

The use of alternatives to testing on animals for the REACH Regulation

Fourth report under
Article 117(3) of the
REACH Regulation

June 2020

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**The use of alternatives to testing on animals for the REACH Regulation
Fourth report (2020) under Article 117(3) of the REACH Regulation**

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Foreword by the executive director

Dear reader,

This is now the fourth time that we are presenting our findings to the European Commission on how companies are using alternatives to testing on animals under REACH.

One of the main fundamentals of REACH is to strike a balance between gathering information on possible hazards of chemicals to protect human health and the environment, and, at the same time, avoiding unnecessary tests on animals by ensuring registrants only conduct them when there is no other choice.

This report serves as our vehicle for documenting the current status on alternative methods and testing strategies that companies are adopting to avoid animal tests. It confirms our earlier findings that registrants are successfully sharing data and that they are making extensive use of the different options at their disposal to avoid testing on animals testing.

In particular, we see from the report that many companies are avoiding animal tests by using information on similar substances through read-across. But there is also evidence that they are providing valid justifications for omitting data, combining evidence from different sources using weight-of-evidence approaches, predicting properties using computer models and adopting *in vitro* methods to isolate tissues, organs or cells rather than testing on living organisms.

With the completion of the registration deadline back in 2018, companies have effectively laid their cards on the table. We now have ample data which gives us the opportunity to comprehensively review how companies have avoided animal tests across all tonnage bands.

There remains a concerning number of incompliances in registration dossiers with many still needing to be updated, either voluntarily or after we have requested for this through a compliance check. We are proactively following up with companies to make sure they understand that it is their responsibility to provide information that shows their chemicals can be used safely. I urge companies to take advantage of the guidance, practical guides, webinars and advice available in our other publications, such as those on the progress we have made in evaluation, and to use these resources to strengthen their alternative approaches and avoid unnecessary animal testing.

Chemicals are – and are increasingly going to be – crucial for the survival of Europe's manufacturing industry, so having accurate information available is a must. To be innovative and move towards circularity, we need precise data and in-depth knowledge as these will underpin our efforts to ensure companies produce safe chemicals, replace harmful substances with better alternatives, make materials recyclable, reduce animal testing, and ultimately safeguard our environment and our health.

Our registration database gives us a unique starting point from which to build up a chemicals knowledgebase to further develop alternative approaches to animal testing. Such a knowledgebase will be an integral resource for supporting the goals of the European Green Deal and the Digital Agenda and reinforcing initiatives such as the chemicals strategy for sustainability, a toxic-free EU environment and the circular economy.

We plan to continue pursuing non-animal testing methods by following the development of alternative approaches at OECD-level and grasping opportunities for them to be used in the regulatory arena. And we are also leading and collaborating in various international projects that seek to promote collaboration and dialogue on the scientific and regulatory needs for accepting new approach methodologies into regulatory decision making.

Adopting these approaches will not only allow us to make better informed decisions, but will also help to minimise the need for studies on vertebrate animals even further.

Bjorn Hansen,
ECHA Executive Director

Summary

Every three years, ECHA submits a report to the European Commission on the implementation and use of non-animal test methods and testing strategies used to generate information on intrinsic properties and for risk assessment. This report is the fourth in this series, covering the operational years from 2007 until 2020. It is published in accordance with ECHA's obligations under Article 117(3) of the REACH Regulation. The previous reports were published in 2011, 2014 and 2017.¹

In 2018, as a result of the final REACH registration deadline, ECHA obtained information for all remaining substances brought on the EU market in quantities between 1 and 100 tonnes per year. This data has given us a unique opportunity to comprehensively review the status of the use of alternative methods and testing strategies for industrial chemicals in the EU.

This report recalls the main legal instruments to avoid unnecessary animal testing and presents a comprehensive analysis of REACH registrations with an update on the use of alternative methods. Further discussion on the extent to which adaptations to animal testing are used, as well as aspects of their quality are also provided.

The report also describes ECHA's activities to promote the use of alternative methods and adequate application of adaptation possibilities, and to support registrants in complying with their legal duties.

Finally, it looks ahead to describe potential development areas and to provide thoughts on how alternative methods may be used in the future.

The report's main findings are the following:

REACH **legal instruments**, which are designed to avoid unnecessary animal testing, continue to largely work well. The data-sharing and inquiry processes remain among the most effective tools to reduce animal tests. These provisions ensure that test data is collected, generated and brought together for each substance in one joint registration dossier, instead of potentially leading to individual submissions.

The last registration deadline has made publically available the large amount of existing information previously only available to registrants. This information is now **transparently** available to support the safe and sustainable use of substances and avoiding unnecessary animal testing.

For new and existing registrations, **in vitro studies** for skin corrosion/irritation, serious eye damage/eye irritation and skin sensitisation have been clearly **taken up** since 2016. The amendment of the REACH annexes has certainly played an important role in accomplishing this change.

In general, **no major changes in the use of adaptations** have been observed since the last report in 2017². Furthermore, the following observations can be made:

- Overall, the **most commonly used adaptation is read-across**, followed by data waiving, weight of evidence and quantitative structure–activity relationship (QSAR) models. Experimental studies were available – on average – in 27.1 % of cases (-0.5 % compared to 2016).
- When new studies are needed for repeated dose toxicity and toxicity to

¹ <https://echa.europa.eu/about-us/the-way-we-work/plans-and-reports?panel=animal-testing-reports#animal-testing-reports>

² The data for the 2017 report was extracted in 2016, which is the date used throughout the report.

reproduction screening, these are increasingly performed using the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422). This **significantly reduces the number of animals and costs**.

- There has been a **moderate increase in the availability of pre-natal developmental toxicity and (sub)chronic repeated dose studies**. Decisions related to compliance checks and testing proposals in the last three years are likely to account for this.

In general, Annex VII and VIII dossiers received by the 2018 deadline follow the same patterns in terms of use of adaptations. Furthermore, the following observations can be made:

- The newly received **Annex VIII dossiers follow a similar pattern as dossiers in higher tonnage bands**, with the exception of acute toxicity where the Annex VIII dossiers have fewer experimental studies (-3.1 %), but weight of evidence, QSAR and data waiving have increased.
- Remarkably, at REACH Annex VIII, the percentage of short-term toxicity to fish studies used to fulfill the information requirement decreased since 2016, showing an **effective use of adaptations** for this standard information requirement. However, a minor increase for long-term aquatic experimental studies has been observed.
- For newly received **Annex VII dossiers, fewer experimental studies and less read-across are observed, with more weight of evidence, QSAR and data waiving**. For dossiers at this Annex level with the lowest data requirements, it can be concluded that registrants have used alternative approaches, even more so than in other tonnage bands.
- Annex VII dossiers that were submitted earlier (before 2016) contain **more additional information** on top of the standard minimum requirements than the once submitted later (2018 deadline). Low tonnage substances also needed to be registered before June 2010, if they were classified as carcinogenic, mutagenic or toxic to reproduction, in categories 1 or 2 (CMR Cat 1 and 2). These substances can be expected to have more information than required according to the tonnage band, since this information was likely forming the basis for their classification in the past. Information that is needed **to classify a substance as CMR Cat 1 and 2**, is typically information that is only required starting from Annex IX. In contrast, the substances that were registered later and are not classified as CMR Cat 1 and 2, would not have this 'extra' information, as this is not required.

Yet, there are still many **incompliances** in registration dossiers and many still need to be updated, either voluntarily or after being requested by an ECHA compliance check decision. ECHA has communicated about this, and in this report some key findings are summarised. For this report, a spot check of the compliance of stand-alone **QSAR predictions** was additionally done and it shows that a substantial number of **predictions are not adequate**.

Registrants still have **opportunities to strengthen their alternative approaches**, based on the ECHA guidance and tools, as well as the feedback given in other publications, for example, the progress made in evaluation, according to Article 54 of REACH.

Looking towards the future, the now complete REACH registration database constitutes a

unique starting point of knowledge that can serve the safe use of chemicals as well as the further development of alternative approaches to animal testing. ECHA has developed several initiatives in this direction. Also, stimulated by the emerging global acceptance of the IUCLID data standard to capture and exchange information, ECHA foresees the possibility to develop an **EU chemicals knowledgebase**³ as the basis to support the European Green Deal⁴ and the Digital Agenda and, in particular, to underpin initiatives and concepts such as the chemicals strategy for sustainability (a toxic-free environment)⁵, 'one substance – one assessment' and the circular economy.

With the chemicals knowledgebase as one of the resources, ECHA will pursue its objective of **promoting non-animal testing** methods by developing and maintaining tools and guidance to support registrants. It will continue to follow and contribute to the developments at the OECD and to seize opportunities to translate alternative approaches into the regulatory arena. ECHA is actively supporting the development of the OECD QSAR Toolbox⁶, a software tool increasingly used in computational toxicology and chemical hazard assessment.

ECHA is also exploring ways to exploit **new approach methodologies** (NAMs) with the ambition to reinforce their applicability in a regulatory context. In this regard, it is leading and collaborating in various projects involving NAMs within international consortia such as the APCRA⁷ initiative. These approaches are crucial for high throughput assessment. They will not only allow for better informed decisions but also minimise the need for studies on (vertebrate) animals, for the protection of human health and the environment.

³ [This platform is probably a significant building block for the OECD Global Knowledgebase. How this data-platform relates to the "Feasibility study on a common open platform on chemical safety data" currently executed by DG Environment is to be seen. <https://etendering.ted.europa.eu/cft/cft-document.html?docId=61946>](#)

⁴ https://ec.europa.eu/info/strategy/priorities-2019-2024/european-green-deal_en

⁵ <https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12264-Chemicals-strategy-for-sustainability>

⁶ <http://www.qsartoolbox.org/>

⁷ <https://www.epa.gov/chemical-research/accelerating-pace-chemical-risk-assessment-apcra>

1 Introduction

European context

The EU legislates animal welfare under EU Directive 2010/63/EU⁸ on "the protection of animals used for scientific purposes". This directive is often cited as one of the most stringent ethical and welfare standards worldwide⁹ and implements the '3Rs principle' in EU legislation: "Principle of replacement, reduction and refinement" first described by Russell and Burch in 1959¹⁰.

In February 2020, the European Commission released its 2019 report on the statistics on the use of animals for scientific purposes in the Member States of the EU in 2015-2017.¹¹

The report shows that the number of animals used for regulatory compliance of industrial chemicals is a small fraction of the total number of laboratory animals. In 2017, 9.39 million animals were used for scientific purposes – 69 % were used in research, while 23 % were used to satisfy legislative requirements, ensuring safety for human health and/or the environment.

The regulatory uses accounted for 2.18 million animals. The majority of regulatory uses occurred for medicinal products for humans (61 %) and veterinary medicinal products (15 %). The proportion for industrial chemicals was about 11 %, which represents approximately 2.5 % of the total animals used for scientific purposes¹².

The REACH Regulation

REACH's¹³ primary objective is to ensure that human health and the environment receive a high level of protection. This aim is also balanced with promoting alternative methods for assessing substance hazards, and the need to enhance the competitiveness and innovation of industry. The requirement in the REACH Regulation to use alternative methods whenever possible is based on EU Directive 2010/63/EU on the protection of animals used for scientific purposes.

ECHA

ECHA¹⁴ was established for managing the implementation of the REACH and CLP legislation and, in some cases, carrying out the technical, scientific, and administrative aspects of REACH. It also has to ensure consistency at EU level with respect to these activities. ECHA helps companies comply with the legislation, advances the safe use of chemicals, provides information on chemicals and addresses chemicals of concern.

Scope

Under Article 117(3) of the REACH Regulation, "Every three years, *the Agency, in accordance with the objective of promoting non-animal testing methods, shall submit to the Commission a report on the status of implementation and use of non-animal test methods and testing strategies used to generate information on intrinsic properties and for risk assessment to meet the requirements of this Regulation*". This current report is the fourth edition, fulfilling that obligation.

⁸ <https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32010L0063>

⁹ <https://www.euroscience.org/news/euroscience-supports-directive-201063eu-on-the-protection-of-animals-used-for-scientific-purposes/>

¹⁰ [Russell, W.M.S.; Burch, R.L. \(1959\). The Principles of Humane Experimental Technique. Methuen, London. ISBN 0-900767-78-2.](https://doi.org/10.1002/9780470015862.ch2)

¹¹ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0016&from=EN>

¹² This report covers all testing for the purposes of REACH, irrespective of where the testing takes place i.e. within or outside of the European Union.

¹³ <https://echa.europa.eu/regulations/reach/legislation>

¹⁴ <https://echa.europa.eu/about-us>

REACH registration

A key feature of REACH is the greater level of responsibility placed on companies to ensure safety. REACH is based on the principle that manufacturers, importers and downstream users are responsible for ensuring and showing that they manufacture, place on the market, or use substances that do not adversely affect human health or the environment.

Therefore, registrants are responsible for generating the necessary information to properly identify and manage the hazards and risks of substances. Registrants are also responsible for applying alternative methods to avoid unnecessary animal testing, with REACH stipulating that animal testing is the last resort (Article 13).

REACH specifies the standard information requirements that must be fulfilled in Annexes VII to X to REACH. These requirements are in relation to the expected tonnages on the market. The higher the volume, the more information is needed. These requirements are minimum requirements as they represent the minimum information needed to protect human health and the environment, by means of classification and labelling and/or risk assessment. One generic requirement is that the registration dossier should contain all relevant and available information, regardless of the standard requirements.

Information on intrinsic properties may also be generated in other ways than by tests, as long as the conditions for adaptations of the standard testing requirements set out in Annex XI to REACH are met. To address general requirements for generating information on intrinsic properties of substances, testing on vertebrate animals must only be undertaken as a last resort.

Where more information on the intrinsic properties of substances is needed, tests have to be conducted according to the test methods laid down in a Commission Regulation¹⁵ or in accordance with other international test methods that the Commission or ECHA recognise as being appropriate.

REACH registrations represent the knowledge that companies have on their chemicals, including existing data from animal testing, alternatives to animal testing for certain information requirements, and situations where additional animal tests are needed to ensure safe use (through testing proposals).

The main focus of this report is the analysis of the registration dossiers, as these should contain all available and relevant information on chemicals on the European market. In line with the scope of Article 117(3), the focus of this report is on how the registrants used the alternative methods which are part of the standard requirements (e.g. in-vitro testing), and how they made use of the legal possibilities to adapt the standard information requirements (in particular, alternative methods and data waiving).

IUCLID database

Companies report information on the substances they manufacture or import in a registration dossier submitted to the Agency. The level of information to be submitted depends on the substance tonnage and its hazardous properties. The registration dossier must be in IUCLID¹⁶ format. All non-confidential information is published on ECHA's website to view¹⁷ or for download¹⁸.

¹⁵ <http://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32008R0440>

¹⁶ International Uniform Chemical Information Database

¹⁷ <https://echa.europa.eu/information-on-chemicals>

¹⁸ <https://iuclid6.echa.europa.eu/web/iuclid/reach-study-results>

For this report, ECHA analysed IUCLID registration dossiers for all four tonnage bands (1-10 tonnes per year, 10-100 tonnes per year, 100-1 000 tonnes per year, and 1 000 tonnes per year and above according to Article 10 of REACH) corresponding to each respective information requirement in REACH Annexes VII-X.

Complete view

This fourth edition is the first report published since the 2018 registration deadline¹⁹, and therefore covers all substances manufactured or imported in Europe with a volume of one tonne per year or higher. With this, the coverage of substances in ECHA's REACH registration database is complete. The obligation to update a dossier in case of relevant changes²⁰, as well as the requirement to register new substances, makes that the database gives a complete and up to date view of the industrial chemicals on the European market.

In addition to the availability of experimental studies and the status of implementation and use of non-animal test methods, the registration database was further analysed to answer the following specific questions:

1. What are the most commonly used adaptations?
2. Which options did registrants use to fulfil their information requirements for lower-volume substances (less than 100 tonnes per year)?
3. What are the most noticeable changes for higher-volume substances (100 tonnes per year and above) since the previous (third) Article 117(3) report?
4. How did the situation evolve for the endpoints where alternative methods have been introduced since 2016 as standard information requirements?

For technical reasons, the methodology of data analysis used for the previous reports in this series were redesigned and adapted to take into account significant modifications introduced by the IUCLID 6 release²¹ in 2016. This makes it difficult to directly compare the data between this edition and previous editions. However, the algorithms developed for this fourth Article 117(3) report make it now possible to compare the status of the IUCLID database at different points in time.

The third Article 117(3) report was based on a snapshot of data from 2016. The algorithms used for this fourth version were executed to reflect the state of the IUCLID database at two points in time, namely 31 July 2016 and three years later (i.e. 31 July 2019). It is, therefore, possible to examine the time evolution of testing methods and use of alternatives since the previous report.

For the purpose of this report, a distinction between low-tier and high-tier endpoints was made according to the following considerations. Endpoints outlined in REACH Annexes VII and VIII are considered as low-tier endpoints, while endpoints listed in REACH Annexes IX and X are considered as high-tier endpoints. For the purpose of this analysis, the 28-day repeated dose toxicity and screening studies for reproductive/developmental toxicity (included in REACH Annex VIII) are also considered as high-tier endpoints. These studies are closely related to the high-tier requirements and are often used (in combination with other evidence) in an attempt to fulfil the repeated dose toxicity and reproductive/developmental toxicity requirements.

Low-tier endpoints include acute rodent toxicity, skin corrosion/irritation, serious eye damage/eye irritation, skin sensitisation and short-term toxicity to fish. High-tier human health endpoints include repeated dose toxicity (all routes, all durations), genetic toxicity *in vivo*, developmental toxicity, toxicity to reproduction and carcinogenicity. And, high-tier environmental endpoints include bioaccumulation, long-term fish toxicity and long-term toxicity to birds.

¹⁹ <https://echa.europa.eu/-/21-551-chemicals-on-eu-market-now-registered>

²⁰ Article 22 of REACH "Further duties of registrants"

²¹ <https://echa.europa.eu/-/iuclid-6-is-available>

2 LEGAL INSTRUMENTS TO AVOID UNNECESSARY TESTING

REACH offers different legal instruments to avoid unnecessary testing and to make sure that (animal) testing is only undertaken as a last resort. The main instruments are data sharing, adapting information requirements and testing proposals.

2.1 Data sharing and joint submission

All registrants of the same substance have to share data related to vertebrate animals. They have to agree on the data for their joint REACH registration. It is a collective responsibility, which applies equally to all co-registrants. If they cannot reach an agreement, they can submit a dispute to ECHA, which may give them access to data, if appropriate. ECHA also provides data if a period of more than 12 years has passed after its submission. In this case, the data can be re-used freely by others for registration.

Data sharing applies to old experimental studies as well as new studies conducted either spontaneously by registrants to fulfil an information requirement, in preparing their registration dossier or updating it, or after receiving a request from ECHA following an evaluation decision.

There are two possible routes for data sharing: **pre-registration** and establishment of substance information exchange forums (SIEFs) for existing (phase-in) substances and **inquiry** to ECHA for all other substances. Pre-registration ended on 31 May 2017 for phase-in substances under certain conditions²². After this date, the obligatory inquiry route is the only way to get in contact with other registrants of the same substance.

New contacts between companies for sharing data have continued since the previous report. For phase-in substances, the earlier trend of around 14 000 pre-registrations each year on average continued, with 15 000 pre-registrations in 2016. In 2017, there seemed to be a rush before the closure of pre-registration with over 580 000 pre-registrations for getting access to SIEFs, and to fulfil the obligatory data-sharing rules.

The inquiry process facilitates data sharing for all registrants who cannot benefit from the pre-registration mechanism. Since the closure of pre-registration, all substances enter the system in this way, which led to a significant rise in the number of inquiries to around 4 200 inquiries per year, with a peak of 6 104 inquiry dossiers around the 2018 deadline. The vast majority of inquiries are to share data for substances previously registered, with on average only 200-250 substances per year that are new to the database.

In anticipation of the 2018 registration deadline, the Commission issued an Implementing Regulation²³ in 2016 to clarify the data-sharing principles and the requirement that ECHA must ensure that all registrants of the same substance are part of the same joint submission, even where a registrant separately submits some information (opt-out). This prompted the need to revise the *Guidance on data-sharing*²⁴. ECHA also modified REACH-IT, to prevent submissions outside of existing joint submissions. This ensures that co-registrants discuss sharing of all relevant data for the substance and avoid duplicating animal tests following the 'one substance, one registration' (OSOR) principle.

²² Phase-in substances below 100 tonnes per year, within six months after exceeding the one tonne per year threshold.

²³ Commission Implementing Regulation (EU) 2016/9 of 5 January 2016 on joint submission of data and data-sharing in accordance with Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

²⁴ https://echa.europa.eu/documents/10162/13631/guidance_on_data_sharing_en.pdf

With the improvements in IT systems and processes, the number of parallel new submissions has been reduced to zero. Especially with the high number of additional registrations related to the 2018 deadline, this change in process and IT has enforced more data sharing, and has avoided duplicate data generation, including animal testing.

2.2 Adaptation possibilities of REACH

REACH Annex XI(1) specifies the general rules for adaptation of the standard testing regime set out in annexes VII to X. It provides different options for deviating from the standard requirements and for using alternative approaches, provided they are duly justified and scientifically sound. These options are listed as possible adaptations in REACH Annex XI(1) and include:

- 1) use of existing data, including historical human data;
- 2) use of a weight-of-evidence approach;
- 3) information generated using quantitative structure activity relationships (QSARs);
- 4) *in vitro* test methods; and
- 5) grouping of substances and read-across.

Adaptations can be used either individually or combined in a weight-of-evidence approach (for example, use of QSAR and information from read-across in combination with literature evidence or some properties indicating the possible fate of a substance). In all cases, the data used must be adequate, reliable and relevant for the particular endpoints, and must follow the criteria set out in Annex XI.

It is also possible to omit (i.e. waive) the standard information required for an endpoint by other means than the options listed above. REACH Annex XI provides data-waiving possibilities when testing is not technically possible (REACH Annex XI(2)) or based on exposure considerations (for example, where no significant exposure can be shown) (REACH Annex XI(3)).

In addition, for some endpoints, Column 2 of REACH Annexes VII-X gives specific rules for other adaptation or data-waiving possibilities (for example, based on considerations of other hazardous properties).

For the analyses conducted for this report, omitting studies as a result of REACH Annexes VII-X Column 2 adaptations is not distinguished from omitting studies according to REACH Annex XI adaptations. As such, both options are marked as “data waiver” in the presented results.

2.3 Testing proposals and third party consultations

For the purposes of registration under REACH, registrants must not undertake any new studies involving vertebrate animals required by REACH Annex IX or X before submitting a testing proposal to ECHA and only after receiving ECHA’s decision requiring the test to be performed, and under which conditions. When they submit their proposal, the registrants must show that they have considered alternatives²⁵ in their IUCLID dossier.

ECHA organises third party consultations for all testing proposals involving vertebrate animals, for the endpoints specified in REACH Annexes IX and X. The aim is to ensure that there is no scientifically valid, existing data that could address the hazard endpoint covered by the testing proposal. Such information, if it can be used to fill the data gap, may mean that the proposed testing is no longer required and is sent to the registrant

²⁵ https://echa.europa.eu/view-article/-/journal_content/title/considerations-for-alternative-methods-need-to-be-included-in-your-testing-proposal

together with the draft decision for their consideration. ECHA, in consultation with the Member States, adopts the decision based on the registrant's proposal, the information submitted by third parties and any readily available information identified by ECHA.

Many comments received from third parties are about potential strategies that the registrant could use, for example, information supporting weight of evidence, references to open literature and, seldom, potentially relevant studies. However, the registrant may face challenges to make use of this information. One difficulty is to get reliable and adequate documentation so that the information can be used for classification and risk assessment and to establish that the information has adequate and reliable coverage of the key parameters addressed in the corresponding test method. Another challenge is to get access to study reports identified by third parties and compensate the data owner.

During the last years, the number of comments received decreased significantly. Before 2015, almost all initiated consultations received third party comments, while between 2017 and 2019, only one-third of initiated consultations²⁶ received third party comments. As reported previously, the impact of third party consultations has remained relatively limited for the reasons outlined above. Nevertheless, there are a limited number of examples of third party comments that pushed registrants to adapt their testing strategies.

As of 31 December 2019, there were 1 348 information requests stemming from adopted testing proposal decisions for endpoints concerning vertebrate animal tests (see Table 1 below). It is not possible to directly correlate these requests with the number of animal tests that may result. Such requests may address sequential testing strategies involving the prior conduct of invertebrate tests or may accept the use of data from tests conducted with another substance (for example, read-across) as plausible.

The most frequent requests in testing proposal decisions are for information for pre-natal developmental toxicity studies, repeated dose toxicity 90-day studies and toxicity to reproduction.

Table 1: Number of requests for tests in adopted decisions with testing proposals taken since the last report (2017-2019) and cumulative number of all requests since 2009.

Endpoint (concerning vertebrate animals only)	Number of requests in adopted decisions with testing proposals adopted since the last report (2017-2019)	Total number of requests in adopted decisions with testing proposals (2009-2019)
Bioaccumulation	7	25
Long-term toxicity to fish	21	69
Repeated dose toxicity (90-day, all routes)	103	462
Mutagenicity/genotoxicity <i>in vivo</i>	35	90

²⁶ <https://echa.europa.eu/information-on-chemicals/testing-proposals/previous/outcome>

Pre-natal developmental toxicity	157	624
Toxicity to reproduction ²⁷	72	78
Total	395	1 348

3 Analysis of REACH registrations

Under REACH, registrants are responsible for collecting and generating the necessary information, including the application of alternative methods, to properly identify and manage the hazards and risks. They have to make their data and knowledge on substances transparent, by submitting an electronic REACH registration dossier to ECHA, using the IUCLID software.

3.1 Scope: a complete view

With this report, the low tonnage phase-in substances, which were registered by the 2018 deadline are also included, providing a complete overview for substances on the European market within the scope of REACH.

With the update of the data analysis approach, a new feature was introduced to compare the situation at different time periods. For this report, the situation of 31 July 2016 (the date when data was extracted for the third 117(3) report), is compared to the current situation, using data taken from the complete database on 31 July 2019. Comparing the results for the two cut-off dates gives an insight into the way information requirements have been fulfilled in 2019 and 2016.

In total, 98 017 dossiers were analysed for this report (see Table 2). These included all the latest submissions of the 7 553 and 12 184 substances that had been registered before 31 July 2016 and 31 July 2019, respectively. The analysis was done on substances for which at least the full Annex VII information requirements are applicable²⁸. For these substances, all the dossiers that (potentially) contain animal tests or alternative methods to animal testing were considered.

Table 2: Number of substances for each of the REACH annexes (VII – X) which define the standard information requirements, for the cut-off dates of 31 July 2016 and 31 July 2019.

REACH Annex	31 July 2016	31 July 2019
VII	2 254	4 884
VIII	903	2 642

²⁷ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015R0282&from=CS>

²⁸ Dossiers for strictly controlled intermediates (article 17 and 18) were excluded, as well as some of the NONS substances which were notified under the previous directive 67/548/EEC. More details in Annex 1

IX	2 156	2 331
X	2 240	2 327
Total	7 553	12 184

3.2 Method

ECHA develops algorithms and uses powerful, dedicated data mining tools to screen and analyse the submitted dossiers. For this report, ECHA also used its in-house scientific data analysis platform.

As REACH stipulates that registrants need to provide all available and relevant information, there is often a multiplicity of data and information available for each required endpoint. This makes it complex to analyse what type of alternative approach was used.

