ECHA
EUROPEAN CHEMICALS AGENCY

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

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

June 2023

The use of alternatives to testing on animals for the REACH Regulation. Fifth report under Article 117(3) of the REACH Regulation

Reference: ECHA-23-R-07-EN
ISBN: 978-92-9468-292-5
Cat. Number: ED-04-23-558-EN-N
DOI: 10.2823/805454
Date: June 2023
Language: English

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LIST OF ABBREVIATIONS

3Rs	Reduction, refinement, replacement of animal testing
AOP	Adverse Outcome Pathway
APCRA	Accelerating the Pace of Chemical Risk Assessment
CLP	Classification, Labelling and Packaging
CSS	Chemicals Strategy for Sustainability
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EPAA	European Partnership for Alternative Approaches to Animal Testing
EU	European Union
GD	OECD Guidance document
GHS	Globally Harmonised System of classification and labelling of chemicals
IATA	Integrated Approach to Testing and Assessment
IRS	Integrated Regulatory Strategy
IUCLID	International Uniform ChemicaL Information Database
MSC	Member State Committee
NAM	New Approach Methodologies
NGO	Non-Governmental Organisation
OECD	Organisation for Economic Cooperation and Development
PARC	Partnership for the Assessment of Risks from Chemicals
QAF	QSAR Assessment Framework
QSAR	Quantitative Structure-Activity Relationship
RAAF	Read-Across Assessment Framework
RAC	Committee for Risk Assessment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RDT	Repeated Dose Toxicity
TG	OECD Test Guideline
TP	Testing proposal
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drugs Administration
WoE	Weight of evidence

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FOREWORD

This is the fifth report on the use of alternative methods to animal testing that we present to the European Commission.

Since its entry into force in 2007, REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) is the EU's main regulatory framework on chemicals and has resulted in the largest knowledge base on chemicals globally. REACH ensures that industry provides adequate data, using as a last resort tests on animals, to assess chemicals' hazardous properties.

Together with the Classification, Labelling and Packaging (CLP) Regulation, it provides a horizontal framework for the management of risks to human health and the environment arising from the use of industrial chemicals.

The analysis of the REACH registration database confirms the findings reported in the previous edition of this report. Registrants continue using existing information and alternatives to avoid unnecessary animal testing.

While the current regulatory system achieves its main objectives - protecting human health and the environment, whilst ensuring that animal testing is done as a last resort - stakeholders and policymakers recognise the increasing expectations to accelerate the pace of replacing animal tests.

This increased expectation is demonstrated by the European Citizens' Initiative with 1.2 million signatures. This initiative urges prompt action from the European Commission to strengthen the ban on animal testing for EU cosmetics, modernise EU safety science, and revamp EU chemicals legislation by committing to an action plan to phase out animal testing.

Over the past twelve months, we have stepped up our efforts to better support scientific and regulatory developments that seek to replace the use of animal testing. This report highlights the progress made.

We are particularly proud of the work to effectively implement New Approach Methodologies (NAMs) to identify and address risks of chemicals of concern within the current regulatory context. We have invested in multiple international activities, particularly APCRA (Accelerating the Pace of Chemical Risk Assessment), PARC (Partnership for the Assessment of Risks from Chemicals) and OECD (Organisation for Economic Co-operation and Development) to enhance regulatory knowledge on how we can protect health and the environment and reduce our reliance on animal testing. Thanks to all this work, ECHA is ready to support the European Commission and other institutional partners for moving towards full replacement of animal testing. Furthermore, we provide advice to the Commission on the use of alternatives to replace animal testing in the context of the current REACH review. We are also exploring the potential of NAMs for defining information requirements for polymers.

As part of our commitment to promoting alternatives to animal tests, we are organising a workshop in 2023 to discuss how we can collectively work towards an animal free regulatory system for industrial chemicals. This event will bring together regulators, policy makers, scientists and stakeholders (industry, animal welfare NGOs, environmental NGOs). It is only by sharing our collective knowledge and expertise that we can move away from animal testing in the future.

We in ECHA look forward to contributing to regulatory and scientific understanding of how New Approach Methodologies can play their part in ensuring protection of our health and the environment.

Sharon McGuinness
Executive Director

EXECUTIVE 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. It is published in accordance with ECHA's obligations under Article 117(3) of the REACH Regulation.

Under the REACH Regulation, (EC) No 1907/2006, testing on vertebrate animals (e.g. rats, other mammals or fish) can only be used as a last resort to fulfil information requirements for registration.

REACH foresees several ways to avoid unnecessary animal testing. Data sharing and joint submission of information are the main principles behind the registration process which significantly reduce the need for animal testing. In addition, the regulation foresees the possibility to justify waiving of tests or use of adaptations to fulfil the information requirements. This report provides an update on the use and implementation of non-animal testing methods and testing strategies used by companies to meet the information requirements. At the same time, the report provides an overview of ECHA's activities to promote the development and use of alternatives and discusses opportunities and challenges in moving away from animal testing for the risk assessment of chemicals in a regulatory context.

The data presented follows a similar format compared to previous editions, covering the availability of experimental data, the options used to comply with information requirements, and the period when the studies were conducted. The cut-off date for data analysis for the purpose of this report has been set to 31 July 2022, three years after the previous edition.

For the first time, this report provides a separate data analysis of newly registered substances since the previous edition, covering the period from 2019 to 2022, after the final REACH registration deadline in 2018.

The key findings from the data analysis are:

- Overall, adaptations continue to be used by registrants more than experimental studies to fulfil the information requirements; read-across is the most frequent adaptation followed by waivers, weight of evidence and QSAR.
- The majority (53%) of the available experimental studies in the REACH database is legacy data generated before the entry into force of REACH.
- *In vitro* test methods are increasingly used in registration dossiers, especially for skin corrosion/irritation and serious eye damage/eye irritation and skin sensitisation. The significant shift from *in vivo* to *in vitro* approaches, reported in the previous edition, continues between 2019 and 2022. About 50% of the studies conducted since 1990 for skin and eye irritation available in the REACH database, are performed in vitro; this percentage rises to about 90% for the most recent studies performed over the last three years.
- Experimental studies are more often used for the low tier testing needed to meet the information requirements for low tonnage substances, while adaptations are more commonly used for the higher tier testing requirements of substances registered at higher tonnage bands.
- There is more data generated through animal testing to investigate long term effects when comparing to three years ago. This is mainly due to the requests made under compliance checks for further testing when non-compliant adaptations were provided. For example, there is more experimental data available for pre-natal developmental toxicity and (sub)chronic repeated dose toxicity.
- When possible, new studies aiming to investigate potential for long term effects are increasingly performed in a combined fashion, to reduce testing on animals. For example, repeated dose toxicity tests are increasingly combined with toxicity to reproduction screening.
- Data analysis for the newly registered substances, over the past three years, shows that the majority, about 70% of these substances, are in the lowest tonnage band (REACH Annex VII) and overall the use of *in vitro* test methods is substantial.

Over the years ECHA has been active in using and promoting the use of alternative methods to animal testing within its mandate. We use alternative methods whenever possible for regulating substances and provide advice and guidance to registrants. ECHA has been active in international collaborations aiming to develop alternative methods such as the initiative on Accelerating the Pace of Chemical Risk Assessment (APCRA), the European Partnership for the Assessment of Risks from Chemicals (PARC) and at the Organisation for Economic Co-operation and Development (OECD) level. In addition, ECHA facilitates the research and development on New Approach Methodologies (NAMs) by making registration data readily available to the wider regulatory and scientific community.

In the OECD context, significant progress has been made with ECHA contributing through several expert and advisory groups to the development of OECD test guidelines, guidance documents as well as the development of case studies. ECHA has also co-led the work to develop a QSAR assessment framework (QAF) establishing criteria to validate QSAR results and has been a co-lead in the steering group to update the OECD guidance on grouping of chemicals. The development and regulatory acceptance of the QSAR toolbox has also progressed (with more than 30 000 users from industry, authorities, and academia), reaching the milestone of being included in the OECD guideline on Defined Approaches on skin sensitisation (OECD TG 497).

Looking forward, ECHA recognises that the topic of replacement of animal testing is highly relevant in the current policy context. We stepped up efforts to contribute to the scientific debate while continuing to implement the regulatory frameworks adopted by the legislator.

New Approach Methodologies currently represent a priority area for ECHA. We provide access to crucial data required for their development. To support this process, ECHA is rebuilding its public dissemination system with a focus to facilitate the re-use of data. The Agency is also expected to play a central role in the EU Common Data Platform which will provide further opportunities in this area. Furthermore, ECHA continues investing in developing the QSAR toolbox to integrate new information. For example, ECHA continues to integrate and use data from various sources such as the contributions from the pharmaceutical industry and from the US Food and Drug Administration (FDA). This will facilitate comparison of animal data and human data and contribute to the development of NAMs and reduction of animal testing.

We are also building internal capacity on NAMs by organising training for ECHA's scientists and Committees (Member State Committee (MSC), Committee for Risk Assessment (RAC)) to increase the level of knowledge on NAMs suitable for regulatory needs.

We have increased co-operation through platforms such as the European Partnership for Alternative Approaches to Animal Testing (EPAA) and APCRA to raise awareness of on-going work and exploit potential synergies. We believe that this will support developing a common understanding on what NAMs can achieve in the short and long term.

Finally, we are playing a more visible and active role in the scientific/regulatory community by steering flagship research projects dedicated to NAMs via PARC or Horizon Europe.

Moving forward, we recognise that a full replacement of animal testing will require advancement in scientific developments as well as policy changes. In this shift, two key questions will need to be addressed: how a new approach can cover the most relevant (adverse) effects and diseases of concern for society (for example, carcinogenicity, mutagenicity, reproductive toxicity, immunotoxicity, endocrine disruption, etc.) and how to ensure a similar or better level of protection for human health and the environment.

Such fundamental changes ultimately represent policy options. ECHA has the competence and is ready to support policy makers in developing suitable and robust approaches for regulating chemicals based on an increased use of NAMs and eventually, phasing out animal testing.

USE OF ADAPTATIONS IN REACH REGISTRATION DOSSIERS

Under REACH, registrants are responsible for collecting and generating information on substances manufactured in, or imported into Europe, above one tonne per year, in order to properly assess the hazards and potential risks. This information is communicated to ECHA through a registration dossier. Information on the REACH registration statistics is regularly updated and made publicly available through the ECHA dissemination website[1].

This report describes the status of implementation and use of non-animal test methods by analysing the information on experimental studies and adaptations used to fulfil REACH information requirements for the endpoints required by REACH. For this report, the situation was analysed using data extracted from the REACH database on **31 July 2022.**

The data analysis is reported in two main sections. Section 1.1 analyses **all dossiers** submitted to ECHA until 31 July 2022 (i.e. over the period **2008 – 2022**), and section 1.2 analyses only dossiers submitted in the last three years for **newly registered substances**, i.e. substances first registered between **2019 and 2022**.

Each section includes the following three analyses (or data projections), the two first provide substance-centric information while the third analysis provides study-centric information:

1. Availability of experimental studies This analysis reports the **percentage of substances for which guideline studies** were used to fulfil the standard information requirements.
2. Options used to address the information requirements This analysis reports the **percentage of substances** using each option (e.g. experimental test, different types of adaptations, data waiver).[2]
3. Experimental study period This analysis reports the **number of experimental studies conducted before and after** the adoption of REACH.

Furthermore, certain endpoints for which recent changes in the legal text introduced non-animal test methods as standard information requirements, such as skin corrosion/irritation, serious eye damage/eye irritation and skin sensitisation, are analysed separately. The report contains key results of the data analysis, while more detailed information is included in the Annexes to this report.

Throughout this report, the following terms are frequently mentioned and are worth distinguishing at the outset: "adaptations" and "alternative (test) methods". The definition of these terms and the context of their use is more explicitly described in Annex 1. Briefly, adaptations refer to adaptations from the standard testing regime to fulfil the REACH information requirements, while alternative test methods are used as opposed to animal test methods.

1.1. Current status of registration data (2008-2022)

The number of substances included in the analysis of the whole REACH database is shown in Table 1. The substance dossiers analysed for this report included submissions of all qualifying registrations by the cut-off date 31 July 2022, (i.e. in the period 2008 – 2022). Substances were included in the analysis if by the cut-off date there has been at least one registration received under REACH that fulfilled the information requirements.

1 https://echa.europa.eu/registration-statistics

2 The options used to fulfil the information requirements are described in Annex 1 to this report.

The section "Dossier and substance selection" (see Annex 1) to this report describes in detail the registrations in scope of this report.

REACH Annex	Number of substances
VII	4901
VIII	2857
IX	2346
X	2335
Total	**12439**

TABLE 1: Number of substances registered for each of the REACH Annexes (VII – X) which define the standard information requirements (cut-off dates of 31 July 2022).

1.1.1. Availability of experimental studies

This section gives an overview of the availability of experimental study results, whilst Annexes 1 to 3 to this report provide additional details. An important part of the analysis is based on the availability of experimental studies conducted with the registered substance according to one of the acceptable guideline methods to fulfil the corresponding information requirement. The absence of such a study means that an adaptation has been used to fulfil the information requirement. However, an experimental study is not necessarily a test on animals, as the information requirement for certain endpoints asks for *in vitro* testing, which are also considered to be experimental studies.

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

Data analysis shows that the **endpoints with the highest percentage of guideline studies correspond typically to low tier endpoints**[3]: genetic toxicity *in vitro*, acute toxicity and short-term toxicity to aquatic invertebrates. **For high tier endpoints, there is a higher percentage of substances using adaptations to fulfil the information requirements.** This demonstrates that indeed, registrants consider animal testing as a last resort. Whenever possible, they follow a tiered testing strategy which results in fewer studies on animals for higher tier endpoints. This is in line with the requirements and the overall goal of REACH and other policy objectives to reduce animal testing.

In general, no significant change is noted from the data analysis for experimental studies since the last article 117(3) report three years ago[4]. An analysis of the trend in the data availability was performed to quantify the difference in the percentage of substances for which guideline studies were used to fulfil the standard information requirements since the last edition. The data is provided in Annex 2 to this report. A slight increase in the proportion of experimental studies in the last three years has been observed. However, that is due partly to an improvement in ECHA's tools to identify the test material more reliably in the registration dossiers which allows more precise identification of the experimental studies and thus improved data analysis, as further detailed in Annex 1 to this report.

Furthermore, the following observations were made:

3 The definition of low- and high-tier endpoints is consistent with the previous editions of this report

4 https://echa.europa.eu/documents/10162/0/alternatives_test_animals_2020_en.pdf

First, **for skin sensitisation, skin corrosion/irritation and serious eye damage/eye irritation, the significant shift observed from 2016 to 2019 from in vivo to in vitro approaches reported in the previous edition, is substantiated in the current database.** Indeed, the difference in the percentage of substances for *in vitro* studies at Annex VII are respectively 4.7, 7.7 and 8.1%, as shown in Figure A 2. A slight increase of the percentage of substances with *in vivo* studies for skin sensitisation, however, was also observed. It is between 4.1 and 6.2% depending on the tonnage of the substances. For skin corrosion/irritation, the increase is not significant, it is between 0.7 to 2.8%. The same applies for serious eye damage/eye irritation where the increase is between 1.4 and 3%. A **manual spot check for *in vivo* skin sensitisation** studies was performed to understand the reasons and justifications to perform these studies. It was observed that the registrants justified *in vivo* studies mainly because i) the *in vitro* study was not possible due to the physico-chemical properties of the test substance (e.g., low solubility, metal), and ii) the in vitro results were inconclusive for classification and *in vivo* study information was necessary to fulfil the information requirement for the skin sensitisation endpoint. No manual spot check for *in vivo* skin corrosion/irritation and serious eye damage/eye irritation was performed as the increase in *in vivo* studies is not significant.

Second, an **increase in the percentage of substances with experimental studies for pre-natal developmental toxicity and (sub)chronic repeated dose for REACH Annex IX and X substances** (up to +7.9% and +6.6%, respectively, for Annex IX substances) is observed, which is likely related to the decisions ECHA has taken in compliance checks and testing proposals on these endpoints and the subsequent submission of the studies requested[5]. There is also an indication of an increase of experimental studies (+3.7%) at Annex VIII for OECD Test Guideline 422: *Combined repeated dose toxicity with the reproduction/developmental toxicity screening test.*

Annex 2 to this report provides the data related to the availability of experimental studies.

1.1.2. Options used to address the information requirements

The different options to fulfil the information requirements considered in this analysis, are:

1. Experimental study
2. Read-across/category
3. Quantitative structure–activity relationship (QSAR)
4. Weight of evidence (WoE)
5. Data waiver
6. Testing proposal (TP)
7. Other
8. No requirement[6].

The definition of the various options and the approach taken for the analysis are provided in the previous editions of this report and are also mentioned in the Annexes of this edition. Adaptations to information requirements include read-across and grouping, QSAR, WoE and waivers. Registrants also have the option to combine approaches for fulfilling the information requirements in a weight of evidence approach. For example, a read-across can be combined with QSAR predictions. In all cases, the data used must be adequate, reliable, and relevant for each particular endpoint, and must follow the criteria set out in REACH Annex XI. For the purposes of this analysis we used a cascade of rules to derive a single option for a given dossier and IUCLID section. The algorithmic details are the same as given in the previous reports and are explained in the Annexes to this report.

5 Article 54 of REACH provides the statistics on the progress in dossier and substance evaluation. https://echa.europa.eu/progress-in-dossier-evaluation

6 This category denotes the absence of a mandatory information requirement by default. Most commonly this reflects that providing information for the endpoint is not required and therefore only provided if data is available. Another reason for this category is that the endpoint is part of an integrated testing strategy, and the test requirement depends on the outcome of other tests. This category was labelled no information in the previous editions, and was modified for clarity and upon request of the report readers.

Data were aggregated at IUCLID section level[7], from all processed dossiers regardless of the tonnage band. Figure 1 shows the options used by registrants to fulfil the information requirements, whereas Figure 2 provides the breakdown per REACH Annex of the options used.

Experimental studies carried out according to specific test guidelines outlined in the REACH Annexes were available for about 30.9% of cases[8]. Adaptations were submitted in 32.7% of cases. **Read-across was the most commonly used adaptation** (22.8%), where information on a substance is used to predict the properties of another similar substance. The other most commonly used adaptations are: data waiving, 7.1% (i.e. justifications for omitting data); weight of evidence 4.1% (i.e. combining information from different sources) and QSARs, 2.8% (i.e. predicting properties using computer models).

Overall, adaptations continue to be used more than guideline studies although it may appear to be less than reported previously. This is due to the improvement mentioned earlier and described in more detail in the annexes. This technical improvement of ECHA data mining tools to identify the test material in the registration dossiers resulted in an apparent increase in the type of information identified as experimental (+3.8) and decrease in read-across (-2.3) and the category "other" (-1.5), when compared to 2019.

