EUROPEAN CHEMICALS AGENCY

Helsinki, 24 July 2019

Addressee: [redacted]

Decision number: CCH-D-2114476044-51-01/F
Substance name: 4-hydroxybutyl acrylate
EC number: 219-606-3
CAS number: 2478-10-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 13.02.2013
Registered tonnage band: 100-1000T

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. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

2. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

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

4. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

5. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.) by providing an adaptation in accordance with the second column of Annex IX section 9.1. by explaining that the chemical safety assessment according to Annex I indicates that there is no need to further investigate the effects on aquatic organisms;**

6. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6) by providing an adaptation in accordance with the second column of Annex IX section 9.1. by explaining that the chemical safety assessment according to Annex I indicates that there is no need to further investigate the effects on aquatic organisms;**

7. **Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment: include in the registration dossier an exposure**

assessment for all relevant exposure scenarios and the revised risk characterisation.

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 to the REACH Regulation. 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***31 January 2022***. You also have to 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 and 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, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Hazard Assessment

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

Appendix 1: Reasons

INFORMATION RELATED TO PREDICTION OF TOXICOLOGICAL PROPERTIES

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

In the registration, you have adapted the standard information requirements for

- Sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.); and
- Pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.)

by applying a weight of evidence adaptation following REACH Annex XI, Section 1.2.

Weight of evidence

Article 13(1) of the REACH Regulation stipulates that information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met.

In that respect, ECHA notes that you have adapted two of the information requirements addressed in the present decision with weight of evidence approaches. Section 1.2 of the Annex XI of the REACH Regulation sets out the prerequisites of weight of evidence approaches as follows:

> *"There may be 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, while the information from each single source alone is regarded insufficient to support this notion".*

Therefore, an evidence based approach involves an assessment of the relative values/weights of different pieces of the available information that have been retrieved and gathered in previous steps. To this end, a value needs to be assigned to each piece of information. These weights/values can be assigned either in an objective way by using a formalised procedure or by using expert judgement. The weight given to the available evidence depends on factors such as the quality of the data, consistency of results, nature and severity of effects and relevance of the information for the given regulatory endpoint.

In the present case, the weight of evidence approach that you have developed for the endpoints under consideration is based on information obtained from structurally similar substances in a grouping and read-across approach: substances 2-hydroxyethyl acrylate, CAS No 818-61-1 (EC No 212-454-9; hereafter referred to as '**HEA**'); 2-hydroxypropyl acrylate, CAS No 25584-83-2 (EC No 247-118-0; hereafter referred to as '**HPA**'); and methyl acrylate, CAS No 96-33-3 (EC No 202-500-6; hereafter referred to as '**MA**'). Such sources of information are themselves adaptations, which are described in respective sections of Annex XI and subject to specific conditions. The fulfillment of all or parts of these conditions determines the quality and reliability of these sources of information for assuming or concluding that a substance has or has not a particular dangerous property.

You have provided a justification for the weight of evidence adaptation in an endpoint study record referring to a "*read-across justification*" included in section 13 of the IUCLID dossier. In this document you outline the elements of structural similarity between HEA, HPA, MA and the substance subject to this decision 4-hydroxybutyl acrylate CAS No 2478-10-6 (EC number: 219-606-3; hereafter referred to as the '**HBA**') and specify the structural differences between these substances. In order to support the use of data from the structurally similar substances, you elaborated on similarities in some physicochemical properties between HEA, HPA, MA and HBA. In the section of this document addressing toxicological endpoints you indicated that following systemic absorption, "*all esters are hydrolysed in local tissues as well as in blood by carboxyl esterases (high activity within many tissues and organs like liver, GI tract, nasal epithelium and skin) forming acrylic acid and the respective alcohol*". On that basis you consider that "*From a toxicological point of view the acrylate group represents the reactive group and will mainly trigger the toxicological profiles at least for systemic toxicity*". Comparisons of the available toxicological data on HBA, HPA, HEA and MA are presented for the endpoints skin sensitisation, repeated dose toxicity, developmental toxicity and mutagenicity.

You concluded that "*Overall, the information available for different analogous methacrylate esters demonstrates that a read-across approach is adequate and scientifically justified to support the relevant endpoints for the test item's WoE approach. Taking the small structural differences, the similar physicochemical properties as well as the behaviour in physiological media into account it was possible to conduct a sound and scientifically valid assessment of the test item's hazard properties with regards to the toxicological endpoints skin sensitisation, repeated dose toxicity, reproduction and developmental toxicity as well as genetic toxicity. In conclusion the data set available allows a scientifically valid evaluation of all endpoints that have to be addressed under REACH*".