Different graphs and projections are presented, where choices are made depending on the nature of the analysis. In some cases, the focus is on all the available information, for instance, when analysing trends on the use of guideline studies. For other analyses, the focus is on how registrants fulfilled their requirements.

Therefore, a certain hierarchy needs to be implemented to keep the output graphs readable. A more detailed technical description of the data extraction, data processing and graph explanation can be found in Annex 1.

3.3 Results and discussion

The results and discussion are presented from different angles to answer four main questions for this analysis.

In addition to the availability of experimental studies and the status of implementation and use of non-animal test methods, the registration database was further analysed to answer the following specific questions:

1. What are the most commonly used adaptations?
2. Which options did registrants use to fulfil their information requirements for lower-volume substances (less than 100 tonnes per year)?
3. What are the most noticeable changes for higher-volume substances (100 tonnes per year and above) since the previous (third) Article 117(3) report?
4. How did the situation evolve since 2016 for the endpoints where alternative methods have been introduced as standard information requirements?

The evolution of the skin corrosion/irritation, serious eye damage/eye irritation and skin sensitisation endpoints are described in more detail in dedicated sections at the end of this chapter.

3.3.1 Availability of experimental studies

First, information was compiled on all substances for which guideline²⁹ studies were

²⁹ Guideline/experimental study means, an experimental study according to (one of the) guidelines appropriate

available. A comparison between 2016 and 2019 data has been performed to have an overview of changes in the availability of experimental studies since the last report. An intuitive way to obtain this overview is to first look at the percentage of substances for which registrants have provided at least one guideline study for each information requirement³⁰.

Figures 1 and 2 show the results of the study availability analysis. The rows in both figures represent the endpoints, and each column represents the REACH Annex to which the substance belongs. Within each cell, the percentage of substances is shown for which the information requirement is fulfilled with the standard guideline study. This is colour-coded: the darker the shade of blue, the more guideline studies were provided, this means that e.g. for developmental toxicity, 19.5 % of substances had a guideline study at Annex IX level, which means that 80.5% of substances used some form of an adaptation.

The standard information requirements for skin corrosion/irritation and serious eye damage/eye irritation³¹ were updated in the legal text on 31 May 2016, and on 10 May 2017 for skin sensitisation³², making non-animal testing the default requirement. Subsequently, *in vitro* and *in vivo* studies have been separated in this analysis.

Figure 3 shows the percentage-point difference between 2019 and 2016 (the 2019 percentage minus the 2016 percentage). An increase in the number means that between 2016 and 2019, a higher percentage of substances have at least one reliable (Klimisch score 1 or 2, as determined by the registrant) guideline study, while a decrease means that the percentage of substances with such experimental information was reduced and registrants have used alternative approaches or waiving to fulfil the information requirement. In some specific cases (for example, skin sensitisation), the changes also reflect changes in the standard requirements.

It should be noted that non-vertebrate endpoints related to aquatic toxicity have also been included in the analysis since REACH foresees the use of integrated strategies, where invertebrates are also considered, which can ultimately affect the number of studies performed on vertebrate animals.

to meet the requirement for the endpoint.

³⁰ The values behind the figures in this chapter can be found in Annex 1.3

³¹ <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32016R0863>

³² <https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32017R0706>

Figure 1: Percentage of substances for which guideline studies were used to fulfil the standard information requirements for each information requirement (2019)

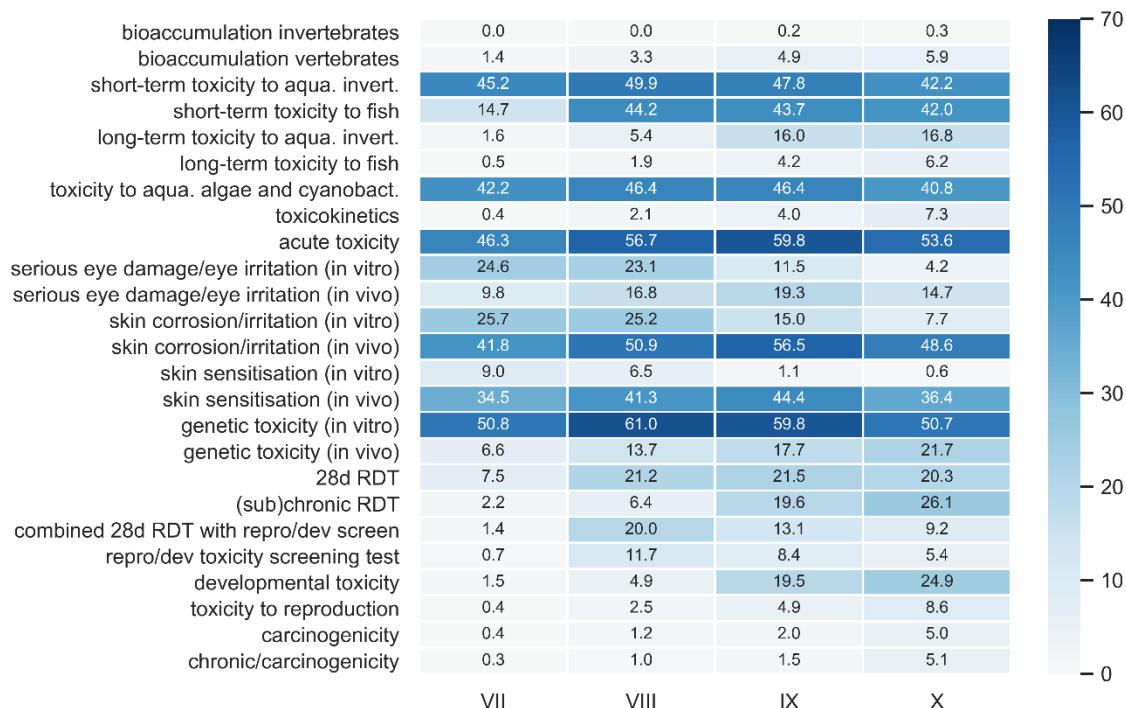


Figure 2: Percentage of substances for which guideline studies were used to fulfil the standard information requirements for each information requirement (2016)

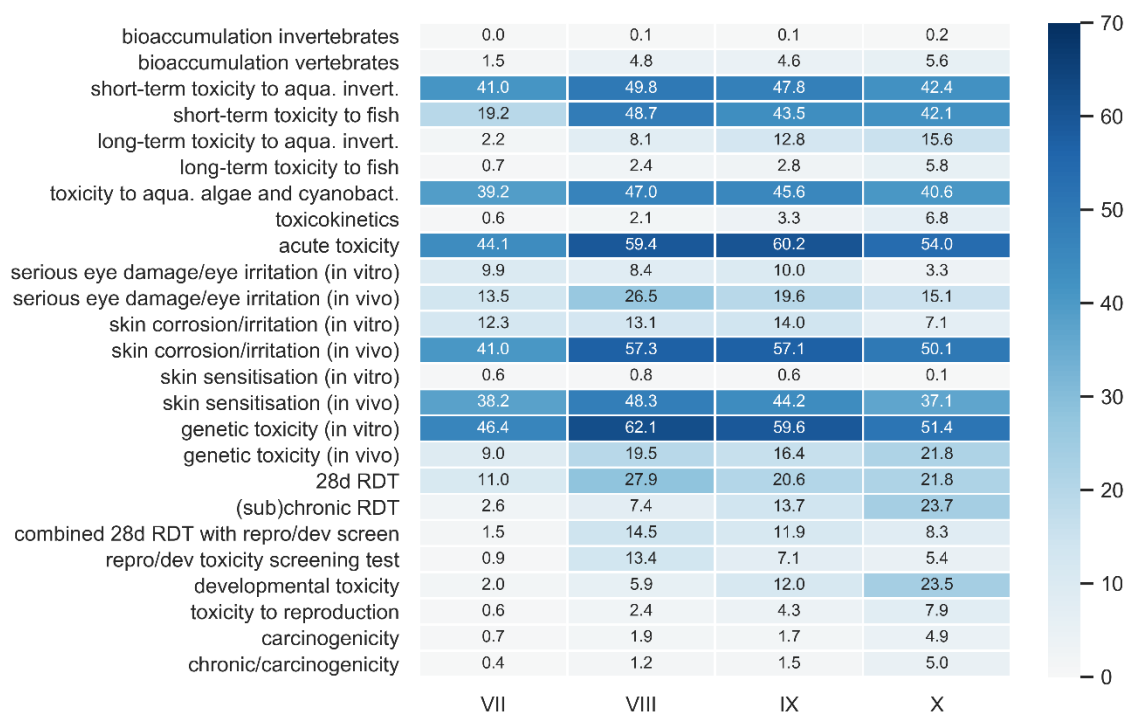
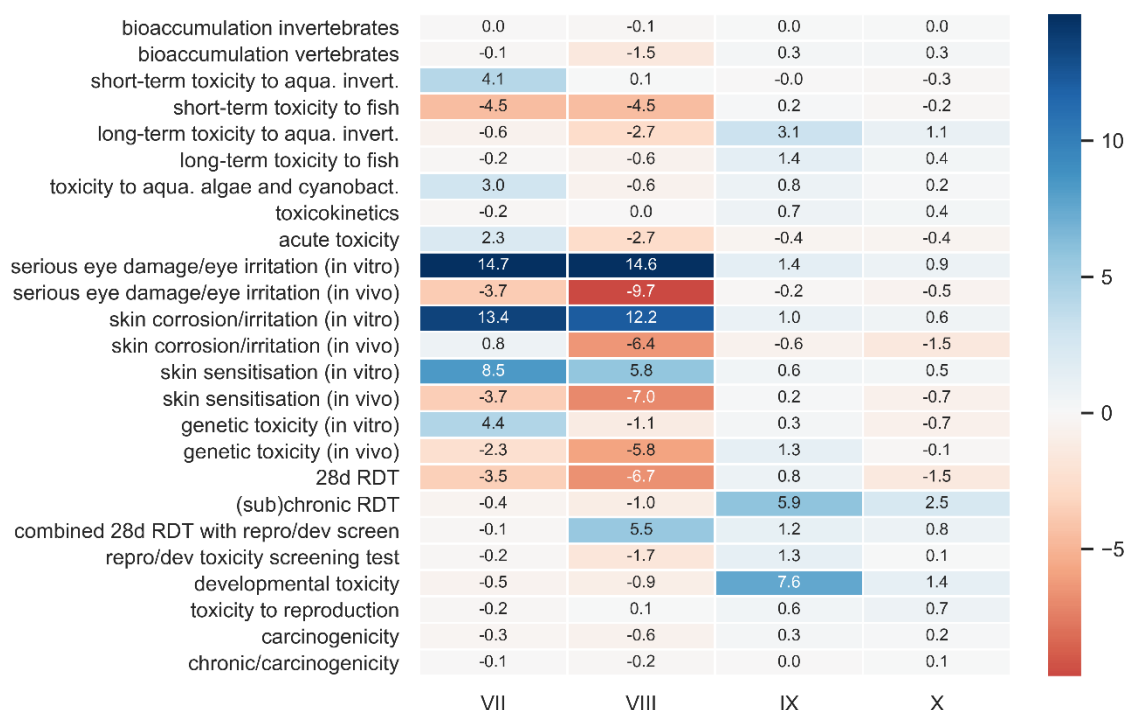


Figure 3: Difference in the percentage of substances for which guideline studies were used to fulfil the standard information requirements for each information requirement (percentage in 2019 minus percentage in 2016)



In general, Figure 2 shows that endpoints with the highest percentage of guideline studies were in 2019 for genetic toxicity *in vitro*, with a percentage of around 50 % to 60 % depending on tonnage, acute toxicity (~ 46–60 %), skin corrosion/irritation *in vivo* (42–50 %) and short-term toxicity to fish are at almost the same percentage.

On the other hand, bioaccumulation (vertebrates and invertebrates) (<6 %), carcinogenicity (1–5 %) and toxicity to reproduction (1–8 %) are endpoints for which typically relatively few guideline studies were available.

On a high level, no significant changes are observed between 2016 and 2019 except in four areas.

The first area is skin sensitisation, skin corrosion/irritation and serious eye damage/eye irritation where a significant shift is visible from *in vivo* to *in vitro* approaches between 2016 and 2019. This suggests that the Commission Regulation 2016/863 amending Annexes VII and VIII to the REACH Regulation in 2016³³ has had an impact in terms of the way registrants are fulfilling information requirements and has contributed to avoiding animal testing. A further analysis of these endpoints is presented in Sections 3.3.7 and 3.3.8.

The second area that stands out and is visible in Figure 3, is the moderate increase in the percentage of pre-natal developmental toxicity and (sub)chronic (90-day/28-day) repeated dose studies for Annex IX and X substances, which is likely to be related to the decisions ECHA has taken in compliance checks and testing proposals on these endpoints.

Thirdly, there is an increase in the propensity of the combined repeated dose toxicity

³³ <http://data.europa.eu/eli/reg/2016/863/oj>

with the reproduction/developmental toxicity screening test (OECD 422) at Annex VIII while at the same time, the percentage of repeated dose toxicity (short-term) and toxicity to reproduction screening studies has lowered compared to 2016. These studies do not require a testing proposal and can be done on the initiative of registrants. This increase seems to indicate that when new data has to be generated to ensure safe use, registrants favour combined tests instead of separated studies which brings significant reductions in the number of animals and costs.

Fourthly, it can be observed that the percentage of short-term toxicity to fish studies is lower in 2019 than in 2016, which indicates that the use of adaptations for this standard information requirement in REACH Annex VIII has increased. It is noticeable that there is a significant number of short-term fish studies for Annex VII substances, even if there is no standard information requirement. In addition, a slight increase in experimental data for long-term aquatic studies in 2019 is visible, which might be a consequence of industry initiatives to improve dossiers through testing proposals and compliance check actions by ECHA.

3.3.2 Options used to fulfil requirements in 2016 compared to 2019

REACH gives many options to fulfil the information requirements, and at the same time, calls for the use of all relevant and available information. The different options that REACH registrants have as defined in this analysis, are:

- Experimental: the use of an experimental study according a guideline which is in line with the information requirement.
- Read-across: the use of a guideline study on a different but similar substance to read-across the results. This includes category approaches of read-across within groups of substances.
- QSAR: a mathematical prediction relating one or more quantitative parameters, which are derived from the chemical structure, to a quantitative measure of a property or activity.
- Weight of evidence: the use of all available and relevant information which combined would suffice to allow for a conclusion on hazard and risk assesment, including classification and labelling, without further studies. In Annex 1 , the combinations of information that lead to the labelling of weight of evidence are defined.
- Data waiver: omitting the standard information required for an endpoint either by means of the general REACH Annex XI adaptations (testing is not technically possible as defined in REACH Annex XI(2)) or based on considerations of exposure (REACH Annex XI(3)), or by specific Column 2 adaptations of REACH annexes VII–X.
- Testing proposal: It should be noted that testing proposals remain only for a period in the database, as they are processed within set deadlines. The number represented in the graphs reflects the testing proposals at the moment the snapshot of the database was taken. For an overview of the number of testing proposal processed, see Chapter 2.3 Testing proposals and third party consultations.
- Other: other combinations of information that do not match the above defintions, e.g. literature data.
- No information: the absence of information, most commonly this reflects that the endpoint is not required and therefore not provided. Another reason for this category is that the endpoint is part of the integrated testing strategy, and the test is not required depending on the outcome of other tests.

A direct comparison of the options to fulfil the information requirements, other than through experimental (animal) testing, is difficult to make because registrants have the option to combine approaches. For example, a read-across can be combined with QSAR

predictions and literature experimental evidence, where none of these pieces of evidence is adequate on its own.

The approach taken for the analysis is a combination of applying a hierarchy and taking (arbitrary) decisions on how to label endpoint data. For instance, if an endpoint has a reliable guideline study, together with a QSAR prediction, this is counted as a guideline study. The Klimisch score, as assigned by the registrant, was used as a guide to distinguish reliable information (Klimisch 1 and 2) from other information. If the registrant used a combination of pieces of information to cover an endpoint, this was counted as weight of evidence. The approach is explained in full detail in Annex 1.

The results of the analyses are shown in Figures 4 and 5. They show the options used by registrants to fulfil the information requirements on 31 July 2016 and on 31 July 2019. In these two figures, data was aggregated (at IUCLID section level) from all processed dossiers regardless of the tonnage band. Endpoints (listed on the vertical axis) are blue or red. Blue represents obligatory endpoints, and the percentage is expressed using only the substances for which the endpoint is requirement. The red endpoints are not obligatory which means they are either:

- part of an integrated testing approach, and therefore not always obligatory as these tests are conditional (relevant for Figures 4-11), or
- not required at the level of the annex, and information is provided on top of the standard minimum requirements (relevant for Figures 6-11)

For the endpoints listed in red on the Y-axis, all substances in their respective tonnage bands are used to express the percentages. This explains why for the red endpoints "no information" is a much larger category than for the blue endpoints, as this represents optional endpoint information.

A more detailed technical description of the data extraction, data processing and graph explanation can be found in Annex 1. The numerical results can be found in Annex 3.

Figure 4: Frequency of the different options to fulfil the information requirements in 2019 (aggregated at IUCLID section level).

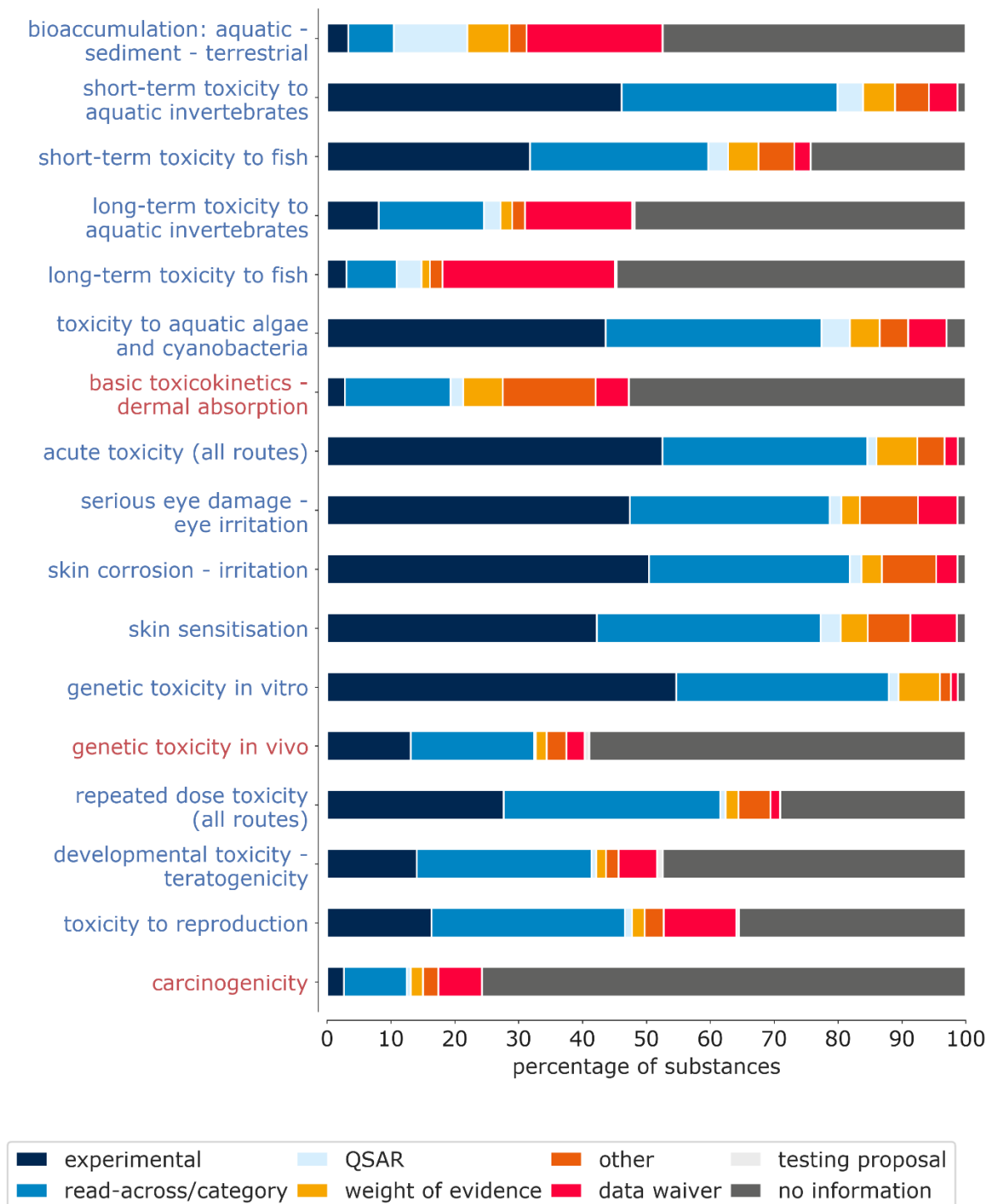
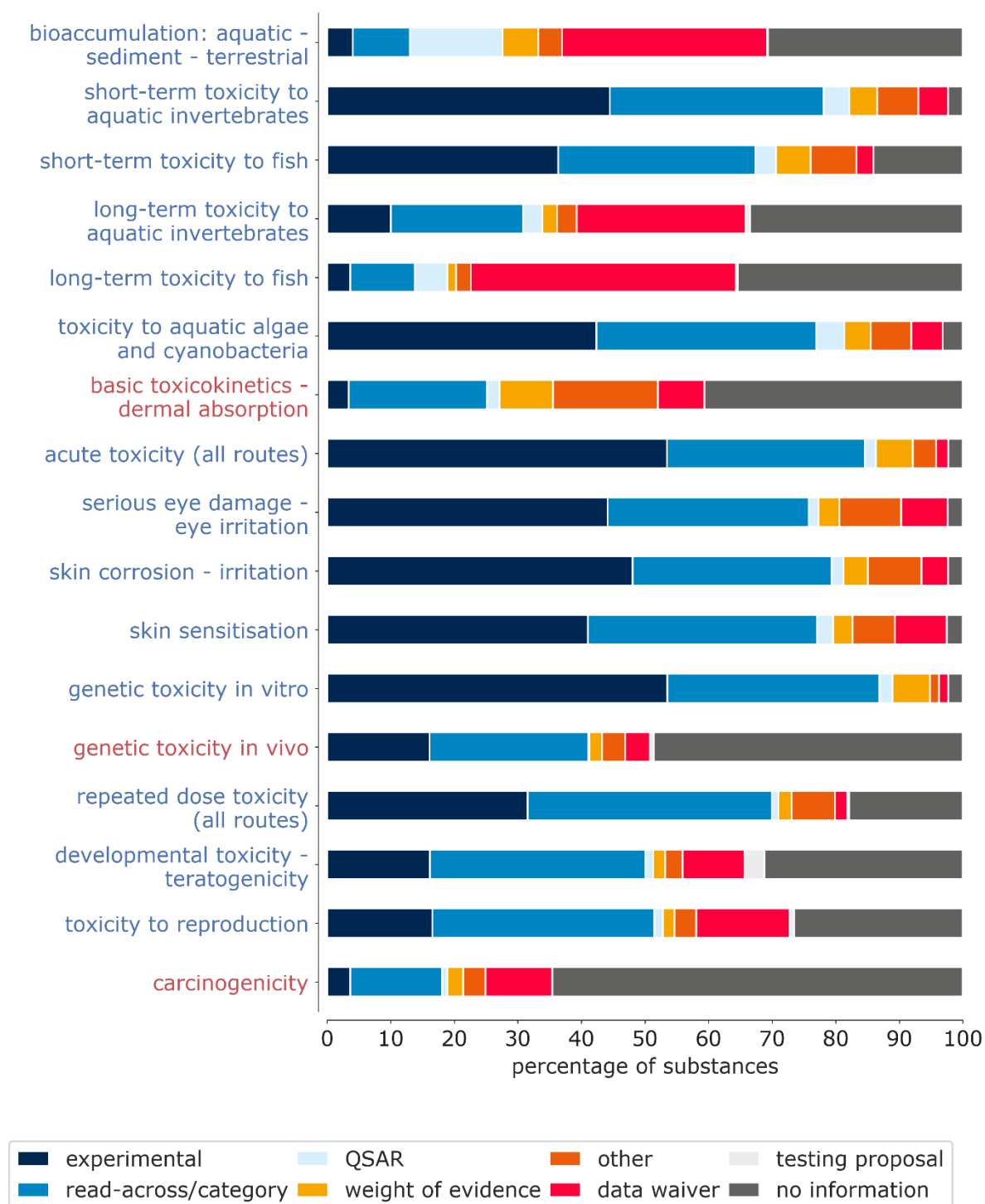


Figure 5: Frequency of the different options to fulfil the information requirements in 2016 (aggregated at IUCLID section level).



From the results presented in Figures 4 and 5, it can be observed that at the highest level of aggregation, there are no remarkable differences between the approaches used to fulfil the information requirements in 2016 and 2019. The overall picture has not changed despite the fact that many lower tonnage dossiers were added due to the 2018 registration deadline, and at least six years of maintaining the existing dossiers (2010 and 2013 deadline) as reflected in Table 3.

Table 3: options used to fulfil the information requirements on average, 2019 compared to 2016

Option used	2019 average [%]	2016 average [%]
Experimental	27.1	27.6
Read-across/category	25.1	27.7
QSAR	2.6	3.0
Weight of evidence	3.7	3.7
Other	4.8	5.6
Data waiver	7.7	10.8
Testing proposal	0.2	0.3
No information	28.7	21.2

There are two areas that are worth highlighting as, even in this highly aggregated overview, they stand out.

Firstly, as can be seen in Figure 4, waiving is used as the most frequent adaptation for long-term toxicity to fish, suggesting that information on short-term aquatic toxicity and long-term toxicity for non-vertebrate species has often been considered sufficient to carry out a chemical safety assessment.

Data on invertebrates for environmental endpoints have been included in the data analysis so the impact of testing strategies to avoid vertebrate testing with fish can be explored. REACH *Guidance R.7* stipulates that fish testing can be omitted if the fish is less sensitive than aquatic invertebrates or algae. While the percentage of short-term toxicity studies with fish is only slightly lower than the percentage of short-term toxicity studies with aquatic invertebrates (*daphnids*) and algae, the percentage of experimental long-term fish studies is substantially lower than that of long-term studies with aquatic invertebrates. This suggests that the promoted testing strategy to avoid vertebrate testing has been widely applied. Similarly to the situation in 2016, bioaccumulation (11.5 %), long-term toxicity to fish (almost 4 %) and short-term toxicity to fish (3.1 %) are the endpoints that require vertebrate animal testing for which (Q)SARs were used most frequently to fulfil the information requirements without relying on other information.

Secondly, for a number of endpoints the level of 'no information' seems higher in 2019 than in 2016. The higher tier endpoints especially show this: carcinogenicity (11 % difference), toxicity to reproduction (9 % difference), developmental toxicity (16 % difference). These results suggest that there was more additional information, beyond the minimum requirements, in the dossiers submitted earlier. Further detailed analysis reveals that this is due to the nature of the 2019 dossiers (See Chapter 3.3.4).

