and for ENV because waiving referred to an Annex, Column 2 criteria was applied or acceptable standard tests were conducted.

Next to these general tendencies large differences occurred among the endpoints with respect to the endpoint conclusion categories and in addition, several underlying reasons are endpoint-specific. Therefore, the results for HH and ENV endpoints will be discussed separately in the following chapters.

3.4.2 Discussion of Human Health Results

The conclusions for each endpoint were obtained based on the respective decision tree. The documentation of the reason for each conclusion as well as of additional information in memos allowed for a closer look on the underlying situation. Several aspects and problems applied to all HH endpoints, however, endpoint-specific issues were also observed and both are summarised and discussed in the following section.

"Compliant" conclusions

The endpoint conclusion category "compliant" applied if all standard information requirements were fulfilled by presenting appropriate experimental studies. Additionally, for Muta and TRep, it was assigned if the substance had a certain harmonised classification according to CLP.

Almost 25% of the dossiers were "compliant" for the endpoints RDT and Muta. In contrast, only 5% of all dossiers were in compliance with the REACH requirements according to our approach for TRep. With more than 80% of the category "compliant", this mainly comprised substances with a harmonised classification as toxic for reproduction category 1A or 1B. The appropriate experimental studies were only provided in less than 20% of the "compliant" endpoint conclusions, which corresponds to a percentage of 1% of all dossiers. This might be due to the complexity of the studies which are required according to the REACH Regulation and which are very frequently waived or adapted.

"Non-compliant" conclusions

For 11 to 28% of the dossiers depending on the HH endpoint the conclusion resulted in "non-compliant" because adequate standard studies were not presented according to our concept and registrants did not adapt or waive the information requirements.

One major reason was the situation that studies in a particular case have not been carried out with the registered substance or provided information were inconsistent regarding substance conformity. This applied to approximately 30% of all "non-compliant" conclusions for all HH endpoints. It is important to note that the remaining data in the same endpoint study record appeared sufficient for most of the dossiers according to the screening concept. There are several reasons which are supposed to contribute to this issue. According to Annex XI, 1.5 registrants can use data with another test substance if a grouping/read-across approach is applied. However, this has to be clearly announced and requires a valid justification. Moreover, there are formal rules how to announce such an approach and it is the responsibility of the registrant to provide information free of doubt. At least one of these requirements was not fulfilled in the respective dossiers according to our screening approach. One other reason might be that the registrant simply made a formal mistake in filling out the ESR which resulted in inconsistent information with respect to the test substance and its conformity with the registered substance. However, especially if studies are not publically available, it is difficult to elucidate if the correct substance was used and, as already mentioned, it is the responsibility of the registrant to make this clear. Test substance identity is an important issue and registrants should take care that they use the adequate substance for testing, correctly fill out ESRs and clearly announce and justify if a grouping/read-across approach was used.

A second important reason contributing to 19 to 27% of all "non-compliant" endpoint conclusions was the situation that test data were only accepted if the registrant has stated that the studies were performed according or similar to the appropriate OECD guideline or comparable guidelines. One likely reason might be that older studies did not fulfil the criteria of current testing guidelines and were therefore not flagged by the registrant to be according or comparable to a guideline. A more detailed analysis of the study design might lead to the conclusion that information requirements were fulfilled. However, such a comprehensive evaluation could not be addressed in this project.

The endpoint Muta had the highest percentage of "non-compliant" conclusions of all HH and ENV endpoints. As already mentioned, if studies were not flagged to be according or similar to appropriate guidelines, they were regarded as "non-compliant". This was especially observed for testing on gene mutation in bacteria, probably due to the fact that the Ames test is already used for a long time. Older studies might not fulfil the requirements of the current respective test guideline. An additional reason might be that in contrast to other endpoints, e.g. RDT, data on at least three study types have to be provided and some tests were simply not addressed. Moreover, the necessity to perform certain tests,

such as the gene mutation test in mammalian cells or the in vivo soma and germ cell tests, depends on the outcome of previous testing, e.g. an in vivo soma cell test has to be performed if the respective in vitro testing indicated the occurrence of adverse effects. This is obviously required when the results of all previous tests were positive. For ambiguous results, which often include availability of multiple studies, e.g. several Ames tests, the evaluation of how to proceed might be more difficult and/or less obvious and registrants sometimes missed to provide at least an appropriate adaptation/waiving. To document cases with inconsistent data a corresponding memo ("Widerspruch" – "inconsistency", Annex 1) was introduced. However, this memo only occurred in 19 dossiers with the endpoint conclusion "non-compliant" for Muta.

Interestingly, tests on gene mutation in bacteria and cytogenicity in mammalian cells were most often missing in "non-compliant" as well as "complex" dossiers. On the one hand, this is an obvious result because both tests are the minimum standard requirements for Muta at the production level of 10 tpa or more per year according to REACH Annex VIII. On the other hand, it is surprising because both tests are well established and do not involve in vivo testing. One reason might be that the studies were not performed according/similar to the respective OECD testing guidelines as discussed above.

Besides the reasons for "non-compliance" discussed above, another reason for TRep was the referencing to screening studies such as OECD TG 421 and 422 (1995b, 1996). Although screening studies might give basic information on adverse effects for reproduction and development, they are not considered to be appropriate to fully address these issues (ECHA, 2014c). Additional reasons might be that, as data on two study types have to be provided for TRep, one of the study types was simply not addressed or that registrants referred to other, inadequate toxicity studies such as RDT studies. According to Column 2 criteria, low toxicity in other studies can only be accepted as an adaptation if the substance shows no systemic absorption and there is no or no significant human exposure. This has to be clearly stated and justified using a waiving option.

"Complex" conclusions

The endpoint conclusion category "complex" was the predominant assignment for all HH endpoints ranging from 47 to 73% of the dossiers. In these cases a conclusion on the "compliance" with the REACH information requirements was not achieved because they require a more in-depth analysis which could not be performed in the screening of this project. This high rate of "complex" endpoint conclusions was expected as it is known that this approach is frequently used in registration dossiers (ECHA, 2011b, 2014d). The vast majority of the category "complex" included a waiving justification or adaptation of the standard information, reflected by the percentages of 93 to 100%, depending on the endpoint. The most frequent reason for all endpoints was the indication that a grouping/read-across approach had been applied according to Annex XI, 1.5 of the REACH Regulation. In about half of all adaptations/waivers this approach has been presented as surrogate data. The actual numbers are certainly even higher because a grouping/read-across can be part of other adaptation options such as "scientifically not justified" and WoE. As long as a harmonised procedure for assessing grouping/read-across is not available, these cases have to be resolved on an individual basis. At the time this report is prepared, ECHA is in the process of finalising their "Read-Across Assessment Framework (RAAF)" and the results are expected to improve the situation considerably, putting both registrants and assessors in a better position. However, even after this framework will be installed, decisions on grouping/read-across approaches will - by their nature - always require a case-by-case assessment.

The categories "scientifically not justified" and WoE were also frequently used. The first also comprises the use of surrogate data according to Annex XI No. 1 such as *in vitro* data or (Q)SAR. In WoE approaches the information from multiple non-standard studies is accumulated to allow for a conclu-

sion on the toxic potential of a particular substance. In conclusion, grouping/read-across, "scientifically not justified" and WoE rely on the use of substitute data and if summed up contribute with 86% to all adaptations/waivings. Therefore, one can conclude that the majority of registrants used non-standard data to fulfil the REACH requirements for Muta, RDT and TRep. This is in general in accordance with the REACH demand to avoid new experimental studies whenever possible by using all information available. Moreover, it is a rational approach to keep costs and resources low. To what extent the adaptations/waivers applied in the registrations fulfilled the specific rules set out in Annex VII to X, Column 2 and Annex XI was not addressed in this screening. In order to get a complete overview on data availability in REACH registrations this will be a focus of a planned second project phase.

Important to note is that adaptations/waivers were documented as specified by the registrants in the corresponding IUCLID fields. If the correct option was selected for a particular case could not be proved. It was also observed that registrants often selected multiple adaptation/waiving categories for one study type. Although this is rather a formal issue, registrants have to be aware that REACH demands to clearly state and justify adaptations and waiving of standard information. This includes an unambiguous and consistent indication of the adaptation/waiving category.

A minority of the "complex" endpoint conclusions for HH were related to a special design of the decision tree.

Conclusion "TP"

If registrants proposed new experimental studies for at least one of the required study types the endpoint conclusion category "TP" was assigned for the endpoint. This was especially relevant for the endpoints TRep and RDT with 11% and 7% of all dossiers, respectively. The higher number in contrast to Muta might be due to the situation that both endpoints require one or two so-called "higher-tier" studies as standard information whereas for Muta in vivo studies have only to be provided under certain conditions. With respect to the dossiers conclusions, endpoints with testing proposals were counted as "complex" cases. One has to keep in mind that the screening was conducted with dossier entries from a cut-off date in March 2014. Dossiers might have been updated since then and meanwhile include data on the proposed studies which were approved by ECHA.

Noting the high numbers of "complex" conclusions for all HH endpoints, one can assume that most of the registrants who did not provide the experimental data required for substances with a production volume of equal or more than 1000 tonnes per year were aware of the necessity to at least adapt this standard information or justify data waiving.

With respect to RDT, this awareness was lower for dossiers in which a subacute test was provided. One reason might be that registrants were not aware of providing data on subchronic testing, e.g. because the registered substance was previously produced/imported at a lower tonnage level. Another possible reason might be that registrants intended to adapt subchronic testing with the provided 28-day study, but did not accurately announce this approach.

Regarding Muta, registrants were mostly aware to substitute missing standard information for the required in vitro tests by an adaptation or waiver. In contrast, for the majority of the cases for which an in vivo study was required and no appropriate experimental data were available, an adaptation or waiver was not provided.

With respect to TRep registrants frequently missed to adapt or waive the developmental toxicity study in the second species if no appropriate experimental data were available. Although the testing in a second species is a standard requirement, the necessity to perform this study depends on the outcome of the test in the first species and all other available data. A justification why the study was not conducted should be provided. ECHA also recently addressed the lack of compliance with the second-

species developmental toxicity standard information requirement and pointed again to the necessity to (at least) waive the study in the second species (ECHA, 2014a).

3.4.3 Discussion of Environmental Results

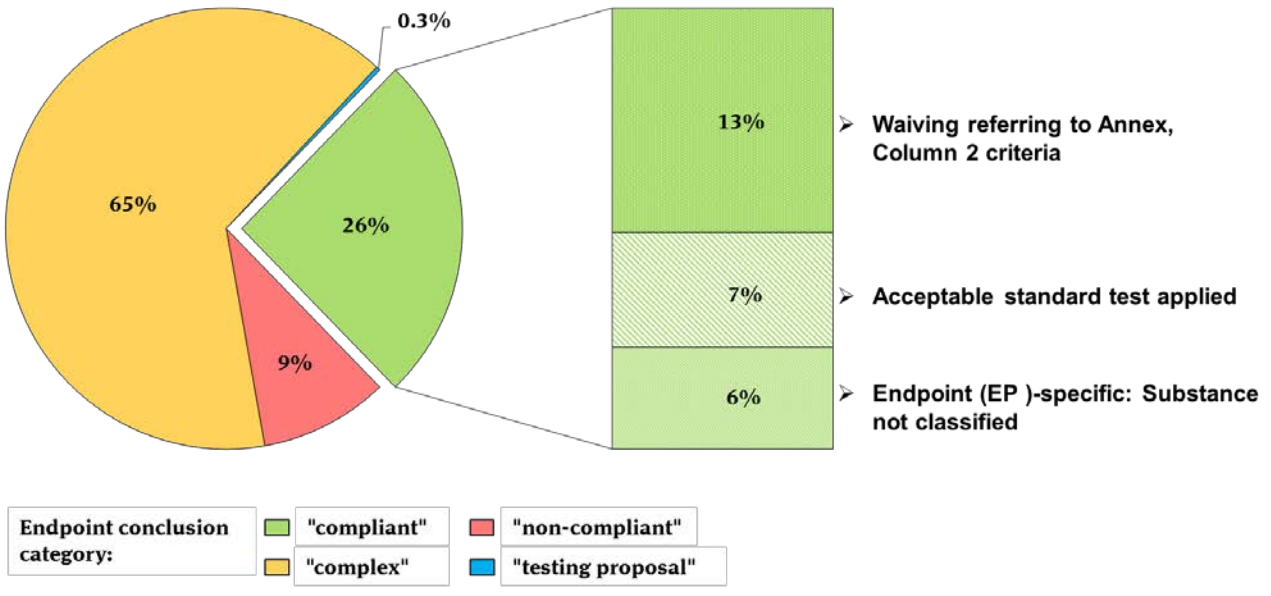
The conclusions for each endpoint were generated during the screening based on the fixed structure of the respective decision tree. This allowed a subdivision of conclusions in several underlying reasons. In addition, the recording of memos was a helpful tool to specify these reasons or to add further information. The results from the environmental endpoints reveal some distinctive differences between the endpoints as well as several cross-cutting issues. Both will be discussed together with respect to the conclusion categories in the following section.

"Compliant" conclusions

Registration information considered as "compliant" spanned a wide range of percentages (4 - 45%) for the environmental endpoints, with Ecotox at the lower and BioDeg at the upper end of the scale. The dominant cross-cutting reasons for "compliant" conclusions were either waiving in accordance with a REACH Annex criterion from Column 2 (predominantly AbioDeg, Bioaccu) or the availability of standard tests (predominantly BioDeg and Ecotox). The only reason why the conclusion for the endpoint Expo could be considered "compliant" was that the substance was not classified referring to Annex I of the CLP Regulation and was not considered to be a PBT/vPvB-substance (Figure 31).

With respect to BioDeg the distribution of information considered "compliant" or "complex" deviated considerably from those of other endpoints. The relatively high percentage of "compliant" endpoint conclusions was due to the fact that inorganic substances can be waived in accordance with Annex VII. This was responsible for nearly half of the conclusions classified as "compliant". If the distribution of the conclusion categories stated in Table 26 is calculated without this substance group, the proportions for "compliant" and "complex" conclusions will be approximately 30% and 55%, respectively. Hence, these are similar percentages for both categories than for most other endpoints. Furthermore, it was striking to note that the requirements for simulation tests were seldom fulfilled.

Figure 31: Summarised reasons why ENV endpoint conclusions were "compliant"



The low amount of "compliant" cases for Ecotox was expected. All possible options to achieve a "compliant" conclusion, as shown in Table 29, depend on the availability of long-term standard tests. Concurrently, these tests were quite often performed according to non-standard tests or data waiving was practised, particularly via read-across. Therefore, these conclusions were classified as "complex" (see below).

"Non-compliant" conclusions

Conclusions assigned as "non-compliant" represented percentages from 3% to 15%. Two main crosscutting reasons responsible for conclusions classified as "non-compliant" could be observed at the endpoints BioDeg, AbioDeg, Bioaccu and Ecotox (Figure 32). First, the test material identity given in the ESR was not in agreement with the identification presented in IUCLID section 1.1 (test material inconsistent). And second, the experimental data were obtained without any reference to a standard or non-standard guideline. The combined share of both reasons accounted for more than three quarters of "non-compliant" conclusions at BioDeg, Bioaccu and Ecotox, and only 30% at AbioDeg (Table 31). At Ecotox and BioDeg these cases were clearly dominated by incorrect test material identities, whereas these reasons were equally distributed at Bioaccu. For AbioDeg other reasons were more important, for example, that a test on hydrolysis was not available because the necessity to conduct it, taking into account the outcome of the pre-test, may not have been realised by the registrants.

In 266 cases the endpoint conclusion for Exposure was "non-compliant", since an exposure assessment was missing, although a classification according to REACH Art. 14(4) was available. A common (non-valid) justification for the absence of the assessment was that a non-environmental classification indicated no need to assess environmental exposure. While the paragraph clearly defines this, it can be helpful to improve the communication of the underlying conditions, e.g. by providing more details.

Figure 32: Summarised reasons why ENV endpoint conclusions were "non-compliant"

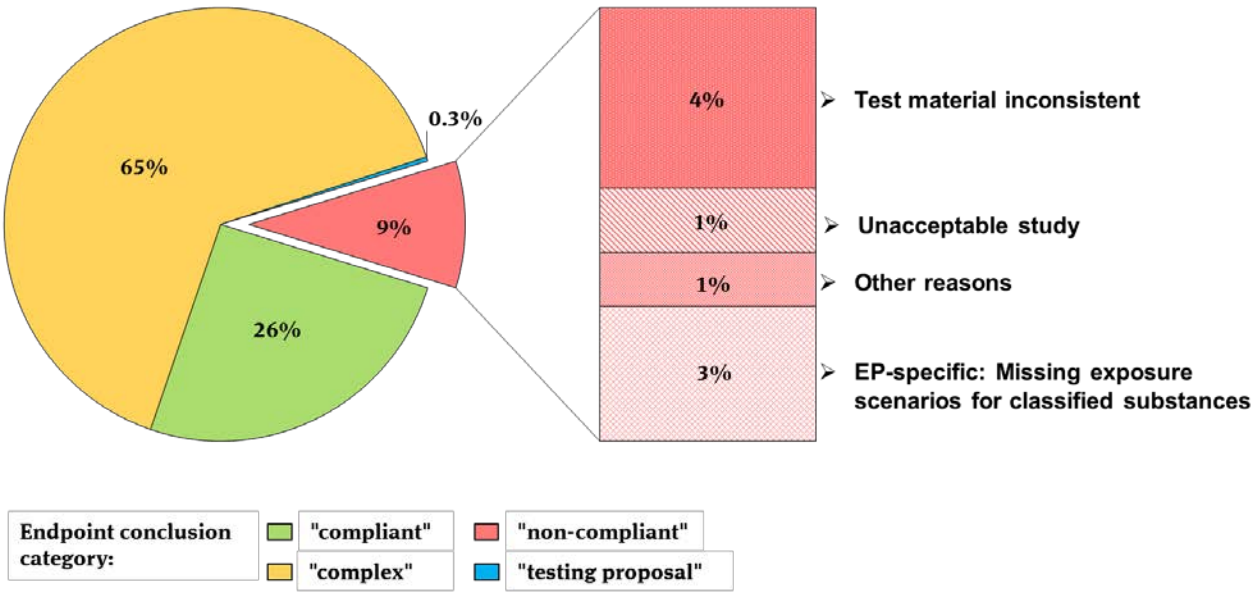


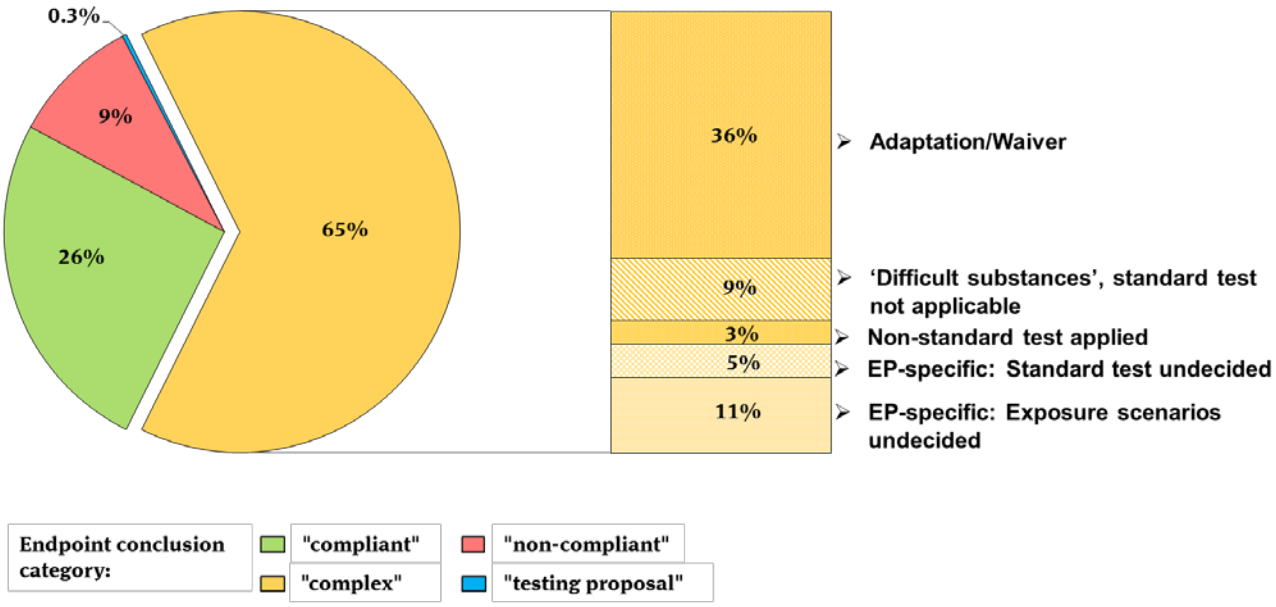
Table 31: Main cross-cutting reasons for endpoint conclusions considered "non-compliant". Reasons were registered through memos (Annex 2) during the screening.

