ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 31 August 2018

Addressee: [redacted]

Decision number: CCH-D-2114440629-43-01/F
Substance name: Benzyl methacrylate
EC number: 219-674-4
CAS number: 2495-37-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 06/11/2013
Registered tonnage band: 100-1000

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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

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

3. **Robust study summary for key study "key Long-term toxicity to aquatic invertebrates: [redacted]_2012_OECD211", Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5. in conjunction with Annex I, Section 1.1.4.);**

4. **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;**

5. **Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment: generate an exposure assessment for all relevant exposure scenarios and revise the risk characterisation accordingly.**

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 **7 September 2020**. 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, 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 2004

Reasons

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), provided that the conditions set out in Annex XI are met".

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

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

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context.

0.1. Information provided on the grouping and read-across approach

You have provided read-across justifications in Sections 5.6.3 and 5.9.3 of the CSR and Section 7.8 of the technical dossier.

You propose to use grouping and read-across approach to adapt the following standard information requirements for, the registered substance subject to this decision, benzyl methacrylate (EC no 219-674-4, CAS no 2495-37-6, the 'target' substance) by using the following source substances:

- Methyl methacrylate (CAS no 80-62-6, EC no 201-297-1) for a sub-chronic (90-day) study and a pre-natal developmental toxicity study,
- n-Butyl Methacrylate (CAS no 97-88-1, EC no 202-615-1) for a sub-chronic (90-day) study and a pre-natal developmental toxicity study,
- 2-Ethylhexyl Methacrylate (CAS no 688-84-6, EC no 211-708-6) for a sub-chronic (90-day) study.

You have also provided the following hypothesis for repeated dose toxicity:

"*For alkyl methacrylate esters in principal, there is strong and consistent evidence for a uniform metabolism. The first step is always cleavage of the ester to methacrylic acid (cf reference below) and the regarding alcohol catalyzed by unspecific esterases which are present in all tissues relevant for metabolism, including liver, skin and lung tissues. Thereafter, the methacrylic acid is further metabolised via the valine pathway of the citric acid cycle and the alcohol may be further metabolised by the standard metabolic pathways for fatty alcohols. Consequently, results of the repeated dose studies on the structurally*

related esters Methyl methacrylate, n-Butyl methacrylate and 2-Ethylhexyl are considered as representative for the subchronic and chronic toxicity of Benzyl methacrylate.
Concerning the metabolite benzyl alcohol, its relevant metabolite Benzoic acid and its salts are in widespread use as food preservatives in the EU. The Scientific Committee for Food (SCF) recognized an overall NOAEL of 500 mg/kg bw/day from long-term and multigeneration studies (2002, reference see below).
Taken as a whole there are sufficient data available for assessment purposes so for the sake of animal welfare it is not proposed to conduct further repeated dose studies.

References:
SCF (Scientific Committee on Food) (2002) Opinion of the Scientific Committee on Food on Benzoic acid and its salts. SCF/CS/ADD/CONS/48 Final, 17 Sept 2002, available online: http: //ec. europa. eu/food/fs/sc/scf/out137_en. pdf
US EPA, 2008United States Environmental Protection Agency, Office of Pollution Prevention and Toxics: METHACRYLIC ACID, interim acute exposure guideline levels. Interim 10/2008; available online: http: //www.epa.gov/opptintr/aegl/pubs/methacrylci_acid%20interim_de_oct_2008_c. pdf

The following information is taken into account for any hazard / risk assessment:
In an OECD Guideline 422 and GLP study with Benzyl methacrylate, the NOAEL for repeated dose toxicity is determined to 500 mg/kg/day which was the highest dose tested. Moreover, there is sufficient information to confirm the absence of a critical potential by read –across to data on structurally related substances and the relevant metabolites methacrylic acid, benzyl alcohol and benzoic acid", and the following hypothesis for pre-natal developmental toxicity:

