Helsinki, 31 May 2024

Addressee
Registrant of JS_412-050-4 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
30 October 2019

Registered substance subject to this decision ("the Substance")
Substance name: β-methyl-3-(1-methylethyl)benzenepropanal
EC/List number: 412-050-4

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***7 December 2026***.

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

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

1. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490).

2. Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats.

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

3. Sub-chronic toxicity study (90 days), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) 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. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210).

The reasons for the requests 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.

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 request(s)
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 request(s)

Contents

Reasons related to the information under Annex VIII of REACH

1. *In vitro* gene mutation study in mammalian cells

1 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

1.1. Triggering of the information requirement

2 Your dossier contains negative results for both an Ames test and an *in vitro* cytogenicity study.

3 Therefore, the information requirement is triggered.

1.2. Information provided

4 You have not submitted any information for this requirement.

5 Therefore, the information requirement is not fulfilled.

6 In your comments to the draft decision, you agree to perform the requested study.

1.3. Study design

7 To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

2. Screening study for reproductive/developmental toxicity

8 A screening study for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1.

2.1. Information provided

9 You have provided:

(i) a 14-days repeated dose toxicity study (2010) with the Substance.

10 In addition, you have adapted this information requirement and provided the following justification:

> "*the study does not need to be conducted because (i) the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), (ii) it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and (iii) there is no or no significant human exposure*"

11 Based on your comments to the draft decision and information provided in IUCLID sections 7.1.1. and 7.8.1., ECHA understands that you intend to adapt the information requirement at Annex VIII, Section 8.7.1. by using Annex XI, Section 1.2. (weight of evidence). To support your adaptation, you have provided study (i) and:

(ii) Publication ([redacted] 2017) (IUCLID 7.1.1.);

(iii) Publication ([redacted] 2020) (IUCLID 7.1.1.);

(iv) Publication ([redacted] 2022) (IUCLID 7.1.1.);

(v) *In vitro* study on metabolism of Florhydral (the Substance) compared with Lilial in primary rat hepatocytes (2023) (IUCLID 7.1.1.);

(vi) *In vitro* study on metabolism and formation of Coenzyme A esters by Florhydral (the Substance) compared with Lilial (2023) (IUCLID 7.1.1.).

2.2. Assessment of the information provided

2.2.1. The provided study (i) does not meet the specifications of the test guideline(s)

12 To fulfil the information requirement, a study must comply with EU B.63/OECD TG 421 or EU B.64/OECD TG 422 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the highest dose level aims to induce toxicity or aims to reach the limit dose;
b) at least 10 male and 12-13 female animals are included for each dose and control group;
c) the exposure duration is at least four weeks for males, including a minimum of two weeks prior to mating, and approximately 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation;
d) gross pathology of reproductive organs is performed, and the presence or absence, incidence and severity of abnormalities is evaluated;
e) histopathology of reproductive organs and tissues is performed, and the presence or absence, incidence and severity of abnormalities is evaluated.
f) parameters for sexual function and fertility such as those for mating and fertility/duration of gestation, parturition and lactation are reported;
g) oestrous cycles are monitored;
h) offspring parameters such as number and sex of pups, stillbirths and live birth, gross abnormalities, pup body weight, litter weight, anogenital distance, and nipple retention in male pups are reported.

13 In study (i):

a) the highest dose levels tested was 250 mg/kg bw/d (i.e., below the limit dose of the OECD TG 421or 422) and no adverse effect were observed and no justification for the dose setting was provided;
b) no females were included in the study;
c) the exposure duration was 14 days for males (i.e., less than 4 weeks for males);
d) gross pathology of female reproductive organs, including incidence and severity of abnormalities, are not investigated;
e) histopathology of female reproductive organs and tissues, including incidence and severity of abnormalities, are not investigated.
f) parameters for sexual function and fertility such as those for mating and fertility/duration of gestation, parturition and lactation are missing;
g) data on oestrous cycles is missing;
h) data on number and sex of pups, stillbirths and live births, gross abnormalities, pup body weight, litter weight, anogenital distance, and nipple retention in male pups are missing.