3.3.3 Overall trends in the use of alternative methods with an emphasis on higher tier endpoints

The third edition of the Article 117(3) report focused mostly on the higher tonnage substances (Annex IX and X) as most substances in these tonnage bands were registered before the deadlines in 2010 (Annex X) and 2013 (Annex IX). So, for the purposes of this fourth edition of the report we investigated if and how the use of alternative methods for substances in these tonnage bands has evolved. It is important to note that the pool of substances for these two tonnage bands has been very stable between 2016 and 2019: 4327 substances were present both in 2016 and 2019 (Annex IX and X combined). Only few new substances occurred in these tonnage bands: 331 new substances from 2016 to 2019. Even less substances no longer exist at this tonnage band: -69 substances from 2016 to 2019. Changes in how registrants used the different options to meet the requirements for these tonnage bands are therefore expected to be caused by changes of the existing registrations, e.g. spontaneous updates, testing proposals, and ECHA's compliance check decisions.

Figures 6 to 9 provide the results for Annex IX and X dossiers for 2016 and 2019. As in Figures 4 and 5, endpoints in red font are part of an integrated testing approach and are not always required as they may also depend on the tonnage band.

Figure 6: Frequency of the different options to fulfil the information requirements for Annex X substances in 2019 (aggregated at IUCLID section level).

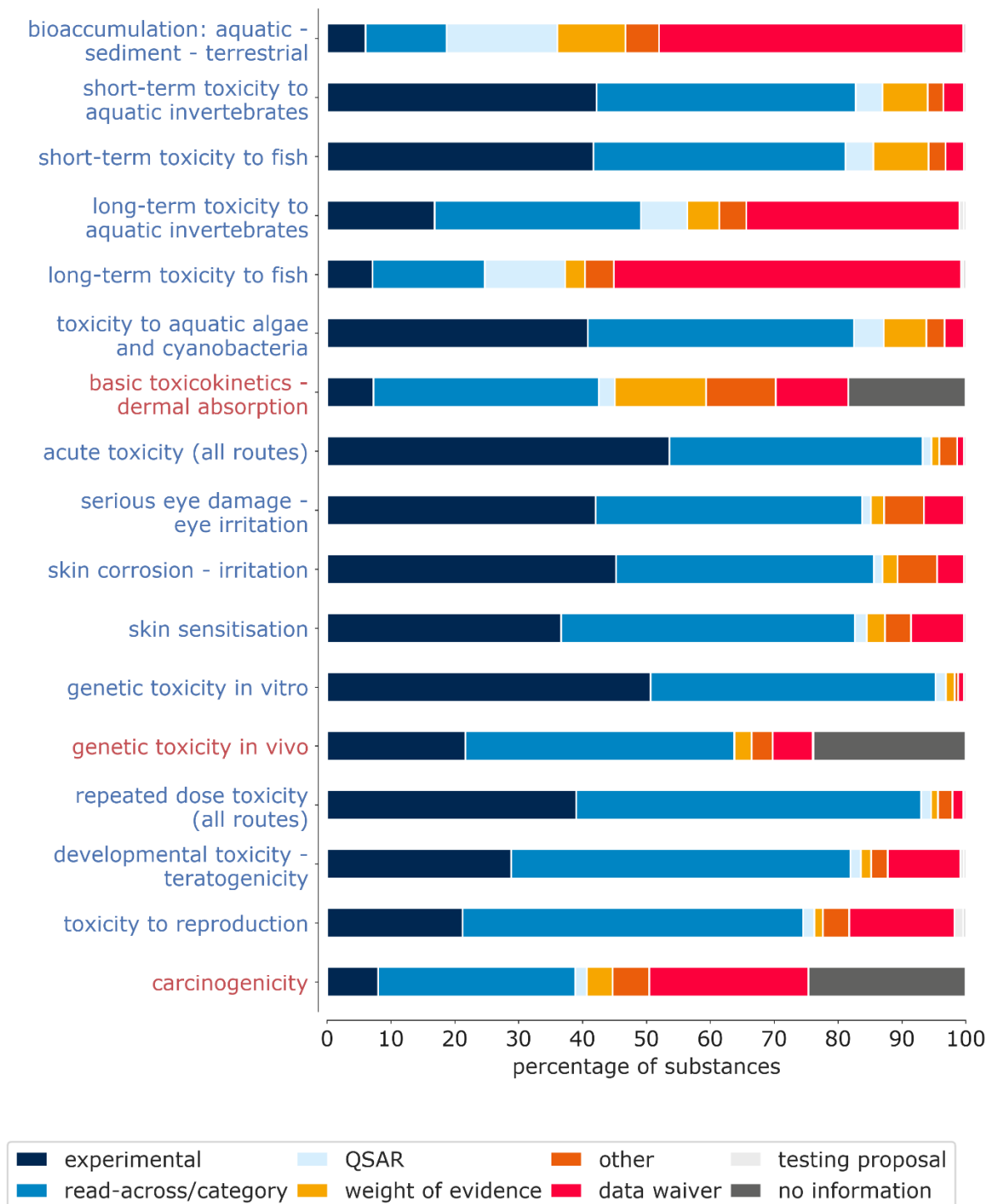


Figure 7: Frequency of the different options to fulfil the information requirements for Annex X substances in 2016 (aggregated at IUCLID section level)

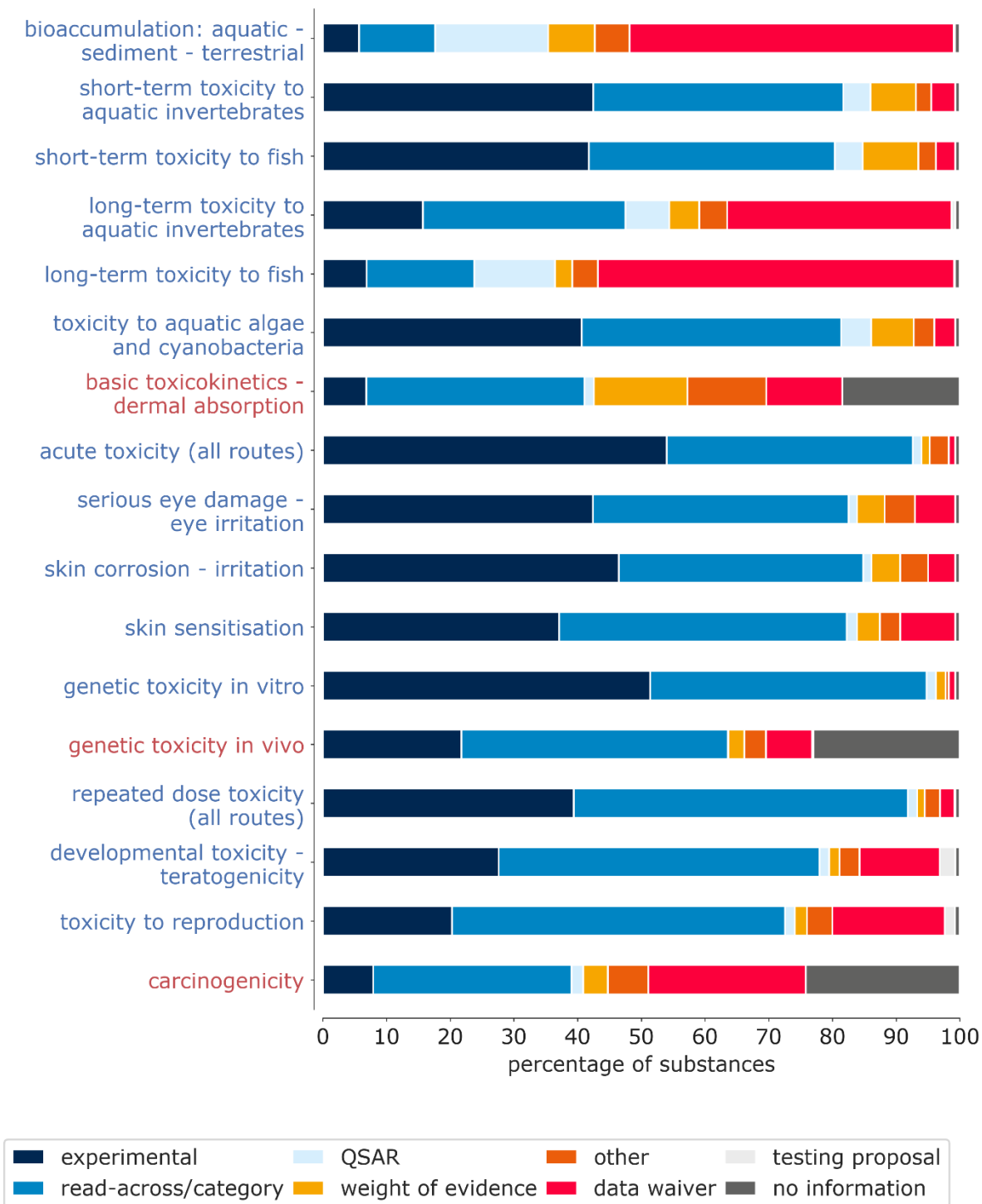


Figure 8: Frequency of the different options to fulfil the information requirements for Annex IX substances in 2019 (aggregated at IUCLID section level)

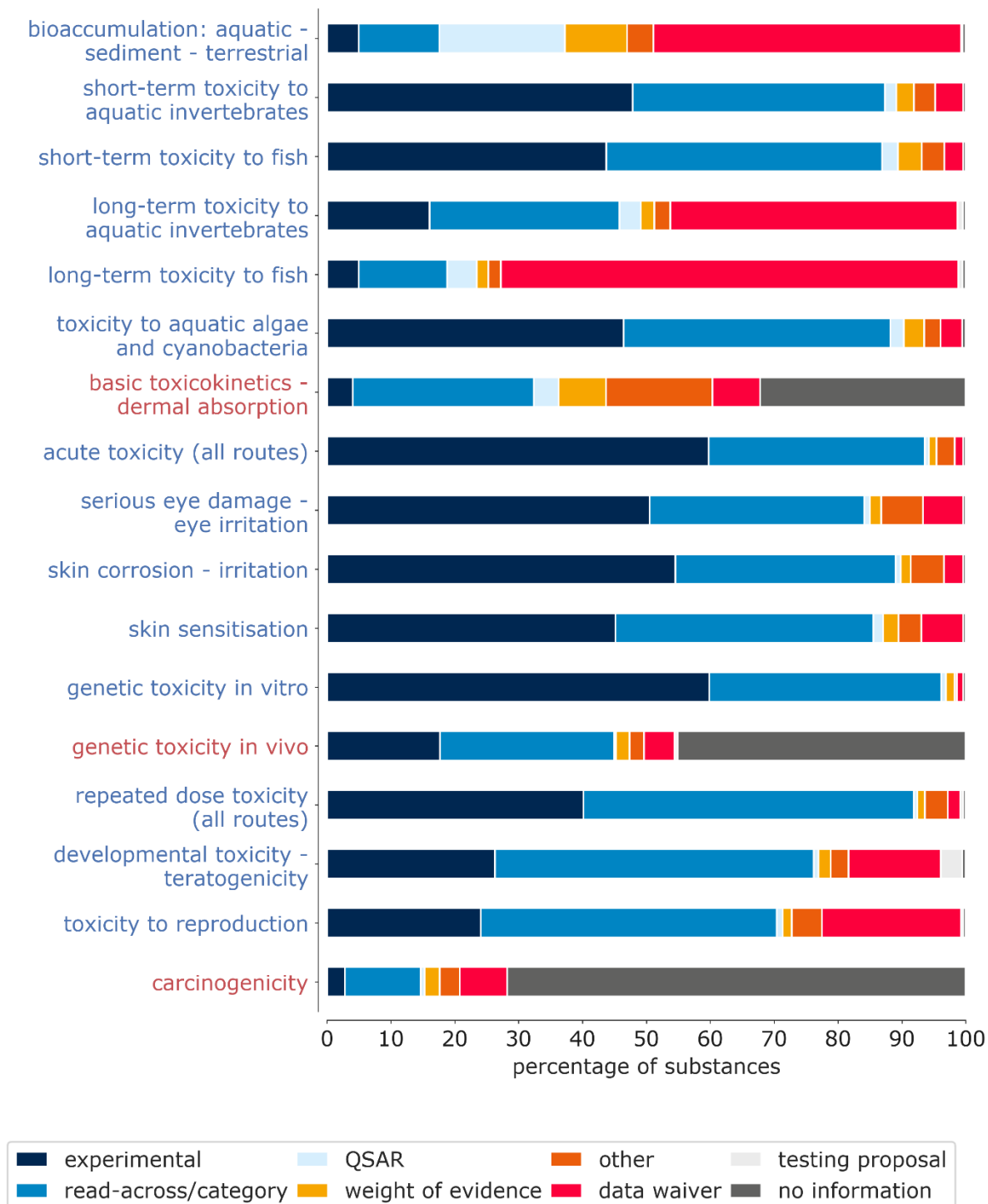
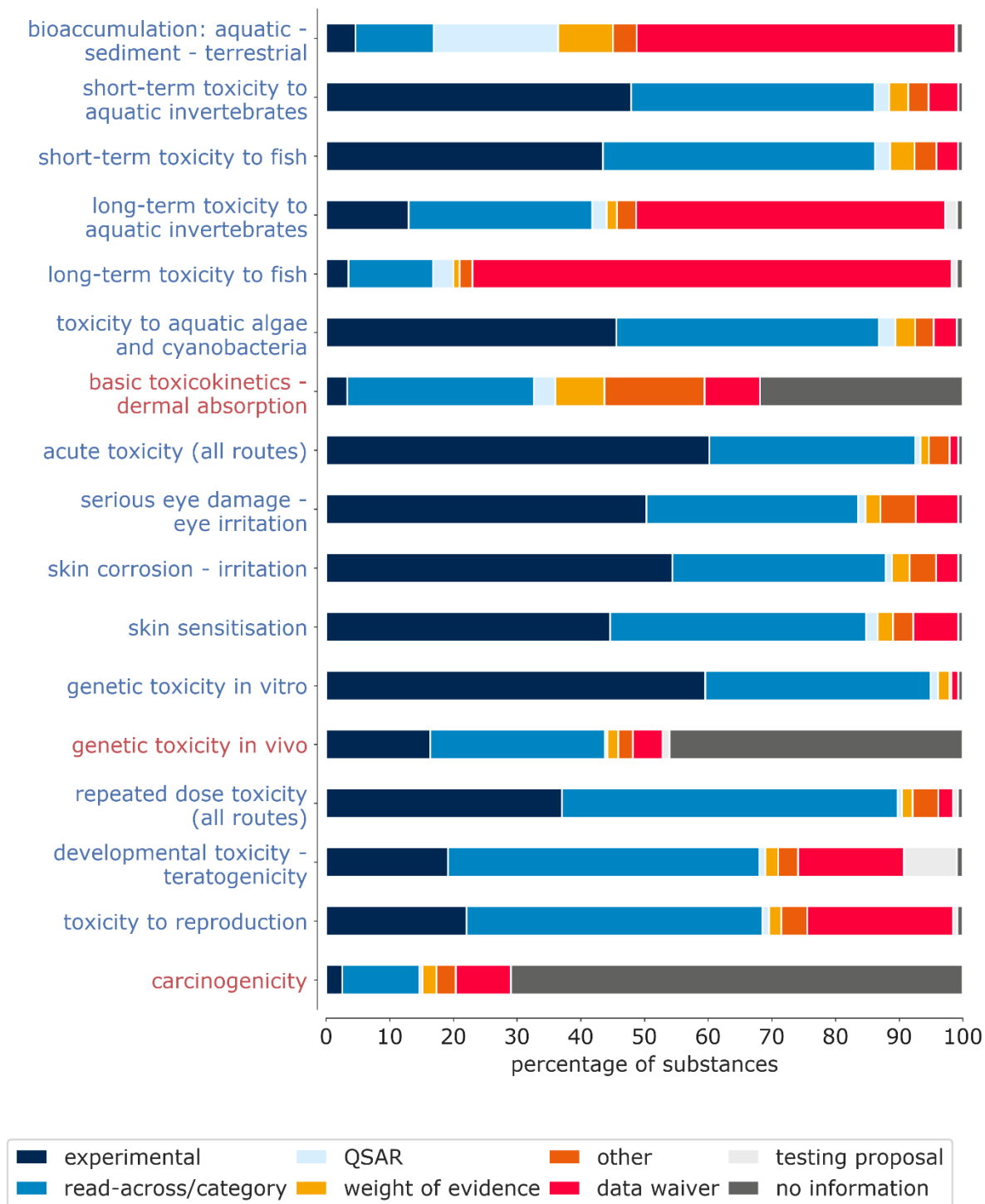


Figure 9: Frequency of the different options to fulfil the information requirements for Annex IX substances in 2016 (aggregated at IUCLID section level)



Figures 6 and 7 show that for Annex X substances there are hardly any changes detectable between 2016 and 2019. The largest change, with an increase of 3 % for weight of evidence and a decrease of around 3 % for the use of data waiver, is observed in bioaccumulation.

Developmental toxicity – teratogenicity sees a small increase in experimental studies (1.2 %), and an increase in read-across (2.8 %), somewhat balanced with fewer testing proposals (-1.9 %) and less data waiving (-1.2 %).

Skin corrosion – irritation and serious eye damage – eye irritation endpoints see a shift from weight of evidence (2.2 % less in both endpoints) to read-across (2 % for skin corrosion – irritation and 1.6 % for serious eye damage – eye irritation). These examples represent the biggest changes, which indeed confirms that these dossiers have been stable in how endpoints are addressed.

For Annex IX (Figures 8 and 9), the overall picture is also very similar between 2016 and 2019 but some changes are more clearly visible, especially for higher tier human health endpoints and long-term toxicity to aquatic invertebrates.

Developmental toxicity – teratogenicity has shifted from testing proposal (5 % lower in 2019) to an increase in experimental studies (7.1 % higher) in the 2016-2019 period. For repeated dose toxicity, an increase in experimental tests of 3.1 % can be observed in the period of analysis. There has also been a slight increase in the percentage of experimental long-term toxicity to fish studies (+1.4 % and +0.3 % for Annex IX and Annex X, respectively), although the overall percentage of substances with experimental data for this endpoint remains low (5 % and 7.1 % for Annex IX and X in 2019, respectively).

Generally speaking, adaptations continue to be used more than experimental studies, with read-across being the most popular option used. A small shift in experimental studies for some endpoints is visible, but this doesn't change the overall picture.

3.3.4 A more complete view on options used for lower tonnage substances

As this is the first time ECHA has been able to execute the analysis with all the lower tonnage dossiers (Annex VII and VIII) available, this has allowed us to focus on how alternative methods have been used for this group of substances.

Figures 10 and 11 provide the results for Annex VIII and VII dossiers for 2019.

Figure 10: Frequency of the different options to fulfil the information requirements for Annex VIII substances in 2019 (aggregated at IUCLID section level). Endpoints labelled in red font are not part of the standard information requirements at the given tonnage level, or are part of an integrated approach and are not always required.

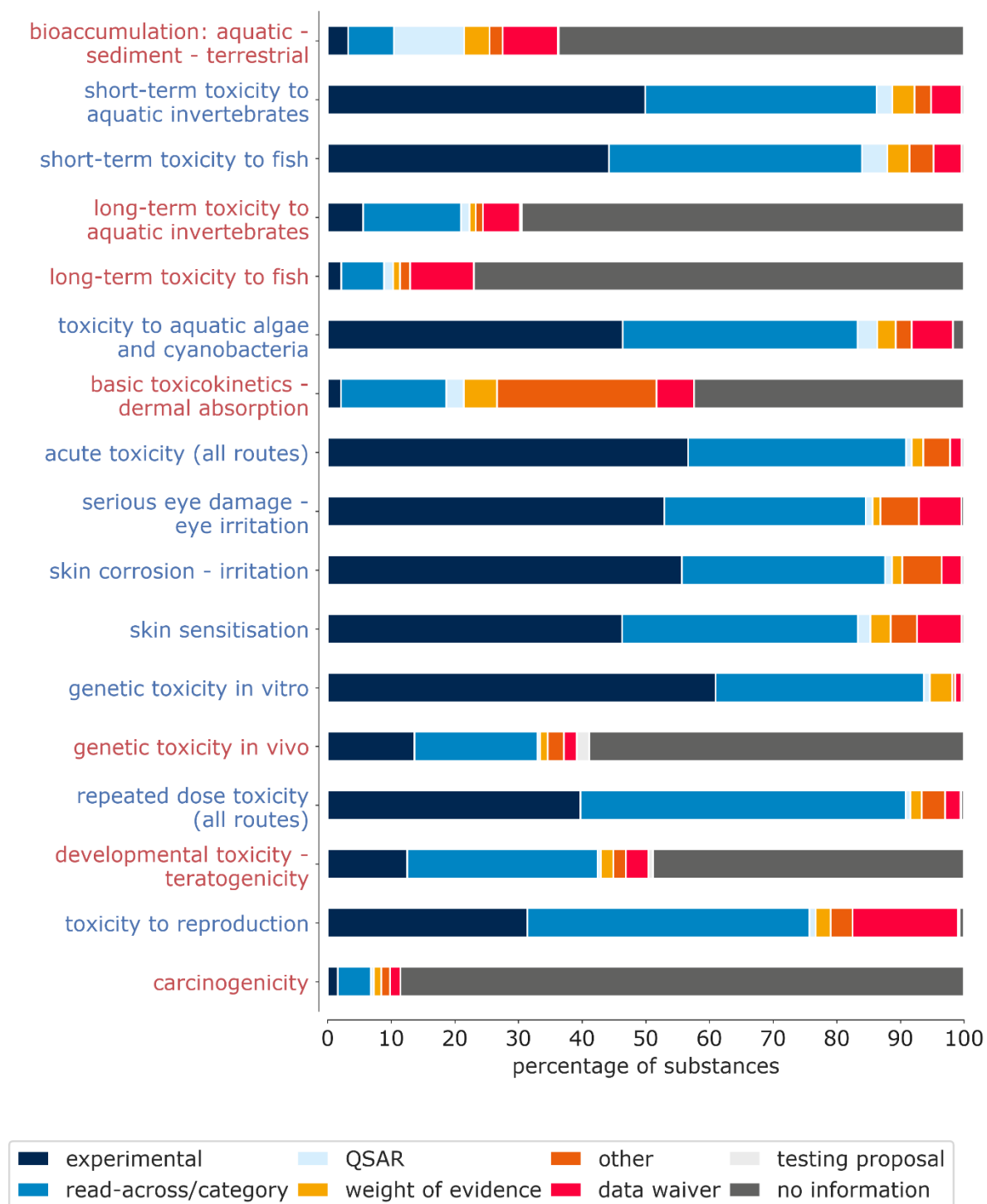
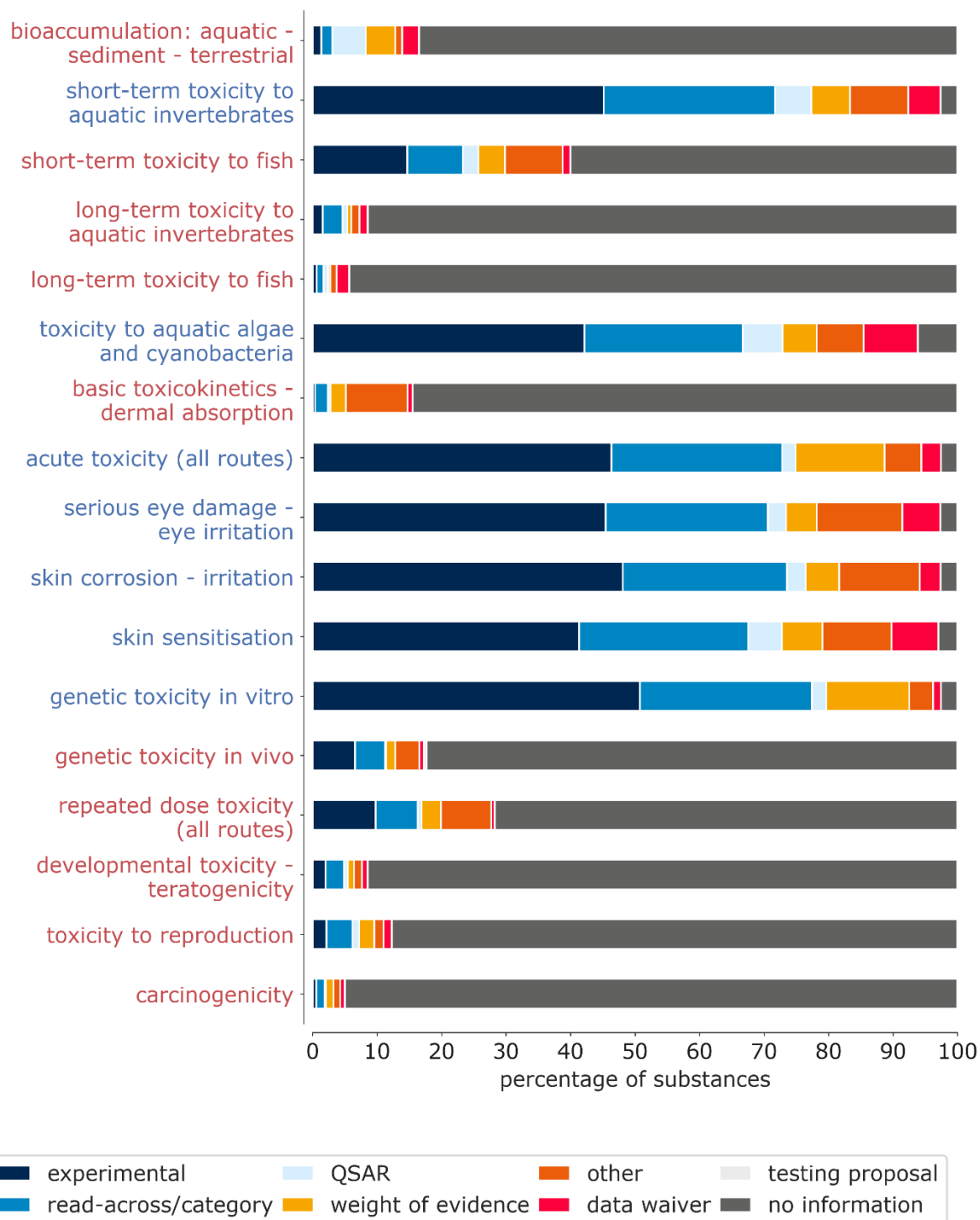


Figure 11: Frequency of the different options to fulfil the information requirements for Annex VII substances in 2019 (aggregated at IUCLID section level). Endpoints labelled in red font are not part of the standard information requirements at the given tonnage level, or are part of an integrated approach and are not always required (genetic toxicity in vivo for this annex).



The general distribution of the adaptation options for Annexes VII and VIII follows the overall pattern observed previously for the higher tier endpoints: read-across is the most popular, followed by data waiving, weight of evidence and QSARs.

When comparing 2019 Annex VIII dossiers (Figure 10) with 2019 Annex XI (Figure 8) for the endpoints that are required at both tonnage bands, no significant differences are observed, with the exception of acute toxicity where Annex VIII has fewer experimental studies (-3.1 %), which is compensated by an increase in the other options (weight of evidence, QSAR and data waiver).

When comparing 2019 Annex VII dossiers (Figure 11) with 2019 Annex XI (Figure 8) for the endpoints that are required at both tonnage bands, a generic trend can be observed of fewer experimental studies, less read across, balanced with more weight of evidence, QSAR and data waiver at the lower tonnage band. It can be concluded that for the dossiers with the lowest data requirements, registrants have used alternative approaches, even more than in the other tonnage bands.