"According to REACH regulation, Annex XI, 1, a prenatal developmental toxicity study is scientifically not necessary. The available data are sufficient for classification, labelling and risk assessment. Thus, no further testing is proposed.
BENZYL METHACRYLATE has been screened for reproductive and developmental toxicity in a study according to OECD guideline 422. The results indicate that the substance has a low potential for adversely affecting fertility and development: There were no effects of BENZYL METHACRYLATE on reproductive indices including number of external anomalies of delivered pups.
This is further supported by the fact that BENZYL METHACRYLATE is rapidly metabolised in vivo and the primary metabolites, methacrylic acid as well as benzyl alcohol, demonstrate an absence of concern for specific reproductive toxicity.
For Benzyl alcohol, its metabolite Benzoic acid and its derivatives, developmental toxicity has been evaluated by SCF (2002): no teratogenic effects were described; fetotoxic effects have been observed at 1000 mg Benzyl acetate/kg bw/d leading to a NOAEL of 500 mg/kg bw/d.
For Methacrylic acid no "signs of toxicity related to embryolethality or teratogenicity were observed " when administered to pregnant rats from day 6 to 20 of gestation as cited in US EPA, 2008.
Supportingly, there is extensive information available for structurally analogous methacrylate esters which are metabolized to methacrylic acid and the regarding alcohol.
In an inhalation developmental toxicity study with methyl methacrylate in rats (OECD 414), exposure to concentrations up to 8.3 mg/L (2028 ppm) resulted in no embryo or fetal toxicity or malformations even at exposure levels that resulted in maternal toxicity.
In a study comparable OECD guideline no. 414, groups of 22-25 pregnant female rats were given whole-body inhalation exposures to n-butyl methacrylate at target concentrations of

0, 100, 300, 600 or 1200 ppm for 6 hr/day, during days 6 to 20 of gestation. Maternal toxicity was observed at 300 to 1200 ppm. The NOAEL for developmental toxicity was 300 ppm n-BMA. There was no evidence of embryolethality or teratogenicity with n-butyl methacrylate.

With methyl methacrylate an oral OECD 414 study in rabbits was performed with doses of 50, 150, and 450 mg/kg/d. The no observed adverse effect level (NOAEL) for prenatal developmental toxicity was 450 mg/kg bw/d. No adverse foetal findings of toxicological relevance were evident at any dose, even in the presence of maternal toxicity. Considerations on a molar basis with respect to methacrylate esters lead to the result that the NOAEL of 450 mg/kg/d obtained for Methyl methacrylate is equivalent to a NOAEL of > 800 mg/kg/d for Benzyl methacrylate due to the higher molecular weight of the latter. In conclusion, based on studies in experimental animals, there is no evidence for toxicity of Benzyl methacrylate to the reproductive system.

References:
SCF (Scientific Committee on Food) (2002) Opinion of the Scientific Committee on Food on Benzoic acid and its salts. SCF/CS/ADD/CONS/48 Final, 17 Sept 2002, available online: http: //ec. europa. eu/food/fs/sc/scf/out137_en. pdf
US EPA, 2008United States Environmental Protection Agency, Office of Pollution Prevention and Toxics: METHACRYLIC ACID, interim acute exposure guideline levels. Interim 10/2008; available online: http: //www. epa. gov/opptintr/aegl/pubs/methacrylci_acid%20interim_de_oct_2008_c. pdf

The following information is taken into account for any hazard / risk assessment:
In an OECD Guideline 422 and GLP study with Benzyl methacrylate in rats, the NOAEL for development of offspring was at the highest test dose of 500 mg/kg/day. Supportingly, there is extensive information available for structurally analogous methacrylate esters. The absence of a teratogenic potential was demonstrated in teratogenicity studies in rats and rabbits (OECD 414) for methyl methacrylate and n-butyl methacrylate.

There is no evidence for critical effects on developmental toxicity or teratogenicity in animal studies with the relevant metabolite benzyl alcohol and benzoic acid.
In conclusion, based on studies in experimental animals, there is no evidence for toxicity of Benzyl methacrylate to the reproductive system."

