ECHA
EUROPEAN CHEMICALS AGENCY

Survey results - Analysis of higher tier studies submitted without testing proposals

Submission of higher tier studies on vertebrate animals
for REACH registration without a regulatory decision on testing proposals
- a follow-up on the Article 117(3) report (2014)

Survey results - Analysis of higher tier studies submitted without testing proposals

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Introduction

This report is an analysis following the second report of the series on "*The Use of Alternatives to Testing on Animal for the REACH Regulation*" (hereinafter called "the report") (published on 2 June 2014). It provides an overview of the latest quantitative findings and the steps ECHA has taken to clarify the possible reasons why registrants have submitted new higher-tier studies on vertebrate animals (i.e. studies primarily referred to in Annexes IX and X to the REACH Regulation) without submitting a testing proposal (TP) and awaiting a prior regulatory decision to conduct the testing.

ECHA has contacted a number of registrants to better understand the reasons why they have provided such information in their registrations and not submitted a testing proposal.

1. Background

ECHA published the first report on "*The Use of Alternatives to Testing on Animal for the REACH Regulation*" in 2011. At that time, ECHA reported that a computer-based search conducted for statistical purposes showed that 107 higher tier studies in vertebrate animals appeared to have been conducted in the absence of an ECHA decision on a testing proposal.

This finding did not necessarily mean that registrants' obligations under REACH, to submit a testing proposal and await ECHA's decision, had not been followed. If new tests are available (e.g. not conducted for REACH purposes) and fall within the information requirements, registrants are obliged by REACH to include them in their registrations.

ECHA has previously reported that a number of the reported tests had been requested under previous EU legislation and has recommended that registrants include their reasons why the testing was conducted, if known, and which may explain why there was no need for a testing proposal.

As a follow up to these findings, ECHA sent a request to the respective Member State competent authorities (MSCAs) and national enforcement authorities (NEAs) to consider investigating whether there were instances of new animal tests being conducted where obligations to submit testing proposals and await ECHA's decision may have been breached.

In general, the feedback received by ECHA from the MSCAs/NEAs was that investigating the cases did not lead to the need for enforcement actions and that some registrants were reminded to observe their REACH obligations in this regard.

The second report of the series on "*The Use of Alternatives to Testing on Animal for the REACH Regulation*" (hereinafter called "the report") was published on 2 June 2014. The computational searches that were conducted for that report showed that, after excluding the 107 cases identified in 2011, a further 295 higher-tier vertebrate studies[1] appeared to have been submitted without a prior testing proposal and an ECHA decision permitting the test.

A computerised screening of the 295 cases also showed that there were possible explanations for 126 cases. The remaining cases were then subject to a telephone survey to find out the possible explanations, the

1 The report mentions 293 studies, not taking into account two studies that had been overlooked.

results of which are presented in this report.

When ECHA observes that a registrant has performed or is performing a higher-tier vertebrate test without having sought a prior regulatory decision from ECHA approving their testing strategy, the Agency informs the relevant Member State authorities in accordance with the relevant provisions of the REACH Regulation. This is so that the authorities have the opportunity to consider the need for any necessary investigations and enforcement actions, in accordance with Articles 125 and 126 of REACH.

2. Legal provisions

The aim pursued by the REACH Regulation in relation to testing proposals is explicitly described in the preamble of the regulation and in the legislative documents:

"*It is also necessary to ensure that generation of information is tailored to real information needs. To this end evaluation should require the Agency to decide on the programmes of testing proposed by manufacturers and importers*" (Recital 63 of the REACH Regulation, emphasis added).

According to Articles 10(a)(ix), 22(1)(h) and 40, as well as Annexes IX and X to the REACH Regulation, registrants are obligated to submit a testing proposal to ECHA and await its decision before conducting higher-tier animal tests to meet the information requirements specified in Annexes IX to X. Furthermore, in some cases, tests specified in Annexes IX and X may also need to be proposed where, for example, the conditions of Annex VIII 8.4, column 2, and the need to consider *in vivo* mutagenicity studies, are met.

It is here also noted that, according to Article 13(1), registrants have an obligation to consider "*whenever possible […] means other than vertebrate animal tests*" when information is generated to fulfil an information requirement. Under REACH, the steps registrants are to take before considering new testing in vertebrate animals for the purposes of registration are laid out in Annex VI, Guidance Note on Fulfilling the Requirements of Annexes VI to XI.

Furthermore, in line with Article 40(2) of the REACH Regulation, ECHA runs a public consultation on its website for all proposed vertebrate tests. The public consultation invites third parties to provide scientifically valid information that address the relevant substance and hazard endpoint.

If a registrant fails to make a testing proposal for a higher-tier vertebrate study and there are no explanations removing any concerns, the registrant may be presumed to have unnecessarily performed such a test in breach of Article 25 of the REACH Regulation, which provides that testing on vertebrate animals must only be undertaken as a last resort.

3. Methodology and findings

As explained in the 2014 report, ECHA identified new higher tier tests using computational analysis. As such, the analysis relies on the data provided by registrants in their dossiers (that were available on 1 October 2013) and is limited to what can be found using computational algorithms.