Under Figure 10, it is remarkable that for 37 % of the substances, some information on the bioaccumulation endpoint was submitted, even though bioaccumulation at Annex VIII only needs to be followed up, if screening information indicates a potential persistent, bioaccumulative and toxic (PBT) concern. As context, for the Annex IX and X substances this information was present for roughly 50 %. Bioaccumulation does not need to be assessed for substances that have a low potential for bioaccumulation (for example, based on a low octanol/water partition coefficients ($\log K_{ow}$)) or a low potential to cross biological membranes (in the case of high molecular weight substances).

When discussing the overall difference between 2019 and 2016 dossiers (see Chapter 3.3.2), it was observed that the level of 'no information' seems higher in 2019 than in 2016 for a number of endpoints. This is particularly shown for the higher tier endpoints: carcinogenicity (11 % difference), toxicity to reproduction (9 % difference) and developmental toxicity (16 % difference). This significant difference does not occur in any of the other annexes (Annex X and Annex IX). It is, therefore, the result of differences in the Annex VII and VIII dossiers received until 2016 and the Annex VII and VIII dossiers received until 2019, respectively. Low tonnage substances also needed to be registered before June 2010, if they were classified as carcinogenic, mutagenic or toxic to reproduction, in categories 1 or 2 (CMR Cat 1 and 2). These substances can be expected to have more information than required according to the tonnage band, since this information was likely forming the basis for their classification in the past. Information that is needed to classify a substance as CMR Cat 1 and 2 is typically information that is only required starting from Annex IX. In contrast, the substances that were registered later and are not classified as CMR Cat 1 and 2 would not have this 'extra' information, as this is not required.

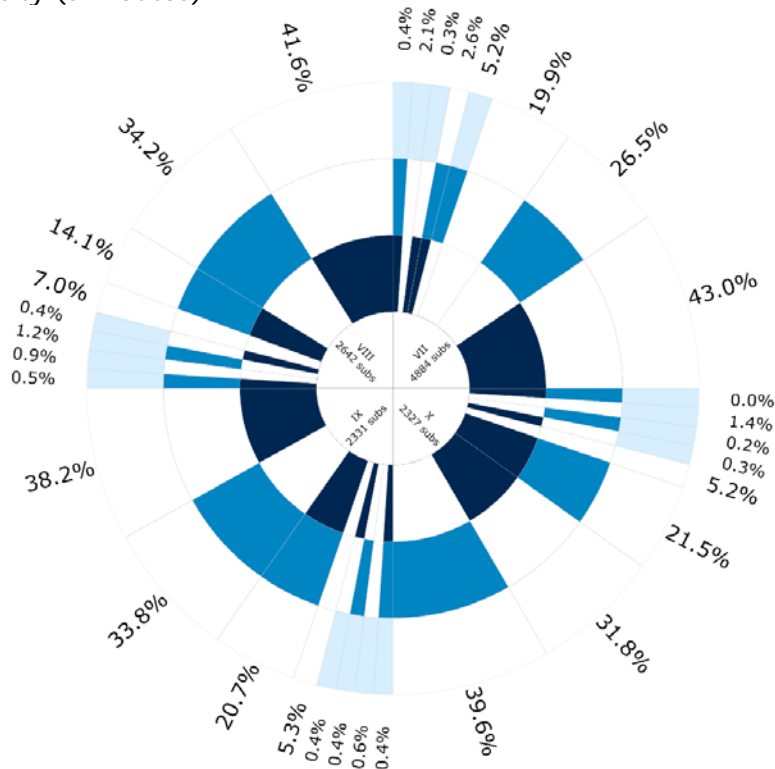
3.3.5 A complete, detailed view per endpoint

Registrants often submit multiple pieces of evidence to cover an information requirement. Consequently, the projections discussed earlier only show the main adaptation option per endpoint and cannot fully represent reality. To illustrate that, a further analysis of the main types of information submitted per tonnage band was performed, regardless of whether the information was required or not.

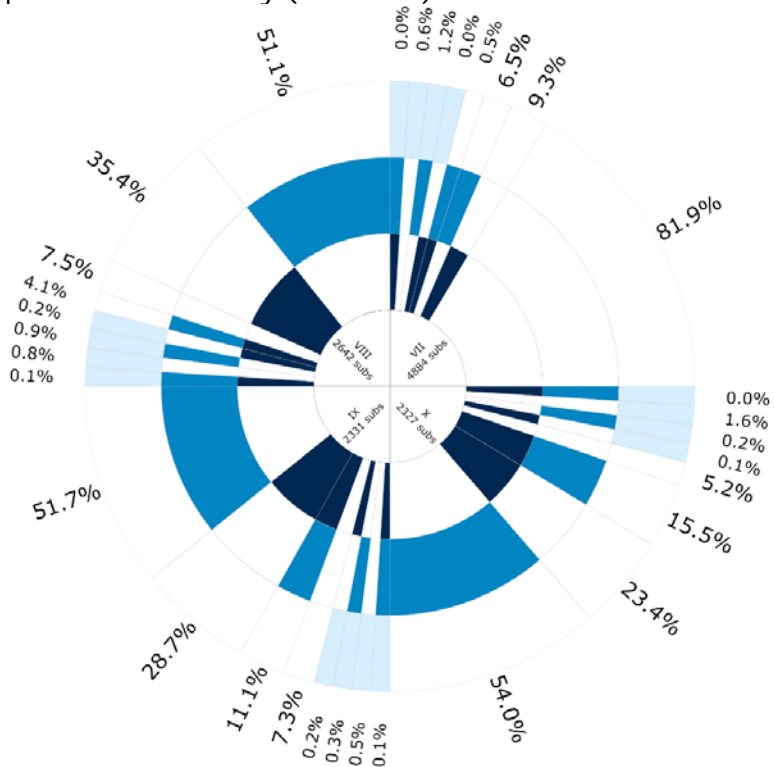
Figure 12 shows how registrants can combine the main ways of fulfilling the information requirements for one endpoint under REACH, for example, experimental data, read-across and QSAR. Weight of evidence is not shown separately because it is mostly a combination of different study result types (experiment, read-across, QSAR or data waiver). In Figure 12, example a) of one low tier (acute toxicity) and b) of one high tier endpoint (repeated dose toxicity) is presented, to illustrate the information available. The corresponding plots for all endpoints analysed can be found in Annex 2.

Figure 12: For each annex, the slice shows the options used to fulfil the information requirement: dark blue = experimental, blue = read across/category approach, light blue = QSAR. See the text for a detailed explanation.

a) Acute Toxicity (all routes)



b) Repeated dose toxicity (all routes)



Acute toxicity is the lower tier endpoint requiring testing on vertebrate animals for which there is the highest proportion of experimental data, with more than 50 % of substances covered by reliable guideline studies (Figure 1). However, for a significant percentage of substances, experimental studies are often submitted together with read-across or QSARs. In addition, there is quite a significant proportion of adaptations, which are combined with other evidence. In general, for approximately one-third of the substances, acute toxicity is covered by multiple options. If we take, for example, the 2 327 substances covered by Annex X (substances registered above 1 000 tonnes per year), we see that there are actual test data for 53.6 % of the substances. However, for 21.5 % of the total, there are additional read across/category justifications provided in the dossiers whereas for another 0.3 % QSARs are also provided. For a very small fraction, the dossiers contain information using all options. For substances for which no tests are available, the majority of the justifications are using the read across/category option.

Repeated dose toxicity is the higher tier endpoint for which most guideline studies are available. Here, the standalone read-across is the most frequently used option (for over 48 % of substances at Annexes VIII-X, read-across is used to cover this endpoint) followed by standalone experimental studies (approximately 30 %). Other substances are covered by multiple options, for example, approximately 30 % use read-across and experimental studies.

These two examples show that there is a significant proportion of endpoints covered with multiple options. These alternative options are in fact more abundantly applied than might appear from the earlier sections, which give a more simplified view of the data.

3.3.6 When were studies conducted?

Information on when guideline studies were executed gives insight into:

1. the extent to which REACH makes studies available, that already existed, but were not transparently available in one database;
2. how newly introduced alternative methods are taken up; and
3. how many new studies had to be done by registrants to ensure the safe use of the chemicals on the market, where alternatives to the guideline testing were not a viable option according to the registrants.

Figure 13 shows the distributions of the study period of the experimental studies (i.e. when the study was carried out) as reported in the REACH registration database. For each endpoint, the distribution is visualised as a boxplot, with the box showing the quartiles ($Q_1=25\%$ and $Q_3=75\%$) of the distribution.

The whiskers are drawn at 1.5 times the interquartile range ($IQR=Q_3-Q_1$) outside the low and high quartiles. Points outside the whiskers are identified as outliers and drawn as open circles. The vertical line within the boxplots corresponds to the median of the study period distribution of the corresponding endpoint.

The annotations to the right of each boxplot show the number of unique “new” (2009 and later) and “old” (before 2009) studies. As in the previous version of this report, 2009 is taken as a significant point in time, as it defined the studies that generally should be conducted and motivated by the REACH requirements – new studies that had to be done by registrants to ensure the safe use and no viable alternative was available. Other drivers such as other (global) legislative requirements cannot be excluded and will also have contributed to the number of new studies executed.

The green vertical lines represent the different deadlines to give a more precise orientation on how the REACH requirements may have influenced the behaviour of registrants. Technical details on how the algorithms deduce the study period and on how they establish the uniqueness of experimental studies can be found in Annex 1.

Figure 13: Distribution in the period of study per endpoint. “New” means studies dated 2009 or later; “old” before 2009. The vertical green lines correspond to the three REACH registration deadlines. See the text for a detailed explanation.

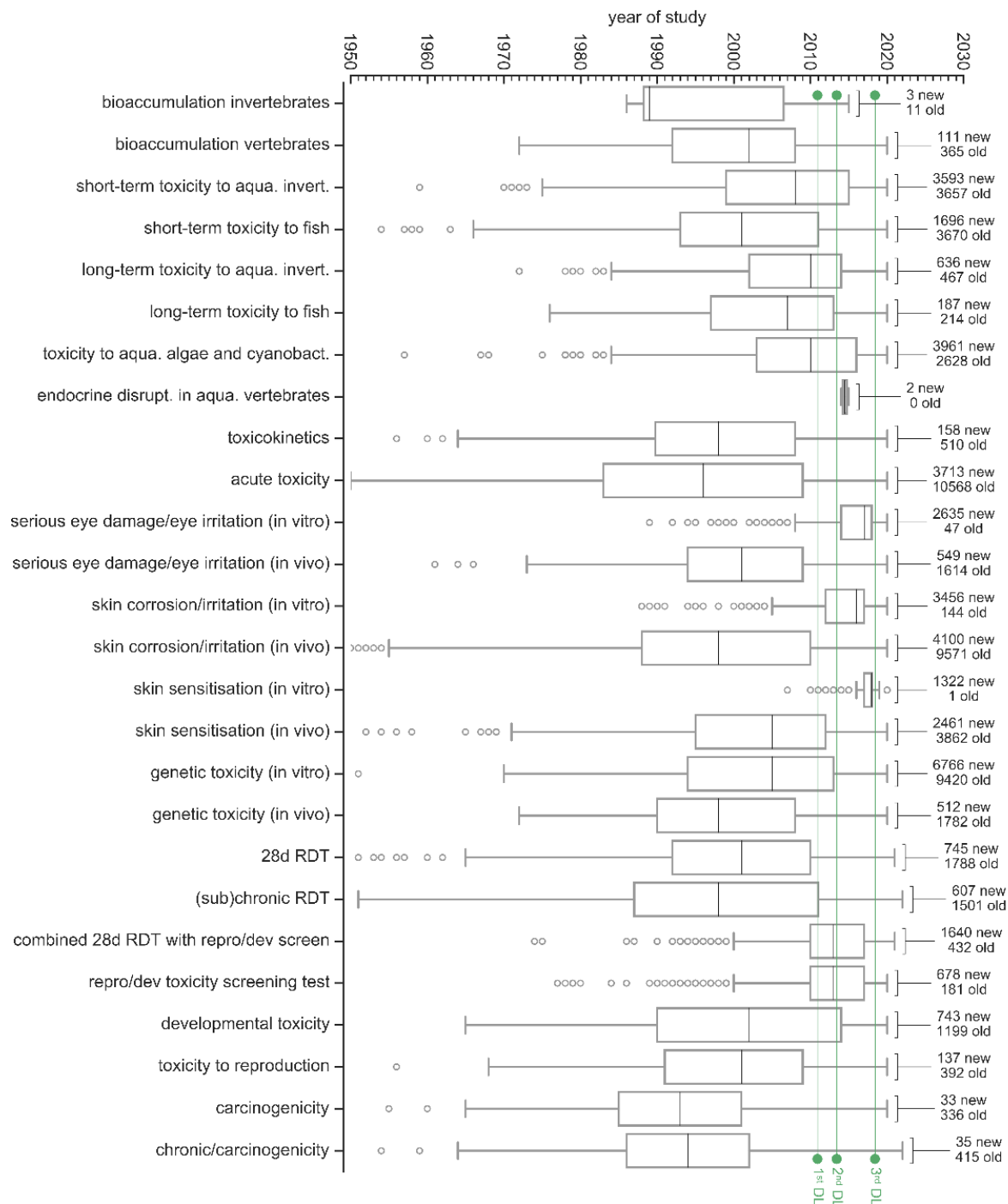


Figure 13 shows that REACH has brought transparency and availability to an enormous collection of existing studies. The figure also illustrates that REACH seems to have stimulated additional testing, revealing the existence of information gaps needed to ensure safe use, where no other options were available.

In addition, the figure shows the evolvement towards integrated testing, and avoiding of animal testing in general. An illustration of integrated testing is the use of the test

guideline combining 28-day repeated dose and reproductive toxicity screening (shown as “combined 28d RDT with repro/dev” in Figure 13).

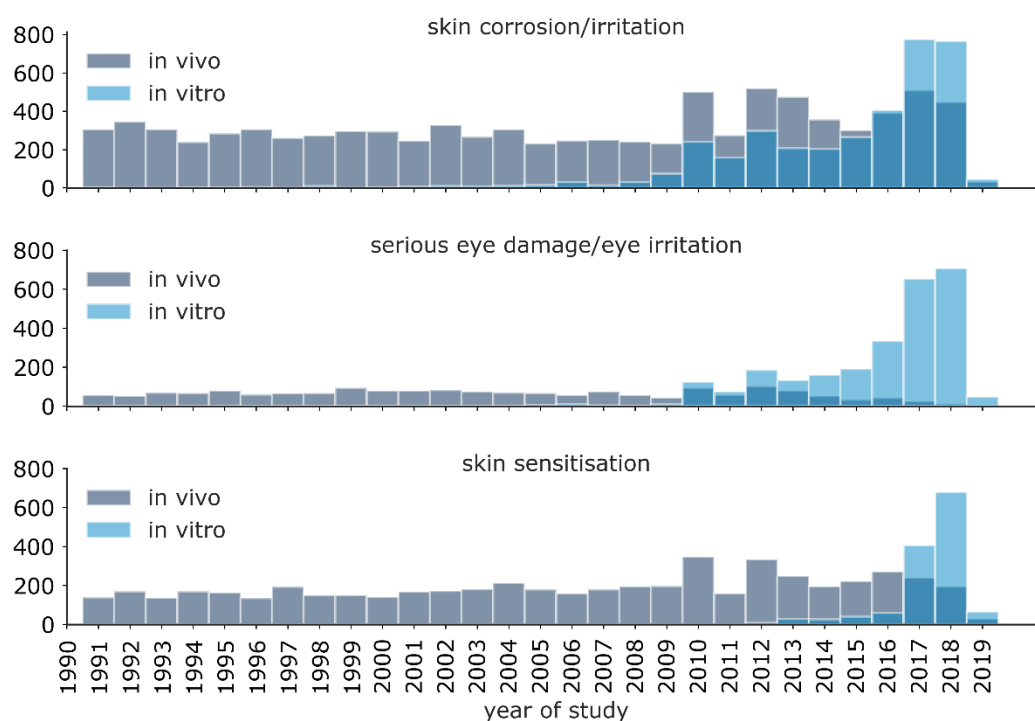
In 2016, 802 new studies (i.e. performed in or after 2009) were reported, along with 374 old ones. In 2019, 1 627 new ones were reported (an increase of 825), along with 423 old ones. This suggests that REACH, with most provisions starting to apply in 2008 and with the last registration deadline in 2018, has been the driver for most of the studies combining 28-day repeated dose and reproductive toxicity screening.

Furthermore, REACH has also driven the use of *in vitro* skin corrosion/irritation, serious eye damage/eye irritation and sensitisation tests. A striking example is the change for *in vitro* serious eye damage/eye irritation studies, which quadrupled (from 655 to 2 608). Similarly, *in vitro* skin corrosion/irritation tests tripled (from 1 126 to 3 401).

The most important increase is for *in vitro* skin sensitisation tests. In 2016, there were only 56 tests, but in 2019, 1 311 tests were reported.

Figure 14 shows the occurrence of *in vivo* and *in vitro* studies for skin corrosion/irritation, serious eye damage/eye irritation and sensitisation tests in time. It illustrates that registrants choose more often the *in-vitro* route after the implementation of the alternative *in vitro* method in the regulation as the first option; 2016 for *in vitro* studies for skin corrosion/irritation as well as serious eye damage/eye irritation and 2017 for *in vitro* skin sensitisation.

Figure 14: Occurrence of *in vivo* and *in vitro* studies for skin corrosion/irritation, serious eye damage/eye irritation and skin sensitisation tests over the years 1990- 2019



3.3.7 In-depth analysis: Skin corrosion/irritation and serious eye damage/eye irritation

Since the last report, an increased amount of substances have been registered under REACH, therefore the assessment of *in vitro* methods performed between 2016 and July 2019 will only focus on the number of *in vitro* studies performed without going into the approaches used at substance level. In addition, no manual verification of the compliance of the reported studies was performed due to the large amount of data submitted.

For skin corrosion/irritation, most of the *in vitro* studies performed have been conducted according to OECD TG 439 (In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method) or 431 (In vitro skin corrosion: reconstructed human epidermis (RHE) test method). During this period, approximately 2 050 *in vitro* studies were performed. Most of the studies were performed for substances registered between 1 and 100 tonnes per year (ca. 1 950 studies). The majority (more than 65 %) of the studies were performed according to OECD TG 439 for skin irritation, followed by OECD TG 431 for skin corrosion. Fewer than 100 studies were performed according to OECD TGs 430 (In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test) or 435 (In Vitro Membrane Barrier Test Method).

For eye serious eye damage/eye irritation, most of the *in vitro* studies have been conducted according to OECD TGs 437, 438 or 492. During this period, approximately 1 700 *in vitro* studies were performed. Again, the majority of the studies (ca. 1 150 studies) were performed for substances registered at tonnages between 1 and 100 tonnes per year. The Bovine Corneal Opacity and Permeability Test Method (OECD TG 437) was the most frequently used assay (ca. 900 studies performed), followed by OECD TG 492 i.e. Reconstructed human Cornea-like Epithelium test method (ca. 600 studies performed), and followed by OECD TG 438 i.e. the Isolated Chicken Eye test method (ca. 230 studies performed). This demonstrates clearly that registrants are following the amended information requirements and are only performing *in vivo* studies in exceptional circumstances.

3.3.8 In-depth analysis: Skin sensitisation

Since the data mining performed for the previous report, the REACH information requirements for skin sensitisation were amended and entered into force in May 2017. The new legal requirements specify that if new data needs to be generated, the testing would start with *in vitro* methods (covering three key events as described in the adverse outcome pathway, OECD 2012). Only if the *in vitro* methods are not suitable for the substance, or the results are not adequate for classification and, where required, for risk assessment, can an *in vivo* study be performed.

Due to the 2018 registration deadline for the lower tonnage substances, an increased number of *in vitro* studies for the skin sensitisation endpoint were generated for the tonnage band of 1 to 100 tonnes per year. The whole of ECHA's registration database covering all tonnage bands currently contains approximately 1 500³⁴ studies for *in vitro* methods among the different key events (55 studies were identified in the previous report).

Most of the studies are covering inflammatory response in the keratinocyte key event (40 %), followed by the molecular interaction with skin proteins key event (38 %) and the activation of dendritic cells key event (22 %). For ca. 680 substances from all

³⁴ This number i.e. ca. 1 500 studies differs from the number provided in Section 3.3.6 (1 311 studies) as: i) *in vitro* studies reported regardless of reliability were included, ii) non-standard *in vitro* studies were included, and iii) multiple *in vitro* studies reported under one endpoint study record were calculated separately.

tonnage bands, data were generated using *in vitro* methods. Of those substances, registrants are using information derived only from *in vitro* methods for about 70 % of the substances (ca. 490 substances) to fulfil the information requirement and for 30 % of the substances (ca. 190 substances) the information was derived from both *in vitro* and *in vivo* methods.

The majority of the studies have been performed for substances registered at tonnages from 1 to 100 tonnes per year (ca. 640 substances). The registration database seems to indicate that following the amendment of the REACH standard information requirements for skin sensitisation, registrants who needed to generate new information have started testing using *in vitro* methods, where possible. Depending on the substance or results obtained from the *in vitro* studies, *in vivo* testing (the Local Lymph Node Assay being the preferred test method) may still be needed.

With the amendment of information requirements for skin sensitisation in 2017, it also became mandatory to consider skin sensitisation potency for skin sensitising substances. To this date, there is no internationally agreed way on how to do this based on *in vitro* methods only. Therefore, currently this has to be done based on a weight-of-evidence approach. To date, registrants have used the following approaches to estimate the skin sensitisation potency of their substance by:

- i) using *in vitro* study results only (for example, reactivity results based on OECD TG 442C or induction of cell surface markers at very low concentrations);
- ii) using *in vivo* results obtained from a similar substance (Local Lymph Node Assay EC3 values) together with the *in vitro* study results; or
- iii) using the QSAR Toolbox to estimate the potency based on analogue search together with *in vitro* study results.

Under the OECD test guideline programme there is work ongoing to develop a guideline for defined approaches for skin sensitisation. The guideline aims to provide a fixed data interpretation procedure, to be used with a defined set of non-animal data, for the identification of the skin sensitisation hazard, including the prediction of its potency.

3.4 Conclusions from the data analysis

With the inclusion of the 2018 phase-in substances, registered at the lower tier, the coverage of substances in ECHA's REACH registration database is complete. The extensive analysis of the registration database, the availability of experimental studies and the use of alternative options to fulfil the information requirements provide answers to the questions posed earlier in this report:

What are the most commonly used adaptations?

A similar picture as in earlier editions of this report emerges. For all endpoints where animal testing is or was the standard requirement, in practice, other means to fulfil these requirements are more frequently used. This is with the exceptions of acute toxicity and skin corrosion/irritation, where for just over 50 % of the substances an *in vivo* testing approach was used, mostly based on studies conducted before 2009.

For the more complex, higher tier endpoints, read-across is the preferred option to meet the information requirements. In chapter 4 we will further discuss the quality of the information submitted.

What are the most noticeable changes for higher-volume substances (100 tonnes per year and above) since the previous (third) Article 117(3) report?

Again, a similar picture as in the earlier editions of this report can be observed. For Annexes IX and X registrations, the overall situation did not change. For Annex X substances there are hardly any changes detectable between 2016 and 2019. The

highest change, with an increase of 3 % for weight of evidence and a decrease of around 3 % for the use of data waivers, is observed in bioaccumulation. Developmental toxicity – teratogenicity has seen a small increase in experimental studies (1.2 %), and an increase in read-across (2.8 %), somewhat balanced with fewer testing proposals (-1.9 %) and less data waiving (-1.2 %).

For Annex IX, the overall picture is also very similar between 2016 and 2019 but some changes are more clearly visible, especially for higher tier human health endpoints and long-term toxicity to aquatic invertebrates. Developmental toxicity – teratogenicity has shifted from testing proposal (5 % lower in 2019) to an increase in experimental studies (7.1 % higher) in the 2016-2019 period. For repeated dose toxicity, an increase in experimental tests of 3.1 % can be observed in the period of the analysis. Besides the initiative by registrants (through testing proposals) to conduct studies for these endpoints, these are also the endpoints that typically are requested after compliance checks.

There has also been a slight increase in the percentage of experimental long-term toxicity to fish studies (+1.4 % and +0.3 % for Annex IX and Annex X, respectively), although the overall percentage of substances with experimental data for this endpoint remains low (5 % and 7.1 % for Annex IX and X in 2019, respectively).

Which options did registrants use to fulfil their information requirements for lower-volume substances (< 100 tonne per year)?

The general distribution of the adaptation options for Annex VII and VIII follows the overall pattern observed previously for higher tier endpoints: read-across is the most popular, followed by data waiving, weight of evidence and QSARs.

The 2019 Annex VIII dossiers have a similar use of adaptations as the 2019 Annex XI dossiers, with the exception of acute toxicity where the Annex VIII dossiers have fewer experimental studies (-3.1 %), which is compensated by an increase in the other options (weight of evidence, QSAR and data waivers).

When comparing 2019 Annex VII dossiers (Figure 11) with 2019 Annex IX dossiers (Figure 8) for the endpoints that are required at both tonnage bands, a generic trend can be observed of fewer experimental studies and less read-across, balanced with more weight of evidence, QSAR and data waiving. It can be concluded that for the dossiers with the lowest data requirements, registrants have used alternative approaches, even more than in the other tonnage bands.

Also remarkable is that for 37 % of all substances some information on the bioaccumulation endpoint was submitted, even though bioaccumulation only needs to be followed up at Annex VIII if screening information indicates a potential PBT concern. As context, this information is present for roughly 50 % of the Annex IX and X substances. Bioaccumulation does not need to be assessed for substances that have a low potential for bioaccumulation (for example, based on a low octanol/water partition coefficient ($\log K_{ow}$)) or a low potential to cross the biological membranes (in the case of high molecular weight substances).

Finally, it was observed that for low tonnage substances the earlier registrations (2016) had more additional information provided beyond the standard minimum requirements, than those submitted more recently (2019). For substances in the lower tonnage bands that are classified as carcinogenic, mutagenic or toxic to reproduction (CMR), categories 1 or 2, an earlier deadline applied (2009). It can be understood that these older dossiers contain more information at a higher level than presently required by the tonnage band, and that this led to their classification in the past.

How did the situation evolve for the endpoints where alternative methods have been introduced since 2016 as standard information requirements?

For new and existing registrations, **in vitro studies** for skin corrosion/irritation, serious eye damage/eye irritation and skin sensitisation have been clearly taken up since 2016. The amendment of the REACH annexes has certainly played an important role in driving this change.

4 Robustness of the used adaptations

In its General Report on the operation of REACH³⁵, the European Commission acknowledges that the development and consideration of alternative methods have greatly improved during the last 10 years of REACH operation. The report also acknowledges that registrants are attempting to minimise animal testing, while recognising that some challenges still exist and that there are still gaps for some endpoints – in particular, the high-tier ones.

The public consultation conducted for this report showed that while stakeholder views concerning the achievements of REACH differed depending on their objectives, they were consistently very positive concerning the promotion of alternative methods to animal testing.³⁶

4.1 Testing strategies and adaptations

As can be seen from the data analysis, adaptations are used more often than guideline studies. Registrants have used all options available to them, often combining many lines of evidence. The underlying requirement is to ensure safe use through information suitable for classification and risk assessment.

Unfortunately, many dossiers do not meet this requirement to ensure safe use as the adaptations are not applied in a scientifically robust manner.