0.2. ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

ECHA understands that your read-across hypothesis is based on:

- structural similarity of the substances: *"results of the repeated dose studies on the structurally related esters Methyl methacrylate, n-Butyl methacrylate and 2-Ethylhexyl are considered as representative for the subchronic and chronic toxicity of Benzyl methacrylate"* and *"there is extensive information available for structurally analogous methacrylate esters which are metabolized to methacrylic acid and the regarding alcohol"*,

- similar metabolism: *"For alkyl methacrylate esters in principal, there is strong and consistent evidence for a uniform metabolism. The first step is always cleavage of the*

ester to methacrylic acid (cf reference below) and the regarding alcohol catalyzed by unspecific esterases which are present in all tissues relevant for metabolism, including liver, skin and lung tissues. Thereafter, the methacrylic acid is further metabolised via the valine pathway of the citric acid cycle and the alcohol may be further metabolised by the standard metabolic pathways for fatty alcohols".

Structural similarity

In order to meet the provisions in Annex XI 1.5 to predict physicochemical and toxicological properties from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

You state that the target and source substances are structurally related esters and that methyl methacrylate, n-butyl methacrylate and 2-ethylhexyl methacrylate are considered as representative source substances for the sub-chronic and chronic toxicity of benzyl methacrylate.

ECHA observes that while both the target and source substances share some similarity of structure, i.e. methacrylate moiety, the target substance however has a benzyl side chain while the source substances have alkyl (methyl/n-butyl/2-ethylhexyl) side chains. ECHA notes that you have not provided information to support the argument how these structural differences impact the predicted environmental and human health hazard properties. More specifically, you have not explained how these structural differences such as different chain lengths, and an alkyl versus a benzyl moiety attached to oxygen atom, relate to their toxicokinetic properties, especially metabolism, and their toxicological properties. Consequently, there is not a robust basis for predicting the properties of the registered substance from the data of the source substances.

Toxicokinetics

Annex XI 1.5 provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances.* One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the comparison of absorption, distribution, metabolism and elimination of source and target substances to allow assessment of the qualitative and quantitative internal systemic exposure of the test organism when exposed to source(s) and target, respectively.

You claim that "*Ester hydrolysis has been established as the primary step in the metabolism of methacrylate esters. Ester hydrolysis of BNMA would result in Methacrylic acid and Benzyl alcohol. Benzyl alcohol is authorised as food additive without limitations (EFSA, 2012). It is oxidised to Benzoic acid, which is subsequently conjugated with glycine and excreted via the urine. In case high doses of Benzyl alcohol are taken up, "formation of the glycine conjugate is limited; when glycine is depleted, free benzoic acid may sequester acetyl coenzyme A or be excreted unchanged or as the glucuronic acid conjugate" (EFSA, 2012). It is concluded that "benzyl derivatives [...] are rapidly absorbed, distributed, metabolised and excreted.*

Mammals, birds and fish share a similar metabolic capacity to handle these compounds and produce hydrophilic metabolites with low affinity for tissues which are excreted efficiently in the urine. Methacrylic acid is cleared rapidly from blood by standard physiological pathways, with the majority of the administered dose being exhaled as CO2."

ECHA notes that you have provided only a general statement regarding the ester hydrolysis and that no experimental information has been provided to demonstrate that similar hydrolysis with similar rate resulting in (dis)similar hydrolysis products occurs with the registered substance and the source substances. More specifically, you have not provided experimental evidence and toxicokinetic information to support the claimed similarity between the target and source substances regarding (i) the hydrolysis/metabolism pathway, (ii) identification of similar breakdown products and dissimilar breakdown products, and (iii) the rate of the hydrolysis/metabolism, and how these (dis)similarities may influence the toxicological profile of the substances.

ECHA further notes that due to differences in the moieties in the target and the source substances, that the ester hydrolysis of methacrylate esters will result in the common metabolite methacrylic acid while, depending on the different moieties in the parent substances, different non-common alcohols will be formed : benzyl alcohol, methyl alcohol, n-butyl alcohol and 2-ethylhexyl alcohol. ECHA observes that different metabolites (alcohols) may have different toxicities which need to be considered as they may impact the basis for prediction. This is further addressed in the next section.

ECHA also identifies that the read-across justification should include experimental evidence from the hypothesised breakdown products (benzyl alcohol and methacrylic acid) regarding repeated dose toxicity and developmental toxicity.

ECHA therefore concludes that due to lack of evidence of hydrolysis and hydrolysis rate of the registered and source substances there is no adequate basis for predicting the properties of the registered substance from the source substances.