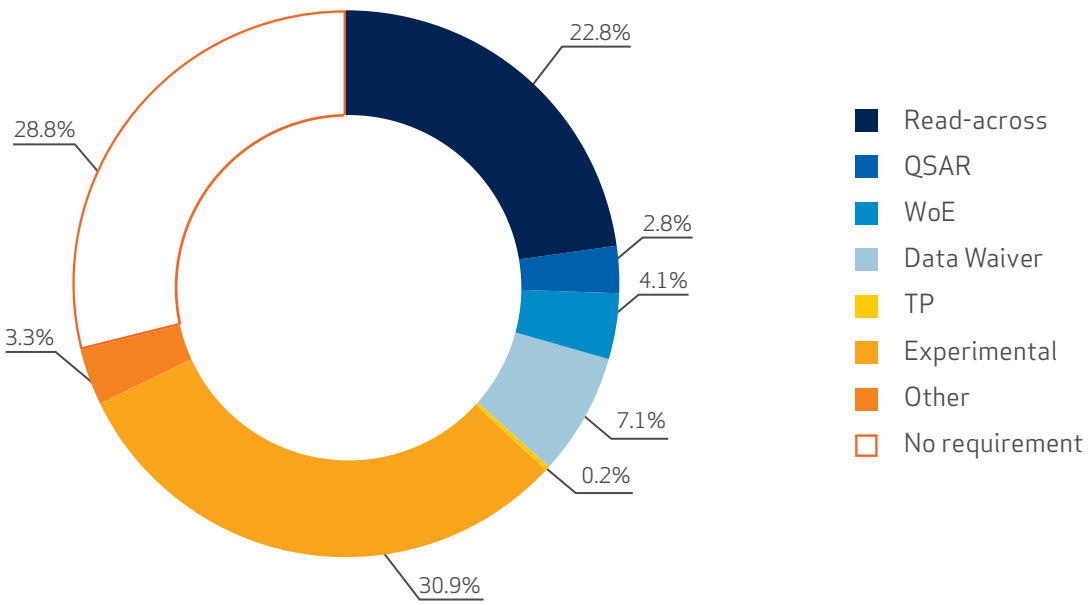

FIGURE 1: Options used to fulfil the information requirements

Figure 2 displays the breakdown per REACH Annex of the options used by registrants to fulfil the information requirements. It shows that when additional information is required at higher tonnage bands (i.e. reduced "No requirement" category percentage), **registrants gradually use more adaptations**. The cumulative percentage of the read-across, QSAR, WoE and Data Waiver options, changes from about 20% at Annex VII, to 35.3% at Annex VIII, 50.1% at Annex IX and 59.4% at Annex X. The percentage of experimental studies are 25.4%, 33.9%, 36.5% and 33.0% at Annexes VII to X respectively.

7 Section levels reflect the organisation of study records within IUCLID based on the REACH Annexes, e.g. IUCLID section 6.1.1 contains information on Short-term toxicity to fish, that corresponds to section 9.1.3 of REACH Annex VIII.

8 This means that on average, taking into account all IUCLID sections, and considering all the registered substances at all Annexes, 30.9% of the 12439 substances used an experimental study to fulfil the information requirement.

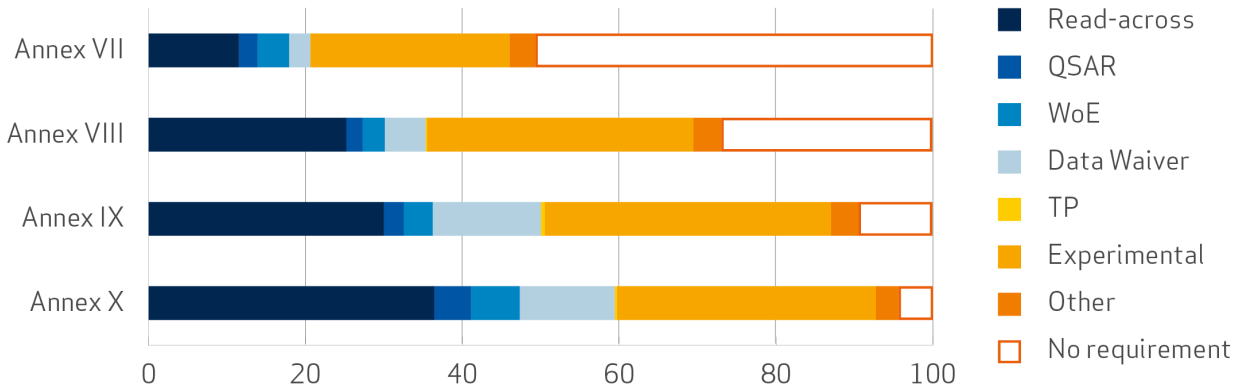

FIGURE 2: Options used to fulfil the information requirements (breakdown per REACH Annex)

The frequency of the different options to fulfil information requirements per endpoint, aggregated at the IUCLID section level and for all REACH Annexes, are shown in "Figure 3". For completeness, the breakdown per REACH Annex is provided in "Figure A 3" to "Figure A 6", together with a detailed technical description of the data extraction, data processing and graph explanation.

"Figure 3" shows that **acute toxicity has the highest proportion of experimental data in comparison to other lower tier endpoints requiring testing on vertebrate animals, with more than 50 % of substances covered by reliable guideline studies (Klimisch score 1 or 2)**.

Repeated Dose Toxicity (RDT) is the high tier endpoint for which most guideline studies are available, with an equivalent proportion of adaptations (approximately 30% each).

Waiving is used as the most frequent adaptation for long-term toxicity to fish, long-term toxicity to invertebrates and also bioaccumulation. This suggests that information on short-term aquatic toxicity and long-term toxicity for non-vertebrate species has often been considered by registrants sufficient to carry out a chemical safety assessment. A Board of Appeal decision in 2020[9] clarified that studies pertaining to long-term toxicity to aquatic organisms is not triggered by the chemical safety assessment but is a standard information requirement for Annex IX and Annex X substances, which limits the waiving possibilities perceived by some registrants. Data waiving for long-term toxicity to aquatic organisms is indeed used less for newly registered substances (see chapter 1.2). For bioaccumulation, information is required for Annex IX and X substances but can be waived for substances that have a low potential for bioaccumulation (e.g. based on a low octanol/water partition coefficient (logKow), or a low potential to cross biological membranes).

The analysis in this section takes into account the evolution of the whole registration database. Changes in how registrants fulfil the information requirements are caused by both newly registered substances and dossier updates of existing registrations. The latter include spontaneous updates and requested updates following a Compliance Check or Testing Proposal evaluation.

An assessment as to the quality of the information submitted by registrants is not discussed in this report. However, experience from evaluation indicates that 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 and deficiencies have been described and discussed in the previous editions of this report[10].

9 Case number A-011-2018, https://echa.europa.eu/documents/10162/32082059-2870-0322-e26d-b1630c2cc6da

10 https://echa.europa.eu/report-archive-specific-reports

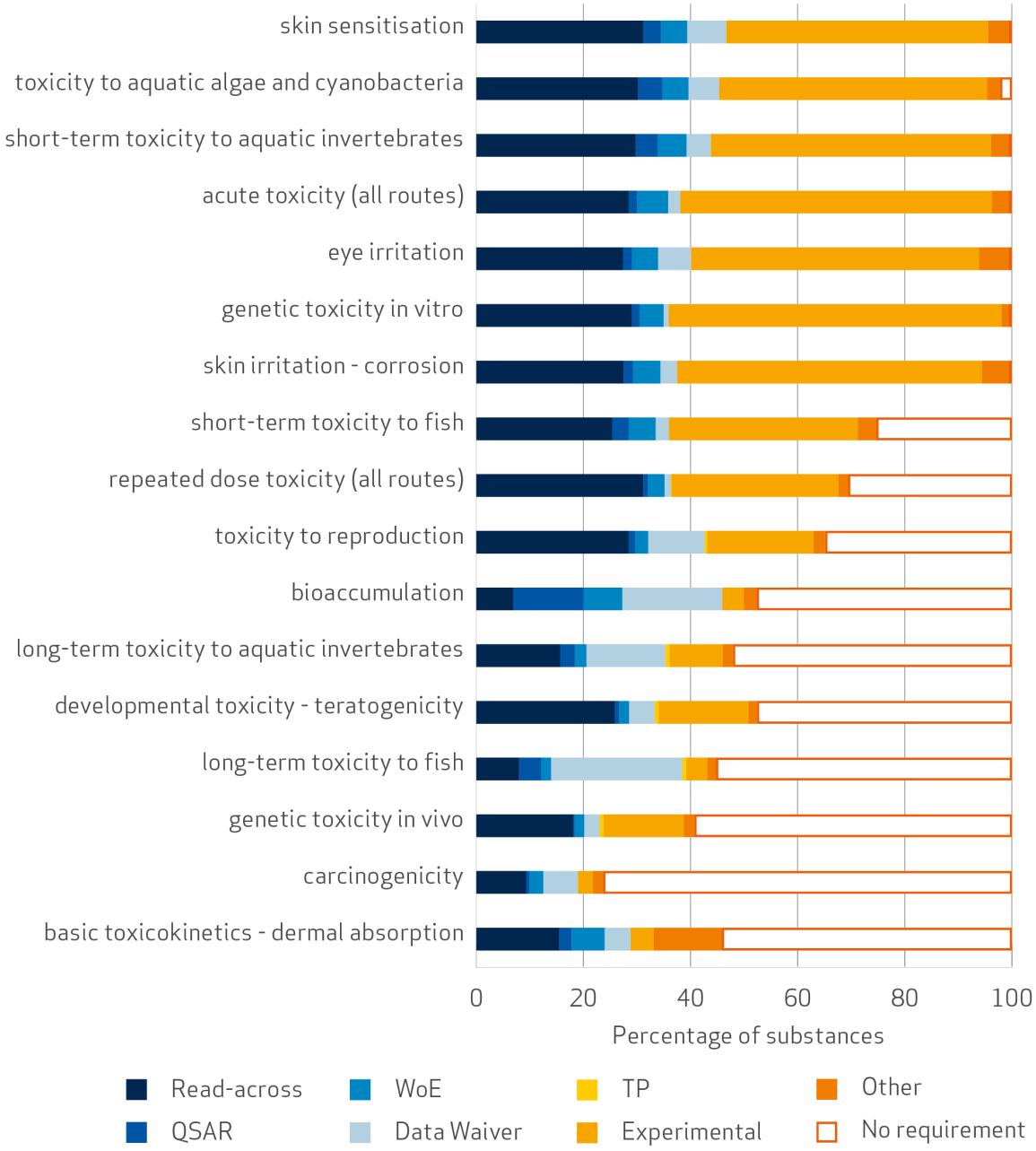

FIGURE 3: Frequency of the different options to fulfil the information requirements for the 12439 substances within the scope of this report (aggregated at IUCLID section level)

1.1.3. Experimental studies period

Information on the experimental studies available in the REACH database and the time they were conducted (pre- or post- REACH, cut-off date 2009) is provided. The analysis assumes that studies conducted as of 2009 have been motivated by the REACH information requirements. However, other drivers such as other (global) legislative requirements cannot be excluded.

The number of experimental studies available in the REACH database in July 2022 is shown in "Figure 4". Each bar represents the total number of experimental studies available for a specific endpoint. The grey portion represents existing studies from before 2009 that are considered legacy data. The blue portion of the bar represents the

studies generated after 2009 and thus assumed to be primarily triggered by REACH. It is important to note that there are technical limitations to establish the uniqueness of experimental studies. The limitations of the algorithm used have been described in the previous edition of this report.

A first major observation is that overall, **more than half of the available experimental studies in the REACH database were conducted before the entry into force of REACH (53%)**. This shows clearly that REACH has brought transparency and availability to an enormous collection of existing experimental studies. In particular, as shown in "Figure 4", most of the acute toxicity (70%), in vivo skin irritation/corrosion (85%), serious eye damage/eye irritation (79%) and skin sensitisation studies (58%) were performed before REACH. For high tier human health endpoint studies, the percentages of legacy data are also high, they represent 65% of (sub)chronic repeated dose toxicity studies, 61% of toxicity to reproduction, and 52% of developmental toxicity studies.

When information gaps have been identified to ensure safe use, REACH has stimulated additional testing where no other options were available. For high tier human health endpoint studies, REACH has been the driver for the generation of safety data. However, reduction possibilities are available and applied. Indeed, when new studies are required for repeated dose toxicity (OECD 407) and toxicity to reproduction screening (OECD 421), **these are increasingly performed using the *combined repeated dose toxicity study with the reproduction/developmental toxicity screening test* (OECD 422).**

Also, **REACH has driven changes in assessing aquatic toxicity by shifting away from short-term fish toxicity studies**. Before REACH, short-term aquatic toxicity was predominately assessed with fish, while after 2009, aquatic toxicity is predominantly assessed using aquatic invertebrates, such as daphnids, as well as algae.

The regulatory changes introduced by **REACH have also driven the use of in vitro test methods for the endpoints skin corrosion/irritation, serious eye damage/eye irritation and sensitisation tests.**

"Figure 5"zooms in on the endpoints skin corrosion/irritation, serious eye damage/eye irritation and skin sensitisation, showing the occurrence of both *in vivo* and *in vitro* studies for these specific endpoints. It is clear that for these endpoints, *in vivo* legacy data, existing before REACH, is widely available in registration dossiers, while *in vitro* data is scarcer. ***In vitro* studies have been primarily generated under REACH.** In general, for the data generated under REACH, *in vitro* studies are used more often than *in vivo*, except for skin sensitisation for which *in vivo* studies continue to be conducted. For this specific endpoint, the REACH information requirements amendment entered into force in May 2017, i.e. just before the last REACH registration deadline, which specifies that testing should start with *in vitro* methods (covering three key events as described in the adverse outcome pathway[11]). 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. An in-depth analysis of the whole database in 2019 was provided in the previous edition, and the conclusions are confirmed with the analysis of the current status of the database. In general, the registrants are using *in vitro* methods where possible, as required under the REACH regulation.

11 OECD (2012). The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins. OECD Environment, Health and Safety Publications Series on Testing and Assessment 168.

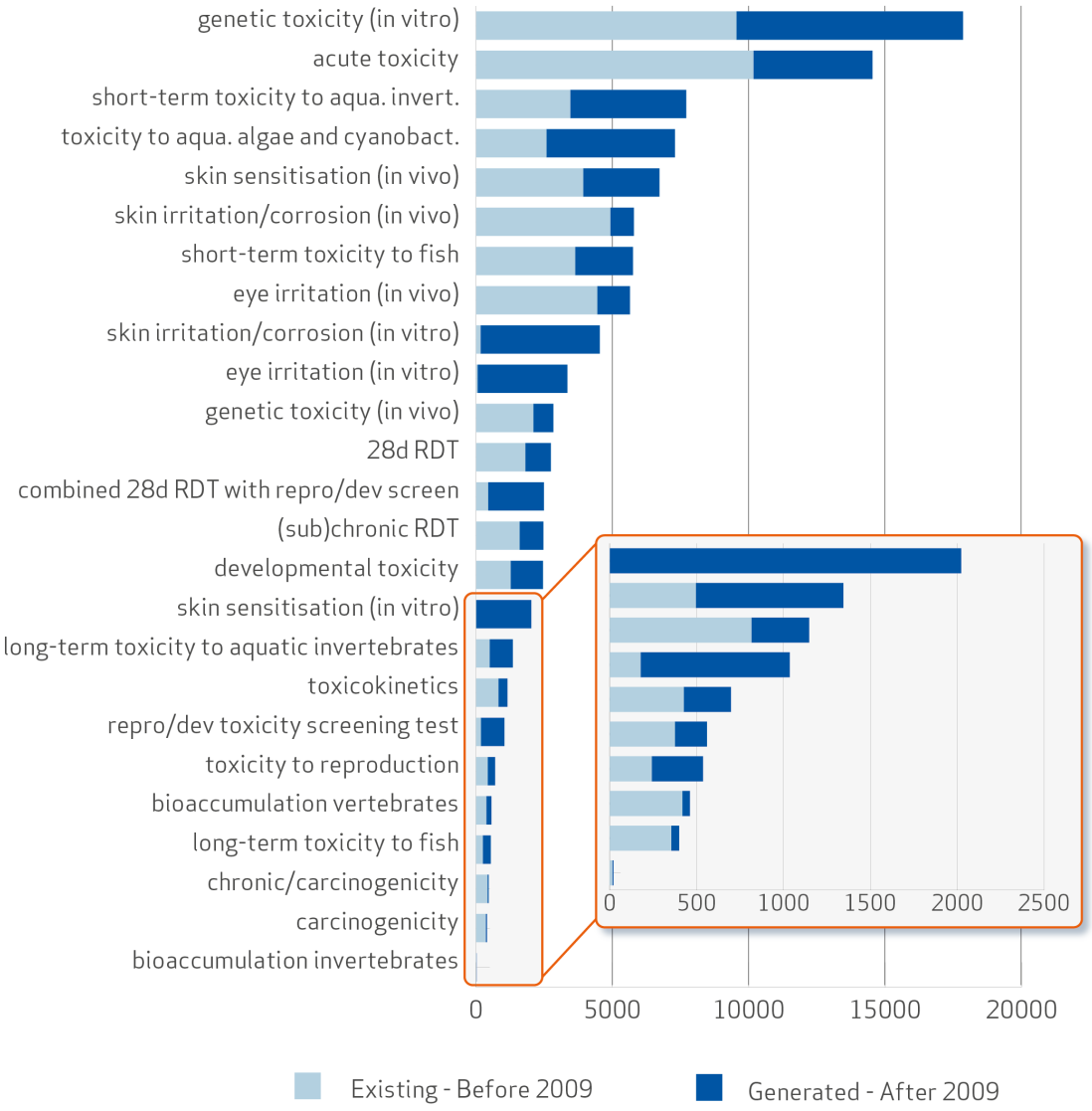

FIGURE 4: Number of unique experimental studies per information requirement partitioned according to the study period (before/after 2009).

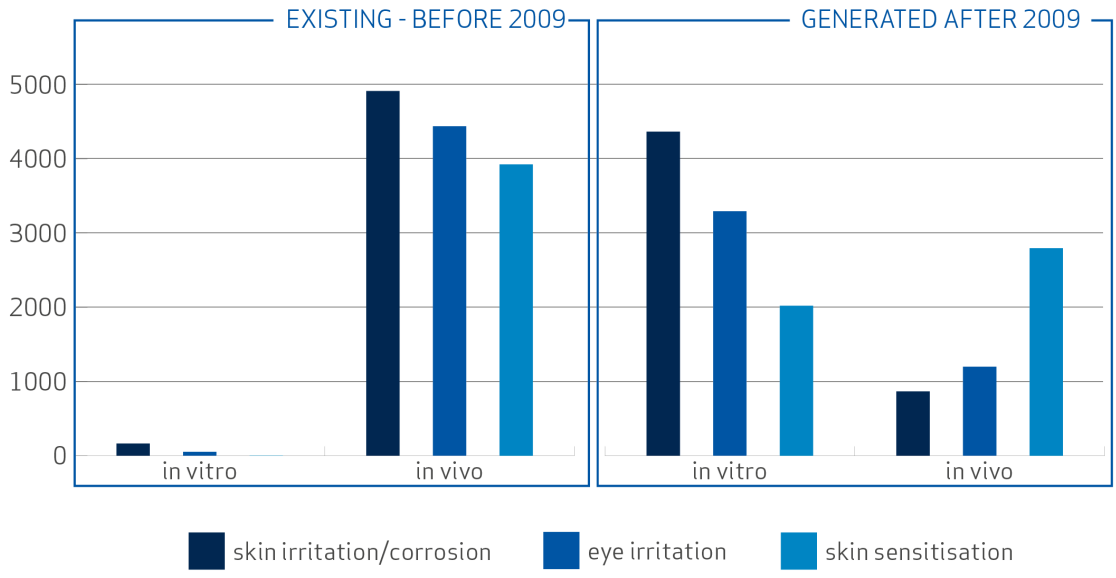

FIGURE 5: Number of unique in vivo/vitro experimental studies for skin irritation/corrosion, eye irritation and skin sensitisation, partitioned according to the study period (before/after 2009).