4.2 Use of read-across

Read-across is considered one of the main possible adaptations for higher tier human health endpoints such as repeated dose toxicity, developmental and reproductive toxicity, presuming that a scientifically plausible hypothesis can be justified and used to derive a quantitative result for targeted substances.

If grouping and read-across are applied correctly, experimental testing can be reduced, as there is no need to test every substance in a group for all required endpoints³⁷. However, experience from evaluation indicates that such adaptations provided by registrants often fail to comply with the legal requirements and are inadequate to ensure the safe use of chemicals. The most common shortcomings include:

- poor documentation, insufficient substance identification, significant deficiencies in the quality of the source studies, lack of or low quality of supporting data;
- lack of qualitative and quantitative data to support predictions based on toxicokinetics; and
- shortcomings in the hypothesis and justification of the toxicological prediction.

The deficiencies related to the supporting evidence are particularly relevant for high-tier human health and high-tier environmental endpoints. To increase the robustness and regulatory acceptance of those adaptations for high-tier human health endpoints, additional data is needed, particularly related to toxicological mechanisms and

³⁵ [Commission General Report on the operation of REACH and review of certain elements Conclusions and Actions](#)

³⁶ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018SC0058&from=EN>

³⁷ https://echa.europa.eu/documents/10162/22931011/non_animal_approcches_en.pdf

absorption, distribution, metabolism and excretion (ADME) properties. The presence of “mid-tier” screening studies like the 28-day repeated dose toxicity and/or screening for reprotoxic effects can also strengthen the soundness of categories.

New approach methodologies (for example, high throughput *in vitro* screening) have the potential to further substantiate the hypotheses of read-across approaches. As these approaches often use starting points which are directly relevant for humans (such as human liver cells), more relevant data can be obtained. One of the great challenges is currently that these methods lack the integrated complexity of a higher organism (metabolism, toxicokinetics, covering all effects etc.).

In March 2017, ECHA published the Read-Across Assessment Framework (RAAF)³⁸. It was first developed for human health endpoints and has later been extended to cover environmental fate and effects, as well as considerations on multi-constituent and UVCB substances.

The concepts of the RAAF were also incorporated in the OECD QSAR Toolbox. Although the RAAF is an assessment framework intended for ECHA or Member State assessors, it is a useful tool for registrants to self-assess the read-across/category developed in the dossier, and also for strengthening their case to avoid testing all required endpoints for all substances that are part of the read-across/category.

Based on the dossiers manually opened (for example, in compliance check), the impression is that registrants have not in a significant number of cases taken the RAAF as a guideline to proactively improve the read-across/category approaches in their dossiers. This is one of the reasons that has led to an increased effort on compliance by ECHA and the Commission.³⁹

4.1 Weight of evidence and data waiving

For weight of evidence and data waiving, experience from evaluation also indicates that such adaptations provided by registrants are often found to be non-compliant. Weight of evidence and data waiving are often not supported by any reliable data or justification.

For weight of evidence, registrants often do not include reliable sources of information. Moreover, ECHA's evaluation experience indicates that, in most cases, weight of evidence is not documented sufficiently (for example, the relevance of each line of evidence is not described). In addition, registrants often do not ensure that each element of the standard requirement is sufficiently covered in the proposed weight of evidence.

To support registrants, ECHA published in 2017 a new reporting template to illustrate the main required elements, with a background document on its use in human health and environmental hazard assessments, in line with ECHA guidance.⁴⁰

4.2 Use of QSARs

In 2016, before the 2018 deadline, ECHA released a *Practical Guide on How to use and report (Q)SARs*⁴¹, extended by practical examples on how to assess the reliability of QSAR predictions with the most popular QSAR programs. For this report, ECHA performed a manual screening assessment on a limited number of substances on the quality of the information generated by QSAR models used by registrants as standalone evidence. This use means that the information requirement was entirely covered by

³⁸<https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

³⁹<https://echa.europa.eu/-/improving-compliance-is-echa-s-key-priority>

⁴⁰<https://echa.europa.eu/support/guidance-on-reach-and-clp-implementation/formats>

⁴¹https://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf

QSAR predictions (QSAR as the unique endpoint study record marked as “key study”).

Only dossiers submitted between 2016 and 2018 have been considered for this analysis. The endpoints selected were short-term toxicity to fish, short-term toxicity to daphnia and bioaccumulation. These endpoints have the highest percentage of QSAR predictions used as standalone evidence, and if used adequately, reliable predictions can be made due to the relatively high number of experimental data available and the lower levels of complexity of the effect.

During the screening, adequacy of the input structure, applicability domain and the coverage of the specific chemical space were verified. Overall, 75 predictions fulfilling the criteria listed above were screened.

Out of the 50 QSAR predictions used as standalone information for short-term aquatic toxicity, about one-third (32 %) were found not to be adequate in light of the conditions for using QSAR predictions to adapt standard information requirements as listed in REACH Annex XI, Article 1.3.

The most common reasons for non-reliable predictions were that the target substance did not correspond to the registered substance, there was an insufficient number of data points in the training set of the model, and a lack of coverage of the structural fragments in the training set. Nevertheless, the remaining (68 %) QSAR predictions were found to be adequate by this screening assessment, and accompanied by the appropriate QSAR reporting format (QMRF and QPRF⁴²) as required by REACH Annex XI, Article 1.3, showing that QSARs can be a useful alternative to testing for short-term aquatic toxicity, when used adequately.

Regarding bioaccumulation, 18 of the 25 selected substances had a logK_{ow} above 3, indicating a general potential for bioaccumulation in fat tissues. In our analysis, we observed that more than two-thirds of these substances had shortcomings regarding the assessment of the applicability of the model, which is a requirement for the use of QSAR predictions as an adaptation to testing according to Annex XI, Article 1.3. While for one-third of the substances, the reporting of the applicability domain check was limited to logK_{ow} and molecular weight (parametric domain), the other ca. 40 % of substances had no applicability domain check reported at all.

To conclude, the majority of predictions for bioaccumulation (over 70 %) were found to have shortcomings related to the applicability domain of the model. In addition, the reliability of the prediction is often not sufficiently scrutinised by registrants. In particular, this applies to the structural domain covered by the model, and the anticipated biotransformation rate of the substance in cases where it significantly reduces the predicted bioaccumulation potential of a substance.

The overall conclusion is that for aquatic toxicity, the QSAR approach as applied by the registrants worked well in the majority of cases (68 %) while for bioaccumulation, the majority (70 %) had issues.

⁴² QMRF = QSAR Model Reporting Format and QPRF = QSAR Prediction Reporting Format

5 Promotion of non-animal test methods

One of the objectives of REACH is to promote the use of alternative methods. To address these challenges, ECHA is active in four areas:

1. Developing and maintaining **tools and guidance** (many in collaboration with the OECD). ECHA has general as well as detailed guidance on the use of alternatives, including specific guidance and manuals for specific topics (such as RAAF). In addition, ECHA is the main financial contributor to the development of the OECD QSAR Toolbox⁴³, which is a tool that supports data gap filling through re-using existing data (including the REACH registration data), as well as different predictive approaches. A simplified and user-friendly version was released in 2020 with multiple new features helping users to obtain reliable predictions, including category consistency assessment, automated workflow for skin sensitisation and aquatic toxicity, and an exportable data matrix. Another example is the practical guide released in July 2016 on how to use (Q)SARs, which provides examples to assess the validity of predictions based on OECD principles and REACH requirements.⁴⁴
2. Development and maintenance of **OECD test guidelines and related activities**⁴⁵. ECHA is (as part of the EU delegation) an active participant in the OECD's Working Group of National Coordinators of the TGs programme (WNT)⁴⁶ which develops test guidelines, the OECD harmonised templates to capture, share and reuse test data electronically (IUCLID) and other activities to explore the possibility of new approach methods in a regulatory context.
3. Exploring if and **how new approach methods can be integrated** in chemicals management (international collaboration and OECD) mostly through APCRA.⁴⁷
4. Keeping ECHA staff **up to date on the latest developments in (eco)toxicology** relevant in a regulatory context, through training, conferences, expert fora and exchange (internal and external).

5.1 Building the knowledgebase of chemicals

As all substances on the European market should be registered by now, the focus of the work has moved on from registration to aspects of REACH that ensure data are compliant and are adequate to demonstrate safe use. The ultimate objective is to further build and improve the IUCLID chemicals knowledgebase⁴⁸, which will support avoiding (additional) animal testing, the development of alternative methods, green/sustainable chemistry, substitution and form a basis for the circular economy.

5.1.1 Further work needed by registrants

The further application and development of alternatives and the further development of this chemicals knowledgebase is reliant on the receipt of updated and compliant registrations that guarantee safe use, while utilising alternative methods in a sound

⁴³ <https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm>

⁴⁴ <https://echa.europa.eu/practical-guides>

⁴⁵ <https://www.oecd.org/env/ehs/testing/>

⁴⁶ <https://www.oecd.org/env/ehs/testing/national-coordinators-test-guidelines-programme.htm>

⁴⁷ Accelerating the Pace of Chemical Risk Assessment

⁴⁸ <https://newsletter.echa.europa.eu/home/-/newsletter/entry/working-towards-one-global-iuclid> How this data-platform relates/is part of the "Feasibility study on a common open platform on chemical safety data" currently executed by DG Environment is to be seen. <https://etendering.ted.europa.eu/cft/cft-document.html?docId=61946>

manner. This calls to mind some of the recommendations to registrants⁴⁹ in ECHA's annual reporting under Article 54 REACH,⁵⁰ particularly those on adaptation possibilities.⁵¹ Here it should be emphasised that in addition to *in vitro* methods, read-across and QSAR are available as options to consider for avoiding testing on animals. In the past decade, ECHA has clearly defined the conditions needed to construct read-across/category and QSAR arguments that can withstand regulatory scrutiny and reliably replace animal testing. These are crystallised in ECHA's *Practical Guide on How to use and (Q)SARs* and in the Read-Across Assessment Framework. If registrants choose to use read-across and QSAR, they should take advantage of these to augment the robustness of their adaptations.

5.1.2 Maximising the availability and use of data

Given the amount and complexity of the information collected, ECHA has developed additional tools to help companies, authorities and researchers make the best use of it.

Since 2017, data from the dossiers has been made available for IUCLID users as a downloadable file. This file contains all non-confidential substance data that has been submitted to ECHA under REACH and reports study results for physical-chemical properties, environmental fate and pathways, and (eco)toxicological information. The file was last updated in April 2020⁵². This dataset has been integrated in the latest version of the OECD QSAR Toolbox.

Besides the European efforts, many jurisdictions in the world have started to collect their data using the same IUCLID software. Health Canada uses the IUCLID software as their main scientific database for existing chemicals assessments. Switzerland and the US have also started to accept data in IUCLID format for some parts of their chemical legislation. Other countries, such as Australia and New Zealand, started using IUCLID now that the tool is configured⁵³ to fit their regulatory contexts. This strengthens interoperability among stakeholders and makes sharing and comparing practical.

The more widely the IUCLID format is accepted globally, the better this is for industry, authorities and animal welfare organisations. It contributes to avoiding duplicate testing, supporting international harmonisation of chemical data and reducing trade barriers. Using a universal format based on IUCLID will in particular support the mutual acceptance of test data since all authorities would ultimately have the same basis for their assessments. In the long run, this would improve the efficiency of the work and also increase the reliability of data which contributes significantly to the avoidance of animal testing.

To really maximise the use of existing data, ECHA's future vision is to support setting up one international IUCLID platform: the Chemicals Knowledgebase. This would mean that all parties involved, whether authorities or industry, would be able to contribute by generating and entering data in the system.

Mutual acceptance of chemical safety data⁵⁴ is already a reality and having one harmonised IT format for it might not be that far away. If and when this happens, IUCLID has the potential to become the platform where chemical safety data can be uploaded and viewed, but also managed, exchanged and improved by all parties. The future platform would integrate the functionalities and options from other tools and

⁴⁹ <https://echa.europa.eu/recommendations-to-registrants>

⁵⁰ <https://echa.europa.eu/overall-progress-in-evaluation>

⁵¹ <https://echa.europa.eu/adaptations-recommendations>

⁵² https://iuclid6.echa.europa.eu/view-article/-/journal_content/title/reach-study-results-have-been-updated

⁵³ <http://www.oecd.org/chemicalsafety/risk-assessment/customisation-opportunities-of-iuclid-for-the-management-of-chemical-data.pdf>

⁵⁴ <https://www.oecd.org/env/ehs/mutualacceptanceofdatamad.htm>

databases. For instance, in the coming years, the OECD QSAR Toolbox will be further developed so that some of its key functionalities, like chemical similarity searches and predicting hazard properties, could be made available through the Chemicals Knowledgebase.

Currently, this is still a vision with a number of concrete building blocks operational. ECHA will continue working towards this goal together with interested parties, such as the OECD, which has recently agreed to further develop its OECD Global Chemicals Knowledgebase in which the IUCLID Chemicals Knowledgebase will play a central role. In the short term, the aim remains to make the data and knowledge gathered in the framework of European chemicals legislation easier to access and use.

5.1.3 Using the REACH data for alternatives development: an example

With acute toxicity being one of the endpoints with the highest proportion of animal tests in mind, ECHA collaborates with the US Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)⁵⁵. One of their priority projects is to develop alternative methods for the “six-pack” tests; a set of basic tests – of which acute oral, dermal and inhalation systemic toxicity tests are a part. While developing their models, ECHA offered REACH registration data to extend their training and test sets. ECHA supported ICCVAM by:

- investigating what acute oral toxicity data could be used for this purpose;
- extracting and filtering the data from ECHA’s database to provide data of adequate quality for model development and validation; and
- giving advice to the model developers on the best possible use and interpretation of the data.

When the models are finalised, they will be publicly available for all companies and researchers to use free of charge. Discussions are ongoing on whether these models could also be included in the QSAR Toolbox. Data exchange for the remaining endpoints is also ongoing.

5.2 ECHA activities to promote the development of suitable alternatives

REACH has as an objective to minimise the unnecessary use of animals in regulatory hazard assessment. In addition, ECHA is facing many challenges, such as a large number of incompliant dossiers, especially for higher tier endpoints, the need to improve methodologies for risk assessment for ‘difficult’ scenarios (for example, substances with complex compositions, mixture effects), the increasing expectations on high quality information on chemicals that can be used to support policy objectives that move towards using sustainable chemicals and the complexity of interpreting hazard data and its translation to effective risk assessment and risk management measures.

ECHA is exploring ways to exploit new approach methodologies (NAMs) with the ambition to test and demonstrate their applicability in a regulatory context. This approach is envisaged to also enhance the pace of chemicals management, to have better informed decisions and reduce or replace the need for studies on (vertebrate) animals, for the protection of human health and the environment. The benefits of NAMs should be observed in terms of:

- Throughput;
- Robustness;

⁵⁵ <https://ntp.niehs.nih.gov/whatwestudy/niceatm/iccvam/index.html>

- Bringing mechanistic knowledge;
- Providing appropriate protection levels for human health and environment.

Recent ECHA reports that relate to this topic include the Integrated Regulatory Strategy report,⁵⁶ the Applicability of non-animal approaches (ANAA) report (2017)⁵⁷, the proceedings of a scientific workshop on New Approach Methodologies in Regulatory Science⁵⁸, and the reporting under Article 54. With these in mind, ECHA's regulatory and scientific activities continue to promote non-animal test methods and testing strategies.

However, the conclusions from the ANAA⁵⁹ report remain valid. For complex endpoints, such as repeated dose toxicity or reproductive toxicity, non-animal approaches are not yet foreseeable. New approaches, such as *in vitro* microsystems and high-throughput/high-content methods, are under development. They aim to provide better insight into the mechanisms of toxicity. Still, they require further standardisation and validation before they can be accepted for regulatory use. A continuous dialogue between researchers and regulatory authorities is necessary to ensure that innovations in non-animal approaches to chemical safety assessment can be considered for regulatory use without undue delay.

5.3 Prospects for scientific development

As early as 2013, ECHA has stated in its Multi-Annual Work Programme 2014–2018: *"Significant and rapid development is being made, especially in (eco)toxicology, with an emphasis on better understanding the biological mechanisms leading to an adverse effect, rather than just observing the effect. Systems biology, bioinformatics, increased understanding of modes of action and adverse outcome pathways will also affect the way chemicals are tested, or how their properties can be predicted, thus enabling reduction in traditional animal testing"*.

Among the priorities outlined in its strategy, ECHA emphasised regulatory science activities related to *non-standard methods and new approaches methodologies to hazard assessment, in particular rational integration of different lines of evidence (ITs, IATAs, AOPs;⁶⁰ with links to the QSAR Toolbox, omics and high-throughput screening methodologies)*.

So far, most of the alternatives were developed by researchers with little attention to their potential regulatory application. They were based mostly on *in vitro* systems. In terms of opportunities, capturing mechanistic (for example, toxicokinetics, biomarkers) data in parallel to adversities will allow to better understand the mode of action and better predict potential adversities across species without actually relying on animal data.

We see two main branches for development in the future:

For the short/medium term: a continuation of strengthening the ECHA knowledgebase. An example is to use existing animal test systems (REACH standard information requirement) and complement them when possible with multiple, relevant NAMs data. The ambition is to bridge classical toxicological findings related to apical endpoints with mechanistic knowledge. Moreover, this NAM-based information can work as bridging studies, strengthening read-across and category arguments while reducing animal testing.

⁵⁶ <https://echa.europa.eu/substances-of-potential-concern>

⁵⁷ <https://echa.europa.eu/-/more-progress-needed-to-replace-animal-tests-under-eu-chemicals-laws>

⁵⁸ https://echa.europa.eu/documents/10162/22816069/scientific_ws_proceedings_en.pdf

⁵⁹ https://echa.europa.eu/documents/10162/22931011/non_animal_approaches_en.pdf

⁶⁰ Integrated testing strategy, integrated approach for testing and assessment, adverse outcome pathway.

For the long term: to predict systemic effects, new approaches need to cover a wide range of tissues, organs, and chemical interactions within the organism (i.e. toxicodynamics). Such a wide toxicological space cannot be covered by a single *in vitro* assay. An intelligent combination of high throughput, high content assays and computational tools could potentially fulfil these requirements. In addition to elements of toxicodynamics, these methods need to cover toxicokinetics or ADME, namely: Adsorption (estimates of systemic concentration), Distribution, Metabolism (biotransformation) and Excretion.

It is still challenging nowadays to provide this wide coverage in both the toxicodynamic and toxicokinetic aspects, as well as maintaining quality and throughput. The approach presented in the United States Environmental Protection Agency's research project ToxCast, that deploys hundreds of high-throughput screening assays to generate biological activity data, is trying to reach this ambitious goal, although it is premature to estimate its impact on regulatory chemical safety.⁶¹

In contrast to the well-developed understanding of the utility and limitations of NAM-based biomarkers in the hazard assessment of pharmaceuticals, the practical utility of these techniques for industrial chemicals is poorly understood. Another limiting factor is that some industrial chemicals do not have suitable properties for *in vitro* testing (for example, there are issues with solubility or volatility). To address this lack of understanding, ECHA participates in an international consortium of regulatory agencies "Accelerating the Pace of Chemical Risk Assessment" (APCRA), which is exploring ways to use NAM-based information to inform the grouping of industrial chemicals in the context of hazard assessment.

In the longer-term, APCRA is conducting a retrospective study to compare NAM-delivered points of departure (mainly from high throughput assays) to those determined by classical *in vivo* studies. The preliminary outcome of this study shows that in 92 % of cases, NAMs can provide a conservative point of departure as protective or more compared to classical *in vivo* data⁶². Based on this outcome, ECHA, together with partners, continues to refine the methodology to show its utility in providing realistic estimates for systemic toxicity, i.e. neither over-conservative nor under-protective. The majority of substances in this part of the project are data-poor chemicals (i.e. for which *in vivo* studies are not available).

With these actions, ECHA aims to cover both the short/medium-term and the long-term prospects in NAM development, both making use of the huge amounts of toxicological data, already available or being generated, and also by expanding and building on its own knowledgebase.

⁶¹ <https://www.epa.gov/chemical-research/toxcast-data-generation-chemical-workflow#phaseIII>

⁶² Katie Paul Friedman, et al., Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization, *Toxicological Sciences*, Volume 173, Issue 1, January 2020, Pages 202–225, <https://doi.org/10.1093/toxsci/kfz201>

6 Conclusions

For new and existing registrations, **in vitro studies** for skin corrosion/irritation, serious eye damage/eye irritation and skin sensitisation have been clearly **taken up** since 2016. The amendment of the REACH annexes has certainly played an important role in accomplishing this significant change in the **use of alternative methods**.

In general, **no major changes in the use of adaptations** have been observed since the last report in 2017⁶³ for the existing registrations. Furthermore, the following observations can be made:

- Overall, the **most commonly used adaptation is read-across**, followed by data waiving, weight of evidence and quantitative structure–activity relationship (QSAR) models. Experimental studies were available – on average – in 27.1 % of cases (-0.5 % compared to 2016).
- When new studies are needed for repeated dose toxicity and toxicity to reproduction screening, these are increasingly performed using the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422). This **significantly reduces the number of animals and costs**.
- There has been a **moderate increase in the availability of pre-natal developmental toxicity and (sub)chronic repeated dose studies**. Decisions related to compliance checks and testing proposals in the last three years are likely to account for this.

In general, Annex VII and VIII dossiers received by the 2018 deadline follow the same patterns in terms of use of adaptations. Furthermore, the following observations can be made:

- The newly received 2019 **Annex VIII dossiers follow a similar pattern as dossiers in higher tonnage bands**, with the exception of acute toxicity where the Annex VIII dossiers have fewer experimental studies (-3.1 %), but weight of evidence, QSAR and data waiving have increased. This seems to point to a lower availability of historical data, as well as an increased use of adaptations for this group of substances.
- Remarkably, at REACH Annex VIII, the percentage of short-term toxicity to fish studies used to fulfill the information requirement decreased since 2016, showing an **effective use of adaptations** for this standard information requirement. In addition, a minor increase for long-term aquatic experimental studies has been observed.
- For newly received **Annex VII dossiers, fewer experimental studies and less read-across are observed, balanced with more weight of evidence, QSAR and data waiving**. For dossiers with the lowest data requirements, it can be concluded that registrants have used alternative approaches, even more so than in other tonnage bands. As these dossier have not been assed under Compliance Check in significant number, it is for now unclear if the approaches used are appropriate.
- Annex VII dossiers that were submitted earlier (before 2016) contain **more**

⁶³ The data for the 2017 report was extracted in 2016, which is the date used throughout the report.

additional information on top of the standard minimum requirements than the once submitted later (2019). Low tonnage substances also needed to be registered before June 2010, if they were classified as carcinogenic, mutagenic or toxic to reproduction, in categories 1 or 2 (CMR Cat 1 and 2). These substances, can be expected to have more information than required according to the tonnage band, since this information was likely forming the basis for their classification in the past. Information that is needed **to classify a substance as CMR Cat 1 and 2**, is typically information that is only required starting from Annex IX. In contrast, the substances that were registered later and are not classified as CMR Cat 1 and 2, would not have this 'extra' information, as this is not required.

In terms of robustness of the applied alternatives, the picture of years before remains, with frequent incompliances. This is despite the update and development of tools and guidance, especially between the second (2013) and third deadline (2018).

As there are still many incompliances, many dossiers will need to undergo updates, either voluntarily or after compliance check. Registrants still have opportunities to strengthen their alternative approaches, based on ECHA Guidance and tools, as well the feedback made available through other publications, such as the Article 54 reporting.

Despite the current issues with the robustness of the alternative approaches used in registration dossiers, the REACH registration database, is a unique starting point for a knowledgebase that can serve safe use of chemicals, sustainable chemistry development, circular economy as well as the further development of alternative approaches to animal testing. ECHA has developed a number of initiatives in this direction and, stimulated by the emerging global acceptance of the IUCLID data standard to capture and exchange study information, sees possibilities to develop such a chemicals knowledgebase.

ECHA will continue to follow the developments at the OECD to seize opportunities to bring alternative approaches into the regulatory context, as well as working together with international partners in the APCRA⁶⁴ initiative to explore the use of more advanced new approach methods.

⁶⁴ <https://www.epa.gov/chemical-research/accelerating-pace-chemical-risk-assessment-apcra>

Annex 1

The purpose of this annex is to provide technical details on how the data analysis has been carried out. Such technical details were kept intentionally out of the main body of the report for brevity. The annex assumes that the reader is familiar with IUCLID and the registration process, but reading it is not necessary for understanding the key messages of the report. However, the annex may assist technical experts who wish to know the conventions underpinning the data analysis and data visualisation, and it is provided for completeness and transparency.

A1.1 Description of dossier and substance selection

The registration dossier list that was subjected to data analysis was constructed by obtaining the submission of each registration that has the most recent submission date, given that the submission date was on or before 31 July 2019. Both active and inactive registrations were included in the data analysis. However, registrations that have been revoked, annulled or invalidated were excluded.⁶⁵

Dossiers submitted by registrants that are members in the joint submission were included in the analysis in case they provide fate and (eco) toxicity information not present in the dossier submitted by the lead or individual registrants of the same registered substance.

The analysis included NONS registrations that have been updated under REACH, given that at least one dossier update has been received under REACH and that it has been subject to full technical completeness check.⁶⁶

To analyse the evolution over time, we repeated the data analysis by applying a second cut-off date, namely 31 July 2016 that roughly corresponds to the dataset used for the purposes of the third Article 117(3) report. It is not possible to directly compare the numbers included in this fourth Article 117(3) report with the numbers in the third Article 117(3) report because of changes in the data analysis approach due to the IUCLID update. The comparison of the results for the two cut-off dates nevertheless provides an insight on the time evolution of how the information requirements have been fulfilled.

Overall, we processed the data from 87 485 and 47 457 registrations for the 31 July 2019 and 31 July 2016 cut-off dates, respectively. The corresponding number of substances can be found in Table 2.

Substances were allocated to REACH annexes according to the registration with the highest information requirements at each point in time. As an illustration, a substance has been considered as Annex IX if there is at least one REACH registration according to Article 10 (so-called full registrations) with a tonnage of 100-1 000 tonnes per year and no Article 10 registration with a higher tonnage.

The analysis covered only substances for which there is at least one registration that provides all endpoint information as in Annex VII of REACH or higher. This means that

⁶⁵ The registration status is not readily available as a function of time and, as such, registrations that were active in the past and were annulled, invalid or revoked when the data analysis was carried out have been removed even for result sets that refer to the past. This artefact has negligible effect on the obtained results.

⁶⁶ NONs registrations pass through full technical completeness check if they have become the lead or they have increased their tonnage band leading to increased information requirements compared to the original NONs submission. It is likely that more NONs registrations have undergone full technical completeness check although these criteria do not apply. Such NONs registrations were not included in the analysis. NONs registrations that have not passed full technical completeness checks were excluded because of the incomplete migration of the original NONS IUCLID dossiers to the latest IUCLID format that may skew the analysis.

substances for which registrants only provided the reduced information requirements (physicochemical) of REACH Annex VII according to Article 12 1(b) were excluded because such registrations typically do not contain tests on vertebrate animals or their alternatives.

However, substances for which there has been at least one transported intermediate registration for more than 1 000 tonnes per year have been included given that the registrants are required to provide the full information requirements of REACH Annex VII.

Once a substance was considered to be within the scope of the report then all registrations were processed and analysed regardless of their own tonnage band.

