~~Confidential~~

Helsinki, 27 May 2024

Addressee
Registrant of JS_270586-78-2 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
30 May 2023

Registered substance subject to this decision ("the Substance")
Substance name: [bis(4-methylphenyl)phosphoryl](mesityl)methanone
EC/List number: 884-585-5

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

DECISION ON TESTING PROPOSAL(S)

Under Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***4 December 2026***.

Requested information must be generated using the Substance unless otherwise specified.

Information required from all the Registrants subject to Annex VII of REACH

1. In vivo mammalian alkaline comet assay combined with in vivo mammalian erythrocyte micronucleus test also requested below (triggered by Annex VII, Section 8.4., column 2)

Information required from all the Registrants subject to Annex VIII of REACH

2. In vivo mammalian alkaline comet assay combined with in vivo mammalian erythrocyte micronucleus test also requested below (triggered by Annex VIII, Section 8.4., column 2)

Information required from all the Registrants subject to Annex IX of REACH

3. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats

4. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

5. In vivo mammalian alkaline comet assay combined with in vivo mammalian erythrocyte micronucleus test (triggered by Annex IX, Section 8.4.4)

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressee(s) of the decision and their corresponding information requirements based on registered tonnage band are listed

in Appendix 3.

In the requests above, the same study has been requested under different Annexes or for different information requirements.

In the case of the same study requested under different Annexes, this is because some information requirements may be triggered at lower tonnage band(s). In such cases, only the reasons why the information requirement is triggered are provided for the lower tonnage band(s). For the highest tonnage band, the reasons why the standard information requirement is not met and the specification of the study design are provided.

In all cases, only one study is to be conducted; all registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the others under Article 53 of REACH.

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report**, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

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 Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 1: Reasons for the decision

Contents

Reasons related to the information under Annex VII of REACH

1. In vivo mammalian alkaline comet assay combined with in vivo mammalian erythrocyte micronucleus test

1 Under Annex VII, Section 8.4., Column 2, an appropriate *in vivo* mammalian somatic cell genotoxicity study as referred to in Annex IX, point 8.4.4, must be performed in case of a positive result in any of the *in vitro* studies referred to in Annex VII, Section 8.4. The *in vivo* study must address the concern(s) raised by the *in vitro* study results, i.e. the chromosomal aberration concern or the gene mutation concern or both, as appropriate.

1.1. Triggering of the information requirement

2 Your dossier contains positive results for the *in vitro* micronucleus test (OECD TG 487, 2023) which raise the concern for chromosomal aberrations.

3 Therefore, the information requirement is triggered.

1.2. Information provided and its assessment

4 For the assessment of the testing proposal, see Section 5.

Reasons related to the information under Annex VIII of REACH

2. In vivo mammalian alkaline comet assay combined with in vivo mammalian erythrocyte micronucleus test

5 Under Annex VIII, Section 8.4, Column 2, an appropriate *in vivo* study is an information requirement in case of a positive result in any of the *in vitro* genotoxicity studies referred to in Annex VII or Annex VIII, which gives rise to concern. The *in vivo* study must address the concern(s) raised by the *in vitro* study results, i.e. the chromosomal aberration concern or the gene mutation concern or both, as appropriate.

2.1. Triggering of the information requirement

6 Your dossier contains positive results for the *in vitro* micronucleus test (OECD TG 487, 2023) which raise the concern for chromosomal aberration.

7 Therefore, the information requirement is triggered.

2.2. Information provided and its assessment

8 For the assessment of the testing proposal, see Section 5.

Reasons related to the information under Annex IX of REACH

3. Sub-chronic toxicity study (90 days)

9 A sub-chronic toxicity study (90 days) is an information requirement under Annex IX, Section 8.6.2.

3.1. Information provided

10 You have submitted a testing proposal for a sub-chronic toxicity study (90 days) according to OECD TG 408 with the Substance.

11 Your registration dossier does not include any information for this information requirement.

12 ECHA requested your considerations for alternative methods to fulfil the information requirement for repeated dose toxicity. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

13 ECHA agrees that a sub-chronic toxicity study (90 days) is necessary.

3.2. Study design

14 You proposed testing in the rat. ECHA agrees with your proposal because the rat is the preferred species according to the OECD TG 408. Therefore, the study must be conducted in the rat.

15 You proposed testing by the oral route. ECHA agrees with your proposal because this route of administration is appropriate to investigate systemic toxicity; Guidance on IRs and CSA, Section R.7.5.4.3.2.