1.2. Newly registered substances (2019 - 2022)

In 2018, after the final REACH registration deadline for phase-in substances, ECHA obtained information for all existing substances present on the EU market in quantities of 1 tonne per year or more. The previous edition of this report provided a comprehensive review of the status of the use of alternative methods and testing strategies for industrial chemicals in the EU. Since there were no major REACH amendments[12] or a new registration deadline, it was anticipated that the information in the REACH database will remain relatively stable since the last registration deadline. This is confirmed as shown in the previous chapter. For this edition of the report, additionally we also analysed the hazard data in registrations of **substances that were registered for the first time over the three years since the previous edition[13], i.e. between 2019 and 2022**. This data provides a unique opportunity to inform on the practices registrants adopt to fulfil the information requirements, after 15 years of REACH. Therefore, this report includes for the first time an additional analysis of the newly registered substances over the last three years, following the last REACH registration deadline in 2018.

Table 2 shows the number of substances registered between 1 August 2019 and 31 July 2022. On average, about 300 new substances are brought to the EU market every year[14], most of them, about 85%, are manufactured or imported in quantities below 100 tonnes a year (Annex VII and VIII substances) and less than 5% are manufactured or imported at more than 1000 tonnes per year (REACH Annex X substances).

REACH Annex	Number of NEW substances
VII	624
VIII	149
IX	72
X	44
Total	**889**

TABLE 2: Number of new substances, registered between 2019 and 2022.

The analysis of the newly registered substances was performed in the same manner as for the whole database and are briefly presented below.

1.2.1. Availability of experimental studies

Experimental studies carried out according to specific test guidelines outlined in the REACH Annexes were available for about 31% of cases. This is consistent with the percentage in the whole database. The "No requirement" category, that indicates the absence of information, is much higher for the newly registered substances, mainly due to the prevalence of Annex VII substances (about 70%) in scope of this analysis, where the information requirements are limited. The same reasoning applies for the use of adaptations, that are lower than the average for the whole database, but still with read-across being the most frequent option. The use of QSAR, WoE and data waivers follows a similar pattern for new registrations as for the whole database.

12 Since 2020, new provisions were introduced to complement the registration requirements for nanoforms, but given the change is very recent, information on nanoforms was not separately considered in this report.

13 In practice, the analysis looks into new registrations for substances that before were either not registered or the registration was not in the scope of the report (e.g. previously registered as an onsite isolated intermediate or transported isolated intermediate below 1000 tonnes/year, but that are now registered for 1-10 tonnes).

14 There are also newly registered substances that do not require hazard information as they are only registered as intermediates, that are not included in this analysis.

1.2.2. Options used to address information requirements

Looking at the higher tonnage bands, we also observe a reduced use of adaptations at Annex IX. However, caution should be used since these observations are based on a small number of substances (72 substances newly registered according to Annex IX) in comparison overall to the 12 439 substances in the whole REACH database, which is the main scope of this report.

The frequency of the different options to fulfil the information requirements per endpoint, aggregated at the IUCLID section level and for all Annexes, are shown in "Figure 8". For completeness, the breakdown per REACH tonnage band is provided in Annex 2 to this report. "Figure 8" shows that for the low tier endpoints, e.g. genetic toxicity *in vitro*, acute toxicity and short-term toxicity to aquatic invertebrates, more experimental studies are being used than adaptions for information requirements under Annex VII. On the contrary, for high-tier endpoints that usually correspond to higher tonnage bands, the category "no requirement" is predominant since only a small proportion of substances are registered at Annexes VIII, IX and X.

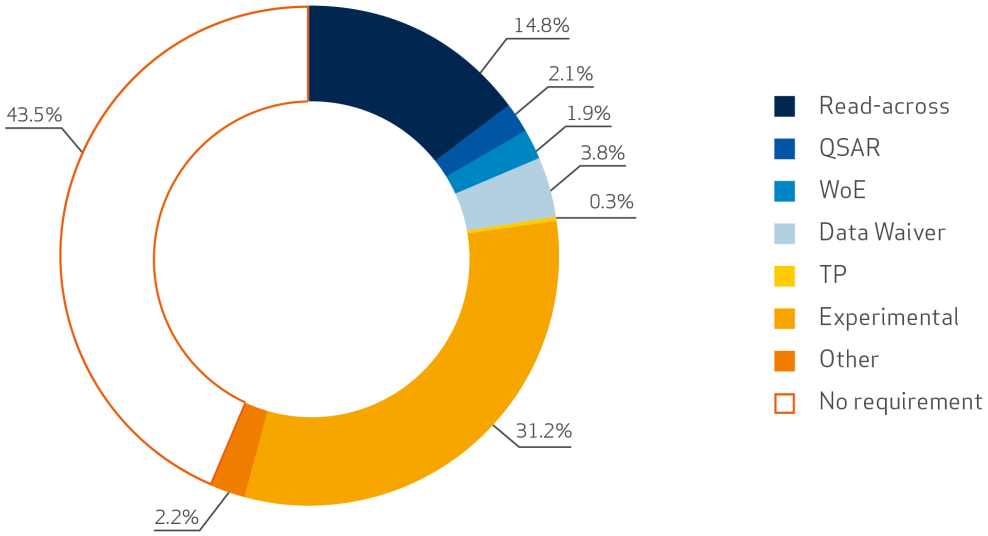

FIGURE 6: Options used to fulfil the information requirements for newly registered substances.

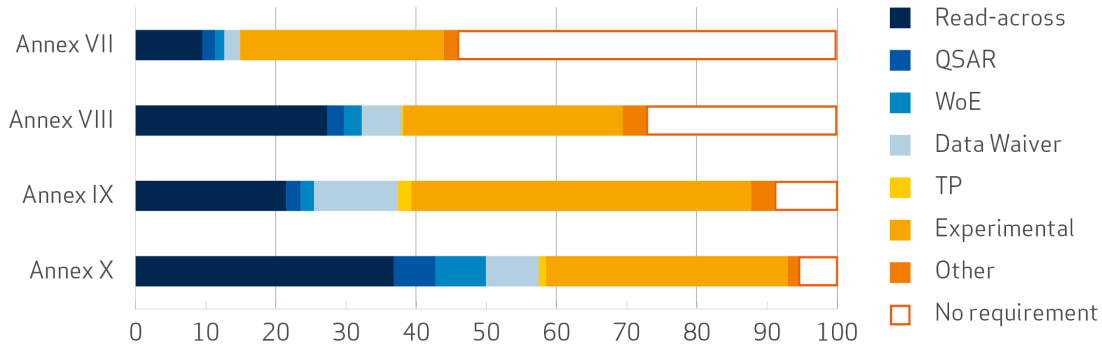

FIGURE 7: Options used to fulfil the information requirements for newly registered substances (breakdown per REACH Annex).

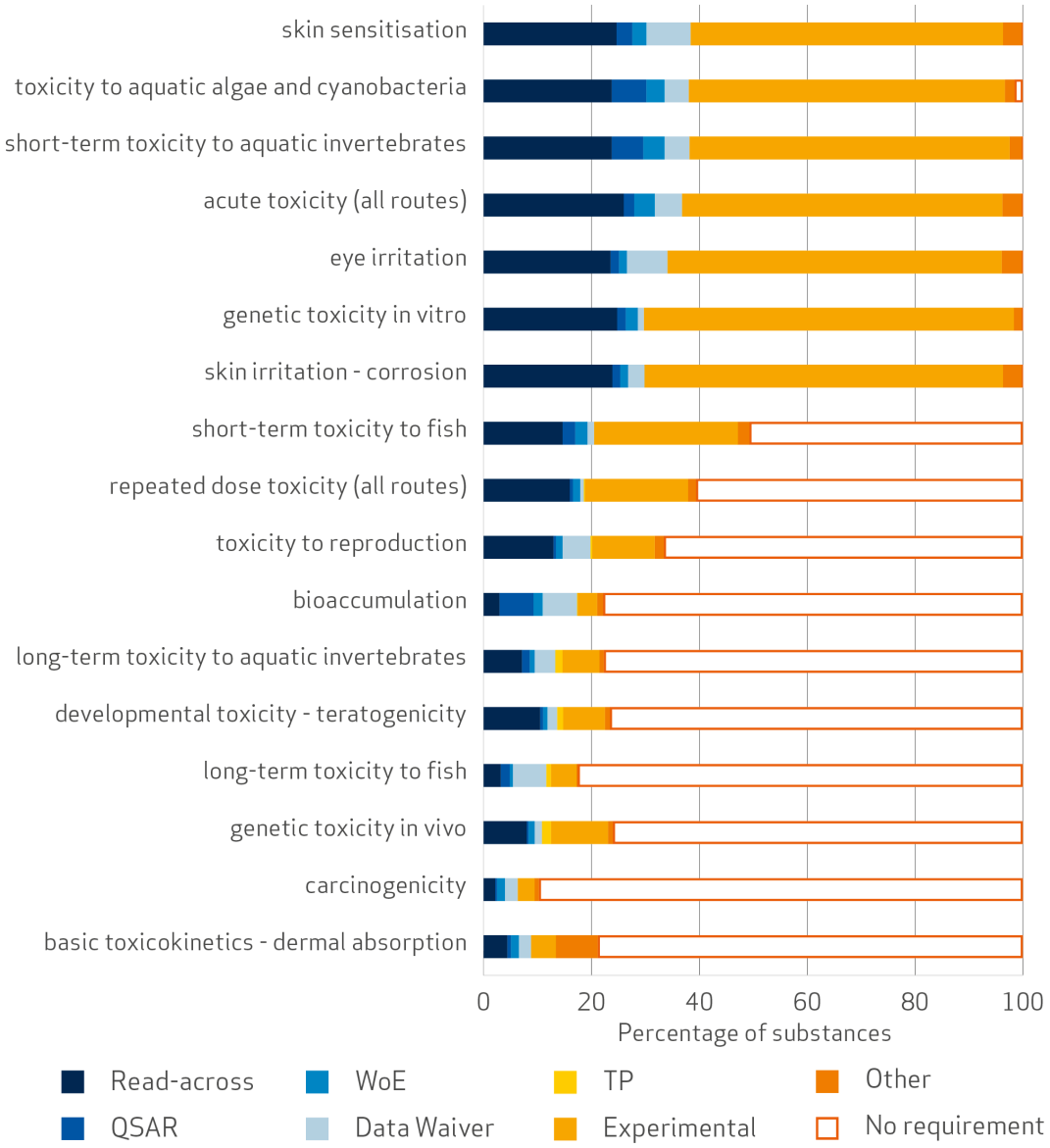

FIGURE 8: Frequency of the different options to fulfil the information requirements for the 889 newly registered substances in the last three years (aggregated at IUCLID section level)

1.2.3. Experimental studies period

The analysis of the studies available in the REACH database for the newly registered substances is summarised in "Figure 9". Each bar represents the total number of studies available for a specific endpoint. Similar to "Figure 4", the grey portion represents existing studies and the blue studies generated after 2009.

A first major observation is the **significant availability of *in vitro* experimental studies** for the three endpoints skin irritation/corrosion, serious eye damage/eye irritation and skin sensitisation. These studies are exclusively triggered by REACH, i.e. new studies conducted after 2009. Even so, *in vivo* studies have been submitted for these endpoints, although for skin irritation/corrosion, serious eye damage/eye irritation the majority of in vivo studies derived from legacy data. Only for skin sensitisation were there more new studies reported than already existing studies.

For the specific endpoint of **skin sensitisation**, the findings already reported in the previous edition were confirmed. The registrants are correctly following the testing strategy as laid down in the REACH regulation i.e.

testing needs to start with *in vitro* methods and only in case the substance is not suitable for *in vitro* methods or the results cannot be used for classification, can an *in vivo* test then be performed.

Furthermore, "Figure 9" also indicates that the proportion of fish studies to assess short term aquatic toxicity is further decreasing. The overall number of fish studies to assess long-term aquatic toxicity and bioaccumulation is very low compared to other endpoints.

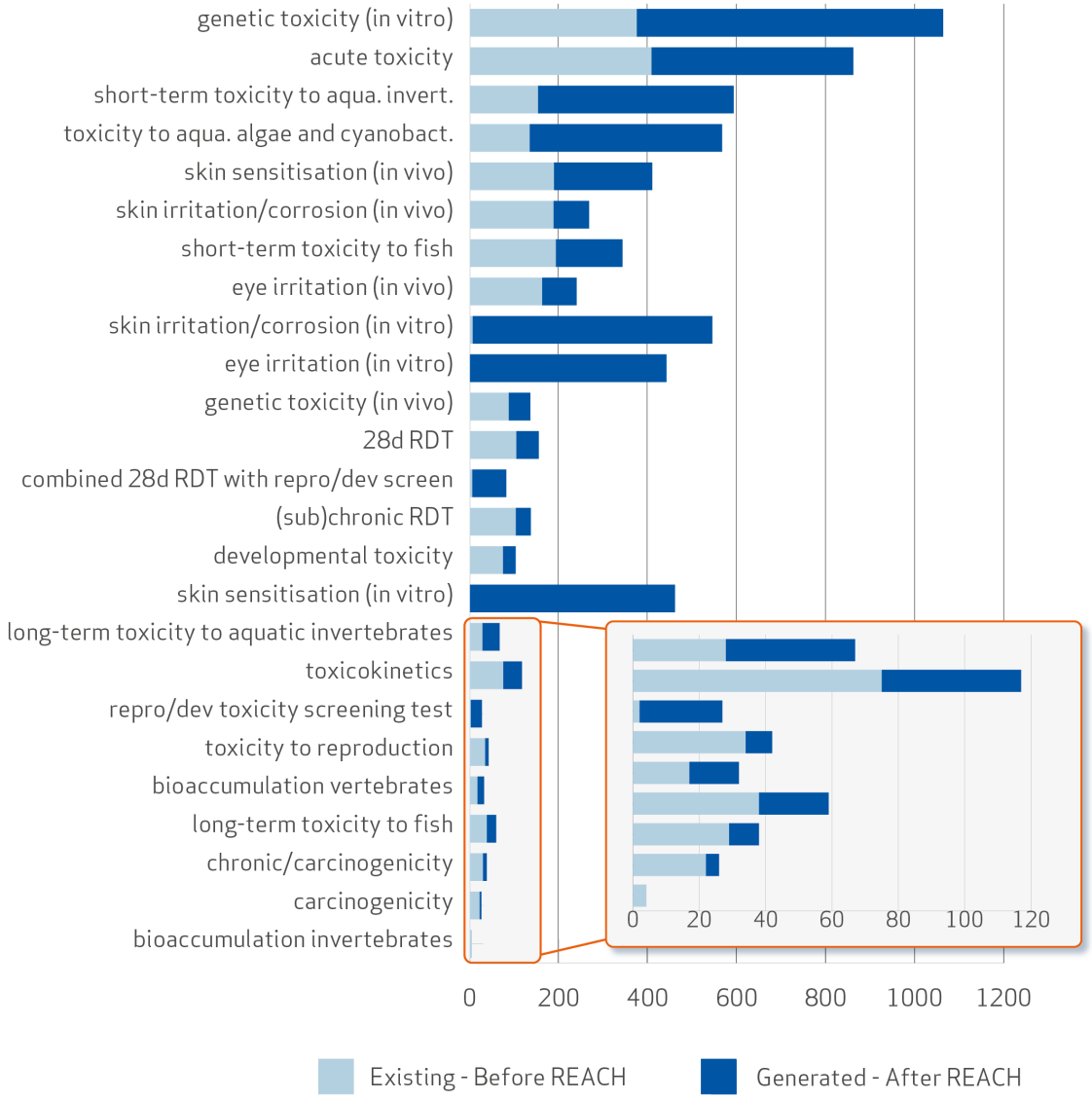

FIGURE 9: Number of unique experimental studies per information requirement partitioned according to the study period (before/after 2009) for substances newly registered in the last three years. The endpoints are ordered as in Figure 4.

1.3. A detailed view on study period

The time (exact year) when *in vivo* and *in vitro* studies were conducted for the three endpoints **skin irritation/corrosion, serious eye damage/eye irritation and skin sensitisation** is provided in Table 4 of Annex 3. The table shows the occurrence of the tests over the years 1990- 2022.

In brief, the data provided in "Table 4" shows that of all studies in the REACH database, conducted between 1990 and 2022, and performed to fulfil the information requirement for skin irritation/corrosion, about half

were performed in vitro (55.4%). This percentage increases drastically to about 9 out of 10 (88.6%) for studies performed in the last 3 years (2019 - 2022).

The same trend applies to serious eye damage/eye irritation with an increase from 48.4% (all studies in the database) to 89.9% (2019 - 2022).

For skin sensitisation, the trend is similar as regards seeing an increase of *in vitro* studies, however, when taking into consideration all the studies available in the whole REACH database, only a quarter were performed *in vitro* (25.6%) for this endpoint between 1990 and 2022. Notably, the percentage increases substantially to about 3 quarters (74.4%) for studies performed in the last 3 years (2019 - 2022).

These findings are derived from "Table 4" of Annex 3 and summarised in "Figure 10".

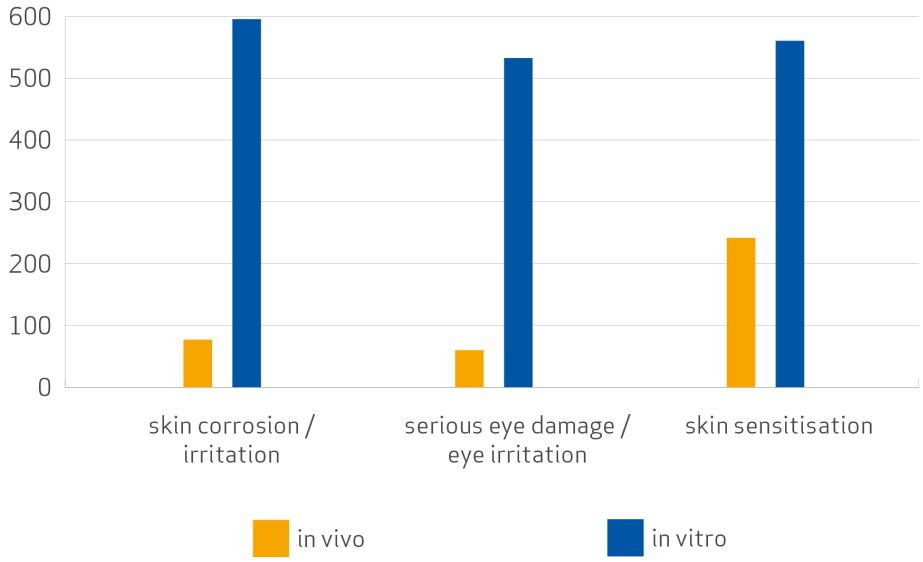

FIGURE 10: Occurrence of studies over the years 2019- 2022

1.4. Summary of data analysis

The analysis of the REACH registration database presented here includes information on the use of adaptations to fulfil information requirements and on the availability of experimental studies, and provides answers to the following key questions:

What are the most commonly used adaptations?

For all endpoints where animal testing is or was the standard requirement, the registrants applied in most cases other means to fulfil these requirements other than by using experimental tests, except for acute toxicity, where for about 60% of the substances, an *in vivo* testing approach was used (mostly for studies conducted before 2009). A similar picture was observed in the previous editions of this report.

For the more complex, higher tier endpoints, read-across is the preferred option to meet the information requirements, followed by data waiving, WoE and QSARs.

