ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 14 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114365547-39-01/F
Substance name: butyl glycollate
EC number: 230-991-7
CAS number: 7397-62-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08.10.2013
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance;**

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

3. **Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: Daphnia sp. Acute immobilisation test, EU C.2./OECD TG 202) with the registered substance;**

4. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203) with the registered substance;**

5. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;**

6. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;**

In order to ensure use of the integrated testing strategy for the environmental requests, the aquatic short-term toxicity testing (points 3 and 4 above) are to be conducted first before long-term testing (points 5 and 6 above) is commenced, as further explained in Appendix 1 of this decision.

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **21 January 2020**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

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, shall 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.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

[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

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by using a rodent species (rat). According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you agreed with the information requirement in the draft decision, i.e. to address the non-compliance for the endpoint in question.

Furthermore, you have explained the intention to close the information gap by applying a read-across approach on the basis of common breakdown products and similar biological effects following Annex XI, 1.5 of the REACH Regulation. You provided new information that has not been available earlier in the registration dossier.

You have provided the justification for read-across within your comments and provided an additional document entitled "[redacted]". Within the document, you claimed that "*Based on the well-established metabolism of esters, glycollic acid and n-butanol were selected as suitable read-across substances for butyl glycollate. These substances represent metabolic/chemical breakdown products of butyl glycollate. Ethylene glycol is selected as an appropriate source substance because it is a substance with the same main metabolite, i.e. glycollic acid...Comparing the target organ and adverse effects of butyl glycollate, ethylene glycol and glycollic acid shows that all three substances cause similar effects in the kidneys (i.e. the same pattern of toxicological activity). This corroborates the presence of similar metabolites, which then further supports use of these substances as read across substances...Following the hydrolysis of butyl glycollate to its metabolites, reproductive and developmental effects, if present, would most likely be related to the glycollic acid.*"

You have provided an analysis addressing the following elements in support of the read-across hypothesis:

- *Hydrolysis of Butyl Glycollate*
- *Metabolism of Butyl Glycollate*
- *Biotransformation to common compounds*
- *Metabolism of ethylene glycol*
- *Estimation of metabolic pathway concentrations of butyl glycollate upon hydrolysis*
- *Comparison of data from human health endpoints – Reproductive and developmental toxicological effects*

ECHA has assessed the information provided in your comments and the read-across justification document.

ECHA agreed that the registered substance and the analogue substance (ethylene glycol) have a common metabolite (glycollic acid). Although there is no experimental hydrolysis data for the enzymatic breakdown of butyl glycollate, the hypothesis based on: (i) predictive models, (ii) information from analogue esters and (iii) the comparative analysis of systemic effects between the registered substance, the analogue (ethylene glycol) and the common metabolite (glycollic acid), support the argument that the toxicity of butyl glycollate is driven by the formation of glycolic acid. Information on the non-common metabolite (butanol) has been provided showing no significant impact on the toxicity of the parent compound.

The experimental evidence from systemic toxicity, developmental toxicity and reproductive toxicity studies performed with ethylene glycol and glycolic acid when compared with the systemic toxicity and developmental toxicity studies performed with butyl glycollate show good dose-response and temporal concordance regarding the specific kidney effects (attributed to glycolic acid) and similar malformations in rodent developmental toxicity studies occurring only at high doses.

The information requirement of developmental toxicity in a non-rodent species (rabbit) has been addressed with experimental data performed with glycolic acid and ethylene glycol. ECHA concluded that the prediction between the source and the target substances is possible.

ECHA agreed with the arguments presented regarding potential species differences for glycolic acid mediated developmental toxicity. ECHA agreed that the information

requirement regarding a second species developmental toxicity study can be fulfilled with the experimental studies (rabbit pre-natal developmental toxicity) from ethylene glycol.

ECHA considered that the information in your comments and "[redacted]" document that you provided is adequate to support the read-across hypothesis. Therefore, on this basis the read-across approach was, at that time, considered plausible to fulfill the information gap addressed in the draft decision.

Subsequently, a Proposal for amendment (PfA) has been submitted during the MSCA commenting period that considered the read-across proposal required additional scientific justification. In particular the PfA concluded that there was:

1. insufficient "scientific justification of the hydrolysis rate in mammalian species (e.g. rats, rabbit, and/or humans) and thereby not sufficient scientific evidence that continuous systemic exposure to the parent compound, butyl glycollate would be negligible, i.e. that the hydrolysis of glycollate in vivo will lead to so low systemic exposure / blood levels that any developmental / reproductive effects as measured in PNDT study on rabbits or EOGRTS can be disregarded" and

2. insufficient "scientific justifications relating to the metabolites of the registered substance which are currently lacking from the Registration dossier".