16 ECHA acknowledges your intention to include additional satellite groups of 5 animals per sex in the control and in the high dose groups and that the '*satellite animals treated on the same regime will be subsequently used for 14-day post-treatment observation for the potential reversibility or persistence of any toxic effects*.'

17 According to OECD TG 408, para. 22, '*The observation period should be at least 90 days. If a satellite group is included in the study, animals in the satellite recovery group scheduled for follow-up observations should be kept for an appropriate period without treatment to detect persistence of, or recovery from toxic effects'*.

18 Your proposal is in line with OECD TG 408. Therefore, you may include the additional satellite groups at your own discretion as long as their inclusion does not compromise the integrity of the OECD TG 408 study design.

3.3. Outcome

19 Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test, as specified above.

4. Pre-natal developmental toxicity study in a first species

20 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX, Section 8.7.2.

4.1. Information provided

21 You have submitted a testing proposal for a PNDT study according to the OECD TG 414 with the Substance.

22 Your registration dossier does not include any information for this information requirement.

23 ECHA requested your considerations for alternative methods to fulfil the information requirement for developmental toxicity. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

24 ECHA agrees that a PNDT study in a first species is necessary.

4.2. Study design

25 You proposed testing in the rat as a first species.

26 You may select between the rat or the rabbit because both are preferred species under the OECD TG 414 (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

27 You proposed testing by the oral route.

28 As the Substance is a solid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1). Therefore, ECHA agrees with your proposal.

29 You propose to use the following dose levels for the main OECD TG 414 study: 100, 350, and 700 mg/kg bw/day. You indicate that the selection of these dose levels is based on a dose range finding (DRF) study which has been conducted. However, you have not provided the results of the DRF study in your registration dossier. Therefore, ECHA cannot assess the validity of your proposed dose level selection. You remain responsible for complying with OECD TG 414.

30 ECHA emphasizes that according to paragraph 14 of the OECD TG 414 '*the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering*', or the limit concept shall be used[2].

4.3. Outcome

31 Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test, as specified above.

5. In vivo mammalian alkaline comet assay combined with in vivo mammalian erythrocyte micronucleus test

32 Under Annex IX, Section 8.4.4., an appropriate *in vivo* mammalian somatic cell genotoxicity study is an information requirement if there is a positive result in any of the *in vitro* genotoxicity studies referred to in Annex VII or VIII, which gives rise to concern. The *in*

[2] For more information and recommendations, see '*Advice on dose-level selection for the conduct of reproductive toxicity studies (OECD TGs 414, 421/422 and 443) under REACH*': https://echa.europa.eu/documents/10162/17220/211221_echa_advice_dose__repro_en.pdf/27159fb1-c31c-78a2-bdef-8f423f2b6568?t=1640082455275.

vivo mammalian somatic cell genotoxicity study must address the chromosomal aberration concern or the gene mutation concern or both, as appropriate.

5.1. Triggering of the information requirement

33 Your dossier contains positive results for the *in vitro* micronucleus test (OECD TG 487, 2023) which raise the concern for chromosomal aberration.

34 Therefore, the information requirement is triggered.

5.2. Information provided and its assessment

35 You have submitted a testing proposal for an *in vivo* mammalian alkaline comet assay to be performed with the Substance.

36 ECHA requested your considerations for alternative methods to fulfil the information requirement for Genetic toxicity *in vivo*. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement for which testing is proposed. ECHA has taken these considerations into account.

37 ECHA received third party information concerning the testing proposal during the third-party consultation.

38 The third party has indicated that "*The Registration Dossier for the substance (EC 884-585-5) contains a positive in vitro micronucleus assay (OECD 487), indicating that the substance has the potential to cause chromosomal aberrations. No further in vitro genotoxicity data are available for the registered substance. The testing proposal is for an in vivo comet assay (OECD 489). This test method is designed to investigate the potential of the substance to cause gene mutations, which has not yet been investigated in vitro. If the requirement for a study in vivo is confirmed, the study guideline used should take into account the nature of any positive response(s) seen in vitro. In order to minimise the extent of animal testing and prevent repeated testing, all genotoxic endpoints should be investigated in vitro prior to any testing in vivo*".

39 ECHA is not in agreement with the 3rd party comment regarding the *in vitro* data provided: while it is correct that the registration dossier contains a positive *in vitro* micronucleus test (OECD TG 487, 2023) that raises a concern for chromosomal aberrations, ECHA notes that the dossier also contains a negative bacterial reverse mutation (Ames) test (OECD TG 471, 2023), which investigates gene mutation *in vitro*. Consequently, contrary to the statement in the third-party comment, the *in vitro* data available for this substance do '*investigate all [required] genotoxic endpoints in vitro*'.