Which options are used in the registration dossiers to fulfil the information requirements for the different REACH Annexes?

There is no significant difference between the type of adaptations applied by registrants across the different Annexes. The only exception is at Annex VII where the weight of evidence adaptation is slightly more frequently used. An additional difference among the Annexes is that the overall percentage of adaptations increases correlatively with the tonnage band, and is highest for substances produced or imported above 1000 tonnes per year and lowest for substances produced or imported at 1-10 tonnes per year.

What is the overall situation for the endpoints where non-animal test methods have been introduced as standard information requirement?

There is a consistent and clear trend towards the use of non-animal methods for endpoints where alternatives have been already introduced as standard information requirements. In such cases the proportion of newly performed *in vivo* tests are seen to rapidly decrease. However even when a full replacement method is available, *in vivo* tests are still performed and submitted as in certain cases it is not possible to conduct studies according to the new methods or the results of the new methods are inconclusive. Registrants have justified the performance of *in vivo* tests mainly with the testability limitations and applicability domains of the newly introduced *in vitro* methods. The possibility of *in vivo* studies performed to fulfil a regulatory requirement outside the EU also exists, but the extent to which this is the case has not been analysed further.

What is the status of the low tier endpoints?

For low-tier endpoints, experimental data are more often used than adaptations to fulfil information requirements. However, at Annex VII, the only standard information requirement that still relies exclusively on animal testing is acute oral toxicity, which does not contribute significantly to the overall number of animals used to ensure safety within REACH.

What is the status of the high tier endpoints?

Registrants of substances at the high tonnage bands continue to follow the requirement of replacement and reduction of animal testing by choosing various adaptations, starting with read-across as the preferred option. However, it must be noted (besides the observed artefacts) that the percentage of experimental data is slowly growing over the years; this is due to the low quality of adaptations (especially read-across) submitted which are subsequently replaced by experimental data as a result of compliance check decisions. This trend might persist in the upcoming years.

What are the most noticeable observations or changes for the newly registered substances?

The overall pattern of adaptations is consistent with what was observed for the whole REACH database, with read-across as the most frequently used adaptation, followed by data waivers, weight of evidence and QSAR. The overall percentage of experimental data in newly submitted dossiers is significantly higher than in the whole database and consequently the percentage of adaptations is lower. However, this difference reflects essentially the fact that newly submitted substances are predominantly low tier and meet Annex VII information requirements, and as stated above, low tier endpoints are covered with experimental data more often than adaptations.

TOWARDS AN ANIMAL TESTING-FREE REGULATORY SYSTEM FOR INDUSTRIAL CHEMICALS

REACH's aim to promote alternatives to animal testing has been part of ECHA's mandate since its establishment. Stakeholders and policymakers have clear and pressing expectations to ensure protection for human health and the environment, and follow the 3Rs principle to **replace** animals with non-animal methods where possible, **reduce** the number of animals used in testing, and **refine** methods to minimise animal suffering.

In general, New Approach Methodologies (NAMs) denote alternatives to traditional toxicity methods that typically involve animal testing. These alternatives are useful for predicting and assessing chemical risks and hazards, by providing mechanistic information for biologically complex endpoints. They include, e.g. *in vitro, in chemico* methods and in silico computational models, which may be used alone or in combination with other methods and have the potential to be quicker, cheaper and use less animals.

2.1. Regulatory context

The development of NAMs is closely linked with the overall ambition to replace animal testing. The use of NAMs to evaluate the effects of chemicals on humans and the environment is a topic of increasing interest. For example, a number of roadmaps and implementation plans have been developed recently e.g., by the US EPA[15] and EFSA[16], to support the implementation of NAMs and aim towards a full replacement of animal testing. There is however, no consensus on how to best increase the use of NAMs in regulatory decision-making by authorities on chemicals, mainly because of the differences in the regulatory frameworks and requirements under the different legislations and jurisdictions.

The European Commission's 2018 report on REACH[17] shows that the regulation is achieving its goals of protecting health and the environment. REACH provides a comprehensive mechanism for generating and evaluating data for chemicals used in the EU. The report also acknowledges the significant progress made in developing and promoting alternative testing methods, with registrants reducing their reliance on animal testing, although challenges remain for certain endpoints.

The recent Chemicals Strategy for Sustainability (CSS) aims to improve chemicals regulation by ensuring hazards and risks are properly characterised. The CSS also seeks to reduce dependence on animal testing, while encouraging scientific advancements in the field. However, anticipated changes to REACH and CLP[18] may increase animal testing to safeguard human health and the environment from chemicals that exhibit, for example, endocrine disruptive properties.

In parallel, the European Parliament passed a resolution to 'Accelerate a Transition to Innovation without the use of Animals in Research, Regulatory Testing and Education[19]' in September 2021, calling for ambitious objectives, reduction targets and timelines for replacing animal testing with alternative methods.

15 US EPA (2021) New Approach Methods Work Plan. EPA/600/X-21/209

16 EFSA (2022) Development of a Roadmap for Action on New Approach Methodologies in Risk Assessment. doi: 10.2903/sp.efsa.2022.EN-7341

17 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018DC0116&from=en

18 EU regulation for classification, labelling and packaging of chemical substances and mixtures

19 European Parliament resolution of 16 September 2021 on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education (2021/2784(RSP)).

More recently, a European Citizen's Initiative[20] garnered more than 1.2 million signatures, urging prompt action from the European Commission to strengthen the ban on animal testing for EU cosmetics, modernise EU safety science, and revamp EU chemicals legislation by committing to a roadmap to phase out animal testing.

Within this context, ECHA is committed to promoting alternatives to animal testing and, within its mandate, has been actively addressing this topic since the agency's establishment.

2.2. ECHA's activities to promote NAMs

ECHA's work on NAMs is structured around three main pillars:

1. **The effective implementation of ECHA's regulatory processes to identify and address risks of chemicals of concern by:**

- Selecting chemicals for regulatory prioritisation and grouping them to reduce data generation[21].
- Supporting registrants to develop, e.g. within pilot projects, testing strategies based on read-across to reduce animal testing.
- Implementing mechanisms such as data sharing, testing proposal examinations and consultations to reduce unnecessary animal testing.
- Supporting the European Commission on promoting alternatives to animal testing, including through partnerships such as the EPAA[22].

2. **The investment in collaborations and international activities promoting alternatives by:**

- Financing and co-managing the development of the OECD QSAR Toolbox, which is a well-known global tool for assessing chemical hazards based on similarities in toxicological profiles and modelling biotransformation pathways.
- Contributing, through ECHA's experts, to the development of OECD test guidelines with a focus on replacement, reduction and refinement of animal testing. For example, ECHA significantly contributed to the development and adoption of non-animal testing methods for skin and serious eye damage/eye irritation, and skin sensitisation.
- Steering flagship research projects that aim to develop suitable alternatives for regulatory needs such as the European Partnership for the Assessment of Risks from Chemicals (PARC) and other Horizon 2020-funded initiatives. ECHA has also collaborated with authorities from other regions, such as the US or Canada within the Accelerating the Pace of Chemical Risk Assessment initiative (APCRA). This collaboration aims to promote the acceptance of alternative methods across regulatory frameworks.

3. **Making sure toxicological data and related information is readily accessible to the wider regulatory and scientific community to facilitate research and development on NAMs by:**

- Sharing information with the chemicals community by making datasets available for download in a harmonised IUCLID format. This includes REACH study results, contributions from the pharmaceutical industry, and toxicity data from the US FDA.

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20 Save cruelty free cosmetics - commit to a Europe without animal testing, Commission registration number: ECI(2021)000006.

21 This does not refer to data generation by registrants to meet standard Information requirements. It is rather in the context of the IRS, when there is a need of additional information or assessment before it is possible to identify whether further regulatory action should be proposed. A detailed description is available in ECHA's 2022 Integrated Regulatory Strategy Annual Report.

22 European Partnership for Alternative Approaches to Animal Testing

The next sections provide a short description of selected initiatives and efforts undertaken by ECHA to implement NAMs and promote their use. These examples illustrate the key activities in this regard.

2.2.1. ECHA's use of NAMs in the framework of the regulatory strategy

ECHA's Integrated Regulatory Strategy (IRS)[23] aims to foster collaboration between ECHA, the European Commission, and Member States to identify and address substances of concern identify suitable regulatory action for them.

To increase the pace and efficiency of identifying and addressing substances of concern, ECHA has moved from examining substances one-by-one to grouping together structurally similar substances. The assessment of substances in groups ensures that all available information is used more effectively and enhances the coherence and consistency of authorities' work when progressing with similar substances.

The main source of information is ECHA's database, however external sources or prediction tools might be used to screen and assess consistency of groups for a given potential hazardous property.

Generally, NAMs are used within ECHA's regulatory strategy in a three-level model namely i) individual tools and databases that form a common library of modules, ii) standardised workflows to address specific scenarios and iii) NAMs to cover ECHA's operational needs. Figure 11 provides an overview of this structure. A brief description of the levels and examples are also provided.

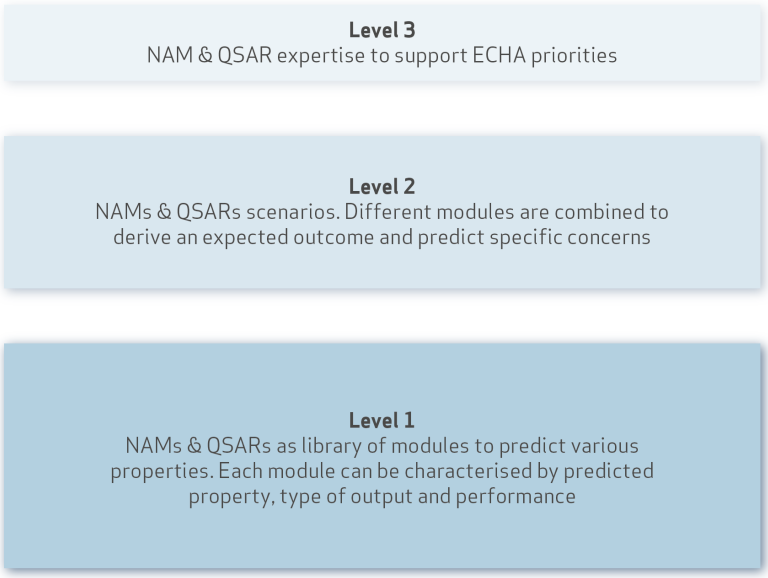

FIGURE 11: NAMs used in ECHA's regulatory strategy

At level 1, a library of individual tools, including publicly available, free and commercial software tools and QSAR modules, is collected to provide computed estimates and predictions of a set of properties of interest to support prioritisation activities. Every module has its own characteristics in terms of coverage of the chemical space and performance (e.g. sensitivity and specificity). This set of predictive tools and external datasets are used as building blocks for specific applications (e.g. specific scenarios to predict fate, (eco)toxicity and toxicokinetic properties). A high degree of automation and throughput is expected at this level. In this context, NAMs support prioritisation of groups of substances for screening and further assessment.

23 https://echa.europa.eu/substances-of-potential-concern

The second level makes use of manually pre-defined combinations of individual modules defined in level 1. For example, to assess the endocrine disruption potential of (groups of) substances of interest, specific screening workflows have been developed upon request for the EATS modalities (estrogen, androgen, thyroid, steroidogenic). These workflows combine various types of evidence from common prediction tools and databases. These tools include QSAR models (single and consensus), structural alerts (SARs) and are combined with metabolism predictions. Available databases include the ToxCast/Tox21 in vitro assays, and the outcomes of the ToxCast models for estrogen receptor (ER) and androgen receptor (AR) interaction. This information may be used, for example, to identify supporting evidence for a specific concern when assessing a group of substances and most suitable further regulatory step.

The third level covers ECHA's operational needs, for instance, dossier or substance evaluations. ECHA uses in-house expertise on NAMs and QSAR to assess if adaptations to standard information requirements are used according to REACH Annex XI and when non-standard information is used as supporting evidence.

While levels 1 and 2 allow for a direct application of NAMs in data generation and use for specific regulatory applications, reducing the reliance on animal data, level 3 supports the interaction with registrants, e.g. through guidance on the use of NAMs.

2.2.2. APCRA

ECHA, together with the US EPA, Health Canada, and other regulatory agencies are part of the Accelerating the Pace of Chemical Risk Assessment (APCRA)[24], a collaborative initiative to promote the use of NAMs in chemical risk assessment.

The collaboration aims to establish a common global understanding of the current state of the science of NAMs and promotes the adoption of NAMs in chemical regulations. This aim addresses several key elements in order to widen the acceptance of NAMs, such as strengthening the scientific foundation for using NAMs, increasing public confidence, and supporting the inclusion of NAMs in regulatory policymaking.

APCRA organises workshops and webinars to share knowledge and data for applying emerging science in regulatory decision-making. Collaborative case studies on alternative methods in regulatory contexts have been performed and the outcomes are disseminated through public webinars. The case studies investigate a wide range of topics including; the use of *in vitro* bioassays in combination with exposure estimates; the use of NAMs for updating chemical categorisations; helping to increase the understanding of exposure and human health toxicity resulting from various chemicals. They explore new ways of describing hazard (i.e., pathway perturbations as a measure of adversity) and new ways of describing risk (i.e., using NAMs to identify protective levels without necessarily being predictive of a specific hazard)[25]. A list of the ongoing case studies within APCRA is provided in the consortium dissemination website.

ECHA has been involved in a number of these case studies by, e.g. providing curated toxicological datasets, participating in chemical selection, and helping in experimental designs and data analysis where relevant.

More particularly, ECHA has been active in case studies related to repeated dose toxicity. The approach investigated consists of attempting to directly correlate NAM data to regulatory "triggers", such as DNELs (Derived no-effect levels). For this reason, two case studies have been initiated, first a retrospective study using only existing data, followed by a prospective study where a strategy for NAM data generation was designed and implemented by the case study partners. The NAM battery includes a suite of in silico tools and computational models, *in vitro* methods for broad profiling and targeted screening. The retrospective study, now completed, demonstrates the feasibility

24 https://apcra.net/

25 Robert J. Kavlock, et al. Chem. Res. Toxicol. 2018, 31, 5, 287–290. doi :10.1021/acs.chemrestox.7b00339

of using *in vitro* bioactivity as a conservative estimate of *in vivo* adverse effect levels[26] using mainly existing high throughput *in vitro* data, e.g. Toxcast. The ongoing prospective case study addresses some of the uncertainties identified previously and attempts to extend the applicability of NAMs to 90-day repeated dose toxicity studies.

2.2.3. PARC

The European Partnership for the Assessment of Risks from Chemicals (PARC)[27] is a seven-year research and innovation programme funded by the EU under Horizon Europe.

Its main objective is to improve chemical risk assessment by advancing research, sharing knowledge, and enhancing skills. The programme aims to push the boundaries of current paradigms in risk assessment in line with the Green Deal's zero-pollution ambition and the European Commission's Chemicals Strategy for Sustainability (CSS).

PARC is expected to address several challenges in the assessment of chemicals risks, including the growing number and diversity of chemicals, incomplete data on exposure, gaps in (eco)toxicological information, separate policy frameworks, and limited access to information and data. Additionally, PARC is expected to contribute to a shift towards using alternative non-animal methods in chemical risk assessment. It will do so by developing research and innovation projects in the following key areas:

"Monitoring and exposure" aims to monitor and measure exposure to humans and to the environment.

"Hazard assessment" contributes to the consideration of new mechanism-based approaches and methods. It will link to OECD activities, current frameworks, e.g. adverse outcome pathway (AOP), and serve some of the tasks in the CSS.

"Innovation in regulatory risk assessment" contributes to the development of regulatory workable risk assessment methods. Reviews of existing regulatory assessment systems are carried out to prioritise research and facilitate the uptake of new approaches.

ECHA plays an active role in PARC by bringing its regulatory expertise on industrial chemicals and biocides. ECHA ensures that the projects adopted and implemented within PARC address regulatory challenges related to chemical risk assessment and contributes to establishing priorities for research and innovation in chemicals risk assessment.

Currently, PARC has about 61 ongoing projects. ECHA has evaluated the majority of them. For a selected number of projects where ECHA sees the highest regulatory relevance, ECHA follows and provides advice on the work ongoing. Some of these projects are relevant or related to NAMs, e.g. development of AOPs and Integrated Approaches to Testing and Assessments (IATAs) for relevant regulatory endpoints.

In the short term, PARC is expected to expand the overall knowledge base of NAMs and stimulate the development of functional, applicable, relevant and, where possible, validated methods in readiness for the current regulatory framework, and supports ECHA's Integrated Regulatory Strategy.

For the long term, ECHA expects PARC to provide several breakthroughs such as combined toxicokinetic and toxicodynamic methods that allow systemic endpoints to be predicted. By exploring the edges of chemical risk assessment research, ECHA expects a paradigm shift where further research and communication within PARC should help to overcome barriers to the usability of non-animal methods for regulatory purposes.

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26 Katie Paul-Friedman, et al. Toxicol Sci. 2020 Jan 1;173(1):202-225. doi: 10.1093/toxsci/kfz201.

27 https://www.anses.fr/en/content/european-partnership-assessment-risks-chemicals-parc

2.2.4. OECD

ECHA provides scientific and technical support to the European Commission on its contributions to the Organisation for Economic Co-operation and Development (OECD), especially for areas linked to the activities of its Task Force on Hazard Assessment and Working Group on National co-ordinators of the TGs programme. ECHA supports the OECD Environment, Health and Safety (EHS) Programme, which promotes the harmonisation of chemicals management globally. ECHA is further involved in the IUCLID (International Uniform ChemicaL Information Database) Expert Group Panel, is a co-lead of the QSAR assessment framework (QAF) project and provides important input to the development of the QSAR Toolbox, as well as the eChemPortal and harmonised templates. ECHA is also a co-lead of the Steering Group for the update of the OECD Guidance on Grouping of Chemicals. In addition, ECHA is involved in the Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST), and its adverse outcome pathway (AOP) programme, as well as in the new Advisory Group on Emerging Science in Chemicals Assessment (ESCA).

ECHA's aim is to encourage the regulatory use of NAMs for safety assessments across jurisdictions. Ultimately, the uptake of NAMs is and will be, demonstrated through the adoption of regulatory test guidelines, the drafting of guidance documents as well as the implementation of advanced hazard assessment methodologies.

Uptake of NAMs in OECD Test Guidelines

In the past decade, the OECD has published approximately 75 new and revised test guidelines (TG) including about 35 *in vitro* test methods for mostly human health endpoints. Several *in vitro* methods provide information on some of the most commonly requested six short-term, high dose acute toxicity tests ("acute toxicity six pack") used for agrochemicals, biocides, industrial chemicals, and cosmetics ingredients. In addition to these test guidelines, a number of guidance documents have been developed on the application, interpretation, and use of these methods in sequential testing strategies, and circumstances when test data may not be needed.

ECHA contributes to the development of OECD TGs and guidance documents (GDs) through the endpoint specific expert groups (EGs). The role of the EGs is to critically assess the methods to be considered, preferably after the scientific validity has been confirmed, and to ensure that the TG clearly specifies the regulatory scope, limitations and applicability of a given method in view of its adoption.

ECHA has been active in multiple expert groups such as those discussing skin corrosion/irritation, serious eye damage/eye irritation, skin sensitisation, endocrine disruptors, developmental neurotoxicity, non-genotoxic carcinogens, mutagenicity, environmental endpoints etc. by providing feedback during the discussions, commenting on draft documents, and drafting parts of the documents.

