Bis(2-ethylhexyl) adipate (BEHA)

Bis(2-ethylhexyl) adipate major uses is plasticizer, commonly blended with general purpose plasticizers, such as di-n-octyl phthalate and diisooctyl phthalate in processing polyvinyl and other polymers. It is also used as solvent in the following cosmetics: bath oils, eye shadow, cologne, foundations, rouge, blusher, nail-polish remover, moisturizers and indoor tanning preparations. This chemical substance is not classified in the Annex I of Directive 67/548/EEC. In addition, in the MSDS related to Bis(2-ethylhexyl) adipate, limited evidence to carcinogenic effect with risk phrase (R40) was specified.

An assessment of the PBT status of BEHA using the algorithm described in the toolbox is explained below step by step.

Step1: Substance identification

Identifiers on BEHA have been obtained from the most recent reliable sources (www.chemfinder.com) and chemIDplus which are listed in step1. The smiles notation for BEHA was obtained form chemspider and chemID plus sources. These identifiers are shown in Table1 below.

Identifier of BEHA	
EINECS or ELINCS number	203-090-1
CAS name and CAS number	103-23-1
Name(s) in the IUPAC nomenclature or other international chemical name(s)	Hexanedioic acid, bis(2-ethylhexyl) ester
Other names (usual name, trade name, abbreviation)	ADO (lubricating oil) AI3-28579 Adimoll DO Adipic acid, bis(2-ethylhexyl) ester Adipol 2EH Arlamol DOA BEHA BRN 1803774 Bis(2-ethylhexyl) adipate Bis(2-ethylhexyl) hexanedioate Bis-(2-ethylhexyl)ester kyseliny adipove

	[Czech] Bisoflex DOA CCRIS 236 Crodamol DOA DEHA DOA Di(2-ethylhexyl)adipate Di-2-ethylhexyl adipate Dioctyl adipate Dioctyl adipate (VAN) Effomoll DA Effomoll DOA Ergoplast ADDO Flexol A 26 Flexol plasticizer 10-A Flexol plasticizer A-26 HSDB 343 Hatcol 2908 Hexanedioic acid, dioctyl ester Jayflex DOA 2 K 3220 Kemester 5652 Kodaflex DOA Lankroflex DOA Mollan S Monoplex DOA Morflex 310 NCI-C54386 NSC 56775 Octyl adipate Octyl adipate (VAN) PX-238 Plasthall DOA Plastomoll DOA Reomol DOA Rucoflex Plasticizer DOA Sansocizer DOA Sicol 250 Staflex DOA Truflex DOA USS 700 Uniflex DOA Vestinol OA Vistone A 10 Wickenol 158 Witamol 320
Information related to molecular and structural formula of BEHA	
Molecular Formula	$C_{22}H_{42}O_4$

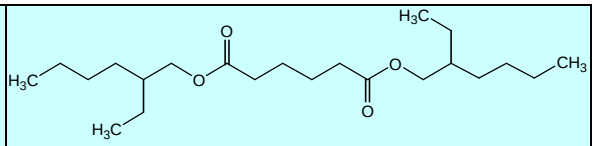
Structural Formula	
Smiles Notation	C([C@@H](CCCC)CC)OC(CCCCC(OC[C@@H](CCCC)CC)=O)=O

Table1: BEHA identification parameters.

Step 2: Data needed for the assessment

These are divided into the followings:

- Physical-chemical properties (water solubility, Partition coefficient n-octanol/water, Soil Adsorption Coefficient (Koc/Kd), and Henry's Law Constant)
- Degradation, (biodegradation, half lives)
- Accumulation (BCF)
- Environmental Partitioning (MacKay)
- Ecotoxicity data of the substance (LC_{50}, NOEC)

Step 3: Collecting the available information and identifying the data gap

1- Information on the physical-chemical properties for BEHA

The following table provides a summary of the

1. Chemical and physical properties required for the assessment as explained in the algorithm.

2. The available chemical and physical properties of BEHA along with the source for these data. As explained in the algorithm, in this step you have to make sure that the data studies were conducted according to EU-approved methods (e.g. those specified in Annexes V and VIII of Directive 67/548/EEC, or REACH Annex X methods) and in compliance with the principles of GLP. This only applies for degradation, accumulation and ecotoxicity studies not for the physical-chemical one.