A1.2 Processing of endpoint study records

This section of the annex summarises how individual endpoint study records were extracted from the IUCLID database and processed. The next section describes how the endpoint study record information has been aggregated at substance level to generate the graphs.

The number of endpoint study records for the different IUCLID sections is shown in Table 4. The rows in this table correspond to the horizontal bars in the barplots in Figures 4 - 11, i.e. for some endpoints, we counted together the endpoint study records in more than one IUCLID section, as is for example the case for acute toxicity where oral, inhalation and dermal studies are reported in separate IUCLID sections but are counted here together.

Endpoint study records in category substances embedded in the registration dossiers were excluded from the analysis, i.e. only the endpoint study records of the substance that is the dossier subject were processed. Endpoint study records in IUCLID templates embedded in the registered substance dataset were included in the analysis.

Table 4: Number of IUCLID endpoint study records in 2016 and 2019 dataset

Endpoint	Number of endpoint study records in 2016 dataset	Number of endpoint study records in 2019 dataset	Increase (%)
bioaccumulation: aquatic - sediment - terrestrial	21 014	29 498	40.37
short-term toxicity to aquatic invertebrates	32 817	48 836	48.81
short-term toxicity to fish	28 539	39 552	38.59
long-term toxicity to aquatic invertebrates	16 237	21 648	33.33

long-term toxicity to fish	11 395	14 547	27.66
toxicity to aquatic algae and cyanobacteria	25 070	39 226	56.47
basic toxicokinetics - dermal absorption	22 012	29 543	34.21
acute toxicity (all routes)	67 279	94 551	40.54
serious eye damage - eye irritation	26 083	43 841	68.08
skin corrosion - irritation	36 120	55 534	53.75
skin sensitisation	23 094	44 009	90.56
genetic toxicity <i>in vitro</i>	50 733	75 191	48.21
genetic toxicity <i>in vivo</i>	13 661	17 941	31.33
repeated dose toxicity (all routes)	48 092	66 329	37.92
developmental toxicity - teratogenicity	18 077	26 460	46.37
toxicity to reproduction	15 070	23 852	58.27
carcinogenicity	11 008	12 621	14.65
Total	466 301	683 179	46.51

Table 4 shows that the number of endpoint study records increased by approximately 50 % between 2016 and 2019. The increase is primarily due to the last registration deadline on 31 May 2018. The number of reliable, guideline experimental studies is smaller than the number of endpoint study records shown because many endpoint study records

contain adaptations. Moreover, the same experimental study or adaptation may have been reported in more than one endpoint study record in different dossiers for the same or a different substance. For the purposes of this report, we have also attempted to count the unique experimental studies as explained later on in this section.

With the introduction of IUCLID 6 there has been a significant change with regard to the way registrants need to report read-across adaptations. While before registrants only needed to provide one endpoint study record with the read-across information, with the introduction of IUCLID 6, registrants are required to provide two endpoint study records, one containing the experimental study with the source substance and one containing the read-across adaptation for the registered substance that makes reference to the endpoint study record with the source experimental study.

A side effect of this change is the fact that endpoint study records for which the type of information has been indicated by the registrants to be an experimental study may refer to an experiment carried out with a substance different to the one that has been registered. This is one of the main reasons for which the data analysis approach developed for the purposes of the third edition of the Article 117(3) report has been modified.

A very large number of dossiers were submitted before the introduction of IUCLID 6 and so the database contains all possible ways to report read-across and category adaptations. For this reason, and in contrast to the methodology used for earlier editions of the Article 117(3) report, judging whether an experimental study was carried out with the registered substance or an analogue was not simple to establish using the administrative information of the endpoint study records, so a more elaborate algorithm was constructed. The main steps of this algorithm are shown in Table 5.

Table 5: Main elements of the algorithm to establish whether a test has been carried out with the registered substance (test material algorithm)

Type of information	Test material matches registered substance ¹	Endpoint study record refers to read-across source ²	Algorithm outcome
experimental study	no	it does not matter	read-across
	no structured test material information	yes	read-across application
	no structured test material information	no	test with registered substance
	yes	yes	read-across application

	yes	no	test with registered substance
migrated information: read-across based on grouping of substances (category approach)	it does not matter	it does not matter	test with analogue
migrated information: read-across from supporting substance (structural analogue or surrogate)	it does not matter	it does not matter	test with analogue
read-across based on grouping of substances (category approach)	no	it does not matter	test with analogue
	no structured test material information	it does not matter	read-across application
	yes	it does not matter	read-across application
read-across from supporting substance (structural analogue or surrogate)	no	it does not matter	test with analogue
	no structured test material information	it does not matter	read-across application
	yes	it does not matter	read-across application

¹ "yes" means that the test material contains at least one numerical identifier of the type EC number or CAS number that matches the corresponding numerical identifier of the registered substance, "no" means that the test material contains at least one identifier (e.g. a chemical name) and neither the EC number nor CAS number (if contained) matches the corresponding identifiers of the registered substance, "no structured test material information" means that the test material does not contain any identifier (this can be an artefact of the automated migration to IUCLID 6).

² "yes" means that the type of information in the administrative part of the endpoint study record is "experimental study" and the endpoint study record contains at least one cross reference of the type "read-across source" for which the corresponding cross-referenced document has been provided.

An endpoint study record was considered as an experimental study for the registered substance if the test material matching the algorithm outcome was “test with registered substance”. To count the percentage of substances with at least one experimental study for the purposes of the barplots in Figures 4 - 11 and the circular plots in Figure 12 and Figures in Annex 2, the endpoint study record should additionally have been identified as reliable according to the registrant (Klimisch score 1 or 2, i.e. reliable without and with restrictions, respectively) and, additionally, the study has been carried with one of the guidelines mentioned later on in this section of the annex.

Most of the analysis and graphs presented in the report refer to the percentage of substances that have an experimental study or for which a given adaptation has been used. For these applications, it is not necessary to identify which endpoint study records report the same original information. As an illustration, this often happens in cases of read-across when both the source and the target substances of the read-across adaptation have been registered. It is also frequent that the same experimental study is used as the source in read-across adaptations for more than one registered substance.

For the purposes of the study period distributions shown in Figure 13, it was necessary to count the unique experimental studies that have been identified as reliable according to the registrant and executed according to one of the guidelines mentioned later in this section of the annex. This was accomplished by creating study “signatures” in the form of strings concatenating key information from the endpoint study record and, in particular, from the study period, the guideline, the literature reference and the test material.

Although more accurate signatures could have been created by using additional fields from the endpoint study records, the benefit of the simple signatures is that they only use fields that are present in all harmonised templates (<http://www.oecd.org/ehs/templates/>). This allows duplicate studies present in different IUCLID sections to be detected, as can be the case, for example, for combined repeated dose toxicity with reproduction/developmental toxicity screening studies.

It is important to emphasise though that any unique study identification algorithm based on string equality like we used, may identify two endpoint study records that refer to the same experimental study as distinct if one of the elements used to compile the signature has been reported even slightly differently. This can, for instance, happen when in one of the two literature references for the same study, the registrants provided the authors of the study while in the other this information was missing although the bibliographic reference may otherwise be identical. This suggests that Figure 13 overestimates the number of unique studies. ECHA is currently investigating the possibility to use machine learning for the purposes of un-duplicating studies, but this approach is still considered experimental and not sufficiently developed to be used for the purposes of this report.

The study period distributions in Figure 13 also require a single characteristic date to be computed that provides the time at which the experimental study has been conducted, even though in reality the study took place over a period of time that can span several months. A separate algorithm has been constructed to work out a single year that roughly captures the time the study was conducted.

The algorithm uses all available sources of information and, in particular, the literature reference year, the report date range and the study period provided by the registrant in the administrative part of the endpoint record. The latter is a free text and dates were extracted using natural language processing. From all dates, we only kept the year and in cases of multiple extracted years, we retained only the latest that was used for calculating the study period distributions visualised in the boxplots in Figure 13.

The last part of this section describes the way in which it was determined whether an experimental study has been carried out with one of the generally acceptable guidelines.

As registrants may not always have used the IUCLID picklists, particularly for recently developed *in vitro* methods that are important information for this report, we relied on text pattern matching. The algorithm looked in all fields where guideline information may have been provided. We ensured that the text patterns also correctly understood IUCLID picklists if the registrants provided the guideline information in a structured manner, which is the case for older studies for which guidelines have been available for several years.

In some cases the same study has been tagged as matching more than one practically equivalent guideline, for example, because the registrant provided both the EU and OECD test guidelines. Such cases lead to the same study tag. In rare situations, the registrants may have provided more than one guideline that lead two different study tags, in which case the algorithm increased the study counts for both study tags.

Table 6 shows the assigned study tags (shown in Figures 1 - 3 and Figure 13), the IUCLID sections where the study tags were applied to and the text patterns capturing the generally acceptable guidelines. The text patterns are expressed in the form of regular expressions and are only provided for transparency and completeness.

Table 6: Text patterns should for detecting guideline studies

Study tag	IUCLID section	Guideline
(sub)chronic RDT	7.5.1	(?i)(TG OECD)[^0-9]*408([\^d] \$) or (?i)B[\.\s]*26([\^d] \$) or (?i)(OPPTS)[^0-9]*870[\.\s]+3100([\^d] \$) or (?i)(OPP)[^0-9]*82[-\s]+1([\^d] \$) or (?i)(OTS)[^0-9]*798[\.\s]+2650([\^d] \$) or (?i)(OTS)[^0-9]*795[\.\s]+2600([\^d] \$) or (?i)(TG OECD)[^0-9]*409([\^d] \$) or (?i)B[\.\s]*27([\^d] \$) or (?i)(OPPTS)[^0-9]*870[\.\s]+3150([\^d] \$) or (?i)(OPPTS)[^0-9]*870[\.\s]+8700([\^d] \$) or (?i)(TG OECD)[^0-9]*424([\^d] \$) or (?i)B[\.\s]*43([\^d] \$)
(sub)chronic RDT	7.5.1, 7.5.2, 7.5.3	(?i)(TG OECD)[^0-9]*452([\^d] \$) or (?i)B[\.\s]*30([\^d] \$) or (?i)(OPP)[^0-9]*83[-\s]+1([\^d] \$) or (?i)(OPPTS)[^0-9]*870[\.\s]+4100([\^d] \$) or (?i)(OTS)[^0-9]*798[\.\s]+3260([\^d] \$)
(sub)chronic RDT	7.5.2	(?i)(TG OECD)[^0-9]*413([\^d] \$) or (?i)B[\.\s]*29([\^d] \$) or (?i)(OPP)[^0-9]*82[-\s]+4([\^d] \$) or (?i)(OPPTS)[^0-9]*870[\.\s]+3465([\^d] \$) or (?i)(OTS)[^0-9]*798[\.\s]+2450([\^d] \$)
(sub)chronic RDT	7.5.3	(?i)(TG OECD)[^0-9]*411([\^d] \$) or (?i)B[\.\s]*28([\^d] \$) or (?i)(OPP)[^0-9]*82[-\s]+3([\^d] \$) or (?i)(OPPTS)[^0-9]*870[\.\s]+3250([\^d] \$) or (?i)(OTS)[^0-9]*798[\.\s]+2250([\^d] \$)
28d RDT	7.5.1	(?i)(TG OECD)[^0-9]*407([\^d] \$) or (?i)B[\.\s]*7([\^d] \$) or (?i)(OPPTS)[^0-9]*870[\.\s]+3050([\^d] \$) or (?i)(TG OECD)[^0-9]*419([\^d] \$) or (?i)B[\.\s]*38([\^d] \$) or (?i)(OPP)[^0-9]*81[-\s]+7([\^d] \$) or (?i)(OPP)[^0-9]*82[-\s]+5([\^d] \$) or (?i)(OPP)[^0-9]*82[-\s]+6([\^d] \$)
28d RDT	7.5.2	(?i)(TG OECD)[^0-9]*412([\^d] \$) or (?i)B[\.\s]*8([\^d] \$)

28d RDT	7.5.3	(?) (TG OECD)[^0-9]*410([^\d] \$) or (?) B[\.\s]*9([^\d] \$) or (?) (OPP)[^0-9]*82[-\s]+2([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+3200([^\d] \$)
acute toxicity	7.2.1	(?) (TG OECD)[^0-9]*401([^\d] \$) or (?) (TG OECD)[^0-9]*420([^\d] \$) or (?) (TG OECD)[^0-9]*423([^\d] \$) or (?) (TG OECD)[^0-9]*425([^\d] \$) or (?) B[\.\s]*1([^\d] \$) (?)bis (?)tris or (?) B[\.\s]*1[-\.\s]*bis or (?) B[\.\s]*1[-\.\s]*tris or (?) (OPP)[^0-9]*81[-\s]+1([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+1100([^\d] \$) or (?) (OTS)[^0-9]*798[\.\s]+1175([^\d] \$)
acute toxicity	7.2.2	(?) (TG OECD)[^0-9]*403([^\d] \$) or (?) (TG OECD)[^0-9]*433([^\d] \$) or (?) (TG OECD)[^0-9]*436([^\d] \$) or (?) B[\.\s]*2([^\d] \$) or (?) B[\.\s]*52([^\d] \$) or (?) (OPP)[^0-9]*81[-\s]+3([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+1300([^\d] \$) or (?) (OTS)[^0-9]*798[\.\s]+1150([^\d] \$)
acute toxicity	7.2.3	(?) (TG OECD)[^0-9]*402([^\d] \$) or (?) (TG OECD)[^0-9]*434([^\d] \$) or (?) B[\.\s]*3([^\d] \$) or (?) (OPP)[^0-9]*81[-\s]+2([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+1200([^\d] \$) or (?) (OTS)[^0-9]*798[\.\s]+1100([^\d] \$)
bioaccumulation invertebrates	5.3.1	(?) (OPPTS)[^0-9]*850[\.\s]+1710([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1830([^\d] \$) or (?) (TG OECD)[^0-9]*315([^\d] \$) or (?) (OPPTS)[^0-9]*835[\.\s]+4100([^\d] \$) or (?) (OPPTS)[^0-9]*835[\.\s]+4200([^\d] \$) or (?) 600[-/\s\\]+R[-/\s\\]+94[-/\s\\]+024([^\d] \$) or (?) (ASTM)[-/\s\\]+E[-/\s\\]*1688([^\d] \$) or (?) (OPP)[^0-9]*72[-\s]+6([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1850([^\d] \$)
bioaccumulation invertebrates	5.3.2	(?) (TG OECD)[^0-9]*317([^\d] \$) or (?) C[\.\s]*30([^\d] \$) or (?) (ASTM)[-/\s\\]+E[-/\s\\]*1676([^\d] \$) or (?) (ASTM)[-/\s\\]+E[-/\s\\]*1688([^\d] \$)
bioaccumulation vertebrates	5.3.1	(?) (TG OECD)[^0-9]*305([^\d] \$) or (?) C[\.\s]*13([^\d] \$) or (?) (OPP)[^0-9]*165[-\s]+4([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1730([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1520([^\d] \$)
carcinogenicity	7.7	(?) (TG OECD)[^0-9]*451([^\d] \$) or (?) B[\.\s]*32([^\d] \$) or (?) (OPP)[^0-9]*83[-\s]+2([^\d] \$) or (?) (OTS)[^0-9]*798[\.\s]+3300([^\d] \$)
chronic/carcinogenicity	7.5.1, 7.5.2, 7.5.3, 7.7	(?) (TG OECD)[^0-9]*453([^\d] \$) or (?) B[\.\s]*33([^\d] \$) or (?) (OPP)[^0-9]*83[-\s]+5([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+4300([^\d] \$) or (?) (OTS)[^0-9]*798[\.\s]+3320([^\d] \$) or (?) (OPP)[^0-9]*83[-\s]+5([^\d] \$)

combined 28d RDT with repro/dev screen	7.8.1, 7.8.2, 7.5.1, 7.5.2, 7.5.3	(?) (TG OECD)[^0-9]*422([^\d] \$) or (?) (OPPTS)[^0-9]*870[\\.\s]+3650([^\d] \$)
developmental toxicity	7.8.1, 7.8.2	(?) (TG OECD)[^0-9]*426([^\d] \$) or (?) B[\\.\s]*53([^\d] \$) or (?) (OPP)[^0-9]*83[-\s]+6([^\d] \$) or (?) (OPPTS)[^0-9]*870[\\.\s]+6300([^\d] \$) or (?) (OTS)[^0-9]*795[\\.\s]+2500([^\d] \$)
developmental toxicity	7.8.2	(?) (TG OECD)[^0-9]*414([^\d] \$) or (?) B[\\.\s]*31([^\d] \$) or (?) (OPP)[^0-9]*83[-\s]+3([^\d] \$) or (?) (OTS)[^0-9]*798[\\.\s]+4900([^\d] \$) or (?) (OPPTS)[^0-9]*870[\\.\s]+3600([^\d] \$) or (?) (OPPTS)[^0-9]*870[\\.\s]+3700([^\d] \$) or (?) (OTS)[^0-9]*798[\\.\s]+4350([^\d] \$)
eye irritation/corrosion (<i>in vitro</i>)	7.3.2	(?) (TG OECD)[^0-9]*437([^\d] \$) or (?) B[\\.\s]*47([^\d] \$) or (?) (TG OECD)[^0-9]*438([^\d] \$) or (?) B[\\.\s]*48([^\d] \$) or (?) (TG OECD)[^0-9]*491([^\d] \$) or (?) (TG OECD)[^0-9]*492([^\d] \$) or (?) (TG OECD)[^0-9]*460([^\d] \$)
eye irritation/corrosion (<i>in vivo</i>)	7.3.2	(?) B[\\.\s]*5([^\d] \$) or (?) (OPP)[^0-9]*81[-\s]+4([^\d] \$) or (?) (OPPTS)[^0-9]*870[\\.\s]+2400([^\d] \$) or (?) (OTS)[^0-9]*798[\\.\s]+4500([^\d] \$)
genetic toxicity (<i>in vitro</i>)	7.6.1	(?) (TG OECD)[^0-9]*471([^\d] \$) or (?) (TG OECD)[^0-9]*472([^\d] \$) or (?) B[\\.\s]*13([^\d] \$) or (?) B[\\.\s]*14([^\d] \$) or (?) (TG OECD)[^0-9]*473([^\d] \$) or (?) B[\\.\s]*10([^\d] \$) or (?) (TG OECD)[^0-9]*487([^\d] \$) or (?) (TG OECD)[^0-9]*476([^\d] \$) or (?) B[\\.\s]*17([^\d] \$) or (?) (TG OECD)[^0-9]*490([^\d] \$) or (?) (TG OECD)[^0-9]*479([^\d] \$) or (?) B[\\.\s]*19([^\d] \$) or (?) (OPPTS)[^0-9]*870[\\.\s]+5900([^\d] \$) or (?) (OTS)[^0-9]*798[\\.\s]+5900([^\d] \$)
genetic toxicity (<i>in vivo</i>)	7.6.2	(?) (TG OECD)[^0-9]*474([^\d] \$) or (?) B[\\.\s]*12([^\d] \$) or (?) (TG OECD)[^0-9]*475([^\d] \$) or (?) B[\\.\s]*11([^\d] \$) or (?) (TG OECD)[^0-9]*488([^\d] \$) or (?) B[\\.\s]*58([^\d] \$) or (?) transgenic\s+(rodent rat mouse mice) or (?) (TG OECD)[^0-9]*489([^\d] \$) or (?) Comet or (?) (TG OECD)[^0-9]*485([^\d] \$) or (?) B[\\.\s]*25([^\d] \$) or (?) (TG OECD)[^0-9]*483([^\d] \$) or (?) B[\\.\s]*23([^\d] \$) or (?) (TG OECD)[^0-9]*478([^\d] \$) or (?) B[\\.\s]*22([^\d] \$) or (?) dominant\s+lethal or (?) spermatogonial\s+chromosom(e al)\s+aberration or (?) heritable\s+translocation
long-term toxicity to aquatic invertebrates	6.1.4	(?) (TG OECD)[^0-9]*211([^\d] \$) or (?) (TG OECD)[^0-9]*242([^\d] \$) or (?) (TG OECD)[^0-9]*243([^\d] \$) or (?) C[\\.\s]*20([^\d] \$) or (?) (OPPTS)[^0-9]*850[\\.\s]+1300([^\d] \$) or (?) (OPPTS)[^0-9]*850[\\.\s]+1350([^\d] \$) or (?) (OTS)[^0-9]*797[\\.\s]+1330([^\d] \$) or (?) (OTS)[^0-9]*797[\\.\s]+1950([^\d] \$)

long-term toxicity to fish	6.1.2	(?) (TG OECD)[^0-9]*210([^\d] \$) or (?) (TG OECD)[^0-9]*212([^\d] \$) or (?) (TG OECD)[^0-9]*215([^\d] \$) or (?) C[\.\s]*14([^\d] \$) or (?) C[\.\s]*15([^\d] \$) or (?) C[\.\s]*47([^\d] \$) or (?) (OPP)[^0-9]*72[-\s]+5([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1400([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1500([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1000([^\d] \$)
long-term toxicity to fish	6.1.2, 6.1.4	(?) (OPP)[^0-9]*72[-\s]+4([^\d] \$)
repro/dev toxicity screening test	7.8.1, 7.8.2	(?) (TG OECD)[^0-9]*421([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+3500([^\d] \$) or (?) (OTS)[^0-9]*798[\.\s]+4420([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+3550([^\d] \$)
short-term toxicity to aqua. invert.	6.1.3	(?) (TG OECD)[^0-9]*202([^\d] \$) or (?) (TG OECD)[^0-9]*235([^\d] \$) or (?) C[\.\s]*2([^\d] \$) or (?) (OPP)[^0-9]*72[-\s]+2([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1010([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1020([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1025([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1035([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1045([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1055([^\d] \$) or (?) (OTS)[^0-9]*795[\.\s]+1200([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1300([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1800([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1930([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1970([^\d] \$) or (?) (ISO)[^0-9]*6341([^\d] \$)
short-term toxicity to fish	6.1.1	(?) (TG OECD)[^0-9]*203([^\d] \$) or (?) C[\.\s]*1([^\d] \$) or (?) (OPP)[^0-9]*72[-\s]+1([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1075([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+1085([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1400([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1460([^\d] \$) or (?) (ISO)[^0-9]*7346[-.\s\+]+1([^\d] \$) or (?) C[\.\s]*49([^\d] \$) or (?) (TG OECD)[^0-9]*236([^\d] \$)
short-term toxicity to fish	6.1.1, 6.1.2	(?) (TG OECD)[^0-9]*204([^\d] \$)
short-term toxicity to fish	6.1.1, 6.1.3	(?) (OPP)[^0-9]*72[-\s]+3([^\d] \$)
skin irritation/corrosion (<i>in vitro</i>)	7.3.1	(?) (TG OECD)[^0-9]*430([^\d] \$) or (?) (TG OECD)[^0-9]*431([^\d] \$) or (?) reconstructed\s+human\s+epidermis or (?) (TG OECD)[^0-9]*439([^\d] \$) or (?) B[\.\s]*40([^\d] \$)
skin irritation/corrosion (<i>in vivo</i>)	7.3.1	(?) (TG OECD)[^0-9]*404([^\d] \$) or (?) B[\.\s]*4([^\d] \$) or (?) (OPP)[^0-9]*81[-\s]+5([^\d] \$) or (?) (OTS)[^0-9]*798[\.\s]+4470([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+2500([^\d] \$) or (?) transcutaneous\s+electrical\s+resistance or (?) human\s+skin\s+model or (?) (TG OECD)[^0-9]*435([^\d] \$) or (?) membrane\s+barrier\s+test or (?) B[\.\s]*46([^\d] \$)

skin irritation/corrosion (<i>in vivo</i>)	7.3.2	(?) (TG OECD)[^0-9]*405([^\d] \$)
skin sensitisation (<i>in vitro</i>)	7.4.1	(?)B[\.\s]*59([^\d] \$) or (?) (TG OECD)[^0-9]*442\s*C or DPRA or (?)direct peptide reactivity or (?)in chemico skin sensitiation or (?)B[\.\s]*60([^\d] \$) or (?) (TG OECD)[^0-9]*442\s*D or (?)keratinosens or (?)RE[-\s]*Nrf2\s+Luciferase or (?)RE[-\s]*Nrf2 or (?)LuSens or (?)SENS[-\s]+IS or (?)h[-\s]*CLAT or (?)U[-\s]+SENS or (?)IL[-\s]*8[-\s-]*Luc
skin sensitisation (<i>in vivo</i>)	7.4.1	(?)(?<!non[-\s])LLNA or (?)local\s+lymph\s*node or (?)B[\.\s]*42([^\d] \$) or (?) (TG OECD)[^0-9]*429 or GPMT or (?)guinea\s*pig\s+maximisation or (?)B[\.\s]*6([^\d] \$) or (?) (TG OECD)[^0-9]*406
toxicity to aqua. algae and cyanobact.	6.1.5	(?) (TG OECD)[^0-9]*201([^\d] \$) or (?)C[\.\s]*3([^\d] \$) or (?) (OPP)[^0-9]*122[-\s]+2([^\d] \$) or (?) (OPP)[^0-9]*123[-\s]+3([^\d] \$) or (?) (OPPTS)[^0-9]*850[\.\s]+5400([^\d] \$) or (?) (OTS)[^0-9]*797[\.\s]+1050([^\d] \$) or (?) (ISO)[^0-9]*8692([^\d] \$) or (?) (ISO)[^0-9]*10253([^\d] \$)
toxicity to reproduction	7.8.1	(?) (TG OECD)[^0-9]*415([^\d] \$) or (?)B[\.\s]*34([^\d] \$) or (?) (TG OECD)[^0-9]*443([^\d] \$) or (?)B[\.\s]*56([^\d] \$) or EOGRTS or (?)extended[-\s]+one[-\s]+generation or (?) (TG OECD)[^0-9]*416([^\d] \$) or (?)B[\.\s]*35([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+3800([^\d] \$)
toxicity to reproduction	7.8.1, 7.8.2	(?) (OPP)[^0-9]*83[-\s]+4([^\d] \$) or (?) (OTS)[^0-9]*798[\.\s]+4700([^\d] \$)
toxicokinetics	7.1.1	(?) (TG OECD)[^0-9]*417([^\d] \$) or (?)B[\.\s]*36([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+8500([^\d] \$) or (?) (OTS)[^0-9]*795[\.\s]+2350([^\d] \$) or (?) (OPP)[^0-9]*85[-\s]+1([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+7485([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+8223([^\d] \$) or (?) (OTS)[^0-9]*798[\.\s]+7485([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+8320([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+8340([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+8360([^\d] \$) or (?) (OPPTS)[^0-9]*870[\.\s]+8380([^\d] \$) or (?) (OTS)[^0-9]*795[\.\s]+2230([^\d] \$) or (?) (OTS)[^0-9]*795[\.\s]+2280([^\d] \$) or (?) (OTS)[^0-9]*795[\.\s]+2300([^\d] \$) or (?) (OTS)[^0-9]*795[\.\s]+2310([^\d] \$) or (?) (OTS)[^0-9]*795[\.\s]+2320([^\d] \$) or (?) (transformation.dissolution.*metal.*aqueous\s+media OECD Series on Testing and Assessment.*\s+29([^\d] \$)) or (?) (OPPTS OCSPP)[^0-9]*870[\.\s]+8245([^\d] \$)

A1.3 Aggregation of study information at substance level

This section of the annex builds on the previous one and summarises how the endpoint study record information has been aggregated at substance level.