You have provided in response to the PfA information including some additional scientific justifications addressing the elements of hydrolysis rate/extent and its potential impact on the systemic exposure to the parent compound and impact of the metabolites in regard to the plausibility of the read-across.

ECHA notes that the additional information provides some more scientific elaboration regarding the plausibility of the read-across for the endpoint prenatal developmental toxicity.

However, following the PfA and the additional information provided by you, ECHA also notes that in order for the read-across approach to be acceptable, evidence of

1. the rapid hydrolysis of the registered substance by esterases should be provided, which would confirm your claim that repeated oral exposure to the registered substance would lead to such a low systemic exposure that is it unlikely that the parent substance impacts the pre-natal developmental toxicity, i.e. that this toxicity is mediated only via the common metabolite glycolic acid, and

2. relative contribution of the activity of esterases (leading to formation of the common metabolite glycolic acid) in comparison with the activity of aldehyde dehydrogenase/aldehyde oxygenase (leading to non-common metabolites glyoxylic acid butyl ester and oxalic acid mono butyl ester) should be provided to confirm that these non-common metabolites have negligible impact on toxicity of the registered substance.

ECHA considers that the read-across should be further strengthened by additional evidence with the registered substance, e.g. toxicokinetic (hydrolysis/metabolism) information and/or modelling, to address the shortcomings described above.

Further, the supporting information for the read-across must be in the registration dossier in order to comply with Section 1.5 last indent of Annex XI of REACH.

However, you are reminded that irrespective of the plausibility of the adaptation argument presented at the stage of commenting the decision-making procedure, this decision does not take into account any updates submitted after 17 October 2016. All the new information in later update(s) of the registration dossier, including the substantiation of the adaptation argument and missing studies, will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation after passing of the deadline set by this decision for provision of the further information.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit) by the oral route, which is not included in the dossier under evaluation (submission number: [redacted]).

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

ECHA took note of your data waiving justification in the technical dossier that "according to EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008, the substance is classified as reproductive toxicant category 2 (Repr. 2) based on the observed developmental toxicity in rats. The basis for this proposed classification is also supported by an expert judgement ([redacted], 2010)."

However, this classification does not allow for an adaptation of the standard information required, neither in accordance with column 2 of Annex X, Section 8.7.3. nor with the general rules of Annex XI. In particular, ECHA observes that your adaptation does not meet the specific rule for adaptation in Annex X, Section 8.7., column 2, third paragraph for substances known to cause developmental toxicity, as that provision concerns substances

meeting the classification as Repr Cat 1A or 1B. Therefore, your adaptation of the information requirement is rejected.

In your comments to the draft decision you agreed with the information requirement in the draft decision, i.e. to address the non-compliance for the endpoint in question.

Furthermore, you have explained the intention to close the information gap by applying a read-across approach on the basis of common breakdown products and similar biological effects and you provided new information that has not been available earlier in the registration dossier.

You have provided the justification for read-across within your comments and provided an additional document entitled "[redacted]". Within the document, you claimed that "*Based on the well-established metabolism of esters, glycollic acid and n-butanol were selected as suitable read-across substances for butyl glycollate. These substances represent metabolic/chemical breakdown products of butyl glycollate. Ethylene glycol is selected as an appropriate source substance because it is a substance with the same main metabolite, i.e. glycollic acid...Comparing the target organ and adverse effects of butyl glycollate, ethylene glycol and glycollic acid shows that all three substances cause similar effects in the kidneys (i.e. the same pattern of toxicological activity). This corroborates the presence of similar metabolites, which then further supports use of these substances as read across substances...Following the hydrolysis of butyl glycollate to its metabolites, reproductive and developmental effects, if present, would most likely be related to the glycollic acid.*

You have provided an analysis addressing the following elements in support of the read-across hypothesis:

- *Hydrolysis of Butyl Glycollate*
- *Metabolism of Butyl Glycollate*
- *Biotransformation to common compounds*
- *Metabolism of ethylene glycol*
- *Estimation of metabolic pathway concentrations of butyl glycollate upon hydrolysis*
- *Comparison of data from human health endpoints – Reproductive and developmental toxicological effects*

ECHA has assessed the information provided in your comments and the read-across justification document.