ECHA has evaluated your adaptation with respect to the provision of Annex XI, Section 1.2 of the REACH Regulation and concludes that it cannot be accepted as currently presented for the reasons detailed below.

Based on the information provided, ECHA understands that hydrolysis of the ester function of HBA, HEA, HPA and MA and the formation of acrylic acid and the related alcohols is a key element in your read-across hypothesis: you indicate in your read-across justification document that the "*acrylate group represents the reactive group and will mainly trigger the toxicological profiles at least for sytemic toxicity*".

Hydrolysis of the esters to form acrylic acid and the respective alcohol

As indicated above you have highlighted in your read-across justification document that "*all esters are hydrolysed in local tissues as well as in blood by carboxyl esterases (high activity within many tissues and organs like liver, GI tract, nasal epithelium and skin) forming acrylic acid and the respective alcohol*". You also reported in section 5.1.3 of the Chemical Safety Report (CSR) that "*Animal studies indicated rapid metabolism via hydrolysis of the ester functionality with the subsequent rapid metabolism of the hydrolysis products to produce exhaled CO2 or urinary metabolites (mercapturic acid derivatives)*".
You have provided data from *in vitro* and *in vivo* toxicokinetic investigations conducted via different routes of administration with the analogue substance HEA to support this argument. On the basis of this information, you concluded in the CSR that "*Based on the similarity of the results for HEA with other acrylic acid esters, similar kinetics of 4-hydroxybutyl acrylate are anticipated.*"

ECHA has evaluated this set of toxicokinetic data. The *in vivo* studies conducted with HEA via the oral, dermal, inhalation and intra-peritoneal routes provide reliable information on the metabolism, distribution and elimination of HEA after unique administration to rat. These studies provide global toxicokinetic information integrating all the steps of the metabolic pathway of HEA, *i.e.* from the ester hydrolysis, the formation of the primary metabolites ethylene glycol and acrylic acid and until the elimination of the final metabolites. In the context of this specific weight of evidence approach, the characterization of the kinetics of the ester function hydrolysis and the determination of the formation of acrylic acid and the related alcohol constitutes the most relevant metabolic step. The uniform radio-labelling of the test material prevents from discriminating the formation of the primary metabolites formed, i.e. acrylic acid and ethylene glycol and the global study design does not specifically inform on the kinetics of the metabolic step of interest, i.e. the hydrolysis of the ester function. Further, no information from similar studies conducted with the target substance is available, allowing for a direct comparison of the toxicokinetic parameters derived from these studies between HEA and HBA. Therefore, ECHA considers that the relevance of the information obtained from these in vivo toxicokinetic studies in the context of this weight of evidence approach is not established. However, ECHA accepts that the half-life 1.7 minutes identified from the *in vitro* data generated with HEA in rat blood ([redacted] 1992) indicates that this substance is rapidly bio-transformed to unspecified metabolites in rat blood. This constitutes relevant and reliable information in the context of this weight of evidence approach.

Although information establishing a rapid metabolism of the analogue substance HEA is provided and whilst the general claim of hydrolysis of esters by carboxyl esterases is considered plausible, ECHA emphasises that your adaptation, as currently documented, is missing scientific evidence supporting your assumption that all the other substances involved in this weight-of-evidence approach, and in particular that the target substance HBA, will display kinetics similar to those of documented and characterised in your dossier for HEA. Consequently, ECHA concludes that the relevance of the information obtained from experimental data generated with HEA, HPA or MA is not established, in the context of a weight of evidence approach aimed at identifying toxicological properties of HBA.

Toxicity of the parent compound

ECHA further points out that no information on the systemic properties after repeated administration of the target substance HBA is included in the dossier.
The limited information on the toxicological properties of the target substance HBA after repeated administration does not allow a comparison of the toxicological profiles of HBA with those of the analogue substances HEA, HPA and MA in the context of a weight of evidence approach aimed at identifying toxicological properties of HBA. ECHA is of the opinion that the weight of the evidence presented does not allow to conclude on the toxicological properties of the target substance HBA in its native form.

