Helsinki, 26 January 2023

Addressees
Registrants of "Reaction products of diphenylamine with nonene, branched" as listed on published CoRAP listed in the last Appendix of this decision

Registered substance subject to this decision (the Substance)
Substance name: Reaction products of diphenylamine with nonene, branched
List number: 701-385-4
Previously registered as bis(nonylphenyl)amine (EC number 253-249-4; CAS RN 36878-20-3)

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

DECISION ON SUBSTANCE EVALUATION

Under Article 46 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below:

A. Information required to clarify the potential risk related to PBT/vPvB properties

1. *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211), performed with Monoalkylated diphenylamine (or MNDPA), one nonene branched constituent of the Substance, and specified as follows:
    - The test must be performed with a sufficient number of concentrations allowing to determine a dose-response curve. If less than five concentrations are tested a justification must be provided.
    - All reasonable efforts must be made to achieve exposure concentrations up to the aqueous solubility of the MNDPA in the test medium.
    - You must demonstrate that the concentration of the MNDPA constituent is stable throughout the test (within 80-120% of nominal concentration). A pre-test must be conducted to determine the optimal experimental set-up.
    - Analytical monitoring of the exposure concentrations must be performed at minimum eight times between t = 0 and 21 days, with three sampling points in the first week to ensure stable test conditions.

Deadline

The information must be submitted by **31 January 2025.**

Conditions to comply with the information requested

To comply with this decision, you must submit the information in an updated registration dossier, by the deadline indicated above. The information must comply with the IUCLID robust study summary format. You must also attach the full study report for the corresponding study in the corresponding endpoint of IUCLID.

You must update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You will find the justifications for the requests in this decision in the Appendices entitled 'Reasons to request information to clarify the potential risk'.

You will find the procedural steps followed to reach the adopted decision and some technical guidance detailed in further Appendices.

Appeal

This decision may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] by Mike Rasenberg, Director of Hazard Assessment.

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

Basis for substance evaluation

The objective of substance evaluation under REACH is to allow for the generation of further information on substances suspected of posing a risk to human health and/or the environment ('potential risk').

ECHA has concluded that further information on the Substance is necessary to enable the evaluating Member State Competent Authority (MSCA) to clarify a potential risk and whether regulatory risk management is required to ensure the safe use of the Substance.

The ECHA decision requesting further information is based on the following:

(1) There is a potential risk to human health and/or the environment, based on a combination of hazard and exposure information.
(2) Information is necessary to clarify the potential risk identified; and
(3) There is a realistic possibility that the information requested would allow improved risk management measures to be taken.

Appendix A – Reasons to request information to clarify the potential risk related to PBT/vPvB properties

1. Potential risk

1.1 Potential hazard of the Substance

The Substance is a UVCB substance, consisting of three main constituents (isomers) with nonene (branched) -monoalkylated, -dialkylated or -trialkylated substituted diphenylamine (DPA). The log K_{ow} (>7) and log K_{oc} (>5) values for the three constituents increase with the increasing number of alkylated substitutions. The Substance exhibits a low water solubility (<5µg/L).

Details on the Substance and its constituents are indicated below.

Table 1

	Substance (UVCB)	**Constituent 1 (isomer)**	**Constituent 2 (isomer)**	**Constituent 3 (isomer)**
Acronym	-	MNDPA	DNDPA	TNDPA
List number	701-385-4	-	-	-
Name	Reaction products of diphenylamine with nonene, branched	Ar-nonyldiphenyl-amine (Monoalkylated diphenylamine, branched)	4-nonyl-N-(4-nonylphenyl)aniline (Dialkylated diphenylamine, branched)	N-phenyl-tris(ar-nonyl, branched)aniline (Trialkylated diphenylamine, branched)
Boundary composition		[redacted]	[redacted]	[redacted]
Mol formula	-	C21 H29 N1	C30 H47 N1	C39 H65 N1
Mol weight (g/mol)	295 - 548	295.47	421.72	547.96
Log K_{ow} (KOWWIN EPI suite)	-	7.58	11.87	16.17
Log K_{oc} (K_{ow} method EPI suite)	-	5.075	7.448	9.826
Water solubility (µg/L)	<5 (OECD TG 105)	4.4 (25°C EPI suite) 11.3 (20°C, pH 6/ EU Method A.6)	1.6 E-04 (25°C EPI suite)	5.496 E-012 (25°C EPI suite)

a) P/vP properties

If a substance fulfils the criteria in Section 1.1.1 or 1.2.1 of Annex XIII to REACH, it is considered that it has persistent (P) or very persistent (vP) properties.

For the purpose of the P/vP assessment and to check whether the criteria are fulfilled, the information listed in Section 3.2.1 to Annex XIII, including results from simulation tests, must be considered using a weight of evidence approach. If no such data are available, it is necessary to consider the screening information of Section 3.1.1 to Annex XIII, such as QSAR predictions.

Evidence based on model prediction

You provided Catalogic 301C predictions on ready biodegradability for the three main constituents of the Substance in response to a compliance check (CCH) decision. CATALOGIC, as well as an alternative software for predicting degradation pathways, EAWAG PPS, predicted that the Substance could be hydroxylated at various positions as a first step.

The results for biochemical oxygen demand (BOD) value were of 0.24 after 28d for the MNDPA, 0.31 after 28d for the DNDPA and 0.09 after 28d for the TNDPA. The probabilities for the transformations suggest that the constituents are not ready biodegradable, thus potentially P/vP.

The evaluating MSCA (eMSCA) ran QSAR models to estimate the biodegradability of the Substance by applying EPIsuite BIOWIN v4.10 from three estimation models (2, 3 and 6). Based on the BIOWIN prediction models, the three main constituents of the Substance are considered not ready biodegradable (Table 2). These estimates indicate that the Substance is potentially P or vP, according to screening criteria specified in the ECHA Guidance for PBT assessment, Chapter R.11[2].