ECHA agreed that the registered substance and the analogue substance (ethylene glycol) have a common metabolite (glycollic acid). Although there is no experimental hydrolysis data for the enzymatic breakdown of butyl glycollate, the hypothesis based on:
(i) predictive models, (ii) information from analogue esters and (iii) the comparative analysis of systemic effects between the registered substance, the analogue (ethylene glycol) and the common metabolite (glycollic acid), support the argument that the toxicity of butyl glycollate is driven by the formation of glycolic acid. Information on the non-common metabolite (butanol) has been provided showing no significant impact on the toxicity of the parent compound.

The experimental evidence from systemic toxicity, developmental toxicity and reproductive toxicity studies performed with ethylene glycol and glycolic acid when compared with the systemic toxicity and developmental toxicity studies performed with butyl glycollate show good dose-response and temporal concordance regarding the specific kidney effects

(attributed to glycolic acid) and similar malformations in rodent developmental toxicity studies occurring only at high doses.
The experimental data available indicate that glycolic acid mediated toxicity is not likely to cause adverse effects on reproduction. This is based on: (i) the absence of fertility related effects in the repeated dose toxicity study performed with butyl glycollate, (ii) the evidence that butyl glycollate toxicity is driven by glycolic acid formation, (iii) the supportive evidence from the experimental rodent generation studies performed with glycolic acid and ethylene glycol that indicate no effects on fertility.

ECHA agreed with the arguments presented and the information requirement regarding a reproductive toxicity study can be fulfilled with the experimental studies available from ethylene glycol and glycolic acid. ECHA concluded that the prediction between the source and the target substances is possible.

ECHA considered that the information in your comments and "[redacted]" document that you provided is adequate to support the read-across hypothesis. Therefore, on this basis the read-across approach was, at that time, considered plausible to fulfill the information gap addressed in the draft decision.

Subsequently, a Proposal for amendment (PfA) has been submitted during the MSCA commenting period that considered the read-across proposal required additional scientific justification. In particular the PfA concluded that there was:

1. insufficient "scientific justification of the hydrolysis rate in mammalian species (e.g. rats, rabbit, and/or humans) and thereby not sufficient scientific evidence that continuous systemic exposure to the parent compound, butyl glycollate would be negligible, i.e. that the hydrolysis of glycollate *in vivo* will lead to so low systemic exposure / blood levels that any developmental / reproductive effects as measured in PNDT study on rabbits or EOGRTS can be disregarded" and

2. insufficient "scientific justifications relating to the metabolites of the registered substance which are currently lacking from the Registration dossier".

You have provided in response to the PfA information including some additional scientific justifications addressing the elements of hydrolysis rate/extent and its potential impact on the systemic exposure to the parent compound and impact of the metabolites in regard to the plausibility of the read-across.

ECHA notes that the additional information provides some more scientific elaboration regarding the plausibility of the read-across for the endpoint reproductive toxicity.

However, following the PfA and the additional information provided by you, ECHA also notes that in order for the read-across approach to be acceptable, evidence of

1. the rapid hydrolysis of the registered substance by esterases should be provided, which would confirm your claim that continuous oral exposure to the registered substance would lead to such a low systemic exposure that is it unlikely that the parent substance impacts the reproductive toxicity, in particular fertility and perinatal developmental effects, i.e. that this toxicity is mediated only via the common metabolite glycolic acid, and

2. relative contribution of the activity of esterases (leading to formation of the common metabolite glycolic acid) in comparison with the activity of aldehyde dehydrogenase/aldehyde oxygenase (leading to non-common metabolites glyoxylic acid butyl ester and oxalic acid mono butyl ester) should be provided to confirm that these non-common metabolites have negligible impact on toxicity of the registered substance.

ECHA considers that the read-across should be further strengthened by additional evidence with the registered substance, e.g. toxicokinetic (hydrolysis/metabolism) information and/or modelling, to address the shortcomings described above.

If needed depending on the toxicokinetic information to be provided, information on the reproductive toxicity (e.g. Reproductive/Developmental Toxicity Screening study, e.g. OECD 421) of the registered substance would allow comparison of the toxicological profiles between the registered and the source substance and may further strengthen the read-across.

Further, the supporting information for the read-across must be in the registration dossier in order to comply with Section 1.5 last indent of Annex XI of REACH.