14 The information provided does not cover the specifications required by the OECD TG 421 or 422.

2.2.2. Your justification to omit the study has no legal basis

15 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex VIII, Section 8.7.1., Column 2.

16 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex VIII, Section 8.7.1., Column 2. Although not explicitly stated, ECHA understands that your justification refers to the adaptation possibility at Annex IX/X, Section 8.7, column 2, first paragraph, third indent. However, since such adaptation possibility is not set out in Annex VIII, Section 8.7.1, column 2, it is not applicable for this information requirement.

17 Therefore, you have not demonstrated that this information can be omitted.

2.2.3. Weight of evidence adaptation is rejected

18 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

19 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

20 According to ECHA Guidance R.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 and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude on the corresponding information requirement.

2.2.3.1. Lack of documentation justifying the weight of evidence adaptation

21 Annex XI, Section 1.2. requires that adequate and reliable documentation is provided to describe a weight of evidence approach.

22 You have not included a justification for your weight of evidence, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude on the information requirement under consideration.

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

24 Information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.7.1. includes similar information that is produced by EU B.63/OECD TG 421 or EU B.64/OECD TG 422. OECD TGs 421/422 require the study to investigate the following key parameters:

(1) sexual function and fertility,

(2) toxicity to offspring, and

(3) systemic toxicity.

2.2.3.2. Sexual function and fertility

25 Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

26 The source of information (i) provides information only on male reproductive organs and tissues, and sperm parameters (see also Section 2.2.1.), while the source of information (ii) provides information on male and female reproductive organs. However, the sources of information (i) and (ii) do not inform on the other aspects of sexual function and fertility described above. The source of information (iii) provides limited information only on metabolism in testis but do not inform on the aspects of sexual function and fertility.

27 The sources of information (iv) to (vi) do not provide any relevant information on sexual function and fertility as studies focus on *in vitro* metabolism.

2.2.3.3. Toxicity to offspring

28 Toxicity to offspring must include information on pre- and perinatal developmental toxicity reflected by litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations, postnatal developmental toxicity reflected by survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.

29 The sources of information (i) to (vi) provide no information on toxicity to offspring.

2.2.3.4. Systemic toxicity

30 Systemic toxicity on both sexes must include clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

31 The source of information (iii) to (vi) provide no information on the aspects of systemic toxicity described above.

32 The sources of information (i) and (ii) provide information on systemic toxicity. However, we have identified the following issue that significantly affects the reliability of these sources of information:

2.2.3.4.1. Methodological deficiencies in the sources of information (i) and (ii)

33 The evaluation of the reliability of the contribution of each relevant line of information to the weight of evidence approach includes an assessment of each source of information against the specifications of the test guideline followed.

34 The sources of information (i) and (ii) are described as short-term repeated dose toxicity studies. The OECD TGs 421 and 422 requires the investigations of the following aspects on systemic toxicity:

a) at least 10 male and 12-13 female animals are included for each dose and control group;
b) the exposure duration is at least four weeks for males, including a minimum of two weeks prior to mating, and approximately 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation;
c) body weights are measured at least weekly;
d) food consumption is measured at least weekly;
e) terminal organ and body weights are reported.

35 In the sources of information (i) to (ii):

a) no females included in (i) and only 5 males and 5 females were included in (ii);
b) the exposure duration is only 14 days in (i) and the exposure duration is too short for females in (ii), i.e. 28 days, and do not cover premating, conception,

pregnancy and at least 13 days of lactation;
c) no information on body weights in (ii);
d) no information on food consumption in (ii);
e) no terminal organ and body weights are reported in (ii).

36 The methodological deficiencies listed above affect significantly the reliability of the sources of information (i) and (ii) to the conclusion on the aspects of systemic toxicity.