Table 2

Episuite Probability of Rapid degradation (Biowin models v.4.10)		
MNDPA CCCC(C)CC(C)(C)c1ccc(Nc2ccccc2)cc1	DNDPA CCCC(C)CC(C)(C)c1ccc(Nc2ccc(C(C)(C)CC(C)CCC)cc2)cc1	TNDPA CCCC(C)CC(C)(C)c1ccc(Nc2ccc(C(C)(C)CC(C)CCC)cc2C(C)(C)CC(C)CCC)cc1
Biowin2 : 0.0466	Biowin2 : 0.0002	Biowin2 : 0.0000
Biowin3 : 2.2212	Biowin3 : 1.7080	Biowin3 : 1.2169
Biowin6 : 0.0112	Biowin6 : 0.0014	Biowin6 : 0.0002
Ready Biodegradability Prediction: NO	Ready Biodegradability Prediction: NO	Ready Biodegradability Prediction: NO

Annex XIII to REACH provides that the identification of PBT/vPvB substances must also take account of the PBT/vPvB properties of relevant transformation and/or degradation products. The results from CATALOGIC and EAWAG-BBD pathway models predict that the expected most common degradation/ transformation products from the MNDPA and DNDPA constituents are not readily biodegradable. The predictions support that the two main constituents of the Substance would not undergo ultimate degradation and that the metabolites are potentially persistent. Therefore, the Substance may form persistent transformation and/or degradation products.

Evidence based on experimental data

- Information on the Substance

Since the Substance has a low solubility in water, hydrolysis is not applicable. Moreover, it has no functional group subject to hydrolysis. Therefore, hydrolysis of the Substance is not expected.

[2] Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11: PBT/vPvB assessment Section R.11.4.1.1.2 (June 2017)

A simulation testing on ultimate degradation in surface water according to OECD TG 309 was performed for the Substance following a CCH decision. No significant mineralization (max 0.6% after 60d) was observed. The constituents are highly adsorptive, and a significant part of the Substance was adsorbed to the glass vessels. Thus, only a reduced recovery of the total applied radioactivity was possible (below the acceptable range of 90-110% recommended in the guideline) leading to low mass balance recovery at the end of the experiment (approximately 75% for the highest concentration of 10 µg/L and approximately 89% for the lowest concentration of 2 µg/L).

It was difficult to distinguish between primary degradation and adsorption in this study, therefore primary degradation cannot be excluded and might have occurred to a certain extent, although identification or quantification of the degradation products was not possible. DT50 (50% disappearance time) values were calculated: 0.3 d for MNDPA and 4.2 d for DNDPA at 12°C and 10 µg/L. The results from the OECD TG 309 should be considered as inconclusive, due to the low mass balance and recovery of radioactivity thus preventing any direct comparison with the degradation half-lives criteria of Annex XIII to REACH. However, since no significant mineralization (max 0.6% after 60d) was observed, the surface water simulation degradation study provides supporting evidence that the Substance does not degrade rapidly in surface water.

- Information on the MNDPA constituent

One inherent biodegradability test according to the draft OECD TG 302D performed on MNDPA (test material [redacted]) is included in the dossier. This study is of good quality and has Klimisch score of 1. Compound-specific analyses conducted on days 0, 28 and 56 indicate that no significant chemical or biological degradation of the test material occurred. No degradation of the test material based on carbon dioxide production was observed after 56 days. Therefore, MNDPA is not inherently biodegradable. This study is considered as a key study.

Evidence based on monitoring data from literature

Monitoring data showed detection of the MNDPA and DNDPA constituents in wastewater treatment plant (WWTP) effluents, surface water and sediments in various locations in Canada (Environment and Climate Change Canada (ECCC), Health Canada (HC), 2017; Lu et al., 2016b; Lu et al., 2017). The detection from biomonitoring studies of the MNDPA and DNDPA constituents in various taxa (Lu et al., 2016b; Lu et al., 2019b) and in livers and eggs of seabird's species living in a remote subarctic region of Canada (Lu et al., 2019a) are also indicative of a potential for persistency of the Substance.

Conclusion

Based on the available information from model prediction (QSAR estimates), experimental results (abiotic and biotic degradation; especially the draft OECD TG 302D inherent test on MNDPA), and monitoring data (from literature), the eMSCA considers that the P criteria is fulfilled for the MNDPA constituent.

Based on structural considerations, and as predicted by Catalogic and Biowin modelisations, it would follow that the DNDPA and TNDPA constituents would also be persistent. Therefore, based on the weight of evidence, the available and current information is sufficient to show that the Substance, based on its main constituents (MNDPA, DNDPA & TNDPA) is persistent.

b) B/vB properties

If a substance fulfils the criteria in Section 1.1.2 or 1.2.2 of Annex XIII to REACH, it is considered that it has bioaccumulative (B) or very bioaccumulative (vB) properties.

For the purpose of the B/vB assessment and to check whether the criteria are fulfilled, the information listed in Section 3.2.2 of Annex XIII must be considered using a weight of evidence approach, including bioconcentration factor (BCF) values. Notably, if the BCF-value is > 2000, the Substance fulfils the criteria for B.

Evidence based on model prediction

You provided BCF and Diamax predictions for the constituents based on Catalogic 5.11.19 model v.02.09. According to the Catalogic model, TNDPA is out of the applicability domain of the model for BCF prediction. Thus, the prediction is relevant for MNDPA and DNDPA constituents only.

According to EPI Suite BCFBAF model prediction v.3.01, constituents that have a log K_{ow} value greater than 11.26 are considered out of the applicability domain of the model and BCFBAF model may be highly uncertain for chemicals that have estimated log K_{ow} values > 9 (Arnot and Gobas, 2003). Thus, the prediction is relevant for MNDPA but not for DNDPA and TNDPA. Results of model predictions are summarised below.

Table 3

	MNDPA	**DNDPA**	**TNDPA**
SMILES	CCCC(C)CC(C)(C)c1ccc(Nc2ccccc2)cc1	CCCC(C)CC(C)(C)c1ccc(Nc2ccc(C(C)(C)CC(C)CCC)cc2)cc1	CCCC(C)CC(C)(C)c1ccc(Nc2ccc(C(C)(C)CC(C)CCC)cc2C(C)(C)CC(C)CCC)cc1
Catalogic Diamax average (Å)	16.6	20	20.8
Catalogic 5.11.19 (Bioaccumulation baseline model v2.09) Log BCF L/kg corrected	2.92 ± 0.404 (BCF 328-2108)	0.88 ± 0.109 (BCF 5.9-9.7)	0.89 ± 0.0922 * (BCF 6.3-9.6)
BCFBAF v.3.01 BCF L/kg (regression-based estimate)	6893	54.4*	3.2*
BCFBAF v3.01 (incl. biotransformation, upper trophic) BCF L/kg	721.6	1.7*	0.9*

*Out of the applicability domain of the model.