However, you are reminded that irrespective of the plausibility of the adaptation argument presented at the stage of commenting the decision-making procedure, this decision does not take into account any updates submitted after 17 October 2016. All the new information in later update(s) of the registration dossier, including the substantiation of the adaptation argument and missing studies, will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation after passing of the deadline set by this decision for provision of the further information.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. which is not included in the dossier under evaluation (submission number: [redacted]). The following refers to the specifications of this required study.

b) *The specifications for the study design*

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015), the starting point for deciding on the length of the premating exposure period should 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 because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

As no information is yet available from the dossier under evaluation (submission number: [redacted]), pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

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

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. You may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

3. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

Pursuant to Articles 10(a) (vi) and 12(1) (e) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Short-term toxicity testing on aquatic invertebrates", is a standard information requirement as laid down in Annex VII, Section 9.1.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record for a short term toxicity test on invertebrates (key, reliability 1, GLP, [redacted] 1986/[redacted] 2009, species *Daphnia magna Straus* exposed for 24 hrs) in a static, freshwater system on the registered substance according to guideline DIN 38 412 Part 11. However, this study does not provide the information required by Annex VII, Section 9.1.1. because as you did not provide data generated by the corresponding test method referred to in Article 13(3) of the REACH Regulation, i.e. *Daphnia sp.* acute immobilisation test (test method EU C.2. / OECD TG 202). Therefore, ECHA considers, that you sought to adapt the information requirement in accordance with Annex XI, Section 1.1.2.

In accordance with Annex XI, Section 1.1.2., data generated by another than the corresponding test methods referred to in Article 13(3) of the REACH Regulation shall be considered equivalent if the following conditions are met:

(1) adequacy for the purpose of classification and labelling and/or risk assessment;
(2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

ECHA notes that the exposure duration was set at 24 hours. A standard test duration for a short-term toxicity test on invertebrates according to OECD 202 (2004), *Daphnia sp.* Acute Immobilisation Test, is 48 hours.

ECHA concludes that the toxicity study on *Daphnia magna* provided in the registration dossier does not fulfil the conditions of Annex XI, 1.1.2. for being recognised as equivalent to data from the test method referred to in Article 13(3). Furthermore, ECHA observes that there is no information provided in the technical dossier on the pH and the dissolved oxygen concentration of the test solutions.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 3.0, February 2016) *Daphnia sp*. acute immobilisation test (test method EU C.2. / OECD TG 202) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.1.

You have proposed in your comments to the draft decision a weight of evidence approach to cover the information gap for this endpoint. You have provided a separate document "[redacted]" as an attachment to your comments ([redacted]). This document contains details on your weight of evidence approach, which is based "*on existing data and non-testing data in a read-across approach together with information derived from validated QSAR models.*"

ECHA has assessed the information presented in your comments on the draft decision and in the separate document according to Annex XI, Section 1.2., weight of evidence. You have provided the following justification for the weight of evidence adaptation: "*calculations with accepted QSAR models were conducted with butyl glycollate and its metabolite glycollic acid to confirm the results of the available aquatic toxicity studies for fish and daphnids for butyl glycollate in terms of suitability for the chemical safety assessment. Although some of the QSAR modelling results for butyl glycollate are not in the order of magnitude of the experimental values the EC0 value of 50 mg/L as derived from the submitted short-term toxicity study with fish can still be regarded as the lowest value hence representing a reasonable worst case. As no mortality occurred at this test concentration, this value is more protective than a L(E)C50 value and hence in line with the precautionary principle. New short-term toxicity studies on fish and daphnids are therefore not needed. A revision of the PNEC is therefore not necessary: In the chemical safety report prepared for butyl*

glycollate, all RCR values for the environment are clearly below the trigger value of 1, indicating a low risk of butyl glycollate to the environment."

To support the weight-of-evidence adaptation you have used the following sources of individual information:

- key study on the registered substance (reliability 1, GLP, [redacted] 1986/[redacted] 2009, species *Daphnia magna Straus* exposed for 24 hrs), provided in the technical dossier.
- read-across approach based on the hypothesis of (bio)transformation to a common compound, presented in your comments and in the separate document "[redacted];QSAR predictions, presented in your comments and in the separate document "[redacted]".

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific hazardous properties of the registered substance with respect to a short-term toxicity study on aquatic invertebrates (EU C.2. / OECD TG 202). Relevant elements are in particular exposure duration and exposure concentrations.

Furthermore, the relative values/weights of different pieces of the provided information needs to be assessed as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4., Section 4.4 (version 1.1, December 2011). In particular relevance, reliability and consistency of results/data and coverage (completeness) need to be considered.