Contrary to earlier editions of the Article 117(3) report this edition does not include multiple aggregation levels because they are not deemed necessary to convey the key

findings and are detrimental to readability. Instead, with the exception of Figure 13 that displays the distribution of study periods without aggregating at substance level, all other figures in the report have aggregated the endpoint study record information at substance level, even when the endpoint study records have been retrieved from different IUCLID dossiers for the same substance. Moreover, the figures can be categorised into two main families:

- Figures 1 - 3 have grouped together the endpoint study records according to the study tags assigned to them as described in the previous section. This means that endpoint study records within the same IUCLID section may have been assigned to different study tags because the IUCLID section encapsulates information that refers to more than one information requirement as delineated in the REACH annexes. As an example, this is the case for skin sensitisation where both *in vitro* and *in vivo* studies are included in the same IUCLID section. Figures 1 - 3 only examine the presence or absence of a study for each study tag for each substance.

Figures 4 - 12, on the other hand, have grouped together the endpoint study records according to the IUCLID section they belong. The technical reason for doing so is that when the same IUCLID section encapsulates more than one information requirement, it is technically challenging to assign all endpoint records in the same section to each information requirement. For example, it is not always straightforward to algorithmically assign a data waiver to a particular information requirement, especially for dossiers that have not been recently updated. Such dossiers have automatically been migrated to the latest IUCLID format and may not have passed the latest set of technical completeness check rules that only started applying after their submission. For these reasons it has not been technically possible to construct all figures so that the endpoint study records are always grouped together according to the study tags, although this would have been preferable for consistency.

A distinction is made between the endpoints on the vertical axis in red and in blue. The endpoints in blue are required, depending on the relevant annex for the substance. Some requirements are valid for all annexes (e.g. acute toxicity), some only occur at a higher annex (repeated dose toxicity). To calculate the percentages, only the substances in the corresponding annexes were used. Substances for which the endpoint was not a requirement were left out. This was done, to provide a picture with the highest resolution. Endpoints indicated in red are either optional or part of an integrated testing approach and are not always required, regardless of the tonnage band. For this reason, all categories have to be expressed versus all substances, regardless of the tonnage bands. The category 'no information' is therefore relatively high.

The next part of this section explains how the information has been aggregated at substance level for the purposes of the barplots in Figures 4 - 11. A cascade of rules was applied after all endpoint study records in a given IUCLID section for the same substance were pulled together regardless of whether they have been included in the same or different IUCLID dossiers. All repeated dose toxicity IUCLID sections for the different routes and duration were binned together. The same approach has been followed for acute toxicity information, bioaccumulation and toxicokinetics. The aggregation rules can be summarised as follows:

1. if there are no endpoint study records in the IUCLID section, the endpoint was marked as "no information"; otherwise
2. if the only endpoint study records provided are one or more data waiver, the endpoint was marked as "data waiver"; otherwise
3. if the only endpoint study records provided are one or more testing proposal the endpoint was marked as "testing proposal"; otherwise
4. if at least one reliable (Klimisch score 1 or 2) experimental study with the

registered substance with one of the generally accepted guidelines under REACH has been provided, the endpoint was marked as “experimental” regardless of the presence of additional information; otherwise

5. if the only reliable (Klimisch score 1 or 2) information provided is one or more read-across (but not reliable experimental study or QSAR prediction), the endpoint was marked as “read-across/category”; otherwise
6. if the the only reliable (Klimisch score 1 or 2) information provided is one or more QSAR prediction (but not reliable experimental study or read-across), the endpoint was marked as “QSAR”; otherwise
7. if both reliable (Klimisch score 1 or 2) read-across and QSAR prediction information has been provided (but no reliable experimental study), the endpoint was marked as “weight of evidence”; otherwise
8. if the total number of unique endpoint study records that belong to one of the following types:
 - o reliable experimental study with a generally not accepted guideline
 - o unreliable experimental study regardless of guideline
 - o unreliable read-across
 - o unreliable QSAR
 - o other information, not understood to be experimental study, read-across or QSAR prediction

is two or more and there is there is no reliable experimental study, read-across or QSAR prediction information, then endpoint was marked as “weight of evidence”; otherwise

9. the endpoint was marked as “other”.

The above scheme is to some extent arbitrary and different hierarchy rules could have been constructed. Despite this limitation, the use of hierarchical rules was deemed essential to provide an overview that is otherwise impossible to convey if we enumerate all possible combinations of endpoint study record types used to fulfil the information requirements.

It is true that both the nature but also the sequence of hierarchical rules affect the obtained results to some extent. However, the qualitative conclusions drawn in the report would not differ significantly even with different rules. For this reason, and in the interests of simplicity, this report does not contain results obtained with different sets of hierarchical rules. Moreover, the effect of the adopted conventions is less significant when the focus is on the way registrants have been changing the way they fulfil the information requirements, given that both 2016 and 2019 datasets have been analysed in a consistent way.

The next part of this section explains how the information has been aggregated at substance level for the purposes of the circular graphs in Figure 12 and Figures in Annex 2. To some extent, these figures compensate for the shortcomings of the hierarchical rules used for the barplots of Figures 4 - 11 by providing quantitative information on how registrants combined different ways to fulfil the information requirements for the same endpoint.

The colour coding of these circular graphs is consistent with the colour coding of the barplots. To reduce the complexity of the graphs, we only show the percentage of substances that:

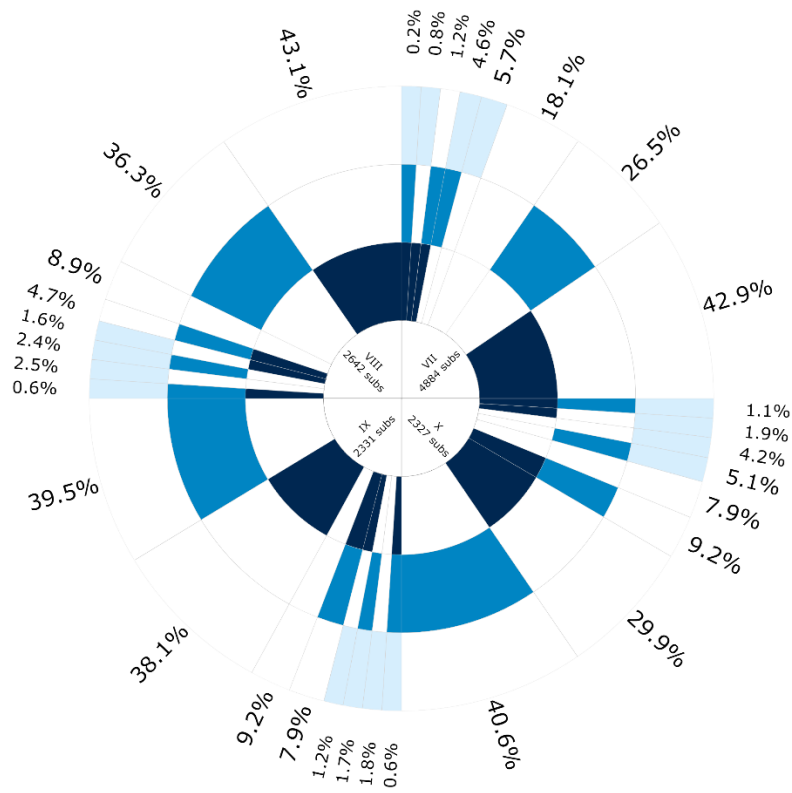
1. have at least one endpoint study record that contains a reliable (Klimisch score 1 or 2) experimental study with the registered substance with one of the generally accepted guidelines under REACH (dark blue);
2. have at least one endpoint study record that contains a reliable (Klimisch score 1 or 2) read-across (blue); or

3. have at least one endpoint study record that contains a reliable (Klimisch score 1 or 2) QSAR prediction (light blue).

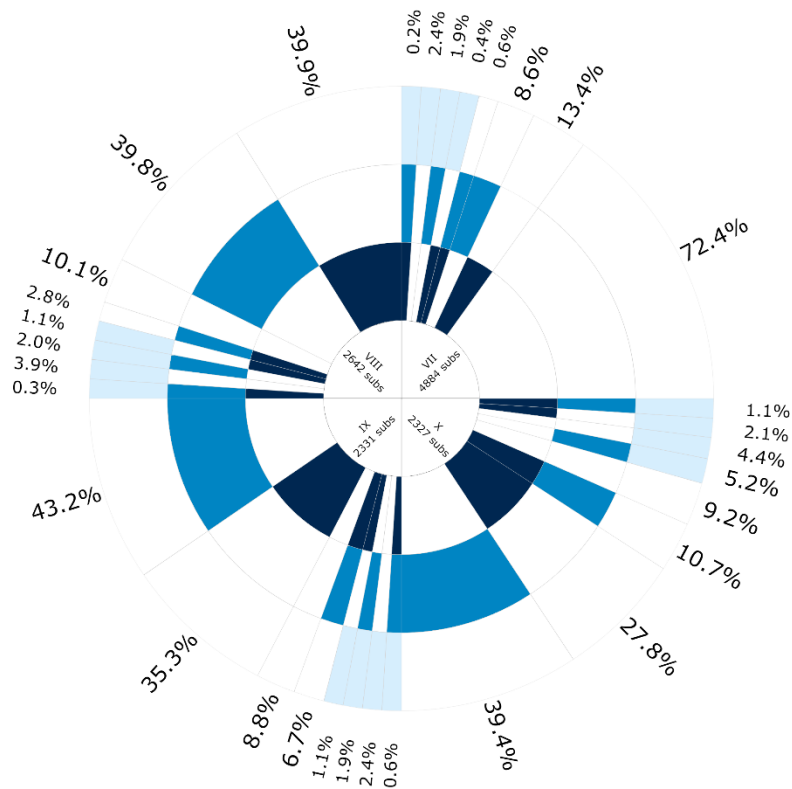
All other endpoint study records have not been colour coded. However, this does not mean that the corresponding IUCLID section is devoid of any hazard information. It is possible that the combination of multiple pieces of evidence of lower reliability may be sufficient to demonstrate the absence of hazard for some substances, or that the registrant may have opted to conservatively assume that the substance is hazardous as a worst case even though no definitive testing information is available.

In certain cases, this may be sufficient to ensure safe use if the classification and risk assessment have also been conservatively applied.

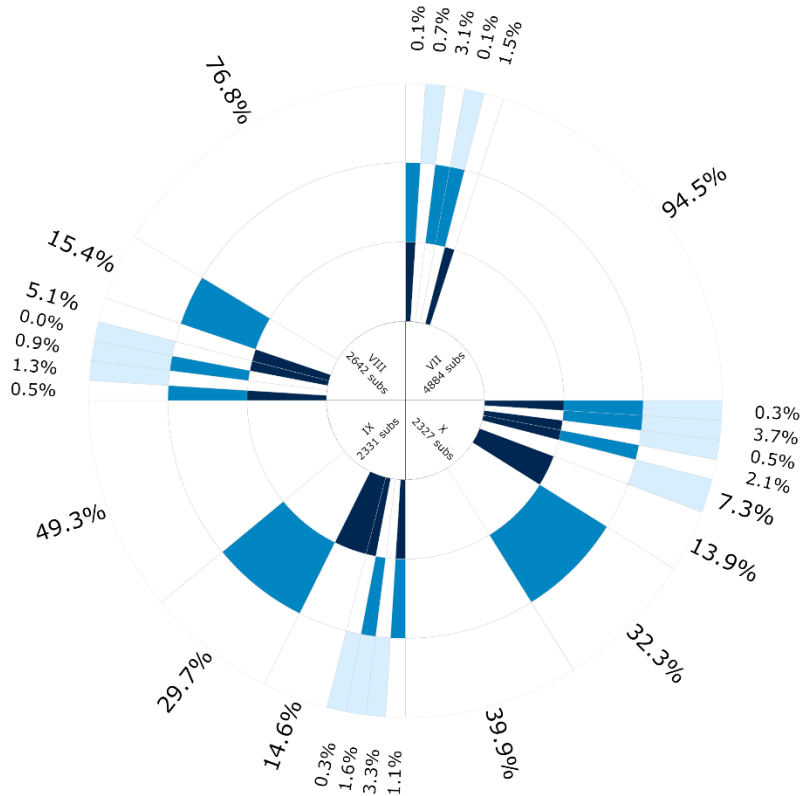
b) Short-term toxicity to aquatic invertebrates [short-term toxicity to aquatic invertebrates_2019]



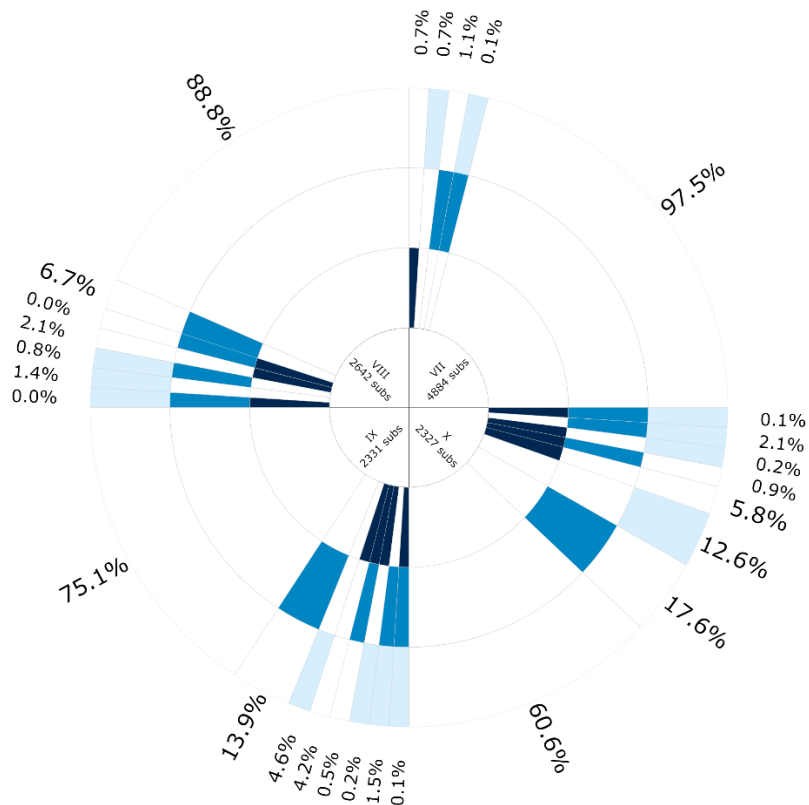
c) Short-term toxicity to fish



d) Long-term toxicity to aquatic invertebrates



e) Long-term toxicity to fish



f) Toxicity to aquatic algae and cyanobacteria

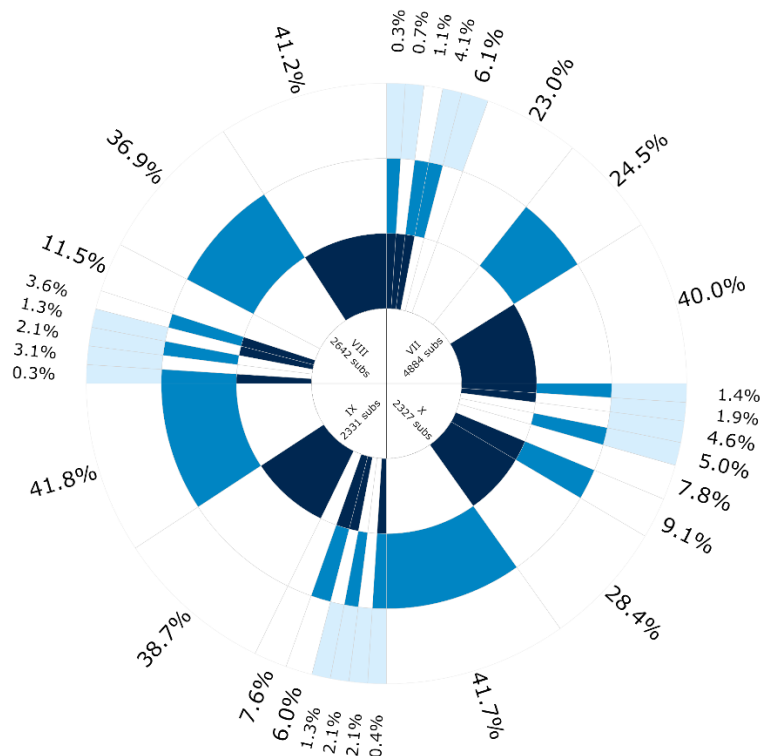
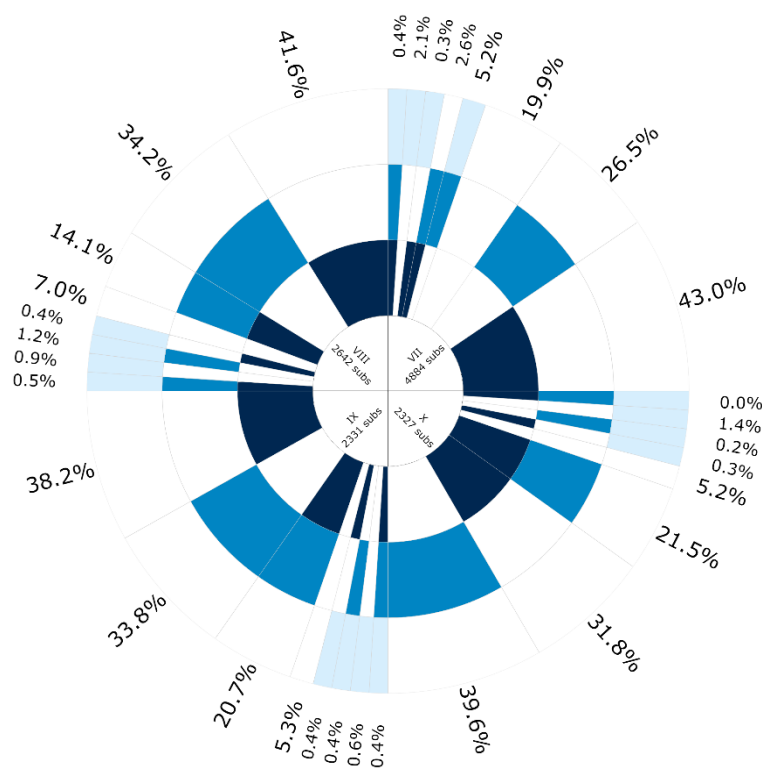
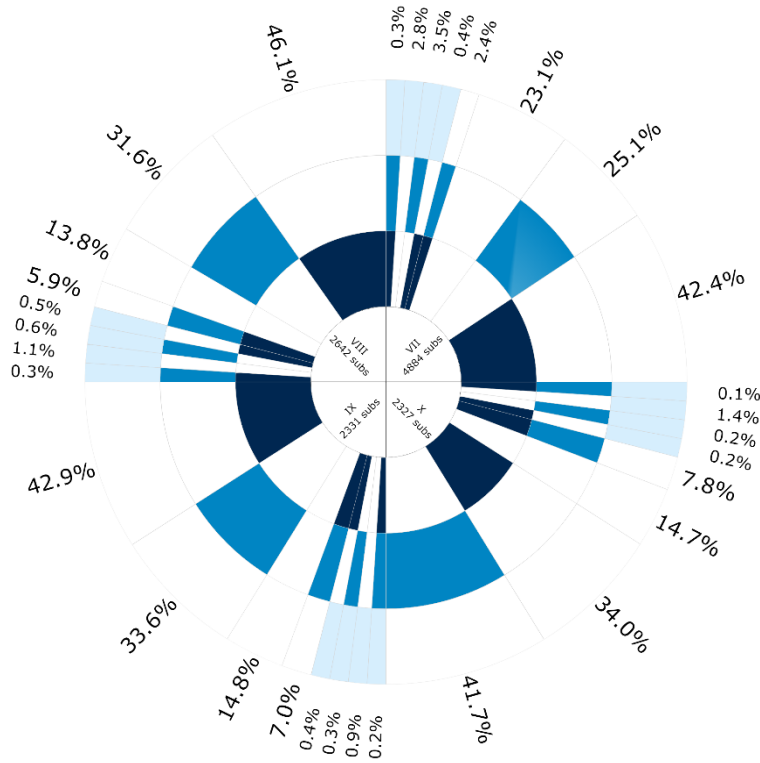


Figure 16. Detailed view for human health lower tier endpoints 2019

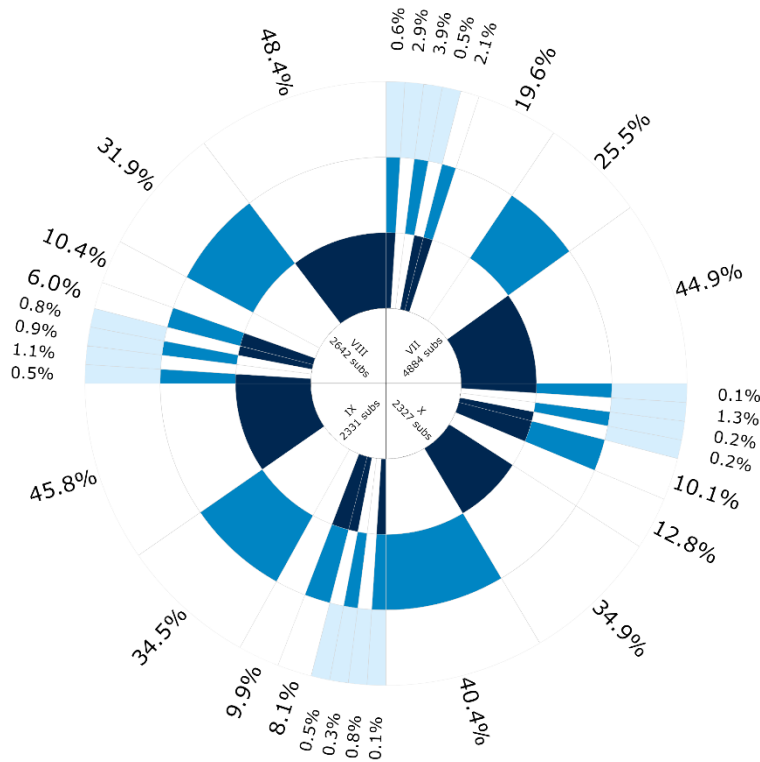
a) Acute toxicity (all routes)



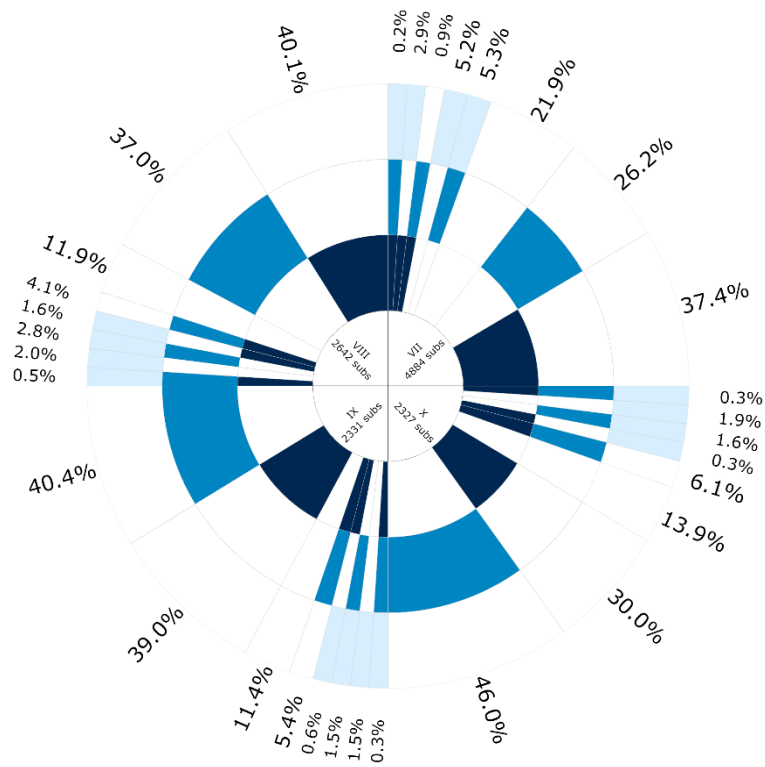
b) Serious eye damage - eye irritation



c) Skin corrosion - irritation



d) Skin sensitisation



e) Genetic toxicity *in vitro*

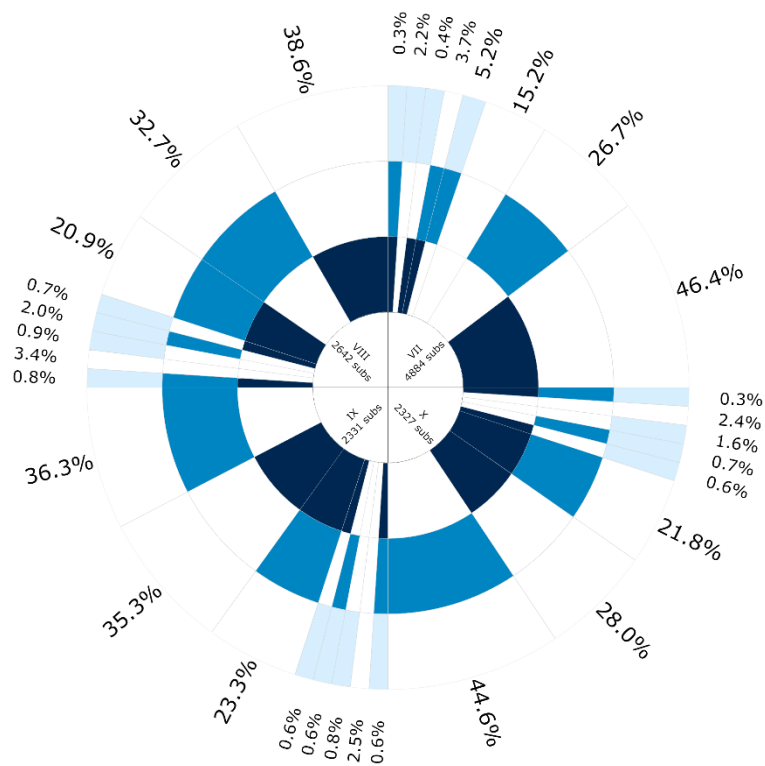
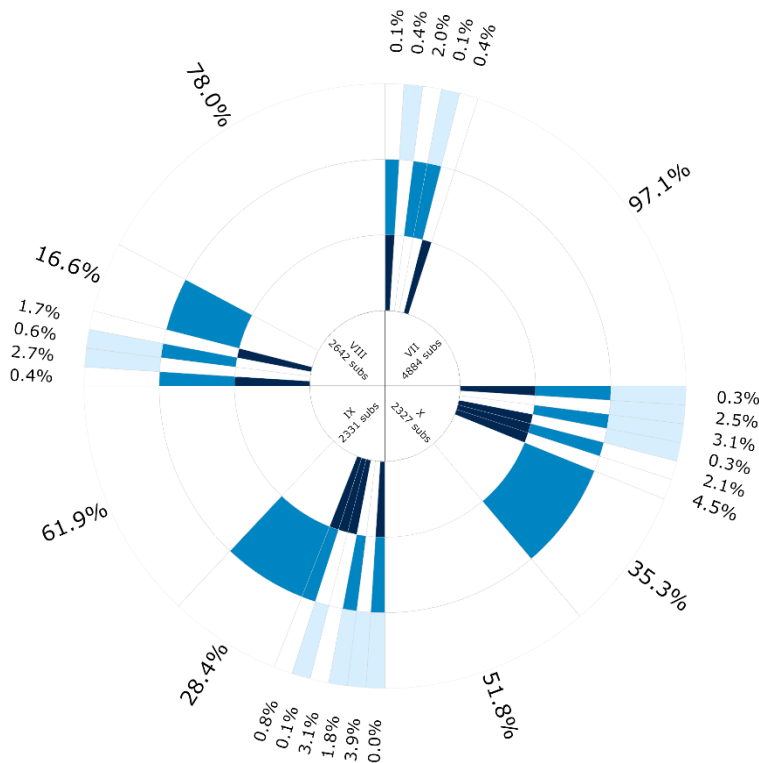
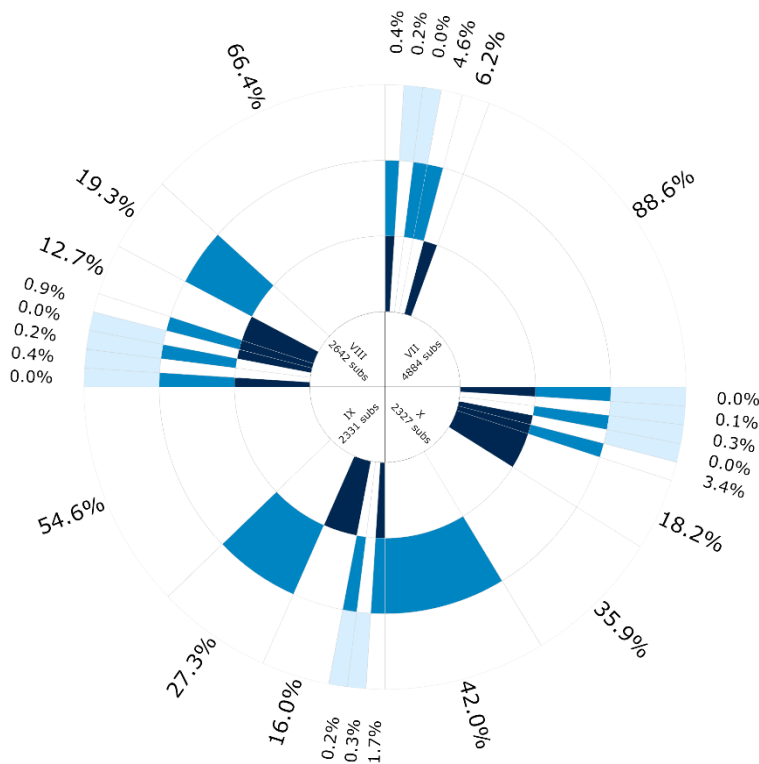