Evidence based on experimental data

- Information on the Substance

There is no experimental data evaluating the bioaccumulative properties of the Substance.

- Information on the MNDPA constituent

One study following a guideline similar to OECD TG 305 was performed on fish with the

MNDPA constituent (test material [redacted]). The bioconcentration factors (BCF) calculated from the results were used to evaluate the potential of bioaccumulation in *Cyprinus carpio*. At a concentration of 10 µg/L, a BCF of 1730 was calculated by the authors. Following the recommendations of the OECD TG 305, the eMSCA calculated a new BCF value by kinetic approach taking into account lipid normalisation. The new BCF calculated BCF_{KLip}=2219 L/kg (CI_{95} 2060-2377) reaches the threshold value for bioaccumulation (BCF>2000).

In your comments on the draft decision, you mentioned that:

(i) the study performed in 2000, according to the requirement of the Japanese authorities, is difficult to evaluate with today's standards of the OECD TG 305 and has several significant shortcomings. You suggested to perform a new OECD TG 305 study to meet its requirements and criteria.

ECHA disagrees with your comment and considers that the study is valid although some deviations are noted. In the OECD TG 305, a minimum of four fish should be analysed at each sampling point. In the case of this study, four fish were sampled at each sampling point. However, the analysis was conducted on two pools of two fish. Deviations were noted regarding the recommendations on the water quality measurements (dissolved oxygen, temperature, and frequency of measurements). During the exposure test, the dissolved oxygen and temperature were measured when the test water was sampled. During the elimination period, they were measured once a week and in addition when test fish was sampled. The pH was measured at the beginning and at the end of each of the exposure and elimination periods. Water quality and composition were measured one month before the beginning of the study as described in an Appendix, but repetition is not mentioned. These are considered as minor deviations to the guideline, and they do not invalidate the study.

(ii) the tested concentrations were above the maximum solubility of the test material based on the water solubility of the Substance (<5 ug/L) and that there are no details on the substance identity used in the water solubility test (based on test Method A.6, an equivalent to OECD TG 105) performed in 2002.

As indicated in the registration dossier[3], the test performed in 2002 assessed the water solubility of the MNDPA constituent (test material [redacted]) and it was determined to be 11.3 µg/L at 20°C and pH6. The concentration of the test material was selected in the bioaccumulation test study to be 10 and 100 µg/L. Therefore, only the lower concentration of 10 µg/L was considered for further assessment and for BCF calculation. This concentration is lower than the water solubility of the test material. Moreover, the test material was measured and determined to be stable in the test medium.

(iii) the OECD TG 305 does not recommend the use of solubilizers.

The use of solvents and dispersants (solubilising agents) is not recommended but the use of solvents is allowed in the limit of 100 mg/L (or 0.1 mL/L). In the present study, the solvent and dispersant concentrations were 0.4 mg/L for HCO-30 and <25 ppm (v/v, 0.025 mL/L) for 2-methoxyethanol, and thus considered acceptable.

(iv) a dietary exposure study on the basis that you considered this more appropriate than an aqueous study and that the use of 14C labelled test material is required

[3] https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14820/4/9/?documentUUID=956b788a-8465-4b5d-b5aa-73f3837b8b53

to allow for a mass balance analysis.

The tested substance has a log K_{ow} of 7.6 and a dietary exposure study might indeed be considered as more appropriate and thus recommended, especially when the stability of the substance in the media is difficult to maintain and an uptake of the substance needs to be insured. However, it is not mandatory neither is the use of a 14C labelled test material. The OECD TG 305 (2012) only mentions that radiolabelled test substances can facilitate the analysis, but it is not a requirement. The study conducted with MNDPA showed that an acceptable and stable exposure was reached, and an uptake of the constituent occurred from fishes. Also, as the available study is reliable, it is not deemed necessary to ask for a further study on the same substance.

(v) changes in weight and length of fish were not monitored but could have a great impact on BCF values. You further indicated that the absence of a growth correction may lead to an overestimation of the BCF values.

Due to the lack of information on individual fish length (only a range 6.7-8.7 cm) and to the absence of significant variation of the weight based on the measurements on the days of sampling during the study, growth correction was not considered possible nor relevant. It should be mentioned that weight is the preferred measure of growth for the purpose of correcting kinetic BCF values for growth dilution. In contrast to your statement, the increase in fish mass during the test can result in a decrease of the test material concentration in growing fish (so-called growth dilution). Thus, the kinetic BCF could be underestimated if not corrected for growth (OECD TG 305, 2012, paragraph 20).

(vi) to meet the requirement of the OECD TG 305 (2012) the test design (from 2000) needs to be adjusted regarding the monitoring of individual test fish parameters, the exposure and depuration durations, the sampling intervals, and the amount of test fish. More precisely, in your comments you mentioned that 60 fish were treated at each exposure level, yet only two fish were analysed to determine the highest accumulated organs/tissues and that basing a conclusion around the bioaccumulation potential of a substance on two fish is not statistically significant nor representative of current practices.

Although highest accumulated organs/tissues (viscera in this case) give relevant information regarding to the toxicokinetic profile of a substance, it is important to note that this information was not used for BCFk calculation and statistical analysis. On the contrary, for the assessment of the bioaccumulation potential, and as described above, four fish were sampled from each group, paired, and subjected to whole body analyses for test compound. ECHA reminds that the OECD TG 305 advice a minimum of four fish at each sampling point, but it is not a requirement as condition for the validity of the test. Furthermore, it should be noted that for every sample day, consistent concentration of the MNDPA constituent were found between both fish.

(vii) to get the accurate kinetic constant of k2, the depuration phase should last until 95% of the mass is removed or for a maximum of 56 days while in the present bioaccumulation study only 82% of the substance had been removed within 42 days of depuration time. You argued that the partially k2 can't be extrapolated to the whole k2 when the k value fluctuated a lot over the time. In addition, you indicate that a single compartment model cannot be judged.