Concerning the key study performed with the registered substance, ECHA has assessed above the information presented in your technical dossier. In this study, performed according to DIN 38 412, an EC50 (24h) of 280 mg/L (nominal) was obtained. As discussed above, the exposure duration of 24 hours is shorter than the standard test duration of 48 hours (EU C.2. / OECD TG 202) and the robust study summary lacks information on some parameters (e.g. pH and dissolved oxygen concentration of test solutions). However, this study might be acceptable in a weight of evidence approach if there are several studies available for the same test substance for the same endpoint which indicate an effect at approximately the same concentration and time. ECHA notes a scientifically underpinned attempt could have been made to extrapolate the 24h EC50 to a 48h EC50 value, but this has not been done.

Concerning the read-across approach, ECHA has assessed the information presented in your comments and in the separate document according to Annex XI, Section 1.5., grouping of substances and read-across approach. You use the following arguments to support the prediction of properties of the registered substance: *"Esters are directly broken down in vivo through the function of esterase enzymes, forming the corresponding acid and alcohol.*

Hydrolytic breakdown of esters by means of enzymes takes places in humans and animals [9]
In the absence of in vivo data on metabolism of a substance, there are computational tools available that allow the modeling and/or prediction of metabolism. These tools are well-recognized, with one of the primary tools, the OECD's QSAR toolbox, being recognized directly by ECHA. Using these tools, the metabolism of butyl glycollate was predicted, and the results support the hypothesis that butyl glycollate is hydrolyzed to n-butanol and glycolic acid in vivo.(..) The focus for the read-across approach is on glycolic acid since n-butanol is classified as "neutral organic" acting mainly via narcosis."

ECHA considers that your read-across hypothesis is based upon (bio)transformation to a common product (glycolic acid), which mediates the properties of the substance. However, there is insufficient information to support this element of your read-across hypothesis provided in your comments and in the separate document:

Your read-across hypothesis is supported by a prediction of a possible metabolic pathway of the registered substance using the OECD QSAR Toolbox. ECHA notes that for a read-across prediction to be valid, the information supporting the read-across should be reliable and of good quality. However, you have not provided any experimental information, or other adequate and reliable information, about the extent and the rate of the biotransformation of the registered substance in aquatic organisms. Without information addressing this issue, it is not possible to reliably and quantitatively predict the formation of the common product in aquatic invertebrates.

For the reasons presented above and on the basis of the information provided in your comments and in the separate document, there is not sufficient support for your proposal that the registered substance is enzymatically hydrolysed to a common product in aquatic invertebrates, and accordingly your hypothesis is not substantiated. For this reason, your hypothesis based upon enzymatic hydrolysis to a common product is not a reliable basis whereby the properties of the registered substance may be predicted from data for reference substance(s). In conclusion, the read-across information provided is currently not sufficient to fulfil the requirements of Annex XI section 1.5. and ECHA cannot accept the proposed information on its own or as part of a weight of evidence approach.

Concerning the QSAR predictions, ECHA has assessed the information presented in your comments and in the separate document according to Annex XI, Section 1.3., Qualitative or Quantitative structure-activity relationship (QSAR). You provide calculations for short-term toxicity to aquatic invertebrates of the registered substance, using the following models: ECOSAR model for esters (US EPA); Leadscope, SciQSAR and Battery models for aquatic toxicity from the Danish QSAR database, which you describe as "*well-accepted methods*". The predicted EC50 (48h) values range from 334.2 mg/L (Leadscope) to 615.6 mg/L (SciQSAR). However, these predictions are not correctly documented, since QMRFs and QPRFs have not been submitted.
According to the requirements set for acceptance of QSAR models in Annex XI section 1.3., adequate and reliable documentation of the applied methods must be provided. You indicate in the separate document that "*The QMRF reports for ECOSAR, Leadscope and SciQSAR are provided in the annex of this document*" (*Step 6 – (Q)SAR*). However, ECHA notes that the reports are not present neither as annex of the separate document nor in any of the attachments to your comments. For the ECOSAR and Danish QSAR database ECHA concludes – without the information being available in the dossier – that the substances are within the domain. However, the QSAR results are somewhat variable and indicate EC50

values that are higher than the information in the dossier (=> QSARs predict less toxicity). As explained above, the EC50 value is not fully reliable as the test duration was shorter than required in the current test guidelines and the real EC50 values are likely even lower than the values currently reported. Therefore, the QSAR result do not confirm the non-worst case EC50 value in the dossier. In conclusion, the QSAR information submitted is currently not fully supporting the experimental study and is not sufficient to fulfil the requirements of Annex XI section 1.3. and ECHA cannot accept the proposed information on its own or as part of a weight of evidence approach.