3. The data gap which is highlighted as red in the table.

Required Property	Value	Source
Water solubility	0.78mg/l at 22^{0}C Insoluble. <0.01 g/100 ml at 22 ^{0}C	ChemID plus and HSDB (References cited in the report).
Partition coefficient n-octanol/water	No measured logK_{ow} is available. Log K_{ow} = 6.11 and 8.114 (calculated)	chemIDplus and IUCLID
Soil Adsorption Coefficient (Koc/Kd)	No measured log Koc value is available for BEHA only estimated Koc = 49,000	HSDB
Henry's Law Constant	4.34E-07 at 20 ^{0}C (EXP)	ChemID plus

Table2: Physical chemical data available for BEHA.

2- Accumulation data of BEHA

According to HSDB result (Hazardous substances data bank) bioaccumulation of Bis(2-ethylhexyl) adipate was studied with blue-gill fish. The whole-fish BCF observed from this study was 27. This value is considered to give sufficient evidence on a very low bioaccumulation of BEHA.

3- Degradation data of BEHA

The following table provides a summary of the

1. Degradation properties required for the assessment as explained in the algorithm.
2. The available degradation data of BEHA along with the source for these data. As explained in the algorithm, the data should be reliable.
3. The data gap which is highlighted as red in the table.

Required Property	Value	Source
Biodegradation	Biodegradation studies with Bis(2-ethylhexyl) adipate using an activated sludge seed indicates substance to be ready biodegradable. 66% of Bis(2-ethylhexyl) adipate (100 ppm) degraded after 28days in the standard biodegradability test of the Japanese Ministry International Trade and Industry (MITI), a BOD test utilizing a mixed inoculum of activated sludge, sewage and surface water. (study conducted according to OECD TG 301C guideline)	MITI , HSDB and IUCLID
Half lives-$t_{1/2}$		
1-Hydrolysis as a function of pH	Bis(2-ethylhexyl) adipate is expected to hydrolyse producing 2-ethylhexanol and hexandioic acid. A base-catalyzed second-order hydrolysis rate constant of 0.07 L/mole-sec was estimated using a structure estimation method; this corresponds to half-lives of 3 years and 120 days at pH values of 7 and 8, respectively. (EST)	HSDB
2-Photolysis (Atmospheric OH Rate Constant)	No measured data is available only estimated 2.45E-11 cm^3/molecule-sec at 25 ^0C	ChemID plus and HSDB

Table3: Degradation data available for BEHA.

4- Environmental Partitioning (MacKay)

No data is available.

5- Aquatic toxicity information of BEHA

The results of toxicity tests carried out with Bis(2-ethylhexyl) adipate on fish (acute), aquatic invertebrates (acute) and plants (algae) have been collated from IUCLID. The data are summarised below in Table 4.

Required Property	Value	Source
Fish Acute toxicity to fish (96hrs LC_{50}) mg/l Long term toxicity to fish (28days NOEC) mg/l	LC_{50} > water solubility and therefore is not reliable (study conducted according to the OECD method) No data available	IUCLID
Daphnia Acute toxicity to Daphnia (48hrs EC_{50}) mg/l Long term toxicity to Daphnia (21days NOEC) mg/l	EC50 >1.6 mg/l (Study carried out according to the Directive 92/69/EEC method following GLP and has been validated) No data available	IUCLID
Algae Acute toxicity to algae (72hrs EC_{50}) mg/l	EC50 >1.4 mg/l (Study carried out according to the Directive 92/69/EEC method following GLP and has been validated)	IUCLID

Table4: Aquatic toxicity data available for BEHA.

Step 4: Filling the data gap by using QSAR

In this step the above endpoints (both the available and not) will be predicted using QSARs tools and software listed in step 1 (EPIWIN, Danish(Q)SAR data base and PBT profiler). The reason for doing this is to compare the QSAR results with the experimental one to identify the accuracy of the QSAR.

