EUROPEAN CHEMICALS AGENCY

Helsinki, 19 May 2020

Addressees
Registrants of Diphenyl ether Joint listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
25 April 2016

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Diphenyl ether
EC number: 202-981-2
CAS number: 101-84-8

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***24 August 2023***.

A. Requirements applicable to all the Registrants subject to Annex VII of REACH

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method EU B.13/14. / OECD TG 471) with the fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP 2 uvrA (pKM101) with the Substance;

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) with the Substance;

C. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rabbit), oral route with the Substance;

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route (gavage or diet) specified as follows:

   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity); and
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

   You must report the study performed according to the above specifications. Any expansions of the study design must be scientifically justified. You must justify the selection of gavage or diet, as described in Appendix C.

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses issues relevant for several requests while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix on general considerations

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested information was 30 months from the date of adoption of the decision. In your comments on the draft decision you requested ECHA to extend the standard granted time to a total of 36 months due to sampling, drying and characterisation process of the Substance.

ECHA has agreed with your request for the deadline extension due to time needed for availability of the test material and granted 6 months extension to the original deadline. Therefore, the deadline is set to 36 months.

Appendix A: Reasons for the requests to comply with Annex VII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to REACH.

1. In vitro gene mutation study in bacteria with the fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP 2 uvrA (pKM101) (Annex VII, Section 8.4.1.)

An *In vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

You have provided following studies with the Substance:

i. [redacted] 1978 – Key study, Rel. 2.; Bacterial reverse mutation assay (Ames test) according to standard Ames method (non-GLP compliant);
ii. [redacted] 1983 – Supporting study, Rel. 2.; Bacterial reverse mutation assay (Ames test) according to standard Ames method (GLP not specified).

We have assessed this information and identified the following issue(s):

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997). The key parameter(s) of this test guideline include that the test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

You have provided negative bacterial reverse mutation assays (similar to OECD TG 471; studies i-ii) covering the following strains: *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 with and without metabolic activation.

However, the reported data for the studies did not include the appropriate 5 strains, as the information provided does not include results in the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).

The information provided does not cover key parameter(s) required by OECD TG 471. Therefore, the information requirement is not fulfilled.

In your comments on the draft decision, you agreed to conduct the requested test as specified in the decision.

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) with the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is considered suitable.

Appendix B: Reasons for the requests to comply with Annex VIII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have provided following study with the Substance:

i. [redacted]., 1987 – Key study, Rel. 2. *In vitro* cytogenicity / chromosome aberration study in CHO cells according to a standard test ([redacted], 1973) similar to OECD TG 473 (GLP compliant).

We have assessed this information and identified the following issue(s):

To fulfil the information requirement, the study has to be an *in vitro* chromosomal aberration test or an *in vitro* micronucleus test, conducted in mammalian cells in accordance with OECD TG 473 or OECD TG 487, respectively[2].

You have provided an *in vitro* chromosomal aberration study similar to OECD TG 473 (1987). The key parameters of the OECD TG 473 include, among others, that at least 300 well-spread metaphases must be scored per concentration.

In the provided study, only 100 well-spread metaphases were scored per concentration. Therefore, the study does not provide equivalent statistical power to detect chromosomal aberrations.

In conclusion, the information provided does not cover key parameter(s) required by the relevant OECD TG.

In your comments on the draft decision you referred to the *in vitro* cytogenicity data discussed above, as well as mutation data and uncheduled DNA synthesis (USD) assay data provided in the dossier with the Substance. You stated that the weight of evidence for the Substance genotoxicity clearly indicates that this substance is not genotoxic nor does it react with DNA.

Therefore, ECHA has evaluated the provided information according to Annex XI, Section 1.2 of REACH (weight of evidence).

In support of your adaptation, you have provided the following sources of information:

(i) [redacted] 1987 – Key study, Rel. 2. *In vitro* cytogenicity / chromosome aberration study in CHO cells according to a standard test ([redacted] 1973) similar to OECD TG 473 (GLP compliant);
(ii) [redacted] 1978 – Key study, Rel. 2.; Bacterial reverse mutation assay (Ames test) according to standard Ames method (non-GLP compliant);
(iii) [redacted] 1983 – Supporting study, Rel. 2.; Bacterial reverse mutation assay

[2] ECHA Guidance R.7a, Table R.7.7-2

(iv) (Ames test) according to standard Ames method (GLP not specified); and [redacted] 1987 - Key study, Rel. 2. Unscheduled DNA synthesis in vitro study in rat hepatocytes (GLP compliant).

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude that the Substance is not genotoxic nor does it react with DNA.

We have assessed your adaptation and note the following deficiencies:

Annex XI, Section 1.2 states that there may be sufficient weight of evidence weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory information requirement. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You have not included a justification with an assessment, integration and weighing of the individual sources of information for relevance, reliability, consistency and results, and subsequently decided whether they together provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2 at Annex VIII includes information on *in vitro* cytogenicity by detection and quantification of chromosomal aberrations or micronuclei in cultured mammalian cells.

The study (i) is the only source of information providing relevant information on *in vitro* cytogenicity as it includes detection and quantification of chromosomal aberrations. Studies (ii., iii.) provide information on the ability of the Substance to cause gene mutations and not on *in vitro* cytogenicity.