In conclusion, the results from the key study are the only relevant source of information on short-term aquatic toxicity to aquatic invertebrates and would constitute a worst-case approach with respect to the QSAR predictions for the registered substance. However, due to the limitations of the key study indicated above, this information alone does not adequately address the short-term toxicity to aquatic invertebrates to the extent required at this tonnage level that it can be assumed/conclude on the hazardous properties of the registered substance.

Hence, the sources of information you provided do not allow to conclude on the dangerous (hazardous) property of the registered substance with respect to the information requirement for Annex VII, Section 9.1.1.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

Consequently, there is an information gap and it necessary to provide information for this endpoint.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: short-term toxicity testing on invertebrates - *Daphnia sp.* Acute immobilisation test (test method EU C.2./OECD TG 202).

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203)

Pursuant to Articles 10(a) (vi) and 12(1) (e) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Short-term toxicity testing on fish", is a standard information requirement as laid down in Annex VIII, Section 9.1.3. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record for a short term toxicity test on fish (key, reliability 2, GLP, unknown author 1977 / [redacted]. 2009, species *Leuciscus idus* exposed for 48 hrs) in a static, freshwater system on the registered substance according to guideline DIN 38 412 Part 15. However, this study does not provide the information required by Annex VIII, Section 9.1.3. because you did not provide data generated by the corresponding test method referred to in Article 13(3) of the REACH

Regulation, i.e. Fish, acute toxicity test (test method: EU C.1./OECD TG 203). Therefore, ECHA considers that you sought to adapt the information requirement in accordance with Annex XI, Section 1.1.2.

In accordance with Annex XI, Section 1.1.2., data generated by another than the corresponding test methods referred to in Article 13(3) of the REACH Regulation shall be considered equivalent if the following conditions are met:

(1) adequacy for the purpose of classification and labelling and/or risk assessment;
(2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

ECHA notes that the exposure duration was set at 48 hours. A standard test duration for a short-term toxicity test on fish according to OECD TG 203 (1992), Fish, acute toxicity test is 96 hours.

ECHA concludes that the toxicity study on fish provided in the registration dossier does not fulfil the conditions of Annex XI, 1.1.2. for being recognised as equivalent to data from the test method referred to in Article 13(3). Furthermore, ECHA observes that there is no information provided in the technical dossier on the experimental conditions, such as concentrations, pH and the dissolved oxygen concentration of the test solutions.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 3.0, February 2016) fish acute toxicity test (test method EU C.1. / OECD TG 203) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.1.3.

You have proposed in your comments to the draft decision a weight of evidence approach to cover the information gap for this endpoint. You have provided a separate document "[redacted]" as an attachment to your comments ([redacted]). This document contains details on your weight of evidence approach, which is based "*on existing data and non-testing data in a read-across approach together with information derived from validated QSAR models.*"

ECHA has assessed the information presented in your comments on the draft decision and in the separate document according to Annex XI, Section 1.2., weight of evidence. You have provided the following justification for the weight of evidence adaptation: "*calculations with accepted QSAR models were conducted with butyl glycollate and its metabolite glycollic acid to confirm the results of the available aquatic toxicity studies for fish and daphnids for butyl glycollate in terms of suitability for the chemical safety assessment. Although some of the QSAR modelling results for butyl glycollate are not in the order of magnitude of the*

experimental values the EC0 value of 50 mg/L as derived from the submitted short-term toxicity study with fish can still be regarded as the lowest value hence representing a reasonable worst case. As no mortality occurred at this test concentration, this value is more protective than a L(E)C50 value and hence in line with the precautionary principle. New short-term toxicity studies on fish and daphnids are therefore not needed. A revision of the PNEC is therefore not necessary: In the chemical safety report prepared for butyl glycollate, all RCR values for the environment are clearly below the trigger value of 1, indicating a low risk of butyl glycollate to the environment."

To support the weight-of-evidence adaptation you have used the following sources of individual information:

- key study on the registered substance (reliability 2, GLP, unknown author 1977 / [redacted] 2009, species *Leuciscus idus* exposed for 48 hrs), provided in the technical dossier.
- read-across approach based on the hypothesis of (bio)transformation to a common compound, presented in your comments and in the separate document "[redacted]";QSAR predictions, presented in your comments and in the separate document "[redacted]".