40 ECHA agrees that an appropriate *in vivo* follow up genotoxicity study is necessary to address the concern identified *in vitro*.

5.3. Test selection

41 The positive *in vitro* results available in the dossier indicate a concern for chromosomal aberration.

42 To address this concern, you proposed performing the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489). While the comet assay can detect primary DNA damage that may lead to gene mutations and/or structural chromosomal aberrations, the *in vivo* mammalian erythrocyte micronucleus test ("MN test", OECD TG 474) can detect both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy).

43 The MN test and the comet assay can be combined in a single study (OECD TG 474, paragraph 37c; OECD TG 489, paragraph 33; Guidance on IRs & CSA, Section R.7.7.6.3).

44 The combined study, together with the results of the *in vitro* mutagenicity studies, can be used to make definitive conclusions about the mechanism(s) inducing *in vivo* mutagenicity and lack thereof. Furthermore, the combined study can detect effects in both distant organs, such as the bone marrow or the liver, and at site(s) of contact, such as the glandular stomach, the duodenum or the lung. Investigating several genotoxic endpoints and different tissues in a combined study is necessary to reduce the uncertainties associated with not testing all organs and to generate complementary information that provides a comprehensive overview of the genotoxic potential of the Substance. Moreover, the combined study can help limit the number of tests performed and the number of animals used.

45 Therefore, the comet assay combined with the MN test is the most appropriate study for the Substance.

5.4. Specification of the study design

46 You proposed testing in the rat. According to the test method OECD TG 489, rats are the preferred species. Other rodent species can be used if scientifically justified. According to the test method OECD TG 474, the test may be performed in mice or rats. Therefore, the combined study must be performed in rats, or if justified, in mice.

47 You proposed testing by the oral route. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

48 In line with the test method OECD TG 489, the test must be performed by analysing tissues from the liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

49 According to the test method OECD TG 474, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen (OECD TG 474, paragraph 25, Table 1).

50 The combination of the OECD TGs 489 and 474 should not impair the validity of the results from each individual study. Careful consideration should be given to the dosing, and tissue sampling for the comet analysis alongside the requirements of tissue sampling for the mammalian erythrocyte micronucleus test (see OECD TG 489, e.g. Bowen et al. 2011 [1]).

[1] Bowen DE et al. (2011) Evaluation of a multi-endpoint assay in rats, combining the bone-marrow micronucleus test, the comet assay and the flow-cytometric peripheral blood micronucleus test. *Muta Res.*;722:7–19.

5.4.1. Assessment of aneugenicity potential

51 If the result of the *in vivo* MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance. In line with the OECD TG 474 (paragraph 42), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei

is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

5.4.2. Investigation of target tissue exposure

52 The applicable test method OECD TG 474 states that "*If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test*". Additionally, a negative test result can be considered reliable only if "*Bone marrow exposure to the test substance(s) occurred*".

53 Therefore, to ensure that the data generated are adequate for hazard identification, you must take blood samples at appropriate times and measure plasma levels of the Substance and/or its metabolites (OECD TG 474, paragraph 40), unless exposure of the bone marrow can be demonstrated through other means, e.g. by showing a depression of immature to mature erythrocyte ratio (OECD TG 474, paragraph 48).

54 If the Substance is negative in this test, but it is not possible to demonstrate that bone marrow exposure to the Substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the Substance and whether to request any further information.

5.4.3. Germ cells

55 You may consider collecting the male gonadal cells from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

5.5. Outcome

56 Under Article 40(3)(b) your testing proposal is accepted under modified conditions, and you are requested to conduct the test with the Substance, as specified above.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2023).
Guidance on intermediates; ECHA (2010).

All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs); ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 26 May 2023.

ECHA held a third-party consultation for the testing proposal(s) from 30 June 2023 until 14 August 2023. ECHA received information from third parties (see corresponding Appendix/Appendices).

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA did not receive any comments within the commenting period.

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 3: Addressee(s) of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third-party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. Test methods, GLP requirements and reporting

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

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

(3) 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 on How to report robust study summaries[3].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the boundary composition(s) of the Substance,
- 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.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[4].

[3] https://echa.europa.eu/practical-guides
[4] https://echa.europa.eu/manuals

2. General recommendations for conducting and reporting new tests

References to Guidance on REACH and other supporting documents can be found in Appendix 1.