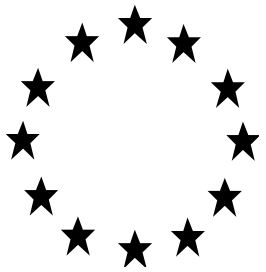
Competent Authority Report

Programme for Inclusion of Active Substances in Annex I to Council Directive 98/8/EC



Amines, N-C10–C16-alkyltrimethylenedi-, reaction products with chloroacetic acid; Ampholyt (PT 2, 3, 4)

CAS-No. 139734-65-9

DOCUMENT IIIA (A1-A3)

Evaluation Report

Rapporteur: Ireland

April 2015

Ampholyt (PT2, 3, 4)

Document A1-A3

CONTENTS

Section A1 Annex Point IIA1	Applicant	
Applicant	**Name:**	Evonik Industries AG
	Address:	Rodenbacher Chaussee 4 63457 Hanau-Wolfgang Germany [redacted]
Manufacturer of Active Substance (if different)	As given in Section A1.1 above.	
Manufacturer of Products (if different)	As given in Section A1.1 above.	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16/07/2013
Materials and Methods	**X – 1.1 Applicant** Since the submission of the dossier for Ampholyt 20, there have been several administrative and organisational changes. The initial submission of the dossier was submitted on behalf of the applicant "Goldschmidt GmbH" in July 2007. Goldschmidt was later taken over by "Evonik", who in turn modified their organisational structure after the Goldschmidt take-over. As a result, the first amendment to the dossier (February 2009) was therefore submitted on behalf of "Evonik Goldschmidt GmbH", and a second amendment (April 2012) on behalf of "Evonik Industries AG".
Results and discussion	Evonik Industries AG is the correspondence address and the contact person belongs to this legal entity. Furthermore he has full power of attorney for the other legal entity Evonik Goldschmidt GmbH. Therefore the following contact details are correct: **Name:** Evonik Industries AG **Address:** Rodenbacher Chaussee 4 63457 Hanau-Wolfgang Germany [redacted] The contact details for the legal manufacturing facility: **Name:** Evonik Goldschmidt GmbH **Address:** Goldschmidtstraße 100 45127 Essen Germany
Conclusion	The current name of the applicant is Evonik Industries AG. The contact details for the manufacturing facility refer to Evonik Goldschmidt GmbH.
Reliability	1
Acceptability	Acceptable
Remarks	No further information required under Section A1 (1.1 – 1.3).
	COMMENTS FROM
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Section A2
Annex Point IIA2

Identity of Active Substance

		Official use only
Common name (IIA2.1)	Ampholyt 20 *Remark:* The active substance as manufactured is obtained as a "product-by-process", resulting in an aqueous solution containing 20% (w/w) active ingredient. The trade names of this product are "Ampholyt 20" or "TEGO 2000" and "TEGOL 2000". Pure, water-free active substance is usually not available. For the purpose of physical-chemical characterisation of the active itself, however, a small quantity was purified by lyophilisation. This purified active substance is termed Ampholyt 20/100, to discriminate the purified active substance from the active as manufactured. Since the 20 % aqueous solution (product-by-process) constitutes the active substance as manufactured and marketed, the data used in this dossier were typically generated using "Ampholyt 20", i.e. the a.s. as manufactured, except where explicitly indicated otherwise, e.g. physicochemical tests and a limited number of (eco-) toxicological investigations. Endpoints are, however, given in terms of active substance, i.e. excluding water.	
Chemical name (IIA2.2)	Amines, N-C_{10}–C_{16}-alkyltrimethylenedi-, reaction products with chloroacetic acid	X
Manufacturer's development code number(s) (IIA2.3)	None	
CAS No and EC numbers (IIA2.4)		
CAS-No	139734-65-9	X
EC-No	None assigned	
Other	None assigned	
Molecular and structural formula, molecular mass (IIA2.5)		
Molecular formula	Not applicable	
Structural formula	[redacted] Note: The above structural formulas cover the majority of species in the UVCB substance. All of these species are in a thermodynamic equilibrium with their protonated forms. The pH of the solution in water is approximately around 8 – 8.5 in the presence of acetic acid and hydrochloride which is being released from chloroacetic acid after the reaction with the primary and secondary amines.	X
Molecular mass	280.79 g/mol (average weighted molecular mass)	X

Section A2 Annex Point IIA2	Identity of Active Substance	
		Official use only
Method of manufacture of the active substance (IIA2.6)	The information on the method of manufacture is considered to be a trade secret of Goldschmidt and therefore claimed to be CONFIDENTIAL. Thus, the manufacturing process is summarised in Appendix 1 to Document III-A (confidential information).	
Specification of the purity of the active substance, as appropriate (IIA2.7)	The information on the specification of the purity is considered to be a trade secret of Goldschmidt and therefore claimed to be CONFIDENTIAL. Thus, the specification is summarised in Appendix 1 to Document III-A (confidential information).	X
Identity of impurities and additives, as appropriate (IIA2.8)	See Annex Confidential Data and Information.	X
The origin of the natural active substance or the precursor(s) of the active substance (IIA2.9)	See Annex Confidential Data and Information.	

	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	

EVALUATION BY RAPPORTEUR MEMBER STATE (*)

Date

16/07/13

Materials and Methods

X - Chemical name:

Ampholyt 20 is best described as a UVCB (Substances of Unknown or Variable composition, Complex reaction products or Biological materials).

The RMS considers that Ampholyt 20 is best described as a UVCB for two reasons:

(1) The number of constituents is relatively large and
(2) The variability of composition is relatively large.

It was decided during APCP WG III 2014, that the current name that is being used by the applicant remains applicable:
"Amines, N-C10-C16-alkyltrimethylenedi- reaction products with chloroacetic acid".
The WG members agreed that the current chemical name that is being used by the applicant is more descriptive than the name that would apply if REACH was strictly applied. The meeting also noted that the current chemical name is only a very slight deviation with respect to the naming proposal according to REACH.

X – CAS and EC numbers:

It was decided during APCP WG III 2014, that the current CAS name for Ampholyt 20 should continue to apply. Requesting another CAS number for exactly the same chemical substance would cause confusion and unnecessary market disturbance on a global basis.

X – Structural formula:

The structures provided by the applicant above are considered to be the „major components" of Ampholyt 20, however Ampholyt 20 also contains „minor components" which have been identified in the 7-batcha analysis. It is important to note that the sum of the „minor components" account for < 2% of the total active ingredient. The structures for the „minor components" are provided below for completeness:

X - Molecular mass:

It should be noted that it is not possible to provide an accurate molecular mass for Ampholyt 20 as it consists of *ca.* 20+ individual components with varying molecular weights.
However, the applicant calculated a "weighted average" molecular mass for Ampholyt 20 in their dossier on the basis of 7-batch analysis results (average % w/w values for the individual components) and the individual molecular weights of the components making up Ampholyt 20. The weighted mean value of 280.79 g/mol was calculated.
However, it is acknowledged that the specification of a weighted molecular mass for

UVCB provides little practical relevance or information since UVCB substance by their nature have a variable composition.

X - Specification of the purity of the active substance, as appropriate:
There are two main issues to consider in relation to the specification of the active substance:

(1) Minimum purity of "total active ingredient" &
(2) Minimum and maximum concentration range for individual components making up the "total active ingredient".

Minimum purity of total active ingredient:
The active ingredient includes everything identified in the final reaction product.

The applicant and RMS have agreed on the following purity values for active ingredient:

Aqueous Ampholyt 20:
Average = 19.0% w/w
Mean – 3sd = 16.0% w/w
Mean + 3sd = 22.0% w/w

Dry Ampholyt 20 (20/100):
APCP WG III 2014 decided that the min. purity for Ampholyt 20 in the Inclusion Regulation should be min. 100% w/w.

Note in relation to aqueous Ampholyt specification proposals:
It should be noted that components of the active ingredient having a C10 carbon chain length were not analysed in the supporting 7-batch analysis and have not been taken into account in the aqueous Ampholyt specification proposals above. The specification proposals above assume that the C10 components are not present in aqueous Ampholyt 20. The applicant stated that they did not analyse the 7-batches of aqueous Ampholyt 20 for C10 components because the raw material used in the synthesis of the 7-batches had a very low C10 content at that time. The 7 batch analysis of aqueous Ampholyt 20 was completed in May 2007.
However, the applicant stated in June 2013 that an analysis of 60 samples of raw starting material between June 2007 and May 2013 indicated the following % C-chain distribution:

		C_{10}	C_{12}	C_{14}	C_{16}
Avg		0,4	71,9	22,5	1,0
Std Dev		0,6	1,8	1,0	0,6
Min		0,1	68,4	20,1	0,1
Max		4,0	76,6	24,0	2,7

The analytical results from the 60 batches of starting material indicates that C10 contributes to a maximum of 4% of the c-chain distribution of the starting material.

The applicant has proposed specification values for the C10 components in aqueous Ampholyt 20 by using the C-chain distribution results from the starting material.
The applicant assumed the following when proposing specification values for the C10 components in aqueous Ampholyt 20:

(1) An average level of 0.4% C10 was assumed to be present in Ampholyt 20 (aqueous) technical and
(2) 0.4% is distributed evenly between C10-PDA and the sum of C10-Gly components - 0.2% each for C10-PDA and the sum of C10-Gly components in Ampholyt 20 (aqueous) technical.

The applicant calculated the following results for C10 in Ampholyt 20 (aqueous):

Synonym	Mean % w/w	S.D.	3S.D.	Mean-3SD % w/w	Mean+3SD % w/w
[redacted]	0.2	0.06	0.19	0.01	0.39
[redacted]	0.2	0.07	0.2	0	0.4

The RMS does not know how the applicant calculated the S.D. for the C10 components. The applicant should explain how they calculated the S.D. for the C10 components.

The RMS considers that it would be more appropriate to use the S.D. (0.6) from the raw material results when calculating the Mean -3SD and Mean + 3SD values for the C10 components:

Synonym	Mean % w/w	S.D.	3S.D.	Mean-3SD % w/w	Mean+3SD % w/w
[redacted]	0.2	0.6	1.80	0	2.0
[redacted]	0.2	0.6	1.80	0	2.0

It is reasonably safe to assume that the C10 values calculated by the RMS will be much greater than the C10 levels that are actually in Ampholyt 20 (aqueous).

The RMS considers that the applicant should analyse at least 5-batches of Ampholyt 20 (aqueous) for C10 components so that their specification values for C10 can be confirmed – the C10 components are part of the active substance and could potentially have a bearing on the minimum specification level of active ingredient in Ampholyt 20.

The RMS also notes that the applicant needs to identify the methods of analysis that were used for raw material analysis – the methods of analysis should be fully validated if they are going to be used to set technical specification valules for C10 which in turn will have an impact on the overall active ingredient content.

The applicant has subsequently confirmed that they intend to carry out a batch analysis for C10 components in Ampholyt 20. The results of this analysis should be provided to the RMS at least 6 months before the date of entry into force.

It is noted by the RMS that the applicant has not referred to the C16-diGly components in either their technical specification or their supporting 7-batch analysis report, however it can be assumed that the sum of C16-diGly components are only expected to contribute to no more than 1% of the total active ingredient in Ampholyt 20.
The applicant included C16-PDA and "C16-Gly as sum" in their 7-batch analysis and specification. "C16-Gly as sum" is the sum of the structural isomers N-C16-Gly and N'C16-Gly.

X - Identity of impurities and additives, as appropriate:
A UVCB substance can be described as a reaction product between two or more reactants. UVCB substances do not differentiate between major constituents, minor constituents or impurities according to REACH guidance – UVCB substances do not contain impurities in the classical sense of the word.

Results and discussion	APCP WG III 2014 decided that the min. purity for Ampholyt 20 in the Inclusion Regulation should be min. 100% w/w. The specification values for total active ingredient in aqueous Ampholyt 20 are considered acceptable pending verification of the C10 content (% w/w) in the final product: Average = 19.0% w/w Min. = 16.0% w/w (Mean – 3sd). Max. = 22.0% w/w (Mean + 3sd) APCP WG III 2014 decided that the minimum purity of the dry Ampholyt (100% w/w) will be the minimum purity included in Inclusion Regulation.
Conclusion	Further clarifications are required in relation to the C10 content in aqueous Ampholyt 20.
Reliability	2
Acceptability	Acceptable pending clarification of C10 content in aqueous Ampholyt 20.
Remarks	Further clarity required from the applicant. The results of this analysis should be provided to the RMS at least 6 months before the date of entry into force.
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Melting point, boiling point, relative density (IIA3.1)								
Melting point	EC method A.1 (92/69/EEC) OECD guideline 102 (1995) Differential scanning calorimetry (DSC)	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	No melting or freezing point, considered as amorphous solid (solidified melt). Liquefied under decomposition at 140–145°C.	Key study	Y	1	**A3.1.1/01:** [redacted] Ampholyt 20/100 ES64A25143 Melting Point A.1. (OECD 102) Boiling Point A.2. (OECD 103), Siemens AG, Frankfurt a. M., Germany, report no. 20050230.01, June 20, 2005 (unpublished).	X
Boiling point	EC method A.2 (92/69/EEC) OECD guideline 103 (1995) Differential scanning calorimetry (DSC)	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	No boiling point at atmospheric pressure, since the test item decomposed first (approx. at 145°C).	Key study	Y	1	Cross-reference: **A3.1.1/01**	X
Bulk density/ relative density	EC method A.3 (92/69/EEC) OECD guideline 109 (1995) Air comparison pycnometer for solids	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99%	$D_4^R = 1.03$	Key study	Y	1	**A3.1.3/01:** [redacted] Ampholyt 20/100 ES64A25143 Relative Density A.3. (OECD 109), Siemens AG, Frankfurt a. M., Germany, report no. 20050230.02, June 20, 2005 (unpublished).	X

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Vapour pressure (IIA3.2)	EC method A.4 (92/69/EEC) OECD guideline 104 (1995) Effusion method	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99%	Measurements carried out above 34°C to 94°C. The calculated vapour pressure values are extrapolated: p (20°C) = 1.9×10^{-4} Pa p (25°C) = 4.0×10^{-4} Pa p (50°C) = 1.0×10^{-2} Pa	Key study	Y	1	**A3.2/01:** [redacted] Ampholyt 20/100 ES64A25143 Vapour Pressure A.4. (OECD 104), Siemens AG, Frankfurt a. M., Germany, report no. 20050230.03, June 20, 2005 (unpublished).	X
Henry's Law Constant	Calculation based on vapour pressure (p) and water solubility (c) $H = \frac{p \cdot MW}{c}$	Not applicable (calculation)	$H = 2.67 \cdot 10^{-7} \frac{Pa \cdot m^3}{mol}$		n.a.	0 (model calculation)	**A3.2.1/01:** [redacted] Calculation of Henry's law constant of Ampholyt 20. EBRC Consulting GmbH, Hannover, Germany, Report no. GOL-070417-01, June 2007 (unpublished)	X
	QSAR model calculation by bond contributions using program HENRYWIN (U.S. EPA)	Not applicable (model calculation)	It can be summarised briefly that for the bulk of the components, this value was clearly below that of water, so that all components and thus also the product Ampholyt 20 itself may be considered as essentially non-volatile form aqueous solution/media.		n.a.	0 (model calculation)	**A3.2.1/02:** [redacted] Model calculation of Henry's law constant of Ampholyt 20. EBRC Consulting GmbH, Hannover, Germany, Report no. GOL-070606-01, June 2007 (unpublished)	
Appearance (IIA3.3)								