Impact of the non-common compounds

In accordance with your read-across hypothesis, and without prejudice to the deficiencies in the scientific documentation of the hydrolysis identified above, ECHA accepts that HBA, HEA, HPA and MA have the potential to be metabolized after systemic absorption to form acrylic acid and the respective alcohols, i.e. 1,4-butanediol, ethylene glycol, 1,3- or 1,2-propanediol and methanol, respectively.

You have indicated in your justification document that you consider that the toxicity is due to the acrylate group, which is the common structural feature for all these substances and which will give rise to the common primary metabolite acrylic acid. However, your adaptation is missing considerations and information on the potential impact of the non-common primary metabolites, i.e. the different alcohols, on the toxicological properties of the substances for the endpoints under consideration. According to the information provided in the OECD SIDS for 1,4-butanediol (http://www.inchem.org/documents/sids/sids/110634.pdf), findings with neurobehavioral/neurotoxicity have been reported in repeated-dose toxicity studies, in a combined repeat dose an reproductive/developmental screening toxicity test conducted in rats and in a developmental toxicity study performed in mice conducted with the alcoholic primary metabolite of the target substance HBA. Such findings are particularly relevant for the systemic endpoints under consideration.

In your technical dossier, you have reported information from a sub-chronic neurotoxicity study conducted in rats with HEA via the intra-peritoneal route ([redacted] 1992). This study reveals multiple behavioural effects (e.g. transient decrease in hindlimb grip, impaired righting reflex in males dosed with 60 mg/kg/d). Modifications of the gait are reported, without a dose-response relationship. Bloating, described as "*extreme*" was suspected of being responsible for some of the changes noted in the functional observation battery. You indicate that "*the authors did not comment about how bloating (pear-shaped belly) could have eventually affected gait scores. Behavioural effects observed after i.p. administration of HEA where neither dose- nor time-related*". You consider that "the neurotoxic potential of HEA appears to be minimal" and conclude that "*based on the data from the analogue 2-hydroxyethyl acrylate, the neurotoxic potential of HBA appears to be minimal, too*". However, ECHA stresses that your adaptation is missing information establishing whether and how the behavioural findings observed with HEA may inform about the above-mentioned properties of HBA or of its alcoholic primary metabolite 1,4-butanediol in the context of a weight of evidence adaptation.

In the endpoint-specific read-across justification that you have provided in your read-across justification document for the endpoint repeated dose toxicity, you have indicated that "*Based on the structural similarity of the three hydroxy acrylate compounds 2-hydroxyethyl acrylate, 2-hydroxypropyl acrylate and 4-hydroxybutyl acrylate similar toxicological behaviour after repeated exposure can be expected for 4-hydroxybutyl acrylate as observed for the other two substances as a WoE approach*". In contradiction with this statement, ECHA underlines that no information is available in the technical dossier on the properties of the target substance HBA after repeated administration to compare the behaviour of the target substance HBA with that of the analogue substances HEA and HPA. The information on the analogue substances HEA, HPA and MA provided in the weight of evidence approach, as currently documented, does not address the potential impact of exposure to 1,4-butanediol formed from HBA, i.e. in conjunction with exposure to the other primary metabolite acrylic acid, on the toxicological properties of HBA. In the absence of this information, ECHA considers that the possibility that the information currently provided in the weight of evidence approach may under estimate the properties of the HBA for the endpoints under consideration cannot be dismissed. Therefore, ECHA concludes that the weight of the information provided in your adaptation for the endpoints repeated dose toxicity and pre-natal developmental toxicity, as currently documented, is not sufficient to assume that HBA has or has not a particular dangerous property for the endpoints under consideration.

Hence, for the reasons presented above, ECHA considers that the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude on the dangerous (hazardous) property of the registered substance with respect to the information requirement for Annex IX, Sections 8.6.2. and 8.7.2.

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.

Your comments on the initial draft decision

In your comments to the initial draft decision, you disagreed with ECHA's rejection of your read-across /weight of evidence approach. You have attached a revised read-across justification to your comments. The read-across hypothesis is now based on RAAF, Scenario 2 (biotransformation into common products); i.e. that the target substance HBA hydrolyses to the common metabolite acrylic acid (AA) and the non-common metabolite butane-1,4-diol (BD). You assume that the toxicity of the target substance can be accurately predicted from data available on AA and BD. However, you also assume that the effect of the common metabolite AA can be predicted from other acrylates (i.e. HEA, HPA, MA and n-butyl acrylate (nBA)) where it is also formed following hydrolysis. You have provided additional information on the non-common metabolites and HPA in the revised read-across justification document.

In your comments you highlight that there is *in vitro* toxicokinetic information available on HEA which shows that this substance hydrolyses in blood with a half-life of less than 2 minutes.

It is a well-known fact that the rate of hydrolysis of an ester-bond decreases with the length of the "side-chain". The rate is also influenced by the amount of branching and type, number and position of substituents on the side-chain[2]. Currently, there is no information available on the rate of hydrolysis of any other acrylate than HEA. Given that the side-chain in HBA differs both in terms of length of the side-chain and in the position (relative to the ester bond) of the hydroxyl-substituent on the side-chain, it is reasonable to assume that the rate of hydrolysis will be longer than 2 minutes because the side-chain is two carbon atoms longer and the hydroxyl-substituent is in a different position in relation to the ester-bond.

ECHA therefore concludes that you have not provided any additional information with regard to the rate of hydrolysis for HBA.

ECHA wants to reiterate the importance of such information to support a read-across approach based on hydrolysis. Without supporting information that allow a side-by-side comparison of the rate of hydrolysis for all the substances involved in a read-across approach based on hydrolysis such read-across cannot be accepted. In addition, when the rate of hydrolysis becomes longer also the influence of the parent compound needs to be considered in the predictions.

1. *In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)*

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

[2] Pharmaceutical chemistry, Watson DG (ed.), 2011, Elsevier Ltd., London

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used 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.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four S. typhimurium strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or S. typhimurium TA102 which have an AT base pair at the primary reversion site.

You have provided a test from the year 1989 according to OECD TG 471 but not-GLP with an assigned reliability score of 2. The test used four different strains of S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

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.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

In your comments on the draft decision you agreed to perform the test.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing information from a two-generation reproductive toxicity study conducted according to the OECD TG 416 in rats via the inhalation route with the source substance methyl acrylate ([redacted] 2009) . You conclude in section 5.9.3 of the CSR that *"In a 2-generation-study with the structural analogue methyl acrylate by the inhalation route, no effects on reproductive function (i. e. fertility) were observed. Based on the structural similarities between the substances, it can be safely assumed that 4-hydroxybutyl acrylate does not cause any toxicity to reproduction"*.

In order to support your read-across approach, you have established the elements of structural similarity bewteen the target substance HBA and the source substance methyl acrylate in your read-across justification document. You further specifically justified the selection of this source substance as "*the substance methyl acrylate was used for the read-across as it is the smallest acrylate ester compound*". ECHA understands from the following statement in the read-across justification document included in the technical dossier that you read-across hypothesis is based on the hydrolysis of the acrylate esters to form acrylic acid and the corresponding alcohols:"*From a toxicological point of view the acrylate group represents the reactive group and will mainly trigger the toxicological profiles at least for systemic toxicity. Following absorption into the systemic circulation all esters are hydrolysed in local tissues as well as in blood by carboxyl esterases (high activity within many tissues and organs like liver, GI tract, nasal epithelium and skin) forming acrylic acid and the respective alcohol*".

As detailed in the section Weight of evidence of Appendix 1 above, ECHA has identified deficiencies in the scientific documentation of the hydrolysis of the acrylate esters and has emphasised the absence of information on the toxicological properties of the target substance in its non-hydrolysed form. ECHA also stressed that the information on the analogue substances MA provided in your adaptation, as currently documented, does not address the potential impact of exposure to 1,4-butanediol formed from the target substance HBA, i.e. in conjunction with exposure to the other primary metabolite acrylic acid, on the toxicological properties of HBA. For all these reasons, ECHA considers that your read-across adaptation, as currently documented, does not constitute a reliable for predicting the properties of the registered substance according to the provisions of Annex XI, Section 1.5 of the REACH Regulation. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with 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 6.0, July 2017) R.7a, chapter R.7.6.2.2.1. 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 initial draft decision you did not agree to conduct the requested OECD TG 421/422 study. Instead you propose to cover this information requirement by reading across to other acrylates and their hydrolysis products (as outlined in your revised read across approach). You have identified additional source studies which are currently not in the dossier. Whether or not this approach is acceptable is dependent on whether or not the read-across approach is considered acceptable. Currently, crucial information is missing to support the read-across approach. Without information on the rate of hydrolysis in blood for the acrylates involved in the approach, in particular the registered substance, it is impossible to conclude on the acceptability of the approach; because your read-across hypothesis rely on rapid and complete hydrolysis for the prediction of the properties of the registered substance from the proposed source substances. In order for your approach to be acceptable the rate of hydrolysis for the other acrylates must be similar to or less than the 2 minutes reported for HEA. If the rate of hydrolysis is longer than 2 minutes for the registered substance, then also the toxicity of the parent compounds need to be considered in the predictions. In such case a study according to OECD 422 with the registered substance may serve as a bridging study because it provides screening level information on your substance with regard to reproductive, developmental and repeated-dose toxicity which allow comparison of the toxicity profile with the source substances.
You are in this context reminded that ECHA does not take into account dossier updates submitted after the notification of the draft decision under Article 50(1) of the REACH Regulation for the purpose of this decision. However, ECHA will examine any information submitted in later updates of the registration dossier at the stage of the follow-up to the dossier evaluation in accordance with Article 42 of the REACH Regulation.

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: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, section R.7.5 and 7.6 (version 6.0, July 2017).

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance
(https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017."

3. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. You have provided the following lines of information:

- 100-day repeated dose toxicity study conducted in rats via the oral route using the analogue substance HEA ([redacted] 1967)
- 97-day repeated dose toxicity study conducted in dogs via the oral route using the analogue substance HEA ([redacted] 1967)
- 12+6-month repeated dose toxicity study conducted chronic toxicity/carcinogenicity in rats via the inhalation route using the analogue substance HEA ([redacted] 1979)
- 28-day repeated dose toxicity study conducted in rats via the inhalation route using the analogue substance HEA ([redacted] 1970)
- 21-day repeated dose toxicity study conducted in rats via the inhalation route using the analogue substance HPA ([redacted] 1983)
- 30/31-day repeated dose toxicity study conducted in mice via the inhalation route using the analogue substance HPA ([redacted] 1983)
- 20-day repeated dose toxicity study conducted in dogs via the inhalation route using the analogue substance HPA ([redacted] 1983)
- 20-day repeated dose toxicity study conducted in rabbits via the inhalation route using the analogue substance HPA ([redacted] 1983)

ECHA has assessed the weight of each of these lines of evidence and has evaluated your adaptation with respect to the provisions of Annex XI, Section 1.2 of the REACH Regulation.

ECHA notes that according to the information provided in the endpoint study records, the oral repeated dose toxicity studies conducted by [redacted] 1967 with HEA do not fulfil the conditions described in the current version of the OECD TG 408/409. Based on the information reported in the robust study summaries provided for these studies, ECHA is unable to fully understand how these studies deviate from the current test guideline. It should be noted that the animal numbers in the dog study in half of those required by the OECD TG 409; i.e. at least 4 animals per sex per group. Further, according to the recommendations of the OECD TG 408/409, the "*highest dose should be chosen with the aim to induce toxicity but not death or severe suffering*". In these studies, toxicity was observed up to the highest dose tested, leading to the identification of NOAELs corresponding to the highest test doses used in each of these studies.

Despite these shortcomings, ECHA considers that these lines of evidence provide relevant information on the properties of the test materials, *i.e.* HEA and HPA. However, for the reasons described Appendix 1, section Weight of evidence of this decision, ECHA considers that you have not established how data generated with HEA and HPA can be used to predict the properties of the registered substance. Therefore, ECHA is of the opinion that this information, as currently provided, does not constitute relevant information in the context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration.

In addition to the general information addressed in Appendix 1, section Weight of evidence, ECHA notes that you have provided endpoint-specific considerations section 5.6.3 of the CSR: "*Based on the structural similarity of the three hydroxy acrylates HEA, HPA and HBA, a similar toxicological behaviour after repeated exposure can be expected for 4-hydroxybutyl acrylate as observed for the other two substances. However, vapour pressure for HBA was measured to be considerably respectively to some extent lower than for its structural analogues HEA and HPA. Therefore, read across to HEA and HPA for the inhalation route might represent a worst case assumption for HBA*". ECHA understands that the "*worst-case assumption*" referred to in this statement is based exclusively to the differences in vapour pressures, with the vapour pressure of the target substance HBA being lower than that of the source substances HEA and HPA. Whilst this difference in vapour pressure may inform on the higher relevance and extent of inhalation exposure for HEA and HPA, ECHA considers that a higher vapour pressure does not, by itself and in the absence of further information, establish that the hazard information obtained from inhalation studies conducted by HEA and HPA constitute work-cases with regard to the properties of HBA.

Taking into consideration the weight of each of the lines of evidence provided, ECHA considers that the overall weight of the evidence is not sufficient to conclude that the registered substance has or has not a particular dangerous property in relation to the endpoint under consideration. Therefore, the general rule for adaptation of Annex XI, Section 1.2 is not met and your adaptation of the information requirement cannot be accepted. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size.
Hence, the test shall be performed by the oral route using the test method OECD TG 408.

According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In the comments you did not agree to conduct the requested OECD TG 408 study. Instead you propose to cover this information requirement by reading across to other acrylates and their hydrolysis products (as outlined in your revised read across approach). ECHA has addressed this information under point 2. above.

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: Repeated dose 90-day oral toxicity study (test method: OECD TG 408) in rats.

4. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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.

You have sought to adapt this information requirement according to Annex XI, Section 1.2, weight of evidence. In the read-across justification document included in section 13 of the technical dossier you have provided the following endpoint-specific considerations: *"Similarly, in developmental studies conducted with the structural analogues 2-hydroxyethyl acrylate and 2-hydroxypropyl acrylate in rats by the inhalation route, no signs of developmental toxicity (fetotoxicity, embryotoxicity, teratogenicity) were observed. The results if these studies are supported by a developmental study in rabbits and a further reproductive study in rats conducted via the inhalation route with the simple substance methyl acrylate. Again, based on the structural similarities between the read-across substances and the test item, it can be safely assumed that 4-hydroxybutyl acrylate does not cause developmental toxicity".*

In the technical dossier you have reported results from the following lines of information:

- Developmental toxicity study conducted in rats via the inhalation route using the analogue substance HEA ([redacted] 1999);
- Developmental toxicity study conducted in rats via the inhalation route using the analogue substance HPA ([redacted] 1999);
- Developmental toxicity study conducted in rats via the inhalation route using the analogue substance MA ([redacted] 2009).

ECHA has assessed the weight of each of these lines of evidence and has evaluated your adaptation with respect to the provisions of Annex XI, Section 1.2 of the REACH Regulation.

ECHA considers that these lines of evidence provide relevant information on the properties of the test materials, i.e. HEA, HPA and MA. However, for the reasons described Appendix 1, section Weight of evidence of this decision, ECHA considers that you have not established how data generated with HEA, HPA and MA can be used to predict the properties of the registered substance. Therefore, ECHA is of the opinion that this information, as currently provided, does not constitute relevant information in the context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration.

Taking into consideration the weight of each of the lines of evidence provided, ECHA considers that the overall weight of the evidence is not sufficient to conclude that the registered substance has or has not a particular dangerous property in relation to the endpoint under consideration. Therefore, the general rule for adaptation of Annex XI, Section 1.2 is not met and your adaptation of the information requirement cannot be accepted. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first 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 6.0, July 2017) R.7a, chapter R.7.6.2.2.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In the comments you did not agree to conduct the requested OECD TG 414 study. Instead you propose to cover this information requirement by reading across to other acrylates and their hydrolysis products (as outlined in your revised read across approach). ECHA has addressed this information under point 2. above.

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: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

5. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

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

Under Annex IX, section 9.1., column 2 long-term toxicity is not necessary if the chemical safety assessment indicates that there is no need to investigate further the effects on aquatic organisms.

You have sought to adapt this information requirement according to Annex IX, Section 9.1., column 2. You provided the following justification for the adaptation: "*In Annex IX of Regulation (EC) No 1907/2006, it is laid down that long-term toxicity to aquatic invertebrates shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic invertebrates. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of 4-hydroxybutyl acrylate reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, a long-term toxicity test in aquatic invertebrates is not provided.*"

In your comments on the draft decision, you attached Chapters 9 and 10 of the CSR, with the exposure assessment and risk characterization for both human health and environment. You noted that based on the exposure assessment and risk characterisation (EA/RC) for environment (performed following request 7. below and attached to your commens), the CSA indicates no risks for the registered substance. ECHA acknowledges that in your comment you provided the requested EA/RC showing that the RCRs are below 1. Therefore, ECHA agrees that based on this information long-term aquatic testing is not needed.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to fulfil the information requirement for long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.) by providing an adaptation in accordance with the second column of Annex IX section 9.1. by explaining that the chemical safety assessment according to

Annex I indicates that there is no need to further investigate the effects on aquatic organisms.

6. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

"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 Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

Under Annex IX, section 9.1., column 2 long-term toxicity is not necessary if the chemical safety assessment indicates that there is no need to investigate further the effects on aquatic organisms.

You have sought to adapt this information requirement [according to Annex IX, Section 9.1., column 2. You provided the following justification for the adaptation: *"In Annex IX of Regulation (EC) No 1907/2006, it is laid down that long-term toxicity to fish shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on fish. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of 4-hydroxybutyl acrylate reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, and for reasons of animal welfare, a long-term toxicity test in fish is not provided."*

In your comments on the draft decision, you attached Chapters 9 and 10 of the CSR, with the exposure assessment and risk characterization for both human health and environment. You noted that based on the exposure assessment and risk characterisation (EA/RC) for environment (performed following request 7. below and attached to your comments), the CSA indicates no risks for the registered substance.

ECHA acknowledges that the EA/RC provided in your comments show that the RCRs are below 1. Therefore, ECHA agrees that based on this information long-term aquatic testing is not needed.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to fulfil the information requirement for long-term toxicity testing on fish (Annex IX, Section 9.1.6.) by providing an adaptation in accordance with the second colum of Annex IX section 9.1. by explaining that the chemical safety assessment according to Annex I indicates that there is no need to further investigate the effects on aquatic organisms.

Notes for your consideration for issues 5 and 6

In order to comply with the requests mentioned above in issues 5 and 6 above, you should submit environmental EA and RC (see issue 7 below) which are already included as an attachment to your comments to the initial draft decision.

7. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.).

In accordance with Articles 10(b) and 14(1) of the REACH Regulation, the registration must contain a chemical safety report (CSR) which documents the chemical safety assessment (CSA) conducted in accordance with Article 14(2) to (7) and with Annex I to the REACH Regulation.

Pursuant to Article 14(4), if the substance fulfils the criteria for any of the hazard classes listed in that provision or is assessed to be a PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative), the CSA shall include exposure assessment and risk characterisation.

Annex I, Section 5 of the REACH Regulation requires the Registrant to generate exposure scenarios and exposure estimations for the registered substance. The exposure assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the identified hazards.

Annex I, Section 6 of the REACH Regulation requires the Registrant to characterise the risk for each exposure scenario and to consider the human population (exposed as workers, consumer or indirectly via the environment and if relevant a combination thereof) and the environmental spheres for which exposure to the substance is known or reasonable foreseeable, under the assumption that the risk management measures described under exposure scenario in Section 5 of the same Annex have been implemented. In addition, the overall environmental risk caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments.

ECHA's Guidance on information requirements and chemical safety assessment, Part B: Hazard Assessment, Section B.8.4. (pages 47 to 48) (version 2.1, December 2011) states that "*if no adverse effects have been observed in studies at the highest recommended concentration/doses tested, this would normally indicate that no hazard has been identified and no DNEL or PNEC can be derived and hence exposure assessment for that route of exposure, type of effect or protection target would not be needed*".

In the CSR you provided, the exposure assessment for the environment is missing. You claimed that no exposure assessment is *necessary for the environment by* stating in the CSR "*As no environmental hazard was identified no environmental-related exposure assessment and risk characterization was performed.*"

ECHA notes that you have classified the substance as Acute Tox. 4 (H302), Skin Irrit. 2 (H315), Eye Damage 1 (H318), Skin Sens. 1 (H317); therefore, it fulfils the criteria set out in Article 14(4) of the REACH Regulation to require an exposure assessment and a risk characterisation in the chemical safety assessment.

Additionally, ECHA notes that adverse effects were observed in some environmental toxicity studies. In particular, e.g. in short-term studies on fish, aquatic invertebrates and algae (L(E)C50 values of 14.7 mg/L, 22.5 mg/L and 13.6 mg/L respectively). Although only nominal concentrations are reported for all these studies, the results show that adverse effects are observed for all three trophic levels in short-term studies.

In your comments on the draft decision, you agreed to perform this request. You indicated that the exposure assessment and risk characterisation (EA/RC) for environment has already been performed for the three exposure scenarios and you included it in your comments. ECHA acknowledges that the information provided in the comments is sufficient to address the request. However, ECHA notes that the EA/RC must be included in the technical dossier and reflected in the CSA.

ECHA notes that any new information should be submitted in a form of a dossier update.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to include in your dossier an exposure and risk assessment for the environment.

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 20 February 2017.

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).

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) 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 requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.