Unscheduled DNA synthesis (UDS) test (iv.) does not detect chromosomal aberrations or micronuclei. The UDS test is an indicator test measuring DNA repair of primary damage in liver cells. The UDS test can detect some substances that induce DNA damage because this assay is sensitive to some (but not all) DNA repair. However, a negative result cannot rule out the possibility of DNA damage.

Therefore, the source of information (i.) is the only study that provide relevant information on *in vitro* cytogenicity. However, as described above, this study has a deficiency that affects the reliability of its results.

In the absence of reliable information on ability to induce chromosomal aberrations or micronuclei in cultured mammalian cells, no conclusion can be drawn on *in vitro* cytogenicity as required by the information requirement.

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in *in vitro* cytogenicity study by detection and quantification of chromosomal aberrations or micronuclei in cultured mammalian cells. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, both *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) and *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

Appendix C: Reasons for the requests to comply with Annex X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage abve 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

In order to be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in two species.

You have not provided information on a second species.

In your comments on the draft decision, you agreed to conduct the requested test as specified in the decision.

Information on study design
The test in the first species was carried out by using a rodent species (rat). A PNDT study according to the test method OECD TG 414 must be performed in rabbit as preferred non-rodent species.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

In your dossier you have provided a waiver stating that the potential exposure of workers and consumers is minimal and therefore, no additional testing is proposed by you.

According to Annex X, Section 8.7., Column 2, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, one of them being:

- that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure.

Based on the provided information, the dermal absorption of the 14C-labelled Substance in rats was approximately 19-23 % of the administered dose. In addition, in the attachment to your assessment of the toxicokinetic properties of the Substance included in your technical dossier, you refer to a publication by Law et al. (1983) to evaluate the oral bioavailability of the Substance. You indicate that "in rats, diphenyl oxide (i.e. the Substance) has been reported to absorb rapidly after oral dosing (rate = 0.024 min-1); oral absorption was >90%".

Therefore, you have not met the criteria that no systemic absorption occurs via relevant routes of exposure, and your adaptation according to Annex X, Section 8.7., Column 2 is rejected.

In addition, while an adaptation was not specifically indicated by you, ECHA has also evaluated the above information under the rules set in Annex XI, Section 3. Substance-tailored exposure-driven testing.

According to Annex XI, Section 3, you may adapt the information requirement, provided you fulfil all the identified criteria in paragraphs 3.2(a)(i) to (iii) and submit an adequate and scientifically-supported justification, based on a thorough and rigorous exposure assessment in accordance with Section 5 of Annex I. The criteria in paragraph 3.2(a) specifies, among others, that:

- DNEL or PNEC must be relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes (Annex XI, 3.2(a)(ii)).

You have provided a waiver stating that "*The REACH substance is used as a high temperature heat transfer fluid in enclosed industrial and commercial heat transfer systems. As such the potential for exposure to workers and consumers is minimal (refer to exposure assessment). In the subchronic repeated dose studies (oral, dermal and inhalation), there were no observed effects on fertility or sex organs. Also, there were no embryo- or fetotoxic effects observed in a developmental toxicity test at maternally toxic doses. Therefore, no additional testing is proposed for assessing reproductive toxicity*".

In your Chemical Safety Report (CSR) you have reported the worker, long-term, systemic DNEL for inhalation based on a 90-day oral repeated dose toxicity study, and the worker, long-term, systemic DNEL for dermal effects is based on a 90-day dermal repeated dose toxicity study.

These studies do not provide information on mating, fertility, pregnancy, lactation and postnatal development of the fully exposed F1 generation up to the adulthood as required in EOGRT (OECD TG 443). Therefore, the DNELs you have provided are not relevant nor appropriate both for the information requirement to be omitted and for risk assessment purposes. Therefore, criterion 3.2(a)(ii) cannot be fulfilled, and you do not meet the general rules for adaptation of Annex XI, Section 3.2(a).

Therefore, your adaptation According to Annex XI, Section 3 is rejected.

In conclusion, based on above evaluation, the information you provided does not fulfil the information requirement.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration. [3]

Therefore, the requested premating exposure duration is at least ten weeks.

[3] ECHA Guidance R.7a, Section R.7.6.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and must be included.

Species and route selection

The study must be performed in rats with oral[4] administration.

In your comments to the draft decision you agree with the request to perform the study via oral administration. However, you propose for flexibility to the oral route of administration selection and state that you will use the dose setting study (i.e. the reproductive toxicity screening study) to determine the best method for oral administration.

ECHA agrees that a comparison between the oral gavage and dietary routes should be explored, and the results used to determine the suitable method for oral administration of the Substance in the EOGRTS. The method that provides the highest dose levels without causing severe reduction in food intake (or body weight) that would confound the interpretation of reproductive toxicity (including developmental toxicity) (e.g. by causing reproductive toxicity itself) must be selected and justified.

Therefore, the study should be conducted using oral gavage or dietary dosing and the selection of dosing method justified.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[5].

[4] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[5] ECHA Guidance R.7a, Section R.7.6.

Appendix D: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 9 April 2019.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA took into account your comments and amended the request for Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.), and the deadline of the decision.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix E: Observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[6].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[8]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[9]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[10]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[10] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix F: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.