The data pool consisted of the registration dossiers of the lead registrants that were submitted by the first and second registration deadlines, for phase-in and non-phase-in substances at or above 100 tonnes

per year. A "new" study was one where it could not be established from the registration that the study was conducted before the operational parts of the REACH Regulation came into force on 1 June 2008.

The 107 cases of new higher-tier tests without testing proposals, which were previously identified following the 2011 report and already reported to the MSCAs/NEAs in 2012, were excluded from the 2014 report and from this analysis as were those studies for which the tests were linked to ECHA decision-making on testing proposals.

In addition, after eliminating the clear read-across cases (i.e. using studies conducted on other analogous substances) using computational tools, ECHA has not further manually assessed whether the substance reported as the test material in the studies was always the registered substance. There is a possibility that the study was actually conducted on another substance which itself may, or may not, be subject to obligations under REACH to submit a testing proposal. It is expected, however, that the computational search that has been conducted would have identified new tests conducted on the analogous substances subject if they are present in a registration under REACH and were in the datapool.

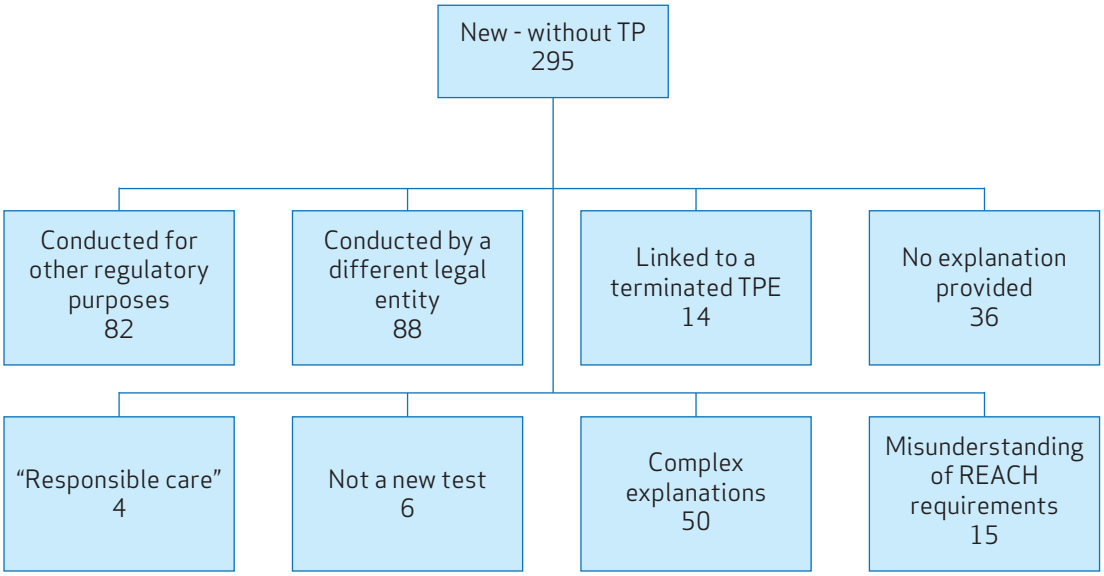
The computerised screening of information extracted from the dossiers indicated that the "new" tests could be assigned to one of three categories. Either they were generated to meet other regulatory purposes (40 cases), were conducted by a different legal entity than the registrant (72 cases) or were linked to the termination by ECHA of a testing proposal evaluation (TPE) (14 cases).

There are limitations to what can be achieved through the computerised search, as information about why the tests were conducted is often not provided in registration dossiers.

In addition, the information may have been present in the registration but could not be detected by the algorithms. So for 169 cases, the possible reasons for the submission of the new studies could not be determined using this approach.

These cases were entered into a survey in which registrants were contacted by telephone and invited to give their reasons why the tests were available to them. After the survey, the responses were collated and ECHA created categories of possible explanations in addition to those mentioned above, to better match the responses of registrants so far as was possible. These are depicted in Figure 1 below.

Figure 1. Categorisation of explanations for not submitting a testing proposal (number of cases based on the combination of data mining and results from the survey)



The studies from companies that ECHA was unable to contact or that did not respond to the survey, were categorised as "No explanation provided" (36 cases).

A breakdown of the cases by substance is in the appendix to this report.

4. Analysis of results

4.1 HIGH RESPONSE RATE FROM SURVEY

ECHA successfully contacted 86 % of the 89 companies identified for the survey by phone. Responses to the survey were obtained from 78% of the 89 identified companies contacted. The high level of cooperation from industry and willingness to contribute to the survey greatly helped ECHA in refining its assumptions and to complete its analysis.

4.2 CATEGORIES OF EXPLANATION

The categories of registrants' explanations identified can be summarised as follows:

- "Conducted for other regulatory purposes": The registrants of the studies assigned to this category have reported that the study may have been performed to fulfil other regulatory requirements, within the EU (e.g. the Biocidal Products Regulation) or outside the EU (e.g. tests conducted to a non-OECD or non-EU-method guideline).