1- Results obtained by using EPIWIN

Table 5 provides the predicted values for the above endpoints using EPIWIN software along with the name of the programme used. The output obtained by EPIWIN for each end point is given. Also included are explanations which could be obtained by clicking on a link to view.

Required Property	EPI QSAR Programme	Predicted Value
Water solubility	WSKOW (result output)	0.0005452 mg/l at 25 C
Partition coefficient n-octanol/water	KOWWIN	Log K_{ow} = 8.12

Bioconcentration Factor (BCF)	BCFWIN	LogBCF = 1.78 (BCF = 60.52)
Soil Adsorption Coefficient (Koc/Kd)	(PCKOCWIN)	K_{oc} = 4.863E+004
Henry's Law Constant	HENRYWIN	5.16E-005 atm-m^3/mole
Half lives-$t_{1/2}$		
1-Hydrolysis as a function of pH	HYDROWIN	Half-Life at pH 8: 117.423 days Half-Life at pH 7: 3.215 years
2-Photolysis (Atmospheric OH Rate Constant)	AOPWIN	Atmospheric Oxidation Rate Constant = 25.3514E-12 cm^3/molecule-sec Half-Life = 5.03 hrs = 0.422 Days
(Atmosph. Oxidation, Ozone)	AOPWIN	No Ozone Reaction Estimation
Biodegradability		
BIOWIN1	BIOWIN	1.1363 (Biodegrades fast)
BIOWIN2	BIOWIN	0.999 (biodegrades fast)
BIOWIN3 (Ultimate biodegradation)	BIOWIN	3.2573 (Days-weeks)
BIOWIN4 (Primary Biodegradation)	BIOWIN	4.3091 (Hours-Days)
BIOWIN5	BIOWIN	0.8893 (Readily Degradable)
BIOWIN6	BIOWIN	0.9316 (Readily degradable)
BIOWIN7	BIOWIN	0.2582 (Does not biodegrade fast)
Ready Biodegradability Prediction:	BIOWIN	Yes
Environmental Partitioning		
(MacKay)	EPI V3.2 (Results output)	Level III Fugacity Model: Mass Amount (percent) / Half-Life (hr) Air 0.527 / 10.1 Water 5.57 / 208 Soil 31.8 / 416 Sediment 62.1 / 1.87e+003
Fish Acute toxicity to fish (96hrs LC50) mol/l Long term toxicity (28days NOEC) mol/l	ECOSAR	Values are not reliable as the chemical does not fit the model domain (Log Kow>5, 6.4 and 8).
Daphnia Acute toxicity to Daphnia (48hrs EC_{50}) mol/l Long term toxicity (21days NOEC) mol/l	ECOSAR	Values are not reliable as the chemical does not fit the model domain (Log Kow>5, 6.4 and 8).

Algae Acute toxicity to Algae (72hrs EC_{50}) mol/l	ECOSAR	Values are not reliable as the chemical does not fit the model domain (Log Kow>5, 6.4 and 8).

Table5: EPIWIN predictions of the required endpoints.

2- Results obtained from Danish(Q)SAR database

The Danish (Q)SAR report for BEHA is shown below (Figures 1 and 2) with some comments. This output contains predictions for physical-chemical, environmental and human health endpoints, however, as we are only interested in selected physical-chemical endpoints along with the environmental endpoints these are highlighted in yellow or blue in the report. The yellow highlighter identifies the values that have been predicted in the Danish (Q)SAR using the EPIWIN suite and therefore we can check whether the results obtained directly with the EPIWIN suite agree (Table 6). The blue highlighter indicates to the values predicted using other QSAR models such as multicase which is used to predict the biodegradability.