Support of a similar or regular pattern as a result of structural similarity

Annex XI, 1.5 provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties or follow a regular pattern. One important aspect in this regard is the data matrix comparing properties of source and target substances.

ECHA notes that for each human health endpoint a different source substance has been used to predict the properties of the registered substance. Therefore, in addition to analysing the read-across approach for each endpoint and proposed source substance, ECHA has analysed the available additional data of the other source substances.

- Repeated dose toxicity

You have provided an oral OECD TG 422 study with the registered substance. No adverse effects were observed up to 500 mg/kg bw/day. In addition, you have provided a sub-chronic (90-day) oral toxicity study in rats (OECD TG 408) conducted with the source

substance n-butyl methacrylate. The NOAEL value is 120 mg/kg bw/day based on effects on the increased liver weight, prolonged prothrombin time, lower serum globulin and triglyceride levels in males and increased absolute kidney weight in females. You have also provided a sub-chronic (90-day) oral toxicity study in rats (OECD TG 408) conducted with the source substance 2-ethylhexyl methacrylate. The NOAEL value is 120 mg/kg bw/day based on effects on body weight gain and some blood chemistry parameters.

ECHA considers that the results from the OECD TG 422 study conducted with the registered substance (no effects up to 500 mg/kg bw/day), and sub-chronic (90-day) toxicity studies conducted with the source substances n-butyl methacrylate (liver and blood chemistry effects) and 2-ethylhexyl methacrylate (body weight gain and blood chemistry changes) show differences in effects and do not support a similar or regular pattern of toxicity.

ECHA also considers, taking into account the elements described under the Toxicokinetics section above, that the source substances are hydrolysed to different metabolites than the target substance. ECHA concludes that the information from these studies might only be useful regarding the toxicity of methacrylic acid but do not cover the toxicity profile of benzyl alcohol.

You further refer to "*an overall NOAEL of 500 mg/kg bw/day*" based on studies conducted with benzoic acid and its salts (Opinion of The Scientific Committee for Food (SCF)). ECHA observes that only an abstract is available (Ishigureo et al. Teratological studies on benzyl acetate in pregnant rats, 1993, http://agris.fao.org/agris-search/search.do?recordID=JP19970152385) and that the NOAEL value is obtained from a teratogenicity study, which is not considered adequate to cover sub-chronic (90-day) toxicity.

ECHA notes that information from benzoic acid can be considered as additional supportive evidence. However benzoic acid is a secondary metabolite compared to the primary metabolite of the target substance (benzyl alcohol) that is more likely to be bioavailable following hydrolysis of the target substance.

ECHA further notes that several studies conducted with benzyl alcohol (the hypothesised metabolite of the registered substance) are publicly available, which you have not included in your registration dossier: e.g. in a 13-week oral study benzyl alcohol caused mortality, severe effects including clinical signs indicative of neurotoxicity (staggering, respiratory difficulty, and lethargy) and haemorrhages at 800 mg/kg bw/day (Toxicology and carcinogenesis studies of benzyl alcohol (CAS NO. 100-51-6) in F344/N rats and B6C3F1 mice (gavage studies), NTP Technical Report Series No 343).

ECHA considers that the presented evidence does not support a similar or regular pattern of repeated dose toxicity as a result of structural similarity. Thus, there is no adequate basis for predicting properties of the registered substance from the source substance(s).

- Pre-natal developmental toxicity

You have provided an oral prenatal developmental toxicity study (OECD TG 414) in rabbits conducted with the source substance methyl methacrylate. The NOAEL for maternal toxicity is 50 mg/kg bw/day based on reduced food consumption and body weight gain, while the NOAEL for developmental toxicity is 450 mg/kg bw/day. You have provided an inhalation prenatal developmental toxicity study (OECD TG 414) in rats conducted with the source

substance methyl methacrylate. The LOAEC for maternal toxicity is 99 ppm based on reduced body weight gain, while the NOAEC for developmental toxicity is 2028 ppm.