The OECD TG 305 bring some recommendations about the time of depuration phase. It takes as example the reference value of 95% of the reduction of body burden of the substance, which usually corresponds to half the duration of the uptake phase. The

guideline does not consider this value as a mandatory reference to apply a kinetic approach to derivate BCF values. ECHA's guidance (R.7c)[4] mentioned that a BCF kinetic assumes that the organism can be mathematically represented as a homogeneously mixed single compartment, and that first order kinetics applies. In addition, as recommended in Annex 5 of OECD TG 305, visual inspection of the modelled uptake and depuration curves when plotted against the measured data can be used to assess and compare the goodness of fit. The guideline also indicates that if the goodness of fit is poor this may be an indication that first order kinetics do not apply, and other more complex models should be employed. However, in the case of the bioaccumulation study with the MNDPA constituent, the Box-Cox transformed optimisation procedure, followed by visual inspection of the model diagnostics (one data outlier was removed) and statistical testing, provides a consistent fit for the uptake and depuration phase. This finding indicates that first order kinetics can be applied.

ECHA considers that, since the validity criteria for this study are met and there are no significant shortcomings, it is therefore not justified to perform a new OECD TG 305 study and the available study can be used to assess the bioaccumulation potential of MNDPA. Furthermore, the calculation of the BCF value by kinetic approach taking into account lipid normalisation is justified and can be used in the weight of evidence approach to assess the B/vB criteria.

Evidence based on monitoring data from literature

Biomonitoring data on aquatic and air-breathing organisms suggest that the two main constituents of the Substance (MNDPA and DNDPA) are effectively transferred in the food chain and revealed the possibility of a maternal transfer of MNDPA to bird's eggs (Lu et al. 2016a; Lu et al. 2016b; Lu et al., 2018; Lu et al., 2019a; Lu et al. 2019b). These results give additional indications that MNDPA and DNDPA are taken up from food in an efficient way and that the Substance and its constituents are not easily eliminated (e.g., excreted and/or metabolized) by the organism.

On the other hand, although biomonitoring data indicate a potential uptake of the DNDPA from various taxa (invertebrate, fish and bird), there is no experimental bioaccumulation study on this specific constituent nor on the Substance. Moreover, data on the physico-chemicals properties of DNDPA (molecular size and Log K_{ow}), rather indicate a hindered potential for B/vB properties. QSAR modelisations also suggest that, with the highest bioaccumulation potential, MNDPA is the worst-case constituent when considering the B/vB criteria of the Substance.

Conclusion

A conclusion that the Substance is bioaccumulative is not possible based on the model prediction and no experimental data are available to confirm the B criterion on the Substance.

Based on the QSAR model predictions and its physico-chemical properties, MNDPA is the most bioavailable constituent of the Substance. The calculated BCF for MNDPA reaches the threshold for bioaccumulation and this result is consistent with evidence based on monitoring data.

[4] Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7c: Endpoint specific guidance Section R.7.10.1.1 (June 2017)

Based on the weight of evidence presented, the available and current information is sufficient to draw a conclusion on the property of MNDPA which is considered to be bioaccumulative.

c) Potential T properties

If a substance fulfils the criteria in Section 1.1.3 of Annex XIII to REACH, it is considered that it fulfils the toxicity (T) criterion. For the purpose of the assessment of T and to check whether the criteria are fulfilled, the information listed in Section 3.2.3 of Annex XIII must be considered, such as results of long-term toxicity tests.

Environmental toxicity

- Information on the Substance

A long-term toxicity study in fish is available (OECD TG 210, GLP compliant, 2020) from which a No-Observed Effect Loading Rate (NOELR) 34d > 10mg/L was derived. Two algae studies (OECD TG 201, GLP compliant, 1997 and 2020) are also available with the following results, based on nominal concentrations: NOEC (96h) >33 mg/L, EC50 (72h) >600 mg/L, EC50 (96h) >870 mg/L for the first study and EL10 (72h) >100 mg/L, EL50 (72h) >100 mg/L for the second study. None of these studies indicates that the Substance fulfils the T criteria, as defined in Annex XIII to REACH.

Terrestrial and sediment toxicity studies with the Substance are also available for:

- microorganisms (OECD TG 216, GLP compliant, 2018), for which EC10 (28d)> 1000 mg/kg dw,
- vascular plants (OECD TG 208, GLP compliant, 2019), for which NOEC (28d)> 1000 mg/kg dw, and
- macroorganisms (OECD TG 222, GLP compliant, 2014 and OECD TG 225, GLP compliant, 2018), for which NOEC (28d)> 1000 mg/kg dw, and NOEC (28d)= 100 mg/kg dw respectively.

The results of these studies do not show that the Substance exerts toxic effects to terrestrial and sediment organisms.

However, one long term study on *Daphnia magna* (OECD TG 211, GLP compliant, 2020) indicates toxic effects: a significant reduction in number of offspring per introduced parental daphnid was observed at the nominal loading rates of 6.67 and 10.0 mg/L (NOELR of 4.42 mg/L). A significant trend in increasing mortality was observed reaching 50% mortality at the highest loading rate tested (NOELR adult mortality: 6.67 mg/L). The calculated EL10 (21d) for the Substance provided by the registrants based on the nominal loading rate was 4.12 mg/L.

The chemical-specific analysis showed that only MNDPA (one of the two main constituents) could be detected. The measured concentrations in the fresh media, at the beginning of the exposure-renewal interval, were in the range of below the limit of quantification (LOQ) (1 µg test item/L) to 4.65 µg/L. At the end of the exposure-renewal interval (24 hours), most of the measured concentrations were below LOQ.

As indicated in the section on poorly water-soluble substances of the Guidance R7b[5] ("summary of difficult substance testing issues" in table R.7.8-3): *"Toxicity may be observed at concentrations nominally in excess of water solubility, or below the detection*

[5] Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7b : Endpoint specific guidance Appendix R.7.8-1 (June 2017)

limit of the analytical method. Such data are not automatically invalid since the original solubility estimate may be uncertain, and the solution may have been prepared appropriately (e.g., provided any undissolved substance is removed prior to testing). If physical effects are not obvious, then as a realistic worst case, the lowest effect concentration may be based on either the water solubility limit or detection limit of the analytical method, whichever is the lower."