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex point)	Method/ Guideline	Purity/ Specification	Results	Remarks/Justification	GLP (Y/N)	Reliability	Reference	Official use only
Physical state	Visual inspection	Specification as given in Section A2	Ampholyt 20/100 solid Condition at 20 °C, 101,3 kPa: sticky, agglomerated		N	1	**A3.3.1/01:** [redacted] Determination of the appearance of Ampholyt 20/100. EBRC Consulting GmbH, Hannover, Germany, Report no. DEG-20060922-01, Sept 2006 (unpublished)	
	Visual inspection	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	**Ampholyt 20/100:** solid For the physical-chemical characterisation Ampholyt 20 was purified and called Ampholyt 20/100.		Y	1	Cross-reference: **A3.4.1/01**	
		Purity: 20 % of the pure active (≥ 99 %) in water.	**Ampholyt 20:** liquid The active substance as manufactured is obtained as a "product by process", resulting in an aqueous solution containing 20% (w/w) active ingredient and called Ampholyt 20.		Y	1	Cross-reference: **A3.4.1/01**	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex point)	Method/ Guideline	Purity/ Specification	Results	Remarks/Justification	GLP (Y/N)	Reliability	Reference	Official use only
Colour	Visual inspection	Specification as given in Section A2	Ampholyt 20/100 solid Colour at 20 °C, 101,3 kPa: white to light yellow (at diffused daylight)		N	1	Cross-reference: **A3.3.1/01:**	
	Visual inspection	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	**Ampholyt 20/100:** white For the physical-chemical characterisation Ampholyt 20 was purified and called Ampholyt 20/100.		Y	1	Cross-reference: **A3.4.1/01**	
	Visual inspection	Purity: 20 % of the pure active (≥ 99 %) in water.	**Ampholyt 20:** light yellowish The active substance as manufactured is obtained as a "product by process", resulting in an aqueous solution containing 20% (w/w) active ingredient and called Ampholyt 20.		Y	1	Cross-reference: **A3.4.1/01**	
Odour	Olfactory assessment	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	**Ampholyt 20/100:** product-specific For the physical-chemical characterisation Ampholyt 20 was purified and called Ampholyt 20/100.		Y	1	Cross-reference: **A3.4.1/01**	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex point)	Method/ Guideline	Purity/ Specification	Results	Remarks/Justification	GLP (Y/N)	Reliability	Reference	Official use only
	Olfactory assessment	Purity: 20 % of the pure active (≥ 99 %) in water.	**Ampholyt 20:** slight, typical The active substance as manufactured is obtained as a "product by process", resulting in an aqueous solution containing 20% (w/w) active ingredient and called Ampholyt 20.		Y	1	Cross-reference: **A3.4.1/01**	
	Olfactory assessment	Specification as given in Section A2	**Ampholyt 20/100:** solid Odour at 20 °C, 101.3 kPa: faint, ammonia-like		N	1	Cross-reference: **A3.3.1/01**	
Absorption spectra (IIA3.4)								X
UV/VIS	OECD guideline 101 (1981)	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	Molar absorption coefficient ε (290 nm): pH < 2: 4.4 L $mol^{-1}cm^{-1}$ pH 5: 2.8 L $mol^{-1}cm^{-1}$ pH 7: 2.2 L $mol^{-1}cm^{-1}$ pH 9: 3.0 L $mol^{-1}cm^{-1}$ pH > 12: 2.8 L $mol^{-1}cm^{-1}$ Graphical presentations are given in Figure A3- 1 to Figure A3- 5.	Key study	Y	1	**A3.4.1/01:** [redacted] Determination of spectral properties of Ampholyt 20/100, Aqura GmbH, Marl, Germany, August 22, 2006 (unpublished).	
IR	Guideline: not applicable Method: Infrared spectroscopy	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	The IR spectrum is in accordance with the proposed structure of the test item. A graphical presentation of the IR spectrum is given in Figure A3- 6	Key study	N	1	Cross-reference: **A3.4.1/01**	

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
^{1}H-NMR	Guideline: not applicable Method: ^{1}H-NMR spectroscopy	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	The ^{1}H-NMR spectrum of the test item is in accordance with the proposed structure of the test item. Mean carbon chain length of the alkyl group: 12.5 [R = $CH_3(CH_2)_{11.5}$] A graphical presentation of the ^{1}H-NMR spectrum is given in Figure A3- 7.	Key study	N	1	Cross-reference: **A3.4.1/01**	
^{13}C-NMR	Guideline: not applicable Method: ^{13}C-NMR spectroscopy	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	The ^{13}C-NMR spectrum is in accordance with the proposed structures of the test item. The quantitative composition was determined and is presented in Table A3- 1. A graphical presentation of the ^{13}C-NMR spectrum is given in Figure A3- 8.	Key study	N	1	Cross-reference: **A3.4.1/01**	
MS	Guideline: not applicable Method: LC-MS	Specification as given in Section A2 Batch no.: ES00056A06 Expiry date: October 30, 2007 Purity: ≥ 99 %	The MS spectrums are in accordance with the components of the test item. Graphical presentations of the MS spectrums are given in Figure A3- 9 till Figure A3- 21.	Key study	N	1	**A3.4.4/01:** [redacted] Test report no. A070012787 according to DIN EN ISO/IEC 17025, AQura GmbH, Hanau, Germany, June 27, 2007 (unpublished).	

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Solubility in water (IIA3.5)	Non-guideline method: The product "Ampholyt 20", constituting an aqueous solution of the pure active substance, was freeze-dried and the mass of the residue determined gravimetrically.	Specification as given in Section A2 for the active substance as manufacture Batch no.: 17 EM 17	> 20.83 % (m/m) (≥ 200 g/L)	In view of the fact that the active substance as manufactured constitutes an aqueous solution as a "product by process" which is identical to the biocidal product, the chosen method is considered to be fully justified.	Y	4	**A3.5/01:** [redacted] Determination of physico-chemical properties of TEGO 2000. Infracor GmbH, Marl, Germany, Report no. AN-ASB 0198, April 04, 2002 (unpublished).	X

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
(3.5 continued…)				Although the above study was not conducted according to guideline EEC A.6, it is nevertheless established without reasonable doubt that the a.s. is soluble in water at concentrations of at least 200 g/l. Determination of a more accurate figure would be entirely immaterial for the risk assessment. Thus, the conduct of a water-solubility study following EEC A.6 would not provide a relevant contribution to the existing knowledge and is therefore considered to be scientifically unjustified.				
Dissociation constant (-)				The determination of the dissociation constant is technically not feasible in view of the detergent nature of this complex aqueous mixture, in which individual components are soluble in water.Sol				X

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Solubility in organic solvents, including the effect of temperature on solubility (IIIA3.1)	CIPAC Handbook Volume H (1998), MT 181	Specification as given in Section A2 Batch no.: ESL00S4B05 Expiry date: June, 12 2007 Purity: 99 %	The solubility of Ampholyt 20/100 in methanol was determined to be 33–40 g/L (10°C), 40–50 g/L (20°C) and 160–200 g/L (30°C), respectively. In n-heptane, p-xylene, 1,2-dichloroethane, acetone and ethyl acetate the solubility was classified as < 10 g/L at the tested temperatures.	Key study	Y	1	**A3.7/01:** [redacted] Ampholyt 20/100, Solubility in organic solvents. Dr. U. Noack-Laboratorien, Sarstedt, Germany, Report no. CLS117241, July 18, 2007 (unpublished).	X
Stability in organic solvents used in b.p. and identity of relevant breakdown products (IIIA3.2)				According to the TNsG, such data are only required if organic solvents are included in the biocidal product. Since the biocidal products do not contain organic solvents, data on stability in organic solvents are not considered to be required.				

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Partition coefficient n-octanol/water (IIA3.6)	EC method A.8 – Shake flask method –	Specification as given in Section B2 Batch no.: 490486 Expiry date: not applicable Purity: 100 %	log Pow, estimate ≤ - 0.76 (25°C)	The test substance is an amphoteric surfactant. The methods to determine the partition coefficient described in Directive 92/69/EC A.8 are not applicable to surface-active materials. Furthermore, since Ampholyt 20 is not a pure substance, but a complex mixture, this parameter cannot be determined experimentally on a scientifically valid basis.	Y	4	**A3.9/01:** [redacted] The partition coefficient n-octanol/water of TEGO 2000, TNO Prins Maurits Laboratory, AA Rijswijk, The Netherlands, report no.: 213194726a, December 1994 (unpublished)	
	QSAR model calculation by bond contributions using program KOWWIN (U.S. EPA)	Not applicable (model calculation)	log Pow 3.81 at 25°C (QSAR estimate, weighted average)		n.a.	0 (model calculation)	**A3.9/02:** [redacted] Model calculation of partition coefficient of Ampholyt 20. EBRC Consulting GmbH, Hannover, Germany, Report no. GOL-070524-01, July 2007 (unpublished)	X

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Thermal stability, identity of relevant breakdown products (IIA3.7)	OECD 113 Differential scanning calorimetry (DSC)	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	The DSC-measurement in the closed glass crucible showed no exothermal effect in the temperature range of 25–400 °C. Thus, the substance is considered to be stable.		Y	1	Cross-reference: **A3.1.1/01**	X
Flammability, including auto-flammability and identity of combustion products (IIA3.8)	Flammability: EC method A.10 Auto-flammability: EC method A.16	Specification as given in Section A2 Batch no.: ES64A25143 Expiry date: October 30, 2007 Purity: 99 %	*Flammability:* Not flammable; the test item melted in the preliminary test. *Auto-flammability:* Not auto-flammable; no exothermal reaction up to the maximum test temperature of 402°C.	Key study	Y	1	**A3.11/01:** [redacted] Ampholyt 20/100 ES64A25143 Flammability (solids) A.10 Auto-Flammability A.16 (solids-determination of relative self-ignition temperature), Siemens AG, Frankfurt a. M., Germany, report no. 20050230.04, June 20, 2005 (unpublished).	X

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Flammability in contact with water				Experimental data are not submitted since these are considered to be scientifically unjustified: From the structural formula and the composition of the substance it can be safely concluded that the substance does not evolve any flammable gases in contact with water or humid air. In particular, since the a.s. as manufactured is obtained as a “product-by-process” in the aqueous phase, any flammability in contact with water can be safely excluded.				X

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Pyrophoric properties				Experimental data are not submitted since these are considered to be scientifically unjustified: From the structural formula and the composition of the substance, as well as from experience in use over decades, it can be safely concluded that the substance is stable in air at room temperature and is not pyrophoric.				
Flash-point (IIA3.9)				A test on this endpoint must be provided for liquids whose vapours can be ignited; this does not apply to Ampholyt 20/100, which is a solid.				X

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Surface tension (IIA3.10)	EC method A.5 (1992), OECD 115 (1995)	Specification as given in Section B2 Batch no.: S9B10B Expiry date: 01 December 2002 Purity: 100%	The surface tension of 1.004 g TEGO 2000/L (0.2008 g active ingredient/L) was 27.2 mN/m; it is considered to be a surface active material	The surface tension should be measured using an aqueous solution of sufficient concentration such that any surface activity potential is expressed. In view of the fact that the active substance as manufactured constitutes an aqueous solution as a "product by process" which is identical to the biocidal product, the chosen method is considered to be fully justified.	Y	1	**A3.13/01:** [redacted] Determination of the surface tension of an aqueous solution of TEGO 2000. NOTOX B.B. 's-Hertogenbosch, The Netherlands, report no. 283444, March 31, 2000 (unpublished).	
Viscosity (-)				The substance Ampholyt 20/100 is solid, which is why viscosity cannot be determined. Thus, this data requirement is not applicable.				X
Explosive properties (IIA3.11)	Benson`s method of group additivity using program CHETAH (ASTM; 2001)	Not applicable (model calculation)	Structural aspects and estimated thermodynamic properties indicate that Ampholyt 20 must not be considered to have explosive properties.		n.a.	0 (model calculation)	**A3.15/01:** [redacted] Explosive properties of Ampholyt 20/100; Expert statement. EBRC Consulting GmbH, Hannover, Germany, Report no. GOL-070713/01, July 2007 (unpublished)	

Section A3	Physical and Chemical Properties of Active Substance							
Subsection (Annex point)	**Method/ Guideline**	**Purity/ Specification**	**Results**	**Remarks/Justification**	**GLP (Y/N)**	**Reliability**	**Reference**	Official use only
Oxidizing properties (IIA3.12)	Benson`s method of group additivity using program CHETAH (ASTM; 2001)	Not applicable (model calculation)	Structural aspects and estimated thermodynamic properties indicate that Ampholyt 20 must not be considered to have oxidising properties.		n.a.	0 (model calculation)	**A3.16/01:** [redacted] Oxidising properties of Ampholyt 20/100; Expert statement. EBRC Consulting GmbH, Hannover, Germany, Report no. GOL-070713/02, July 2007 (unpublished)	
Reactivity towards container material (IIA3.13)				Ampholyt 20 has been manufactured for more than 30 years. From experience in use, no reactivity with the employed container materials has become known. Ampholyt 20 is supplied in polyethylene containers. In addition, the chemical structure of the active ingredient does not indicate particular reactivity with the proposed container materials.				