Reasons	Degradation				Bioaccu		Ecotox	
	BioDeg		AbioDeg					
	n	[%]	n	[%]	n	[%]	n	[%]
Test material inconsistent	144	71	7	7	21	38	185	79
No reference to a guideline	14	7	23	23	21	38	16	7
Other	44	22	68	69	14	25	34	14
Total	202	100	98	100	56	100	235	100

"Complex" conclusions

Not surprisingly, the vast majority of the endpoints has been categorised as "complex" (43 – 82%). For the endpoints BioDeg, AbioDeg, Bioaccu and Ecotox this was primarily due to the use of data waiving and to a lesser extent because non-standard tests were executed (Figure 33). Moreover, specific groups of substances, for example inorganic or ionisable substances at AbioDeg and Bioaccu, had to be classified as "complex" as well ("difficult substances"), since neither appropriate assessment methods nor uniform adaptation/waiving criteria were applicable. Therefore a case-by-case analysis with more time on each dossier is necessary.

Figure 33: Summarised reasons why ENV endpoint conclusions were "complex"



Data waiving by means of read-across or WoE approaches that contain at least one ESR based on read-across were considered "complex" in this project. The endpoint Ecotox had the highest percent-

age of adaptations based on read-across and WoE approaches among the environmental endpoints, followed at some distance by Bioaccu. This reflects that more expansive tests than for other endpoints are required, and simultaneously it shows the attempt by the registrants to reduce testing to cut costs and/or for animal welfare reasons. Furthermore, to assess aquatic toxicity several tests have to be conducted and if at least one of those compulsory tests was waived via read-across or WoE this endpoint was classified as "complex".

The quantities of adaptation/waiving categories reported in Table 25 can give valuable hints with respect to the distribution of waiving categories. However, at a first sight during the screening the assignment of adaptation/waiving categories was partly inconsistent, i.e. the actual reason was filed under a wrong category, particularly, if omission of data was justified with one of the following categories: "scientifically", "other", "exposure", "technically". Therefore, the data have to be interpreted with caution.

Non-standard tests were predominantly applied to investigate aquatic toxicity and to a much lesser extent for the environmental fate. Almost 10% of the conclusions for the endpoint Ecotox were considered "complex" in the screening, but the actual percentage is possibly much higher. First, non-standard methods could have been used in parallel for different tests under evaluation, for key as well as for supporting studies, and second, it is expected that adaptation based on a read-across or WoE approaches also contributed to the amount of non-standard tests. Important sources of experimental data were studies conducted prior to the entry into force of the REACH Regulation. To reduce the uncertainty, whether these tests fulfil the standard requirements, an in-depth analysis has to be carried out to compare the application of non-standard methods with those of the current standard guidelines.

There were some cases for the endpoint Ecotox in which the answer to one question was inconsistent. If no effects occurred in the short-term tests, for example in limit tests with 100 mg/L, question 8 in the decision tree (Figure 8) should be answered with "No" (no effect). If at least one of the tested concentrations was below the 1.25 fold water solubility, but higher than 100 mg/L the question was answered with "Yes" (effect) and a memo was placed (Annex 2). However, this answer should be corrected to "No", since independent from the effect criteria "EC_{50} or LC_{50} < 1.25 fold water solubility" in these cases no toxic effect was observed. Overall 87 of such conclusions were recorded, in 85 of these cases the respective conclusion was considered to be "complex" and in two "compliant". A revised evaluation, as a consequence, would classify the conclusion also mainly in the endpoint conclusion category "complex". However, a very few cases may be assigned as "non-compliant" if no adaptation/waiving is given.

For AbioDeg the need to conduct a test on hydrolysis may be conditioned on the findings from the endpoint BioDeg. If the substance was classified as "readily biodegradable" in the ESR of BioDeg, the hydrolysis test can be waived according to Annex VIII, Column 2. In the screening the statement "readily biodegradable" was not accepted as "compliant" if it based on waiving, non-standard testing or on a questionable test material identity. These cases were assigned as "complex" and have to be checked in more detail to classify them either as "compliant" or "non-compliant".

For more than half of the dossiers the endpoint Exposure was categorised as "complex". Even, if this is a smaller number than for several other endpoints, a much higher effort would be required to make final conclusions on these cases. The exposure scenarios have to be checked in detail for 90% of the conclusion category "complex", and the work associated with this depends particularly on the number of uses of the substance under evaluation. For this reason, a group of dossiers may be selected to evaluate the data quality of the exposure scenarios. In addition, the quality of exposure assessments (10% of "complex" endpoint conclusions) would have to be checked in more detail, since it is assumed that the required description was not provided in all cases.

Entries with respect to the harmonised classification in IUCLID were mainly correct, however in 51 dossiers deviations from the CLH presented in the C&L Inventory were observed. These deviations could be subdivided in two groups. First, in some entries only minor deviations were recorded, where, for example, the hazard statement differs slightly between both entries, e.g. H 224 instead of H 225. On the other hand, entries with major differences were documented, e.g. a lack of several hazard statements in the dossier. In the latter case an in-depth analysis may lead to a revised classification as "non-compliant". A reason for deviations can be, for example, that the C&L Inventory has been updated after the 7th March 2014, the data assessed were "frozen" data from the registration dossiers (see Chapter 2.1).

Furthermore, the assessment of UVCB substances and substances which are part of "chemical categories" with respect to the classification were challenging. The respective GHS section in IUCLID frequently contained a large amount of entries without any substance-specific references as reported in the C&L inventory; hence, these substances were classified as "complex".

Conclusion "TP"

The total number of testing proposals, whether or not they led to a respective endpoint conclusion, was very small for the environmental endpoints. It can be assumed that the registrants instead of making a testing proposal used all kind of available data for ecotoxicity and bioaccumulation, even if the underlying testing method could be questionable with regard to the standard requirements, or applied adaptation/waiving categories.

3.4.4 Comparison to Previously Published Studies

The comparison of our screening results to results of other studies on data availability in REACH registration dossiers was possible only to a limited extent, since the methods of data collection and assessment as well as the group of substances under review differed considerably.

An overall result to compare with was ECHA's official full compliance check: For 59% of checked high tonnage chemicals dossiers in 2014 and for 60.8% in 2013, respectively, ECHA concluded draft decisions [(ECHA, 2015), (ECHA, 2014b)].This means that for around 60 % of the checked high tonnage chemicals dossiers the REACH information requirements have not been fulfilled to the full extent. This complies with the screening result of the current study where in 59% of lead and individual dossiers at least one endpoint was "non-compliant".

3.4.4.1 Comparison of Human Health Results

ECHA recorded the amount of experimental data and alternatives to the required tests for phase-in substances at or above 1000 tpa (ECHA, 2011b). In this study, all endpoint study records (ESRs) for each endpoint have been counted. Therefore, a direct comparison to the screening results of this project seems to be difficult. The ECHA study was related to 1862 lead registrant dossiers which is similar to the number (1814) that was investigated in this project. Therefore, some aspects of the results might be comparable.

RDT theoretically requires (at minimum and assumed that the 28-day study was waived) only one ESR per dossier on a 90-day study for one route. In the ECHA report, all routes were considered. Nevertheless, the amount of 42% ESRs with experimental data found in 2011 by ECHA complies approximately with the 38% "compliant" and "non-compliant" dossiers (summation) found in the current study provided that in most of the "non-compliant" dossiers a least some experimental data was existent. The latter fact was proven for 48% of "non-compliant" dossiers in the current study where either the test substance did not correspond to the registered substance (25%) or the studies were conducted according to an appropriate guideline (23%). Further, for 28% of "non-compliant" dossiers regarding RDT at least data from a 28-day study were provided by the registrants. Moreover, the

amount of read-across, data omitting and weight of evidence (alternatives to testing) of 57% of the ESRs found by ECHA is well in accordance to the results found in the current study: 56% of the dossiers regarding RDT were found to be "complex". The number of testing proposals found in the current study (120) complies well with 104 ESRs with proposals found by ECHA in 2011.

For Muta, only the in vitro ESRs considered by ECHA were compared to the screening results of the current study. The basic information requirements for Muta are data on at least two in vitro studies. With respect to this, one should expect that the number of ESRs was much higher than for RDT. Surprisingly, ECHA observed almost the same number of ESRs for RDT (10790 in total) compared to Muta in vitro (10322 in total). Although several studies are required for Muta and only one for RDT, this might be due to the fact that all routes have been counted regarding RDT or that in the majority of substances a 28-day study was also available.

For Muta experimental in vitro data were found by ECHA in 57% of the ESRs which is in the same range as in the current study (52% "compliant" and "non-compliant" dossiers). Adaptations/waivers were found in 43% of the ESRs. This may correspond to the percentage of 47% "complex" dossiers regarding Muta in the current study. Again, the tendency to apply alternatives for testing found by ECHA was confirmed in the presented study. The amount of existing experimental data cannot be directly derived from the screening approach used in this study. Similar to the above explained endpoint, a part of the "non-compliant" data was related to tests on other substances than the registered one or tests that were not conducted according to current guidelines.

ReproTox and developmental toxicity DevTox were separately considered by ECHA. Alternatives to testing were used in 74% of the ESRs on reproductive toxicity, whereas only 54% of the ESRs for developmental toxicity applied alternatives to testing. The overall results of the current study showed 73% "complex" dossiers for TRep including both, ReproTox and DevTox. This generally complies with ECHA's results for reproductive toxicity. The differentiation ReproTox and DevTox regarding the amount of "complex" conclusions was not yet available for the current study. This will be investigated in detail in a follow-up project. In contrast to RDT, testing proposals were detected in the current study at a slightly lower number than they were detected in the ECHA study: The screening found 136 testing proposals for ReproTox (ECHA: 150) and 145 testing proposals for DevTox (ECHA: 151).

3.4.4.2 Comparison of Environmental Results

Sobanska *et al.* (2014) analysed ecotoxicity data from REACH registration dossiers of 2887 substances based on data submitted to ECHA until 28 February 2011. These data include phase-in substances at or above 1000 tonnes a year and substances of lower tonnages with hazardous properties (CMRs and R50/53). One of the applied methods investigated the options, as specified in the picklists of IUCLID, which were used by the registrants to characterise the required information in the ESR. The selected options were: Experimental studies; WoE; (Q)SAR; Read-across; Data waiving; and additionally, cases for which no data were required and substances from a category approach were recorded. The assignment of data options followed a prioritisation scheme and ensured that for each endpoint only one option was chosen. At first, substances which are part of a category approach were identified and excluded from further investigation. Then, the entries of an endpoint were assigned to the aforementioned options in the order as shown. An entry was classified as "experimental data" when at least in one ESR this option was chosen. Then it was checked whether at least one entry referred to WoE and so on. The results were sorted by environmental compartments and taxonomic groups; hence, short-term and long-term studies were combined for fish and invertebrates.

The adaptation/waiving categories in the screening scheme of this project were recorded from a multiple choice question, to record if different categories may contribute to the conclusion. Therefore, these results are not appropriate for a comparison with those from Sobanska *et al.* (2014). However,

the percentages for the experimental data could be contrasted after the results from the screening of this project had been slightly rearranged. All conclusions with regard to an experimental result as listed in Table 29 were added, independently of the assigned endpoint conclusion category (Ecotox-CT1-3, NC1, and CX1-3). The overall percentage is 48.6%. This is considerably lower than the fraction of 54.7% for fish and 60.8% for invertebrates reported by Sobanska *et al.*, all the more as the percentage documented for the "category substances" (12%) was part of the calculation and may have resulted in an underestimation. Reasons which could explain these differences are for example that the classification as "experimental data" was neither restricted to key studies nor was the Klimisch reliability score of the ESRs considered. Therefore, experimental studies could have contributed to the outcome in the study from Sobanska *et al.* which were rejected during the screening in this project.

Similar problems arose from comparing the data availability of the screening with those of ECHA report "The Use of Alternatives to Testing on Animals for the REACH Regulation" (ECHA, 2011b). ECHA used data extraction tools to assess the data availability in registration dossiers for the same substances as described by Sobanska *et al.* The investigation was limited to the ESRs of vertebrate studies and consisted mainly of two approaches.

First, in the "ESR approach" the data availability of all ESRs submitted for each dossier was cumulatively analysed to generate an overall quantitative picture regarding the predefined options to fulfil the information requirements in IUCLID; these are experimental data, testing proposals, and adaptation/waiving categories separated as stipulated in the pick-lists. The proportion of options to fill in the ESR as recorded in the "ESR approach" (ECHA, 2011b, p. 43f.) deviates clearly from the findings in this project. It might be assumed that the cumulative approach in which one or more entries for each ESR are summarised, lead to a considerable shift in the relative frequency of options in comparison to those results recorded from key studies exclusively in the screening. Hence, it is not suitable to compare both results.

In the "substance approach" the analysis focussed on the key ESR entries as chosen by the registrant, subdivided in three principal options "experimental study", "testing proposal" and "alternative approaches"; each of these counted once per endpoint (ECHA, 2011b, p. 22.). In contrast, the findings discussed here are based on phase-in substances at or above 1000 tpa, with the deadline for inclusion being the 28 February 2011. To compare the results from this project with those from the "substance approach", the screening data of the ESR for Bioaccumulation were filed into three options as carried out in the "substance approach". In this context, ESRs based on adaptation/waiving filed into the group "alternative approaches", and all experimental data, either from the category "compliant", "complex" or "non-compliant" were summarised. All substances which were classified as inorganic or ionisable during the screening were excluded from the list, because for these groups the data required to assign one of the three options was not recorded. The remaining number of substances is 1079; hereof the percentages for experimental data, testing proposals and adaptation/waiving documented in the ESR are 13.5%, 0.5% and 86.1%, respectively. The relative proportions of the principal options as reported in the "substance approach" for 1453 substances range in the same order of magnitude: 14.8% experimental data, 0.8% testing proposal and 84.4% "alternative methods" (ECHA, 2011b, p. 48.). This is particularly remarkable, since invertebrate studies on bioaccumulation had been excluded in ECHA approach, while the analysis during the screening was independent of the taxonomic group of the test species. The data for aquatic toxicity could not be compared, since ECHA approach subdivided the outcome in short-term and long-term fish tests while this is not possible for the results of this project due to the structure of the information gathering.

The need of an in-depth analysis of the ESRs from aquatic toxicity with respect to the guidelines used, as stated before, is supported by findings of Tarazona *et al.* (2014). They investigated the data availability of aquatic toxicity data in REACH registrations for the same dossiers as Sobanska *et al.*,

(2014). The analysis of the distribution of test guidelines for short-term and long-term tests for fish and invertebrates indicated that in 25.5 – 36.7% of the ESRs a test method was not reported. Additionally, in another 4.5 – 8.1% of the ESRs the option "other" was chosen in IUCLID and none of the preselected guidelines from the pick-list were used. These relatively high percentages may reflect that both key and supporting studies were evaluated. It can be assumed that a higher portion of non-guideline studies is available in ESRs of the supporting studies than in those of the key studies, which were exclusively analysed in this project.

4 Comparison with ECHA Compliance Check of Registrations Referred to REACH Regulation Art. 41

4.1 Aim and Approach

A screening of REACH registration dossiers as carried out within the current study could easily result in wrong conclusions due to the rather superficial character of the procedure. It was therefore desirable to double-check results of the current study by comparison with ECHA's dossier evaluation results. The aim was to better interpret and classify the results of the current study.

According to REACH Art. 41 it is ECHA's task to evaluate whether registration dossiers comply with the requirements of REACH (compliance check, CCH). In case of non-compliance the evaluation process results in an ECHA decision, in which the missing information is requested and that request is justified. Non-confidential versions of these decisions are published on the web[7] and were considered for the comparison. Furthermore, member states' competent authorities are provided with confidential draft and final decisions as they are involved in the process. Draft or final decisions available at the BfR were, therefore, also considered.

For carrying out the comparison, the starting point was a list provided by ECHA of phase-in substances at the high tonnage level (≥1000 tpa) which underwent full CCH until 28th February 2014. The comparison was performed for those substances for which the reason for selection for CCH was indicated as "random" or "concern-full CCH". Therefore, substances which were under compliance check within the scope of CoRAP[8] or "Area of concern" (AoC) targeted compliance were not considered.

Substances of this list, which were under consideration in the current study, were then examined. The available decisions were opened and chapter II "information required" and chapter III "statement of reasons" were considered for comparison to screening results.

For the human health endpoints special attention regarding results of the current study was drawn to whether available tests had been rejected because

- of the fact that the wrong substance was used or
- the test was not carried out according or similar to a guideline,
- it was only a screening test.