Taking into account the measured concentrations, the effects on reproduction occurred at concentrations below the water solubility limit of the Substance, which is < 5 µg/L (OECD TG 105).

- Information on the MNDPA constituent

Acute aquatic toxicity studies are available and were performed at the concentration corresponding to the limit of solubility of MNDPA (0.0113 mg/L). The results were calculated based on the time-weighted mean measured test concentrations of the centrifuged test media:

- For the acute toxicity in *Oncorhynchus mykiss* (OECD TG 203, GLP compliant, 2003) under semi-static condition: LC50(96 h) >0.0013 mg/L.
- For the acute toxicity in *Daphnia Magna* (OECD TG 202, GLP compliant, 2003): the effect concentration was EC50(48h) >0.0014 mg/L.
- For the acute toxicity in *Scenedesmus subspicatus* (OECD TG 201, GLP compliant, 2003): the effect concentration was EC50 >0.00222 mg/L.

Hence no adverse effects were observed.

- Conclusion

The toxic effects of the Substance were observed in the chronic toxicity study on *Daphnia Magna*. No toxicity of MNDPA was observed in the aquatic short-term tests and no long-term aquatic toxicity study is available. However, MNDPA was the only constituent detected in the long-term toxicity test on *Daphnia magna* with the Substance, suggesting that MNDPA, as the most water-soluble constituent, could be the driver of toxicity of the Substance.

Thus, further information is needed on MNDPA to clarify whether it fulfils the T-criterion according to Annex XIII to REACH.

Human health toxicity

- Information on the Substance

In the subchronic 90-day gavage study (OECD TG 408, GLP compliant, 2013) and in the reproduction and developmental toxicity screening test (OECD TG 421, GLP compliant, 2020) performed with the Substance, effects on liver and thyroid were observed at 100 mg/kg, although with limited magnitude and severity.

The liver was identified as the main target organ of substituted diphenylamines (SDPA) in the different reports dedicated to this SDPA chemical group (OECD 2016, Environment and Climate Change Canada (ECCC), Health Canada (HC) 2017, ECHA 2018). Registrants were also invited to consider the liver/thyroid effects observed in the different studies and whether classification is needed in the conclusion of COLLA project for SDPA (ECHA, 2018).

In addition, reprotoxic effects were observed in the OECD TG 421 study, which can justify a classification of the Substance for reproductive toxicity (decreased ovary weights, decreased number of implantation sites and correlated decreased litter size).

In your comments on the draft decision, you considered that the classification criteria for reproductive toxicity according to CLP are not fulfilled. You further proposed to clarify the effects observed in the OECD TG 421 study in the proposed OECD TG 443 study with the Substance (testing proposal submitted on 14 January 2022, under assessment by ECHA).

ECHA considers that, despite being observed in a screening study with a small number of animals (10/sex/dose), which limits the statistical power to detect effects, the reproductive effects (i.e., decreased ovary weight, decreased mean number of implantation sites and consequently decreased litter size) are observed from the mid-dose and are statistically significant and dose related. Therefore, they are clearly established, and treatment related. As a result, the litter size at PND0 (number of delivered pups) is reduced by 19% and 31% at the mid- and high doses, respectively, which is considered a severe impact on fertility/reproductive function. In the absence of excessive systemic toxicity, the reproductive toxicity potential of the Substance is therefore considered well established.

- Information on the MNDPA constituent

In the OECD case study dedicated to SDPA grouping (OECD, 2016), a short-term 28-day repeated dose gavage study (performed according to a Japanese guideline similar to OECD TG 407, GLP compliant, 1995), carried out with MNDPA (doses at 15, 150 and 500 mg/kg bw/d) in rats is reported (Unpublished study report, 1999). In this study, liver and blood were identified as target organs and the NOAEL was determined to be 15 mg/kg bw/day based on clinical signs of toxicity (increased salivation), increased relative liver weights, histopathological effects in the liver and spleen, as well as changes in haematological and clinical chemistry parameters in both sexes at 150 mg/kg bw/day.

Based on the assessment of the full study report, increased liver weight was associated with significant organ damage (centrilobular hypertrophy and lipid vacuolation from 150 mg/kg bw/d in males and females) and significant adverse change in clinical biomarkers of liver function such as cholestasis (increased ALP from 150 mg/kg bw/d in males and females), decreased in protein synthesis (decreased albumin from 150 mg/kg bw/d in females and at 500 mg/kg bw/d in males and decreased coagulation factors from 150 mg/kg bw/d in males and at 500 mg/kg bw/d in females) as well as lipid metabolism alteration (increased triglyceride levels from 150 mg/kg bw/d in females).

However, the magnitude and the severity of the observed effects at 150 mg/kg bw/d are not considered sufficient to trigger a classification STOT RE (according to CLP threshold value of 300 mg/kg bw/d for STOT RE Cat2, based on a 28-day oral repeated dose study).

- Conclusion

Overall, the eMSCA considers that the Substance fulfils the T criteria for reproductive toxicity.

The concentration range of MNDPA in the Substance is at a lower percentage than DNDPA. MNDPA has a lower molecular weight, lower $LogK_{ow}$ and higher water solubility compared to the major constituent DNDPA; it also has a higher bioavailability than DNDPA. This was identified also in the OECD report (2016), where the oral bioavailability estimated for MNDPA and DNDPA were 21.53% and 0.06%, respectively, using the model ACD Percepta PK Explorer for an oral dose of 5 mg/kg in human (ACD 2012). Based on the comparative

oral bioavailability data of the constituents, the effects observed in the OECD TG 408 and OECD TG 421 performed with the Substance can be suspected to be mainly driven by the toxicity of MNDPA.

In your comments on the draft decision, you highlighted that the ADME estimates in the OECD report (2016) should be considered carefully with regards to their reliability since, as mentioned in the OECD case study report, the ACD Percepta PK Explorer model does not provide information on reliability or applicability domain. Therefore, OECD considered the reliability of the quantitative values reported as low. While the eMSCA acknowledges that the estimated quantitative values are not reliable as such, it however considers (as mentioned in the OECD report) that the results are useful for a comparative analysis.