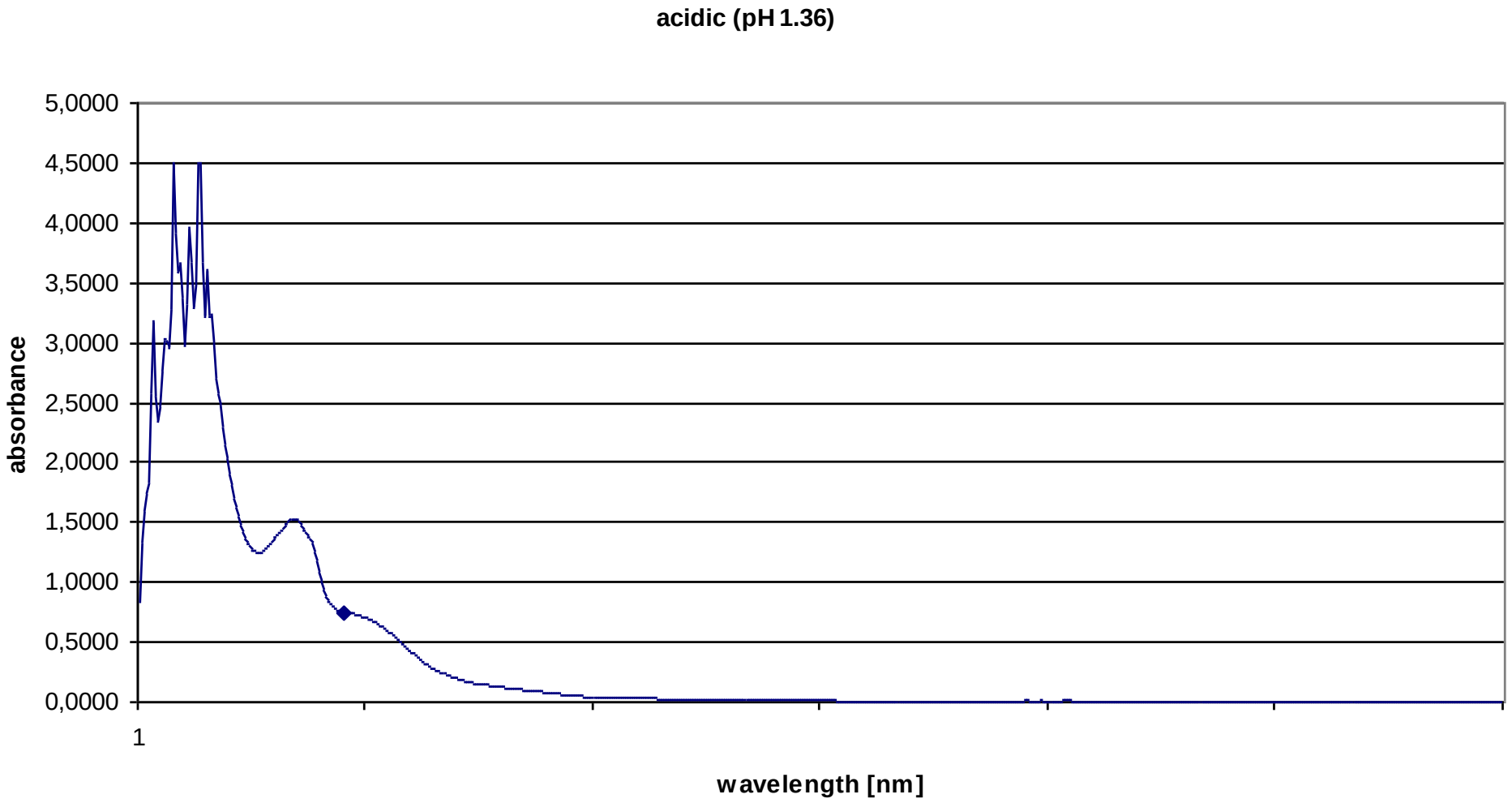


Figure A3- 1: UV/VIS spectrum of Ampholyt 20/100 at pH 1.36.

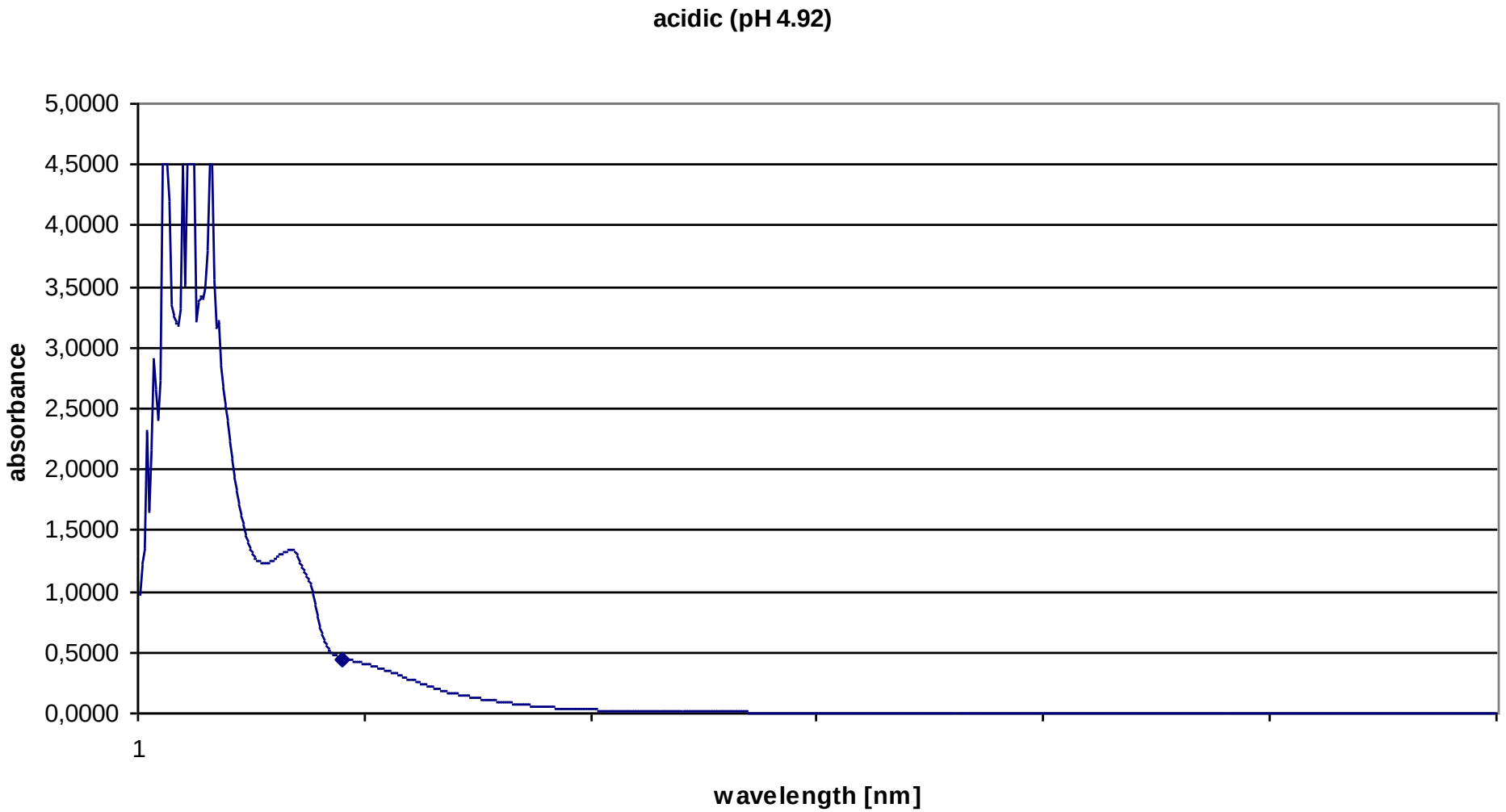


Figure A3- 2: UV/VIS spectrum of Ampholyt 20/100 at pH 4.92.

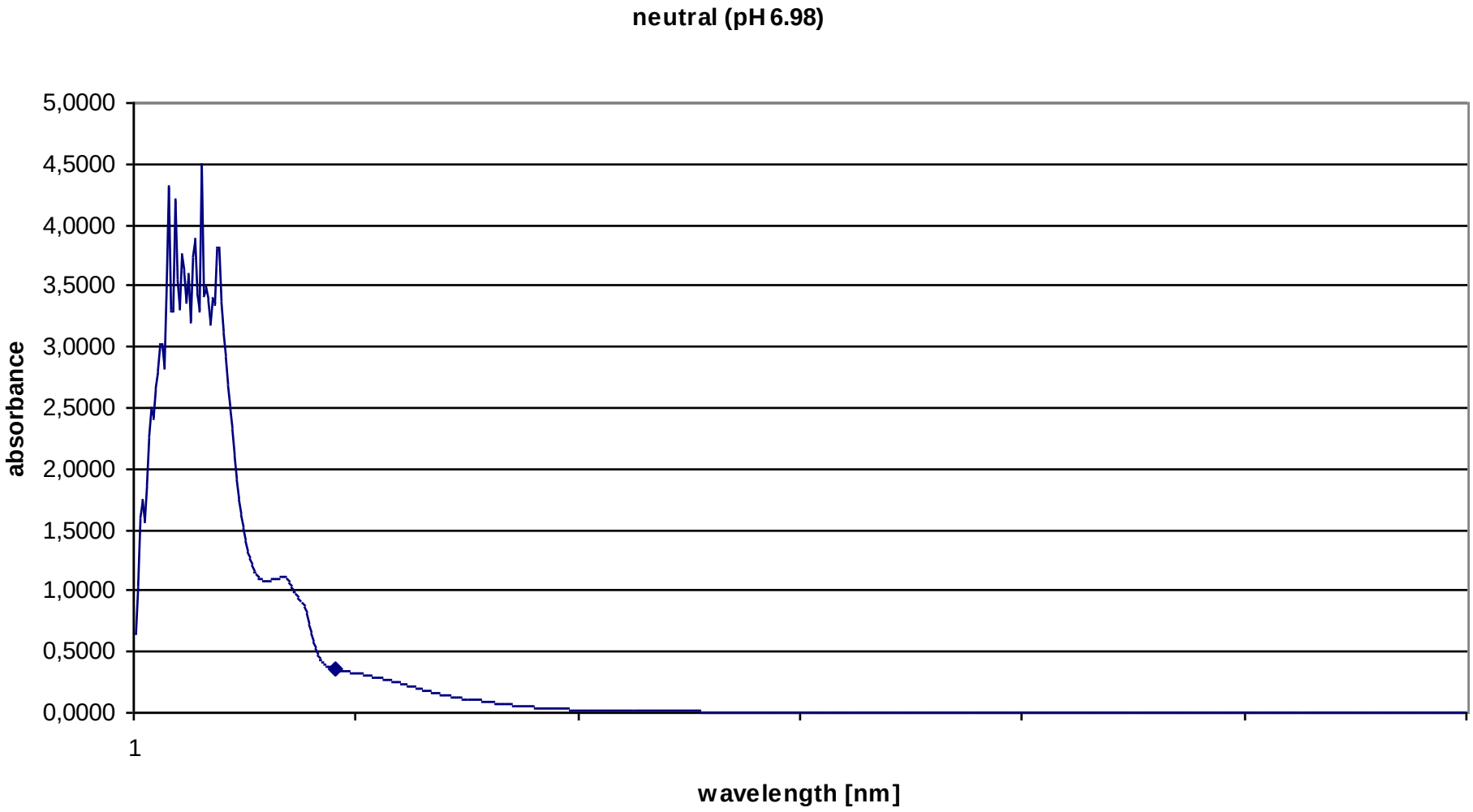


Figure A3- 3: UV/VIS spectrum of Ampholyt 20/100 at pH 6.98.

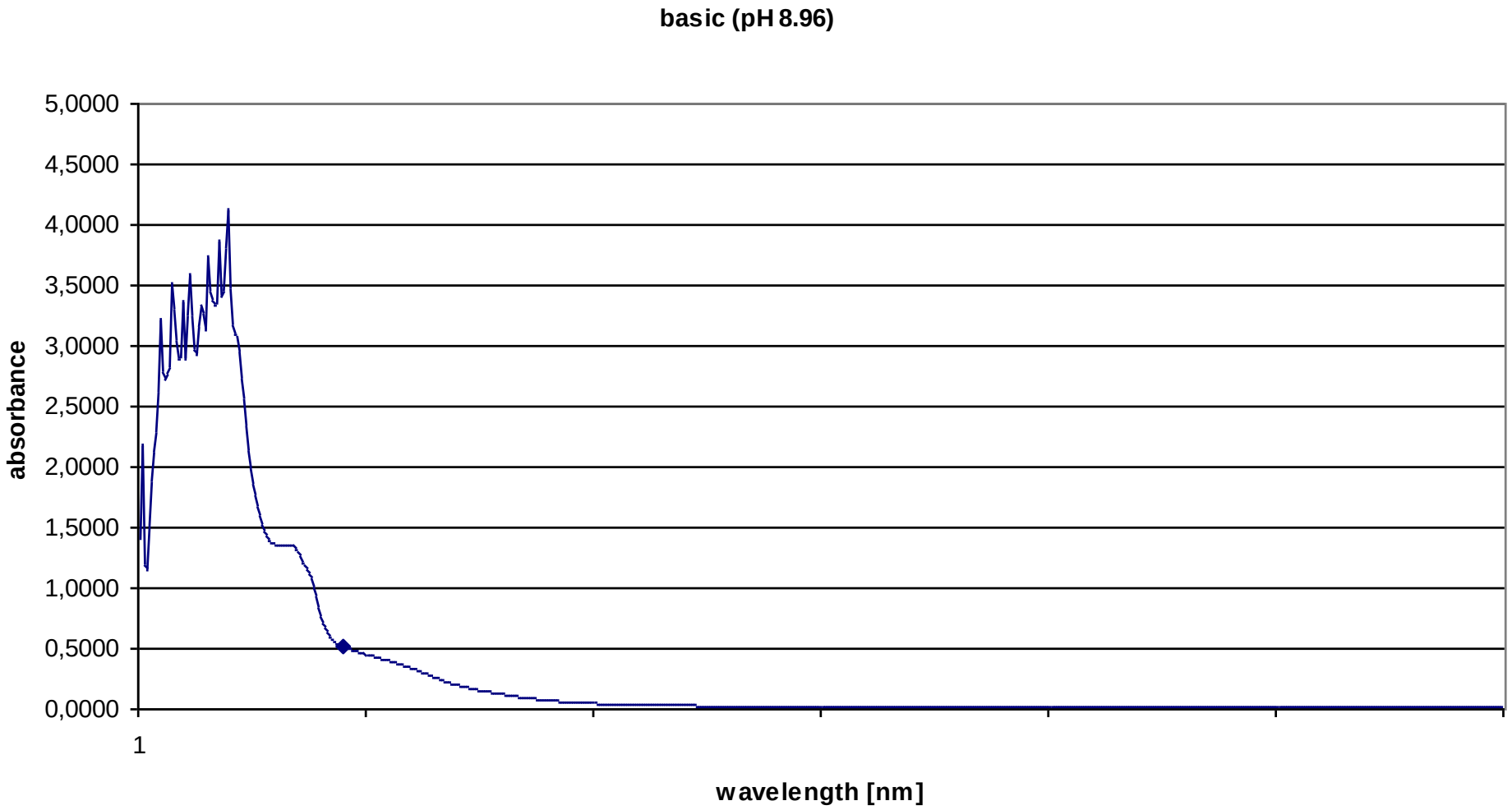


Figure A3- 4: UV/VIS spectrum of Ampholyt 20/100 at pH 8.98.

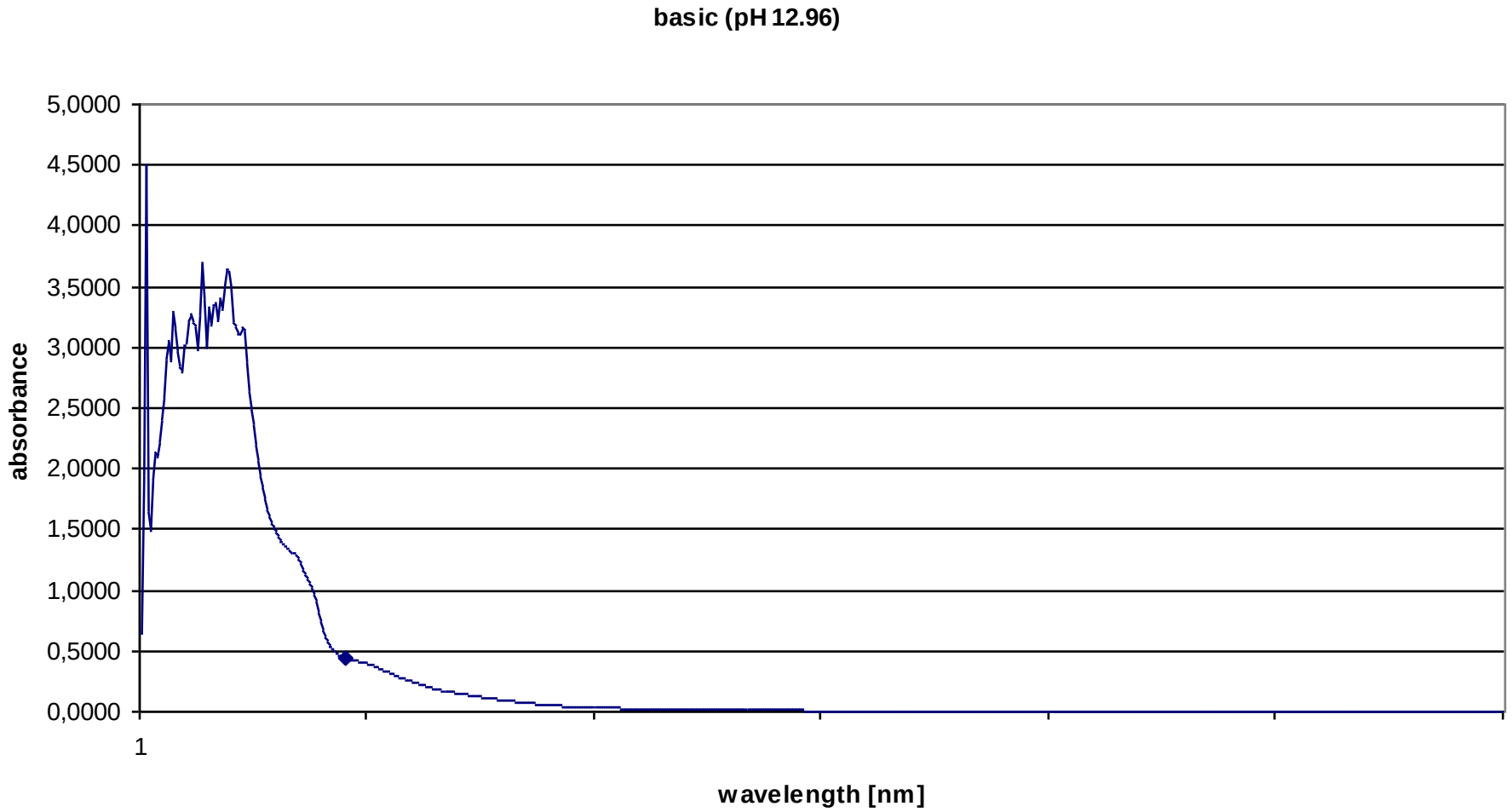


Figure A3- 5: UV/VIS spectrum of Ampholyt 20/100 at pH 12.96.

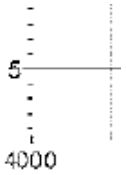


Figure A3- 6: IR spectrum of Ampholyt 20/100.

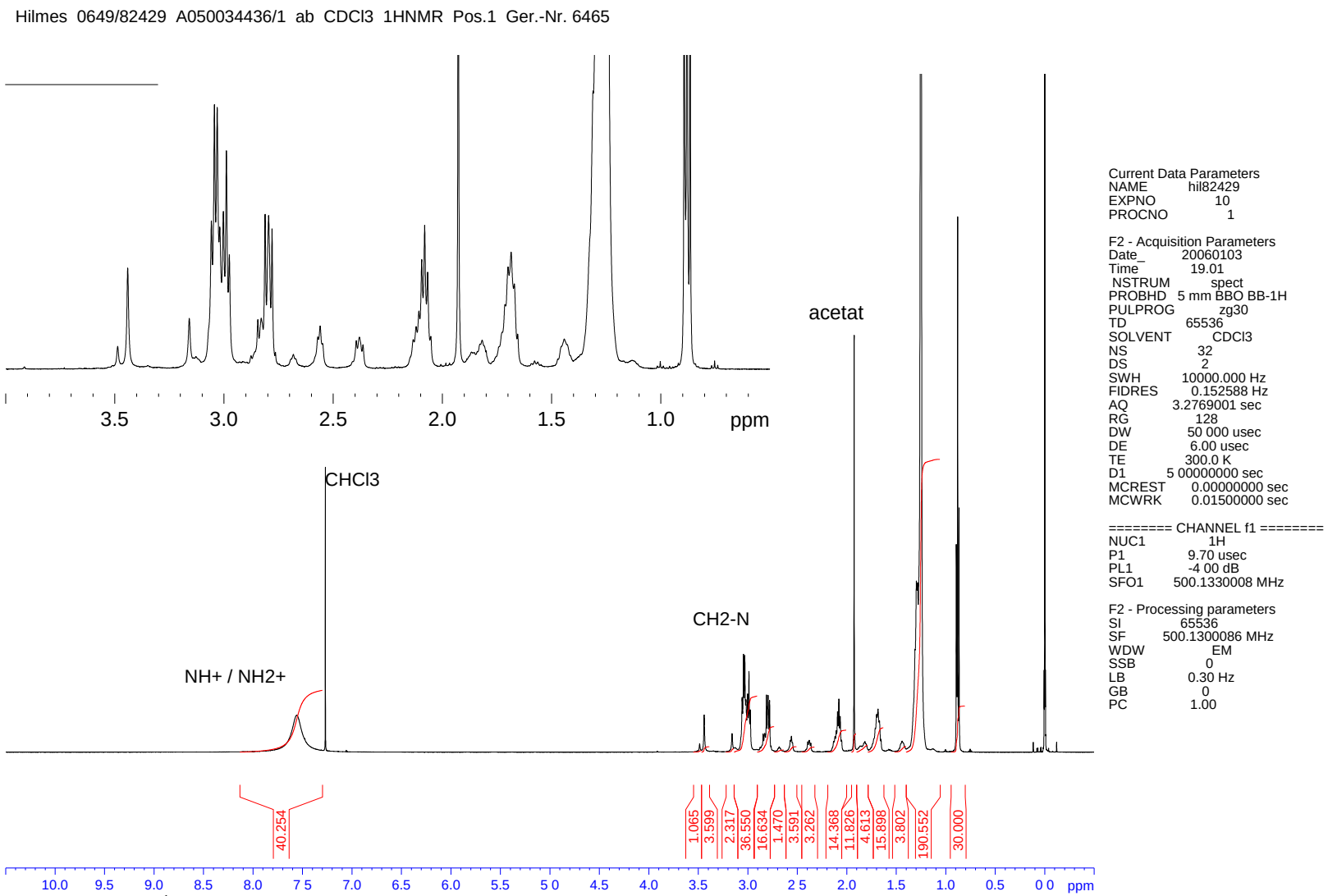


Figure A3- 7: ^{1}H-NMR spectrum and chemical shifts of Ampholyt 20/100.

Table A3- 1: Quantitative composition of Ampholyt 20/100.

Component	Composition [mol %]	Composition (considering acetate [mol %]	Composition [w / w]
[redacted]	**59.4**	**41.2**	**48.8**
[redacted]	**12.7**	**8.8**	**12.8**
[redacted]	**20.1**	**13.9**	**20.3**
[redacted]	**5.3**	**3.7**	**6.4**
[redacted]	**2.5**	**1.7**	**3.0**
[redacted]	**–**	**30.7**	**8.8**

On the basis of the ^{13}C-NMR signal intensities the molar and, taking into account the molecular weight of the basic amines, the weight composition was calculated. However, calculations consider only components assigned in the NMR spectrum.

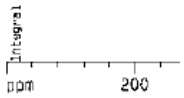


Figure A3- 8: ^{13}C-NMR spectrum.

[redacted]

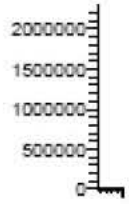


Figure A3- 9: MS spectrum of C_{12}-PDA.

[redacted]

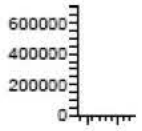


Figure A3- 10: MS spectrum of N-C12 Gly.

[redacted]

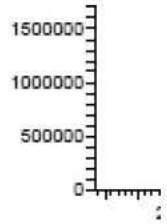


Figure A3- 11: MS spectrum of N'-C_{12} Gly.

[redacted]

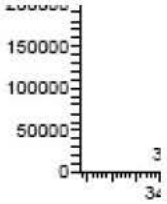


Figure A3- 12: MS spectrum of N,N'-C_{12} diGly.

[redacted]

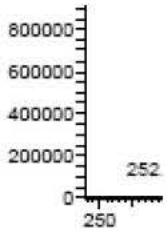


Figure A3- 13: MS spectrum of C14-PDA.

[redacted]

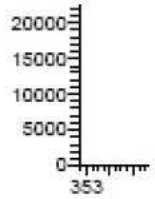


Figure A3- 14: MS spectrum of N`-C_{12} diGly.

[redacted]

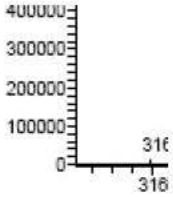


Figure A3- 15: MS spectrum of N-C_{14} Gly.

[redacted]

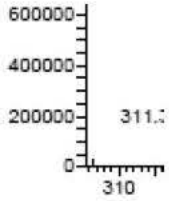


Figure A3- 16: MS spectrum of N`-C_{14} Gly.

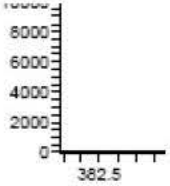


Figure A3- 17: MS spectrum of N,N'-C_{14} diGly.

[redacted]

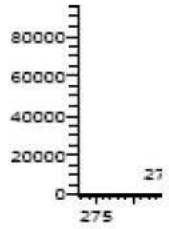


Figure A3- 18: MS spectrum of C_{16}-PDA.

[redacted]

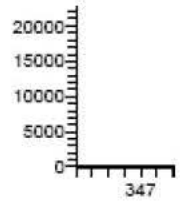


Figure A3- 19: MS spectrum of N-C_{16} Gly.

[redacted]

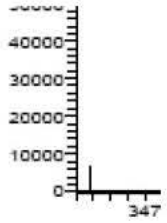


Figure A3- 20: MS spectrum of N'-C_{16} Gly.

[redacted]

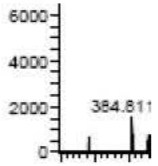


Figure A3- 21: MS spectrum of N'-C_{14} diGly.

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**General note on the test item used for Phys.Chem. studies** The technical material as manufactured is a liquid - Ampholyt 20 is a 'product by process' (*ca.* 20% w/w active ingredient) which consists of *ca.* 80% w/w water. A purified form of the technical material (dry technical material) is not manufactured or sold for commercial purposes. There is a requirement for the vast majority of phys.chem. studies to be carried out with purified test material. The applicant has freeze dried the aqueous technical material in order to produce a small quantity of purified active substance (dry test material) with a minimum purity of 99% w/w. The applicant has named the purified active substance "Ampholyt 20/100" in order to distinguish it from the Technical Material as manufactured (Ampholyt 20). Purified active substance (Ampholyt 20/100) was used in the following phys.chem studies: (1) Melting point. (2) Boiling point. (3) Relative Density. (4) Vapour pressure. (5) Appearance. (6) IR & NMR spectra. (7) Solubility in organic solvents. (8) Flammability (9) Auto-flammability Technical material as manufactured (Ampholyt 20) was used in the following studies: (1) Surface tension
Results and discussion	The applicant has freeze dried technical material in order to produce a purified form (dry form) of the active substance.
Conclusion	The use of freeze dried test material is acceptable.
Reliability	1
Acceptability	Acceptable.
Remarks	The freeze dried test material is acceptable
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

	Evaluation by Competent Authorities

	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**<u>X – Melting Point and Boiling point</u>** The applicant used a purified form of Ampholyt 20 (dry material with the removal of water). The dry form of Ampholyt 20 is called Ampholyt 20/100. Ampholyt 20/100 is not commercially available and was used in the Phys.Chem. studies in order to achieve a purified form of the active substance (min. 99% w/w). Differential scanning calorimetry (DSC) was used in order to determine the melting point and boiling point. No obvious endothermal or exothermal peaks were observed over the temperature range of 25 – 325ºC. However, loss of mass, change in colour and physical state were observed: (1) Significant weight lossof the test sample was observed over the range of 140 – 160ºC (a minimum weight loss of 72% of the original sample weight). (2) The test substance turned from white to black. (3) The test substance went from a solid (<140ºC) to a frothy solid (140ºC), to a viscous liquid (150ºC) during the scan. The results of the DSC scan indicate that Ampholyt 20/100 decomposes (*ca.* 140ºC) before a melting point or boiling point can be determined.
Results and discussion	A melting point range cannot be determined due to the decomposition of the test substance.
Conclusion	The study is acceptable. Decomposition of the product occurs before a melting point range can be determined.
Reliability	1
Acceptability	Acceptable.
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Bulk / Relative Density** The relative density = 1.027 at 23°C.
Results and discussion	The study is acceptable
Conclusion	The relative density value of 1.027 at 23°C is considered acceptable.
Reliability	1
Acceptability	Acceptable.
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Vapour pressure** The vapour pressure was measured using a vapour pressure balance (Effusion Method). It should be noted that the active substance is a UVCB and therefore the vapour pressure of Ampholyt 20 could be predominantly affected by a single component. Prioir to the initiation of the vapour pressure study, the applicant „screened" the major constituents in Ampholyt 20 for their likely vapour pressure via QSAR calculations. The QSAR calculations have been recentlyrepeated by the applicant using the up-to-date version of EPISUITE (v.4.1) – see Table below. The up-to-date EPISUITE results indicated that a significant number of the constituents and a significant % w/w of the active ingredient are predicted to have vapour pressures around or below *ca.* 10^{-10} Pa, and are thus practically non-volatile. However, the predicted vapour pressures of the remaining main components (alkyl-propylenediamine moieties with chain lengths C=10, C=12 and C=14) are in the range 10^{-2} to 10^{-3} Pa; since this substantial portion of Ampholyt20 is expected to drive the overall vapour pressure, the choice of the "vapour pressure balance" method appears reasonably well justified The experimental vapour pressure values for Ampholyt 20 (2.5 x 10-3 – 1.1 Pa at test temperatures of 34.3 – 93.7°C) lie within the specified range of the OECD test guideline.
Results and discussion	The extrapolated value of 0.4 x 10^{-3} Pa indicates that Ampholyt 20 exhibits low volatility at 25°C.
Conclusion	Ampholyt 20 exhibitis low volatility.
Reliability	1
Acceptability	Acceptable.
Remarks	No further information required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Table 1: QSAR - calculated vapour pressure values for the "major constituents" of Ampholyt 20

Structure class	R	% w/w (dry	Vapour pressure**	Sum of the upper

		weight basis)	[Pa]	limits in % w/w (dry weight basis)
[redacted]	[redacted]	NA	$7.54*10^{-2}$	47.74
	[redacted]	29.94 – 35.44	$1.3*10^{-2}$	
	[redacted]	8.26 – 10.73	$2.34*10^{-3}$	
	[redacted]	0.02 – 1.57	$4.33*10^{-4}$	
[redacted]	[redacted]	NA	$2.36*10^{-10}$	44.98
	[redacted]	8.51 – 10.16	$5.41*10^{-11}$	
	[redacted]	1.64 – 2.85	$1.23*10^{-11}$	
	[redacted]	NA	$2.76*10^{-12}$	
[redacted]	[redacted]	NA	$2.17*10^{-10}$	
	[redacted]	13.13 – 15.43	$4.97*10^{-11}$	
	[redacted]	4.07 – 5.86	$1.13*10^{-11}$	
	[redacted]	0 – 1.21*	$2.25*10^{-12}$	
[redacted]	[redacted]	NA	$1.56*10^{-8}$	
	[redacted]	3.51 – 4.36	$3.63*10^{-10}$	
	[redacted]	0.91 – 1.75	$8.35*10^{-11}$	
	[redacted]	0 – 1.21*	$1.9*10^{-11}$	
[redacted]	[redacted]	NA	$1.56*10^{-9}$	
	[redacted]	2.07 – 2.48	$3.63*10^{-10}$	
	[redacted]	0.52 – 0.88	$8.35*10^{-11}$	
	[redacted]	0 – 1.21*	$1.9*10^{-11}$	

NA = Not analysed in supporting 7-batch analysis.
* C16-Gly as sum.
** Calculations performed for 25°C.

Evaluation by Competent Authorities	
Evaluation by Rapporteur Member State	
Date	09/08/13

Materials and Methods	**X – Henry's Law Constant** The applicant provided two Henry's Law Constant calculations: (1) Henry's Law Constant calculated using molecular weight (weighted mean value), the water solubility and the vapour pressure. (2) Henry's Law Constant calculated using an Epi Suite Model Calculation (HENRYWIN). (1) Henry's Law Constant calculated using molecular weight (weighted mean value), the water solubility and the vapour pressure. Tha Henry's Law Constant value of 2.67 x 10^{-7} Pa m3/mol was calculated using the following parameters – Vapour pressure at 20°C: 1.9x10-4 Pa Weighted molecular weight of the main components: 280.79 g/mol Solubility in water at 20°C: 200 g/l The calculated value indicates that Ampholyt 20 will not be volatile from water. The value should only be treated as an orientation because of the high water solubility value for Ampholyt used in the calculation. Ampholyt 20 is a mixture of *ca.* 20 „major constituents" which all have different water solubilities. The applicant has provided QSAR calculations of the water solubility of the individual components as suppplementary data (see Table below). The QSAR calculated water solubility values range from < 1 – 824 mg/L for the main components of Ampholyt 20. The QSAR calculations for water solubility were performed using EPI SUITE WATERNT (v1.01). Technical Ampholyt 20 is a clear solution and miscible with water in a wide range (>200 g/l), the reason being that it is likely that the soluble surface-active constituents facilitate solubilisation of the less soluble species. Because of the heterogeneity of the constituents, a QSAR calculation for the individual Henry's constants is the most suitable option for Ampholyt 20. The QSAR calculations for Henry's Law Constants were performed using EPI SUITE HENRYWIN (v3.12). The surfactant properties of the mixture probably masks the variance in solubilities of the individual constituents therefore making a Henry's Law Constant calculation by the method referred to in (1) only an indicator of the volatility from water. (2) Henry's Law Constant calculated using an Epi Suite Model Calculation (HENRYWIN). Henry's law constant values were calculated for the major and minor components of Ampholyt 20. The calculated values ranged from 1.29 x 10^{-9} to 1.22 x 10^{-2} Pa.m^3/mol for the „major components" and from 8.94 x 10^{-10} to 3.05 x 10^{1} for the „minor components". The QSAR calculations are provided in the Tables below. It should be remembered that the sum of the „minor constituents" account for < 2% of the active ingredient. The values refer to the unprotunated species. The Henry's Law Constants for the vast majority of components are similar or well below that of water even in the unprotunated form. All QSAR-predicted Henry's constants for the "major" Ampholyt constituents are below 0.03 Pa•m^3/mol, most of which are several orders of magnitude lower. It must also be considered that due to the basic nature of the more volatile constituents, these will predominantly exist in neutral aqueous solution in a protonated (ionic) form, whereas the QSAR predictions intrinsically reflect only the non-protonated species. Consequently, the volatility from water will be even further reduced in reality.
Results and discussion	The QSAR predictions together with the basicity/ionisation aspect of the components act as valid and adequate arguments to conclude on the non-volatility of Ampholyt 20 from water.
Conclusion	Ampholyt 20 is considered to be essentially non-volatile from water.

Reliability	1
Acceptability	Acceptable.
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Table 1: QSAR - calculated water solubility values for the constituents of Ampholyt 20

Structure class	R	Water solubility* [mg/L]	% w/w (dry weight basis)
[redacted]	[redacted]	824.61	NA
		78.635	29.94 – 35.44
		7.3982	8.26 – 10.73
		0.68856	0.02 – 1.57
[redacted]	[redacted]	44.144	NA
		4.1058	8.51 – 10.16
		0.37855	1.64 – 2.85
		0.034648	NA
[redacted]	[redacted]	96.907	NA
		9.0132	13.13 – 15.43
		0.83101	4.07 – 5.86
		0.07606	0 – 1.21*
[redacted]	[redacted]	34.779	NA
		3.1817	3.51 – 4.36
		0.28929	0.91 – 1.75
		0.026165	0 – 1.21*
[redacted]	[redacted]	34.779	NA
		3.1817	2.07 – 2.48
		0.28929	0.52 – 0.88
		0.026165	0 – 1.21*

*EPI Suite QSAR calculations with WATERNT (v1.01)

Table 2: QSAR - Calculated Henry's Law values for the major constituents of Ampholyt 20

[redacted]

* Henr

Table 3: QSAR - Calculated Henry's Law values for the minor constituents of Ampholyt 20

[redacted]

* Henry

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Absorption Spectra** The available spectra (NMR, UV, IR and MS) support the proposed structures of the components making up the active ingredient.
Results and discussion	The spectra are acceptable.
Conclusion	The spectra are acceptable.
Reliability	1
Acceptability	Acceptable.
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13

Materials and Methods	**<u>X – Solubility in water</u>** An aqueous solution of test substance (approximately 20%; colourless to slightly yellow) was weighed, freeze dried and then reweighed. The non-aqueous component of the solution was found to be 20.83% by weight and the solubility was concluded to be >20.83% (w/w). The pH dependence of the water solubility was checked by adjusting three solutions of test substance to pH 4.0, 7.0 and 9.0. At pH 4 and 7 the solution appeared clear. At pH 9 the solution appeared viscous and foamy and appeared clear after several hours. It was concluded the solubility of test substance was not pH dependent over the range tested. Ampholyt 20 remained a clear solution regardless of the pH range tested. It can be concluded from the study that the solubility of the Ampholyt 20/100 is at minimum of 208 g/L. The solubuility result essentailly equates to miscible in all proportions. It is also noted that Ampholyt 20 is manufactured as an aqueous solution (*ca.* 20% in water). It is known from its use to be completely miscible in water at all proportions. The applicant applicant has statetd that they did not conduct a conventional solubility study on the basis that the technical material as manufactured is known to be extremely soluble based on decades of use – the technical material is a "product by process" containing *ca.* 80% w/w water. The remaining *ca.* 20% w/w is made up of non aqueous matter. The applicant has not tested the effect of temperature on the solubility of Ampholyt 20 as part of the referenced study report. However, taking into account the high solubility of the technical material in water at 20^{o}C, it can be assumed that Ampholyt 20 will also be reasonably soluble in water at either 10 and 30^{o}C. Ampholyt 20 has always been characterised and described as a clear solution during several decades of handling. The applicant is not aware of any reports of turbidity or descriptions alluding to any kind of dispersion of the solution. However, it should be noted that the applicant attempted to determine the critical micellization concentration (CMC) of Ampholyt 20 in July 2013 but they ran into technical difficulties during the study and were not able to come to a final conclusion regarding the CMC. The applicant used the ring method (ISO 4311:1979) in their attempt to determine the CMC. The applicant has indicated that they intend to carry out another CMC study as soon as possible.
Results and discussion	Ampholyt 20 is considered to be highly soluble with a solubility > 208 g/L. The solubuility result essentailly equates to miscible in all proportions. The technical material is a clear solution when manufactured and continues to remain clear over the environmental pH range. Temperature (10 – 30^{o}C) is not expected to have a significant effect on its solubility.
Conclusion	Solubility > 208 g/L.
Reliability	2 – The applicant did not use a conventaional method in order to determine solubility. The applicant intends to present a CMC study so that they can comment on the possibility of colloid and miscelle formation.
Acceptability	Acceptable.
Remarks	The applicant should present a CMC study as soon as possible.
	Comments from
Date	*Give date of the comments submitted*

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Partition coefficient n-octanol/water** The test substance Ampholyt 20 is an amphoteric surfactant. It constitutes a complex mixture of partially carboxymethylated alkyl-propylene-diamines, obtained as a "product-by-process". The LogKow cannot be experimentally determined by any of the recommended OECD methods (Flash method, HPLC method) because the active substance is surface active. Other suggested approaches such as deriving a calculated value or an estimate based on individual n-octanol and water solubilities are also intrinsically not applicable to Ampholyt 20. Ampholyt 20 consists of at least 20 components, therefore it is not possible to determine a single LogKow value which is representative of all 20 + components, however the partition coefficients for the various individual components of Ampholyt 20 can be calculated by the applicant using quantitative structure activity relationship (QSAR). The applicant presented two complimetary study reports where QSAR was used for LogKow determination: 1st report – *Reference:* *‚Model Calculation of Partition Coefficient of Ampholyt 20', Evonik EBRC Consulting, [redacted], May 2013.* The first report used EpiSuite-KOWWIN for LogPow determination. The individual LogPow values generated by KOWWIN are presented in the Tables 1 and 2 below. The Log Pow values of the individual components of Ampholyt 20 range between 0.33 and 6.71. It is reasonable to suggest that the LogPow values should be considered in light of the relative proportion of each constitunet in Ampholyt 20. The relative proportions (mean % w/w values according to the 7-batch analysis results) of the indivdual components (major and minor components) that were used in the calculation can be found in Tables 3 and 4. The majority of the components present in Ampholyt 20 are of moderate lipophilicity. The applicant reported a weighted mean LogPow of 3.82. It is important to note that all of the components making up Ampholyt 20 are ionisable. KOWWIN QSAR does not consider hydrochlorides. KOWWIN ignores hydrochlorides and predicts a LogKow for non-ionised species. The relative content of hydrochlorides leads to a more hydrophilic nature than what may be expected from the calculated LogPow data. 2nd report – *Reference:* *‚Complex QSAR calculations of partition coefficients for Ampholyt 20 under consideration of pH dependency', Evonik EBRC Consulting, [redacted] June 2013.* LogDow values are considered to be more meaningful for ionised species with regards to environmental risk assessment. According to REACH guidance "the value of the dissociated molecule determined around a pH of 7 is considered more realistic for PBT and chemical safety assessment". LogDow values take into consideration ionised and nonionised species. The applicant performed their LogPow and LogDow caculations for the second

	report using MarvinSketch (CheAcxon, 2012). Unlike EPISuite-KOWWIN, The MarvinSketch QSAR programme allows for the determination of LogP values for non-ionic species, as well as pH dependent LogD values for ionisable species. MarvinSketch applies calculation algorithms according to methods described by: - Viswanadhan and Ghose (VG) (Viswanadhan, 1989) - Klopman (KLOP) (Klopman, 1994) - logP data from PHYSPROP© database (PHYS) - a weighted approach, where the results of the three methods are weighted by using the same factor, resulting in a contribution of 33.3% for each method. The weighted Log Pow and Log Dow values at the isoelectric point and pH 7 were calculated for each molecular constituent in Ampholyt 20. The MarvinSketch results are presented in Table 5 below. The weighted Log Pow values ranged from 2.83 to 5.73, the Log Dow values at the isoelectric point ranged from -2.36 to 3.10, and the LogDow values at pH 7 ranged from -2.37 to 2.33. A graphical representation of the effect of pH on LogDow for the indivdual components is presented in Figure 1 (weighted Log D values). The LogPow determinations obtained from MarvinSketch generally support the LogPow determinations obtained from using EPISuite-KOWWIN. The maximum Log Pow determined by MarvinSketch for any Ampholyt 20 constituent is 5.73, when applying QSAR considerations that are restricted to uncharged molecules. However as previously noted, the LogPow approach is purely theoretical and does not reflect the fact that all constituents possess ionisable functional groups, which renders their charge and consequently their overall lipophilicity as being pH dependant. LogDow values were calculated which take into account all (including ionisable) dissociation species of a molecule. From a plot of each LogDow curve, the intersect with pH=7 gives a value for the partition coefficient which is considered to be more relevant than LogPow for environmental risk assessment according to REACH guidance. Overall, at neutral pH (pH 7) the LogDow values for the individual constituents of Ampholyt 20 ranged between -2.37 and 2.33. A comprehensive comparison of the LogP and LogD results obtained from the various calculated algorithms used by MarvanSketch (Viswanadhan and Ghose (VG), Klopman (KLOP), logP data from PHYSPROP© database (PHYS), and the weighted approach) are presented in Tables 6-29 below.
Results and discussion	It is not technically possible to experimentally determine LogKow values for Ampholyt 20. The applicant has used QSAR to determine LogPow and LogDow values for the individual components of Ampholyt 20.
Conclusion	The applicant has provided QSAR generated LogPow and LogDow values for the individual components of Ampholyt 20. LogDow values are more applicable for PBT and chemical safety assessment for ionisable species according to REACH Guidance. All of the components included in Ampholyt 20 are ionisable.
Reliability	2 – It was not possible to obtain experimental LogKow values. QSAR generated data was presented by the applicant.
Acceptability	Acceptable
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Table 1: LogPow values for the major constituents of Ampholyt 20 according to EPISuite - KOWWIN

(1) logP

Table 2: LogPow values for the minor constituents of Ampholyt 20 according to EPISuite - KOWWIN

(1) $\log P_{ow}$

Table 3: Relative proportions (mean % w/w values) for the major constituents in technical Ampholyt 20

C

(2) represe

Table 4: Relative proportions (mean % w/w values) for the minor constituents in technical Ampholyt 20

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Table 5: Weighted LogPow and LogDow at the isoelectric point and pH 7 according to MarvanSketch

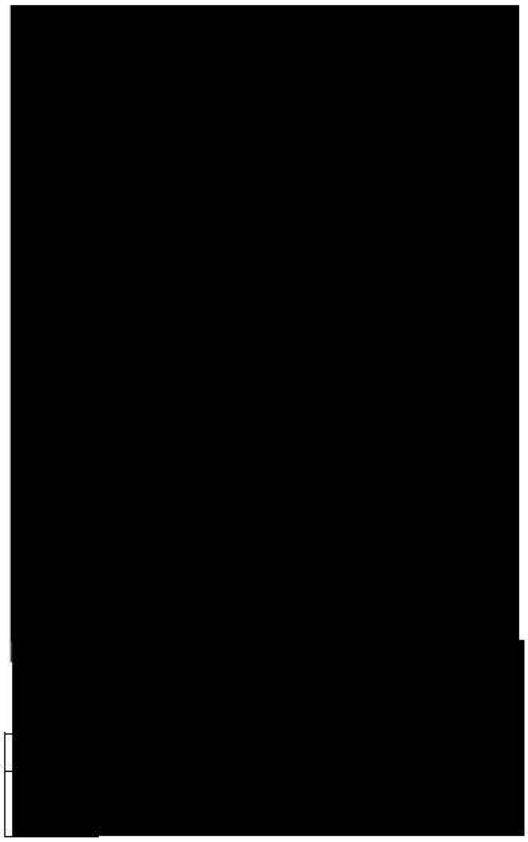


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Table 6: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 5.02 KLOP: 6.17 PHYS: 6.00 Weighted: 5.73	0.00	-2.03	0.03	0.36	-0.55
		0.50	-2.03	0.03	0.36	-0.55
		1.00	-2.03	0.03	0.36	-0.55
		1.50	-2.03	0.03	0.36	-0.55
		2.00	-2.03	0.03	0.36	-0.55
		2.50	-2.03	0.04	0.36	-0.55
		3.00	-2.03	0.04	0.36	-0.54
		3.50	-2.02	0.04	0.36	-0.54
		4.00	-1.99	0.05	0.37	-0.53
		4.50	-1.90	0.08	0.39	-0.49
		5.00	-1.71	0.17	0.45	-0.39
		5.50	-1.37	0.37	0.59	-0.16
		6.00	-0.93	0.71	0.87	0.20
		6.50	-0.41	1.15	1.27	0.66
		7.00	0.20	1.67	1.75	1.19
		7.50	0.92	2.28	2.29	1.80
		8.00	1.71	2.96	2.90	2.50
		8.50	2.47	3.65	3.53	3.21
		9.00	3.12	4.28	4.13	3.84
		9.50	3.67	4.82	4.66	4.38
		10.00	4.15	5.29	5.13	4.86
		10.50	4.54	5.69	5.52	5.25
		11.00	4.81	5.95	5.79	5.52
		11.50	4.94	6.09	5.92	5.65
		12.00	4.99	6.14	5.97	5.70
		12.50	5.01	6.16	5.99	5.72
		13.00	5.02	6.16	6.00	5.73
		13.50	5.02	6.17	6.00	5.73
		14.00	5.02	6.17	6.00	5.73
Structure (incl. pka values)	[redacted]					

Table 7: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 4.23 KLOP: 5.23 PHYS: 5.06 Weighted: 4.84	0.00	-2.82	-0.90	-0.58	-1.44
		0.50	-2.82	-0.90	-0.58	-1.44
		1.00	-2.82	-0.90	-0.58	-1.44
		1.50	-2.82	-0.90	-0.58	-1.44
		2.00	-2.82	-0.90	-0.58	-1.44
		2.50	-2.82	-0.90	-0.58	-1.43
		3.00	-2.82	-0.90	-0.58	-1.43
		3.50	-2.81	-0.90	-0.57	-1.43
		4.00	-2.78	-0.89	-0.57	-1.42
		4.50	-2.69	-0.86	-0.55	-1.38
		5.00	-2.50	-0.77	-0.49	-1.28
		5.50	-2.16	-0.57	-0.35	-1.05
		6.00	-1.72	-0.23	-0.07	-0.69
		6.50	-1.20	0.22	0.33	-0.23
		7.00	-0.59	0.74	0.82	0.30
		7.50	0.13	1.34	1.36	0.92
		8.00	0.92	2.02	1.96	1.61
		8.50	1.68	2.71	2.60	2.32
		9.00	2.32	3.34	3.19	2.95
		9.50	2.87	3.88	3.72	3.49
		10.00	3.35	4.36	4.19	3.97
		10.50	3.75	4.75	4.59	4.36
		11.00	4.01	5.02	4.85	4.63
		11.50	4.15	5.15	4.98	4.76
		12.00	4.20	5.20	5.04	4.81
		12.50	4.22	5.22	5.06	4.83
		13.00	4.22	5.23	5.06	4.84
		13.50	4.23	5.23	5.06	4.84
		14.00	4.23	5.23	5.06	4.84
Structure (incl. pka values)	[redacted]					

Table 8: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 3.43 KLOP: 4.29 PHYS: 4.13 Weighted: 3.95	0.00	-3.62	-1.84	-1.51	-2.32
		0.50	-3.62	-1.84	-1.51	-2.32
		1.00	-3.62	-1.84	-1.51	-2.32
		1.50	-3.62	-1.84	-1.51	-2.32
		2.00	-3.62	-1.84	-1.51	-2.32
		2.50	-3.62	-1.84	-1.51	-2.32
		3.00	-3.61	-1.84	-1.51	-2.32
		3.50	-3.60	-1.84	-1.51	-2.32
		4.00	-3.57	-1.83	-1.50	-2.31
		4.50	-3.49	-1.80	-1.48	-2.27
		5.00	-3.29	-1.71	-1.43	-2.16
		5.50	-2.96	-1.51	-1.28	-1.94
		6.00	-2.51	-1.17	-1.01	-1.58
		6.50	-1.99	-0.72	-0.60	-1.12
		7.00	-1.39	-0.20	-0.12	-0.59
		7.50	-0.66	0.40	0.42	0.03
		8.00	0.13	1.08	1.03	0.73
		8.50	0.88	1.78	1.66	1.43
		9.00	1.53	2.40	2.25	2.06
		9.50	2.08	2.94	2.78	2.60
		10.00	2.56	3.42	3.26	3.08
		10.50	2.96	3.81	3.65	3.47
		11.00	3.22	4.08	3.91	3.74
		11.50	3.36	4.21	4.05	3.87
		12.00	3.41	4.26	4.10	3.92
		12.50	3.43	4.28	4.12	3.94
		13.00	3.43	4.29	4.12	3.95
		13.50	3.43	4.29	4.13	3.95
		14.00	3.43	4.29	4.13	3.95
Structure (incl. pka values)	[redacted]					

Table 9: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted] [redacted]	VG: 2.64 KLOP: 3.35 PHYS: 3.19 Weighted: 3.06	0.00	-4.41	-2.78	-2.45	-3.21
		0.50	-4.41	-2.78	-2.45	-3.21
		1.00	-4.41	-2.78	-2.45	-3.21
		1.50	-4.41	-2.78	-2.45	-3.21
		2.00	-4.41	-2.78	-2.45	-3.21
		2.50	-4.41	-2.78	-2.45	-3.21
		3.00	-4.41	-2.78	-2.45	-3.21
		3.50	-4.40	-2.78	-2.45	-3.21
		4.00	-4.36	-2.77	-2.44	-3.19
		4.50	-4.28	-2.73	-2.42	-3.16
		5.00	-4.08	-2.65	-2.36	-3.05
		5.50	-3.75	-2.45	-2.22	-2.83
		6.00	-3.31	-2.11	-1.94	-2.47
		6.50	-2.78	-1.66	-1.54	-2.01
		7.00	-2.18	-1.14	-1.06	-1.48
		7.50	-1.46	-0.54	-0.51	-0.86
		8.00	-0.66	0.14	0.09	-0.16
		8.50	0.09	0.84	0.72	0.54
		9.00	0.74	1.46	1.32	1.17
		9.50	1.29	2.00	1.85	1.71
		10.00	1.77	2.48	2.32	2.19
		10.50	2.16	2.87	2.71	2.58
		11.00	2.43	3.14	2.98	2.85
		11.50	2.56	3.27	3.11	2.98
		12.00	2.62	3.32	3.16	3.03
		12.50	2.63	3.34	3.18	3.05
		13.00	2.64	3.35	3.19	3.06
		13.50	2.64	3.35	3.19	3.06
		14.00	2.64	3.35	3.19	3.06
Structure (incl. pka values)	[redacted]					

Table 10: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 4.92 KLOP: 5.85 PHYS: 6.00 Weighted: 5.59 logD at pI VG: 1.77 KLOP: 3.33 PHYS: 3.71 Weighted: 2.94	0.00	-2.33	-0.44	-0.01	-0.93
		0.50	-2.31	-0.40	0.04	-0.89
		1.00	-2.24	-0.30	0.16	-0.80
		1.50	-2.11	-0.13	0.36	-0.63
		2.00	-1.94	0.08	0.59	-0.43
		2.50	-1.81	0.24	0.74	-0.28
		3.00	-1.75	0.31	0.82	-0.21
		3.50	-1.72	0.34	0.85	-0.18
		4.00	-1.70	0.35	0.86	-0.17
		4.50	-1.66	0.37	0.87	-0.15
		5.00	-1.55	0.41	0.91	-0.09
		5.50	-1.32	0.52	0.99	0.04
		6.00	-0.97	0.75	1.18	0.30
		6.50	-0.53	1.11	1.51	0.69
		7.00	-0.05	1.55	1.94	1.14
		7.50	0.43	2.02	2.40	1.62
		8.00	0.90	2.48	2.86	2.08
		8.50	1.30	2.89	3.26	2.48
		9.00	1.59	3.17	3.55	2.77
		9.50	1.74	3.32	3.69	2.91
		10.00	1.77	3.34	3.71	2.94
		10.50	1.71	3.26	3.63	2.86
		11.00	1.57	3.06	3.42	2.68
		11.50	1.42	2.80	3.13	2.43
		12.00	1.31	2.57	2.87	2.23
		12.50	1.27	2.43	2.70	2.12
		13.00	1.25	2.38	2.63	2.08
		13.50	1.24	2.36	2.60	2.07
		14.00	1.24	2.36	2.59	2.06
Structure (incl. pka values)	[redacted]					

Table 11: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	**VG**	**KLOP**	**PHYS**	**WEIGHTED**
[redacted]	VG: 4.13 KLOP: 4.91 PHYS: 5.06 Weighted: 4.70 logD at pI VG: 0.98 KLOP: 2.40 PHYS: 2.78 Weighted: 2.05	0.00	-3.12	-1.38	-0.94	-1.82
		0.50	-3.10	-1.34	-0.90	-1.78
		1.00	-3.04	-1.24	-0.78	-1.69
		1.50	-2.91	-1.06	-0.58	-1.52
		2.00	-2.74	-0.85	-0.35	-1.32
		2.50	-2.61	-0.70	-0.19	-1.17
		3.00	-2.54	-0.63	-0.12	-1.10
		3.50	-2.51	-0.60	-0.09	-1.07
		4.00	-2.49	-0.59	-0.08	-1.05
		4.50	-2.45	-0.57	-0.06	-1.03
		5.00	-2.34	-0.53	-0.03	-0.98
		5.50	-2.12	-0.42	0.05	-0.85
		6.00	-1.76	-0.19	0.25	-0.59
		6.50	-1.32	0.17	0.58	-0.20
		7.00	-0.84	0.62	1.00	0.25
		7.50	-0.36	1.09	1.47	0.73
		8.00	0.10	1.54	1.92	1.19
		8.50	0.51	1.95	2.32	1.59
		9.00	0.80	2.23	2.61	1.88
		9.50	0.94	2.38	2.75	2.02
		10.00	0.98	2.40	2.78	2.05
		10.50	0.92	2.32	2.69	1.97
		11.00	0.78	2.13	2.49	1.79
		11.50	0.62	1.86	2.20	1.54
		12.00	0.52	1.63	1.93	1.34
		12.50	0.47	1.50	1.76	1.23
		13.00	0.46	1.44	1.69	1.19
		13.50	0.45	1.42	1.66	1.18
		14.00	0.45	1.42	1.65	1.17
Structure (incl. pka values)	[redacted]					

Table 12: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 3.34 KLOP: 3.97 PHYS: 4.12 Weighted: 3.81 logD at pI VG: 0.18 KLOP: 1.46 PHYS: 1.84 Weighted: 1.16	0.00	-3.92	-2.32	-1.88	-2.70
		0.50	-3.89	-2.28	-1.83	-2.67
		1.00	-3.83	-2.18	-1.72	-2.58
		1.50	-3.70	-2.00	-1.51	-2.41
		2.00	-3.53	-1.79	-1.29	-2.21
		2.50	-3.40	-1.64	-1.13	-2.06
		3.00	-3.33	-1.57	-1.05	-1.99
		3.50	-3.30	-1.54	-1.02	-1.96
		4.00	-3.28	-1.53	-1.01	-1.94
		4.50	-3.24	-1.51	-1.00	-1.92
		5.00	-3.14	-1.47	-0.97	-1.87
		5.50	-2.91	-1.36	-0.88	-1.74
		6.00	-2.55	-1.13	-0.69	-1.47
		6.50	-2.11	-0.77	-0.36	-1.09
		7.00	-1.63	-0.32	0.07	-0.64
		7.50	-1.15	0.15	0.53	-0.16
		8.00	-0.69	0.61	0.99	0.30
		8.50	-0.28	1.01	1.39	0.70
		9.00	0.00	1.30	1.68	0.99
		9.50	0.15	1.44	1.82	1.13
		10.00	0.18	1.46	1.84	1.16
		10.50	0.12	1.38	1.76	1.08
		11.00	-0.01	1.19	1.55	0.90
		11.50	-0.17	0.92	1.26	0.65
		12.00	-0.27	0.69	0.99	0.45
		12.50	-0.32	0.56	0.83	0.35
		13.00	-0.34	0.50	0.75	0.30
		13.50	-0.34	0.48	0.73	0.29
		14.00	-0.34	0.48	0.72	0.28
Structure (incl. pka values)	[redacted]					

Table 13: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 2.55 KLOP: 3.03 PHYS: 3.19 Weighted: 2.92 logD at pI VG: -0.61 KLOP: 0.53 PHYS: 0.91 Weighted: 0.27	0.00	-4.71	-3.26	-2.82	-3.59
		0.50	-4.69	-3.22	-2.77	-3.56
		1.00	-4.62	-3.12	-2.65	-3.47
		1.50	-4.49	-2.94	-2.45	-3.30
		2.00	-4.32	-2.73	-2.22	-3.10
		2.50	-4.19	-2.58	-2.06	-2.95
		3.00	-4.13	-2.51	-1.99	-2.88
		3.50	-4.10	-2.48	-1.96	-2.85
		4.00	-4.08	-2.47	-1.95	-2.83
		4.50	-4.03	-2.45	-1.94	-2.81
		5.00	-3.93	-2.41	-1.90	-2.76
		5.50	-3.70	-2.30	-1.82	-2.63
		6.00	-3.35	-2.07	-1.62	-2.36
		6.50	-2.90	-1.70	-1.30	-1.98
		7.00	-2.43	-1.26	-0.87	-1.52
		7.50	-1.94	-0.79	-0.41	-1.05
		8.00	-1.48	-0.33	0.05	-0.59
		8.50	-1.08	0.07	0.45	-0.19
		9.00	-0.79	0.36	0.74	0.10
		9.50	-0.64	0.50	0.88	0.25
		10.00	-0.61	0.53	0.91	0.27
		10.50	-0.67	0.44	0.82	0.19
		11.00	-0.81	0.25	0.62	0.01
		11.50	-0.96	-0.02	0.33	-0.24
		12.00	-1.07	-0.25	0.06	-0.44
		12.50	-1.11	-0.38	-0.11	-0.54
		13.00	-1.13	-0.44	-0.18	-0.59
		13.50	-1.13	-0.45	-0.21	-0.60
		14.00	-1.13	-0.46	-0.22	-0.60
Structure (incl. pka values)	[redacted]					

Table 14: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	**VG**	**KLOP**	**PHYS**	**WEIGHTED**
[redacted]	VG: 4.97 KLOP: 6.09 PHYS: 5.86 Weighted: 5.64 logD at pI VG: 1.92 KLOP: 3.61 PHYS: 3.78 Weighted: 3.10	0.00	-2.23	-0.34	0.09	-0.83
		0.50	-2.21	-0.31	0.13	-0.80
		1.00	-2.16	-0.22	0.23	-0.72
		1.50	-2.03	-0.06	0.42	-0.56
		2.00	-1.86	0.16	0.65	-0.35
		2.50	-1.72	0.32	0.83	-0.19
		3.00	-1.64	0.40	0.91	-0.11
		3.50	-1.61	0.44	0.95	-0.08
		4.00	-1.58	0.46	0.96	-0.06
		4.50	-1.51	0.49	0.98	-0.02
		5.00	-1.34	0.58	1.03	0.07
		5.50	-1.05	0.78	1.14	0.27
		6.00	-0.64	1.11	1.39	0.60
		6.50	-0.17	1.54	1.76	1.03
		7.00	0.31	2.01	2.20	1.50
		7.50	0.79	2.48	2.66	1.98
		8.00	1.23	2.92	3.10	2.42
		8.50	1.59	3.28	3.46	2.77
		9.00	1.81	3.50	3.68	3.00
		9.50	1.91	3.60	3.78	3.10
		10.00	1.92	3.61	3.78	3.10
		10.50	1.87	3.53	3.71	3.03
		11.00	1.73	3.36	3.52	2.86
		11.50	1.54	3.10	3.22	2.60
		12.00	1.40	2.85	2.89	2.36
		12.50	1.33	2.70	2.65	2.21
		13.00	1.30	2.63	2.52	2.14
		13.50	1.29	2.61	2.47	2.12
		14.00	1.29	2.60	2.45	2.11
Structure (incl. pka values)	[redacted]					

Table 15: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 4.18 KLOP: 5.15 PHYS: 4.92 Weighted: 4.75 logD at pI VG: 1.13 KLOP: 2.67 PHYS: 2.85 Weighted: 2.21	0.00	-3.03	-1.28	-0.85	-1.72
		0.50	-3.01	-1.25	-0.81	-1.69
		1.00	-2.95	-1.16	-0.70	-1.61
		1.50	-2.83	-0.99	-0.51	-1.45
		2.00	-2.65	-0.78	-0.28	-1.24
		2.50	-2.51	-0.62	-0.11	-1.08
		3.00	-2.44	-0.53	-0.02	-1.00
		3.50	-2.40	-0.50	0.01	-0.97
		4.00	-2.37	-0.48	0.03	-0.95
		4.50	-2.30	-0.44	0.04	-0.91
		5.00	-2.14	-0.36	0.09	-0.82
		5.50	-1.84	-0.16	0.21	-0.62
		6.00	-1.43	0.17	0.45	-0.29
		6.50	-0.96	0.60	0.82	0.14
		7.00	-0.48	1.07	1.26	0.61
		7.50	-0.01	1.54	1.73	1.09
		8.00	0.44	1.98	2.17	1.53
		8.50	0.80	2.34	2.52	1.89
		9.00	1.02	2.56	2.75	2.11
		9.50	1.12	2.66	2.84	2.21
		10.00	1.13	2.67	2.85	2.21
		10.50	1.07	2.60	2.77	2.14
		11.00	0.93	2.42	2.58	1.97
		11.50	0.75	2.16	2.28	1.71
		12.00	0.61	1.91	1.96	1.47
		12.50	0.54	1.76	1.71	1.32
		13.00	0.51	1.69	1.59	1.26
		13.50	0.50	1.67	1.53	1.23
		14.00	0.50	1.66	1.52	1.22
Structure (incl. pka values)	[redacted]					

Table 16: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 3.38 KLOP: 4.22 PHYS: 3.98 Weighted: 3.86 logD at pI VG: 0.34 KLOP: 1.73 PHYS: 1.91 Weighted: 1.33	0.00	-3.82	-2.22	-1.78	-2.61
		0.50	-3.80	-2.19	-1.74	-2.58
		1.00	-3.74	-2.10	-1.64	-2.50
		1.50	-3.62	-1.93	-1.45	-2.34
		2.00	-3.45	-1.72	-1.22	-2.13
		2.50	-3.31	-1.56	-1.05	-1.97
		3.00	-3.23	-1.47	-0.96	-1.89
		3.50	-3.19	-1.44	-0.93	-1.86
		4.00	-3.16	-1.42	-0.91	-1.84
		4.50	-3.09	-1.38	-0.89	-1.80
		5.00	-2.93	-1.30	-0.85	-1.71
		5.50	-2.63	-1.10	-0.73	-1.51
		6.00	-2.22	-0.77	-0.49	-1.18
		6.50	-1.76	-0.34	-0.12	-0.75
		7.00	-1.27	0.13	0.33	-0.28
		7.50	-0.80	0.60	0.79	0.20
		8.00	-0.35	1.04	1.23	0.64
		8.50	0.00	1.40	1.59	1.00
		9.00	0.23	1.62	1.81	1.22
		9.50	0.33	1.72	1.91	1.32
		10.00	0.34	1.73	1.91	1.33
		10.50	0.28	1.66	1.84	1.25
		11.00	0.14	1.48	1.65	1.08
		11.50	-0.04	1.22	1.34	0.82
		12.00	-0.19	0.97	1.02	0.58
		12.50	-0.26	0.82	0.78	0.43
		13.00	-0.28	0.75	0.65	0.37
		13.50	-0.29	0.73	0.60	0.34
		14.00	-0.29	0.72	0.58	0.34
Structure (incl. pka values)	[redacted]					

Table 17: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 2.59 KLOP: 3.28 PHYS: 3.05 Weighted: 2.97 logD at pI VG: -0.45 KLOP: 0.79 PHYS: 0.98 Weighted: 0.44	0.00	-4.61	-3.16	-2.72	-3.50
		0.50	-4.59	-3.12	-2.68	-3.47
		1.00	-4.53	-3.04	-2.58	-3.39
		1.50	-4.41	-2.87	-2.38	-3.23
		2.00	-4.24	-2.66	-2.15	-3.02
		2.50	-4.10	-2.49	-1.98	-2.86
		3.00	-4.02	-2.41	-1.90	-2.78
		3.50	-3.99	-2.38	-1.86	-2.75
		4.00	-3.95	-2.36	-1.85	-2.72
		4.50	-3.88	-2.32	-1.83	-2.69
		5.00	-3.72	-2.23	-1.78	-2.60
		5.50	-3.42	-2.04	-1.66	-2.40
		6.00	-3.02	-1.71	-1.42	-2.06
		6.50	-2.55	-1.28	-1.05	-1.63
		7.00	-2.07	-0.81	-0.61	-1.16
		7.50	-1.59	-0.34	-0.15	-0.69
		8.00	-1.15	0.10	0.29	-0.25
		8.50	-0.79	0.46	0.65	0.11
		9.00	-0.56	0.69	0.87	0.33
		9.50	-0.47	0.78	0.97	0.43
		10.00	-0.45	0.79	0.98	0.44
		10.50	-0.51	0.72	0.90	0.37
		11.00	-0.65	0.54	0.71	0.19
		11.50	-0.84	0.28	0.41	-0.07
		12.00	-0.98	0.04	0.08	-0.31
		12.50	-1.05	-0.12	-0.16	-0.46
		13.00	-1.08	-0.18	-0.29	-0.52
		13.50	-1.08	-0.21	-0.34	-0.55
		14.00	-1.09	-0.22	-0.36	-0.55
Structure (incl. pka values)	[redacted]					

Table 18: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 4.87 KLOP: 5.77 PHYS: 5.85 Weighted: 5.50 logD at pI VG: 0.09 KLOP: 1.60 PHYS: 2.13 Weighted: 1.26	0.00	-2.42	-0.79	-0.27	-1.17
		0.50	-2.22	-0.69	-0.19	-1.05
		1.00	-1.89	-0.46	0.01	-0.79
		1.50	-1.46	-0.11	0.34	-0.42
		2.00	-1.02	0.32	0.76	0.01
		2.50	-0.60	0.75	1.20	0.44
		3.00	-0.27	1.13	1.61	0.81
		3.50	-0.06	1.39	1.90	1.06
		4.00	0.05	1.54	2.06	1.20
		4.50	0.09	1.59	2.12	1.25
		5.00	0.09	1.60	2.13	1.26
		5.50	0.06	1.57	2.10	1.23
		6.00	-0.04	1.47	2.00	1.14
		6.50	-0.25	1.26	1.80	0.93
		7.00	-0.59	0.93	1.47	0.59
		7.50	-0.98	0.55	1.09	0.21
		8.00	-1.34	0.22	0.77	-0.13
		8.50	-1.60	0.01	0.57	-0.34
		9.00	-1.73	-0.10	0.48	-0.45
		9.50	-1.79	-0.15	0.43	-0.51
		10.00	-1.85	-0.21	0.36	-0.57
		10.50	-1.96	-0.34	0.23	-0.69
		11.00	-2.13	-0.56	-0.01	-0.91
		11.50	-2.31	-0.83	-0.34	-1.18
		12.00	-2.42	-1.04	-0.64	-1.39
		12.50	-2.46	-1.15	-0.83	-1.50
		13.00	-2.48	-1.20	-0.92	-1.54
		13.50	-2.49	-1.21	-0.95	-1.55
		14.00	-2.49	-1.22	-0.96	-1.56
Structure (incl. pka values)	[redacted]					

Table 19: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 4.08 KLOP: 4.84 PHYS: 4.92 Weighted: 4.61 logD at pI VG: -0.70 KLOP: 0.66 PHYS: 1.19 Weighted: 0.37	0.00	-3.21	-1.73	-1.21	-2.06
		0.50	-3.01	-1.63	-1.12	-1.94
		1.00	-2.68	-1.40	-0.92	-1.68
		1.50	-2.26	-1.05	-0.59	-1.31
		2.00	-1.81	-0.62	-0.17	-0.88
		2.50	-1.39	-0.19	0.27	-0.45
		3.00	-1.06	0.19	0.67	-0.08
		3.50	-0.85	0.45	0.96	0.17
		4.00	-0.75	0.60	1.12	0.31
		4.50	-0.71	0.65	1.18	0.36
		5.00	-0.70	0.66	1.19	0.37
		5.50	-0.73	0.63	1.16	0.34
		6.00	-0.83	0.54	1.07	0.25
		6.50	-1.04	0.33	0.86	0.04
		7.00	-1.38	-0.00	0.53	-0.30
		7.50	-1.77	-0.39	0.16	-0.68
		8.00	-2.14	-0.72	-0.16	-1.01
		8.50	-2.39	-0.93	-0.36	-1.23
		9.00	-2.52	-1.04	-0.46	-1.34
		9.50	-2.59	-1.09	-0.51	-1.40
		10.00	-2.64	-1.15	-0.57	-1.46
		10.50	-2.75	-1.28	-0.70	-1.58
		11.00	-2.92	-1.50	-0.95	-1.80
		11.50	-3.10	-1.77	-1.28	-2.07
		12.00	-3.21	-1.98	-1.58	-2.28
		12.50	-3.26	-2.09	-1.77	-2.38
		13.00	-3.27	-2.13	-1.86	-2.43
		13.50	-3.28	-2.15	-1.89	-2.44
		14.00	-3.28	-2.15	-1.90	-2.45
Structure (incl. pka values)	[redacted]					