Figure 17. Detailed view for human health higher tier endpoints 2019

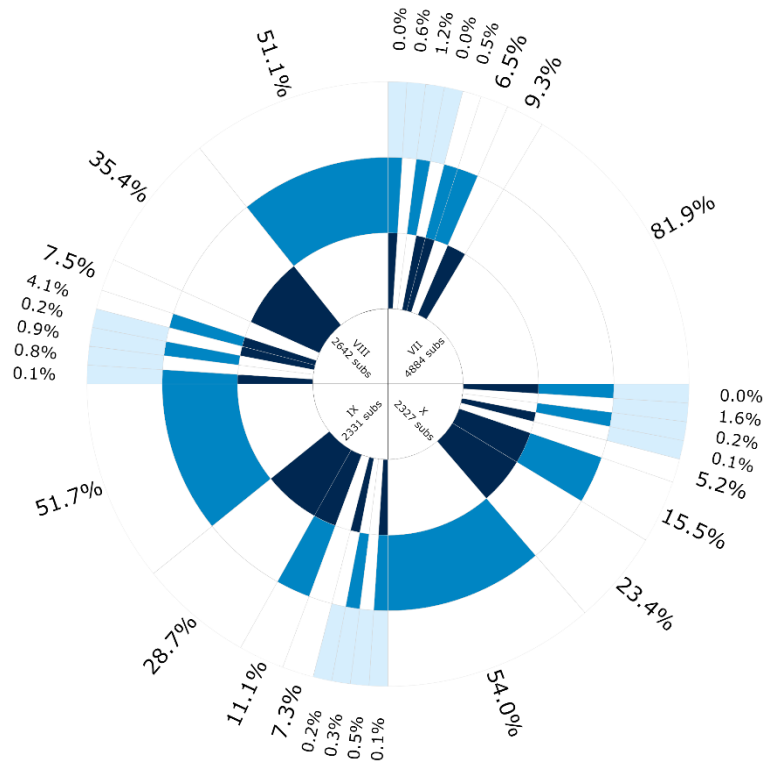
a) Basic toxicokinetics - dermal absorption



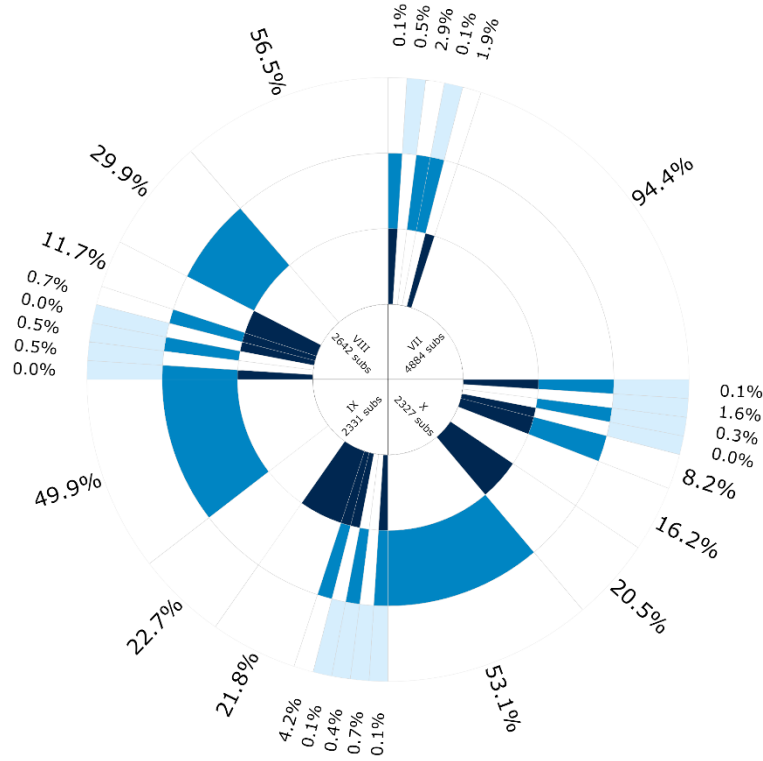
b) Genetic toxicity *in vivo*



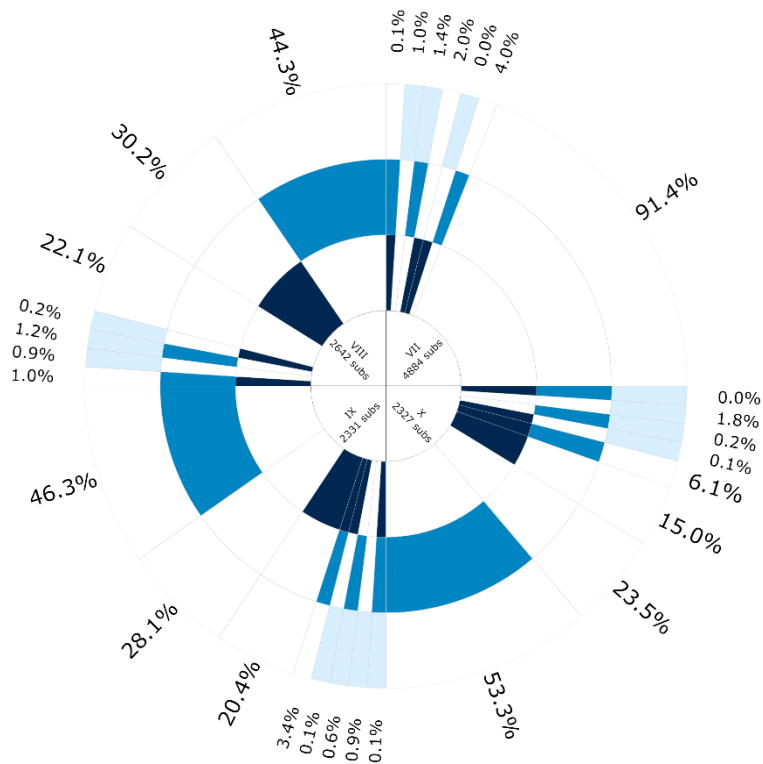
c) Repeated dose toxicity (all routes)



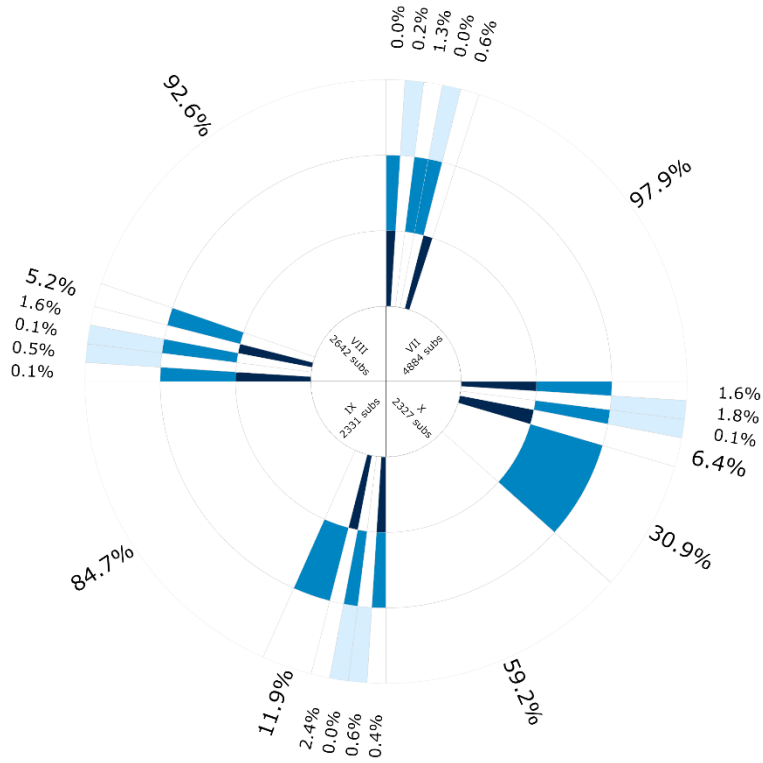
d) Developmental toxicity – teratogenicity



e) Toxicity to reproduction



f) Carcinogenicity



Annex 3

A3.1 Detailed results of the options analysis

This annex contains the detailed results of the option analysis, used to make the figures 4 – 11 in chapter 3.3.2 – 3.3.5

Table 7: Frequency of the different options to fulfil the information requirements in 2019 (aggregated at IUCLID section level), relates to Figure 4.

	Study	Read-across	OSAR	WoE	Waiving	TP	Other	No info
carcinogenicity	2.7	9.8	0.6	1.9	6.8	0.0	2.4	75.7
toxicity to reproduction	16.3	30.3	1.1	2.0	11.4	0.4	3.0	35.5
developmental /teratogenicity	14.1	27.3	0.8	1.5	6.0	0.9	2.0	47.4
repeated dose toxicity (all routes)	27.7	33.9	0.8	2.0	1.4	0.1	5.0	29.0
genetic toxicity <i>in vivo</i>	13.1	19.3	0.2	1.7	2.8	0.7	3.1	58.9
genetic toxicity <i>in vitro</i>	54.7	33.2	1.5	6.5	1.1	0.0	1.7	1.2
skin sensitisation	42.2	35.1	3.2	4.2	7.3	0.0	6.7	1.4
skin corrosion - irritation	50.4	31.4	1.8	3.2	3.3	0.0	8.5	1.3
serious eye damage - eye irritation	47.4	31.3	1.8	2.9	6.2	0.0	9.1	1.3
acute toxicity (all routes)	52.5	32.1	1.4	6.4	2.1	0.0	4.3	1.2
basic toxicokinetics - dermal absorption	2.8	16.6	2.0	6.2	5.2	0.0	14.6	52.7
toxicity to aquatic algae and cyanobacteria	43.6	33.8	4.4	4.6	6.0	0.0	4.5	3.0

long-term toxicity to fish	3.1	7.9	3.9	1.3	27.0	0.2	2.0	54.7
long-term toxicity to aquatic invertebrates	8.1	16.4	2.6	1.8	16.8	0.4	2.0	51.9
short-term toxicity to fish	31.8	27.9	3.1	4.8	2.6	0.0	5.6	24.3
short-term toxicity to aquatic invertebrates	46.2	33.8	3.9	5.0	4.5	0.0	5.3	1.3
bioaccumulation	3.4	7.1	11.5	6.6	21.3	0.1	2.7	47.4

Table 8: Frequency of the different options to fulfil the information requirements in 2016 (aggregated at IUCLID section level), relates to Figure 5

	Study	Read-across	QSA R	WoE	Waiving	TP	Other	No info
carcinogenicity	3.7	14.4	0.9	2.5	10.5	0.0	3.5	64.6
toxicity to reproduction	16.6	34.9	1.4	1.8	14.7	0.7	3.5	26.5
developmental /teratogenicity	16.2	33.9	1.2	1.9	9.7	3.2	2.8	31.2
repeated dose toxicity (all routes)	31.5	38.4	1.0	2.1	1.9	0.3	6.8	17.9
genetic toxicity <i>in vivo</i>	16.1	24.9	0.2	2.0	3.9	0.6	3.6	48.6
genetic toxicity <i>in vitro</i>	53.5	33.4	2.1	5.9	1.5	0.0	1.4	2.3
skin sensitisation	41.0	36.0	2.5	3.0	8.1	0.0	6.7	2.5
skin corrosion - irritation	48.1	31.3	1.8	3.8	4.2	0.0	8.5	2.3

serious eye damage - eye irritation	44.1	31.6	1.5	3.3	7.3	0.0	9.7	2.4
acute toxicity (all routes)	53.4	31.2	1.7	5.8	1.9	0.0	3.7	2.3
basic toxicokinetics - dermal absorption	3.4	21.7	2.0	8.4	7.3	0.0	16.5	40.7
toxicity to aquatic algae and cyanobacteria	42.4	34.6	4.4	4.1	5.0	0.0	6.4	3.2
long-term toxicity to fish	3.7	10.2	5.1	1.3	41.7	0.3	2.3	35.4
long-term toxicity to aquatic invertebrates	10.0	20.8	3.0	2.3	26.6	0.7	3.1	33.5
short-term toxicity to fish	36.4	31.0	3.2	5.5	2.6	0.0	7.2	14.1
short-term toxicity to aquatic invertebrates	44.5	33.6	4.0	4.4	4.7	0.0	6.5	2.3
bioaccumulation	4.1	9.0	14.6	5.6	32.2	0.1	3.7	30.7

Table 9: Frequency of the different options to fulfil the information requirements for Annex X substances in 2019 (aggregated at IUCLID section level), relates to Figure 6

	Study	Read-across	QSAR	WoE	Waiving	TP	Other	No info
carcinogenicity	8.0	30.9	1.8	4.0	24.9	0.0	5.7	24.6
toxicity to reproduction	21.2	53.3	1.8	1.3	16.4	1.5	4.1	0.3
developmental /teratogenicity	28.8	53.1	1.6	1.6	11.3	0.6	2.6	0.3

repeated dose toxicity (all routes)	39.0	54.0	1.6	1.1	1.7	0.0	2.3	0.3
genetic toxicity <i>in vivo</i>	21.7	42.0	0.1	2.7	6.3	0.1	3.3	23.9
genetic toxicity <i>in vitro</i>	50.7	44.6	1.6	1.4	0.9	0.0	0.5	0.3
skin sensitisation	36.7	46.0	1.9	2.8	8.3	0.0	4.1	0.3
skin corrosion - irritation	45.3	40.4	1.3	2.3	4.2	0.0	6.2	0.3
serious eye damage - eye irritation	42.1	41.7	1.4	2.1	6.2	0.0	6.3	0.3
acute toxicity (all routes)	53.6	39.6	1.4	1.2	1.0	0.0	2.8	0.3
basic toxicokinetics - dermal absorption	7.3	35.3	2.5	14.3	11.3	0.0	10.9	18.4
toxicity to aquatic algae and cyanobacteria	40.8	41.7	4.6	6.7	3.0	0.0	2.8	0.3
long-term toxicity to fish	7.1	17.6	12.6	3.1	54.3	0.4	4.5	0.3
long-term toxicity to aquatic invertebrates	16.8	32.3	7.3	5.0	33.4	0.7	4.2	0.3
short-term toxicity to fish	41.7	39.4	4.4	8.6	2.9	0.0	2.6	0.3
short-term toxicity to aquatic invertebrates	42.2	40.6	4.2	7.0	3.2	0.0	2.4	0.3
bioaccumulation	6.1	12.7	17.3	10.7	47.6	0.0	5.2	0.3

Table 10: Frequency of the different options to fulfil the information requirements for Annex X substances in 2016 (aggregated at IUCLID section

level), relates to Figure 7

	Study	Read-across	QSAR	WoE	Waiving	TP	Other	No info
carcinogenicity	7.9	31.1	1.8	3.9	24.7	0.0	6.3	24.2
toxicity to reproduction	20.3	52.3	1.5	1.9	17.6	1.6	4.0	0.8
developmental /teratogenicity	27.6	50.4	1.5	1.6	12.5	2.5	3.2	0.7
repeated dose toxicity (all routes)	39.4	52.4	1.5	1.2	2.3	0.1	2.4	0.7
genetic toxicity <i>in vivo</i>	21.8	41.8	0.1	2.5	7.2	0.3	3.3	22.9
genetic toxicity <i>in vitro</i>	51.4	43.4	1.5	1.5	1.0	0.0	0.5	0.7
skin sensitisation	37.1	45.1	1.7	3.6	8.7	0.0	3.2	0.7
skin corrosion - irritation	46.5	38.4	1.3	4.5	4.3	0.0	4.4	0.7
serious eye damage - eye irritation	42.4	40.1	1.3	4.3	6.3	0.0	4.8	0.7
acute toxicity (all routes)	54.0	38.6	1.3	1.3	1.0	0.0	3.0	0.7
basic toxicokinetics - dermal absorption	6.8	34.2	1.5	14.7	11.9	0.0	12.4	18.4
toxicity to aquatic algae and cyanobacteria	40.6	40.7	4.7	6.7	3.3	0.0	3.2	0.7
long-term toxicity to fish	6.9	16.9	12.7	2.7	55.9	0.1	4.1	0.8
long-term toxicity to aquatic invertebrates	15.7	31.8	6.9	4.7	35.2	0.6	4.4	0.7

short-term toxicity to fish	41.8	38.6	4.4	8.7	3.0	0.0	2.8	0.7
short-term toxicity to aquatic invertebrates	42.5	39.2	4.3	7.1	3.8	0.0	2.4	0.7
bioaccumulation	5.7	11.9	17.8	7.3	50.9	0.2	5.5	0.8

Table 11: Frequency of the different options to fulfil the information requirements for Annex IX substances in 2019 (aggregated at IUCLID section level), relates to Figure 8

	Study	Read-across	QSAR	WoE	Waiving	TP	Other	No info
carcinogenicity	2.8	11.9	0.6	2.4	7.4	0.0	3.2	71.8
toxicity to reproduction	24.1	46.3	0.9	1.4	21.8	0.3	4.7	0.4
developmental /teratogenicity	26.3	49.9	0.7	1.9	14.4	3.3	2.8	0.6
repeated dose toxicity (all routes)	40.2	51.7	0.5	1.2	2.0	0.4	3.6	0.4
genetic toxicity <i>in vivo</i>	17.7	27.3	0.3	2.1	4.8	0.4	2.3	45.1
genetic toxicity <i>in vitro</i>	59.8	36.3	0.8	1.3	0.9	0.0	0.4	0.4
skin sensitisation	45.2	40.4	1.5	2.4	6.5	0.0	3.6	0.4
skin corrosion - irritation	54.5	34.5	0.8	1.5	3.0	0.0	5.2	0.4
serious eye damage - eye irritation	50.5	33.6	0.9	1.8	6.3	0.0	6.6	0.4
acute toxicity (all routes)	59.8	33.8	0.6	1.2	1.3	0.0	2.9	0.4

basic toxicokinetics - dermal absorption	4.0	28.4	3.9	7.4	7.4	0.0	16.7	32.2
toxicity to aquatic algae and cyanobacteria	46.4	41.8	2.1	3.2	3.4	0.0	2.6	0.6
long-term toxicity to fish	5.0	13.9	4.6	1.8	71.6	0.6	2.0	0.5
long-term toxicity to aquatic invertebrates	16.1	29.7	3.3	2.1	45.0	0.8	2.5	0.5
short-term toxicity to fish	43.7	43.2	2.4	3.7	2.9	0.0	3.6	0.4
short-term toxicity to aquatic invertebrates	47.9	39.5	1.8	2.7	4.4	0.0	3.3	0.4
bioaccumulation	5.0	12.6	19.6	9.7	48.2	0.2	4.1	0.5

Table 12: Frequency of the different options to fulfil the information requirements for Annex IX substances in 2016 (aggregated at IUCLID section level), relates to Figure 9

	Study	Read-across	QSAR	WoE	Waiving	TP	Other	No info
carcinogenicity	2.6	12.1	0.5	2.2	8.6	0.0	3.1	71.0
toxicity to reproduction	22.1	46.5	1.0	1.9	22.9	0.7	4.1	0.8
developmental /teratogenicity	19.2	48.9	0.9	2.0	16.6	8.3	3.1	1.0
repeated dose toxicity (all routes)	37.1	52.7	0.7	1.7	2.3	0.8	4.0	0.7
genetic toxicity <i>in vivo</i>	16.4	27.4	0.4	1.8	4.7	1.1	2.3	46.1
genetic toxicity <i>in vitro</i>	59.6	35.3	1.2	1.8	1.1	0.0	0.3	0.7

skin sensitisation	44.6	40.2	1.9	2.4	7.1	0.0	3.2	0.7
skin corrosion - irritation	54.4	33.5	1.0	2.8	3.5	0.0	4.2	0.7
serious eye damage - eye irritation	50.3	33.3	1.1	2.4	6.7	0.0	5.6	0.7
acute toxicity (all routes)	60.2	32.3	0.8	1.3	1.4	0.0	3.2	0.7
basic toxicokinetics - dermal absorption	3.3	29.3	3.4	7.7	8.7	0.0	15.7	31.9
toxicity to aquatic algae and cyanobacteria	45.6	41.2	2.6	3.1	3.6	0.0	2.9	1.0
long-term toxicity to fish	3.6	13.3	3.2	1.0	75.2	0.9	2.0	0.9
long-term toxicity to aquatic invertebrates	13.0	28.8	2.2	1.6	48.5	1.9	3.0	0.9
short-term toxicity to fish	43.5	42.7	2.4	3.8	3.4	0.0	3.5	0.7
short-term toxicity to aquatic invertebrates	47.9	38.2	2.3	3.0	4.7	0.0	3.2	0.7
bioaccumulation	4.6	12.3	19.5	8.6	50.0	0.2	3.8	0.9

Table 13: Frequency of the different options to fulfil the information requirements for Annex VIII substances in 2019 (aggregated at IUCLID section level), relates to Figure 10

	Study	Read-across	QSAR	WoE	Waiving	TP	Other	No info
carcinogenicity	1.6	5.2	0.5	1.2	1.6	0.0	1.4	88.5
toxicity to reproduction	31.4	44.3	0.9	2.4	16.6	0.2	3.4	0.7
developmental /teratogenicity	12.5	29.9	0.5	2.0	3.5	0.8	2.0	48.8
repeated dose toxicity (all routes)	39.7	51.1	0.8	1.7	2.4	0.2	3.7	0.4
genetic toxicity <i>in vivo</i>	13.7	19.3	0.4	1.2	2.0	2.0	2.5	58.9
genetic toxicity <i>in vitro</i>	61.0	32.7	0.9	3.6	1.0	0.0	0.4	0.4
skin sensitisation	46.3	37.0	2.0	3.2	7.0	0.0	4.1	0.4
skin corrosion - irritation	55.7	31.9	1.1	1.6	3.1	0.0	6.2	0.4
serious eye damage - eye irritation	52.9	31.6	1.1	1.2	6.7	0.0	6.1	0.4
acute toxicity (all routes)	56.7	34.2	0.9	1.8	1.8	0.0	4.2	0.4
basic toxicokinetics - dermal absorption	2.1	16.6	2.7	5.2	5.9	0.0	25.1	42.4
toxicity to aquatic algae and cyanobacteria	46.4	36.9	3.1	2.9	6.5	0.0	2.5	1.7
long-term toxicity to fish	2.2	6.7	1.4	1.1	10.0	0.1	1.6	77.0

long-term toxicity to aquatic invertebrates	5.6	15.4	1.3	1.0	5.8	0.3	1.1	69.5
short-term toxicity to fish	44.2	39.8	3.9	3.5	4.4	0.0	3.7	0.4
short-term toxicity to aquatic invertebrates	49.9	36.3	2.5	3.5	4.8	0.0	2.6	0.4
bioaccumulation	3.3	7.2	11.0	4.0	8.7	0.1	2.0	63.7

Table 14: Frequency of the different options to fulfil the information requirements for Annex VII substances in 2019 (aggregated at IUCLID section level), relates to Figure 11

	Study	Read-across	QSAR	WoE	Waiving	TP	Other	No info
carcinogenicity	0.6	1.3	0.2	1.1	0.7	0.0	1.1	95.0
toxicity to reproduction	2.2	4.0	1.0	2.4	1.3	0.0	1.4	87.7
developmental /teratogenicity	2.0	2.9	0.5	1.0	0.9	0.0	1.3	91.4
repeated dose toxicity (all routes)	9.8	6.5	0.6	3.0	0.6	0.0	7.8	71.7
genetic toxicity <i>in vivo</i>	6.6	4.6	0.2	1.4	0.7	0.4	3.7	82.3
genetic toxicity <i>in vitro</i>	50.8	26.7	2.2	12.9	1.2	0.0	3.7	2.6
skin sensitisation	41.3	26.2	5.2	6.3	7.3	0.0	10.7	2.9
skin corrosion - irritation	48.1	25.5	2.9	5.2	3.3	0.0	12.5	2.6
serious eye damage - eye irritation	45.5	25.1	2.8	4.8	5.9	0.0	13.2	2.7

acute toxicity (all routes)	46.3	26.5	2.1	13.8	3.1	0.0	5.7	2.6
basic toxicokinetics - dermal absorption	0.4	2.0	0.4	2.3	0.8	0.0	9.6	84.5
toxicity to aquatic algae and cyanobacteria	42.2	24.5	6.1	5.3	8.4	0.0	7.3	6.2
long-term toxicity to fish	0.7	1.1	0.7	0.3	2.0	0.0	1.0	94.3
long-term toxicity to aquatic invertebrates	1.6	3.1	0.7	0.6	1.3	0.0	1.3	91.4
short-term toxicity to fish	14.7	8.6	2.4	4.1	1.2	0.0	8.9	60.0
short-term toxicity to aquatic invertebrates	45.2	26.5	5.7	6.0	5.0	0.0	9.0	2.6
bioaccumulation	1.4	1.7	5.2	4.5	2.6	0.0	1.1	83.5

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