4.2 Results

Within the scope of the project's data availability screening, lead registration dossiers updated until no later than 07th March 2014 were explored. However, in the majority of cases the investigated ECHA's CCH were based on earlier versions of these dossiers. Therefore, the basis of the examination was not identical to CCH and, moreover, in several cases dossiers had been partly or completely updated meanwhile. Nevertheless, a comparison was carried out considering these differences. Two of ECHA's CCH decisions were included for investigation although they are dated later than March 2014. Furthermore, it must be noted that a comparison of such screening results with a detailed assessment of available toxicological data by ECHA professionals is inherently problematic. Thus, the

7 Dossier evaluation decisions (testing proposal, compliance check): http://echa.europa.eu/information-on-chemicals/dossier-evaluation-decisions.

8 Community Rolling Action Plan (CoRAP) is a list of substances which are or will be evaluated by member states. For more information: http://echa.europa.eu.

information provided by an ECHA decision was not considered in all details, but was generally matched to the aspects covered by the project screening. In addition it is to be noted that for "complex" conclusions the data was partly not assessed in detail.

4.2.1 Human Health

Annex 5 contains a list of 31 substances checked for compliance by ECHA. Due to time restrictions seven other decisions published on the ECHA website have been not considered. The table in Annex 5 includes:

- information on substance identification ,
- requested standard information based on ECHA decisions related to REACH Art. 41,
- dates of decisions and possible notifications related to REACH Regulation Art. 42 on completed dossiers by ECHA,
- results of the current study (result categories), and
- details on the results of the current study.

The table in Annex 5 shows that the most frequent information requests by ECHA for the 31 compared substances concerned the developmental toxicity (DevTox) in general or in a second species (21 substances), followed by information for subchronic toxicity (RDT, 18 substances). Moreover, a two-generation study was requested by ECHA for six dossiers and the gene mutation in bacteria in general or with the 5th strain was necessary for five dossiers. Finally, gene mutation in mammalian cells was requested three times and a cytogenicity test in mammalian cells two times. In total, testing for genetic toxicity (Muta) was requested for seven of the substances compared.

The results of the screening of the 31 substances were in summary and in comparison with ECHA decisions as follows (Annex 5). Thereby, missing information according to the screening is underlined in the table.

First, regarding reproductive and developmental toxicity the screening resulted in only four "non-compliant" dossiers. In these dossiers data for the two-generation study was missed twice and data for developmental toxicity in general and for a second species was missed in total three times. All other dossiers except for one testing proposal and two "compliant" dossiers have been regarded as "complex" in the screening (24 dossiers). From these not further assessed dossiers during screening, for 15 dossiers ECHA had requested the developmental study.

However, during screening most often data of the two-generation study was not available (23 "non-compliant" and "complex" dossiers). From these ECHA had requested this study data only for four dossiers, in total. This comprised one dossier, which was "complex" regarding the screening, and three dossiers, which were "non-compliant".

Second, seven "non-compliant" dossiers regarding RDT was the result of the screening. In addition, eight "complex" dossiers resulted. Additionally, one testing proposal and 15 "compliant" endpoints were found.

Third, for the endpoint Muta the most "non-compliant" dossiers have been decided on during screening (nine dossiers), whereas 13 dossiers resulted in "complex".

Concordance and differences between ECHA CCH decisions and our screening results can be interpreted as follows:

Most often differences between ECHA requests and the screening results were seen in dossiers in which neither waiving justifications nor any adaptations regarding the standard test requirements has been assessed in the screening. While in these cases decisions were issued by ECHA, they were not finally concluded within the current study ("complex" conclusions). Also, classification into the

carcinogen category 1A or 1B or a germ cell mutagen category 1A or 1B of a substance according to CLP (Muta) led to the result "complex" within the screening. In the latter case the registration data were also not further checked whether they were compliant to REACH information requirements.

Further differences between this study and ECHA CCH decisions were as follows: In some dossiers, tests had not followed an official guideline (e.g. OECD TG, EU guideline) so that the data were regarded as not sufficient according to the standards of the project. A detailed assessment of testing designs was not carried out within the screening whereas ECHA does this assessment during CCHs. Moreover, the screening found some cases where the test substance was not identical to the registered substances or not clearly identified, but this fact was not addressed in ECHA CCH decisions. Possibly ECHA has found the related read-across justification elsewhere in the dossier. In any case, a detailed case examination is necessary.

Moreover, some dossiers were already updated so that the missing information requested in the decision was available at the time of the screening. In contrast, in a few cases the dossiers were obviously updated later on in 2014 so that the screening test result now is out of date.

Reproductive and developmental toxicity:

The missing two-generation study (ReproTox) in23 dossiers were less frequently addressed in ECHA decisions regarding this endpoint. This might be due to the fact that waiving/adaptation was regarded as sufficient by ECHA for these substances. Another reason might be that decisions on reproductive toxicity testing have been postponed at the time of the starting of the CCH. Discussions regarding application of the two-generation or the new extended one-generation study might have influenced the process.

The requirement of a 2nd species concerning DevTox found within this study was not always outlined by ECHA decisions. Probably the second species was not necessary due to case-specific reasons. Furthermore, request of this REACH information requirement started only later on (ECHA, 2014a).

Genetic toxicity, repeated dose toxicity:

Differences were recognized in six cases for Muta (substances no. 4, 5, 6, 17, 26, 28 in the table in Annex 5) and four cases for RDT (substances no. 15, 24, 28, 31). In the screened dossiers of these substances, a valid test or an indication on an adaptation of the standard information could not be found during screening (result: "non-compliant") whereas these information gaps were not addressed in the decisions by ECHA or meanwhile the dossier were notified as completed. The reasons could lie in the fact that in the screening only ESRs flagged as key studies were considered. Again, an additional check might resolve the discrepancy.

The requested information by ECHA regarding bacterial gene mutation often concerns a missing bacterial strain according to OECD TG 471 (1997a). Details of test designs could not be considered in the screening. The screening accepted this study as a guideline test if a sufficient reliability was provided (without a detailed analysis of the test strains used).

On the whole, almost all differences between ECHA results and our study are explainable in a direct or indirect way and were either result of the screening methodology or the time differences between the checks.

4.2.2 Environment

For 10 substances/dossiers CCH decisions were available and matched with the screening results of the project for the environmental endpoints. In seven of them the required information referred predominantly to a missing or inadequate exposure assessment and/or risk characterisation (Annex 6). The other information requirements were related to ecotoxicity, partition coefficient, and a set of dif-

ferent endpoints. Environmental endpoints which were not part of the screening were not considered.

For all exposure related decisions of the CCH the respective conclusions in the screening were “complex”. In all CSR of the dossiers was at least some information about environmental exposure scenarios available and in accordance with the screening concept (see Chapter 2.4.4) it could not be further evaluated whether the entries were in agreement with the information requirements. In two cases the CCH criticised that no environmental exposure assessment had been conducted at all. At the time of the screening this information had already been updated and exposure scenarios were available. Additional shortcomings for the endpoint exposure were a missing risk characterisation and an incorrect substance classification. Both deficiencies were also detected during the screening and marked by a memo.

One CCH decision was based on missing information referring to a long-term invertebrate test. In the screening the conclusion was “complex”, because a non-standard method was applied which could not be evaluated in more detail.

For one dossier the decision from the CCH and the screening results seem to be inconsistent. The dossier conclusion was “non-compliant” in this project, since the substance fulfilled at least one criterion of the hazard classes or categories outlined in Annex 1 of the CLP Regulation (1272/2008) however, an environmental exposure assessment according to Article 14(4) was not conducted. This shortcoming was not addressed in the CCH decision. Instead the decision was based on an inadequate adaptation regarding the partition coefficient. In the screening this parameter was not evaluated in detail, however, a memo for the adaptation was recorded.

Another request referred to shortcomings with respect to several endpoints, e.g. AbioDeg with a missing hydrolysis test and Bioaccu with a (Q)SAR calculation where the applicability domain was wrong. The conclusion in the screening was “complex” for all endpoints, since a deeper analysis would have been necessary; e.g. at AbioDeg because the substance is high adsorptive and at Bioaccu a (Q)SAR adaptation was presented.

Due to the limited time in the screening most conclusions regarding the considered 10 substances could not be assigned either to the category “compliant” or “non-compliant” and therefore, a comparison with results from the CCH was very restricted. However, the different shortcomings of the environmental endpoints were detected in most cases. In addition, the results show that “complex” conclusions of the screening have a marked trend to become “non-compliant” when assessed in more detail.

5 "Complex Case" Analysis

5.1 Aim and Introduction of the Analysis

The "complex case" analysis was a preliminary case-by-case examination of dossiers and endpoints for which no firm conclusion could be reached within the screening. It was expected that a considerable percentage of the endpoints and dossier conclusions will be classified as "complex" in the screening of this project due to the simplified nature of the screening approach which for example does not include an assessment of adaptation and waiving justifications. Therefore, a limited number of randomly selected endpoints and dossiers which were allocated to the conclusions "complex" were analysed in more detail. The aim was to identify and categorise concerns which emerged from the entries and information given by the registrant. A revised allocation to the conclusions "compliant" and "non-compliant" should be made, if possible.

In the project plan, four weeks were envisaged for the inspection, documentation and analysis of "complex" conclusions of endpoints and dossiers. From those, approximately two weeks were scheduled for the inspection. Due to the limited time frame only a selected set of endpoints/dossiers was evaluated. Two approaches for selection were applied:

1. "Complex endpoints": For each endpoint a random set of 20 to 30 cases was selected from all cases where the conclusion was "complex".
2. "Complex dossiers": 20 dossiers were randomly selected from the 146 dossiers where all endpoints were categorised as "complex". Each endpoint was evaluated.

The first approach addressed the identification of endpoint-specific concerns, while the second was expected to complement crosscutting issues.

In the first approach ("complex endpoints"), the information given by the registrants in the endpoint study records were compared with the information requirements for the specific endpoints according to the REACH Regulation. One particular focus was the assessment of adaptation and waiving justifications. If the given information was sufficient to revise a conclusion, the endpoint was categorised as "compliant" or "non-compliant". Otherwise, the endpoint remained "complex". The reasons of the revised conclusions were summarised and grouped with respect to the specific and general rules for adaptation and waiving of information requirements stated in the REACH Regulation as well as additional issues. The latter cover harmonised classifications according to CLP, substance-related issues, the route of administration and the lack of information or waiving. The differentiation between adaptation and waiving was adopted from Practical Guide 4 (ECHA, 2010), with adaptation referring to Annex XI, section 1.1 – 1.5 and waiving to Annexes VII-X, Column 2 as well as Annex XI, section 2 and 3. Results are presented in Chapter 5.2.2 for HH and Chapter 5.3.2 for ENV.

In the second approach ("complex dossiers"), all endpoints of the 20 dossiers were re-examined in the same way as in the first approach of "complex endpoints". A re-categorisation of the dossier conclusion could only be made if one of the "complex" endpoints had been categorised as "non-compliant" or all endpoints as "compliant". To analyse crosscutting issues, the revised conclusions for all endpoints and the dossiers were collected and outlined in a table. These results are presented in Chapter 5.4. Additionally, for HH the reasons for endpoint-specific conclusions were integrated into the list of reasons of the first approach. If the reason has not yet been observed, it was added to the list. If the reason has already been listed, the number of cases increased by one case. The respective results are presented in Chapter 5.2.2. In comparison to the "complex endpoint" approach no additional reasons for ENV endpoint conclusions were observed in the "complex dossier" approach. Therefore, the additional reasons from the "complex dossiers" were not inserted in the respective tables.

Adaptations which were solely based on grouping/read-across were not evaluated further in these approaches because these cases require a compound-specific in-depth analysis whether the reference to another substance or one representative of a group is appropriate. This issue could not be addressed within this project.

The endpoints were perused in an explorative manner. This entailed a case-specific evaluation in the majority of cases. However, basic stepwise procedures to examine the data for information gathering have been applied for HH as well as ENV. They are described in more detail in the respective sections below.

5.2 “Complex Endpoints”- Human Health

5.2.1 Information Gathering - Human Health Endpoints

With respect to the first approach (“complex endpoints”), 20 (Muta and TRep) or 30 (RDT) cases from different dossiers were selected for each endpoint. The number was higher for RDT due to very frequent grouping/read-across.

With respect to the second approach (“complex dossiers”), 20 dossiers were selected and all three endpoints were evaluated.

In total, 130 endpoints were assessed. With the scheduled time frame of two weeks, an average time of 45 min was available for each endpoint.

The basic procedure to examine the available data is described in the following section.

First, KnowSEC entries for the respective dossiers were checked to comprehend the preliminary conclusion and to quickly obtain waiving categories as well as additional documented information. Cases for which solely grouping/read-across was available were documented, but not further examined. Next, classification of the substance according to CLP was checked. Subsequently, IUCLID dossiers were opened to evaluate all information given by the registrant in the respective endpoint sections, including endpoint study records, endpoint summaries and included attachments. Cases for which standard information requirements were available required a judgement of the completeness and quality of the reported studies based on the specifications given in the respective OECD test guidelines. Endpoints which were flagged by the registrant as another adaptation/waiving category, but are based on the judgement of grouping/read-across, were documented, but not further assessed. Additional IUCLID sections, e.g. the composition, analytics or uses section, were checked to obtain information required for specific cases, e.g. cases with unclear substance identity or issues regarding the uses of the substance. Moreover, selected cases were discussed with experts in the BfR. Endpoints were allocated to “compliant” or “non-compliant” if the collected information allowed for a conclusion. Relevant information and reasons for the revised conclusion were documented for all cases examined.

5.2.2 Results - Human Health Endpoint Conclusions

5.2.2.1 Overall Observations

A lack of specification of the applied REACH Annex in the adaptation and waiving justifications was frequently observed. However, this specification is urgently required because the information given through the flagged waiver category in IUCLID is rarely sufficient to provide an unambiguous allocation. Especially in case of data waiving according to Annex VII-X, Column 2, flagged waiver categories are hardly ever informative. For example, when a registrant flagged its data waiving for the 90-day study as “scientifically not justified” and none of the adaptations according to Annex XI, section 1applies, there are four options according to Annex IX, 8.6.2., Column 2 which might account for this

choice. An allocation can then only be made if the registrant states the Annex that was applied or provides an unambiguous argumentation in the waiving justification. Unfortunately, this is rarely the case. A further issue is that flagged waiver categories are often not or only partly in accordance with the content of the respective waiving justification. All these issues significantly impede a fruitful evaluation of waiving justifications in a short time. Regarding the aim to group the reasons for the revised endpoint conclusions, adaptations and waiver had to be allocated to the REACH Annexes based on our estimation for the majority of cases.

5.2.2.2 Genetic Toxicity

From the 40 dossiers checked for the endpoint Muta, 27 were not further analysed because evaluation of grouping/read-across would have been required. 19 endpoints were solely flagged as grouping/read-across by the registrant and eight endpoints were flagged as another adaptation/waiving category, but were based on grouping/read-across. Eleven out of the 13 remaining cases allowed for a re-classification to the endpoint conclusion "compliant" or "non-compliant". Two cases could not be resolved within this project phase. The reasons and incidences for the revised conclusions are summarised in Table 32. It should be kept in mind that the last column does not give the number of dossiers, but of cases due to the fact that more than one reason might have been available for a dossier. Single cases are described in more detail in Annex 7 of this report.

Table 32: Reasons leading to revised endpoint conclusions after more detailed analysis of the "complex" endpoint Muta of randomly selected dossiers

Revised conclusion	Reason	Number*
"Compliant"	Waiving sufficient with respect to conditions stated in one of the following Annexes: • Annex X, paragraph 5 (data waiving due to other reasons) • Annex IV	2
"Compliant"	Substance is classified according to CLP as muta. cat. 1 or carc. cat. 1	3
"Non-compliant"	Adaptation insufficient with respect to: • Annex XI (1.2. weight of evidence)	3
"Non-compliant"	Required information is not available • Required studies are incomplete (Annex VII, 8.4.1., Column 1) • Required studies are not available (Annex VIII, 8.4.3., Column 1; Annex IX, 8.4., Column 2)	6
"Complex"	More detailed analysis required with respect to: • Annex XI (1.2. weight of evidence; 2. technically)	2

*More than one reason may be available for a dossier due to the circumstance that multiple study types are required and/or the registrant applied different adaptations. Therefore, this column gives the number of cases and not of dossiers.

With respect to the study type, studies and adaptations for or waiving of the bacterial gene mutation test (Ames test, OECD TG 471 (1997a)) were the decisive factors for the revised conclusion in nine of 13 cases. One reason is that Muta was classified as "complex" in the screening when a harmonised classification as mutagen cat. 1 or carcinogen cat. 1 was present and the bacterial gene mutation assay had been adapted or waived. The revised conclusion was "compliant" because the providence of an adaptation/waiver was only a formal criterion in that specific case and did not require an in-depth

analysis. Another reason is that the required data for the 5th bacterial strain were not available or of inferior quality. This resulted in the endpoint conclusion "non-compliant". In three of these cases the respective studies were flagged as "WoE". Therefore, another group was defined covering "non-compliant" conclusions due to insufficient adaptation of standard information requirements or waiving justifications according to Annex XI. In case that the "WoE" approach was too comprehensive to be sufficiently analysed within the given time frame, the endpoint conclusion remained "complex". The revised conclusion was "compliant" for two cases in which the waiving justification addressed intrinsic properties of the compound. The first case comprised a waiving of the bacterial gene mutation test owing to the bactericide properties of the substance. Sufficient gene mutation data from other tests than the bacterial test were available. In the second case, the compound is expected to be non-toxic because all components of the chemical are listed in Annex IV (exemptions from registration obligations) of the REACH Regulation.

5.2.2.3 Repeated Dose Toxicity

With respect to the first approach ("complex" endpoints), 30 dossiers were assessed for RDT because grouping/read-across was very frequent. In total, 50 dossiers were checked for the endpoint RDT. For 25 endpoints, grouping/read-across was applied without another adaptation or waiver. 13 endpoints were flagged as another category, but were in fact based on grouping/read-across. Seven out of the twelve remaining cases were re-classified as "non-compliant", while for five cases no new conclusion could be made. Table 33 summarizes the grouped reasons and incidences for the revised conclusions. Single cases are described in more detail in Annex 8 of this report.

Table 33: Reasons leading to revised endpoint conclusions after more detailed analysis of the "complex" endpoint RDT of randomly selected dossiers

Revised conclusion	Reason	Number*
"Non-compliant"	Waiving insufficient with respect to conditions stated in one of the following Annexes: • Annex IX, 8.6.2., Column 2 • Annex X, paragraph 4 (corrosive substance) • Annex X, paragraph 5 (data waiving due to other reasons)	6
"Non-compliant"	No adaptation/waiver for standard information requirements, adaptation/waiver exists only for non-required studies	1
"Complex"	More detailed analysis required with respect to: • Annex XI (1.2. weight of evidence; 3. exposure considerations) • Annex IX, 8.6.2., Column 2	5

* More than one reason may be available for a dossier due to the circumstance that multiple study types are required and/or the registrant applied different adaptations. Therefore, this column gives the number of cases and not of dossiers.