You have provided an oral prenatal developmental toxicity study (OECD TG 414) in rabbits conducted with the source substance n-butyl methacrylate. The NOAEL for maternal toxicity is 100 mg/kg bw/day based on reduced food consumption and body weight gain, while the NOAEL for developmental toxicity is 300 mg/kg bw/day (abortions, decreased foetal growth and alterations). You have provided an inhalation prenatal developmental toxicity study (OECD TG 414) in rats conducted with the source substance n-butyl methacrylate. Maternal toxicity (decreased body weight gain) was observed in the 300, 600 and 1200 ppm groups. The NOAEL of 300 ppm for developmental toxicity was based on decreased foetal body weight in female pups (600 and 1200 ppm). Decreased foetal body weight in male pups and increase in skeletal variations were observed at 1200 ppm.

ECHA observes that no major developmental toxicity was observed in studies conducted with methyl methacrylate whereas decreased foetal body weight and increases in skeletal variations were observed with n-butyl methacrylate. ECHA considers that the studies do not support a similar or regular pattern of toxicity.

You state that the study results (OECD TG 422) "*indicate that the substance* [the registered substance] *has a low potential for adversely affecting fertility and development*". ECHA notes that the screening study does not cover the key parameters of a pre-natal developmental toxicity study as explained in section 2. below.

You further refer to studies conducted with benzyl acetate (*developmental toxicity evaluated by SCF (2002): no teratogenic effects were described; fetotoxic effects have been observed at 1000 mg Benzyl acetate/kg bw/d leading to a NOAEL of 500 mg/kg bw/d.*) and methacrylic acid (*no signs of toxicity related to embryo lethality or teratogenicity were observed when administered to pregnant rats from day 6 to 20 of gestation as cited in US EPA, 2008*), and you conclude "*In conclusion, based on studies in experimental animals, there is no evidence for toxicity of Benzyl methacrylate to the reproductive system*".

ECHA notes that developmental toxicity studies in mice and rats conducted with benzyl alcohol (the hypothesised metabolite of the registered substance) are publicly available, which you have not included in your registration dossier (A toxicological and dermatological assessment of aryl alkyl alcohols when used as fragrance ingredients, The RIFM Expert Panel, Food and Chemical Toxicology 50 (2012) 552-599).

ECHA considers that the presented evidence does not support a similar or regular pattern of developmental toxicity as a result of structural similarity. Thus there is no adequate basis for predicting properties of the registered substance from the source substances.In your comments to the draft decision you acknowledge that the current read-across approach submitted in 2013 does not fully meet the current expectations regarding adaptations based on categories and read-across. You indicate that you intend to add another read-across approach for the human health assessment with a higher level of confidence based on information from the primary metabolites of the registered substance and using information on the hydrolysis of methacrylate esters.

Briefly, you explain that existing toxicokinetic data on some shorter and longer chain methacrylates indicate almost complete hydrolysis and thus the hydrolysis products are considered relevant for systemic effects. However, the impact of structurally more complex

methacrylate esters on hydrolysis is not known. You expressed your intention to conduct *in vivo* toxicokinetic studies with mainly cyclic methacrylates (e.g. isobornyl methacrylate) to get information on hydrolysis rate and systemic availability of complex methacrylate esters. You further plan to gather information on hydrolysis of aromatic methacrylate esters via literature search. In case the hydrolysis study with isobornyl methacrylate does not provide sufficient confidence in your revised read-across hypothesis you intend to conduct a hydrolysis study with the registered substance, and further if this study results in low level of confidence the tests requested by ECHA may need to be conducted with the registered substance.

ECHA acknowledges your intention to revise your read-across approach and to assess it using the RAAF by providing further information on the hydrolysis of the registered substance and using information on the metabolites of the registered substance in order to predict the properties of the registered substance.

ECHA stresses that for a read-across approach based on metabolism, corresponding to the RAAF Scenario 1, reliable data establishing rapid and complete hydrolysis of the parent substance is essential to support the read-across hypothesis. If hydrolysis of the registered substance is predicted from data on other, e.g. non-aromatic methacrylates, a sound scientific justification needs to be provided to establish the relevance of this information for the registered substance which has an aromatic structure. Experimental data on the hydrolysis of the registered substance itself may therefore be more relevant. Further, in the context of a prediction based on the metabolites of a substance, adequate and reliable information on the toxicological properties of the metabolites need to be provided. For example, in case of old non-guideline studies e.g. duration of the studies and parameters examined in the studies need to be compared to current OECD/EU guidelines. The impact of possible deficiencies has to be addressed and the relevance and reliability of the studies evaluated accordingly.