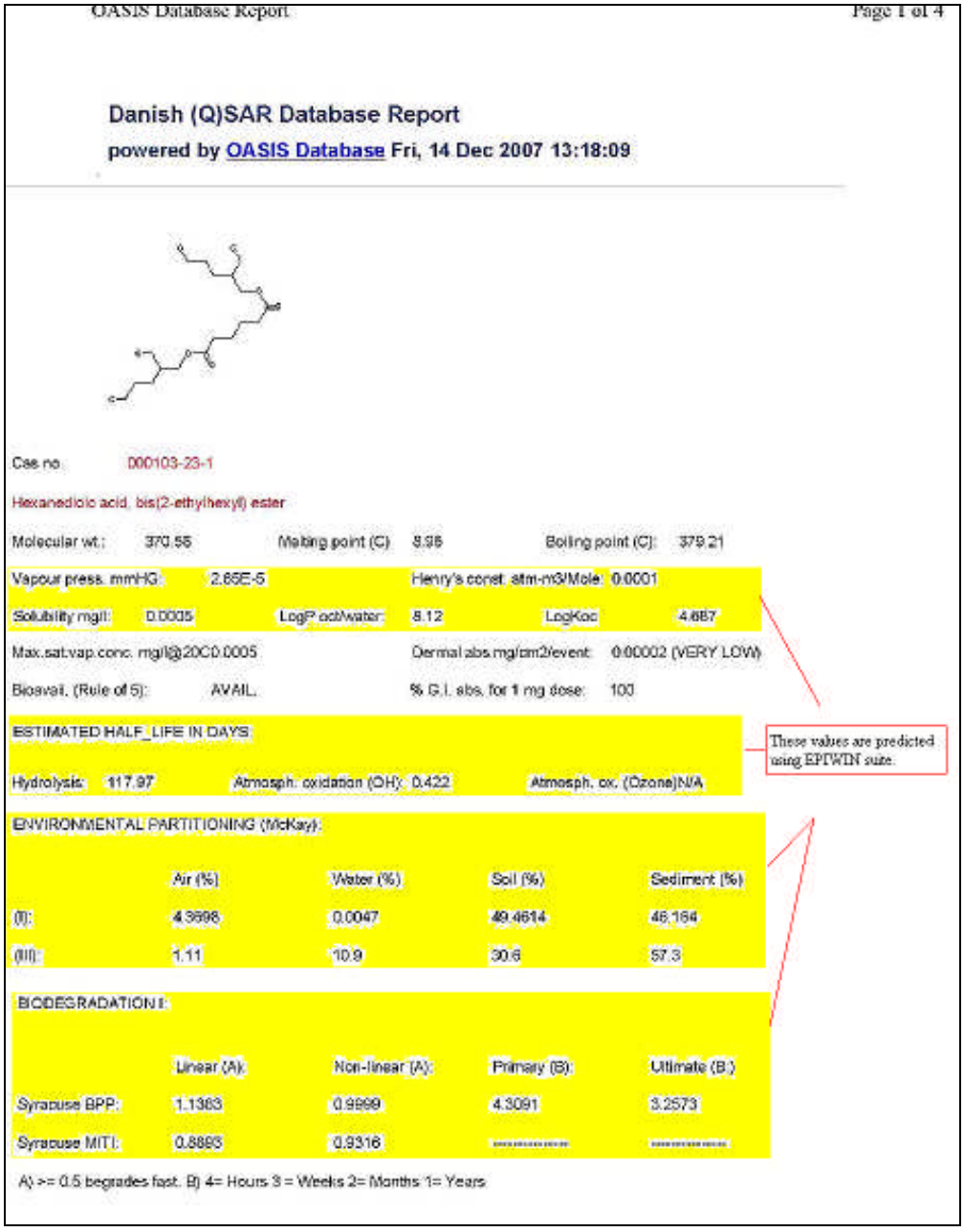


Figure1: Danish(Q)SAR report for BEHA.