- "Conducted by a different legal entity": The studies in this category were those conducted by a legal entity different from the registrant. For example, the registrant indicated that they were not the data owner or had a letter of access. In addition, some registrants may have indicated that these studies were also conducted for other regulatory purposes.

- "Linked to a terminated testing proposal evaluation (TPE)": The studies in this category were ongoing or already completed (according to the dates provided in the registration) although the registrant simultaneously submitted a testing proposal to ECHA. Consequently, ECHA terminated the testing proposal evaluation process and informed the MSCAs about these cases.

- "Responsible care": The registrants of the studies assigned to this category explained that the test was conducted to guarantee safe use of the chemical substance to downstream users. Two companies used the phrasing "responsible care" while two others used "product stewardship reasons".

- "Not a new test": The registrants of the studies designated to this category confirmed that they had commissioned the study before REACH came into force. These six cases can be considered as "false positives" from the data-mining search and on that basis may not warrant any further attention in this analysis.

- "Complex explanations": This category includes the studies, for which registrants provided complex or unclear explanations.

- "Misunderstanding of REACH requirements": The registrants of the studies assigned to this category explained that based on their interpretation, they had not understood that a testing

proposal was necessary before performing the vertebrate study.

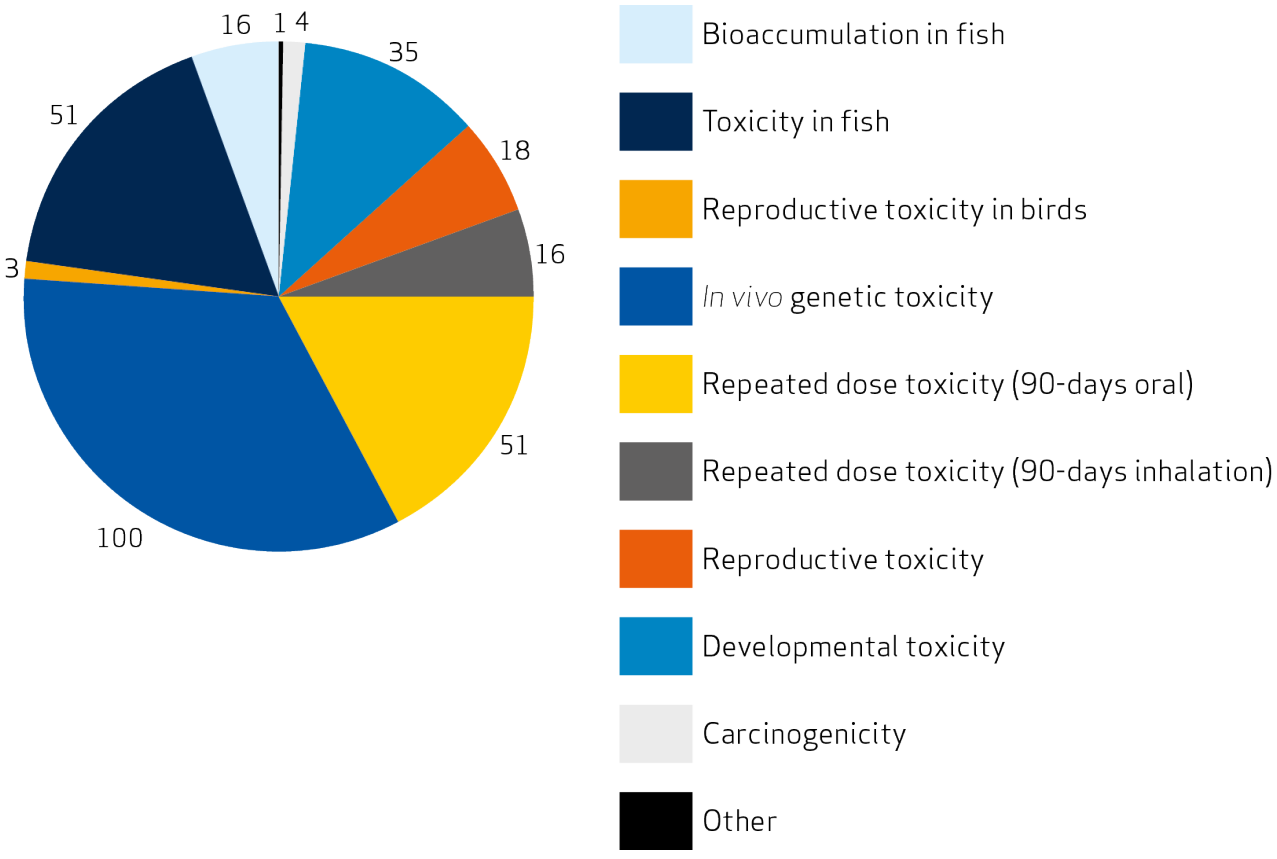
- "No explanation provided": The registrants of the remaining studies identified by data mining could not be contacted by ECHA or did not provide any explanation.

4.3 DISTRIBUTION BETWEEN HUMAN HEALTH AND ENVIRONMENTAL ENDPOINTS

The distribution of the studies is presented in Figure 2. The numbers of studies per category were defined, based on the information from the IUCLID fields "study type" and "study title", in combination.