In your comments on the draft decision, you argued that several effects (haematological parameters and pigment accumulation in spleen) clearly observed in the 28-day study with MNDPA were not observed in the 90-day study with the Substance even though the dose levels were several folds higher when considering the MNDPA content). You concluded that those data do not support that MNDPA is the driver of toxicity of the Substance. ECHA disagrees that the dose levels in the 90-day study performed with the Substance were several folds higher when considering the MNDPA content. The highest dose tested in the 90-day study is 1000 mg/kg bw per day of Substance corresponding to [redacted] MNDPA while the highest tested dose of MNDPA in the 28-day study is 500 mg/kg bw/d. Furthermore, the patterns of liver effects observed in the 28-day study (MNDPA) and in the 90-day study (Substance) are very similar in terms of clinical and histopathology (increased alkaline phosphatase activity triglycerides levels and clotting time, decreased albumin levels and liver hypertrophy associated with fatty change and single cell necrosis). While it is acknowledged that pigment accumulation in the spleen was only observed in the 28-d study with MNDPA, slight decrease of haemoglobin and haematocrit were observed in both studies (28-day study with MNDPA and 90-day study with the Substance) at the highest dose levels. Therefore, this comparison supports that MNDPA could be the driver of toxicity in the Substance.

Thus, further information is needed on MNDPA to clarify whether it fulfils the T-criterion according to Annex XIII to REACH.

d) Conclusion

According to the ECHA Guidance for PBT assessment, Chapter R.11[6], a conclusion that the substance is PBT/vPvB can be drawn when the substance is a *"mono-constituent substance, well-defined multi-constituent substance or UVCB substance, and it contains one or more relevant (group(s) of) constituent(s) which fulfil the PBT and/or vPvB criteria"*.

Due to the well-defined composition of the Substance regarding its constituents and their typical concentration range in the UVCB substance, its assessment was performed taking the relevant constituents into consideration for the PBT/vPvB assessment.

All available data on persistence, bioaccumulation and toxicity of the Substance and its constituents were assessed and, the eMSCA concluded that the Substance may be a PBT substance as defined in REACH Annex XIII because of the potential PBT properties of the constituent MNDPA.

[6] Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11: PBT/vPvB assessment Section R.11.4.1.4 (June 2017)

As presented above:

- The eMSCA considers that MNDPA fulfils the P and B criteria and may fulfil the T criteria. Further information is necessary to clarify the potential toxicity and risk related to PBT properties of this constituent.
- A conclusion that the Substance is PBT can be drawn when the UVCB substance contains one or more relevant constituent(s) which fulfil the PBT criteria. If MNDPA fulfils the PBT criteria, no further information will be needed on the Substance.

1.2 Potential exposure

According to the information you submitted in all registration dossiers, the aggregated tonnage of the Substance manufactured or imported in the EU is in the range of 10,000-100,000 tonnes per year.

Furthermore, you reported that, among other uses, the Substance is used by industrial and professional workers, and by consumers and in metalworking fluids, lubricant additives, lubricants and greases.

The Substance can be released to the environment as emissions from manufacturing plants, emissions from industrial and professional facilities using the Substance and from consumer uses leading to emissions to municipal wastewater treatment plants. Therefore, exposure to consumers, workers, and the environment cannot be excluded.

1.3 Identification of the potential risk to be clarified

Based on all information available in the registration dossier and information from the published literature, there is sufficient evidence to justify that MNDPA, one of the constituents of the Substance, may have PBT properties. As explained in Section 1.1 c) above, the available information is not sufficient to conclude on the potential T property of the constituent MNDPA. Consequently, further data is needed to clarify the potential risk related to PBT properties.

The information you provided on manufacture and uses demonstrate a potential for exposure of the environment.

Based on this hazard and exposure information the Substance poses a potential risk to the environment and human health.

1.4 Further risk management measures

If the PBT properties of the MNDPA constituent, and thus of the Substance, are confirmed, the evaluating MSCA will analyse the options to manage the risk(s). New regulatory risk management measures could be the identification as a substance of very high concern (SVHC) under Article 57 of REACH and subsequent authorisation or restriction of the Substance.

The evaluating MSCA will assess whether the Substance should be proposed for identification as a substance of very high concern (SVHC) under Article 57 of REACH, which could lead to stricter risk management measures than those currently in place. It could acknowledge the PBT status of the Substance, which require minimisation of exposures and emissions to humans and the environment, throughout the lifecycle of the Substance, in accordance with section 6.5 of Annex I of REACH. Consequently, you would have to identify and apply risk management measures to adequately control the risks (REACH, Article 14 and Annex I, Section 6.5).

Furthermore, SVHC identification would trigger information requirements under Articles 7 and 33 of REACH. This could also result in authorisation and allow authorisation to address all the intrinsic properties of the Substance. Alternatively, or additionally, a restriction of the Substance could be proposed if the need for further risk management measures is identified.

2. How to clarify the potential risk

2.1 Development of the testing strategy

According to ECHA Guidance R.11, a conclusion that the substance is PBT/vPvB can be drawn when the substance is a mono-constituent substance, well-defined multi-constituent substance or UVCB substance, and it contains one or more relevant (group(s) of) constituent(s) which fulfil the PBT and/or vPvB criteria.

As presented above, the eMSCA considers that the Substance fulfils the P and T criteria, but no conclusion can be reached regarding the B potential. In contrast, MNDPA is considered to fulfil the P and B criteria and might fulfil the T criteria.

There is evidence that MNDPA may drive the repeated dose and reproductive toxicity in rodents and the aquatic toxicity on *Daphnia magna* observed for the Substance. As MNDPA is considered to meet already the P and B criteria, MNDPA, and thus the Substance, could be identified as SVHC PBT substance if the T criteria is met.

The initial draft decision requested for an OECD TG 422 with the constituent MNDPA. A proposal for amendment (PfA) was submitted by a MSCA to replace the request for an OECD TG 422 study, with a request for an OECD TG 211 with the constituent MNDPA.

In your comments on the PfA, you agreed with the proposal to remove the requested OECD TG 422 study and to instead perform an OECD TG 211 study. Furthermore, in relation to the OECD TG 211, you indicated that the existing OECD TG 211 study performed with the Substance provided inconclusive data to determine T for the environment.