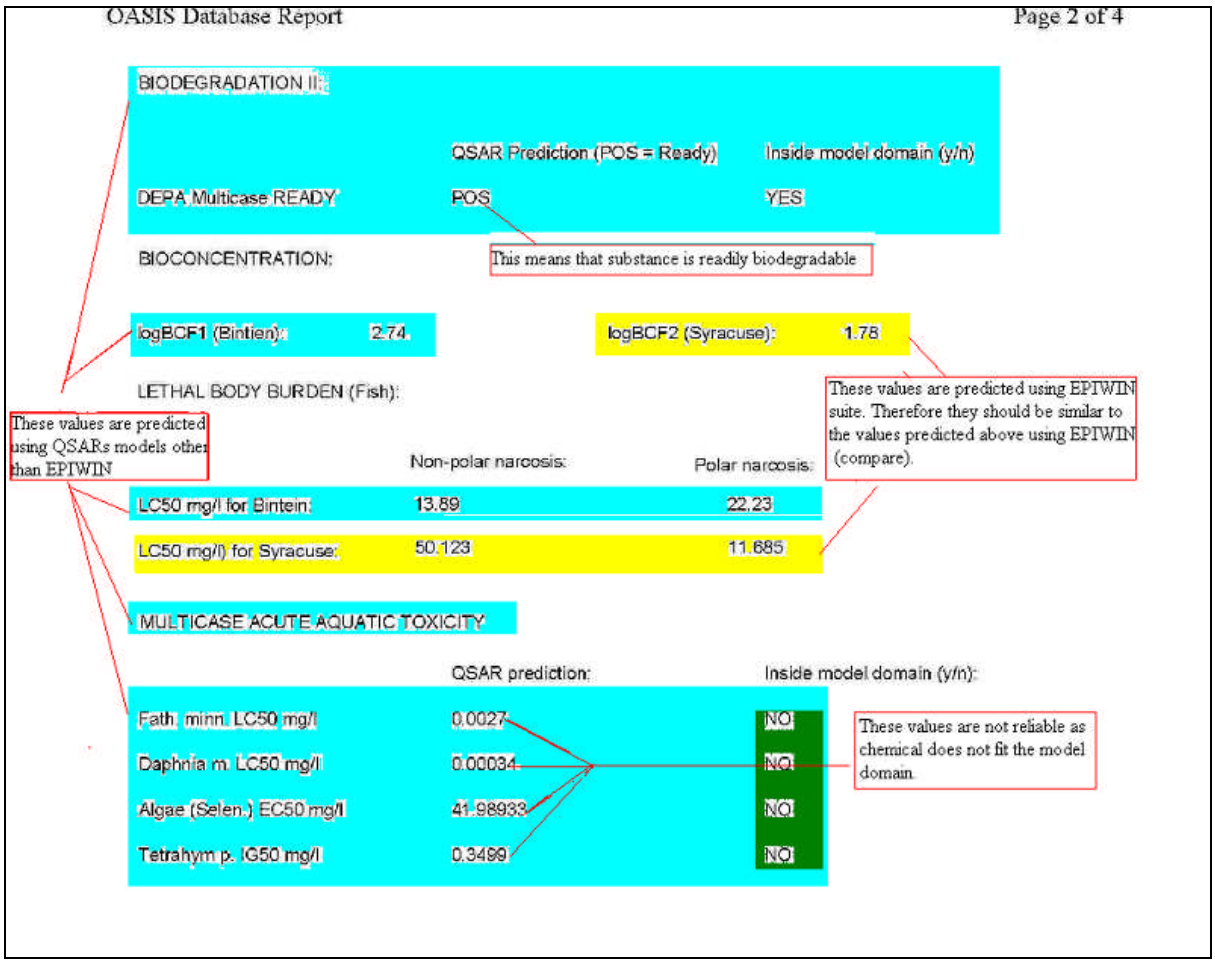


Figure2: Danish(Q)SAR report for BEHA.

Before proceeding to step 5, it is useful to compare the predicted values obtained from EPIWIN with the Danish(Q)SAR database (see Table 6). In this way the reproducibility of EPIWIN predictions can be tested as explained previously.

As expected, we could see that the predictions from the EPIWIN suite are consistent with the one obtained from the Danish(Q)SAR (Log K_{ow}, Log K_{oc} and Henry's Law Constant, see Table 6). Moreover, the predicted parameters from using QSARs other than EPIWIN which are listed in Danish(Q)SAR report are approximately close to EPIWIN estimates. An example for this can be seen in the biodegradability result.