However, since the information supporting your revised adaptation is not yet available, ECHA concludes that the proposed revised adaptation as described in your comments is not justified and therefore cannot be accepted as currently presented.

Your request for an interim evaluation of the revised adaptation is addressed in Appendix 2 of this decision.

0.3. Conclusion of the read-across approach

In the light of the deficiencies as described above, and in particular due to the lack of evidence of rapid hydrolysis of the registered substance and experimental data on the hypothesised metabolite benzyl alcohol, ECHA considers that the read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. of the REACH Regulation. Therefore, the adaptation is not acceptable and there is a data gap for the endpoints covered by this read-across approach.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information

specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

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.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) conducted with the registered substance. However, this study does not provide the information required by Annex IX, Section 8.6.2., because the exposure duration is less than 90 days and the number of animals examined per dose group for histopathology and clinical chemistry is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408).

In addition, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a repeated dose 90-day oral toxicity study in rodents (OECD TG 408) with the analogue substances n-butyl methacrylate (CAS no 97-88-1, EC no 202-615-1) and 2-ethylhexyl methacrylate (CAS no 688-84-6, EC no 211-708-6).

However, as explained in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

As explained above, both the study and the adaptation provided on this endpoint for the registered substance in the technical dossier do not meet the information requirement. 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 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 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 EU B.26./OECD TG 408.

According to the test method EU B.26./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 your comments to the draft decision you indicate that you intend to add another read-across approach for the human health assessment with a higher level of confidence. As explained above in Section 0 of this decision, since the information supporting your revised adaptation is not yet available, ECHA concludes that the proposed revised adaptation as described in your comments is not justified and therefore cannot be accepted as currently presented.

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: EU B.26./OECD TG 408) in rats.

Notes for your consideration

ECHA notes that a revised version of OECD TG 408 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

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

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

A "pre-natal developmental toxicity study" (test method EU B.31./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.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) conducted with the registered substance as a key study. However, this study does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations. Therefore, your adaptation of the information requirement is rejected.

In addition, you have sought to adapt this information requirement according to "Annex XI, 1, study scientifically unjustified" and have provided the following justification: "*According to REACH regulation, Annex XI, 1, a prenatal developmental toxicity study is scientifically not necessary. The available data are sufficient for classification, labelling and risk assessment. Thus, no further testing is proposed. BNMA is rapidly metabolised in vivo and the primary metabolites, methacrylic acid as well as benzyl alcohol, demonstrate an absence of concern for specific reproductive toxicity".*

You have further provided pre-natal developmental toxicity studies (OECD TG 414) as supporting studies in rats (via inhalation route) and rabbits (via oral route) with the analogue substances n-butyl methacrylate (CAS no 97-88-1, EC no 202-615-1) and methyl methacrylate (CAS no 80-62-6, EC no 201-297-1).

ECHA understands that you have adapted the information requirement according to Annex XI, 1.5. However, as explained in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

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

According to the test method EU B.31./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) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid and has a low vapour pressure, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you indicate that you intend to add another read-across approach for the human health assessment with a higher level of confidence. As explained above in Section 0 of this decision since the information supporting your revised adaptation is not yet available, ECHA concludes that the proposed revised adaptation as described in your comments is not justified and therefore cannot be accepted as currently presented.

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: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Notes for your consideration

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

3. Robust study summary for key study "key_Long-term toxicity to aquatic invertebrates: [redacted]_2012_OECD211" (Annex IX, Section 9.1.5. in conjunction with Annex I, 3.1.5

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

Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent

assessment of the study minimising the need to consult the full study report. Guidance on the preparation of the robust study summaries is provided in the Practical Guide on "How to report robust study summaries".

"Long-term toxicity testing on invertebrates (preferred species *Daphnia*)" 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. Furthermore, pursuant to Article 10 (a)(vii) and Annex I, Section 3.1.5., if one study is available, a robust study summary should be prepared for that study.