Altogether, 70 of the 295 studies covered environmental endpoints and 225 studies were for human health endpoints. Notably, the search identified 100 *in vivo* genetic toxicity studies for which no testing proposal had been submitted to ECHA (further discussed in section 4.6 below).

Figure 2. Distribution of studies without a testing proposal according to different endpoints



4.4 CONDUCTED BY A DIFFERENT LEGAL ENTITY

It was established through the analysis that the studies were conducted or owned by a legal entity other than the lead registrant in 88 cases.

In 57 cases, the registrants appeared to have used data from a legal entity which may not have been obligated to submit a testing proposal, for example, under knowledge-sharing agreements. These may be data owners outside the EU or industry associations that do not themselves have obligations to submit a testing proposal under REACH. In the remainder (31 cases), the data owner appeared from a visual check of their address, to be located in the EU.

4.5 SPECIFICITY WHEN TPE WAS TERMINATED

In 14 of the 295 cases identified, a testing proposal had been submitted but the evaluation had subsequently been terminated by ECHA, when the Agency had noted that *in vivo* testing was already on-going or completed, making the examination and the decision-making obsolete. The relevant details of these cases were communicated to Member State authorities at the time of termination.

4.6 MISUNDERSTANDING OF THE REACH INFORMATION REQUIREMENTS RELATED TO THE *IN VIVO* GENOTOXICITY ENDPOINT

Studies in the category "Misunderstanding of REACH requirements" are those studies submitted under the IUCLID endpoint 7.6.2, which corresponds to Annexes IX and X section 8.4 "Further mutagenicity/ genotoxicity study" to the REACH Regulation.

ECHA further noted a potential misunderstanding in the reading of the second column on Annex VIII, section 8.4 of REACH, which provides that "*appropriate in vivo mutagenicity studies shall be considered in case of a positive result in any of the* [*in vitro*] *genotoxicity studies in Annex VII or VIII*".

As already reported in the 2011 report, registrants may have incorrectly interpreted this, to mean that they are not required, at that tonnage level, to submit a testing proposal before conducting an *in vivo* genotoxicity study triggered by positive results from *in vitro* tests. It is, however, the case that new *in vivo* mutagenicity studies, conducted for the purposes of fulfilling the REACH information requirements, require a testing proposal.

In 2013, ECHA introduced a clarification into a draft of the guidance, and the final version is now published (Version 3.0, Chapter R7a - Mutagenicity related sections).

This potential for misunderstanding the REACH information requirement is considered as one possible explanation as to why (100) *in vivo* genetic toxicity studies were identified in the statistical search for which no testing proposal decision was issued (Figure 2).

However, in the course of the survey, ECHA identified that most of the registrants ECHA contacted also had other explanations behind the testing (e.g. responsible care, other regulatory purposes). As a result, 15 of these 100 studies fall solely into the category "Misunderstanding of REACH requirements".

5. Conclusions

As previously reported, ECHA found that while the absolute number of studies, which appeared to have been performed without permission from the Agency, was higher than previously reported (107 in 2011 to 295 in 2014), the proportion of such tests to the total number of new experimental studies *in vivo* has remained similar: 5.5% reported in 2011 and 6% reported in 2014.

As such, the finding of a new higher-tier test, without prior submission of a testing proposal and awaiting an ECHA decision, does not necessarily represent non-compliance with the REACH provisions.

Registrants may have reasons why the studies were available to them and included the studies in their dossiers but these reasons may not be apparent from the information provided in registrations. The fact, for example, that no explanation is also provided in a registration dossier does not itself mean that the registrant has not complied with the requirements of the REACH Regulation. However, in those cases where registrants do transparently provide their reasons, it becomes easier to judge whether a testing proposal should or should not have been submitted.

Computerised screening conducted by ECHA could identify a number of cases where it appears that the studies may have been conducted, for example, to meet other regulatory requirements, among others.

A survey of the registrants provided more details about the remaining cases. After the survey, it was apparent that in the majority of cases, registrants were often willing and able to clarify why the new studies were conducted or were available to them and were submitted for the purposes of registration.

ECHA observes that despite its previous recommendation, registrants do not often include these reasons in their registration dossiers. Providing the reasons, for example, in the respective endpoint study records that are disseminated by ECHA, would allow registrants to demonstrate why the studies were available.

In a number of cases, it is as yet uncertain whether or not there is a potential non-compliance with the registrant's obligations, according to Articles 10(a)(ix) or 22(1)(h), to submit a testing proposal and await ECHA's decision before conducting a higher-tier vertebrate animal study.

Most obviously, this applies to those cases where registrants did not, at the time the survey was conducted (2014), provide any reasons for the submission of the tests (36), or provided complex or unclear responses to the survey (50) or provided only generic reasons such as "responsible care".

The MSCAs and NEAs have the most effective means to clarify whether in the cases described that the registrants are complying with their obligations and whether these cases may warrant investigation by MSCAs/NEAs. ECHA has invited the MSCAs/NEAs to provide feedback on the outcomes of any investigations in such cases.