In March 2023, the European Commission adopted about 100 new and updated test methods, mainly OECD TGs, for the regulatory safety testing of chemicals under REACH, where the majority of the newly approved toxicity test methods are NAMs which do not involve animals[28]. Under the new rules, internationally approved methods (such as OECD test guidelines) are referred to directly in the regulation, reducing the time to include new text methods under REACH. This faster procedure is among the actions taken to speed up the regulatory uptake of non-animal alternatives.

In recent years, substantial developments on the use of NAMs in a regulatory setting have been agreed, for example, through adoption of new Test Guidelines. It is worth mentioning the notable achievements and ongoing work for the following endpoints: Serious eye damage/eye irritation, Skin sensitisation, Endocrine disruption, Aquatic toxicity and Bioaccumulation. In addition, ongoing work on draft TGs and GDs includes the Draft IATA on non-genotoxic carcinogens and the Draft GD on developmental neurotoxicity.

28 https://environment.ec.europa.eu/system/files/2023-03/C_2023_1099_1_EN_ACT_part1_v3.pdf

Update of Guidance on Grouping of Chemicals

The OECD Guidance on Grouping of Chemicals aims to support the consideration of closely related chemicals as a group for assessing the hazards of chemical substances while reducing the need for new experimental studies. The OECD Working Party on Hazard Assessment (WPHA) set up a Steering Group in 2021 to update the second edition from 2014[29], taking into account recent scientific and regulatory developments. Together with the U.S. Environmental Protection Agency, ECHA is co-leading this updating project. ECHA recognises the relevance of read-across approaches as they are widely used in REACH submissions and aims to promote the understanding of read-across concepts, crucial also for the success of the approaches towards fulfilling REACH requirements. ECHA developed the Read-Across Assessment Framework[30] in addition to the ECHA Guidance on grouping of chemicals[31], and also provides recommendations[32] and specific advice to registrants[33].

The Working Party on Manufactured Nanomaterials (WPMN) also set up an *ad hoc* group that includes ECHA to specifically update and extend the nanomaterial-related section of the Guidance. The section update will benefit from/be based on increased knowledge and experience with read-across approaches for nanomaterials since the last version of the Guidance.

The QSAR Toolbox

ECHA co-owns and co-develops the OECD QSAR Toolbox[34] together with OECD. The Toolbox is a free software application that supports reproducible and transparent chemical hazard assessment without needing to perform new experimental (animal) tests.

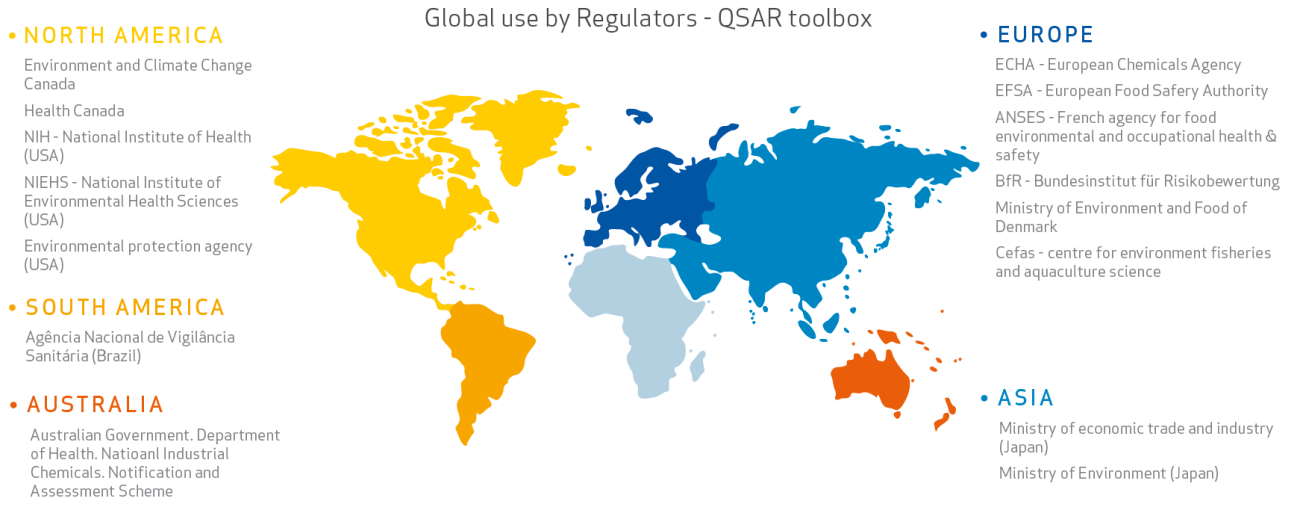


FIGURE 12. Examples of regulatory authorities that use of the OECD QSAR Toolbox in their processes.

According to the latest data collected in 2022, the QSAR Toolbox has been extensively employed by REACH registrants to adapt standard information requirements through QSAR and read-across studies. The Toolbox

29 OECD (2014) Guidance on Grouping of chemicals, 2nd ed, Series on Testing and Assessment No. 194, ENV/JM/MONO(2014)4)

30 https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a

31 ECHA (2008) Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals

32 https://echa.europa.eu/adaptations-recommendations

33 Advice on using read-across for UVCB substances: https://echa.europa.eu/documents/10162/11395738/advice_uvcb_read-across_en.pdf/

34 https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

is mentioned in various endpoints within more than 2 000 registrations, predominantly for assessing skin sensitisation, in vitro genetic toxicity, and short-term toxicity to aquatic invertebrates. For several other endpoints, including acute oral toxicity, toxicity to reproduction, fish short-term toxicity, and bioaccumulation, the standard information requirement mandates the use of vertebrate animals, but the QSAR Toolbox has been significantly used to avoid this. The QSAR Toolbox is also used by other regulatory agencies across the world.

ECHA will continue leading the QSAR Toolbox project and foster collaboration with other stakeholders. An example of such collaboration is with EFSA on implementing a workflow in the QSAR Toolbox to assess the toxicity of pesticides' residues and metabolites.

ECHA, using its extensive expertise in assessing QSAR results under REACH and with the experience gained in establishing various assessment frameworks such as for read across (RAAF), has co-led with the Italian National Institute of Health (ISS) a bi-annual project called the OECD QSAR Assessment Framework (QAF) with the objective to facilitate the use and assessment of QSARs. The QAF establishes four principles for the regulatory assessment of QSAR results, in addition to the five OECD principles for model validity. The four principles include ensuring correct model inputs, substances should be within the model's applicability domain, predictions should be reliable, and the outcomes fit for regulatory purpose. The QAF provides assessment elements for each principle and offers dedicated checklists to assess both QSAR models and results. The guidance and checklists should be published by OECD in September 2023 after their official endorsement.

The QAF benefits model developers, assessors, and users by providing clear guidelines for developing and evaluating models and results for regulatory use. It will increase the availability of models that meet regulatory needs and ensure they meet acceptable standards across regulations at OECD level. Users can compile a QAF checklist and anticipate assessment outcomes. ECHA has played a key role in establishing the QAF, which has the potential to increase regulatory use of QSAR results.

Integrated Approaches to Testing and Assessment (IATA)

Integrated Approaches to Testing and Assessment (IATA) is an OECD project that operates as a forum for sharing information and best practices on developing and applying IATA, with an emphasis on the contributions of NAMs, in regulatory contexts. The IATA Case Studies Project[35] (CSP) has developed examples of chemical hazard assessments for regulatory use, generating around 35 studies in the last decade. The forum also provides detailed presentations and training on different methodologies. The case studies cover various endpoints related to human health and the environment, with a focus on repeated dose toxicity, neurotoxicity, endocrine disruption, reproductive toxicity. All these endpoints are of high relevance within the current EU chemicals regulation and ECHA is actively participating wherever possible. ECHA is also contributing to case studies for ecotoxicity and bioaccumulation.

'Omics reporting framework

ECHA has been involved together with various experts to devise a framework for the reporting of transcriptomics and metabolomics data to be used in regulatory toxicology. This work took place within the Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST)[36], which now concluded a project to establish a framework that assures data quality for reporting and inclusion of omics data in regulatory assessments.

This collective effort resulted in the publication of a OECD draft guidance document, supplemented by specific reporting templates. The guidance document includes four types of reporting modules within the framework, the study summary reporting module; the toxicology experiment reporting module; the data acquisition and

35 https://www.oecd.org/chemicalsafety/risk-assessment/iata/

36 Now the Advisory Group on Emerging Science in Chemicals Assessment (AG ESCA)

processing reporting modules; and the data analysis reporting modules. The omics reporting framework has been implemented in various jurisdictions to test its applicability and regulatory relevance[37]. Such a framework would help establish a baseline for best practice, facilitating regulatory applicability of omics data. Additionally, the reporting framework is currently needed to ensure consistent, transparent, and complete reporting of omics data to various regulatory agencies, including ECHA.

2.2.5. EPAA

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is a public-private collaboration between the European Commission, EU Agencies (ECHA, EFSA and EMA) and industry stakeholders from various business sectors. The partnership envisions to progress the replacement, reduction and refinement (3Rs) of animal use through advanced science. EPAA supports the challenging transition to full replacement by bringing together partners & collaborators to: Promote development and acceptance of 3R methods, foster cross-sector knowledge-sharing, increase international collaboration and facilitate stakeholder dialogue.

EPAA and ECHA are currently joining efforts, together with NGOs and the European Commission, to organise a workshop on new approach methodologies, entitled "Towards an animal free regulatory system for industrial chemicals"[38]. The workshop takes place at the same date of the release of this report, and will be an opportunity to bring stakeholders together and develop a common understanding of what NAMs can achieve in the short and long term, to identify critical needs and steer NAM developments towards an animal testing free regulatory system.

In addition, ECHA participates and brings its expertise wherever possible, e.g. within the project platform, where EPAA manages a number of projects. Also, ECHA hosted a series of workshops, sponsored by EPAA on skin sensitisation organised to support capacity building for national authorities and other stakeholders on the use of in vitro test methods to assess this endpoint. This activity feeds directly into ECHA's work on skin sensitisation and the corresponding ECHA guidance[39].

The EPAA Partners Forum exchanges on the state of knowledge on use of NAMs in various industry sectors and regulatory environments and where the current challenges and the ongoing needs are formulated. Over the past two years, EPAA organised a series of workshops to support developing a common understanding on the use of NAMs across sectors and legislation which lead to a few scientific papers. In addition to the regular events organised by EPAA, where ECHA regularly updates on its activities, priorities and needs, a number of scientific papers and opinions were co-authored jointly, with other partners, to disseminate strategic ideas to improve and increase the applicability, implementation, and acceptance of modern non-animal methods[40].

2.2.6. Research projects

In 2021, three research projects were funded under the EU's research and innovation funding programme, Horizon 2020. These flagship research projects are led respectively by the University of Birmingham (PrecisionTox), Vrije Universiteit Brussels (ONTOX), and Leiden University (RISK-HUNT3R), with the aim of developing NAMs for chemical safety assessment.

ECHA is collaborating with the three projects individually, e.g. within cases studies, as well as contributing at a cluster level (ASPIS) to ensure the research is relevant for regulatory purposes. The ASPIS cluster represents 70 scientific organisations across the EU and aims at providing timely answers about chemicals' effects on human health. Within the regulatory forum, ECHA supported the work of the consortium for the identification

37 Harrill, et al. (2021) Regul Toxicol Pharmacol, 125:105020. doi:10.1016/j.yrtph.2021.105020

38 https://echa.europa.eu/-/new-approach-methodologies-workshop-towards-an-animal-free-regulatory-system-for-industrial-chemicals

39 https://echa.europa.eu/-/new-guideline-reduces-animal-testing-and-protects-from-allergies-caused-by-chemicals

40 Westmoreland et al., (2022) Regul Toxicol Pharmacol;135:105261. doi: 10.1016/j.yrtph.2022.105261

of methods that are potentially applicable under the extended REACH information requirements, as foreseen in the European Commission's CSS.

Besides the regulatory aspect of this research, ECHA participates in practical case studies within the individual projects, such as RISK-HUNT3R, where ECHA contributed to the selection of more than 50 substances registered under REACH that fulfil certain testability criteria and that have repeat dose toxicity from 28-day or 90-day studies. The case study partners generated a series of *in vitro* NAM data to investigate toxicity in the liver, kidney, lung and nervous system. The aim is to demonstrate the feasibility of extensive integration of advanced technologies and data streams, including high throughput transcriptomics, and high throughput screening and imaging techniques in chemical risk assessment with a focus on repeated dose systemic toxicity.

ECHA is also active in various research projects run by industry stakeholders. As an example, the European Chemical Industry Council (Cefic)-funded MATCHING study (MetAbolomics ring-Trial for CHemical groupING) is an international metabolomics ring-trial, focusing on chemical grouping using omics data. The aim is to determine whether this technology can demonstrate high reproducibility in chemical grouping and to propose 'best practice' for metabolomics-based grouping. The international consortium comprises seven industrial, government and academic metabolomics ring-trial partners. ECHA acts as an independent advisor.

2.2.7. Data availability

ECHA invests in developing harmonised data formats and tools to collect and share chemical information globally. A flagship product in this area is IUCLID, which ECHA develops in collaboration with the OECD, particularly around the OECD Harmonised Templates that structure chemicals information by endpoint. The IUCLID format, together with the built-in validation and dissemination modules that ensure harmonised data entry and systematic publication, enable efficient data management by companies and authorities, including the exchange, submission, analysis and public access of chemicals data. ECHA is also developing a series of additional software to extend the set of features available to users to manage data in the IUCLID format:

- Data uploader[41] which supports transforming data to the IUCLID format
- Data extractor[42], Text analytics[43], that enable advanced data analysis

In the past years, ECHA's focus has shifted from collecting data to using it for regulatory processes and making it available to stakeholders. ECHA makes data publicly available on its website, where information about substance properties and their hazards is disseminated as part of the REACH registration dossiers and accessible through web pages. The information is also provided in IUCLID format to facilitate the reuse of data by experts working in several domains, including for the development of alternatives to animal testing: the 'REACH Study Results' database is updated twice a year and contains information for around 23,000 substances including millions of data points. The goal for the coming years is to build a chemicals knowledge base that supports, among others, alternative methods to animal testing and a new public Data availability system that improves the way stakeholders can interact with the information.

By ensuring the use of the harmonised IUCLID format for REACH registration data, ECHA also enables its dissemination through various other channels compatible with the format. As introduced previously, the QSAR Toolbox itself contains the relevant information from REACH registration dossiers and is also updated regularly. Finally, a subset of this information is regularly sent to the OECD eChemPortal, a project co-managed by ECHA, to provide advanced search possibilities.

41 https://iuclid6.echa.europa.eu/data-uploader
42 https://iuclid6.echa.europa.eu/data-extractor
43 https://iuclid6.echa.europa.eu/text-analytics

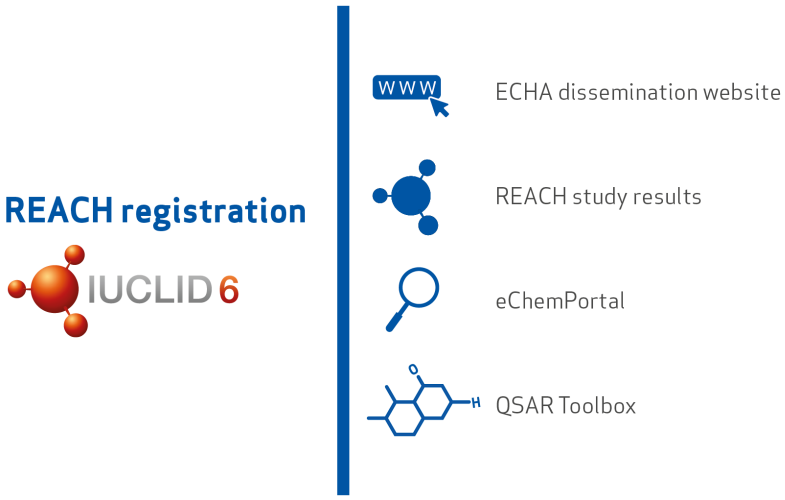


FIGURE 13: one data source, in one format, made available in different ways, the example of REACH registration data

As part of its coordination of the OECD IUCLID Expert Panel and its involvement in cross-organisational projects, ECHA is also promoting IUCLID as a common exchange format for chemicals data. These contacts and collaborations have resulted in the successful publication of new data sets in IUCLID format:

- the use of IUCLID for the EU Pesticides Regulation, in collaboration with EFSA[44]
- previously unpublished data from pharmaceutical companies were made available in the IUCLID format[45]
- relevant toxicity data, previously published by the US FDA, have also been structured according to the IUCLID format and shared publicly[46]

2.3. Outlook – towards a full replacement of animal testing

The primary objective of EU legislation regulating industrial chemicals is to provide a high level of protection of human health and the environment. It relies on the identification of hazardous properties of substances, with REACH and CLP as the essential horizontal EU Regulations.

Since its entry into force in 2007, REACH is the regulatory framework producing the largest knowledge base on chemicals globally. REACH ensures that industry provides adequate data, using as a last resort tests on animals, to assess the hazardous properties of chemicals. CLP enables the classification of chemicals based on the adverse effects observed using standard testing methods, including tests on animals, which are then used to derive safety levels and provide a framework for generic risk management. This system provides predictability and legal certainty for industry to comply with and authorities to enforce.

The generic system under REACH and CLP does not require the intervention of authorities by default – chemicals are not systematically assessed for safety by the regulators before they are put on the market; this assessment is done solely by industry ("the reversal of the burden of proof"). Authorities may scrutinise these assessments and take regulatory actions (e.g. request further information or initiate regulatory risk management), where required. In addition, this system allows adaptations to standard information requirements to be used for supporting hazards and risk assessment.

With regard to the elements above, a **gradual replacement of animal testing in hazard assessment,** within the

44 https://www.efsa.europa.eu/en/applications/toolkit#iuclid-software
45 https://echa.europa.eu/-/pharmaceutical-industry-provides-unpublished-data-on-chemical-substances
46 https://echa.europa.eu/-/new-iuclid-pharmaceuticals-datasets-support-alternatives-to-animal-testing

current regulatory framework, should consider maintaining the fundamental elements that ensure the system functions well, namely:

- defined hazard classes,
- clear criteria to allow consistent classification,
- standard information requirements for conclusive hazard assessment,
- quality data for decision making that are reliable, comparable, and re-usable,
- consistent regulatory actions within chemicals legislation.

Also, it is worth noting that to comply with the requirements for industrial chemicals legislation, animal testing is relatively limited[47] (below 2 % of the overall use of animals for testing, according to the 2019 EU statistics[48]); nevertheless, a full replacement can be envisaged and may be used as a model for other sectors.

The needs for NAMs are different, depending on the type of chemical and regulatory system. NAMs to support screening, prioritisation and read-across are available, continue to be developed and are used to some extent by regulators around the globe in line with the set frameworks and regulatory requirements.

Regarding the full replacement of testing on animals, developments have been successful for a number of endpoints such as skin and eye irritation and skin sensitisation, where a particular adverse effect is investigated and the mechanism(s) leading to it are well understood. In these cases, the use of alternatives allows the classification according to the CLP criteria and setting of appropriate safety levels. However, it has taken considerable time, nearly a decade, to adopt robust, reliable methods to fully replace animal testing for these endpoints.