Required Property	Predicted Value using Danish(Q)SAR database	Predicted Value using EPIWIN	Experimental or found Value
Water solubility	0.0005 mg/l at 25 C	0.0005452 mg/l at 25 C	Insoluble
Partition coefficient n-octanol/water	Log K_{ow} = 8.12	Log K_{ow} = 8.12	Log K_{ow} = 8.114 (calculated)
Bioconcentration Factor (BCF)	LogBCF (Syracuse) = 1.78 LogBCF (Bintien) = 2.74	LogBCF = 1.78 (BCF = 60.52)	
Soil Adsorption Coefficient (Koc/Kd)	K_{oc} = 4.863E+004	K_{oc} = 4.863E+004	Koc = 49,000 (EST)
Henry's Law Constant	0.0001 atm-m^3/mole	5.16E-005 atm-m^3/mole	4.34E-07 at 20 ^{0}C (EXP)
Half lives-$t_{1/2}$			
1-Hydrolysis as a function of Ph	Half-Life at pH 8: 117.423 days	Half-Life at pH 8: 117.423 days Half-Life at pH 7: 3.215 years	half-lives of 3 years and 120 days at pH values of 7 and 8, respectively. (EST)
2-Photolysis (Atmospheric OH Rate Constant)	Atmospheric Oxidation Rate Constant = 25.3514E-12 cm^3/molecule-sec Half-Life = 5.03 hrs = 0.422 Days	Atmospheric Oxidation Rate Constant = 25.3514E-12 cm^3/molecule-sec Half-Life = 5.03 hrs = 0.422 Days	Rate Cons = 45.8X10-12 cm3/molecule-secc (EST)
(Atmosph. Oxidation, Ozone)	No Ozone Reaction Estimation	No Ozone Reaction Estimation	No measured data are available.
Biodegradability			
BIOWIN1	1.1363 (Biodegrades fast)	1.1363 (Biodegrades fast)	
BIOWIN2	0.999 (biodegrades fast)	0.999 (biodegrades fast)	
BIOWIN3 (Ultimate biodegradation)	3.2573 (Days-weeks)	3.2573 (Days-weeks)	
BIOWIN4 (Primary Biodegradation)	4.3091 (Hours-Days)	4.3091 (Hours-Days)	
BIOWIN5	0.8893 (Readily Degradable)	0.8893 (Readily Degradable)	
BIOWIN6	0.9316 (Readily degradable)	0.9316 (Readily degradable)	
BIOWIN (Ready Biodegradability Prediction)	Yes	Yes	Biodegrade fast
Multicase (Ready Biodegradability Prediction)	Yes		

Environmental Partitioning			
(MacKay, (III))	Level III Fugacity Model: Mass Amount (percent) Air 1.11 Water 10.9 Soil 30.6 Sediment 57.3	Level III Fugacity Model: Mass Amount (percent) Half-Life (hr) Air 0.527 10.1 Water 5.57 208 Soil 31.8 416 Sediment 62.1 1.87e+003	No measured data are available.
Fish Acute toxicity to fish (96hrs LC_{50}) mol/l Long term toxicity (28days NOEC) mol/l	Values are not reliable as the chemical outside the model domain	Values are not reliable as the chemical does not fit the model domain (Log Kow>5, 6.4 and 8).	not reliable as > water solubility
Daphnia Acute toxicity to Daphnia (48hrs EC_{50}) mol/l Long term toxicity (21days NOEC) mol/l	Values are not reliable as the chemical outside the model domain	Values are not reliable as the chemical does not fit the model domain (Log Kow>5, 6.4 and 8).	not reliable as > water solubility
Algae Acute toxicity to Daphnia (72hrs EC_{50}) mol/l	Values are not reliable as the chemical outside the model domain	Values are not reliable as the chemical does not fit the model domain (Log Kow>5, 6.4 and 8).	not reliable as > water solubility

Table 6: Comparison between the results obtained from EPIWIN, Danish(Q)SAR and the experimental one.