APPENDIX: List of substances for which registrants submitted at least one higher-tier study without submitting a testing proposal

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
200-663-8	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
200-752-1	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations
200-815-3	7.5.2	Repeated dose toxicity (90-days inhalation)	Conducted by a different LE
200-815-3	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
200-872-4	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
200-879-2	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
200-939-8	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
201-100-9	7.6.2	*In vivo* genetic toxicity	Complex explanations
201-245-8	6.1.2	Toxicity in fish	Conducted by different LE/ Other regulatory purposes
201-297-1, 220-688-8, 212-782-2, 202-597-5, 248-666-3	7.8.1	Reproductive toxicity	Conducted by a different LE
201-297-1, 220-688-8, 212-782-2, 202-597-5, 248-666-3	7.8.2	Developmental toxicity	Not a new test
202-374-2	7.6.2	*In vivo* genetic toxicity	Complex explanations
202-500-6	7.8.1	Reproductive toxicity	Conducted by a different LE
202-613-0, 219-674-4, 202-615-1	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
202-617-2	7.8.2	Developmental toxicity	Conducted by a different LE
202-874-0	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
202-969-7	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
203-004-2	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
203-161-7	7.8.1	Reproductive toxicity	Conducted by a different LE
203-219-1	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
203-308-5	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
203-328-4	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
203-375-0	7.6.2	*In vivo* genetic toxicity	Complex explanations

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
203-474-9	6.1.2	Toxicity in fish	Linked to a terminated TPE
203-474-9	7.5.1	Repeated dose toxicity (90-days oral)	Linked to a terminated TPE
203-474-9	7.5.1	Repeated dose toxicity (90-days oral)	Linked to a terminated TPE
203-497-4	7.5.2	Repeated dose toxicity (90-days inhalation)	Conducted by a different LE
203-497-4	6.1.2	Toxicity in fish	No explanation provided
203-497-4	6.1.2	Toxicity in fish	No explanation provided
203-797-5	6.1.2	Toxicity in fish	Complex explanations
203-846-0	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
203-920-2	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
203-920-2	6.1.2	Toxicity in fish	Other regulatory purposes
203-921-8	7.5.2	Repeated dose toxicity (90-days inhalation)	Conducted by a different LE
203-973-1	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
203-983-6	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
204-815-4	7.8.1	Reproductive toxicity	No explanation provided
204-847-9	6.1.2	Toxicity in fish	Other regulatory purposes
204-847-9	7.8.2	Developmental toxicity	Other regulatory purposes
205-201-9	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
205-491-7	7.5.2	Repeated dose toxicity (90-days inhalation)	No explanation provided
206-696-4	7.8.1	Reproductive toxicity	No explanation provided
208-156-3	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
208-169-4, 215-157-2, 231-158-0, 233-334-2, 200-755-8, 244-166-4, 231-589-4, 205-250-6, 270-601-2, 215-154-6, 233-402-1, 234-614-7, 215-273-3, 216-333-1	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
208-762-8	7.6.2	*In vivo* genetic toxicity	No explanation provided
208-857-4	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
209-062-5	7.8.1	Reproductive toxicity	Linked to a terminated TPE
209-264-3	7.8.2	Developmental toxicity	Other regulatory purposes

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
210-431-8	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by different LE/ Other regulatory purposes
210-871-0	6.1.2	Toxicity in fish	Other regulatory purposes
210-871-0	6.1.2	Toxicity in fish	Other regulatory purposes
210-871-0	7.5.2	Repeated dose toxicity (90-days inhalation)	Other regulatory purposes
211-112-6	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations
211-309-7	7.5.1, 7.7	Carcinogenicity	Other regulatory purposes
211-309-7	7.7	Carcinogenicity	Other regulatory purposes
211-309-7	7.7	Carcinogenicity	Other regulatory purposes
211-309-7	7.7, 7.5.2	Carcinogenicity	Other regulatory purposes
211-471-9	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
211-708-6	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
211-708-6, 202-613-0, 202-615-1	7.8.2	Developmental toxicity	Conducted by a different LE
213-382-0	7.6.2	*In vivo* genetic toxicity	Linked to a terminated TPE
213-537-2	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
213-879-2, 213-561-3	6.1.2	Toxicity in fish	not a new test
214-604-9	7.8.2	Other	Other regulatory purposes
215-183-4	6.1.2	Toxicity in fish	Linked to a terminated TPE
215-214-1	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
215-222-5	7.8.2	Developmental toxicity	Conducted by a different LE
215-222-5	7.5.2	Repeated dose toxicity (90-days inhalation)	Conducted by a different LE
215-239-8	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
215-239-8	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
215-248-7	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
215-266-5	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
215-691-6	6.1.2	Toxicity in fish	Conducted by different LE/ Other regulatory purposes
216-343-6	7.5.1	Repeated dose toxicity (90-days oral)	not a new test
218-561-7	7.5.2	Repeated dose toxicity (90-days inhalation)	Complex explanations
218-561-7	7.6.2	*In vivo* genetic toxicity	Complex explanations

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
218-747-8	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
219-154-7	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
219-372-2	7.6.2	*In vivo* genetic toxicity	Conducted by different LE/ Other regulatory purposes
220-099-6	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
220-237-5	7.6.2	*In vivo* genetic toxicity	Complex explanations
221-209-5	7.6.2	*In vivo* genetic toxicity	Complex explanations
221-641-4	7.5.2	Repeated dose toxicity (90-days inhalation)	Complex explanations
222-020-0	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
222-182-2	6.1.2	Toxicity in fish	Other regulatory purposes
222-429-4	7.6.2	*In vivo* genetic toxicity	Conducted by different LE/ Other regulatory purposes
222-530-3, 228-788-3, 239-898-6	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
222-695-1	5.3.1	Bioaccumulation in fish	No explanation provided
222-695-1	7.8.2	Developmental toxicity	No explanation provided
222-695-1	7.8.2	Developmental toxicity	No explanation provided
222-695-1	7.5.1	Repeated dose toxicity (90-days oral)	No explanation provided
222-695-1	7.6.2	*In vivo* genetic toxicity	No explanation provided
222-852-4	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
223-118-6	5.3.1	Bioaccumulation in fish	Responsible care
223-989-2	7.6.2	*In vivo* genetic toxicity	No explanation provided
224-518-3	7.8.2	Developmental toxicity	Complex explanations
224-809-5	6.1.2	Toxicity in fish	Complex explanations
224-929-8	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
225-266-7	6.1.2	Toxicity in fish	Complex explanations
225-642-0	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
225-730-9	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
228-768-4	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
229-194-7	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
229-563-2	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
230-279-6	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
231-131-3	7.5.2	Repeated dose toxicity (90-days inhalation)	Not a new test
231-391-8	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
231-609-1	6.1.2	Toxicity in fish	Complex explanations
231-869-6	6.1.2	Toxicity in fish	Conducted by a different LE
231-955-3	7.5.2	Repeated dose toxicity (90-days inhalation)	Other regulatory purposes
231-957-4	6.1.2	Toxicity in fish	Conducted by a different LE
232-565-6	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
232-734-4	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
234-217-9	6.1.2	Toxicity in fish	Other regulatory purposes
234-666-0, 240-985-6	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
235-627-0	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations
235-721-1	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
235-721-1, 232-192-9, 237-389-3, 282-217-2, 231-551-7, 235-650-6, 231-107-2, 248-517-2, 234-722-4, 242-637-9, 289-178-0, 215-204-7	6.1.2	Toxicity in fish	Other regulatory purposes
237-537-7	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
237-537-7	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
237-864-5	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations
237-926-1	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
239-407-5	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations
239-407-5	7.8.1	Reproductive toxicity	Complex explanations
239-415-9	7.6.2	*In vivo* genetic toxicity	Complex explanations
239-622-4, 248-227-6	5.3.1	Bioaccumulation in fish	Conducted by a different LE
241-004-4	6.1.2	Toxicity in fish	Other regulatory purposes
241-460-4, 240-969-9	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
241-774-1	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
243-718-1	5.3.1	Bioaccumulation in fish	Conducted by a different LE
244-344-1	6.1.2	Toxicity in fish	No explanation provided
244-344-1	7.5.1	Repeated dose toxicity (90-days oral)	No explanation provided
244-344-1	7.6.2	*In vivo* genetic toxicity	No explanation provided
244-344-1	7.8.2	Developmental toxicity	No explanation provided
244-492-7	7.6.2	*In vivo* genetic toxicity	No explanation provided
246-619-1	5.3.1	Bioaccumulation in fish	No explanation provided
247-979-2	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
248-093-9	5.3.1	Bioaccumulation in fish	No explanation provided
248-093-9	6.1.2	Bioaccumulation in fish	No explanation provided
248-227-6	7.6.2	*In vivo* genetic toxicity	No explanation provided
250-480-2	7.6.2	*In vivo* genetic toxicity	No explanation provided
251-649-3	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
252-558-1	7.8.2	Developmental toxicity	Other regulatory purposes
252-772-5	7.6.2	*In vivo* genetic toxicity	Complex explanations
252-772-5	7.6.2	*In vivo* genetic toxicity	Complex explanations
257-288-8	7.8.1	Reproductive toxicity	Conducted by a different LE
257-573-7	6.1.2	Toxicity in fish	Other regulatory purposes
257-900-3	7.6.2	*In vivo* genetic toxicity	Complex explanations
259-715-3	6.1.2	Toxicity in fish	Other regulatory purposes
262-975-0	7.6.2	*In vivo* genetic toxicity	Complex explanations
263-064-0	6.1.2	Toxicity in fish	Conducted by a different LE
264-261-4	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
265-088-7	7.8.1	Reproductive toxicity	Other regulatory purposes
265-196-4	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
266-047-6, 273-688-5	6.1.2	Toxicity in fish	Conducted by a different LE
266-047-6, 273-688-5	6.1.2	Toxicity in fish	Other regulatory purposes
266-047-6, 273-688-5	6.1.2	Toxicity in fish	Other regulatory purposes
266-358-7	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
266-380-7	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
269-389-4	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
270-704-2	7.5.2	Repeated dose toxicity (90-days inhalation)	Conducted by a different LE
270-704-2	7.8.2	Developmental toxicity	Conducted by a different LE
270-704-2	7.8.1	Repeated dose toxicity (90-days inhalation)	Conducted by a different LE
270-704-2	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
271-756-9	6.1.2	Toxicity in fish	Complex explanations
271-877-7	5.3.1	Bioaccumulation in fish	Conducted by a different LE
272-805-7	6.1.2	Toxicity in fish	Other regulatory purposes
274-581-6	5.3.1	Bioaccumulation in fish	Conducted by a different LE
275-156-8	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
282-217-2, 231-551-7, 235-650-6, 231-107-2, 248-517-2, 234-722-4, 242-637-9, 289-178-0, 215-204-7	5.3.1	Bioaccumulation in fish	Conducted by a different LE
282-217-2, 235-650-6, 248-517-2, 234-722-4, 242-637-9, 289-178-0, 215-204-7	7.8.2	Developmental toxicity	Conducted by a different LE
282-217-2, 248-517-2, 242-637-9, 289-178-0, 215-204-7	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
282-220-9, 909-586-0, 244-492-7, 215-691-6, 231-072-3	6.1.2	Toxicity in fish	Conducted by a different LE
282-758-4	7.8.2	Developmental toxicity	Other regulatory purposes
283-219-6	7.6.2	*In vivo* genetic toxicity	Complex explanations
283-829-2	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
283-829-2	5.3.1	Bioaccumulation in fish	Conducted by a different LE
283-829-2	7.8.2	Developmental toxicity	Conducted by a different LE
283-829-2	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
284-366-9	6.3.5	Reproductive toxicity in birds	Other regulatory purposes
286-304-6	7.6.2	*In vivo* genetic toxicity	Responsible care
290-754-9	7.8.2	Developmental toxicity	Other regulatory purposes
295-556-6	6.1.2	Toxicity in fish	Complex explanations
296-665-1	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
297-049-5	7.5.1	Repeated dose toxicity (90-days oral)	No explanation provided
302-434-9	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
309-712-9	7.8.1	Reproductive toxicity	Conducted by a different LE
309-886-6	7.5.1	Repeated dose toxicity (90-days oral)	Linked to a terminated TPE
310-154-3	7.8.1	Reproductive toxicity	Conducted by a different LE
401-680-5	7.8.1	Reproductive toxicity	Complex explanations
403-030-6	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
403-030-6	6.1.2	Toxicity in fish	No explanation provided
406-080-7	7.8.1	Reproductive toxicity	Other regulatory purposes
406-080-7	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
410-190-0	7.8.2	Developmental toxicity	No explanation provided
412-300-2	6.1.2	Toxicity in fish	Other regulatory purposes
412-300-2	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
412-300-2	7.8.1	Reproductive toxicity	Other regulatory purposes
412-570-1	7.8.2	Developmental toxicity	Linked to a terminated TPE
412-570-1	7.8.1	Reproductive toxicity	Linked to a terminated TPE
415-430-8	7.8.2	Reproductive toxicity	Conducted by a different LE
421-090-1	7.8.1	Reproductive toxicity	Linked to a terminated TPE
423-300-7	7.8.1	Developmental toxicity	Conducted by a different LE
423-630-1	7.8.2	Developmental toxicity	Other regulatory purposes
425-220-8	5.3.1	Bioaccumulation in fish	Other regulatory purposes
425-220-8	6.1.2	Toxicity in fish	Other regulatory purposes
426-040-2	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
428-100-3	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
428-100-3	7.8.2	Developmental toxicity	Conducted by a different LE
436-900-9	7.8.2	Developmental toxicity	Conducted by a different LE
436-900-9	7.8.1	Reproductive toxicity	Conducted by a different LE
447-010-5	6.1.2	Toxicity in fish	Other regulatory purposes
447-010-5	7.5.2	Repeated dose toxicity (90-days inhalation)	Other regulatory purposes
447-060-8	6.1.2	Toxicity in fish	Other regulatory purposes