The evaluating MSCA considered your comments on the PfA as follows:

- The assessment reveals that MNDPA is the worst-case constituent, which is considered to fulfil P and B criteria. T-criterion needs to be investigated further for the constituent MNDPA. As explained in section 1.1.c., toxic effects of the Substance were observed in the chronic toxicity study on *Daphnia Magna*. In this chronic toxicity study, toxic effects appear, and the chemical-specific analysis showed that only the MNDPA could be detected and measured. However, it is not possible to specifically attribute the toxicity to the MNDPA constituent alone.

ECHA amended the decision according to the PfA submitted by the MSCA by requesting an OECD TG 211 study with the constituent MNDPA and by amending the deadline accordingly.

As the T criterion for MNDPA and for the Substance can potentially be clarified by conducting the requested invertebrate study, additional studies on vertebrates are not justified at this stage. This decision is therefore focused on clarifying the long-term aquatic toxicity of MNDPA on *Daphnia magna*. However, if the requested long term toxicity test on *Daphna magna* in the current decision is inconclusive or if no adverse effects fulfilling the

T criteria according to Annex XIII to REACH are observed, a second decision could follow to clarify the remaining concern(s).

2.2 Long-term toxicity testing on aquatic invertebrates: Daphnia magna reproduction test (test method EU C.20. / OECD TG 211) performed with the MNDPA constituent

a) Aim of the study

The requested *Daphnia magna* Reproduction test allows to evaluate long-term aquatic toxicity of MNDPA and to determine whether the constituent fulfils the criteria for toxicity (T) in Annex XIII to REACH. The *Daphnia magna* Reproduction test is a standard information requirement at Annex IX of REACH (Section 9.1.5) and may be subject to a compliance check (Article 41 of REACH). The information requested in this decision aims at clarifying the potential risk that the Substance poses in clarifying the long-term aquatic toxicity of the specified constituent of the Substance (MNDPA). Thus, under the current substance evaluation, the *Daphnia magna* Reproduction test will not be performed on the Substance but instead on the specified individual constituent of the Substance.

b) Specification of the requested study

Test material

MNDPA is a nonene branched constituent present in the Substance at variable concentration levels. It is one of the two main constituents of the Substance.

MNDPA was used as test material under the name [redacted] in a solubility in water EU Method A.6, an inherent biodegradability CONCAWE test (draft OECD TG 302D), in a bioconcentration study with carp (equivalent to OECD TG 305) and in a 28-day toxicity study. Moreover, two ecotoxicity studies were performed with this constituent and described as followed: Reaction products of Benzenamine, N-phenyl, and Nonene, branched (EC 253-249-4; CAS RN 36878-20-3 - previous identifiers for the Substance), followed by purification (distillation) with a 96% mono-alkyl content.

The test material MNDPA was identified as "Monoalkylated diphenylamine (or MNDPA, EC number 248-295-7)" in the initial draft decision. In your comment, you highlighted that MNDPA (EC number 248-295-7), a minor constituent of the UVCB substance, is not readily available and could not be supplied. ECHA noted the inconsistency in the substance identity name and EC number. While the constituent of concern is the nonene branched monoalkylated diphenylamine (referred to as MNDPA), the EC number 248-295-7 (CAS number 27177-41-9) describes the linear alkyl isomer of MNDPA. On this basis, the EC and CAS numbers referring to the MNDPA have been removed from the decision. As the test material focuses on the nonene branched isomer of MNDPA, ECHA considers that there should not be issues with synthetising or isolating the test material, as the nonene branched form of MNDPA is one of the main constituents of the Substance.

Therefore, the eMSCA considers that testing of nonene branched MNDPA is technically feasible for the registrants of the Substance and that this request does not require extensive additional work, e.g., related to test material synthesis.

Test concentrations and study design

The study must be performed with a sufficient number of concentrations allowing to determine a dose-response curve. If less than five test concentrations are tested a justification must be provided. The concentrations and spacing should cover the range of concentrations of MNPDA where effects were seen in the available long-term toxicity test on *Daphnia magna* with the Substance.

Due to its low water solubility and adsorptive properties, MNDPA is considered a difficult to test substance. OECD TG 211 specifies that, for difficult to test substances, you must consider the approaches described in OECD GD 23 (OECD 2019) or other approaches, if more appropriate for MNDPA. In all cases, the approach selected must be justified and documented.

Due to the properties of MNDPA, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, all reasonable efforts must be made to achieve exposure concentrations up to the aqueous solubility of the MNDPA constituent in the test medium. The use of suitable solvent and dispersant as mentioned in paragraph 19 of OECD TG 211 is allowed. A pre-test must be done to characterize the stability of MNDPA constituent.

In the PfA, it was proposed that the study is performed using flow-through test procedure.

In your comments on the PfA, you propose to perform the OECD 211 with MNDPA according to a testing protocol using passive dosing (semi-static loading by swelling approach) due to the poor water solubility and to avoid physical effects due to creation of emulsions.

ECHA observes that OECD GD 23 provides different methodologies for testing difficult substances, such as passive dosing (OECD 2019). ECHA leaves it at your discretion which appropriate methodology should be used to demonstrate that the concentration of the MNDPA constituent is stable throughout the test (within 80-120% of nominal concentration).

You must monitor the test concentrations of MNDPA throughout the exposure duration and report the results. Sampling must be done at minimum eight times between t = 0 and 21 days, with three sampling points in the first week to ensure stable test conditions. Exposure concentrations must be recalculated based on a time-weighted average, as described in Annex 6 of OECD TG 211.

Where the concentrations do not remain within 80-120% of nominal (or if it not possible to demonstrate this), the effect concentrations must be determined and expressed relative to the arithmetic mean concentration as recommended in Appendix R.7.8—1 in Chapter R.7b of the Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA, ECHA, 2017). In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of MNDPA in the test solutions.

If you opt for a flow-through exposure system, to minimize adsorption of the test material, the test vessels must be pre-conditioned using solutions of the test chemical. The concentration of the test chemical used to condition a vessel should not exceed the test concentration appropriate to the vessel; otherwise, the test chemical may desorb during

the test and increase the exposure concentration. Furthermore, such flow-through exposure system must always be equilibrated with the test chemical, regardless of whether an adsorptive test chemical is used, and confirmed by the pre-test samples on e.g., two days at least. In addition to pre-conditioning, the use of test vessels made of non-adsorbing materials should be considered.