2.2.3.5. Conclusion on the weight of evidence adaptation

37 Taken together, only the sources of information (i) and (ii) provide limited information on reproductive organs, and systemic toxicity. The sources of information (i) provides also information on sperm parameters. However, the reliability of these sources of information is significantly affected by the deficiencies described under Section 2.2.3.4.1. Therefore, essential parts of information of the hazardous property is lacking, including information on: mating, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, litter sizes, nursing performance and other potential aspects of sexual function and fertility; and toxicity to offspring.

38 Therefore, it is not possible to conclude based on any source of information alone or considered together, whether your Substance has the particular (hazardous) properties. Thus, your adaptation is rejected.

39 On this basis, the information requirement is not fulfilled.

2.3. Study design

40 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

41 In your comments to the draft decision, you ask that "*ECHA allows the screening for reproductive/developmental toxicity requested in REACH Annex VIII, section 8.7.1 to be combined with the Sub-chronic toxicity requested to fulfil REACH Annex IX, Section 8.6.2.*"

42 ECHA notes that you may consider combining the screening study for reproductive/ developmental toxicity with the sub-chronic toxicity study only if that specific study design does not compromise and interfere with the requirements of OECD TG 421/422 and OECD TG 408. In case you decide to combine the studies, you must have separate groups for the 90-d and fertility parts for the females, and also follow dose-level requirements for a screening study[2] and a 90-d study[3]. ECHA emphasizes that any final determination on the validity of the study will only be possible when the information on the requested study is available in the registration dossier.

43 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex VIII, Section 8.7.1., Column 1).

44 Therefore, the study must be conducted in rats with oral administration of the Substance.

[2] 27159fb1-c31c-78a2-bdef-8f423f2b6568 (europa.eu)
[3] 63e6d895-a80c-f6f4-99c8-c5a3248ce02a (europa.eu)

Reasons related to the information under Annex IX of REACH

3. Sub-chronic toxicity study (90 days)

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

3.1. Information provided

46 Although not explicitly stated, ECHA understands that you have adapted this information requirement by using Annex IX, Section 8.6.2., Column 2, first paragraph, fourth indent. To support the adaptation, you have provided the following information:

(i) *"a sub-chronic toxicity study (90 days) does not need to be conducted because the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test' and human exposure is limited"*

(ii) a short-term 28-days repeated dose toxicity study (1991) with the Substance.

47 Based on your comments to the draft decision, although not explicitly stated, we understand that you intend to adapt this information requirement also by using Annex XI, Section 3.2 (a) (Substance-tailored exposure-driven testing). To support the adaptation, you provide the following justification:

"The risk assessment clearly demonstrates that during its entire life cycle, the handling and use of the registered substance is done in a safe manner. Human exposure, whether workers or consumers, is always below appropriate safety levels. The appropriate safety levels, or DNEL (Derived No Effect Level) were calculated in a highly conservative manner, using appropriate Assessment Factors to account for the sub-acute duration of exposure from the starting point (OECD 407). As such, there is no added value generating the requested OECD 408 study (REACH Annex IX, Section 8.6.2), as the risk assessment is already ensuring the full protection and safety of both workers and consumers in the EU."

3.2. Assessment of the information provided in the registration dossier

3.2.1. Column 2 criteria not met

48 Under Annex IX, Section 8.6.2., Column 2, first paragraph, fourth indent, the study may be omitted if the following cumulative conditions are met:

(1) the substance is unreactive, insoluble and not inhalable;

(2) there is no evidence of absorption; and

(3) no evidence of toxicity in a 28-day 'limit test', particularly if such a pattern is coupled with limited human exposure.

49 You claim that the Substance is unreactive, insoluble and not inhalable (1) as well as that there is no evidence of absorption (2). Furthermore you state that there is (3) no evidence of toxicity in a 28-day 'limit test'. However, you have not provided any information to support these claims.

50 Your assumptions on all conditions (1) to (3) are unsubstantiated and therefore cannot be accepted. You have not provided any evidence to support the claim that the Substance is unreactive and not inhalable. The Substance is liquid, and it is not insoluble although it has low water solubility being 40 mg/L. You have not provided any toxicokinetic information to support that the Substance is not absorbed. In the provided 28-day repeated dose toxicity

study (ii), clinical signs, mortality, and increased kidney and liver weights were observed at the highest dose level. You derived a NOAEL of 300 mg/kg bw/d. These observations provide evidence both for absorption and toxicity.