You have provided a study record for an OECD TG 211 study (*Daphnia magna* reproduction test) "*key_Long-term toxicity to aquatic invertebrates:* [redacted] *_2012_OECD211*" to meet the standard information requirement of Annex IX, Section 9.1.5.

However, ECHA notes that, contrary to Article 3(28) of the REACH Regulation, the documentation of this study is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment. In particular, the following elements are missing: a description of the statistical analysis of the EC10 calculations. ECHA notes that EC10 values are usually slightly higher than NOEC values, although this might depend on parameters such as dose selection, dose-response relationships, etc. However, in this case the difference between the 21 day $EC10_{reproduction}$ (3.34 mg/L) and the 21 day $NOEC_{reproduction}$ (0.291 mg/L) is very large (a factor of 11.5). Since you have not reported how the EC10 and its confidence intervals have been derived, ECHA cannot confirm that the EC10 value can be used instead of the NOEC for this study. ECHA further notes that the substance should be classified Aquatic Chronic 3 if the NOEC value would be used instead of the EC10. Therefore, you need to provide a complete robust study summary with the above missing elements for this study. If you conclude that the EC10 value cannot be used, you should update the endpoint and all related information in your dossier accordingly. Hence, 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.

In your comments to the draft decision you acknowledge that the results of the long-term fish study have indeed been wrongly calculated and have now been corrected by the test laboratory. However, since the correct data are not available in the current dossier, the request is kept in the decision and any new information will be assessed during the follow-up process of this decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: Robust study summary for the OECD TG 211 study (*Daphnia magna* reproduction test) "*key_Long-term toxicity to aquatic invertebrates:* [redacted] *_2012_OECD211*".

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

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

You have sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: "*Long-term testing in fish is waived for BNMA since the substance is readily biodegradable. The risk characterisation shows that the PEC/PNECaqua ratio for the aquatic environment is <1, indicating no need for further information or testing. According to REACH regulation Annex IX, 9.1. column 2, long-term toxicity testing shall only be considered when the chemical safety assessment indicates the need for further investigations. Because there is no indication of major differences in sensitivity between trophic levels and in the absence of any significant long-term bioaccumulation potential it is not necessary to perform further chronic fish tests with the substance. The environmental risk assessment can be performed with sufficient reliability with the available long-term ecotoxicity data. Thus, no long-term toxicity testing is required for BNMA.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6. because ECHA concludes that, contrary to your claim, the information in your dossier indicates the need to investigate further the effects on aquatic organisms, as outlined below.

Firstly, although your statement pointing out that "*the substance is readily biodegradable*" and "*in the absence of any significant long-term bioaccumulation potential*" may allow conclusion of PBT properties of the substance, it does not allow concluding on the risk assessment and thus the entire CSA. Ready biodegradability and lack of significant bioaccumulation do not exclude the potential of toxic effects or exclude exposure to the aquatic environment.

Secondly, you have not provided evidence to justify your claim that "*The risk characterisation shows that the PEC/PNECaqua ratio for the aquatic environment is <1, indicating no need for further information or testing*". ECHA notes that your registration dossier does not include a quantitative risk characterisation (RCR, PEC/PNECaqua ratio) that would allow you to adapt this information requirement. In the CSR you provided, the exposure assessment for the environment is missing (see section 5 of this decision). In the absence of a quantitative risk characterisation, your justification for adapting long-term toxicity to fish based on your assumed PEC/PNECaqua ratio for the aquatic environment of <1 is not substantiated.

Thirdly, you have argued that "*Because there is no indication of major differences in sensitivity between trophic levels and in the absence of any significant long-term bioaccumulation potential it is not necessary to perform further chronic fish tests with the substance.*" ECHA understands that you refer to the integrated testing strategy (ITS) described in ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4). ECHA notes that according to this ECHA Guidance, if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially less sensitive than other trophic levels (i.e., fish, invertebrates, algae), long-term studies may be required on both fish and invertebrates. In such a case, according to the ITS, 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 (i.e. PEC/PNEC<1), no long-term fish testing may need to be conducted. However, ECHA notes that this ITS approach cannot be applied in this case because there is no reliable information provided in the technical dossier on short-term toxicity to *Daphnia* that would allow determination of relative species sensitivity. Therefore, the standard information requirement of long-term toxicity to fish cannot be adapted based on ITS for aquatic pelagic toxicity.