Step 5: Assess your substance to identify whether it is PBT or vPvB

Is your substance persistent? (Degradation properties)

The assessment of persistence is based on the degradation (biotic and chemical) and half life data available. Where no measured environmental degradation data are available, the predicted one can be used as a screen to indicate persistence.

With regard to the chemical degradation, the predicted rate constant and estimated half-life for the reaction of hydroxyl radicals with BEHA in the atmosphere indicated that when it is released to the atmosphere is likely to be **degraded** (not persistence) by this fate process. Moreover, if released in water, Bis(2-ethylhexyl) adipate is expected to undergo hydrolysis due to the presence of hydrolyzable functional groups. Estimated hydrolysis half-lives are 3 years and 120 days at pH values of 7 and 8, respectively. The PBT Profiler has estimated that BEHA is expected to be found predominantly in sediment and its persistence estimate is based on its transformation in this medium. Its half-life in sediment, 78 days, does not exceed the EU criteria of 180 days but exceeds the EPA criteria of >=2 months). As expected, this result is

similar to EPIWIN v3.2 estimate for Level III Fugacity Model (since PBT profile uses EPIWINV3.2 for this). Therefore, BEHA is estimated not to be persistent in the environment.

With regard to the biotic degradation assessment, the ready biodegradability result can be used to determine if a substance meets the P criteria. Based on the biodegradability screening tests available (MITI), BEHA is considered to be readily biodegradable. This is in agreement with both, BIOWIN v4.02 and multicase estimates which give an overall prediction that the substance is **readily biodegradable**.

As a conclusion, based on the degradation and half life data (measured or estimated by PBT profile and EPIWIN), BEHA is considered not to meet the screening criteria for persistence based on the EU criteria.

Is your substance bioaccumlative?

According to HSDB result bioaccumulation of Bis(2-ethylhexyl) adipate was studied with blue-gill fish. The whole-fish BCF observed from this study was 27. This value is considered to give sufficient evidence on a very low bioaccumulation of BEHA.

In addition, BCFWIN v2.17 predicts BCF of 60 (<2000) based on logKow of 8.12. Again this value does not exceed the EU bioconcentration criteria.

Based on the above, BEHA is not expected to bioaccumulate in the food chain and therefore is not considered to meet the screening criteria for bioaccumulation.

Is your substance toxic to the environment organisms?

From the data provided in the IUCLIDs, only the acute toxicity values EC_{50} to Daphnia and algae seem reliable. They are EC_{50}(48h) of 1.6 mg/l for Daphnia and EC_{50}(72hrs) of 1.4 mg/l for Algae. These values are above 0.1mg/l. It is therefore considered reasonably to conclude that the EU criteria for toxicity are not met. However based on the available QSAR data, it was not possible to conclude if the EU

criteria for toxicity are met or not. This is because ECOSAR v0.99 predictions are not reliable as the chemical does not fit the model domain (Log Kow>5, 6.4 and 8) while PBT profiler was unable to estimate the toxicity of Bis(2-ethylhexyl) adipate..

In conclusion, based on the available data, BEHA is not considered fulfilling the T screening criterion according to the EU criteria.

Is your chemical classified as potential PBT?

Based on the predictions data, the substance has been shown to be readily biodegradable and not persistent. In addition, both the estimated and measured BCF for the substance in fish are far below 2000. Therefore the substance does not fulfil the B-criterion. The available aquatic toxicity data for BEHA are clearly above 0.1mg/l, therefore the substance does not fulfil the T-criterion.

Therefore on the basis of the predictions data the substance should not be considered as a potential PBT substance according to the EU criteria. However, the substance should be considered as a potential P under EPA.

What is the preferred environmental compartment of your chemical? (Environmental Distribution)

Adsorption:

According to Mackay level III predictions both the soil and sediment are the preferred environmental compartment (31% and 62%) for BEHA. As the substance has a high K_{oc} value of 4.863E+004 when it is released to soil, is expected to be immobile. Therefore the persistence of BEHA in soil is so significant.