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
447-920-2	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
447-920-2	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
447-920-2	6.1.2	Toxicity in fish	Other regulatory purposes
451-530-8	6.3.5	Reproductive toxicity in birds	No explanation provided
460-100-9	7.6.2	*In vivo* genetic toxicity	Linked to a terminated TPE
460-100-9	7.8.2	Developmental toxicity	Linked to a terminated TPE
460-100-9	7.5.1	Repeated dose toxicity (90-days oral)	Linked to a terminated TPE
460-100-9	6.1.2	Toxicity in fish	Linked to a terminated TPE
471-480-0	7.8.2	Developmental toxicity	Other regulatory purposes
476-700-9	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
476-700-9	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
479-310-7	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
479-310-7	7.8.2	Developmental toxicity	Other regulatory purposes
481-670-5	6.1.2	Toxicity in fish	Other regulatory purposes
481-670-5	7.6.2	In vivo genetic toxicity	Other regulatory purposes
482-070-6	6.1.2	Toxicity in fish	Conducted by a different LE
482-070-6	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
482-220-0	6.3.5	Reproductive toxicity in birds	Other regulatory purposes
482-220-0	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
482-220-0	6.1.2	Toxicity in fish	Other regulatory purposes
482-220-0	5.3.1	Bioaccumulation in fish	Other regulatory purposes
485-390-4	7.8.2	Developmental toxicity	Complex explanations
486-070-7	6.1.2	Toxicity in fish	No explanation provided
486-070-7	7.8.2	Developmental toxicity	Other regulatory purposes
486-070-7	7.8.2	Developmental toxicity	Other regulatory purposes
486-070-7	7.5.2	Repeated dose toxicity (90-days inhalation)	Other regulatory purposes
500-062-3	7.6.2	*In vivo* genetic toxicity	Responsible care
500-655-7	5.3.1	Bioaccumulation in fish	Complex explanations
600-026-8	7.6.2	*In vivo* genetic toxicity	Complex explanations

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
600-736-8	7.6.2	*In vivo* genetic toxicity	Complex explanations
600-736-8	7.6.2	*In vivo* genetic toxicity	Complex explanations
601-238-3	7.8.2	Developmental toxicity	Complex explanations
603-046-5	7.8.2	Developmental toxicity	Complex explanations
603-373-3	6.1.2	Toxicity in fish	Conducted by a different LE
606-330-7	7.6.2	*In vivo* genetic toxicity	Complex explanations
609-066-0	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations
609-066-0	7.8.2	Developmental toxicity	Complex explanations
609-530-2	7.6.2	*In vivo* genetic toxicity	Complex explanations
612-396-8	7.6.2	*In vivo* genetic toxicity	Complex explanations
617-779-3	7.5.2	Repeated dose toxicity (90-days inhalation)	Not a new test
617-903-6	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
617-903-6	7.6.2	*In vivo* genetic toxicity	Misunderstanding of REACH requirements
618-882-6	7.5.1	Repeated dose toxicity (90-days oral)	No explanation provided
627-071-6, 627-083-1	5.3.1	Bioaccumulation in fish	Conducted by a different LE
627-071-6, 627-083-1, 605-717-8	7.5.1	Repeated dose toxicity (90-days oral)	Conducted by a different LE
641-136-6	7.8.2	Developmental toxicity	Other regulatory purposes
690-526-2	7.6.2	In vivo genetic toxicity	Other regulatory purposes
690-526-2	7.8.2	Developmental toxicity	Other regulatory purposes
690-526-2	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
696-026-0	7.6.2	*In vivo* genetic toxicity	Responsible care
700-073-5	7.5.1	Repeated dose toxicity (90-days oral)	Other regulatory purposes
700-459-3	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
700-459-3	6.1.2	Toxicity in fish	Other regulatory purposes
800-838-4	7.6.2	*In vivo* genetic toxicity	Conducted by a different LE
903-945-5	7.6.2	*In vivo* genetic toxicity	No explanation provided
907-672-2	5.3.1	Bioaccumulation in fish	Other regulatory purposes
910-670-4	6.1.2	Toxicity in fish	Conducted by a different LE
911-467-3	7.6.2	*In vivo* genetic toxicity	No explanation provided

REGISTERED SUBSTANCE EC NUMBER	IUCLID SECTION (1)	STUDY TYPE (2)	CATEGORIES OF EXPLANATIONS (3)
914-460-3, 914-475-5, 914-468-7	7.8.2	Developmental toxicity	not a new test
915-926-9	6.1.2	Toxicity in fish	Complex explanations
917-215-9	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
923-400-5	7.6.2	*In vivo* genetic toxicity	No explanation provided
923-725-2	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations
926-191-9	7.6.2	*In vivo* genetic toxicity	Complex explanations
930-592-4	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations
931-257-5	7.5.1	Repeated dose toxicity (90-days oral)	No explanation provided
931-257-5	7.5.1	Repeated dose toxicity (90-days oral)	No explanation provided
931-259-6	7.5.1	Repeated dose toxicity (90-days oral)	Misunderstanding of REACH requirements
931-299-4	7.8.2	Developmental toxicity	Conducted by a different LE
931-915-1	7.5.1	Repeated dose toxicity (90-days oral)	Complex explanations
936-414-1	7.5.2	Repeated dose toxicity (90-days inhalation)	Complex explanations
936-414-1	6.1.2	Toxicity in fish	Conducted by a different LE
939-056-4	7.6.2	*In vivo* genetic toxicity	Complex explanations
939-179-3	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
939-180-9	7.6.2	*In vivo* genetic toxicity	No explanation provided
939-429-1	7.6.2	*In vivo* genetic toxicity	Complex explanations
939-579-8	6.1.2	Toxicity in fish	No explanation provided
939-650-3	6.1.2	Toxicity in fish	Complex explanations
939-727-1	6.1.2	Toxicity in fish	No explanation provided
940-029-4	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes
940-029-4	7.6.2	*In vivo* genetic toxicity	Other regulatory purposes

Notes

(1) Information which was entered under the responsibility of the registrant

(2) Endpoint definition which is matching study report name

(3) Cases may have fallen under multiple categories

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