The application of NAMs for more complex endpoints has been less successful, e.g., for repeated dose toxicity, long term aquatic toxicity, reproductive toxicity and carcinogenicity, and the information requirements still rely on animal testing. There is now wider acceptance across the scientific community and regulators of the challenges to develop one-to-one replacements of animal tests for more complex endpoints.

To identify and characterise the potential hazards for these complex endpoints, NAMs derived information should allow conclusive outcomes regarding the (lack of) hazardous properties of a substance. In addition, the level of the severity should be determined (effect type and potency). Finally, the toxicity values and parameters determined using NAMs should be used to derive safety values amenable for risk assessment and risk management. Therefore, the critical needs to be addressed are, at the minimum:

- the ability to demonstrate that NAMs, (e.g. an integrated *in vitro/in silico* system) can be used to allow a conclusive outcome on the (lack of) hazardous properties for given regulatory endpoint; the conclusion that the substance does (not) have a certain hazardous property should be sound and confirmed by data.
- the ability to reliably identify hazard and derive reference values based on changes at the molecular/cellular level instead of observed adversity in an organism, and to inform how severe the toxic effect is for human health or environment.
- the ability to reliably convert nominal concentrations measured or predicted by NAMs into external doses used to set safety levels, to communicate the hazard and assess the risks.

In addition to the three critical elements described above, combinations of various NAMs will be needed to cover more complex endpoints. Consequently, in addition to the test methods and/or predictive models also the

47 SWD(2022) 199. Summary Report on the statistics on the use of animals for scientific purposes in the Member States of the European Union and Norway in 2019

48 In 2019, the use of animals for scientific purposes was mainly reported for research (72%), followed by regulatory use to satisfy legislative requirements (17%) and routine production (6%). Among the testing carried out for regulatory purposes, the majority involved medicinal products for human use (61%), veterinary medicinal products (18%) and industrial chemicals (9%). Of all animals used for scientific purposes, only about 1.5% were for industrial chemicals legislation.

explicit rules for the evidence integration and derivation of the overall outcome also needs to be developed and implemented.

A full replacement of animal testing would therefore require advancement in the scientific developments accompanied by fundamental policy changes which should address two key questions: how a new approach can cover the most relevant effects and diseases of concern for the society (e.g. CMR, immunotoxicity, EDs, etc.) and how to ensure a similar or better level of protection for human health and environment.

Such fundamental changes ultimately represent policy options. ECHA has the competence and is ready to support policy makers in developing a suitable, consistent approach for regulating chemicals based on an increased use of NAMs and eventually phase out animal testing.

ANNEX I:

METHODS

The main focus of the data analysis is on registration dossiers, as these contain all available and relevant information on chemicals on the European market manufactured or imported above one tonne per year. In line with the scope of Article 117(3), the focus is on how the registrants used the alternative methods to animal testing 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.

REACH specifies the standard information requirements that must be fulfilled in Annexes VII to X to REACH. Where information on the intrinsic properties of substances is needed, tests have to be conducted according to the test methods laid down in Regulation (EC) No 440/2008 or in accordance with other international test methods that the Commission or ECHA recognise.

However, 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.

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 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 (already) existing data,
2. Weight of evidence,
3. Qualitative or Quantitative structure-activity relationship ((Q)SAR);
4. *In vitro* methods; and
5. Grouping of substances and read-across approach.

It is also possible to waive the standard information required for an endpoint 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).

In summary, REACH gives many options to fulfil the information requirements. The different options that REACH registrants have as defined in this analysis, are: experimental study, read-across/category, QSAR, weight of evidence, data waiver, testing proposal (TP) and other.

Definition of the options used to fulfil the information requirements

The different options that REACH offers to fulfil the information requirements and considered in this analysis, are defined as follows:

- Experimental study: the use of an experimental study according to a guideline which is in line with the

information requirement.

- Read-across/category: 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.
- Quantitative structure–activity relationship (QSAR): a mathematical model that can be used to predict the physicochemical, biological and environmental fate properties of compounds from the knowledge of their chemical structure.
- Weight of evidence (WoE): a combination of information from several independent sources that would allow for a conclusion on hazard and risk assessment, including classification and labelling, without further studies. The possible sources of information include: published literature, read-across from chemical analogues, QSAR predictions, data from existing studies, in vitro studies, epidemiological data/human experience.
- Data waiver: the possibility to omit 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 (TP): For endpoints specified in Annexes IX and X under REACH, test proposals involving vertebrate animals are published before the testing is carried out. It should be noted that testing proposals remain only for a period in the database, as they are processed within set deadlines. This report takes into account the testing proposals at the moment the snapshot of the database was taken.
- Other: other combinations of information that do not match the above definitions, e.g. literature data.

In addition, a category "No requirement" is used throughout the report. This category denotes the absence of a mandatory information requirement by default. Most commonly this reflects that providing information for the endpoint is not required and therefore only provided if data is available. Another reason for this category is that the endpoint is part of an integrated testing strategy, and the test requirement depends on the outcome of other tests.

For completeness, the definition of terms frequently used in this report are provided.

An adaptation to a standard information requirement means that instead of providing the specific information required, other information is used. The general rules governing such adaptations are set out in Annex XI, while the specific rules are set out in column 2 of Annexes VII to X.

An alternative (test) method, in the context of REACH, mainly relates to use of *in vitro* methods, QSARs, grouping and read-across. REACH Article 13(1) specifies that: "Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, *in vitro* methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across)". An alternative test method can also be an *in vivo* test, but which uses fewer animals and/or causes less suffering.

An experimental study denotes investigation set up to obtain information on a substance's intrinsic properties or adverse effects. It can cover *in chemico, in vitro* and *in vivo* testing.

Dossier and substance selection

The dossiers analysed for this report included the latest submission of all the qualifying registrations by the cut-off date 31 July 2022. Substances were included in the analysis if by the cut-off date there has been at least one active or inactive registration received under REACH that fulfilled the information requirements according to the full Annex VII of REACH. If a substance is included in the analysis, then all active and inactive registrations for the substance have been processed, regardless of their own tonnage. Registrations that have been revoked,

annulled or invalidated were excluded. The substances were categorised according to the highest REACH Annex that applies to all active and inactive registrations of the substance.

Transported intermediate registrations (REACH Article 18) registered at > 1000 tpa fulfil the information requirements according to the full Annex VII to REACH, and were analysed accordingly. However, NONS[49] registrations notified under the previous directive 67/548/EEC were not analysed, unless if updated under REACH and the update led to an increase of the information requirements and hence triggered a full technical completeness check[50].

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. 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.

ECHA uses in-house developed algorithms and dedicated data mining tools to screen and analyse the submitted dossiers. For this report, the data analysis method was consistent with that used in the previous edition, unless specifically stated otherwise.

A technical limitation with the identification of the test material in 2020 and before, inaccurately identified the reference substance of the test material for some experimental studies. In these cases, where the algorithm was not able to match the test material and the registered substance, it concluded the study as "Read-Across" or "test with analogue". Hence, the reported number of experimental studies was lower than the actual number. Currently the algorithms are more efficient in interpreting the substance identity of the test material reference substance. In addition, the algorithm has improved capabilities in identifying test guidelines, with additional ones encoded. Both of these corrections and improvements have contributed to some of the observed increase of "experimental studies" and decrease of "Read-Across" counts. It was not feasible to investigate further the impact without re-processing hundred of thousands of dossiers from past analyses. Still based on a manual check of hundreds of dossiers for some specific endpoints, we can reasonably assume the average difference to be a few units percent. This difference depends on the endpoint considered and on the amount of data available for that particular endpoint.

Also, although the analysis workflows remain unchanged, there are changes in the context due to IUCLID format updates, data processing algorithm updates, updates in guideline studies and updates in the registration database. Thus, it is not always possible to precisely compare the numbers included in this fifth edition of Article 117(3) report with the numbers in the fourth Article 117(3) report. Numbers reported for the registered substances (e.g. tables 1 and 2) do not add to those reported in the previous editions because of the registration status changes that affect them (e.g. revocation because of the Brexit, status of intermediates, registrations changing tonnage bands, updated NONS registrations, etc.). Another aspect to note is that other REACH related publications might display slightly different counts of unique substances per Annex. Each report counts the number of substances within its own context. In this report the substances have been counted within the inclusion context that is described in this Annex.

Substances were allocated to REACH Annexes according to the registration with the highest information requirements at the time of analysis. 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-

49 Substances notified under the Notification of New Substances (NONS) scheme of Directive 67/548/EEC, that was in place before REACH.

50 NONS registrations that do not meet these criteria were excluded from the analysis due to data quality shortcomings of the automatically migrated legacy IUCLID dossiers. The trigger of the full technical completeness check ensures that the data is reported with enough quality to perform the analysis applied for this report.

1000 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 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. This means that some of the Annex VII substances in the starting pool are in reality transported isolated intermediates, over 1000 tonnes per year.

Dossier and substance selection follows the same approach as in the 4th edition of the 117(3) report.

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

Finally, regarding the newly registered substances (2019 - 2022) analysed in section 1.2, these substances were identified as being registered after 31 July 2019. They are substances that were either registered for the first time after this cut-off date, or that a registrant for that substance became subject to information requirements that are in the scope of this report. These substances are a subset of the complete substance pool that has been analysed in section 1.1. The substances in scope of the previous edition (4th report) have been used as reference to remove the already registered substances. In a rare case that a substance has been in the scope for analysis in even earlier editions of the 117(3) report, but not been in the scope for the fourth edition, it would not have been appeared as a reference substance to be removed, should it have reappeared in the scope again in the 5th edition report.

Processing of endpoint study record

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 registrants only needed to provide one endpoint study record with the read-across information, with the introduction of IUCLID 6, registrants were 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 therefore the database contains a high variety of ways to report read-across and category adaptations. In the methodology used in some earlier editions of the Article 117(3) report, it had not been straightforward to use the administrative information of the endpoint study records to determine whether a study was carried out with the registered substance or an analogue. For this reason, a more elaborate algorithm was constructed already for the fourth edition of the report. A change to the fifth edition of the report is that the algorithms were further improved to better identify the substance identity of the reference substance of the test material. The main steps of this algorithm are shown in "Table 3".

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
	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 in the expected field (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.

TABLE 3: Main elements of the algorithm to establish whether a test has been carried out with the registered substance (test material algorithm)

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 circle/bar plots in Figures 1 to 3, and 6 to 8 (and in the Annexes, Figures A 3 to A 6, and A 8 to A 11), 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.

For the purposes of the study period distributions shown in Figures 4, 5 and 9 (and in the Annexes Figure A 12), 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 that we could detect and interpret.. 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 for some 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 Figures 4, 5 and 9 overestimate 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 work-in-progress and not sufficiently developed to be used for the purposes of this report.

The study period distributions in Figures 4, 5 and 9 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 periods visualised in Figures 4, 5 and 9.

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 to two different study tags, in which case the algorithm increased the study counts for both study tags.

The tags table used in the previous edition of the report (Table 6 in Annex 1 of 4th edition) was updated with the most recent test guidelines. The table contains the assigned study tags (used in Figures A 1 and A 2), the IUCLID sections where the study tags were applied to and the text patterns capturing the generally acceptable guidelines.

Aggregation of study information at substance level

This section summarises how the endpoint study record information has been aggregated at substance level.

All 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 A 1 and A 2 (in the Annexes) 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 A 1 and A 2 only examine the presence or absence of a study for each study tag for each substance.

Figures 1 to 3, and 6 to 8 (and in the Annexes, A 3 to A 6, and A 8 to A 11), 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.

The next part of this section explains how the information has been aggregated at substance level for the purposes of the bar plots in Figures 1 to 3, and 6 to 8 (and in the Annexes, A 3 to A 6, and A 8 to A 11). The source data for a particular substance may come from studies in the same or different dossiers. All of these source data had to be processed, "tagged". In order to count how an endpoint has been reported on a substance level, it was necessary to introduce a technical prioritisation among the tagged studies. Based on the prioritised tags, the results could be aggregated with the tag of highest priority and it became possible to count how a particular substance reports a particular endpoint. To achieve this, it was necessary to develop a set of rules and apply them in a certain order. For the endpoint of repeated dose toxicity, all repeated dose toxicity IUCLID sections for the different routes and duration were grouped 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 requirement"; 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 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:

   - reliable experimental study with a generally not accepted guideline
   - unreliable experimental study regardless of guideline
   - unreliable read-across
   - unreliable QSAR
   - 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.

Also, the qualitative conclusions drawn in the report would not differ significantly even with different 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.

ANNEX II:

DETAILED OVERVIEW OF THE WHOLE REGISTRATION DATABASE (AS OF 31 JULY 2022)

Availability of experimental studies (2008-2022)

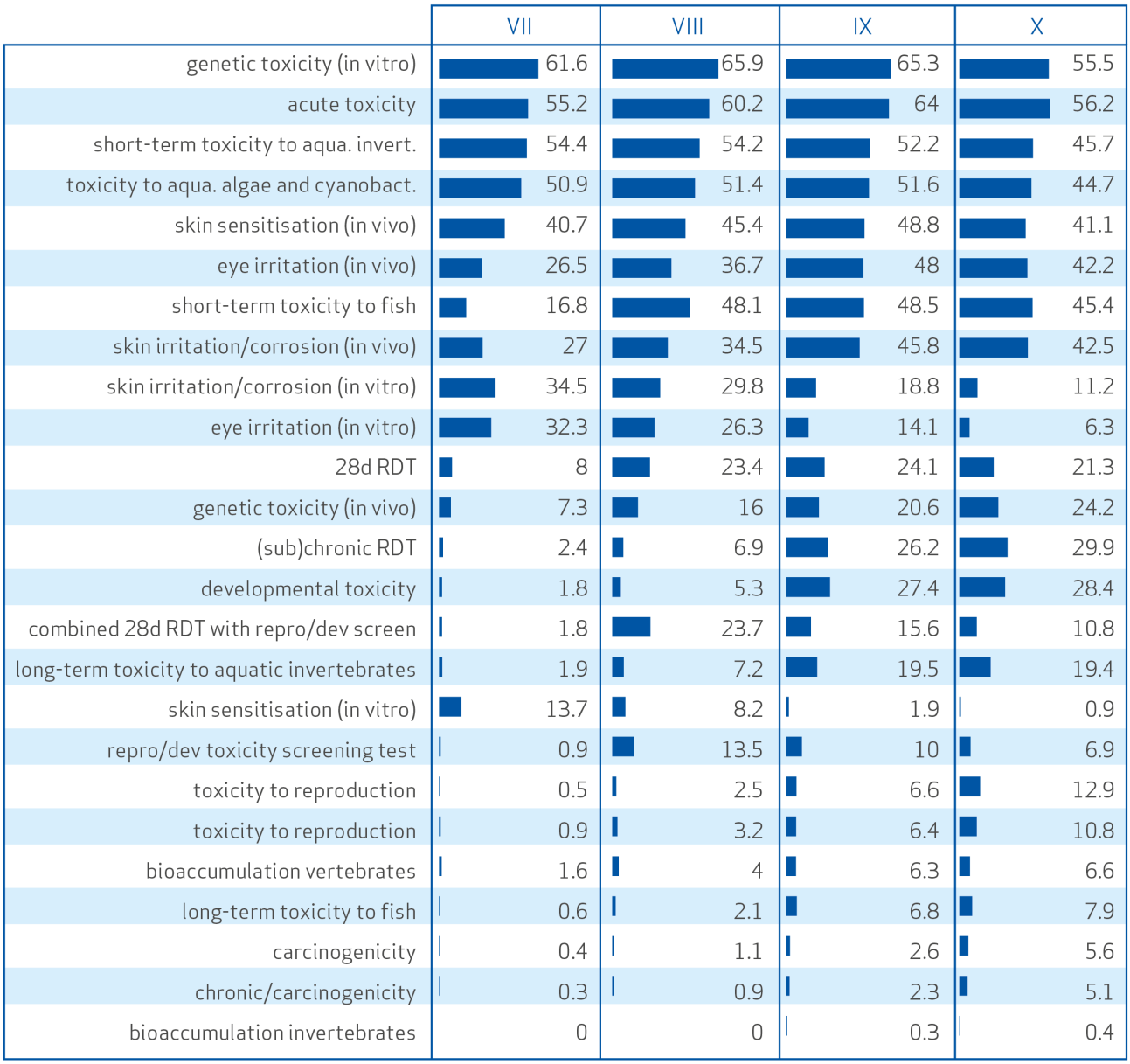
As in the previous editions, the analysis starts with an overview of the experimental studies available in the REACH database.

"Figure A 1" shows the percentage of substances for which guideline studies were used to fulfil the standard information requirements. The rows in the figure represent the endpoints, and each column represents the REACH Annexes to which the substance for which the study have been submitted belongs. Each cell contains the **percentage of substances** for which the information requirement has been covered with the standard guideline study. The endpoints in Figure A 1 were ordered by decreasing percentage of substances per endpoint.

A comparison between 2022 and 2019 data has been performed to have an overview of changes in the availability of experimental studies since the last report.

"Figure A 2" shows the percentage-point difference between 2022 and 2019 (the 2022 percentage minus the 2019 percentage). The 2022 percentage data is presented in Figure A 1, while the 2019 percentage data is reported in the previous edition. An increase in the number means that between 2019 and 2022, 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.

Non-vertebrate endpoints related to aquatic toxicity have 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.



	VII	VIII	IX	X
genetic toxicity (in vitro)	61.6	65.9	65.3	55.5
acute toxicity	55.2	60.2	64	56.2
short-term toxicity to aqua. invert.	54.4	54.2	52.2	45.7
toxicity to aqua. algae and cyanobact.	50.9	51.4	51.6	44.7
skin sensitisation (in vivo)	40.7	45.4	48.8	41.1
eye irritation (in vivo)	26.5	36.7	48	42.2
short-term toxicity to fish	16.8	48.1	48.5	45.4
skin irritation/corrosion (in vivo)	27	34.5	45.8	42.5
skin irritation/corrosion (in vitro)	34.5	29.8	18.8	11.2
eye irritation (in vitro)	32.3	26.3	14.1	6.3
28d RDT	8	23.4	24.1	21.3
genetic toxicity (in vivo)	7.3	16	20.6	24.2
(sub)chronic RDT	2.4	6.9	26.2	29.9
developmental toxicity	1.8	5.3	27.4	28.4
combined 28d RDT with repro/dev screen	1.8	23.7	15.6	10.8
long-term toxicity to aquatic invertebrates	1.9	7.2	19.5	19.4
skin sensitisation (in vitro)	13.7	8.2	1.9	0.9
repro/dev toxicity screening test	0.9	13.5	10	6.9
toxicity to reproduction	0.5	2.5	6.6	12.9
toxicity to reproduction	0.9	3.2	6.4	10.8
bioaccumulation vertebrates	1.6	4	6.3	6.6
long-term toxicity to fish	0.6	2.1	6.8	7.9
carcinogenicity	0.4	1.1	2.6	5.6
chronic/carcinogenicity	0.3	0.9	2.3	5.1
bioaccumulation invertebrates	0	0	0.3	0.4

FIGURE A 1: Percentage of substances registered between 2008 and 2022 for which guideline studies were used to fulfil the standard information requirements

	VII	VIII	IX	X
genetic toxicity (in vitro)	10.8	4.9	5.5	4.8
acute toxicity	8.9	3.5	4.2	2.6
short-term toxicity to aqua. invert.	9.2	4.3	4.4	3.5
toxicity to aqua. algae and cyanobact.	8.7	5	5.2	3.9
skin sensitisation (in vivo)	6.2	4.1	4.4	4.7
eye irritation (in vivo)	2.9	1.4	3	1.9
short-term toxicity to fish	2.1	3.9	4.8	3.4
skin irritation/corrosion (in vivo)	2.8	0.7	2.7	2.3
skin irritation/corrosion (in vitro)	8.1	3.6	2.7	2.4
eye irritation (in vitro)	7.7	3.2	2.6	2.1
28d RDT	0.5	2.2	2.6	1
genetic toxicity (in vivo)	0.7	2.3	2.9	2.5
(sub)chronic RDT	0.2	0.5	6.6	3.8
developmental toxicity	0.3	0.4	7.9	3.5
combined 28d RDT with repro/dev screen	0.4	3.7	2.5	1.6
long-term toxicity to aquatic invertebrates	0.3	1.8	3.5	2.6
skin sensitisation (in vitro)	4.7	1.7	0.8	0.3
repro/dev toxicity screening test	0.2	1.8	1.6	1.5
toxicity to reproduction	0.1	0	1.7	4.3
toxicity to reproduction	0.5	1.1	2.4	3.5
bioaccumulation vertebrates	0.2	0.7	1.4	0.7
long-term toxicity to fish	0.1	0.2	2.6	1.7
carcinogenicity	0	-0.1	0.6	0.6
chronic/carcinogenicity	0	-0.1	0.8	0
bioaccumulation invertebrates	0	0	0.1	0.1

FIGURE A 2: Difference in the percentage of substances for which guideline studies were used to fulfil the standard information requirements (percentage in 2022 reported in Figure A 1 minus percentage in 2019 reported in previous report)

Options used to fulfil requirements (2008-2022)

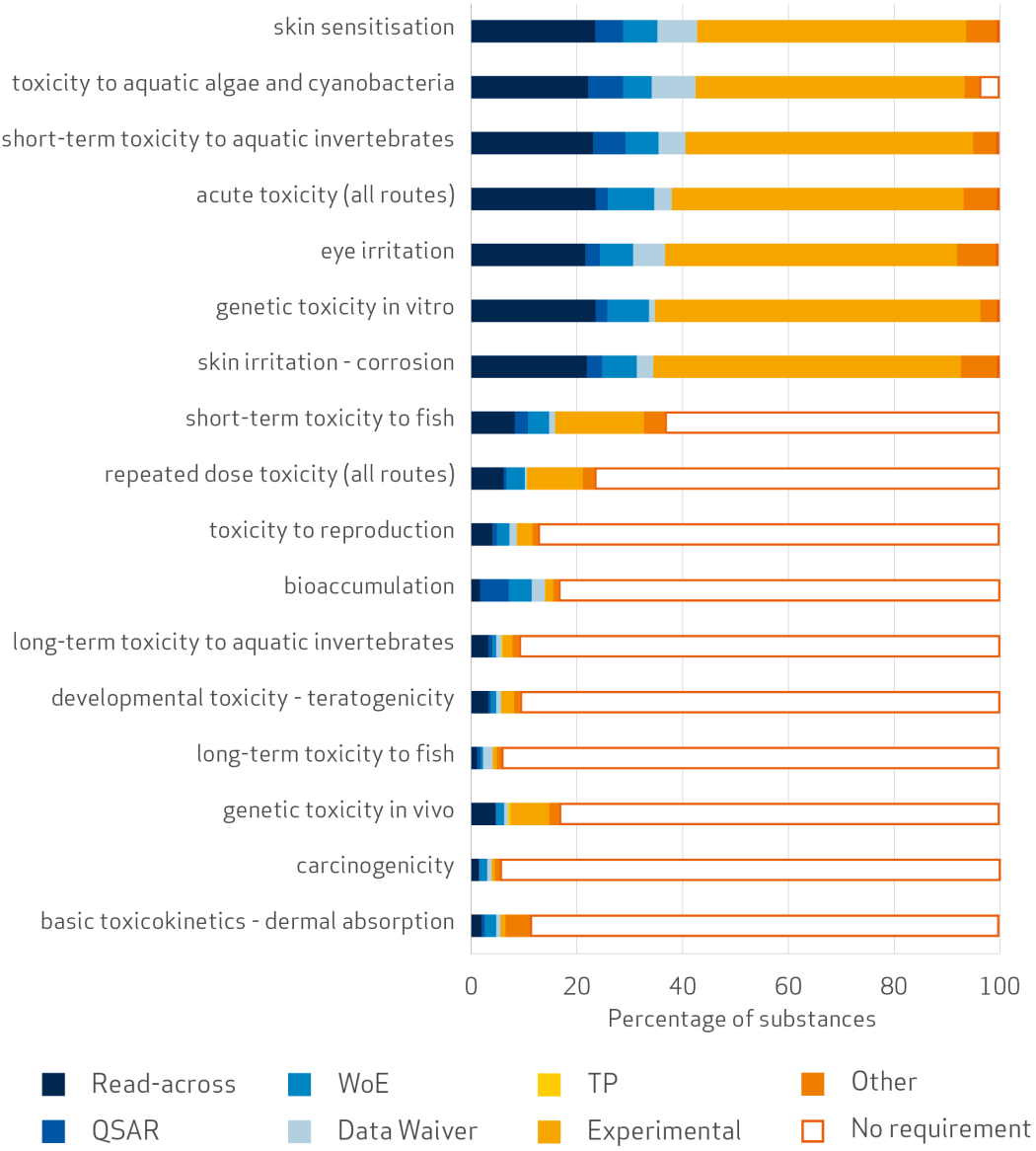


FIGURE A 3: Frequency of the different options used to fulfil the information requirements for the 4 901 substances registered between 2008 and 2022 at Annex VII within the scope of this report

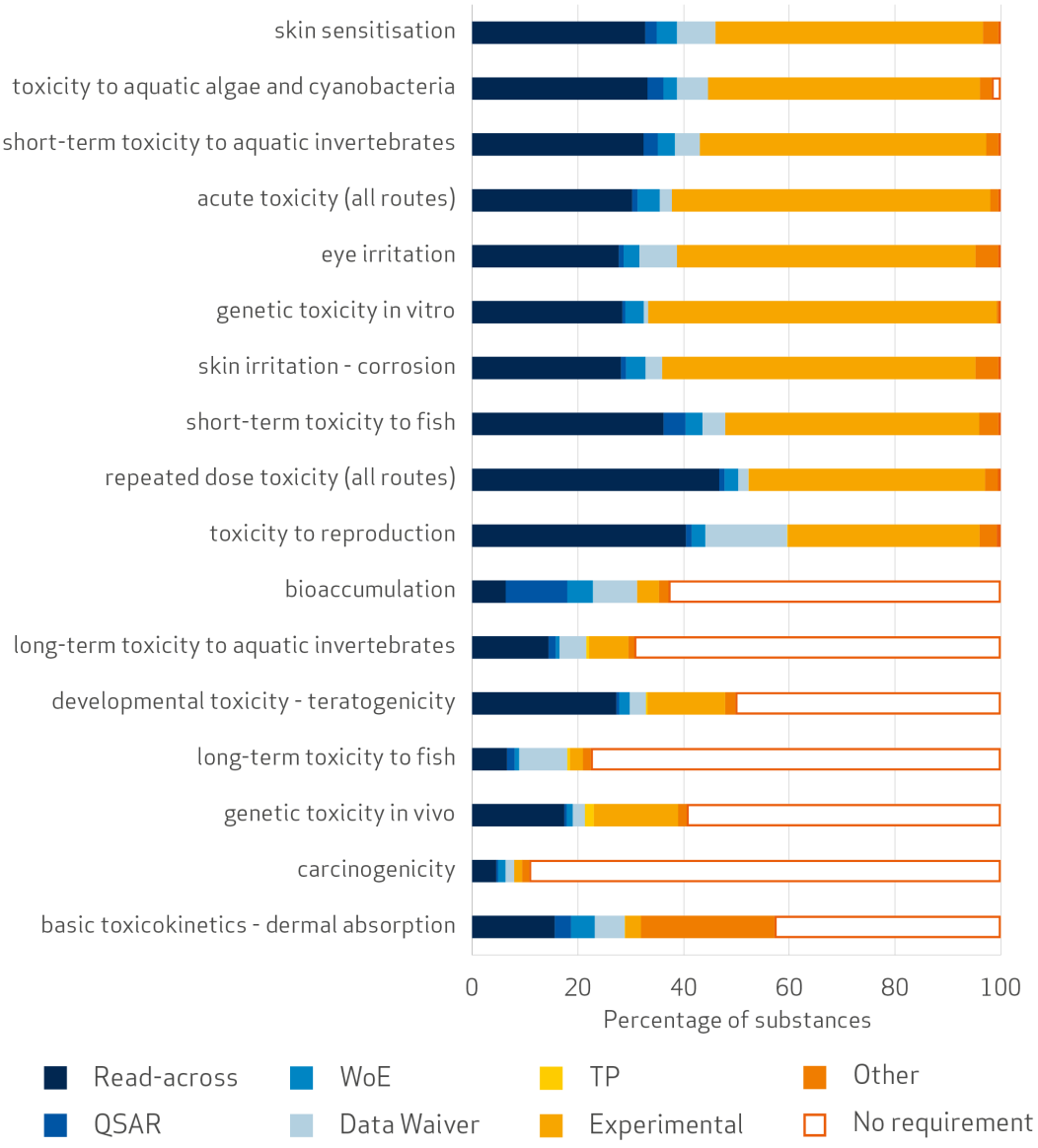


FIGURE A 4: Frequency of the different options used to fulfil the information requirements for the 2 857 substances registered between 2008 and 2022 at Annex VIII within the scope of this report

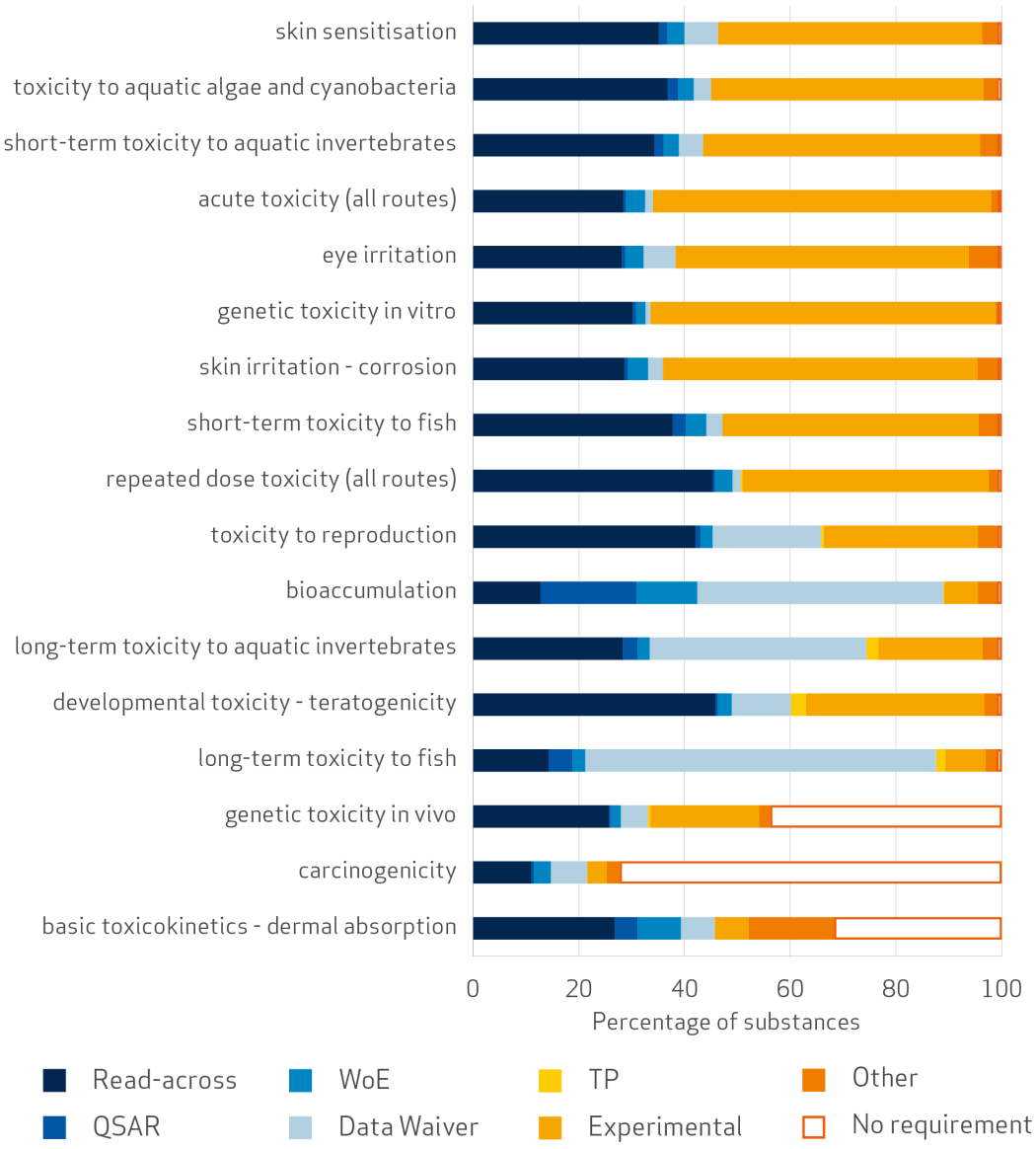


FIGURE A 5: Frequency of the different options used to fulfil the information requirements for the 2 346 substances registered between 2008 and 2022 at Annex IX within the scope of this report

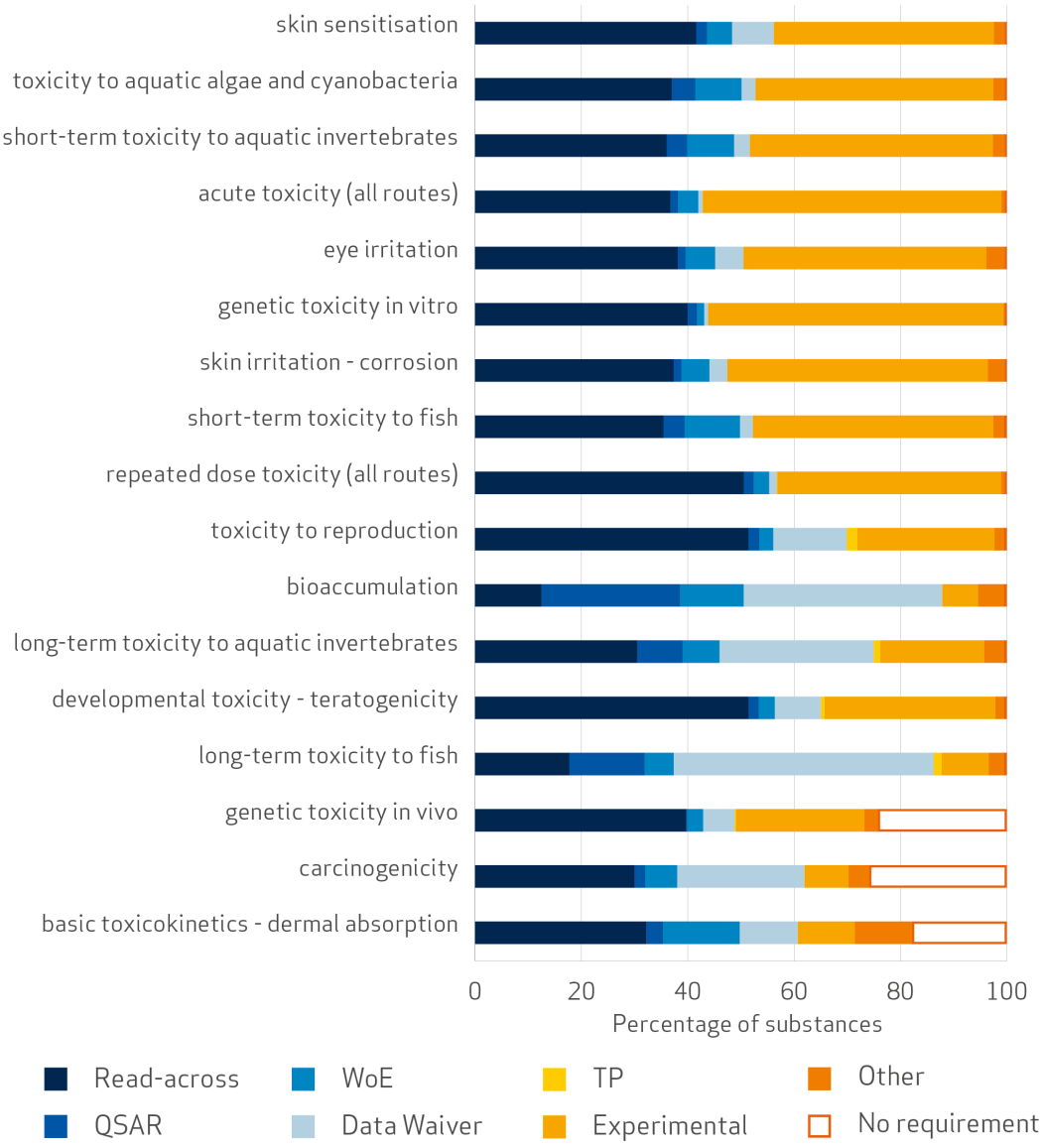


FIGURE A 6: Frequency of the different options used to fulfil the information requirements for the 2 335 substances registered between 2008 and 2022 at Annex X within the scope of this report

ANNEX III:

OCCURRENCE OF STUDIES OVER THE YEARS 1990- 2022

	skin corrosion/irritation		serious eye damage/eye irritation		skin sensitisation	
year	*in vivo*	*in vitro*	*in vivo*	*in vitro*	*in vivo*	*in vitro*
1990	198	1	153	0	110	0
1991	183	1	141	0	147	0
1992	200	0	151	2	175	0
1993	175	1	150	0	153	0
1994	148	7	116	2	188	0
1995	164	1	151	3	171	0
1996	194	7	138	1	146	0
1997	124	0	109	3	185	0
1998	118	15	129	1	144	0
1999	142	1	147	4	158	0
2000	136	2	131	3	132	0
2001	103	5	99	0	148	0
2002	155	9	137	2	165	0
2003	128	9	107	2	167	0
2004	155	15	103	2	195	0
2005	106	16	90	6	180	0
2006	117	23	89	10	156	0
2007	122	12	117	3	164	1
2008	115	34	112	7	193	0
2009	83	99	90	11	189	0
2010	109	282	173	129	358	2
2011	61	154	101	76	158	2
2012	141	320	185	205	369	10
2013	122	252	165	126	259	33
2014	88	209	115	159	185	29
2015	46	278	78	190	230	46
2016	70	423	97	352	301	78
2017	35	815	64	681	263	434
2018	34	941	71	834	243	827
2019	22	269	16	240	109	294
2020	12	183	14	167	57	155
2021	7	113	6	90	47	94
2022	36	31	24	36	29	18

TABLE 4: 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- 2022

ANNEX IV:

DETAILED OVERVIEW OF THE NEWLY REGISTERED SUBSTANCES (2019 – 2022)

Availability of experimental studies (2019 – 2022)

	VII	VIII	IX	X
genetic toxicity (in vitro)	71.5	57	76.4	54.5
acute toxicity	60.7	49	75	50
short-term toxicity to aqua. invert.	62.5	50.3	61.1	38.6
toxicity to aqua. algae and cyanobact.	60.9	51.7	65.3	38.6
skin sensitisation (in vivo)	50.6	33.6	23.6	15.9
eye irritation (in vivo)	48.2	28.9	20.8	13.6
short-term toxicity to fish	37.8	36.2	65.3	40.9
skin irritation/corrosion (in vivo)	22.3	25.5	61.1	43.2
skin irritation/corrosion (in vitro)	16.3	49	63.9	43.2
eye irritation (in vitro)	32.1	12.8	8.3	0
28d RDT	21.2	22.8	55.6	34.1
genetic toxicity (in vivo)	6.6	23.5	31.9	25
(sub)chronic RDT	5.3	20.1	29.2	22.7
developmental toxicity	1.8	9.4	33.3	27.3
combined 28d RDT with repro/dev screen	2.7	6	25	25
long-term toxicity to aquatic invertebrates	1.1	7.4	31.9	29.5
skin sensitisation (in vitro)	1.4	20.1	15.3	6.8
repro/dev toxicity screening test	1.1	5.4	25	18.2
toxicity to reproduction	1.1	5.4	19.4	20.5
toxicity to reproduction	1.3	3.4	20.8	20.5
bioaccumulation vertebrates	1.3	6.7	13.9	9.1
long-term toxicity to fish	0.3	12.1	5.6	4.5
carcinogenicity	0.5	3.4	13.9	11.4
chronic/carcinogenicity	0.2	4	9.7	15.9
bioaccumulation invertebrates	0	0	4.2	2.3

FIGURE A 7: Percentage of substances for which guideline studies were used to fulfil the standard information requirements, where the registered substance appears for the first time after 2019. The date of the study itself is not limited to a particular time period.

Options used to fulfil requirements (2019 – 2022)

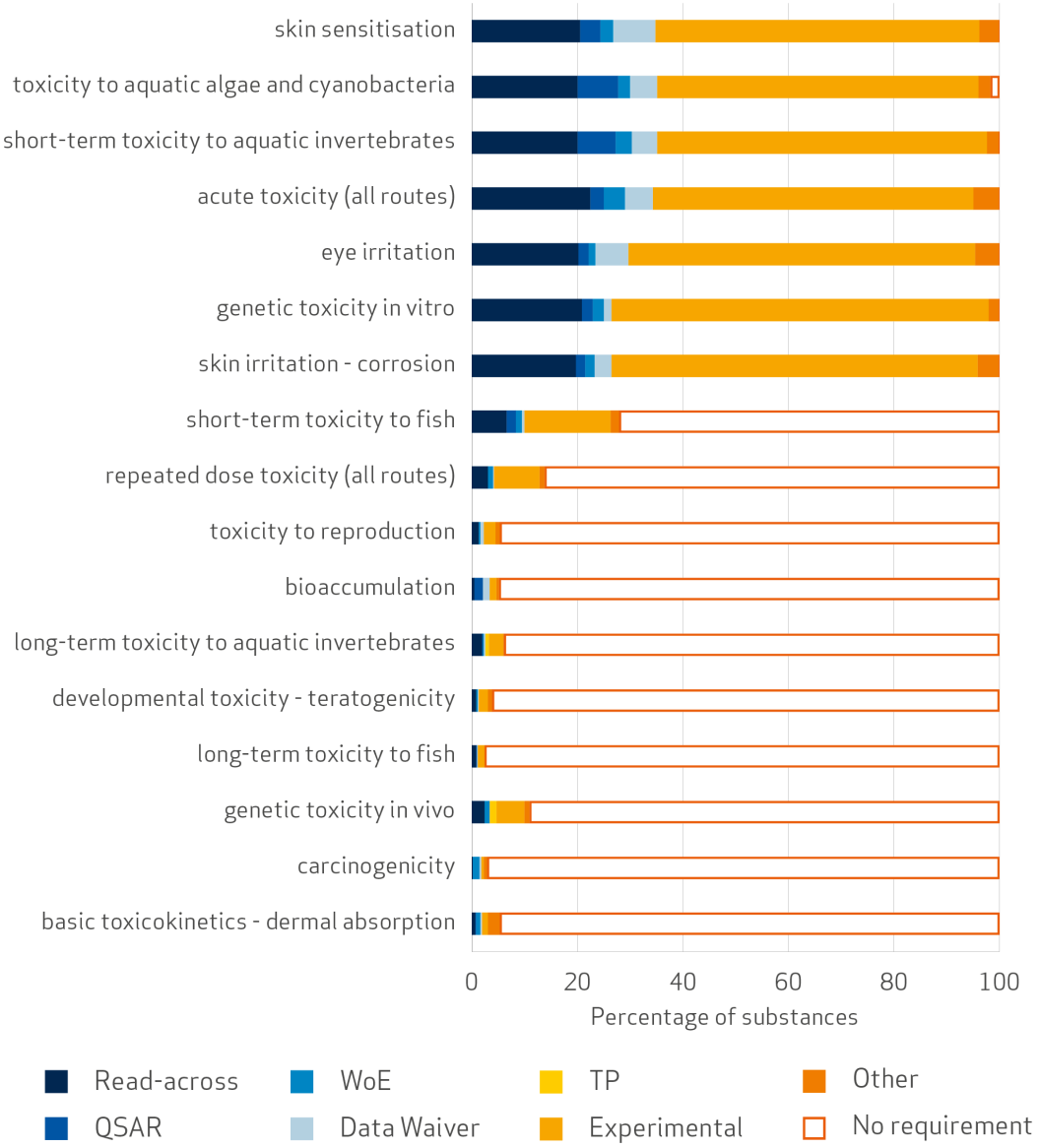


FIGURE A 8: Frequency of the different options used to fulfil the information requirements for the 624 substances registered at Annex VII between 2019 and 2022

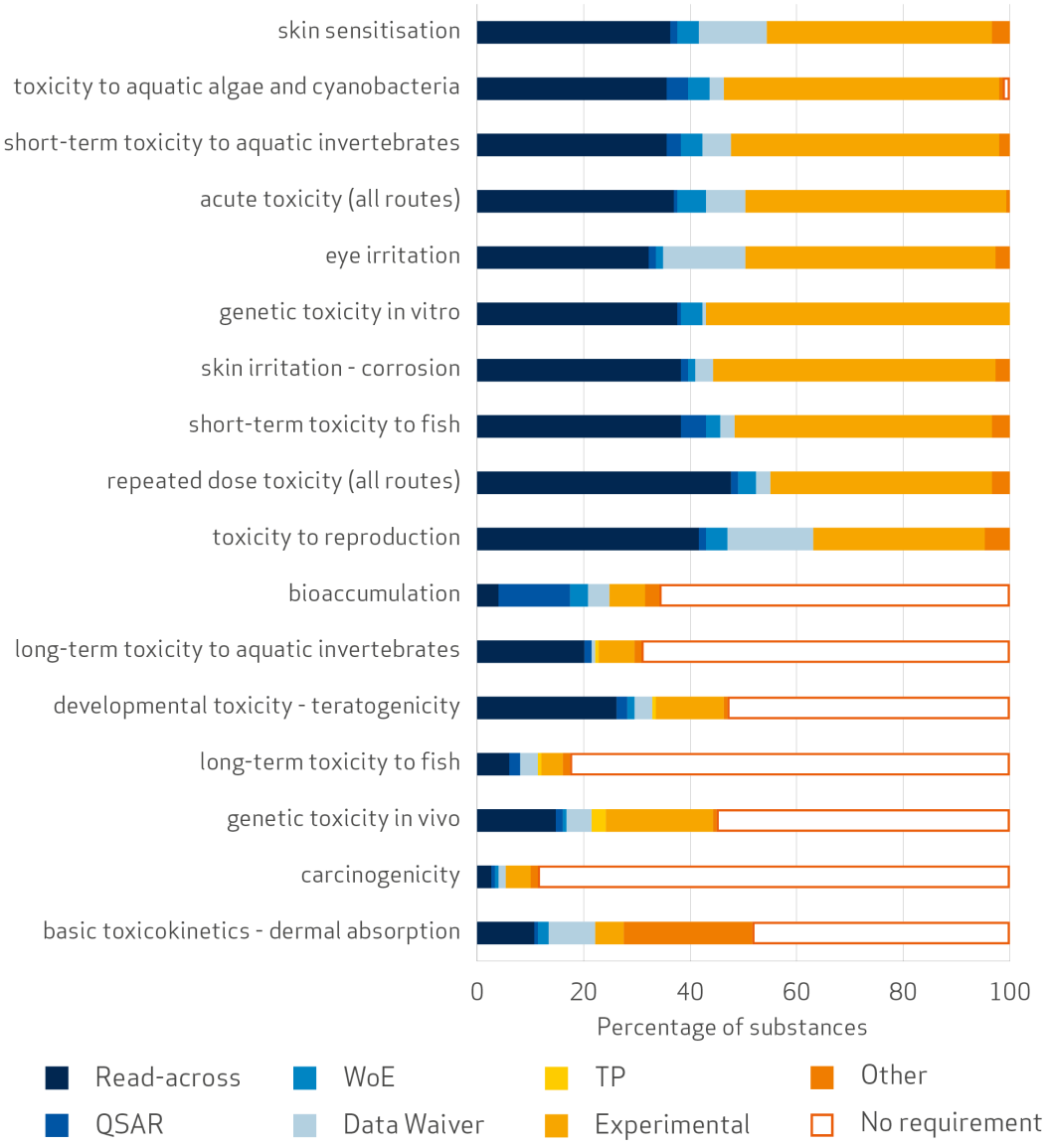


FIGURE A 9: Frequency of the different options used to fulfil the information requirements for the 149 substances registered at Annex VIII between 2019 and 2022

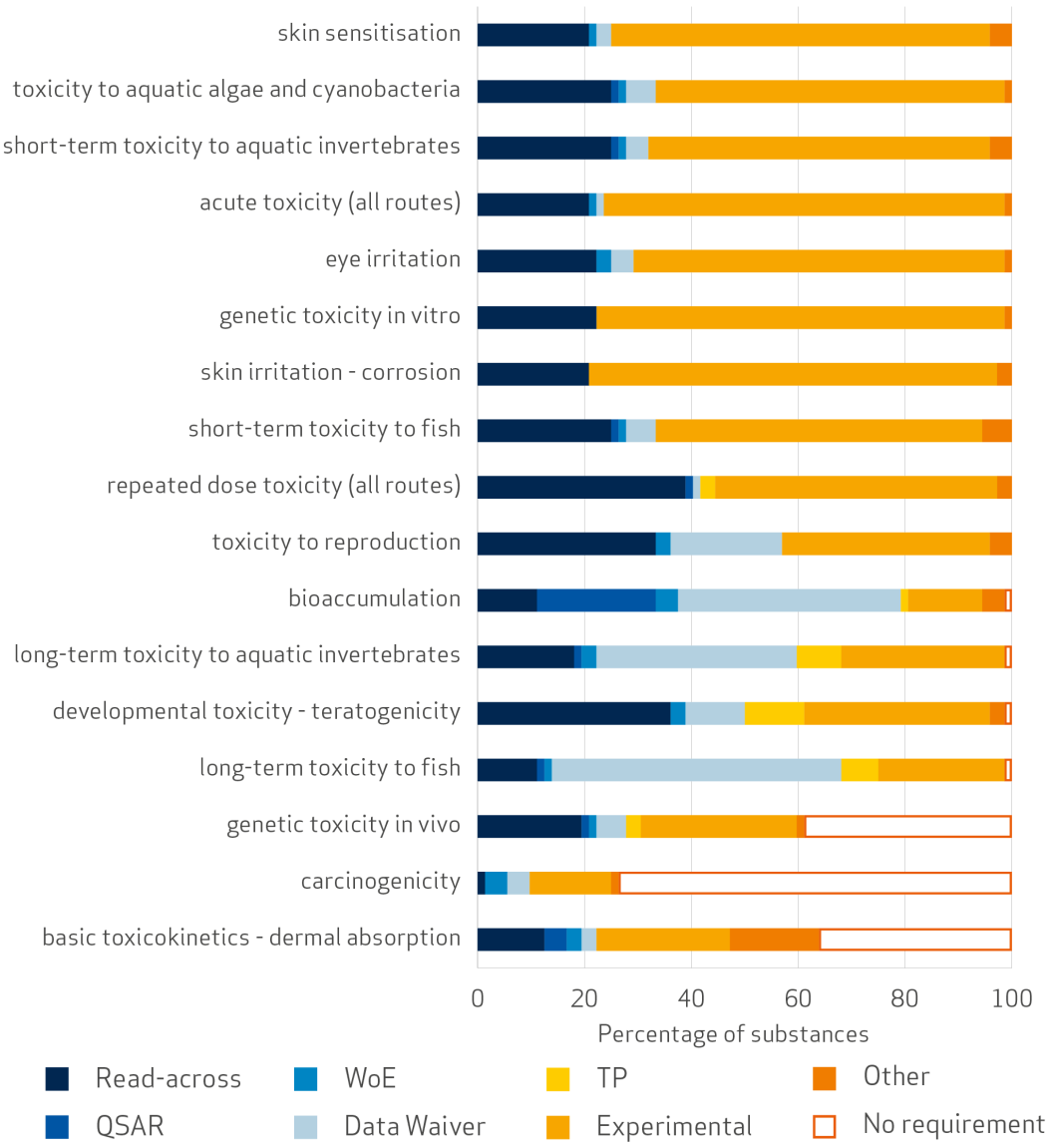


FIGURE A 10: Frequency of the different options used to fulfil the information requirements for the 72 substances registered at Annex IX between 2019 and 2022

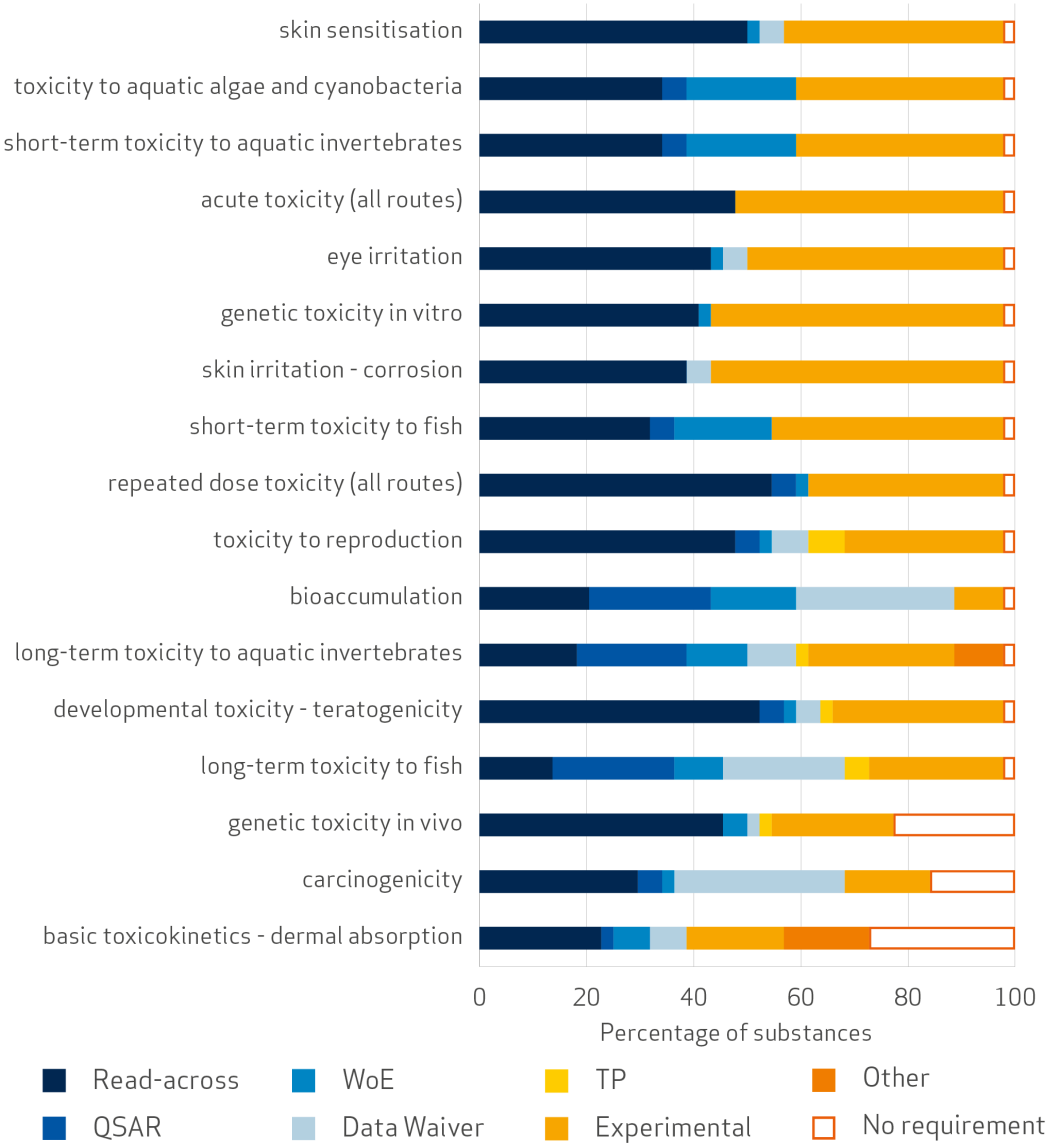


FIGURE A 11: Frequency of the different options used to fulfil the information requirements for the 44 substances registered at Annex X between 2019 and 2022

Experimental studies period (2019 – 2022)

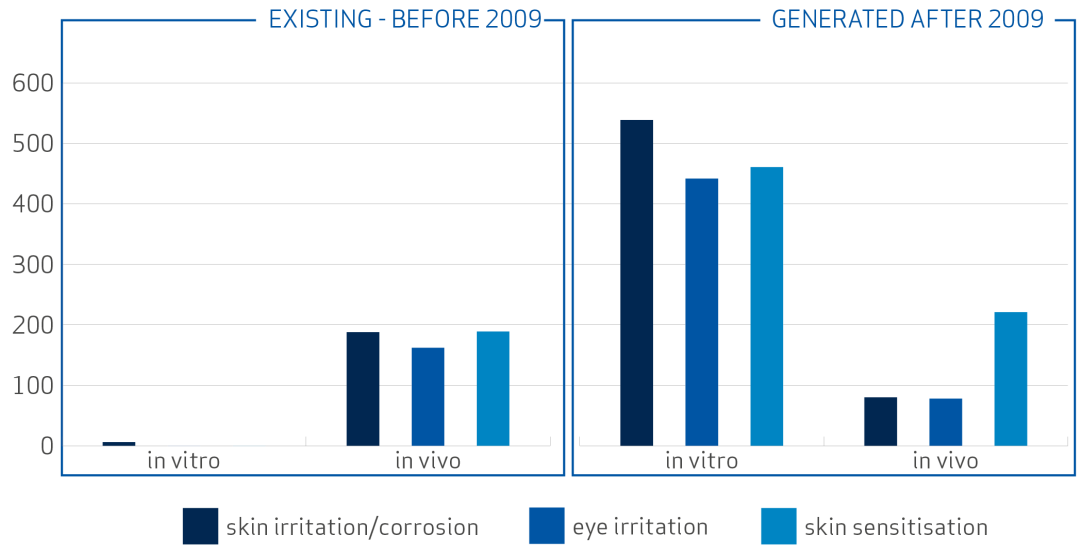


FIGURE A 12: Occurrence of in vivo and in vitro studies for the specific endpoints: Skin irritation/corrosion, eye irritation and skin sensitisation for new registrations (2019 – 2022)

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