3.3. Assessment of the information provided in the comments to the draft decision

3.3.1. Substance-tailored exposure-driven testing adaptation rejected

3.3.1.1. Absence of or no significant exposure not demonstrated

51 Under Annex XI, Section 3(2)(a)(i), the results of the exposure assessment covering all relevant exposure throughout the life cycle of the substance must demonstrate absence of or no significant exposure in all scenarios of the manufacture and all identified uses.

52 The CSR you have provided includes 11 exposure scenarios for manufacture, formulation and re-packing, and for uses at industrial sites, widespread uses by professional workers, and also consumer uses.

53 In various exposure scenarios, the exposure estimates indicate a clearly significant exposure potential to the Substance, e.g. up to 15.83 mg/m^3 in exposure scenarios 1 and 4 (PROC 8b).

54 Therefore, you have not demonstrated absence of or no significant exposure in all scenarios of the manufacture and all identified uses.

3.3.1.2. Lack of appropriate DNEL

55 Under Annex XI, Section 3.2(a)(ii), a relevant and appropriate derived no effect level (DNEL) must be derived. Further, a DNEL derived from a 28-day repeated dose toxicity study must not be considered appropriate to omit a 90-day repeated dose toxicity study.

56 You have used a 28-day repeated dose toxicity study study to derive a DNEL.

57 Therefore, you have not provided a relevant and appropriate DNEL, and risk characterisation cannot be performed since a relevant DNEL is missing.

58 Therefore, you have not demonstrated that this information can be omitted.

59 Based on the above, your adaptation is rejected.

60 Therefore, the information requirement is not fulfilled.

3.4. Study design

61 In your comments to the draft decision you state that "*should ECHA disregard the safe outcome of the Chemical Risk Assessment provided and insist on the registrant performing an OECD 408 to comply with REACH Annex IX, Section 8.6.2, the registrant wishes to object to its below conclusion from the draft decision on the likely route of human exposure". You* provide the following arguments to support the dermal route as the most appropriate route of administration for a repeated dose toxicity study:

- "*The registered substance is a* [redacted] *ingredient. The most likely and predominant route of human exposure of such substances during their life cycle is the dermal route, based on the likelihood of exposure of the skin compared to the digestive or respiratory tract.*"
- "*[…] deriving DNELs via the oral route is not pertinent for professional workers, as oral route is not relevant.*"
- "*There is no relevant opportunity for professional workers manufacturing, compounding or handling the material to be repeatedly orally exposed during*

any of the exposure scenarios […] dermal exposure of workers is highly likely during manufacturing, compounding or handling of the material."

- *"Finally, the dermal exposure of workers is quantitatively defined in the comprehensive Chemical Risk Assessment performed on the registered substance, and further supports that the dermal route is the major route of human exposure to fragrance ingredients at the work place, whereas the oral route is not a relevant route of exposure to humans at all."*
- *"The intended use of the registered* [redacted] *substance is also to be included in consumer products […] None of those final intended uses would be cause for an oral exposure of the consumers to the registered substance in any appreciable amount. They would, however, be the source of extensive skin contact, which is substantiating evidence that the major route of exposure to this fragrance ingredient is indeed the dermal route."*
- *"Finally, the dermal exposure of consumers is quantitatively defined in the comprehensive Chemical Risk Assessment performed on the registered substance, and further supports that the dermal route is the major route of human exposure to* [redacted] *ingredients via the intended use of* [redacted] *consumer products, whereas the oral route is not a relevant route of exposure to consumers at all."*

62 In your comments to the draft decision you state that *"Based on the intended use and handling of the substance and the evidence of its past years on the* [redacted] *market, all available information indicate that workers and consumers are majorly exposed to the registered* [redacted] *substance via dermal contact and not at all orally. As such, the registrant asks that the OECD 408 study be allowed to be conducted via the dermal route, which is the most likely and predominant route of human exposure to the registered substance."*

63 ECHA notes that under Annex IX, Section 8.6.2., Column 2, Paragraph 2, the appropriate route shall be chosen on the following basis:

64 Testing by the dermal route is appropriate if:

(1) skin contact in production and/or use is likely, and

(2) the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin, and

(3) one of the following conditions is met:

- toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test, or
- systemic effects or other evidence of absorption is observed in the skin and/or eye irritation studies, or
- *in vitro* tests indicate significant dermal absorption, or
- significant dermal toxicity or dermal penetration is recognised for structurally-related substances.

65 Your justification for the dermal route is inadequate based on the information you have provided in the registration dossier or in your comments to the draft decision as none of conditions listed under (3) is met:

- acute dermal and oral toxicity studies in rats did not show any clear treatment-related alterations or signs of toxicity when tested up to 2000 mg/kg bw,

- no systemic effects or other evidence of absorption were reported in dermal and eye irritation studies in rabbits,
- no *in vitro* studies available to support significant dermal absorption,
- no data provided to indicate significant dermal toxicity or dermal penetration for structurally-related substances.

66 Following the criteria provided in Annex IX, Section 8.6.2., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.2., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance.

67 According to the OECD TG 408, the rat is the preferred species.

68 Therefore, the study must be performed in rats according to the OECD TG 408 with oral administration of the Substance.

69 In your comments to the draft decision, you ask "*that ECHA allows the screening for reproductive/developmental toxicity requested in REACH Annex VIII, section 8.7.1 to be combined with the Sub-chronic toxicity requested to fulfil REACH Annex IX, Section 8.6.2. in order to reduce the number of vertebrate animals being used to fulfil ECHA's overall requirements for the registration dossier.*".

70 ECHA notes that your request is addressed under request 2 (Section 2.3.).

4. Pre-natal developmental toxicity study in one species

71 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

72 Although not explicitly stated, ECHA understands that you have adapted this information requirement by using Annex IX, Section 8.7., Column 2, first paragraph, third indent. To support the adaptation, you have provided the following justification:

> "*the study does not need to be conducted because the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure*".

73 Based on your comments to the draft decision and information provided in IUCLID sections 7.1.1. and 7.8.1., ECHA understands that you intend also to adapt the information requirement at Annex IX, Section 8.7.2. by using Annex XI, Section 1.2. (weight of evidence). To support your adaptation, you have provided the following sources of information:

(i) a 14-days repeated dose toxicity study (2010) with the Substance (IUCLID 7.8.1.);

(ii) Publication ([redacted]2017) (IUCLID 7.1.1.);

(iii) Publication ([redacted]2020) (IUCLID 7.1.1.);

(iv) Publication ([redacted]2022) (IUCLID 7.1.1.);

(v) *In vitro* study on metabolism of Florhydral (the Substance) compared with Lilial in primary rat hepatocytes (2023) (IUCLID 7.1.1.);

(vi) *In vitro* study on metabolism and formation of Coenzyme A esters by Florhydral (the Substance) compared with Lilial (2023) (IUCLID 7.1.1.).

4.2. Assessment of the information provided

4.2.1. Criteria for the application of the adaptation for Annex IX, Section 8.7., Column 2 not met

74 Under Annex IX, Section 8.7., Column 2, first paragraph, third indent, the study does not need to be conducted if the following criteria are met:

- the substance is of low toxicological activity, demonstrated by a comprehensive and informative dataset showing no toxicity in any of the tests available; and
- that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
- that there is no or no significant human exposure.

75 In the provided 28-day repeated dose toxicity study, as described under Section 3 (above), clinical signs, mortality, and increased kidney and liver weights were observed at the highest dose level, and you derived a NOAEL of 300 mg/kg bw/d. This information provide evidence both for absorption and toxicity.

76 No toxicokinetic data was provided to show that there is no systemic absorption.

77 The uses of the Substance include industrial uses, widespread uses by professional workers and also consumer uses. Therefore, this information indicate that there is significant human exposure which you have not addressed.

78 On this basis, you have not demonstrated that the criteria for this adaptation are fulfilled.

79 Based on the above, your adaptation is rejected.

4.2.2. Weight of evidence adaptation is rejected

80 As explained under Request 2, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information, and it must include adequate and reliable documentation to describe the weight of evidence approach. The sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study. As explained under Request 2, an adequate documentation justifying the weight of evidence adaptation is missing (Section 2.2.3.1.), but ECHA has nevertheless assessed the validity of your adaptation.

81 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex IX includes similar information that is produced by the OECD TG 414 on one species. OECD TG 414 requires the study to investigate the following key parameters:

(1) prenatal developmental toxicity,

(2) maternal toxicity, and

(3) maintenance of pregnancy.

4.2.2.1. Prenatal developmental toxicity

82 Pre-natal developmental toxicity must include information after pre-natal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

83 The sources of information (i) to (vi) provide no information on prenatal developmental toxicity.

4.2.2.2. Maternal toxicity

84 Maternal toxicity must include information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

85 The sources of information (i) to (vi) provide no information on maternal toxicity.

4.2.2.3. Maintenance of pregnancy

86 Maintenance of pregnancy must include information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

87 The sources of information (i) to (vi) provide no information on maintenance of pregnancy.

4.2.2.4. Conclusion on the weight of evidence adaptation

88 Taken together, none of the sources of information (i) to (vi) provide any relevant information on prenatal developmental toxicity, marternal toxicity and maintenance of pregnancy.

89 Therefore, it is not possible to conclude based on any source of information alone or considered together, whether your Substance has the particular (hazardous) properties. Thus, your adaptation is rejected.

90 On this basis, the information requirement is not fulfilled.

4.3. Study design

91 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species.

92 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1).

93 In your comments to the draft decision, you stated that "*considering that the substance is a* [redacted] *substance and based on the intended use and handling of the substance and the evidence of its past years on the* [redacted] *market, all available information indicate that workers and consumers are majorly exposed to the registered* [redacted] *substance via dermal contact and not at all orally*".

94 Therefore, you asked that "*an adaptation could be made and the requested OECD 414 study be allowed to be conducted via the dermal route, which is the most likely and predominant route of human exposure to the registered substance.*".

95 ECHA notes that according to the test methods for reproductive toxicity which focus on the detection of reproductive hazards, the oral route is the default route, except for gases. Testing via dermal route might be necessary under specific circumstances, for example for substances with high dermal penetration and indications for a specific toxicity following dermal absorption (Guidance on IRs and CSA, Section R.7.6.2.3.2.). However, you have not provided any information based on toxicokinetics or route-specific toxicity to support

the dermal route as the most appropriate route of administration in reproductive toxicity study. On this basis, a valid justification for the dermal route is missing.

96 Therefore, the study must be conducted in rats or rabbits with oral administration of the Substance.

5. Long-term toxicity testing on fish

97 Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

5.1. Information provided

98 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following information:

(i) "From the risk assessment performed under the Chemical Safety Report, it is considered that it is not required to propose long-term fish testing (with reference to regulation 1907/2006, Annex IX, Section 9.1, Column 2) considering that (i) all RCRs in freshwater compartment are < 1, despite the application of conservative assessment parameters, and (ii) the unnecessary testing of vertebrate species requires specific authorisation prior to conducting of studies."

5.2. Assessment of the information provided

5.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

99 Under Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to fish referred to under Column 1, Section 9.1.6.

100 Your adaptation is therefore rejected.

101 Therefore, the information requirement is not fulfilled.

102 In your comments to the draft decision, you agree to perform the requested study.

5.3. Study design

103 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

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 (2012).
***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

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

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

The compliance check was initiated on 24 August 2022.

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 took into account your comments and did not amend the request.

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 Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- 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 (https://echa.europa.eu/practical-guides).
(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

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(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 variation in compositions reported by all members of the joint submission,
- 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.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (https://echa.europa.eu/manuals).