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific hazardous properties of the registered substance with respect to a fish acute toxicity test (EU C.1. / OECD TG 203). Relevant elements are in particular exposure duration and exposure concentrations.

Furthermore, the relative values/weights of different pieces of the provided information needs to be assessed as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4., Section 4.4 (version 1.1, December 2011). In particular relevance, reliability and consistency of results/data and coverage (completeness) need to be considered.

Concerning the key study performed with the registered substance, ECHA has assessed above the information presented in your technical dossier. In this study, performed according to DIN 38 412 Part 15, an EC0 (48h) of 50 mg/L (nominal) was obtained. As discussed above, the exposure duration of 48 hours is shorter than the standard test duration of 96 hours (EU C.1. / OECD TG 203) and the robust study summary lacks information on some parameters (e.g. concentrations, pH and the dissolved oxygen concentration of the test solutions). However, this study might be acceptable in a weight of evidence approach if there are several studies available for the same test substance for the same endpoint which indicate an effect at approximately the same concentration and time. ECHA notes a scientifically underpinned attempt could have been made to extrapolate the 48h LC50 to a 96h EC50 value, but this has not been done.Concerning the read-across approach, ECHA has assessed the information presented in your comments and in the separate document according to Annex XI, Section 1.5., grouping of substances and read-

across approach. You use the following arguments to support the prediction of properties of the registered substance: "*Esters are directly broken down in vivo through the function of esterase enzymes, forming the corresponding acid and alcohol. Hydrolytic breakdown of esters by means of enzymes takes places in humans and animals [9]*
In the absence of in vivo data on metabolism of a substance, there are computational tools available that allow the modeling and/or prediction of metabolism. These tools are well-recognized, with one of the primary tools, the OECD's QSAR toolbox, being recognized directly by ECHA. Using these tools, the metabolism of butyl glycollate was predicted, and the results support the hypothesis that butyl glycollate is hydrolyzed to n-butanol and glycolic acid in vivo.(..) The focus for the read-across approach is on glycolic acid since n-butanol is classified as "neutral organic" acting mainly via narcosis."

ECHA considers that your read-across hypothesis is based upon (bio)transformation to a common product (glycolic acid), which mediates the properties of the substance. However, there is insufficient information to support this element of your read-across hypothesis provided in your comments and in the separate document:

Your read-across hypothesis is supported by a prediction of a possible metabolic pathway of the registered substance using the OECD QSAR Toolbox. ECHA notes that for a read-across prediction to be valid, the information supporting the read-across should be reliable and of good quality. However, you have not provided any experimental information, or other adequate and reliable information, about the extent and the rate of the biotransformation of the registered substance in aquatic organisms. Without information addressing this issue, it is not possible to reliably and quantitatively predict the formation of the common product in fish.

For the reasons presented above and on the basis of the information provided in your comments and in the separate document, there is not sufficient support for your proposal that the registered substance is enzymatically hydrolysed to a common product in fish, and accordingly your hypothesis is not substantiated. For this reason, your hypothesis based upon enzymatic hydrolysis to a common product is not a reliable basis whereby the properties of the registered substance may be predicted from data for reference substance(s). In conclusion, the read-across information provided is currently not sufficient to fulfil the requirements of Annex XI section 1.5. and ECHA cannot accept the proposed information on its own or as part of a weight of evidence approach.
Concerning the QSAR predictions, ECHA has assessed the information presented in your comments and in the separate document according to Annex XI, Section 1.3., Qualitative or Quantitative structure-activity relationship (QSAR). You provide calculations for short-term toxicity to fish of the registered substance, using the following models: ECOSAR model for esters (US EPA); Leadscope, SciQSAR and Battery models for aquatic toxicity from the Danish QSAR database, which you describe as "*well-accepted methods*". The predicted LC50 (96h) values range from 68.9 mg/L (Leadscope) to 286.1 mg/L (SciQSAR). However, these predictions are not correctly documented, since QMRFs and QPRFs have not been submitted.

According to the requirements set for acceptance of QSAR models in Annex XI section 1.3., adequate and reliable documentation of the applied methods must be provided. You indicate in the separate document that "*The QMRF reports for ECOSAR, Leadscope and SciQSAR are provided in the annex of this document*" (*Step 6 – (Q)SAR*). However, ECHA notes that the reports are not present neither as annex of the separate document nor in any of the attachments to your comments. For the ECOSAR and Danish QSAR database ECHA concludes – without the information being available in the dossier – that the substances are

within the domain. However, the QSAR results are somewhat variable and indicate LC50 values that are higher than the information in the dossier (=> QSARs predict less toxicity). As explained above, the LC50 value is not fully reliable as the test duration was shorter than required in the current test guidelines and the real LC50 values are likely even lower than the values currently reported. Therefore, the QSAR result do not confirm the non-worst case LC50 value in the dossier. In conclusion, the QSAR information submitted is currently not fully supporting the experimental study and is not sufficient to fulfil the requirements of Annex XI section 1.3. and ECHA cannot accept the proposed information on its own or as part of a weight of evidence approach.

In conclusion, the results from the key study are the only relevant source of information on short-term aquatic toxicity to fish and would constitute a worst-case approach with respect to the QSAR predictions for the registered substance. However, due to the limitations of the key study indicated above, this information alone does not adequately address the short-term toxicity to fish to the extent required at this tonnage level that it can be assumed/conclude on the hazardous properties of the registered substance.

Hence, the sources of information you provided do not allow to conclude on the dangerous (hazardous) property of the registered substance with respect to the information requirement for Annex VIII, Section 9.1.3.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

Consequently, there is an information gap and it necessary to provide information for this endpoint.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Short-term toxicity testing on fish - Fish, acute toxicity test (test method: EU C.1./OECD TG 203).

5. and 6. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211), and long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210).

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. "Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on these endpoints need to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt these information requirements according to Annex IX, Sections 9.1.5 and 9.1.6 column 2. You provided the following justification for both adaptations: '*In accordance with column 2 of REACH Annex IX, long-term toxicity testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation.*' However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Sections 9.1.5 and 9.1.6 because no valid information on short or long-term toxicity to invertebrates and fish is available in the registration technical

dossier. In the absence of valid information on short-term toxicity to invertebrates and fish it is not possible to derive a correct aquatic PNEC, thus there are uncertainties in the risk characterisation.

Therefore, your adaptation of the information requirements cannot be accepted.

As explained above, the information provided on these endpoints for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 3.0, February 2016):

- the *Daphnia magna* reproduction test (test method: EU C.20/OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, section 9.1.5.
- fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

Regarding the long-term toxicity testing on fish pursuant to Annex IX, section 9.1.6.1, ECHA considers that the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, February 2016), *Chapter R7b, Figure R.7.8-4).*

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b*, version 3.0, February 2016).

In your comments on the draft decision for both Long-term toxicity testing on aquatic invertebrates and long-term toxicity testing on fish, you stated the following "*According to Annex IX, sections 9.1.5 and 9.1.6 column 2 Long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. As the results of the chemical safety assessment do not indicate the need for further investigation, long-term studies on fish and daphnids are not needed*".

ECHA notes that your adaptation indicated in your comment on the draft decision, does not meet the specific rules for adaptation of Annex IX, Sections 9.1.5 and 9.1.6 because currently there is no valid information on short or long-term toxicity to invertebrates and fish available in the registration technical dossier. In the absence of valid information on short-term toxicity to invertebrates and fish it is not possible to derive a correct aquatic PNEC, thus there are uncertainties in the risk characterisation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211) and Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210).

Notes for your consideration for long-term aquatic testing

Once you revise the PNEC with valid results of the test on short-term toxicity on aquatic invertebrates and fish (points 3 - 4 above), you may consider the integrated testing strategy as recommended in ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, February 2016), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4), and determine the need to conduct long-term toxicity tests.

Before conducting any of the tests mentioned above in points 5 – 6 you shall consult the ECHA *Guidance on information requirements and chemical safety assessment (version 3.0, February 2016)*, Chapter R7b, Section R.7.8.5 to determine the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on fish.
According to ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, February 2016), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

If you come to the conclusion that no further investigation of effects on aquatic organisms is required, you shall update your technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.5 and 9.1.6. taking into account the new data generated by the short-term toxicity studies requested by the present decision.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 9 August 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and amended the request(s). For the following endpoint: Robust study summary (RSS) for key study, Paulus & Rudolf (2008), report number 07080901G605 according to OECD TG 301B and GLP. Biodegradation in water; screening tests (Annex VII, Section 9.2.1.1. in conjunction with Annex 1, Section 3.1.5; test method: CO2 evolution test, OECD TG 301B with the registered substance), your comments on the draft decision request, submitted as an IUCLID print out, fulfilled the information requirement, resulting in the removal of this request from this decision.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-54 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.