The subchronic study is the only standard information requirement for RDT for substances with a production volume of 1000 tonnes or more per year. Therefore, only one study type has to be adapted or waived. The main reason for the revised conclusion "non-compliant" was insufficiently justified data waiving with regard to endpoint-specific rules (Annex IX) or aspects not covered by REACH Annexes VII-X and XI, e.g. corrosivity or composition of the substance. The latter cases were allocated to Annex X, paragraph 5 which states: "When, for certain endpoints, it is proposed not to provide information for other reasons than those mentioned in Column 2 of this Annex or in Annex XI, this fact and the reason shall also be clearly stated." One example of this group is waiving of the required test

because the compound is a UVCB and has a variable composition. An often observed example for insufficient waiving according to endpoint-specific rules is the waiving of the subchronic test because a subacute study is available showing no or low toxicity. These cases were allocated to Annex IX, 8.6.2., Column 2 4th bullet point and were incomplete because additional properties (e.g. reactivity, solubility, systemic absorption, inhalability) have to be addressed as well. The conclusion remained "complex" when the information was too comprehensive to sufficiently analyse it within the given time frame. This applied to adaptations in the form of a WoE approach and waiving due to exposure considerations which requires checking of the uses of the compound and/or of the CSR. A third case was waiving according to endpoint-specific rules because chronic toxicity studies were available and Annex IX, 8.6.2, Column 2 criteria applies. For deciding on that specific case, the reliability and applicability of these studies has to be checked in more detail.

5.2.2.4 Toxicity to Reproduction

From the 40 dossiers, 14 were not further analysed because grouping/read-across was applied. In eight cases endpoints were solely flagged as grouping/read-across by the registrant and six endpoints were flagged as another adaptation/waiving category, but were indeed based on grouping/read-across. All 26 remaining cases allowed for a re-classification to the endpoint conclusion "compliant" or "non-compliant". The majority of endpoints (23) was re-classified to be "non-compliant". The reasons for and incidences of the revised conclusions are summarised in Table 34. Single cases are described in more detail in Annex 9 of this report.

With respect to the study type, studies and adaptations for or waiving of the two-generation study (OECD TG 416 (2001b)) were the main decisive factors for the revised conclusion. Accordingly, insufficient adaptations/waiver of this study type was frequently observed. A lack of information for the developmental toxicity study (OECD TG 414 (2001a)) in the second species ranked second, followed by the data gap for both study types, the two-generation and the developmental toxicity study. Three cases were allocated to the conclusion "compliant" because the waiving justification according to Annex X, Column 2, 8.7, appeared sufficient, the preliminary conclusion was incorrect because there is a harmonised classification for this endpoint or the most relevant route of administration was chosen in the studies. The route of administration was regarded as acceptable in the screening of this project if the oral route was applied for solids and liquids and the inhalative route for gases. All other cases were allocated to the endpoint conclusion category "complex". In one of these cases, the registrant provided conclusive information that inhalation was the most likely route of human exposure for the registered liquid. The main reason for the conclusion "non-compliant" was the application of insufficient adaptations or waiver. One case which occurred frequently was the waiving of the two-generation study due to no or low toxicity observed in one or more of the following studies: screening (OECD TG 421 or 422 (1995b, 1996)), developmental toxicity, one-generation and RDT. The waiving was allocated to Annex X, 8.7, Column 2, third bullet point and is considered incomplete because further criteria (e.g. absence of absorption) have to be addressed. Another common reason for the conclusion "non-compliant" was that studies for or adaptation/waiving of the second species for the developmental toxicity study was not available. This case had been allocated to the endpoint conclusion category "complex" in the screening. Although a standard information requirement, the need to perform a study in a second species depends on the outcome of the first test and all other relevant data, which requires a more detailed analysis. Meanwhile, ECHA demanded that compliance with the second-species developmental toxicity standard information requirement has to be improved and pointed again to the necessity to (at least) waive the study in the second species (ECHA, 2014a). The revised endpoint conclusion takes these new developments into account. The third reason for the conclusion "non-compliant" dealt with substance-related issues, e.g. studies were not conducted with the registered compound and a grouping/read-across approach was not stated. A minor reason was that the registrant only waived non-required studies for TRep, e.g. chronic and subchronic stud-

ies, while an adaptation/waiver for at least one standard requirement for this endpoint was not available. The fifth reason for the conclusion "non-compliant" was that required studies were either incomplete with respect to the respective OECD testing guidelines or not available.

Table 34: Reasons leading to revised endpoint conclusions after more detailed analysis of the "complex" endpoint TRep of randomly selected dossiers

Revised conclusion	Reason	Number*
"Compliant"	Most relevant administration route was chosen	1
"Compliant"	Waiving sufficient with respect to: • Annex X, 8.7., Column 2	1
"Compliant"	Substance is classified according to CLP as muta. cat. 1	1
"Non-compliant"	Adaptation / waiver insufficient with respect to conditions stated in one of the following Annexes: • Annex X, 8.7., Column 2 • Annex X, paragraph 4 (corrosive substance) • Annex X, paragraph 5 (data waiving due to other reasons) • Annex XI (1.1. use of existing data; 1.2. weight of evidence;2. technically) • Reference to another, inappropriate Annex	17
"Non-compliant"	Study and adaptation/waiving for TG 414, second species, is not available	6
"Non-compliant"	Substance-related issues: • Test was not conducted with registered substance • Composition of the registered chemical is not sufficiently specified, but required for evaluation	3
"Non-compliant"	No adaptation/waiver for standard information requirements, adaptation/waiver exists only for non-required studies	1
"Non-compliant"	Required information is not available • Required studies are incomplete (Annex X, , 8.7.2.), Column 1 • Required studies are not available (Annex X, 8.7.2., Column 1; Annex XI, 1.5 grouping/read-across)	4

* More than one reason may be available for a dossier due to the circumstance that multiple study types are required and/or the registrant applied different adaptations. Therefore, this column gives the number of cases and not of dossiers.

5.2.3 Discussion - Human Health Endpoint Conclusions

The re-examination of "complex" conclusions aimed at identifying and categorising concerns in dossier registrations and, if clarification of the cause of "complex" cases allows, to allocate the endpoints and dossiers to "compliant" or "non-compliant". Within the time limits of this project only a minority of "complex" conclusions could be assessed and this limited number is not expected to represent the entire dossiers. Nevertheless, this analysis already allowed for the identification of some endpoint-specific and -crossing concerns which emerged in REACH registrations. Remarkably, a conclusion

could be made for the majority of "complex" endpoints that were not solely based on grouping/read-across.

In the selected dossiers, grouping/read-across was most often the reason for the conclusion "complex" regarding the endpoints RDT and Muta. This correlates well with the observation that the relative percentage of grouping/read-across is higher for RDT and Muta compared to TRep (Figure 21 in Chapter 3.2.1). Not to forget is that the sample size is very small and that this limited number of cases will certainly not represent the entire "complex" dossiers.

Because grouping/read-across was often applied for RDT and Muta, only 12 and 13 cases, respectively, with other reasons for complexity were evaluated. In contrast, twice as much cases were checked for TRep. This might account for the higher number and diversity of collected reasons for the revised conclusion for this endpoint. Another reason might be that data for two standard information requirements (ReproTox and DevTox) have to be provided in case of TRep, while for RDT only data for one study type, the 90-day study, are requested. For Muta valid information on gene mutation in bacteria and, if required, in mammalian cells as well as on chromosome aberration has to be provided. However, as already mentioned, only half the number of cases were evaluated in comparison to TRep.

With respect to cross-cutting reasons for the conclusions, the reason "insufficient adaptations/waiver" was observed over all endpoints. Due to the fact that most of the cases in the category "complex" are based on adaptations/waiving (Chapter 3.2.1.1), this is obviously a common issue. This reason covers endpoint-specific (Annex VII to X, Column 2) as well as general (Annex XI, Annex X) waiving and adaptation rules and usually results from free text entries in the "waiving justification" field in IUCLID and the Endpoint Summary commenting on why testing is waived. Each adaptation/waiving option has its own requirements as described in the REACH Regulation to sufficiently fulfil the standard information requirements. However, for all in common is that: "The registrant bears the burden of proof to demonstrate that the adaptation is applicable to the registered substance." (ECHA, 2010, practical guide 4) and the lack of justifications or flaws to demonstrate that waiving criteria are fulfilled seems to be a crucial issue in many dossiers. Reasons that were less commonly observed in this "complex case" analysis were "required information is not available" and "no adaptation/waiver for standard information requirements, adaptation/waiver exists only for non-required studies" which also represent an insufficient proof of the applicability of adaptations/waiving.

This analysis, although limited in the number of cases and dossiers examined, also indicated that some provisions on the standard requirements as described in the REACH Annexes may need reconsideration. One example is that a test for gene mutation in bacteria has to be provided for Muta even if a harmonised classification as carcinogenic cat. 1 or germ cell mutagenic cat. 1 or 2 according to CLP exists. In this case a waiver according to Annex VII, 8.4., Column 2 is not envisaged. An adaptation/waiving according to Annex XI cannot be applied as the justification that the substance holds a harmonised classification does not fit to any of the options listed there. From a formal point of view this case would be "non-compliant". An amendment of Annex VII, 8.4., Column 2 referring to a waiving due to harmonised classification as mutagen or carcinogen would obviate redundant testing.

A considerable number of endpoint-specific concerns leading to the allocation as "complex" were identified. These were allocated to different subgroups of reasons according to the adaptation/waiving options provided by the REACH Regulation. Among other reasons the lack of a study or adaptation/waiving with respect to the second species in DevTox and the adaptation of the two-generation study referring to a low toxicity observed in other studies was frequently mentioned for TRep. The latter also applied to the 90-day study required for RDT. The missing 5th strain in the bacterial gene mutation test is a conspicuous issue with Muta.

With respect to the revised endpoint conclusions, a high percentage of the previously assigned "complex" cases were allocated to "non-compliant" for all endpoints. In the "complex case" analysis a few of the random samples were found to be "compliant" for TRep and several cases for Muta. One reason was that they were assigned as "complex" during the screening because a clarification of certain specific issues was required, e.g. an adaptation/waiving for the bacterial gene mutation assay was not available for a compound with harmonised classification (refer to discussion above) or the appropriateness of the administration route had to be checked. In a few other dossiers, adaptations/waivers were sufficiently justified or the initial conclusion was not correct. Of the pool of samples considered in the "complex case" analysis, two cases for Muta and nearly half of the cases for RDT remained "complex". This frequently occurred also for WoE approaches which are often based on comprehensive information and demand further in-depth analysis for evaluation.

The presented "complex case" analysis was a helpful initial step to gain insights into the kind of concerns emerging from REACH registration dossiers and into the complexity of issues. A larger number of dossiers have to be evaluated to reach a representative sample size for all "complex" dossiers and to determine the frequencies of individual concerns. A follow-up project should comprise the development of concepts on how to analyse the available information on the different endpoints and the specific concerns in an efficient and standardised way. The insights obtained here should be one good basis to develop these concepts. Especially the endpoints Muta and TRep allowed for conclusions on the data quality, though the scheduled time during this project was very limited.

5.3 "Complex Endpoints" – Environment

5.3.1 Information Gathering – Environmental Endpoints

For the environmental approach 20 "complex" endpoint conclusions were selected at random for each endpoint to re-examine the "complex" conclusions from the screening. Prior to the evaluation cases in which an adaptation based on a read-across approach were excluded from the list. In total, 100 endpoints were evaluated (for BioDeg and AbioDeg 20 in each case); and the time available to conclude each endpoint conclusion was about 30 min in average.

The overall procedure to gather the information for the analysis was comparable to that for HH (see Chapter 5.2). Briefly, the data already collected for the respective endpoint in KnowSEC were recalled. The registered IUCLID information necessary to assess the endpoint were checked in detail; besides the ESRs and ESS, for example the CSR, additional attached files and further ESRs related to the endpoint under evaluation. Furthermore, selected environmental endpoint conclusions were discussed with experts from the UBA.

The re-examination was performed on a case-by-case basis. Nevertheless, some general evaluation criteria for the environmental endpoints were determined with scientific support from UBA experts:

- Adaptation according to Annex XI, 1.3 ((Q)SAR) without acceptable documentation, e.g. no (Q)SAR Model Reporting Format (QMRF) and (Q)SAR Prediction Reporting Format (QPRF), or without adequate information, e.g. right domain of applicability and appropriate performance (ECHA, 2012c , p. 6ff.), was assessed as "non-compliant". (Q)SAR adaptations with appropriate documentation and information were compiled as "complex" since a deeper analysis of the data is necessary.
- Endpoint study records which based solely on a calculation with a Petrorisk model are insufficient and therefore evaluated as "non-compliant". In a critical review Rorije, Verbruggen et al. (2012, p. 4.) identified different uncertainties in these estimation methodologies regarding the environmental risk assessment.

- Justifications with regard to specific properties of UVCB substances need to be checked in more detail and therefore were assessed as “complex”, if there were no other obviously wrong information given.
- The evaluation of exposure related waiving (Annex XI, 2) mostly has to be categorised as “complex” due to the time-consuming check of exposure scenarios. When the waiving refers to the application of strictly controlled conditions throughout the life cycle of the substance and no releases into the environment are expected this endpoint could be assessed as “compliant”.
- Non-standard test methods, which had not been excluded in advance (see Chapter 2.4), were checked in detail if they presumably fulfil the main information requirements for standard tests. If available, additional sources, e.g. scientific reports, were consulted to compare the requirements and to conclude whether the endpoint has to be classified as “compliant” or “non-compliant”.
- Waiving justifications which were flagged in IUCLID as weight of evidence, scientifically or other justification and emerged as a read-across approach during the analysis remained in the endpoint conclusion category “complex”.

Additional specific selection and testing criteria based on the outcome of the screening were determined for each endpoint. The following chapters are presenting the main procedures of the “complex case” analysis for the environmental endpoints and an overview of the revised conclusions with the underlying reasons.

5.3.2 Specific Analysis Criteria and Results - Environmental Endpoints

5.3.2.1 Overall Observations

In comparison with the screening, altogether, more than half of conclusions could be revised and classified either as “compliant” or “non-compliant” during the approach of “complex endpoints” within the limited time scale. For about one fourth of the endpoints (24) the new conclusion was “compliant”. This was mainly due to revised conclusions in AbioDeg (molecule structure, readily biodegradable) and Bioaccu (K_{ow} trigger value). Nearly one third (29 out of 100) of the endpoint conclusions were categorised as “non-compliant”. The main reasons were insufficient (Q)SAR and the use of Petrorisk models, both predominantly applied for the endpoints BioDeg and Bioaccu. Furthermore, almost half of the conclusions remained “complex”, whereof exposure related waiving considerations were the most frequent reason, and an in-depth analysis will be necessary to finally conclude these assessments.

5.3.2.2 Degradation

The random selection was performed together for the sub-points biotic degradation (BioDeg) and abiotic degradation (AbioDeg). Altogether in 608 dossiers both sub-points were regarded as “complex” during the screening.

The evaluation of AbioDeg is linked to the outcome of the screening test for ready biodegradability, because the standard information requirements for the hydrolysis test could be waived for readily biodegradable substances according to Annex VIII, Column 2, 9.2.2.1.

With regard to the specific rules for adaptation in Annex VII, Column 2, 9.2.1.1, studies on ready biodegradability do not need to be conducted for inorganic substances and therefore the endpoint BioDeg was considered as “compliant” in the screening (see Chapter 2.4.1.1). As a consequence, inorganic substances are not part of the listed substances for AbioDeg as well.

a. Biotic Degradation

Additional criteria for the examination of "complex cases" for BioDeg endpoint conclusions were as follows:

- Non-standard screening tests which fulfil the main requirements of the standard test were accepted. ESRs which were exclusively based on tests like EU C.5 or C.6 (biochemical or chemical oxygen demand, respectively) were assessed as "non-compliant".
- Waiving justification for simulation tests according to Annex IX and X, Column 2, 9.2, e.g. "the CSA has not indicated the need to investigate further the degradation", could not be assessed within the time scale and remained "complex".

Adaptations in BioDeg can take place either for screening tests on ready biodegradability or simulation tests on biodegradation in specific environments like surface water, sediment or soil. Seven out of 20 endpoint conclusions from the first screening were based on adaptations/waiving for screening tests and the other 13 for simulation tests.

In three cases the more detailed evaluation of "complex" cases yielded to the conclusion that the adaptation was considered to be in agreement with the registration requirements and the revised conclusion was "compliant" (Table 35). This included a WoE approach with sufficient information to assess biodegradability as well as a non-standard test conducted according to ISO 10708 which is compatible with standard methods for the screening test (for details see SCHER, 2005).

Table 35: Results from "complex endpoint" analysis for biotic degradation - revised conclusions, their reasons and number

Revised conclusion	Reason	Number
"Compliant"	Adaptation/waiving sufficient with respect to…	
	• Annex XI, section 1.1.2 - Use of existing data Non-standard test but basic requirements fulfilled, ISO 10708	1
	• Annex XI, section 1.2 - WoE Acceptable standard test with registered substance	1
	• Annex IV exemption Multi-constituent composed of listed substances considered to cause minimum risk	1
"Non-compliant"	Adaptation insufficient with respect to…	
	• Annex XI, section 1.1 - Use of existing data Petrorisk calculation, reference to screening results, non-standard test (BOD) and basic requirements not fulfilled	4
	• Annex XI, section 1.3 - (Q)SAR Documentation incomplete	2
"Complex"	In-depth analysis required with respect to…	
	• Annex IX and X, Column 2, 9.2 CSA has not indicated a need to investigate further the degradation	6
	• Annex IX and X, Column 2, 9.2.1.3 & 9.2.1.4 Direct and indirect exposure of soil/sediment is unlikely	2
	• Annex XI, section 1.2 - WoE	1
	• Annex XI, section 2 - Technically Substance related issues, UVCB	2

Six endpoint study records did not fulfil the adaptation requirements according to Annex XI, section 1 and therefore the re-examination led to the endpoint conclusion "non-compliant". Different cases of insufficient use of existing data occurred, such as a not accepted screening test on ready biodegradability (BOD-test, biochemical oxygen demand) as the only source of information, and inadequate waiving for the simulation test justified by a simple reference to the screening result or based on a calculation with the Petrorisk model (see Chapter 5.3.1). In addition, for two endpoint study records with an adaptation via (Q)SAR the necessary documentation forms were attached, but the relevant data were not available.

In about half of the cases the conclusion remained "complex" and an in-depth assessment is necessary to come to a final conclusion. In this context, the simulation test was frequently justified by adaptations according to Annex IX and X, Column 2, 9.2. Furthermore, exposure considerations referring to Annex IX and X, Column 2, 9.2.1.3 and 9.2.1.4 were used for the waiving as well as substance related issues like technically problems conducting the test for UVCB (Annex XI, section 2).

b. Abiotic Degradation

Two major assessment criteria for the re-examination of the endpoint conclusion were defined:

- Waiving justification with respect to the molecule structure was evaluated. For substances with a lack of hydrolysable functional groups, e.g. according to Warren (1990, p. 7-4f.), the endpoint were categorised as "compliant".
- If a re-examination of a BioDeg conclusion led to the conclusion that the substance has to be considered as "readily biodegradable", and the waiving justification in AbioDeg is in accordance with Annex VIII, Column 2, 9.2.2.1, the respective endpoint was re-assessed as "compliant".

From the selected dossiers 17 out of 20 endpoint conclusions were filed as "complex" due to adaptation or waiving for the guideline test on hydrolysis as a function of pH (OECD, 2004c). In three cases the substance was high adsorptive with a log K_{ow} > 4 and therefore regarded as "complex".

The evaluation of "complex cases" for the endpoint study records of AbioDeg resulted in 12 revised conclusions as "compliant" (Table 36). In nine cases the justification was according to a molecule structure with a lack of hydrolysable functional groups. In three cases the waiving justification ('substance is readily biodegradable') was accepted, because of the revised conclusion in BioDeg. Two endpoints conclusions were filed under "non-compliant", since the waiving justification was obviously wrong. First, the indicated water solubility, on which the adaptation based, did not fulfil the criteria according to Annex VIII, Column 2, 9.2.2.1 and second, the WoE approach was insufficient since only one study was available with a reliability of four.

Cases where additional effort is necessary to conclude the evaluation refers to high adsorptive substances with a log K_{ow} > 4 and adaptations according to Annex XI, i.e. an identified read-across which was hidden behind another data waiving category and substance related justifications for non-testing, as for some UVCB.

Table 36: Results from "complex endpoint" analysis for abiotic degradation - revised conclusions, their reasons and number

Revised conclusion	Reason	Number
"Compliant"	Adaptation/waiving sufficient with respect to…	
	• Annex XI, section 1 - Scientifically Molecule structure, lack of hydrolysable functional groups	9
	• Annex VIII, Column 2, 9.2.2.1 Substance is readily biodegradable	3
"Non-compliant"	Adaptation/waiving insufficient with respect to…	
	• Annex XI, section 1.2 - WoE Only one study with reliability 4 available	1
	• Annex VIII, Column 2, 9.2.2.1 Criterion water solubility < 1 mg/L failed	1
"Complex"	In-depth analysis required with respect to…	
	• Annex XI, section 1.5 - Read-across	1
	• Annex XI, section 2 - Technically Substance related issues, UVCB	2
	• Substance adsorptive (log K_{ow} > 4)	3

5.3.2.3 Bioaccumulation

For the evaluation of "complex cases" of the endpoint bioaccumulation the following specific proceedings were made:

- Inorganic, ionisable or hydrolytically unstable substances which were filed as "complex" in the screening (see Chapter 3.3.2.1, Table 26) were excluded from the re-examination due to experiment-related problems with these groups of substances.
- As stated in Annex IX, Column 2, 9.3.2 a bioaccumulation study need not to be conducted for substances with low potential for bioaccumulation. Some registrants performed bioaccumulation studies or adapted the information required by other means, although a waiving according to Column 2 criteria was possible. During the evaluation of "complex cases", the partition coefficient was checked, and for substances with a log $K_{ow} \leq 3$ the conclusion was revised and classified as "compliant" independent from the existing adaptation/waiving.
- Tests conducted according or corresponding to the replaced guideline OECD TG 305C (1981e), such as the Japanese MITI-Test, were still filed as "complex", because the available data stated in IUCLID usually is not sufficient for a rapid check of compatibility with the requirements for the standard test OECD TG 305 (2012a).

In total, the selection was based on 642 dossiers. The endpoint conclusions of the selected dossiers were mainly categorised as "complex" by means of adaptation/waiving of standard information requirements like (Q)SAR, scientifically justifications, exposure consideration and WoE. In addition, three non-standard tests were applied.

Five out of 20 conclusions were corrected to "compliant" as the substances could have been waived due to the low potential of bioaccumulation; however, the registrants did not make use of this possibility (Table 37). Ten revised conclusions filed under "non-compliant", 7 of which had an adaptation by (Q)SAR according to Annex XI, section 1.3, but failed reporting sufficient documentation or the

required specification within the attached document was not available (see Chapter 5.3.1). Two further BCF calculations were performed with the hydrocarbon block model incorporated in the Petrorisk model and therefore, were not accepted (see Chapter 5.3.1). In addition, one waiving was not accepted as the reported partition coefficient exceeded the log K_{ow} threshold stated in Annex IX, Column 2, 9.3.2.

No firm conclusion could be reached for five endpoints, as, for example, the examination of the waiving justification led eventually to a read-across adaptation or the exposure considerations were not possible to assess within the time scale.

Table 37: Results from "complex endpoint" analysis for bioaccumulation - revised conclusions, their reasons and number

Revised conclusion	Reason	Number
"Compliant"	Waiving sufficient with respect to… • Annex IX, Column 2, 9.3.2 Criterion log K_{ow} ≤ 3 fulfilled, without explicit reference	5
"Non-compliant"	Adaptation/waiving insufficient with respect to… • Annex XI, section 1.1 - Use of existing data Calculation method not acceptable, hydrocarbon black method incorporated in Petrorisk model • Annex XI, section 1.3 - (Q)SAR Documentation incomplete • Annex IX, Column 2, 9.3.2 Criterion log K_{ow} ≤ 3 failed	2 7 1
"Complex"	In-depth analysis required with respect to… • Annex XI, section 1.1 - Use of existing data OECD TG 305C • Annex XI, section 1.2, 1.5 - Read-across Based on WoE and Scientific justification • Annex XI, section 3 - Exposure considerations	1 2 2

5.3.2.4 Ecotoxicity

Besides the above mentioned general criteria for the evaluation of "complex cases" the following specifications for the endpoint ecotoxicity were added:

- A waiving justification with respect to Annex IX and X, Column 2, 9.2 is categorised as "compliant", if the chemical safety assessment indicated no risk (PEC/PNEC < 1) and the substance is neither classified according to Annex 1, CLP Regulation nor PBT/vPvB. For substances which are classified the decision-making depends on various details to be taken into account, like water solubility, available tests, effect-concentration, and assessment factor; hence these cases are mostly filed under "complex".
- Non-standard tests, short-term as well as long-term, for fish and invertebrates are presumed to be "compliant" if they are fulfilling the main requirements in comparison with the respective standard guidelines regarding, for example, time of exposure, test species, age, pH and temperature.

The random selection of dossiers in which the endpoint ecotoxicity was rated as "complex" (1493 dossiers) represented all possible conclusions for this endpoint (see Chapter 3.3.4), mainly based on

adaptation or waiving justifications and in addition, referred to an quotient of EC_{50}/LC_{50} between 0.2 – 5.0.

During the re-examination four conclusions for the endpoint ecotoxicity were categorised as "compliant" (Table 38), thereof three cases had an acceptable waiving justification according to Annex IX and X, Column 2, 9.2. Another "compliant" conclusion based on non-standard long-term tests for fish and invertebrates conducted under GLP and fulfilling the basic information requirements. In four cases the review of complex cases led to the conclusion "non-compliant" due to a variety of reasons: a documentation of the (Q)SAR result was not available, a WoE approach was performed where the test material identity was neither in accordance with the registered substance nor a read-across was indicated, a justification based on low water solubility was inconsistent with the range of values reported in IUCLID, and a wrong PNEC calculation leading to an underestimated risk characterisation ratio.

However, for the majority of the dossiers, 12 cases, the endpoint conclusion remained in the category "complex". These waiving justifications related mainly to waiving according to Annex IX and X, Column 2, 9.2, further to exposure considerations, e.g. for gaseous substances, or to adaptations with well documented (Q)SAR calculations that need to be conducted in detail for a final conclusion.

Table 38: Results from "complex endpoint" analysis for ecotoxicity - revised conclusions, their reasons and number

Revised conclusion	Reason	Number
"Compliant"	Adaptation/waiving sufficient with respect to…	
	• Annex XI, section 1.1.2 - Use of existing data Acceptable non-standard long-term tests under GLP	1
	• Annex IX and X, Column 2, 9.2 CSA indicated no risk, substance not classified and not PBT/vPvB	3
"Non-compliant"	Adaptation/waiving insufficient with respect to…	
	• Annex XI, section 1.2 - WoE Inconsistent test material identity	1
	• Annex XI, section 1.3 - (Q)SAR Documentation incomplete	1
	• Annex XI, section 2 - Technically Statement regarding tests and water solubility inconsistent	1
	• Annex XI, section 3 - Exposure considerations Statement inconsistent, wrong PNEC	1
"Complex"	In-depth analysis required with respect to…	
	• Annex IX and X, Column 2, 9.2 CSA indicated no risk, substance classified	6
	• Annex XI, section 1.1 - Use of existing data Only one long- and short-term test	1
	• Annex XI, section 1.3 - (Q)SAR Documentation available	1
	• Annex XI, section 3 - Exposure considerations	4

5.3.3 Exposure

The analysis of "complex cases" of the endpoint exposure was limited through the considerable amount of data given in the exposure scenarios which could not be analysed in detail during this approach. The relevant endpoint-specific criteria are as follows:

- Endpoints with available exposure scenarios which were not obviously wrong remain in the category "complex".
- If the information regarding tonnages and uses do not match between the IUCLID entries and the details given in the chemical safety report, the endpoint conclusion was revised to "non-compliant", since the basis of the exposure calculations was implausible.
- A qualitative exposure assessment which is not justified properly was considered as "non-compliant", e.g. standardised information without exposure-specific considerations. However, if sufficient information was given and no questions left over the endpoint was classified as "compliant".

The screening yielded two possible "complex" conclusions (overall 1012 dossiers) either due to the availability of exposure scenarios or qualitative exposure assessments. In the selected dossiers no conclusion for the endpoint Expo was re-assessed as "compliant" (Table 39). Seven conclusions were categorised as "non-compliant". In three cases inconsistencies regarding the information of tonnage or uses occurred between the entries in IUCLID and the respective chapters of the chemical safety report. Three other exposure scenarios were calculated via a Petrorisk model (see Chapter 5.3.1) and one qualitative exposure assessments had insufficient justifications.

The majority of endpoint conclusions remain in the category "complex" since the exposure scenarios had to be analysed in detail. In addition, the justification of a qualitative exposure assessment has to be checked in more detail.

Table 39: Results from "complex endpoint" analysis for exposure - revised conclusions, their reasons and number

Revised conclusion	Reason	Number
"Compliant"	-	-
"Non-compliant"	Information insufficient with respect to…	
	• Annex I, section 0 Information regarding tonnage and uses inconsistent	3
	• Annex I, section 5 Exposure scenarios calculated via Petrorisk model	3
	• Annex I, section 5 & 6 Qualitative exposure assessment inadequate	1
"Complex"	In-depth analysis required with respect to…	
	• Annex I, section 5 Exposure scenarios	12
	• Annex I, section 5 & 6 Qualitative exposure assessment	1

5.3.4 Discussion - Environmental Endpoint Conclusions

The results from the evaluation of environmental "complex endpoints" gave a short, not representative overview of particular concerns for each endpoint as provided in detail in the previous chapter. Altogether, the outcome showed some frequent problems regarding the dossier registration under REACH Regulation. Besides some endpoint specific features mainly crosscutting issues occurred with an impact on several environmental endpoint conclusions. Both aspects are subsumed within the following thematic groups:

- Substance-related
  - Difficult substances: e.g. inorganic, ionisable, and hydrolytically unstable substances;
  - Complex mixtures: UVCB, multi constituents
  - Physico-chemical properties: n-octanol water partition coefficient –K_{ow}, water solubility - S_w, acid dissociation constant - pK_a; Henry's law constant – k_H;
  - Molecule structure
- Adaptation/waiving
  - (Q)SAR; Petrorisk model
- Exposure related
  - Chemical safety assessment and exposure scenarios;
  - Substance-specific exposure considerations
- Experimental data
  - Non-standard tests

Substance-related issues

As reported, the assessment for "difficult substances" was partially excluded for Bioaccu. For inorganic and ionisable substances a special guidance is needed (ECHA, 2012b, p. 66f.). In addition, according to Annex VII, 7.8 the partition coefficient does not need to be conducted for inorganic substances, as it is not an adequate tool to predict bioaccumulation. Therefore, the information requirements for the bioaccumulation study were usually waived with the justification that the substance is inorganic, although no respective Annex criterion exists.

The data availability for complex mixtures differs considerably between the registration dossiers. While some dossiers provided extensive data for endpoints and physico-chemical parameters, the majority of those, especially UVCB substances from petroleum products, contained insufficient endpoint study records. The use of Petrorisk models is a frequent source of concern (see model-specific issues).

The physico-chemical parameters K_{ow} and S_w are important regulatory triggers (ECHA, 2014c, p. 49ff.), with an impact on most environmental endpoints, as seen in the decision trees in Chapter 2.4. Thresholds of these parameters are used as adaptation criteria in the Column 2 of different Annexes, e.g. log K_{ow} for Bioaccu Annex IX, 9.3.2, S_w for BioDeg Annex IX, 9.2.1.2 and Ecotox VIII, 9.1.3. During the analysis of "complex endpoint" conclusions the method of determination for K_{ow} and S_w was noted for Bioaccu and Ecotox, respectively. For less than half of the 20 cases an experimental K_{ow} and for 13 out of 20 ESR an experimental S_w was derived. Instead of that, data from handbooks, calculations via (Q)SAR and Petrorisk models as well as adaptations via WoE and read-across were stated. Moreover, for complex substances often a defined range of values was presented. Both aspects enhanced the uncertainties in the dossier analysis; and therefore, it is appropriate to pay more attention on the reliability of physicochemical parameters in future assessments.

A frequent waiving justification (9 out of 20 cases) for the hydrolysis test in AbioDeg is the molecule structure of a substance with a lack of hydrolysable functional groups under environmental relevant conditions. This criterion it is not part of the adaptations described in the Annexes. Nevertheless, it is

widely used and a modification with respect to the adaptation criteria for this endpoint may be helpful for the registration procedure.

Adaptation/waiving

(Q)SAR models were applied at three endpoints from the "complex cases", most frequent for Bioaccu, and further for BioDeg and Ecotox, as well as for the calculations of K_{ow} and S_w. Altogether, in 10 out of 11 cases the endpoint conclusion was revised and categorised as "non-compliant" since the entries were not in accordance with Annex XI, 1.3. Either the documentation files QRMF and QRPF were missing or these files were attached but did only contain general statements and no information about the specific calculations. Moreover, for (Q)SAR results which were copied directly into the ESRs the relevant information was often not available, e.g. regarding the applicability domain. Altogether, the basic requirements according to REACH Regulation were rarely met and special attention is needed to achieve sufficient ESRs for the (Q)SAR approach; especially considering its increasingly widespread use.

For petroleum products the Petrorisk models and the incorporated hydrocarbon block model are frequently used to calculate various physicochemical parameters and environmental endpoints. In the analysis of "complex cases" they were applied for calculations of exposure scenarios, BCF and K_{ow}. Together for the endpoints Bioaccu and Expo nine ESRs for substances with an origin indicated as petroleum product were analysed and five of them were classified as "non-compliant" because a Petrorisk model had been applied. During the screening it was not recorded how often a Petrorisk model was used. However, petroleum products represent almost 10% of the investigated dossiers and hence a considerable number of applications are expected. To fulfil the information requirements a more appropriate model for petroleum products is recommended by Rorije, Verbruggen et al. (2012, p. 83.).

Exposure-related issues

The assessment of exposure scenarios, necessary to derive a conclusion for Expo, is the most time-consuming step in dossier evaluation due to the large scale and in several cases the high number of exposure scenarios presented in a CSR. Therefore, the majority of the endpoint conclusions for Expo remained "complex", if no other obvious deficiencies were discovered.

The same was true for most exposure related waiving, as supported by the results for BioDeg and Ecotox. In 15 out of 40 cases waiving was justified with regard to the outcome of the chemical safety assessment (Annex IX and X, Column 2, 9.2), whereof twelve conclusions remained "complex" and has to be checked in detail. Moreover, other exposure related waiving, usually in the context of substance-specific properties, were applied in nine cases for the endpoints BioDeg, Bioaccu, and Ecotox.

Exposure related adaptation/waiving were primarily responsible for the high number of "complex" conclusions at the end of this approach. The focus here was on Expo and Ecotox; therefore, these endpoints are of major interest with respect to an in-depth analysis.

Experimental data

The examination of non-standard methods could be another time consuming step, in particular, if studies were conducted according to old guidelines. Test methods have to be researched and checked for their compatibility with the recommended standard requirements according to Annex XI, 1.1.2. Among the selected "complex endpoints" only three non-standard tests were represented (BioDeg, Ecotox). Nevertheless, the large number of different non-standard tests, conducted especially for the endpoint Ecotox (see Chapter 3.3.4, Table 29), is a huge challenge to assess the compliance of the respective ESRs.

Due to the limited time scale, only a relatively small number of conclusions per each endpoint could be investigated and not all "complex" conclusions could finally categorised as "compliant" or "non-

compliant". In addition, read-across approaches had to be excluded from this analysis. However, within this approach it was possible to identify some important tendencies and concerns regarding the registration procedure under REACH Regulation, both endpoint-specific and crosscutting issues. An in-depth analysis with regard of environmental endpoints should focus on the endpoints Ecotox and Expo, as there is huge demand to assess the data quality either of exposure scenarios, or the non-standard tests. Furthermore, major areas of concern are related to the quality and documentation of calculation models, e.g. (Q)SAR and Petrorisk, and to the registration of UVCB substances, with a special focus on petroleum products.

5.4 "Complex Dossiers"

For 20 random selected dossiers the respective endpoints were analysed as described for the approach of "complex endpoints" in the Chapters 5.2 and 5.3 for HH and ENV, respectively. Besides potential revised conclusions for endpoints and dossiers the aim of the analysis of "complex dossiers" was either to categorise endpoints and overall dossier conclusion as "compliant" or "non-compliant" according the information requirements under REACH Regulation, or may show distinctive features or systematic mistakes across the registered dossier.

Results

The dossier selection encompassed seven "complex endpoints". The endpoint degradation, which consists of the two sub points biotic or abiotic degradation, was considered as "complex", if one of both were classified as "complex", and none of them as "non-compliant". Therefore, a few sub point conclusions of the selection were not "complex", but either "compliant" or "testing proposal".

The results for the revised endpoint and overall dossier conclusions are summarised in Table 40. Nearly one third of the endpoints from the selected dossiers could not be evaluated, since they had been assessed as "complex" due to a grouping/read-across adaptation. The examination showed that another 19 conclusions were also based on a read-across adaptation, mostly as part of a WoE approach and in some cases according to other adaptation groups (e.g. "scientifically"). Read-across was primarily used for the three HH endpoints as well as for Ecotox and BioDeg. The reason of "complex" conclusions with regard to the endpoints AbioDeg, Bioaccu and Expo differed considerably from the above mentioned ones. For Expo the read-across adaptation was not relevant and important reasons for "complex" conclusions for AbioDeg were inorganic substances and for Bioaccu inorganic or ionisable substances.

Nine endpoint conclusions were re-assessed as "compliant", whereas two third of all accounted for AbioDeg due to justifications related to the molecule structure (see Chapter 5.3.2.1). In addition, 20 endpoint conclusions were revised to "non-compliant", focussed on TRep and Bioaccu.

At the outcome of the re-examination no overall dossier conclusion was evaluated as "compliant", in 13 out of 20 cases it was categorised as "non-compliant" and seven conclusions remain unchanged. The "non-compliant" dossiers were mainly based on one or two "non-compliant" endpoint conclusion (seven and four cases, respectively). Another two dossiers had five endpoints classified as "non-compliant".

Discussion

A small number of "complex dossiers" selected at random were analysed in more detail, thus the outcome was quite limited and not representative for the whole group of registration dossiers for substances with high tonnages. Nevertheless, the analysis of "complex dossiers" provided some insights of crosscutting dossier concerns, which went beyond the results from the endpoint-specific evaluation.

As expected, a huge percentage of the "complex" endpoint conclusions based on adaptations via grouping/read-across, especially at those endpoints, which require more expansive tests systems, like Muta, RDT, TRep and Ecotox. Moreover, the revised endpoint conclusions which also based on adaptations containing a read-across approach followed the same pattern. Nearly all selected dossiers contained adaptations via a read-across approach. In many cases read-across adaptations were applied to several endpoints of the same dossier. On the one hand there is an enormous need to validate the read-across application to conclude the overall dossier conclusion; on the other hand the widespread use indicates the huge potential to reduce animal testing.

The percentage of "non-compliant" dossier conclusions was considerably enhanced throughout the analysis. As the justifications for adaptation/waiving were not checked in detail during the screening, they were a major source for potential deficiencies. The dossiers with several endpoints classified as "non-compliant" gave hints for systematic problems. In both dossiers with five "non-compliant" endpoints the overall dossier quality was poor since for various justifications the basic information requirements were not available.

Table 40: Endpoint and overall dossier conclusions for the 20 randomly selected "complex dossiers" after the re-examination

Dossier	Muta	RDT	TRep	Degradation		Bioaccu	Ecotox	Expo	Overall dossier
				BioDeg	AbioDeg				
1	CX (RA)	CX (RA)	CX (RA)	CX (RA)	**CT**	CX (RA)	CX (RA)	CX	CX
2	CX (RA)	CX (RA)	**NC**	CT	CX	CX	CX (RA)	CX	**NC**
3	**CX (RA)***	CX (RA)	CX (RA)	CX (RA)	CX	CX (RA)	**CX (RA)***	CX	CX
4	**CT**	CX	**CT**	CT	CX	CX	CX (RA)	**NC**	**NC**
5	**NC**	**NC**	**NC**	CX	CT	**NC**	**NC**	CX	**NC**
6	**CT**	CX (RA)	**NC**	**NC**	**CT**	**NC**	**NC**	**NC**	**NC**
7	CX (RA)	CX (RA)	**NC**	TP	CX	**NC**	**TP**	CX	**NC**
8	CX (RA)	CX (RA)	CX (RA)	CX (RA)	**CT**	**NC**	CX (RA)	**NC**	**NC**
9	**CX (RA)***	**CX (RA)***	CX (RA)	CX (RA)	**CT**	CX	CX (RA)	CX	CX
10	**NC**	CX	**NC**	CT	CX (RA)	CX	CX	CX	**NC**
11	CX (RA)	**CX (RA)***	**CX (RA)***	CT	CX	CX	**CX (RA)***	CX	CX
12	**CX (RA)***	**CX (RA)***	**CX (RA)***	**NC**	**CT**	CX (RA)	CX	CX	**NC**
13	CX (RA)	**CX (RA)***	**NC**	CX (RA)	CX	CX	CX (RA)	CX	**NC**
14	CX (RA)	CX (RA)	CX (RA)	CT	CX	CX	CX	CX	CX
15	CX (RA)	CX (RA)	**CX (RA)***	CX (RA)	CX	CX	CX (RA)	**NC**	**NC**
16	CX (RA)	**NC**	**NC**	**CX (RA)***	CX	CX	CX (RA)	CX	**NC**
17	**CX (RA)***	**CX (RA)***	**CX (RA)***	CT	CX	CX	CX (RA)	CX	CX
18	CX	CX (RA)	**CX (RA)***	CX (RA)	CX (RA)	CX	CX (RA)	CX	CX
19	CX (RA)	**CX (RA)***	CX (RA)	CX (RA)	**CT**	**CX (RA)***	CX (RA)	**NC**	**NC**
20	CX (RA)	CX (RA)	CX (RA)	**CX (RA)***	CX	CX	CX (RA)	**NC**	**NC**

Highlighted entries indicate revised conclusions. Conclusions without changes are displayed in grey. Abbreviations: CT – "compliant", NC – "non-compliant", CX – "complex", CX (RA) – "complex" conclusion based on grouping/read-across, TP – "testing proposal". * Initially classified as another waiving category by the registrant. The re-examination revealed that evaluation of grouping/read-across is required for further analysis.

These findings emphasize first, the importance of a scientifically justified assessment of grouping/read-across approaches, and second, the opportunity to use the extensive data from this project to identify registration dossiers of concern for future evaluation.

6 Outlook

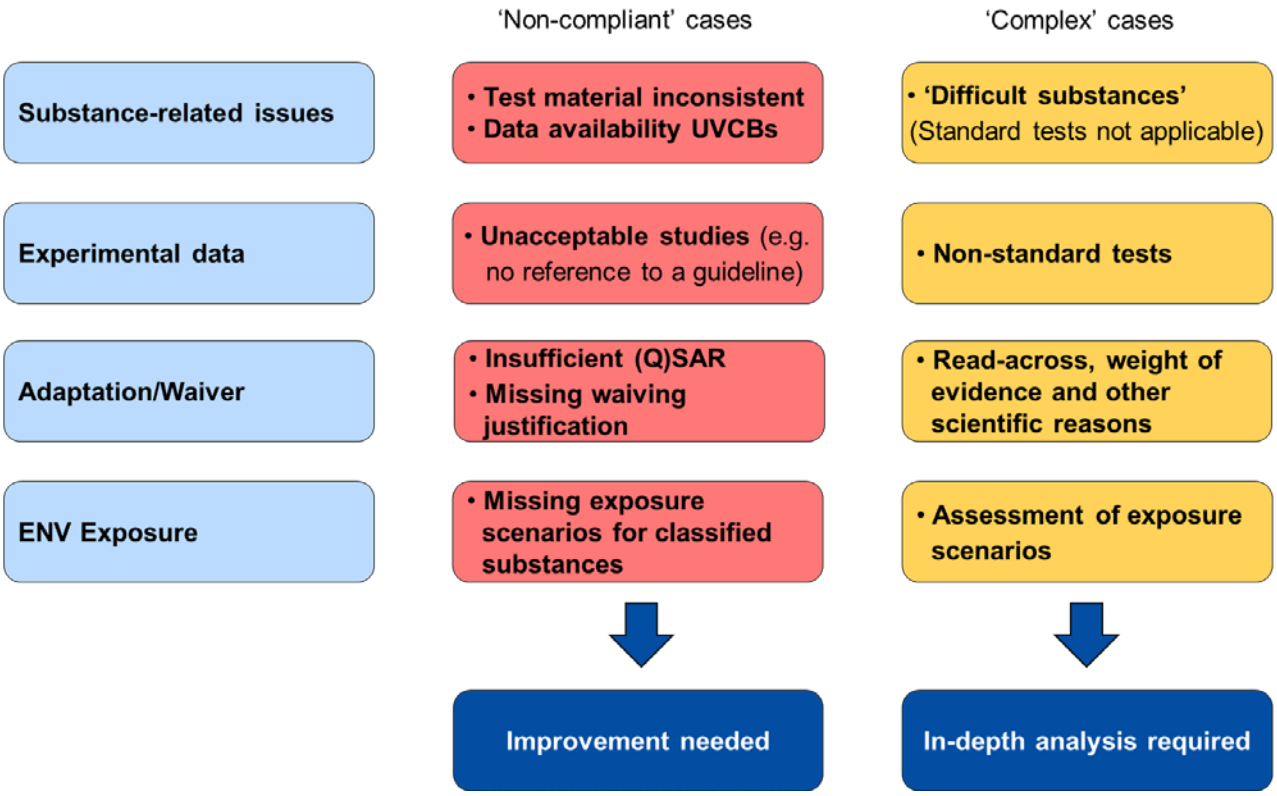
The systematic approach of the project focussed on the data availability and data quality of selected endpoints in dossiers for substances equal or above 1000 tpa. Data gaps occurred in many registration dossiers (58% of 1814 evaluated dossiers), thereof the majority of dossiers had deficiencies for one or two endpoints. For 42% of the dossiers the standard information requirements were adapted or waived at least in one endpoint. Due to the limited time no firm conclusion could be reached with regards to the compliance of the adaptation/waiving to the REACH information requirements. For these cases a future in-depth analysis is necessary.

A number of general cross-cutting concerns which were commonly identified within this project are illustrated in Figure 34. These concerns, grouped into four categories, are related to “non-compliant” as well as “complex” conclusions. The identified deficiencies in the registration dossiers (category “non-compliant”) require further improvement with regard to the data availability and data quality. The observations of this project could help the registrants to overcome common shortcomings. In addition, the concerns related to the conclusion category “complex” point out issues which could not be concluded within the premises of this project and which require a more detailed analysis.

Several of the general issues in the registration dossiers might result from the comprehensiveness and the complexity of the testing requirements for substances at this tonnage level and some ambiguities in the Annexes of the REACH Regulation or guidance documents, e.g. on the need of the second species in developmental toxicity testing. A clarification in the aforementioned documents would be desirable. Similarly, further guidance is needed on the acceptance of applied non-guideline methods and on the reporting of test materials used in experimental studies.

Some of the aforementioned general concerns will be investigated further in a follow-up project from April 2015 to March 2016. Amongst others, an in-depth assessment of the adequacy of the adaptations and waiving justifications referring to the standard information requirements will be conducted. Moreover, it is planned to develop evaluation concepts for specific issues of selected endpoints (toxicity to reproduction, genetic toxicity, ecotoxicity, and environmental exposure). The aim of the project is to gain deeper insight into the data quality of the dossiers and to assign “complex” conclusions to the categories “compliant” or “non-compliant”.

Figure 34: General endpoint concerns identified within this project



The outcome of the project identified unacceptable data gaps in registration dossiers that require improvement. Furthermore, the quantitative recording of shortcomings and the identified areas of improvement offer several possibilities to support the competent authorities' tasks under REACH. German authorities will use the project results to select substances for regulatory measures under REACH and to prioritise substances for immediate and long-term actions. Moreover, ECHA and other member states may apply the results for their IT-screening activities. ECHA may also consider the outcome of the project within their new compliance check strategy. The project results could be used as starting information for activities of ECHA on the dossier evaluation. Registrants with "non-compliant" dossier conclusions could be informed after scrutiny in a formal compliance check procedure. As the number of feasible compliance checks is limited, the project outcome allows to prioritise dossiers with the highest number of inadequate datasets. The identified general shortcomings of the REACH Regulation or its guidance documents that commonly lead to misinterpretations could also be addressed in training programs for registrants.

The considerable number of "non-compliant" conclusions raises the question whether the 5% level for compliance check of registrations (acc. to Art. 41 (5)) is adequate to allow for a safe use of registered substances. Although the project mainly focussed on a screening methodology, it is the first study that examined the total number of lead and individual dossiers of the 1000 tpa registrations of the 2010 deadline. The preliminary results on 1814 dossiers already documented that the majority of dossiers may not be fully compliant to the information requirements of the REACH Annexes.

It is to be noted that the screening within this project is not comparable with a full compliance check that is conducted by ECHA according to Art. 41 (1). Nevertheless the project results suggest that the present 5% level of dossiers/tonnage level seemed to be too low to assure that the registration dossiers comply with the REACH Regulation. The outcome of the project could be understood that all parties involved at level of the Commission, ECHA and the Member States are invited to start a dialogue

on the question whether the 5% level of compliance checks at a tonnage band is sufficient. One option to be discussed is to elevate the percentage of full compliance check as it is foreseen by the REACH Art. 41 (7).

The results of this project support the information note from eight Member States in which the need to improve the quality of REACH registrations is one of the "key issues ... to achieve the long-term goal of a non-toxic environment in the European Union" (EU-Council, 2014, p.3 & 5f). Besides the consideration on the appropriateness of the available REACH instruments from the perspective of the authorities, the project outcome also calls all stakeholders to get actively involved in the improvement of the dossier quality. The huge effort that is needed to meet the requirements of registrations on high tonnage chemicals is acknowledged. However, all registrants are encouraged to make additional efforts to improve the data availability and data quality of their registration dossiers. Only if potential hazards and risks for men and the environment can be reliably identified, a safe use of chemicals is possible.

7 References

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OECD. (1997d). Mammalian Bone Marrow Chromosome Aberration Test. OECD Guidelines for the testing of chemicals No. 475. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (1997e). Mammalian Erythrocyte Micronucleus Test. OECD Guidelines for the testing of chemicals No. 474. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (1997f). Mammalian Spermatogonial Chromosome Aberration Test. OECD Guidelines for the testing of chemicals No. 483. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (1997g). Neurotoxicity Study in Rodents. OECD Guidelines for the testing of chemicals No. 424. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (1997h). Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells In Vivo. OECD Guidelines for the testing of chemicals No. 486. Organisation for Economic Cooperation and Developement (OECD), Paris.

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OECD. (1998b). Repeated Dose 90-day Oral Toxicity Study in Rodents. OECD Guidelines for the testing of chemicals No. 408. Organisation for Economic Cooperation and Developement (OECD), Paris.

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OECD. (2001a). Prenatal Developmental Toxicity Study. OECD Guidelines for the testing of chemicals No. 414. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2001b). Two-Generation Reproduction Toxicity Study. OECD Guidelines for the testing of chemicals No. 416. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2002a). Aerobic and Anaerobic Transformation in Aquatic Sediment Systems. OECD Guidelines for the Testing of Chemicals No. 308. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2002b). Aerobic and Anaerobic Transformation in Soil. OECD Guidelines for the Testing of Chemicals No. 307. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2004a). Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test. OECD Guidelines for the Testing of Chemicals No. 309. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2004b). *Daphnia* spec., Acute Immobilisation Test. OECD Guidelines for the Testing of Chemicals No. 202. Organisation for Economic Cooperation and Developement (OECD), Paris.

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OECD. (2009b). Carcinogenicity Studies. OECD Guidelines for the testing of chemicals No. 451. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2009c). Chronic Toxicity Studies. OECD Guidelines for the testing of chemicals No. 452. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2009d). Combined Chronic Toxicity\Carcinogenicity Studies. OECD Guidelines for the testing of chemicals No. 453. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2009e). Subacute Inhalation Toxicity: 28-Day Study. OECD Guidelines for the testing of chemicals No. 412. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2009f). Subchronic Inhalation Toxicity: 90-Day Study. OECD Guidelines for the testing of chemicals No. 413. 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). Extended One-Generation Reproductive Toxicity Study. OECD Guidelines for the testing of chemicals No. 443. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2012d). Fish Short Term Reproduction Assay. OECD Guidelines for the Testing of Chemicals No. 229. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2013a). Fish, Early-life Stage Toxicity Test. OECD Guidelines for the Testing of Chemicals No. 210. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2013b). Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays. OECD Guidelines for the testing of chemicals No. 488. Organisation for Economic Cooperation and Developement (OECD), Paris.

OECD. (2014). In Vivo Mammalian Alkaline Comet Assay. OECD Guidelines for the testing of chemicals No. 489. Organisation for Economic Cooperation and Developement (OECD), Paris.

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8 Annexes

Annex 1: Memos for Human Health Endpoints

Memo	Question	Description	Frequency (number of memos) *
General			
Ident	All	Contradictory, incorrect or no information with respect to identity of the test material and its conformity with the registered substance. Applies to all information retrieval and to all endpoints. Applies when all other requirements are fulfilled. Respective ESR section in IUCLID: “test material”.	Muta: 297 TRep: 99 RDT: 154
FDA	All	Any guideline according to FDA if it is the only guideline given. Correct study type is given. ESR will be accepted.	Muta: 0 TRep: 9 RDT: 6
ICH	All	Any guideline according to ICH if it is the only guideline given. Correct study type is given. ESR will be accepted.	Muta: 0 TRep: 6 RDT:
NTP	All	Any guideline according to NTP if it is the only guideline given. Correct study type is given. ESR will be accepted.	Muta: 12 TRep: 7 RDT: 16
EPA alt (EPA old)	All	Any old EPA guideline (e.g. EPA OPP, EPA OPPT) if it is the only guideline given. Correct study type is given. ESR will be accepted.	Muta: 12 TRep: 18 RDT: 8
Japan	All	Any guideline according to Japanese chemical regulation if it is the only guideline given. Correct study type is given. ESR will be accepted.	Muta: 14 TRep: 1 RDT: 2
No guide	All	Correct study type is given, but no reference guideline. ESR will not be accepted.	Muta: 138 TRep: 66 RDT: 92
Other guide	All	Correct study type and a guideline is given but it does not belong to the guidelines mentioned above or the OECD/EU/EPA guidelines listed in the endpoint-specific concepts. ESR will not be accepted.	Muta: 22 TRep: 11 RDT: 9

Memo	Question	Description	Frequency (number of memos) *
Muta			
GMbact or Cytvitro or GMvitro or GMbact, GMvitro or GMbact, Cytvitro or Cytvitro, GMvitro or GMbact, GMvitro, Cytvitro	Question 4, answer “no”	The study type is noted for which no or only insufficient standard information is available.	1044
GMbact or Cytvitro or GMbact, Cytvitro	Question 3.D a), answer “no”	The study type is noted for which no or only insufficient standard information is available.	5
GMbact or GMvitro or GMbact, GMvitro	Question 3.D b), answer “no”	The study type is noted for which no or only insufficient standard information is available.	161
Study type, adaptation/waiving category Adaptation/waiving category: • WoE • Grouping/read-across • Scientifically • Technically • Exposure • Other	Question 5, answer “no”	The available single adaptation/waiver and the corresponding study type are noted.	124
Widerspruch (inconsistency)	All	More than one key study is available, at least one with a positive and one with a negative result. ESRs/study type will not be accepted.	23

Memo	Question	Description	Frequency (number of memos) *
TRep			
414 or 416 or 414, 416	Question 3, answer "no-screening 421" and "no-screening 422" and "no-other screening"	Instead of standard information a screening study is available. It is noted to which study type the screening belongs. The OECD guideline number of the respective study type is noted. For ReproTox (IUCLID 7.8.1): 416. For DevTox (IUCLID 7.8.2): 414.	204
414, adaptation/waiving category or 416, adaptation/waiving category or 416, non-rodent Adaptation/waiving category: • WoE • Grouping/read-across • Scientifically • Technically • Exposure • Other	Question 6, answer "no"	The available adaptation/waiver and the corresponding study type or a study for 416 in non-rodents are noted. For ReproTox (IUCLID 7.8.1): 416. For DevTox (IUCLID 7.8.2): 414. Or 416, non-rodent.	62

* This gives the number of memos. A single memo might include comments on more than one study type. Therefore, the respective issue might apply to several study types.

Annex 2: Memos for Environmental Endpoints. The memos are listed with its abbreviations, the related questions from the decision tree, a brief description and the frequency of recording during the screening

Memo	Question	Description	Frequency
BioDeg			
301 A, B, E kH › 1 Sw ‹ 100	Questions 2/4	Tests conducted according to OECD TG 301 guideline, but missing the required physico-chemical criteria with respect to Henry's law constant (kH › 10 Pa*m³/mol) or water solubility (S_w ‹ 100 mg/L).	15
Ident	Question 2	Screening information on ready biodegradability based on inconsistent test material identity.	140
waive	Question 4	Information regarding biodegradability based on adaptation/waiving.	251
test	Question 4	Information regarding biodegradability based on non-standard tests.	58
Ident	Questions 6/9	Simulation test based on inconsistent test material identity.	4
no guide	Questions 6/9	Simulation test was not conducted according to any guideline.	11
AbioDeg			
struct	Question 2	Waiving the test on hydrolysis due to the molecule structure with a lack of hydrolysable functional groups.	241
inorganic	Question 2	Waiving the test on hydrolysis, since the substance is inorganic.	128
waive_BioDeg test_BioDeg Ident_BioDeg	Question 2	Substance is considered ready biodegradable by the registrant in the respective ESR, but that conclusion based on waiving, a non-standard method or a wrong test material. The waiving justification according Annex VIII needs a more detailed analysis.	78 22 15
111	Question 3	The substance is high adsorptive or inorganic and a study according to OECD TG 111 was conducted.	36
Ident	Questions 4/6/9	Hydrolysis test (pre- or main test) based on inconsistent test material identity.	7
noguide	Questions 4/6/9	Hydrolysis test (pre- or main test) was not conducted according to any guideline.	23
Bioaccu			
Ident	Question 3	Experimental BCF based on wrong substance identity.	21
noguide	Questions 3/5	Experimental BCF was not conducted according to any guideline.	21
305 A	Question 5	The use of replaced guidelines OECD TG 305 A, B, or	2

Memo	Question	Description	Frequency
305 B		D is considered non-compliant.	1
305 C 305 E	Question 5	The evaluation of replaced guidelines OECD TG 305 C or E needs a more detailed analysis.	36 8
Kow_QSAR	Question 7	The log Kow used for waiving justification according to Annex IX was derived via (Q)SAR.	56
Ecotox			
204	Question 1	Fish test according to OECD TG 204 not suitable as a long-term study.	17
212 215	Question 1	Long-term fish test according to OECD TG 212 or OECD TG 215.	4 11
cf_xd	Question 1	Long-term fish test (e.g. OECD TG 210) with shorter exposure duration than required.	5
cd_xd	Question 1	Long-term *Daphnia* test (e.g. OECD TG 211) with shorter exposure duration than required.	7
TP	Question 1	"Testing proposals" for long-term tests, which occurred in addition to those recorded as endpoint conclusion.	31
Ident	Question 1	Long-term test based on inconsistent test material identity.	102
noguide	Question 1	Long-term test was not conducted according to any guideline.	52
af_xh	Question 2	Short-term fish test (e.g. OECD TG 203) with shorter exposure duration than required.	14
ad_xh	Question 2	Short-term *Daphnia* (e.g. OECD TG 202) test with shorter exposure duration than required.	23
Ident	Question 2	Short-term test based on inconsistent test material identity.	204
noguide	Question 2	Short-term test was not conducted according to any guideline.	47
Ident	Question 5	Waiving based on inconsistent test material identity.	185
noguide	Question 5	One of the tests relevant for the conclusion was not conducted according to any guideline.	16
no effect?	Question 8	No effects occurred in the short-term tests (e.g. limit tests 100 mg/L), but at least one tested concentration was below the 1.25 fold water solubility of the substance.	87
Expo			
H_diss	Questions 1/5	The harmonised classification according to C&L dissented from that registered in the dossier.	5 46

Annex 3: List of accepted standard guidelines in the screening for long-term and short-term testing of aquatic toxicity for fish and invertebrates

Guideline	Brief description
Long-term fish tests	
OECD TG 210	Fish, Early-life Stage Toxicity (FELS) Test
EPA OPPTS 850.1400	Fish, Early-life Stage Toxicity (FELS) Test
EPA OTS 797.1000	Fish, Early-life Stage Toxicity (FELS) Test
40 CFR 797.1600	Fish, Early-life Stage Toxicity (FELS) Test
EPA OPP 72-4	Fish Early Life-Stage and Aquatic Invertebrate Life-Cycle Studies
EPA OPPTS 850.1500	Fish Life Cycle Toxicity
EPA OPP 72-5	Fish Life Cycle Toxicity
OECD TG 212	Fish Short-term Toxicity Test on Embryo and Sac-Fry Stages
EU C.15	Fish Short-term Toxicity Test on Embryo and Sac-Fry Stages
OECD TG 215	Fish Juvenile Growth Test
EU C.14	Fish Juvenile Growth Test
OECD TG 229	Fish Short-term Reproduction Assay
OECD TG 230	21-day Fish Assay
OECD TG 234	Fish Sexual Development Test
Long-term invertebrate tests	
OECD TG 211	*Daphnia* magna Reproduction Test
OECD TG 202, part 2 (before 1998)	21-d Reproduction Test (old version)
EU C.20	*Daphnia* magna Reproduction Test (equivalent OECD TG 211)
EPA OPPTS 850.1300	Daphnid Chronic Toxicity Test
40 CFR 797.1350	Daphnid Chronic Toxicity Test (equivalent OECD TG 202, part 2)
EPA OTS 797.1330	Daphnid Chronic Toxicity Test
40 CFR 797.1330	Daphnid Chronic Toxicity Test
EPA OPPTS 850.1350	Mysid Chronic Toxicity Test
EPA OTS 797.1950	Mysid Chronic Toxicity Test
40 CFR 797.1950	Mysid Chronic Toxicity Test
EPA OPP 72-4	Fish Early Life-Stage and Aquatic Invertebrate Life-Cycle Studies
Short-term fish tests	
OECD TG 203	Acute Toxicity for Fish
EU C.1	Acute Toxicity for Fish
EU 79/831/EEC, Annex V, C.1*	Acute Toxicity for Fish

Guideline	Brief description
EU 84/449/EEC C.1*	Acute Toxicity for Fish
OECD TG 204	Fish Prolonged Toxicity Test: 14-day Study
EPA OPPTS 850.1075	Fish acute toxicity test, freshwater and marine
EPA OTS 797.1400	Fish acute toxicity test, freshwater and marine
40 CFR 797.1400	Acute Toxicity for Fish (equivalent OECD TG 203)
40 CFR 797.1440	Acute Toxicity for Fish (equivalent OECD TG 203)
EPA 660/3-75-009	Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians
EPA /600/4-90/027*	Methods for Measuring the Acute Toxicity of Effluents to Freshwater and marine organisms
ASTM 729-88a	Acute Toxicity to freshwater Fish
ISO 10229-1	Acute Toxicity for Fish
DIN 38412-15 (L)*	Acute Toxicity for Fish
Short-term invertebrate tests	
OECD TG 202 (part 1 or from 1998)	*Daphnia* sp. Acute Immobilisation Test (48 h)
EU C.2	*Daphnia* sp. Acute Immobilisation Test
EU 79/831/EEC, Annex V, C.2*	*Daphnia* sp. Acute Immobilisation Test
EU 84/449/EEC C.2*	*Daphnia* sp. Acute Immobilisation Test
EPA OPPTS 850.1010	Aquatic Invertebrate Acute Toxicity Test, Freshwater Daphnids
EPA OTS 797.1300	Aquatic Invertebrate Acute Toxicity Test, Freshwater Daphnids
EPA 660/3-75-009	Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians
EPA 600/4-90/027*	Methods for Measuring the Acute Toxicity of Effluents to Freshwater and marine organisms
DIN 38412-11 (L)*	*Daphnia* short-term test

* Methods indicated by an asterisk were part of this list after approximately one third of the screening.

Annex 4: Hazard Categories according to REACH, Art. 14 (4) a-d and CLP Annex I

Hazard statement	Hazard Code
2. Physical Hazards	
2.1 Explosives	H200, H201, H202, H203, H204, H205
2.2 Flammable gases	H220, H221
2.3 Flammable aerosols	H222, H223
2.4 Oxidising gases	H270
2.6 Flammable liquids	H224, H225, H226
2.7 Flammable solids	H228
2.8 Self-reactive substances & mixtures (types A, B)	H240, H241
2.9 Pyrophoric liquids	H250
2.10 Pyrophoric solids	H250
2.12 Substances and mixtures which in contact with water emit flammable gases	H260, H261
2.13 Oxidising liquids (category 1,2)	H271, H272
2.14 Oxidising solids (category 1,2)	H271, H272
2.15 Organic peroxides (types A-F)	H240, H241, H242
3. Health Hazards	
3.1 Acute toxicity	H300, H301, H302, H310, H311, H312, H330, H331, H333
3.2 Skin corrosion/irritation	H314, H315
3.3 Serious eye damage/irritation	H318, H319
3.4 Respiratory or skin sensitisation	H334, H317
3.5 Germ cell mutagenicity	H340, H341
3.6 Carcinogenicity	H350, H351
3.7 Reproductive toxicity	H360, H361
3.8 Specific target organ toxicity-single exposure	H370, H371
3.9 Specific target organ toxicity-repeated exposure	H372, H373
3.10 Aspiration hazard	H304
4. Environmental Hazards	
4.1 Hazardous to the aquatic environment	H400, H410, H411, H412, H413
5. Additional EU Hazard Class	
5.1 Hazardous to the ozone layer	H420 (EUH059)

Annex 5: Comparison of screening results with outcome of ECHA compliance check according to REACH Regulation Art. 41 for human health endpoints investigated in the current study*

No.	Information requested in decision			Decision date	Notification (Art 42): information complete	Screening results			Additional information on screening results where appropriate		
	Muta	TRep	RDT			Muta	TRep	RDT	Muta	TRep	RDT
1		DevTox, oral		30 Oct 2014		"complex"	"complex"	"complex"	GMbact, Cytvitro adaptation/waiving available (no conclusion)	DevTox, ReproTox adaptation/waiving available (no conclusion)	subacute/subchronic adaptation/waiving available (no conclusion)
2		DevTox inhal.; DevTox 2nd species inhal.; ReproTox inhal.	subchronic inhal.	06 Sep 2012		compliant	"complex"	"compliant"		DevTox 2 species, ReproTox available, adminsitration route not standard (no conclusion)	subchronic available
3	GMbact 5th strain			31 Jul 2013	31 Jul 2013	"compliant"	"complex"	"compliant"	GMbact available, number and strains of bacteria were not considered	screening OECD TG 421 available; DevTox, ReproTox adaptation/waiving available (no conclusion)	
4		DevTox 2nd species oral		14 Mar 2013		"non-compliant"	"complex"	"non-compliant"	Cytvivo/Cytvitro not carried out according or similar to required guideline; GMbact available	DevTox 2 species available, ReproTox adaptation/waiving available (no conclusion)	subacute available; subchronic adaptation/waiving not available
5		DevTox inhal.		18 Apr 2013	18 Apr 2013	"non-compliant"	"complex"	"non-compliant"	Cytvivo, GMbact available; GMvitro adaptation/waiving not available	DevTox 1 species available; DevTox 2nd species waiving/adaptation not available (no conclusion); ReproTox adaptation/waiving available (no conclusion)	subchronic was not carried out according or similar to guideline; subacute/subchronic adaptation/waiving not available
6	GMbact 5th strain			21 Oct 2011		"non-compliant"	"complex"	"compliant"	GMbact not carried out according or similar to required guideline; GMbact, GMvitro, Cytvivo: wrong substance was tested; required in vitro adaptation/waivings not available	DevTox 2 species available; ReproTox wrong substance was tested; ReproTox adaptation/waiving available (no conclusion)	
7	GMvitro; GMbact			12 Dec 2011	12 Dec 2011	"complex"	"complex"	"complex"	GMbact available: number and strains of bacteria	DevTox, ReproTox adaptation/waiving available (no	subchronic adaptation/waiving available (no conclusion)

No.	Information requested in decision			Decision date	Notification (Art 42): information complete	Screening results			Additional information on screening results where appropriate		
	Muta	TRep	RDT			Muta	TRep	RDT	Muta	TRep	RDT
	5th strain								were not considered; Cytvitro, GMvitro adaptation/waiving available (no conclusion)	conclusion)	
8		DevTox inhal.	subchronic inhal.	16 Apr 2013	16 Apr 2013	"complex"	"complex"	"compliant"	Cytvivo, GMbact available; GMvitro adaptation/waiving available (no conclusion)	DevTox 1 species available; DevTox 2nd species waiving/adaptation not available (no conclusion); ReproTox adaptation/waiving available (no conclusion)	subchronic available
9		ReproTox oral; DevTox 2nd species oral	subchronic oral	04 Nov 2011		"non-compliant"	"complex"	"complex"	GMbact, Cytvitro available; GMvitro adaptation/waiving not available	DevTox 1 species available; DevTox 2nd species adaptation/waiving available (no conclusion); ReproTox adaptation/waiving available (no conclusion)	subacute available; subchronic adaptation/waiving available (no conclusion)
10		DevTox oral; DevTox 2nd species oral; ReproTox oral	subacute oral	06 Sep 2012		"complex"	"complex"	"complex"	GMbact, Cytvitro: adaptation/waiving available (no conclusion)	DevTox, ReproTox adaptation/waiving available (no conclusion)	subacute/subchronic adaptation/waiving available (no conclusion)
11	GMvitro	DevTox oral	subchronic oral	30 Oct 2014		"complex"	"non-compliant"	"complex"	GMbact, Cytvitro available; GMvitro adaptation/waiving available (no conclusion)	ReproTox available; DevTox was not carried out according or similar to guideline; DevTox adaptation/waiving not available	subacute/subchronic adaptation/waiving available (no conclusion)
12		DevTox oral	subchronic inhal.	02 Jul 2012		"compliant"	"complex"	"compliant"		screening OECD TG 421 available; DevTox 1 species available, ReproTox adaptation/waiving available (no conclusion)	subchronic available
13		DevTox inhal.; DevTox 2nd species inhal.; ReproTox inhal.	subchronic inhal.	19 Apr 2013	19 Apr 2013	"compliant"	"non-compliant"	"compliant"		screening available; ReproTox was not carried out according or similar to guideline; DevTox 1 species available; DevTox 2nd species adaptation/waiving not available (no conclusion); ReproTox adapta-	subchronic available

No.	Information requested in decision			Decision date	Notification (Art 42): information complete	Screening results			Additional information on screening results where appropriate		
	Muta	TRep	RDT			Muta	TRep	RDT	Muta	TRep	RDT
										tion/waiving not available	
14	Cytvitro; in vivo (8.4)			24 Oct 2011		"non-compliant"	"testing proposal"	"testing proposal"	GMbact, Cytvitro available; GMvitro adaptation/waiving not available; GMvivo substance identity unclear	DevTox, ReproTox testing proposal available	subchronic testing proposal available
15		ReproTox		11 Mar 2011		"compliant"	"complex"	"non-compliant"		DevTox 1 species available; DevTox 2nd species waiving/adaptation not available (no conclusion); ReproTox adaptation/waiving available (no conclusion)	subchronic: wrong substance was tested; subacute/subchronic adaptation/waiving not vailable
16		DevTox inhal.; DevTox 2nd species inhal.	subchronic oral	18 Sep 2013	18 Sep 2013	"compliant"	"complex"	"compliant"		DevTox 1 species available; DevTox 2nd species waiving/adaptation not available (no conclusion); ReproTox adaptation/waiving available (no conclusion)	subchronic available
17		DevTox inhal.	subchronic inhal.	18 Jan 2013		"non-compliant"	"complex"	"compliant"	GMbact, Cytvivo available; GMvitro adaptation/waiving not vailable	screening OECD TG 421 available; DevTox, ReproTox adaptation/waiving available (no conclusion)	subchronic available
18			subchronic inhal.			"complex"	"complex"	"compliant"	harmonized classifiaction, GMbact adaptation/waiving available (no conclusion)	DevTox, ReproTox adaptation/waiving available (no conclusion)	subchronic available
19		DevTox inhal.; DevTox 2nd species inhal.; ReproTox inhal.	subchronic inhal.	04 Apr 2013	05 Apr 2013	"complex"	"complex"	"compliant"	GMbact, Cytvitro adaptation/waiving available (no conclusion)	DevTox 1 species, ReproTox available; DevTox 2nd species waiving/adaptation not available (no conclusion)	subchronic available
20		DevTox (with relevant hydrolysis product) oral	subchronic (with registerd substance)	06 Jun 2012		"compliant"	"complex"	"complex"		DevTox, ReproTox adaptation/waiving available (no conclusion)	subacute/subchronic adaptation/waiving available (no conclusion)

No.	Information requested in decision			Decision date	Notification (Art 42): information complete	Screening results			Additional information on screening results where appropriate		
	Muta	TRep	RDT			Muta	TRep	RDT	Muta	TRep	RDT
			inhal.								
21			sub-chronic oral	18 Apr 2013	18 Apr 2013	"complex"	"complex"	"compliant"	GMbact, Cytvivo available; GMvitro adaptation/waiving available (no conclusion)	DevTox, ReproTox adaptation/waiving available (no conclusion)	subchronic available
22		DevTox inhal.; DevTox 2nd species inhal.	sub-chronic inhal.	06 Sep 2012		"complex"	"compliant"	"complex"	harmonized classifiaction, GMbact adaptation/waiving available (no conclusion)	DevTox 2 species, ReproTox available	subacute/subchronic adaptation/waiving available (no conclusion)
23			sub-chronic inhal.	18 Jan 2013		"complex"	"compliant"	"compliant"	harmonized classification, GMbact adaptation/waiving available (no conclusion)		subchronic available
24	GMbact; Cytvitro; GMvitro			16 Aug 2013		"complex"	"complex"	"non-compliant"	GMbact, Cytvitro adaptation/waiving available (no conclusion)	DevTox, ReproTox adaptation/waiving available (no conclusion)	subacute/subchronic adaptation/waiving not available
25		DevTox oral		22 Mar 2013		"complex"	"complex"	"compliant"	Cytvivo available; GMbact, GMvitro adaptation/waiving available (no conclusion)	DevTox 1 species available; DevTox 2nd species waiving/adaptation not available (no conclusion); ReproTox adaptation/waiving available (no conclusion)	
26		DevTox oral; DevTox 2nd species oral; ReproTox oral	sub-chronic oral	19 Apr 2013		"non-compliant"	"non-compliant"	"non-compliant"	all in vivo and in vitro studies not carried out according or similar to guideline; GMbact, Cytvitro adaptation/waiving not available.	DevTox not carried out according or similar to guideline; ReproTox available; DevTox adaptation/waiving not available	subchronic was not carried out according or similar to guideline; subacute/subchronic adaptation/waiving not available
27		DevTox oral		18 Apr 2013		"compliant"	"complex"	"compliant"		DevTox, ReproTox adaptation/waiving available (no conclusion)	
28		DevTox oral		18 Apr 2013	18 Apr 2013	"non-compliant"	"complex"	"non-compliant"	Cytvivo, GMbact available; GMvitro adaptation/waiving not available	DevTox 1 species available; DevTox 2nd species waiving/adaptation not available	subchronic: wrong substance was tested; subacute/subchronic adaptation/waiving not available

No.	Information requested in decision			Decision date	Notification (Art 42): information complete	Screening results			Additional information on screening results where appropriate		
	Muta	TRep	RDT			Muta	TRep	RDT	Muta	TRep	RDT
										(no conclusion); ReproTox adaptation/waiving available (no conclusion)	
29		DevTox inhal.; DevTox 2nd species inhal.	sub-chronic inhal.	09 Oct 2013	18 Apr 2013	"complex"	"complex"	"compliant"	GMbact, Cytvitro adaptation/waiving available (no decsion)	DevTox 2 species available; ReproTox adaptation/waiving available (no decsion)	subchronic available
30		DevTox, ReproTox	sub-chronic	08 Oct 2013	31 Oct 2014	"non-compliant"	"non-compliant"	"non-compliant"	GMbact, Cytvitro available; GMvitro adaptation/waiving not available	DevTox 2 species available; Reprotox not carried out according or similar to guideline; Reprotox adaptation/waiving not available	subchronic: wrong substance was tested; subacute/subchronic adaptation/waiving not available
31	GMbact 5th strain			08 Oct 2013	11 Aug 2014	"compliant"	"complex"	"complex"	GMbact available, number and strains of bacteria were not considered	DevTox 1 species, ReproTox available; DevTox 2nd species adaptation/waiving available (no conclusion)	subchronic test was not carried out according or similar to guideline; subacute/subchronic adaptation/waiving available (no conclusion)

*Muta: Genetic toxicity; TRep: toxicity to reproduction (ReproTox)/developmental toxicity (DEvTox); RDT: repeated dose toxicity; inhal.: inhalative; GMbact: OECD TG 471 (Amestest); Cytvitro: Cytogenicity test in mammalian cells; GMvitro: gene mutation test in mammalian cells. Missing information according to the screening is underlined.

Annex 6: Comparison of screening results with outcome of ECHA compliance check according to REACH Regulation Art. 41 for environmental endpoints investigated in the current study*

No. [a]	Information on compliance check			Information on screening results		
	Information required - statement of reasons (excerpt)	Decision date	Notification (Art 42): information complete	Endpoint	Conclu-sion	Additional information
3	RSS long-term test invertebrates - missing detailed information	31.07.2013	31.07.2013	Ecotox	CX	Non-standard method
11	No regional PEC & RC for ENV compartments; RCR › 1 - revision needed	27.06.2012	-	Expo	CX	ENV exposure scenarios available; no RC (Memo)
14	Degradation (not suitable test); hydrolysis (QSAR invalid - domain); bioaccumulation (without hydrolysis test not acceptable)	24.10.2011	-	BioDeg AbioDeg Bioaccu	CX CX CX	BioDeg: not biodegradable AbioDeg: adsorptive Bioaccu: (Q)SAR
22	No ENV EA & invalid RC	21.11.2013	-	Expo	CX	CSR update; ENV exposure scenarios available
24	log Kow (Klimisch 3 & 4) and no WoE	09.12.2013	-	Expo	NC	No ENV exposure scenarios available; Memo: log Kow
25	Invalid EA & RC	22.03.2013	-	Expo	CX	ENV exposure scenarios available
32	No ENV EA & invalid RC	20.12.2012	20.12.2012	Expo	CX	CSR update; ENV exposure scenarios available
33	Invalid ENV EA & RC; substance classification incorrect; PBT as-sessment missing	11.02.2012	-	Expo AbioDeg	CX NC	ENV exposure scenarios available; Memo: H-diss AbioDeg: pre-test on hydrolysis not sufficient
34	Exposure estimation & RC for marine compartment missing	21.10.2011	-	Expo	CX	ENV exposure scenarios available
35	Exposure estimation & RC for marine compartment missing	25.07.2012	25.07.2012	Expo	CX	ENV exposure scenarios available

* BioDeg: Biotic degradation; AbioDeg: Abiotic degradation; Bioaccu: Bioaccumulation; Ecotox: Ecotoxicity; Expo: Environmental (ENV) Exposure; CX – “complex”; NC – “non-compliant”; EA – exposure assessment; RC(R) – risk characterisation(ratio); RSS – robust study summary. [a] Numbering according to the previous table (Annex 5). Additional numbers from No. 32 onwards for substances not considered for HH endpoints.

Annex 7: Individual examination of the endpoint Muta for the 13 "complex" conclusions in which waiving was not (only) based on grouping/read-across

Type of adaptation/ initial situation	Study type addressed	Problem	Revised conclusion	Reason/explanation
Harmonised classification (CLP): muta. cat. 1 or carc. cat. 1	GMbact (OECD TG 471)	Due to classification testing not required, but waiving not possible according to Annex VII, No. 8.4, Column 2	"Compliant"	"Compliant" due to classification; formally non-compliant
Rejected study, memo "no guide"	GMbact (OECD TG 471)	5th strain missing (other strains: negative results)	"Non-compliant"	"Compliant" in cases where reliable supplementary studies for 5th strain are available; if other strains positive result: missing 5th strain not relevant
Waiving "WoE", supporting studies	GMbact (OECD TG 471)	5th strain was tested, but presented with data of inferior quality (e.g. controls missing, no dose info)	"Non-compliant"	
Waiving "WoE", supporting studies	GMbact (OECD TG 471)	TA1538 was tested; justification for missing 5th strain: reliable according to old version of guideline (TA1538)	"Non-compliant"	TA1538 not regarded as 5th strain
Waiving "WoE", supporting studies	Total standard information	There are many, alone insufficient endpoint study records *in vitro* and *in vivo*	"Complex"	More detailed analysis required
Waiving "scientifically not justified"	GMbact (OECD TG 471)	Justification refers to bactericide properties of substance	"Compliant"	Justification appears valid; compliant provided that sufficient other gene mutation data are available
Waiving "scientifically not justified"	GMvitro (OECD TG 476)	Justification refers to existent negative tests according to Annex VII or VIII, but for gene mutation only Ames test existent with negative result	"Non-compliant"	Justification appears insufficient; GMvitro required due to negative Cytvivo and negative Ames test
Waiving "other justification", multi constitu-	Total standard information	Justification relates to intrinsic properties –no toxicological effects of	"Compliant"	"Compliant", provided that no impurities/additives not listed

Type of adaptation/ initial situation	Study type addressed	Problem	Revised conclusion	Reason/explanation
ent substance		components, all are listed in Annex IV (exemptions from registration)		in Annex IV are existent in the multi constituent substance
Harmonised classification (CLP): muta. cat. 1 or carc. cat. 1	GMbact (OECD TG 471), Cytvitro	Due to classification testing not required; waiving formally required	"Compliant"	"Compliant" due to classification
Waiving "WoE"	GMbact (OECD TG 471)	Cytvivo negative; GMvitro negative; WoE GMbact: 1 negative, 1 positive	"Non-compliant"	Study for GMvivo or adaptation/waiving required
Harmonised classification (CLP): muta. cat. 1 or carc. cat. 1	GMbact (OECD TG 471)	Due to classification testing not required; waiving formally required	"Compliant"	Compliant due to classification
Waiving "technically not feasible" and "other justification"	GMbact (OECD TG 471), Cytvitro	Registrant states that in vitro studies are technically not possible and reliable data can only be derived from in vivo studies; nevertheless in vitro studies are available; Cytvivo only as grouping/read-across for one component of the chemical; no GMvivo study	"Complex"	Reliability and applicability of the available in vitro tests has to be evaluated; if statement of registrant applies non-compliant because required in vivo studies are not available
Waiving "WoE"	GMbact (OECD TG 471)	5th strain missing (other strains: negative results)	"Non-compliant"	"Compliant" in cases where reliable supplementary studies for 5th strain are available; if other strains positive result: missing 5th strain not relevant

Annex 8: Individual examination of the endpoint RDT for the twelve "complex" conclusions in which waiving was not (only) based on grouping/read-across

Type of adaptation/initial situation	Study type addressed	Problem	Revised conclusion	Reason/explanation
Waiving "ether justification"	OECD TG 408 (90-days)	RDT studies are waived because chemical is a UVCB	"Non-compliant"	Required studies or appropriate adaptation/waiving has to be available
Waiving "ether justification" and "exposure considerations"	OECD TG 408 (90-days)	Substance proposed to be an intermediate; oral route: waiving according to Annex XI, 3.2.b (exposure); inhalative route: grouping/read-across studies	"Complex"	Uses of the substance have to be checked comprehensively; evaluation of grouping/read-across is required for further analysis
Waiving "ether justification"	OECD TG 408 (90-days)	Formally non-compliant – studies are not flagged as grouping/read-across or WoE, but an indication for grouping/read-across or WoE is given in a comprehensive form elsewhere; chemical is a UVCB	"Complex"	Information in other dossier sections have to be checked comprehensively; if necessary, evaluation of grouping/read-across is required
Waiving "scientifically not justified"	OECD TG 408 (90-days)	90- days study is waived because 28- days study shows no/low toxicity	"Non-compliant"	Waiving justification not valid
Waiving "scientifically not justified"	OECD TG 408 (90-days)	90- days study is waived because 28- days study shows no/low toxicity; justification according to Annex IX 8.6.2 Column 2 not conclusive and sufficient – data for cleavage products are not available, immediate disintegration not conclusively proved	"Non-compliant"	Waiving justifications not valid/sufficient
Waiving "exposure considerations"	OECD TG 408 (90-days)	Waiving according to Annex XI, 3	"Complex"	CSR of the substance has to be checked comprehensively
Waiving "WoE" and "scientifically not justified"	OECD TG 408 (90-days)	RDT studies are waived because chemical has no toxicity due to its composition (components with	"Non-compliant"	Required studies or appropriate adaptation/waiving has to be available

Type of adaptation/initial situation	Study type addressed	Problem	Revised conclusion	Reason/explanation
		no toxicity, not listed in Annex IV or V)		
Waiving "WoE"	OECD TG 408 (90-days)	Endpoint study records only state: "completely inactive material", nothing else filled out	"Non-compliant"	Required studies or appropriate adaptation/waiving has to be available
Waiving "WoE" and "exposure considerations"	OECD TG 408 (90-days)	WoE for chronic studies which are not according to test guideline – low LOAEC; Harm. Class. as STOT RE1; belongs to group approach	"Complex"	Reliability and applicability of the available chronic studies has to be checked with respect to Annex IX, Column 2, second bullet point– these studies are proposed to be applied to the whole group
Waiving "scientifically not justified"	OECD TG 408 (90-days)	Only subacute study with limited quality and one-generation study available; waiving only for chronic study	"Non-compliant"	Required studies or appropriate adaptation/waiving has to be available
Waiving "other justification"	OECD TG 408 (90-days)	Substance oxidizes in water; waiving according to Annex X, passage 4 – one reaction product is corrosive; grouping/read-across studies for the other reaction product available	"Non-compliant"	Studies with the compound itself at non-corrosive conc. or appropriate adaptation/waiving has to be available (e.g. grouping/read-across for all reaction products)
Waiving "WoE"	OECD TG 408 (90-days)	Several WoE for oral and inhalative, partly based on grouping/read-across	"Complex"	More detailed analysis of WoE required

Annex 9: Individual examination of the endpoint TRep for the 26 "complex" conclusions in which waiving was not (only) based on grouping/read-across

Type of adaptation/initial situation	Study type addressed	Problem	Revised conclusion	Reason/explanation
Waiving "scientifically not justified"	OECD TG 414/416	Two invalid/insufficient waiving arguments are stated without relation to the REACH Regulation; only OECD TG 422 available (no reproductive or developmental toxicity was proven)	"Non-compliant"	"Non-compliant", not all aspects of waiving according to Annex X, 8.7., third bullet were addressed; OECD TG 422 not sufficient to replace 416 and 414
No waiving	OECD TG 414 second species	No study or adaptation/waiving for second species	"Non-compliant"	Study or adaptation/waiving for OECD TG 414, second species, is not available
Waiving "scientifically not justified"	OECD TG 416; OECD TG 414 second species	No study or adaptation/waiving for 414, second species; only 414 and 90- days available (no toxicity to reproduction was proven in these studies)	"Non-compliant"	Study or adaptation/waiving for OECD TG 414, second species, is not available; 416 cannot be replaced by 414 and 90- days studies showing no toxicity to reproduction
Waiving "other justification"	OECD TG 414/416	Endpoint summary references to grouping/read-across studies which are not documented	"Non-compliant"	Data for grouping/read-across studies have to be available
Waiving "other justification"	OECD TG 416	Only chronic and 90- days studies are cited as grouping/read-across (no toxicity to reproduction was proven in these studies)	"Non-compliant"	416 cannot be replaced by chronic and 90- days studies showing no toxicity to reproduction
No waiving	OECD TG 414 second species	No study or adaptation/waiving for second species	"Non-compliant"	Study or adaptation/waiving for OECD TG 414, second species, is not available
No waiving		Substance is a liquid, administration route inhalative	"Compliant"	Most relevant route of administration
Waiving "scientifically not justified"	OECD TG 414/416	Naturally occurring chemical with low toxicity, but not listed in Annex IV or V	"Non-compliant"	Required studies or appropriate adaptation/waiving has to be available
Waiving "other	OECD TG	Only 421, 414 and 90-	"Non-	416 cannot be replaced

Type of adaptation/initial situation	Study type addressed	Problem	Revised conclusion	Reason/explanation
justification"	416	days studies are available (no toxicity to reproduction was proven in these studies)	compliant"	by 414, 421 and 90-days studies showing no toxicity to reproduction
Waiving "scientifically not justified"	OECD TG 416	Study was not conducted due to the relevant inhalative route; data from 421 and repeated dose available	"Non-compliant"	OECD TG 416 inhalative is possible; OECD TG 421 and repeated dose not sufficient
Waiving "scientifically not justified"	OECD TG 414	OECD TG 416 grouping/read-across available, no effect	"Non-compliant"	OECD TG 414 still required
Waiving "scientifically not justified"	OECD TG 414 second species	OECD TG 414 first species not there/insufficient	"Non-compliant"	Waiving for 414, 2. Species available, but study for 414, 1. species, not valid
Waiving "scientifically not justified"	OECD TG 414/416	Reference to Annex XI, No. 1.1. "Use of existing data"; from experiments not carried out according GLP; actually other reasons are indicated such as low bioavailability or existent studies for single components; there is no reference to where the study data is reported (no ESR)	"Non-compliant"	formally "non-compliant"; "compliant" provided that sufficient explanation/reference to study data is given elsewhere in the dossier
Waiving "other justification"	OECD TG 416	Reference to data of screening study	"Non-compliant"	OECD TG 421 not sufficient
Waiving "other justification"	OECD TG 416	Reference to Annex X, 8.7, Column 2: low toxicological effects/no systemic absorption/no significant human exposure; data is only explained in waiving justification (no full study summary)	"Compliant"	"Compliant" provided that sufficient explanation/reference to study data is given elsewhere in the dossier
Waiving "other justification"	OECD TG 416	Reference to Annex IX, that OECD TG 416 is only necessary if 28- or 90-days study indicates adverse effects	"Non-compliant"	Annex X is relevant

Type of adaptation/initial situation	Study type addressed	Problem	Revised conclusion	Reason/explanation
No waiving	OECD TG 414 second species	No study or adaptation/waiving for second species	"Non-compliant"	Study or adaptation/waiving for OECD TG 414, second species, is not available
Rejected study and WoE	OECD TG 414	Study was not conducted with registered substance	"Non-compliant"	
Waiving "scientifically not justified"	OECD TG 416	Waiving based on grouping/read-across, but respective grouping/read-across studies are not included	"Non-compliant"	Grouping/read-across studies have to be included
Grouping/read-across available, no other waiving	OECD TG 414/416		"Compliant"	Substance is classified according to CLP as muta. cat. 1
Waiving "other justification"	OECD TG 416; OECD TG 414 second species	No study or adaptation/waiving for 414, second species; waiving in 416 section only for screening study, one-generation study available	"Non-compliant"	Study or adaptation/waiving for OECD TG 414, second species, is not available; 416 cannot be replaced by one-generation study; waiving or study for 416 is not available
Waiving "scientifically not justified"	OECD TG 414/416	Waiving because one component is classified according to CLP (H340), presence of this compound cannot clearly be deduced from the composition and analytics section in IUCLID	"Non-compliant"	Substance composition has to be specified
Waiving "scientifically not justified"	OECD TG 416	Only 414 and 421 studies are cited as grouping/read-across, 90- days study available (no toxicity to reproduction was proven in these studies)	"Non-compliant"	416 cannot be replaced by 414, 421 and 90-days studies showing no toxicity to reproduction
Waiving "scientifically not justified" and "WoE"	OECD TG 416	Grouping/read-across for 414, 90- days, one-generation and screening studies available (only low toxicity to reproduction was proven in these stud-	"Non-compliant"	416 cannot be replaced by 414, screening, one-generation and 90- days studies showing no toxicity to reproduction

Type of adaptation/initial situation	Study type addressed	Problem	Revised conclusion	Reason/explanation
		ies); low bioavailability		
Waiving "other justification"	OECD TG 414/416	Substance oxidizes in water; waiving according to Annex X, passage 4 – one reaction product is corrosive; grouping/read-across studies for the other reaction product available	"Non-compliant"	Studies with the compound itself at non-corrosive conc. or appropriate adaptation/waiving has to be available (e.g. grouping/read-across for all reaction products)
Waiving "WoE" and "exposure considerations"	OECD TG 414/416	Only one WoE for 414; Waiving for 416 due to low systemic toxicity and 90-days studies available (only low toxicity to reproduction was proven in these studies)	"Non-compliant"	WoE has to comprise more than one study (except new methods were used); 416 cannot be replaced by 90- days studies showing no toxicity to reproduction