Therefore, 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 ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) 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.

However, 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 4.0, June 2017), *Chapter R7b, chapter R.7.8.4.1)*.

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 to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

In your comments to the draft decision, you indicate that long-term toxicity to fish can be waived based on the new information for long-term toxicity to aquatic invertebrates and a generic exposure assessment. However, since the updated information is not available in the current dossier, the request for long-term toxicity to fish is kept in the decision and any new information will be assessed during the follow-up process of this decision.

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: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Once results of the test on long-term toxicity to fish are available and you have updated the robust study summary of the long-term toxicity test to *Daphnia*, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

ECHA notes that there is no short-term study available on aquatic invertebrates for the registered substance. Therefore the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), is not applicable in this case and the long-term studies on both invertebrates and fish are requested to be conducted.

5. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment: generate an exposure assessment for all relevant exposure scenarios and revise the risk characterisation accordingly

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

In the CSR that you provided, the exposure assessment for the environment is missing. You claimed that no exposure assessment is necessary for the environment by stating for each exposure scenario that *"As no environmental hazard was identified no environmental-related exposure assessment and risk characterization was performed."* Similarly, you report in section 9.0.3.1 of your CSR: *"In the chemical safety assessment performed according to Article 14(3) in connection with Annex I section 3 (Environmental Hazard Assessment) and section 4 (PBT/ vPvB Assessment) no hazard was identified. Therefore according to REACH Annex I (5.0) an exposure estimation is not necessary. Consequently all identified uses of the substance are assessed as safe for the environment."*

ECHA notes that you have indicated in your dossier that the substance has a harmonised classification as Skin. Irrit. 2 (H315), Eye Irrit. 2 (H319) and Skin. Sens. 1B (H317) and thus, 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.

With regard to the scope of the required exposure assessment, as stated above and in accordance with Annex I, section 5.0., it has to cover all hazards that have been identified according to sections 1 to 4 of Annex I of REACH Regulation.

It is clear from your dossier that effects were observed in some environmental toxicity studies. For example, in the long-term aquatic invertebrate (*Daphnia*) study, a 21-d $NOEC_{reproduction}$ value of 0.29 mg/L and EC10 value of 3.34 mg/L are reported for the registered substance, in the acute fish study an 96h LC50 value of 4.67 mg/L is reported, in the algae toxicity study the reported 72h NOEC and EC10 values based on growth rate are 0.899 mg/L and 1.08 mg/L. The EC10 of 1.08 mg/L determined from the algae toxicity study is used for the calculation of the PNECfreshwater. Therefore, exposure assessment and risk characterisation for environment are needed to address the hazards identified for the environment.

As further outlined in Guidance *on information requirements and chemical safety assessment*, Part B: Hazard Assessment, Section B.8.1. (version 2.1, December 2011), such identified hazards (among others) necessitating exposure assessment are the *"hazards for which there are classification criteria and there is information on these properties of the substance showing that it does have these properties, but the severity of the effects is lower than the criteria for classification and so the substance is not classified".* Moreover, the above mentioned guidance specifies further (in Section 8.4.2.2.) that *"If there are ecotoxicity data showing effects in aquatic organisms, but the substance is not classified as dangerous for the aquatic environment, an aquatic PNEC can nevertheless be derived thus indicating a hazard to the aquatic environment.(...) Hence, quantitative exposure assessment, i.e. derivation of PECs, is mandatory for the water, sediment and soil environmental compartments."*

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to generate an environmental exposure assessment for all relevant exposure scenarios and subsequently perform the risk characterisation for each exposure scenario to demonstrate the safe use of the substance, and update the dossier accordingly.

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

The compliance check was initiated on 28 August 2017.

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

ECHA took into account your comments and did not amend the request(s).

In your comments on the draft decision, you also requested an interim evaluation with ECHA and interested MSCAs (in the 4th quarter of 2018) of the updated read-across approach, especially with regards to new toxicokinetic studies. According to ECHA's standard policy such evaluations are not provided during decision making.

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.