It is to be noted that the test material may adsorb to the food. Depending on the methodology chosen, detailed information on feeding should be also provided and a feeding schedule should be carefully planned. To investigate sorption on algal biomass, algae may be removed from test solution samples for separate analysis and/or abiotic replicates included in the study design to better characterise exposure levels.

Request for the full study report

You must submit the full study report which includes:
- a complete rationale of test design.
- interpretation of the results.
- access to all information available in the full study report, such as implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.

This will enable the eMSCA to fully and independently assess all the information provided, including the statistical analysis, and to efficiently clarify the potential hazard for the PBT/vPvB properties of the Substance.

c) Alternative approaches and how the request is appropriate to meet its objective

The request for *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211), using MNDPA, nonene branched, is:

- Appropriate, because the test is suitable and necessary to obtain information which will allow clarifying whether MNDPA fulfils the T criterion according to Annex XIII to REACH.
- Regarding the selection of the toxicity test, an alternative could be an experimental toxicity study testing on other aquatic organisms (e.g., algae/plants or fish) and using MNDPA as test material. As vertebrate testing should be avoided, when deemed unnecessary, algae/plant testing is considered a better alternative than fish testing. However, as discussed above, the available ecotoxicity studies (including e.g., fish and algae) do not suggest that T could be fulfilled, with the exception of the long-term toxicity test on *Daphnia magna* (OECD TG 211).
- Regarding bioaccumulation, the alternative of requesting an additional study based on the whole substance approach is not a suitable option. As the Substance is considered to be P and T, testing the bioaccumulation is not considered a possibility because, based on QSAR model predictions and physico-chemical properties, MNDPA is considered to be the most bioavailable constituent. Testing the bioaccumulation on the Substance may not enable the detection of a bioaccumulative potential as the presence of several constituents may interfere in the metabolism of the tested organisms. Therefore, the PBT conclusion for Substance shall be considered on the basis of its most relevant constituents, i.e. MNDPA.

d) Consideration of time needed to perform the requested studies

The deadline in the draft decision was initially based on the request for OECD TG 422. This request has been removed from the decision. Therefore, ECHA has amended the deadline accordingly:

- The deadline of the decision is set based on standard practice for carrying out OECD TG tests, that is 9 months for OECD TG 211. This deadline has been exceptionally extended by 6 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

Furthermore, in your comments on the draft decision, you requested an extension of the timeline. You sought to justify this request as follows:

- Distillation of the test item would require at least 3-4 months and an additional 6-8 months would be required if a synthetic work would be necessary prior to the distillation.

ECHA analysed the time requested and agrees to extend the deadline by an additional 6 months.

Therefore, ECHA has modified the deadline of the decision and set the deadline to 21 months.

2.3 References relevant to the requests (which are not included in the registration dossier)

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Appendix B: Procedure

This decision does not imply that the information you submitted in your registration dossier(s) are in compliance with the REACH requirements. ECHA may still initiate a compliance check on your dossier(s).

12-month evaluation

Due to initial grounds of concern for PBT/vPvB and for mutagenicity, the Member State Committee agreed to include the Substance (List No 701-385-4) in the Community rolling action plan (CoRAP) to be evaluated in 2021. The French Member State is the competent authority ('the evaluating MSCA') appointed to carry out the evaluation.

In accordance with Article 45(4) of REACH, the evaluating MSCA carried out its evaluation based on the information in the registration dossier(s) you submitted on the Substance and on other relevant and available information.

During the evaluation, the evaluating MSCA identified additional concerns for the potential risk related to reproductive toxicity and to specific target organ toxicity (repeated).

The evaluating MSCA completed its evaluation and considered that further information is required to clarify the following concerns on the MNDPA constituent of the Substance: PBT/vPvB.

Therefore, it submitted a draft decision (Article 46(1) of REACH) to ECHA on 17 March 2022.

Decision-making

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

The decision-making followed the procedure of Articles 50 and 52 of REACH as described below.

(i) Registrant(s)' commenting phase

ECHA received your comments and forwarded them to the evaluating MSCA.

The evaluating MSCA took your comments into account (see Appendix A). The request(s) and the deadline (as explained in Section 2.2.d) were amended, including clarification on the test material.

(ii) Proposals for amendment by other MSCAs and ECHA and referral to the Member State Committee

The evaluating MSCA notified the draft decision to the competent authorities of the other Member States and ECHA for proposal(s) for amendment. Subsequently, the evaluating MSCA received proposal(s) for amendment to the draft decision and did not modify the draft decision.

ECHA referred the draft decision, together with your comments, to the Member State Committee.

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

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

(iii) Member State Committee agreement seeking stage

The Member State Committee considered that the draft decision should be amended according to the PfA submitted by an MSCA, which proposed to remove the previous request for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), and instead request a *Daphnia magna* reproduction test (OECD TG 211). The Member State Committee also considered that the draft decision should be amended to reflect your comments on the PfA concerning the testing methodology. Consequently, the draft decision and the deadline were amended accordingly.

As the Member State Committee agreed to request for the OECD TG 211 and removed the request for the OECD TG 422, specific proposals for amendments and comments concerning the OECD TG 422 were no longer needed to be addressed in the decision.

The Member State Committee reached a unanimous agreement during its MSC-80 meeting and ECHA took the decision according to Article 52(2) and 51(6) of REACH.

After the deadline set in this decision has passed, the evaluating MSCA will review the information you will have submitted and will evaluate whether further information is still needed to clarify the potential risk, according to Article 46(3) of REACH. Therefore, a subsequent evaluation of the Substance may still be initiated after the present substance evaluation is concluded.

Appendix C: Technical Guidance to follow when conducting new tests for REACH purposes

Test methods, GLP requirements and reporting

Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[7].

Test material

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

1. *Selection of the Test material(s)*

The Test Material used to generate the new data must be selected taking into account the impact of each impurity on the test results for the endpoint to be assessed.

2. *Information on the Test Material needed in the updated dossier*

   a) You must report the composition of the Test Material selected for each study, under the 'Test material information' section, for each respective endpoint study record in IUCLID.
   b) The reported composition must include all impurities and their concentration values.

Technical instructions on how to report the above is available in the manual "How to prepare registration and PPORD dossiers"[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals