~~Confidential~~

Helsinki, 28 April 2021

Addressee [redacted]

Decision number: CCH-D-2114550865-40-01/F
Substance name: Tetramethylene dimethacrylate
EC number: 218-218-1
CAS number: 2082-81-7
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 13 November 2018

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision CCH-D-2114378296-37-01/F of 23 November 2017 ("the original decision") ECHA requested you to submit information by 30 November 2018 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

Your registration still does not comply with the following information requirement(s):

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

You are therefore still required to provide this information requested in the original decision.

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

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They may consider enforcement actions to secure the implementation of the original decision and exercise the powers reserved to them under Article 126 of Regulation No 1907/2006 (penalties for non-compliance)[1].

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Approved[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] See paragraphs 61 and 114 of the judgment of 8 May of the General Court of the European Court of Justice in Case T-283/15 Esso Raffinage v. ECHA
[2] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

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

In point 2 of the original decision you were requested to submit a 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, i.e., the substance "Tetramethylene dimethacrylate" (the Substance).

In response to that decision you instead adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5 using the following: OECD Guideline 451 (Chronic repeated-dose study) with analogue substance methyl methacrylate (EC 201-297-1) ([redacted] 1964), subacute oral toxicity study in rats with analogue substance 1,4-Butanediol (EC 203-786-5) ([redacted]), OECD Guideline 422 with analogue substance 1,4-Butanediol (EC 203-786-5) ([redacted], 1999), OECD Guideline 408 (subchronic oral study in rats) with analogue substance dihydrofuran-2(3H)-one (γ-butyrolactone, γBL; EC 202-509-5) ([redacted]), OECD Guideline 408 (subchronic oral study in mouse) with analogue substance dihydrofuran-2(3H)-one (γ-butyrolactone, γBL; EC 202-509-5) ([redacted]), OECD Guideline 451 (chronic oral study in rats) with analogue substance dihydrofuran-2(3H)-one (γ-butyrolactone, γBL; EC 202-509-5) ([redacted]), OECD Guideline 451 (chronic oral study in mouse) with analogue substance dihydrofuran-2(3H)-one (γ-butyrolactone, γBL; EC 202-509-5) ([redacted]), OECD Guideline 413 (subchronic inhalation study in rat) with analogue substance methacrylic acid (EC 201-204-4) ([redacted] 2008 [redacted]), OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies in rat by inhalation) with analogue substance methyl methacrylate (EC 201-297-1) ([redacted] 1997), OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies in rat by inhalation) with analogue substance methyl methacrylate (EC 201-297-1) ([redacted] 1986), and read-across documentation.

In the technical dossier you have provided a study record ([redacted], 2013) for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) with the Substance. However, as already explained in page 16 of the original decision this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days.

Assessment of the read-across approach

Legal framework

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[3] and related documents[4, 5].

[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

Information provided

In the original decision you were requested to submit information on a Sub-chronic toxicity study (90-day) with the Substance.

In response to the original decision you instead provided in your updated registration further information on your read across approach based on a multi-step (bio)transformation of the Substance in a read-across "Category Justification" document in the IUCLID Categories section [redacted]).

The category also involves other methacrylates. You propose that the Substance degrades to the metabolites 1,4-butanediol and methacrylic acid. To cover one (bio)transformation product, you provided experimental studies on methacrylic acid and the analogue methylmethacrylate which rapidly forms the common proposed metabolite, methacrylic acid. To cover the other metabolic product, you have provided studies on the metabolite 1,4-butanediol. You further support your read across with information from studies conducted on another substance gamma-butyrolactone as you propose that this substance, and 1,4-Butanediol, can be metabolised to a common metabolite, gamma-hydroxybutyric acid. You provide information showing the ready hydrolysis of the Substance to methacrylic acid and 1,4-butanediol, and in support of the formation of gamma-hydroxybutyric acid from both 1,4-butanediol and gamma-butyrolactone. You also provide information on 1,3-butanediol, stating that "Due to structural analogy to 1,4-BD, analogous metabolic pathways are assumed for 1,3-BD", and also that 1,3-butanediol is an "analogous metabolite for 1,4-BDDMA".

ECHA understands that you propose to predict the properties of the Substance on the basis it readily undergoes biotransformation to metabolites (source substances) and that you can predict the properties of the Substance from the data available on these metabolites and from the data available from other substances which are transformed into common metabolites. For 1,3-butanediol, you do not propose that it is a metabolite of the Substance, but that it is structurally similar to a metabolite of the Substance, i.e. 1,4-butanediol. The properties of your Substance are predicted to be quantitatively equal to those of the source substances.

Evaluation of the adaptation

ECHA has assessed your adaptation in the light of the requirements of Annex XI, Section 1.5 of the REACH Regulation and considers that the read-across cannot be accepted for the reasons presented below.

Read-across hypothesis based on structural similarity for 1,3-butanediol

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled to apply grouping and read-across. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach).

[4] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[5] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the substances[6]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the structural similarity between the source substance, 1,3-butanediol, and the metabolite of your Substance (i.e. 1,4-butanediol) is a sufficient basis for predicting the properties of your Substance.

While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar human health properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source substance(s) and your Substance.

Adequacy and reliability of the source study for 1,3-butanediol

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:
- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3); and
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

In this respect, the source studies should be in the form of the robust study summary(ies), in order to be assessed and to support the read-across justification. According Article 3(28) of REACH a robust study summary means 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.

The standard of a robust study summary is further described in Practical Guide 3: How to report robust study summaries. In particular, section 5.5 Toxicity to Reproduction/Fertility of the Practical Guide specifies among others that details need to be provided of the test animals (species/ strain/ sex, number of animals per sex per dose, and age and weight at the study initiation), that the results are preferably presented in tabular form by sex and generation for each test group with statistical results, and provide information of the reproductive and offspring toxicity in relation to parental toxicity and (proposal of) classification for reproduction (fertility) under interpretation of results.

The source study that you have used in your read-across approach, [redacted], provides information on a Five generation study with embedded continuous breeding study. GLP compliance is not specified, and you do not make reference to an internationally recognised Test Guideline.

For 1,3-butanediol ([redacted]), the reporting of the methods and results falls far short of the standard of a robust study summary and so ECHA cannot make an independent assessment of the study. There is not a description of the methodology to the level provided in a Test Guideline, and for example, the age of parental generation at breeding and the relationship between specific parents and offspring analysed (i.e. whether there are litter effects), together with the statistical basis, is not specified. The reporting should present

[6] *Guidance on information requirements and chemical safety assessment*, Chapter R.6: QSARs and grouping of chemicals.

results preferably in tabular form by sex and generation for each test group with statistical results (as appropriate), yet no numerical data or statistics are provided.

Therefore, on the basis of the information provided ECHA you have not shown that the study:

- is adequate for the purpose of classification and labelling and/or risk assessment;
- does have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3); and
- covers an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

Thus, the read-across for 1,3-butanediol fails to meet the requirements of Annex XI, 1.5.

Read-across hypothesis contradicted by existing data

Annex XI, Section 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. The ECHA Guidance[7] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substances. The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis needs to be provided and supported by scientific evidence.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s).

i) Effects observed with the Substance not observed with the source substances

You have provided a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) conducted with the Substance with oral dosing (gavage) at up to 1000 mg/kg/day ([redacted], 2013). You reported that treatment-related findings were observed at the highest dose in the kidney (increased weight in male and female), thymus (decreased weight only in males), stomach (mild diffuse hyperplasia), and that "*Body weight and body weight gain were lower in the high dose group compared to controls throughout the study*". You consider that the NOAEL based on general toxicity to be 300 mg/kg bw/day. These findings are evidence of treatment-related adverse effects on parental animals at 1000 mg/kg bw/day.

In your comments to the draft decision, you stated the the effects noted in kidneys, thymus and liver were considered as not adverse, due to a more detailed evaluation supported by an expert statement. However, the expert statement does not state that these effects are not adverse, and does not provide an explanation for the increased kidney weight. The expert hypothesises that the stomach lesions are expected on the basis the substance will separate into methacrylic acid and 1,4-butanediol, that the methacrylic acid causes irritation in the stomach, subsequent food reduction, loss in body weight/ body weight gain, hence stress and consequent effects on thymus, spleen, reproduction and offspring, etc.

ECHA considers these effects are caused by treatment with the Substance and further notes that you have specified in your technical dossier under section "Effects levels" and "Basis for

[7] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

effect level" the following "*Significant higher kidney weights (males/females). Thymus weights significant decreased in high dose males.*"amongst other observations. As you have not provided justification for why you consider these effects are non-adverse, ECHA maintains that these effects are caused by treatment with the Substance and are adverse effects.

While the expert report states that "*Even in inhalation studies in Sprague-Dawley rats, histological lesions have been noted in the stomach*", the cited text explicitly refers to lesions in the nose, and not the stomach. Therefore, there remains a difference between effects seen between the Substance and the source substances. ECHA considers that the expert's hypothesis is speculative, and does not provide quantitative (i.e. linking the severity of the putatively causative events [nominally mild diffuse hyperplasia and mild hyperkeratosis at high dose] to the effects caused by stress [reduction in body weight, and subsequently effects on organ weight]) nor other experimental support to show that stress is responsible for these effects in the study itself. Moreover, the expert report does not show that the effects observed with the Substance (as listed above) are seen with the source substances.

In addition, at 1000 mg/kg bw/day the fertility index was markedly reduced (40% compared to 90% of the control group) and litter and/or mean pup weights were lower at PND 1 and 4. ECHA also notes that you report that the "*The percentage of cumulative pup loss on Day 4 post partum starting from the total litter size at birth, was increased in the high dose group*". You consider that "*The pronounced reduction of body weight gain of the premating animals indicates that the reduced reproduction success is likely a secondary effect of general systemic toxicity resulting in a poor condition of the parent females.*" You consider that the NOAEL based on reproduction/developmental toxicity to be 300 mg/kg bw/day. ECHA considers that the toxicity seen in parental animals is comparatively mild, and does not provide a basis for explaining the effects on fertility or pup toxicity (e.g. Birth Defects Res B Dev Reprod Toxicol. 2005 Oct;74(5):431-41.)

In your comments to the draft decision, you considered that the reduced fertlity index and the reduced litter and/or foetal body weights were secondary to maternal toxicity (reduced terminal body weight as a result of reduced food intake). You state that reduced body weight affects the "Leptin-Ghrelin-Kisspeptin-GnRH Pathway" and that consequently, the Substance has no specific impact on the reproductive performance, referring to a paper and expert statement. The expert opinion argues that stress mediates the adverse effects on reproduction, as set out above.

ECHA considers that reference to a pathway does not provide a basis for showing that the adverse effects seen are secondary to maternal toxicity, nor have you provided any other basis for considering that the adverse effects are secondary to maternal toxicity. ECHA considers that the expert's hypothesis is speculative, and does not provide quantitative (i.e. linking the severity of the putatively causative events [nominally mild diffuse hyperplasia and mild hyperkeratosis at high dose] to the effects caused by stress [reduction in body weight, and subsequently effects on reproduction and offpsring]) nor other experimental support to show that stress is responsible for these effects in the study itself. Moreover, the expert report does not show that the effects observed with the Substance (as listed above) are seen with the source substances.

For 1,4-butanediol, you have provided results from:

(1) a study of similar design to OECD TG 422 with oral dosing (gavage) with the source substance 1,4-butanediol up to 800 mg/kg/day ([redacted] 1999). There were no adverse effects on organ weights and no test-substance related histopathological effects in kidney or liver. There were adverse effects on the bladder (diffuse transitional epithelial hyperplasia and fibrosis in the lamina propria). "*Body weight gains were suppressed at 400 and 800 mg/kg*

during the early period of administration..."and on this basis you reported a NOAEL of 200 mg/kg/day. Also observed was a dose-related transient post-dosing change in the activity of the animals with a LOEL of 200 mg/kg day. In addition there were no findings of adverse effects on fertility index or parameters of pup viability or development.

(2) a 28-day study by oral gavage with the source substance 1,4-butanediol up to 500 mg/kg/day ([redacted]). The only effect on organs noted was proliferation of bile ducts and periportal infiltrations with fibroblasts and mononuclear cells in liver of treated animals.

(3) a 13 week rat gavage study with gamma-butyrolactone ([redacted]) at up to 900 mg/kg/day. Animals died in the top dose group, but a dose of 450 mg/kg/day led to a decreased body weight in males. There was inflammation of the nasal mucosa, but no other effects on organs. Rats exposed to 225 and 450 mg/kg/day showed inactivity after dosing only for the first two to three weeks.

(4) a 13 week mouse gavage study with gamma-butyrolactone ([redacted]). There were deaths in the 1050 mg/kg/day group, but at 525 mg/kg/day mice showed signs of sedation immediately after dosing, but the effect diminished after two to three weeks.

(5) a 2 year rat gavage study on gamma-butyrolactone ([redacted]). There were no noted effects on organ weights or non-neoplastic pathology.

(6) a two year mouse gavage study on gamma-butyrolactone ([redacted]). High dose mice (525 mg/kg/day) were partially sedated or lethargic and inactive shortly after dosing, and males in this group showed a lower survival rate to the end of the study. There were no reported non-neoplastic lesions associated with treatment. (7) a non-GLP non-Guideline dietary study with 1,3-butanediol in rats ([redacted] 1981). There were no effects on fertility in F0 and F2, but some of the F1 groups showed a decrease in fertility. There were no effects on pup development.

For Methyl methacrylate, you have provided the results from:

(1) a Two-Generation Reproduction Toxicity Study (OECD TG 416) conducted with the source substance methyl methacrylate with oral dosing (gavage) up to 400 mg/kg/day ([redacted], 2010). This study addresses parameters including fertility index and effects on the pups among others. Under the conditions of this study, no adverse effects on fertility index, litter and mean pup weights, or cumulative pup loss were observed. The NOAEL for systemic toxicity of parental animals was 400 mg/kg/day while dose-related intermittent reductions of bodyweights were noted. In respect of feed consumption the NOEL was 50 mg/kg bw/day and the LOEL was 150 mg/kg bw/day for F0 parental females.

(2) A two-year drinking water study ([redacted] 1964). At 2000 ppm (approximately 160 mg/kg/day), the only effect noted on organs was a significant increase in kidney weight in female rats.

(3) an inhalation study on methacrylic acid which shows no effects on organ weights or histopathology, with the exception of local effects on the nasal cavity.

(4) a two year rat inhalation on methyl methacrylate ([redacted] 1997). There was an increase in absolute and relative organ weights of in the lungs, liver, kidneys, and ovaries in the females exposed to ca. 1.64 mg/L (400 ppm) MMA at week 13. A statistically significant decrease in absolute and relative thyroid and adrenal weights were observed in both males and females in the high-level exposure group at week 52. Absolute thyroid and adrenal weights were

significantly higher in the males exposed to ca. 0.41 mg/L (100 ppm), MMA for 52 weeks. There were no histopathological findings except rhinitis in nasal turbinates. (5) A two year rat inhalation study ([redacted] 1986). This study only showed histopathological effects in the nasal cavity, olfactory epithelium and lung.

First, ECHA notes that for the Substance, you report that treatment-related effects on organ weight were observed in the kidney (both sexes) and thymus (males only)(without histopathological findings) and there are treatment-related histopathological effects (vacuolation) in the liver of females only.

Your studies with the source substances 1,4-Butanediol and gamma-butyrolactone do not show treatment-related effects on these parameters. Your studies on methyl methacrylate do not show differences for these parameters, with the exception that there was an increase in kidney weight in females only after a two year drinking water study ([redacted] 1964) and a transient increase in kidney weight in female in an inhalation study ([redacted] 1997).

In your comments, you have argued that the stomach hyperplasia seen is an adverse effect, is caused by a specific mechanism and such effects "are also observed in an OECD TG 416 and studies on further further methacrylate esters in rats (e.g. with Propylidynetrimethyl trimethacrylate/TMPTMA; Cas No. 3290-92-4; EC No. 221-950-4)". You have not provided the study(ies) with Propylidynetrimethyl trimethacrylate/TMPTMA; Cas No. 3290-92-4; EC No. 221-950-4 in your dossier or in your comment, and ECHA cannot evaluate this information.

Second, for the Substance, you report treatment-related effects on reduced fertility index and effect on post-natal development (reduced litter/pup weights).

Your studies with the source substances 1,4-Butanediol and methyl methacrylate do not show adverse effects on the parameters of reproduction and development such as reduced fertility index and effect on post-natal development (reduced litter/pup weights). Thus the Substance causes toxicological effects which are not caused by the source substances.

The available set of data on the target and source substances shows differences in the toxicological properties of the substances. This information contradicts your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s). Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar given the observation of these differences. Therefore, these data on the sources do not provide a basis on which you can predict the properties of the Substance.

ii) Effects observed with the source substances not observed with the Substance

You have provided a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) conducted with the Substance with oral dosing (gavage) at up to 1000 mg/kg/day ([redacted], 2013). No signs of neurotoxicity were observed in the functional observation battery, grip strength or response to stimuli. The NOAEL based on general toxicity and reproduction/developmental toxicity was reported as 300 mg/kg bw/day.

You have also provided results from a study of comparable design (OECD TG 422 without functional observation battery) conducted with the source substance 1,4-butanediol with oral dosing (gavage) up to 800 mg/kg/day ([redacted] 1999). Treatment-related findings in the bladder and decreases in body weight/gain were reported and the NOAEL for these effects was 200 mg/kg/day. In addition, there was a dose-related transient post-dosing change in the activity of the animals. At 400 mg/kg, there was lower activity which was more severe (coma

and hypoactivity) at 800 mg/kg/day. A LOEL for this neurotoxicity was reported as 200 mg/kg day.

You also reported that clinical signs of CNS depression were observed for 1,4-Butanediol administered in a pre-natal developmental toxicity study (OECD 414; oral dosing) in mouse at the medium dose of 300 mg/kg bw/day with a NOAEL of 200 mg/kg bw/day.

In your Category Justification Document you compared the effects levels with (administered) dose levels (corrected on a molar basis) for the above studies and state: "*Thus, neurotoxicity related clinical signs appear in the alcohol at significantly lower concentration when compared to the parent ester 1,4-BDDMA.*" You state that "*The neurotoxicity seen with 1,4-butanediol and its metabolite γ-hydroxybutyic acid ([redacted], 1996) has not been observed with 1,4-BDDMA up to the highest dose tested (1000 mg/kg/d ester is equivalent to approx. 390 mg/kg/d γ-hydroxybutyic acid) and is perhaps explained by differences in toxicokinetics – particularly because of the complex, multi-step metabolic pathway leading from 1,4-BDDMA to γHB.*" You hypothesise that these differences may be due to toxicokinetics, and you mention the bolus administration of 1,4-butanediol, and the "*complex, multi-step metabolic pathway leading from 1,4-BDDMA to GHB*".

The available set of data on the target and source substances shows that the source substances have additional toxicological properties which are not seen with the Substance. No significant adverse effects on neurotoxicity were observed for the Substance up to 1000 mg /kg bw/day whereas neurotoxicity was reported for the source 1,4-Butanediol and gamma-butyrolactone at lower doses. While you mention possible hypotheses for this difference in toxicity, ECHA notes that the 422 study conducted with the Substance also used oral gavage (i.e. bolus) administration, and so this is not a difference from the 1,4-butanediol study. You have furthermore not explained in what way the complex metabolic pathway from the Substance would be expected to result in different toxicokinetics for the resulting metabolites, and hence different toxic properties. Your hypotheses about the reasons for different toxicity between the Substance and the metabolites is speculative, and does not provide a reliable or quantitative basis for predicting the properties of the Substance.

In your comments to the draft decision, you consider that the neurotoxic effects noted in studies with alcohol 1,4-BD are dose-dependent, and you assert that the alcohol levels necessary to cause systemic neurotoxicity cannot be reached in OECD test guideline studies using the Substance in view of the limit dose. ECHA notes that this conflicts with the statements in your category justification document (vide supra), and that you have not provided a reliable or quantitative basis for predicting the properties of the substance in view of the considerations set out above.

This information does not support your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s). Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be both quantitatively and qualitatively similar despite the observation of these differences. Therefore, these data on the sources do not provide a basis on which you can quantitatively and qualitatively predict the properties of the Substance.

Conclusion

For the reasons presented above and on the basis of the information provided in your registration dossier, ECHA considers that there is not sufficient support for your proposal that the Substance and the source substances have similar toxicological properties as a result of structural similarity, common breakdown products, and similarity in physico-chemical properties. For these reasons, ECHA considers that your hypothesis is not a reliable basis

whereby the properties of the Substance may be predicted from data from the reference substances.

As detailed above, the request in the original decision was not met, and you are still required to provide information on Sub-chronic toxicity study (90-day), via oral route (Annex IX, Section 8.6.2); test method: EU B.26/OECD TG 408 with the registered substance.

This decision is necessary according to Article 42(1) of the REACH Regulation because in your updated registration as a response to the decision CCH-D-2114378296-37-01/F ("the compliance check decision") you have provided information that ECHA has assessed for compliance with the information requirements of the REACH Regulation and the outcome is that your registration still does not comply with the information requirements addressed in the compliance check decision.

Appendix 2: Procedural history

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision CCH-D-2114378296-37-01/F. The Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

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 of this decision was notified to the Member States Competent Authorities according to Article 51(1) of the REACH Regulation.

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 did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Further information, observations and technical guidance

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

2. The Article 42(2) notification for the original decision is on hold until all information requested in the original decision has been received.