Table 20: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 3.29 KLOP: 3.90 PHYS: 3.98 Weighted: 3.72 logD at pI VG: -1.50 KLOP: -0.28 PHYS: 0.26 Weighted: -0.52	0.00	-4.00	-2.67	-2.15	-2.95
		0.50	-3.81	-2.56	-2.06	-2.82
		1.00	-3.47	-2.34	-1.86	-2.57
		1.50	-3.05	-1.99	-1.53	-2.20
		2.00	-2.60	-1.56	-1.11	-1.77
		2.50	-2.18	-1.13	-0.67	-1.34
		3.00	-1.85	-0.75	-0.27	-0.97
		3.50	-1.64	-0.49	0.03	-0.71
		4.00	-1.54	-0.34	0.18	-0.58
		4.50	-1.50	-0.29	0.25	-0.53
		5.00	-1.50	-0.28	0.26	-0.52
		5.50	-1.53	-0.31	0.23	-0.55
		6.00	-1.62	-0.40	0.13	-0.64
		6.50	-1.84	-0.61	-0.08	-0.85
		7.00	-2.17	-0.94	-0.40	-1.18
		7.50	-2.57	-1.32	-0.78	-1.57
		8.00	-2.93	-1.66	-1.10	-1.90
		8.50	-3.18	-1.87	-1.30	-2.12
		9.00	-3.31	-1.97	-1.39	-2.23
		9.50	-3.38	-2.03	-1.45	-2.29
		10.00	-3.44	-2.09	-1.51	-2.35
		10.50	-3.54	-2.21	-1.64	-2.47
		11.00	-3.72	-2.44	-1.89	-2.69
		11.50	-3.89	-2.71	-2.21	-2.96
		12.00	-4.00	-2.92	-2.51	-3.17
		12.50	-4.05	-3.03	-2.70	-3.27
		13.00	-4.07	-3.07	-2.79	-3.32
		13.50	-4.07	-3.09	-2.83	-3.33
		14.00	-4.07	-3.09	-2.84	-3.33
Structure (incl. pka values)	[redacted]					

Table 21: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 2.50 KLOP: 2.96 PHYS: 3.04 Weighted: 2.83 logD at pI VG: -2.29 KLOP: -1.22 PHYS: -0.68 Weighted: -1.41	0.00	-4.80	-3.61	-3.08	-3.84
		0.50	-4.60	-3.50	-2.99	-3.71
		1.00	-4.26	-3.28	-2.80	-3.46
		1.50	-3.84	-2.92	-2.47	-3.09
		2.00	-3.39	-2.50	-2.05	-2.65
		2.50	-2.98	-2.07	-1.60	-2.23
		3.00	-2.65	-1.69	-1.20	-1.86
		3.50	-2.44	-1.42	-0.91	-1.60
		4.00	-2.33	-1.28	-0.75	-1.47
		4.50	-2.29	-1.22	-0.69	-1.41
		5.00	-2.29	-1.22	-0.68	-1.41
		5.50	-2.32	-1.25	-0.71	-1.44
		6.00	-2.42	-1.34	-0.80	-1.53
		6.50	-2.63	-1.55	-1.01	-1.74
		7.00	-2.96	-1.88	-1.34	-2.07
		7.50	-3.36	-2.26	-1.72	-2.46
		8.00	-3.72	-2.59	-2.04	-2.79
		8.50	-3.98	-2.81	-2.24	-3.01
		9.00	-4.11	-2.91	-2.33	-3.12
		9.50	-4.17	-2.97	-2.38	-3.17
		10.00	-4.23	-3.03	-2.44	-3.24
		10.50	-4.34	-3.15	-2.58	-3.36
		11.00	-4.51	-3.38	-2.82	-3.58
		11.50	-4.68	-3.65	-3.15	-3.85
		12.00	-4.79	-3.86	-3.45	-4.06
		12.50	-4.84	-3.97	-3.64	-4.16
		13.00	-4.86	-4.01	-3.73	-4.20
		13.50	-4.86	-4.03	-3.76	-4.22
		14.00	-4.87	-4.03	-3.77	-4.22
Structure (incl. pka values)	[redacted]					

Table 22: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 4.87 KLOP: 5.77 PHYS: 5.85 Weighted: 5.50 logD at pI VG: -1.29 KLOP: 0.76 PHYS: 1.46 Weighted: 0.31	0.00	-2.50	-0.76	-0.21	-1.16
		0.50	-2.40	-0.61	-0.03	-1.02
		1.00	-2.19	-0.32	0.31	-0.74
		1.50	-1.88	0.08	0.74	-0.36
		2.00	-1.59	0.42	1.11	-0.03
		2.50	-1.41	0.63	1.32	0.17
		3.00	-1.33	0.71	1.41	0.26
		3.50	-1.30	0.75	1.45	0.29
		4.00	-1.29	0.76	1.46	0.30
		4.50	-1.29	0.76	1.46	0.31
		5.00	-1.29	0.76	1.46	0.31
		5.50	-1.29	0.76	1.46	0.31
		6.00	-1.29	0.76	1.46	0.31
		6.50	-1.29	0.76	1.46	0.30
		7.00	-1.30	0.75	1.45	0.30
		7.50	-1.31	0.74	1.43	0.28
		8.00	-1.35	0.69	1.38	0.23
		8.50	-1.45	0.56	1.25	0.11
		9.00	-1.61	0.34	1.01	-0.10
		9.50	-1.78	0.08	0.71	-0.35
		10.00	-1.89	-0.14	0.43	-0.55
		10.50	-2.00	-0.32	0.20	-0.72
		11.00	-2.14	-0.53	-0.05	-0.92
		11.50	-2.30	-0.79	-0.35	-1.16
		12.00	-2.41	-1.01	-0.64	-1.37
		12.50	-2.46	-1.14	-0.83	-1.49
		13.00	-2.48	-1.19	-0.92	-1.53
		13.50	-2.49	-1.21	-0.95	-1.55
		14.00	-2.49	-1.22	-0.96	-1.56
Structure (incl. pka values)	[redacted]					

Table 23: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 4.08 KLOP: 4.84 PHYS: 4.92 Weighted: 4.61 logD at pI VG: -2.08 KLOP: -0.18 PHYS: 0.52 Weighted: -0.58	0.00	-3.29	-1.70	-1.15	-2.05
		0.50	-3.19	-1.55	-0.96	-1.91
		1.00	-2.98	-1.26	-0.63	-1.63
		1.50	-2.68	-0.86	-0.20	-1.25
		2.00	-2.38	-0.52	0.17	-0.91
		2.50	-2.20	-0.31	0.39	-0.71
		3.00	-2.13	-0.22	0.48	-0.63
		3.50	-2.10	-0.19	0.51	-0.60
		4.00	-2.09	-0.18	0.52	-0.59
		4.50	-2.08	-0.18	0.52	-0.58
		5.00	-2.08	-0.18	0.52	-0.58
		5.50	-2.08	-0.18	0.52	-0.58
		6.00	-2.08	-0.18	0.52	-0.58
		6.50	-2.09	-0.18	0.52	-0.58
		7.00	-2.09	-0.19	0.52	-0.59
		7.50	-2.10	-0.20	0.50	-0.61
		8.00	-2.15	-0.25	0.45	-0.66
		8.50	-2.24	-0.37	0.32	-0.78
		9.00	-2.40	-0.59	0.08	-0.99
		9.50	-2.57	-0.86	-0.23	-1.24
		10.00	-2.68	-1.08	-0.51	-1.44
		10.50	-2.79	-1.26	-0.74	-1.61
		11.00	-2.93	-1.47	-0.98	-1.81
		11.50	-3.09	-1.72	-1.29	-2.05
		12.00	-3.20	-1.95	-1.58	-2.26
		12.50	-3.25	-2.08	-1.77	-2.38
		13.00	-3.27	-2.13	-1.86	-2.42
		13.50	-3.28	-2.15	-1.89	-2.44
		14.00	-3.28	-2.15	-1.90	-2.45
Structure (incl. pka values)	[redacted]					

Table 24: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 3.29 KLOP: 3.90 PHYS: 3.98 Weighted: 3.72 logD at pI VG: -2.88 KLOP: -1.12 PHYS: -0.41 Weighted: -1.47	0.00	-4.09	-2.64	-2.08	-2.94
		0.50	-3.99	-2.49	-1.90	-2.80
		1.00	-3.78	-2.19	-1.56	-2.52
		1.50	-3.47	-1.80	-1.13	-2.14
		2.00	-3.18	-1.45	-0.76	-1.80
		2.50	-3.00	-1.25	-0.55	-1.60
		3.00	-2.92	-1.16	-0.46	-1.52
		3.50	-2.89	-1.13	-0.43	-1.49
		4.00	-2.88	-1.12	-0.42	-1.48
		4.50	-2.88	-1.12	-0.41	-1.47
		5.00	-2.88	-1.12	-0.41	-1.47
		5.50	-2.88	-1.12	-0.41	-1.47
		6.00	-2.88	-1.12	-0.41	-1.47
		6.50	-2.88	-1.12	-0.41	-1.47
		7.00	-2.88	-1.12	-0.42	-1.48
		7.50	-2.90	-1.14	-0.44	-1.50
		8.00	-2.94	-1.19	-0.49	-1.55
		8.50	-3.04	-1.31	-0.62	-1.66
		9.00	-3.20	-1.53	-0.86	-1.88
		9.50	-3.36	-1.80	-1.17	-2.13
		10.00	-3.48	-2.02	-1.45	-2.33
		10.50	-3.58	-2.19	-1.67	-2.50
		11.00	-3.72	-2.40	-1.92	-2.70
		11.50	-3.88	-2.66	-2.22	-2.94
		12.00	-3.99	-2.89	-2.51	-3.15
		12.50	-4.05	-3.01	-2.70	-3.27
		13.00	-4.06	-3.07	-2.79	-3.31
		13.50	-4.07	-3.09	-2.82	-3.33
		14.00	-4.07	-3.09	-2.84	-3.33
Structure (incl. pka values)	[redacted]					

Table 25: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 2.50 KLOP: 2.96 PHYS: 3.04 Weighted: 2.83 logD at pI VG: -3.67 KLOP: -2.05 PHYS: -1.35 Weighted: -2.36	0.00	-4.88	-3.58	-3.02	-3.83
		0.50	-4.78	-3.43	-2.84	-3.69
		1.00	-4.57	-3.13	-2.50	-3.41
		1.50	-4.26	-2.74	-2.07	-3.03
		2.00	-3.97	-2.39	-1.70	-2.69
		2.50	-3.79	-2.19	-1.49	-2.49
		3.00	-3.71	-2.10	-1.40	-2.41
		3.50	-3.68	-2.07	-1.36	-2.38
		4.00	-3.67	-2.06	-1.35	-2.37
		4.50	-3.67	-2.06	-1.35	-2.36
		5.00	-3.67	-2.05	-1.35	-2.36
		5.50	-3.67	-2.05	-1.35	-2.36
		6.00	-3.67	-2.06	-1.35	-2.36
		6.50	-3.67	-2.06	-1.35	-2.36
		7.00	-3.68	-2.06	-1.36	-2.37
		7.50	-3.69	-2.08	-1.37	-2.39
		8.00	-3.73	-2.13	-1.43	-2.43
		8.50	-3.83	-2.25	-1.56	-2.55
		9.00	-3.99	-2.47	-1.80	-2.77
		9.50	-4.15	-2.74	-2.10	-3.02
		10.00	-4.27	-2.96	-2.38	-3.22
		10.50	-4.37	-3.13	-2.61	-3.39
		11.00	-4.52	-3.34	-2.86	-3.59
		11.50	-4.67	-3.60	-3.16	-3.83
		12.00	-4.79	-3.82	-3.45	-4.04
		12.50	-4.84	-3.95	-3.64	-4.16
		13.00	-4.86	-4.01	-3.73	-4.20
		13.50	-4.86	-4.02	-3.76	-4.22
		14.00	-4.87	-4.03	-3.77	-4.22
Structure (incl. pka values)	[redacted]					

Table 26: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 3.77 KLOP: 4.53 PHYS: 4.47 Weighted: 4.25	0.00	0.32	1.62	1.72	1.22
		0.50	0.32	1.62	1.72	1.22
		1.00	0.32	1.62	1.72	1.22
		1.50	0.32	1.62	1.72	1.22
		2.00	0.32	1.62	1.72	1.22
		2.50	0.32	1.62	1.72	1.22
		3.00	0.32	1.62	1.72	1.22
		3.50	0.32	1.62	1.72	1.22
		4.00	0.32	1.62	1.72	1.22
		4.50	0.32	1.63	1.72	1.22
		5.00	0.33	1.63	1.72	1.22
		5.50	0.34	1.63	1.73	1.23
		6.00	0.39	1.65	1.74	1.25
		6.50	0.51	1.69	1.77	1.31
		7.00	0.76	1.8	1.85	1.44
		7.50	1.13	2.04	2.04	1.72
		8.00	1.58	2.4	2.37	2.11
		8.50	2.06	2.84	2.79	2.56
		9.00	2.54	3.31	3.25	3.03
		9.50	2.98	3.75	3.69	3.47
		10.00	3.35	4.12	4.05	3.84
		10.50	3.59	4.35	4.29	4.08
		11.00	3.7	4.47	4.4	4.19
		11.50	3.74	4.51	4.45	4.23
		12.00	3.76	4.52	4.46	4.25
		12.50	3.76	4.53	4.47	4.25
		13.00	3.76	4.53	4.47	4.25
		13.50	3.76	4.53	4.47	4.25
		14.00	3.76	4.53	4.47	4.25
Structure (incl. pka values)	[redacted]					

Table 27: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 4.56 KLOP: 4.47 PHYS: 5.41 Weighted: 5.14	0.00	1.11	2.56	2.66	2.11
		0.50	1.11	2.56	2.66	2.11
		1.00	1.11	2.56	2.66	2.11
		1.50	1.11	2.56	2.66	2.11
		2.00	1.11	2.56	2.66	2.11
		2.50	1.11	2.56	2.66	2.11
		3.00	1.11	2.56	2.66	2.11
		3.50	1.11	2.56	2.66	2.11
		4.00	1.11	2.56	2.66	2.11
		4.50	1.11	2.56	2.66	2.11
		5.00	1.12	2.57	2.66	2.11
		5.50	1.14	2.57	2.66	2.12
		6.00	1.18	2.58	2.67	2.14
		6.50	1.3	2.63	2.7	2.19
		7.00	1.55	2.74	2.79	2.33
		7.50	1.92	2.98	2.98	2.61
		8.00	2.37	3.34	3.31	3
		8.50	2.85	3.78	3.73	3.45
		9.00	3.33	4.25	4.19	3.92
		9.50	3.77	4.69	4.63	4.36
		10.00	4.14	5.05	4.99	4.73
		10.50	4.38	5.29	5.23	4.97
		11.00	4.49	5.4	5.34	5.08
		11.50	4.54	5.45	5.38	5.12
		12.00	4.55	5.46	5.4	5.14
		12.50	4.56	5.47	5.4	5.14
		13.00	4.56	5.47	5.4	5.14
		13.50	4.56	5.47	5.41	5.14
		14.00	4.56	5.47	5.41	5.14
Structure (incl. pka values)	[redacted]					

Table 28: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 3.06 KLOP: 3.80 PHYS: 3.93 Weighted: 3.60	0.00	-7.65	-5.41	-4.85	-5.97
		0.50	-7.65	-5.41	-4.85	-5.97
		1.00	-7.65	-5.41	-4.85	-5.97
		1.50	-7.65	-5.41	-4.85	-5.97
		2.00	-7.63	-5.4	-4.84	-5.96
		2.50	-7.58	-5.38	-4.83	-5.94
		3.00	-7.46	-5.33	-4.78	-5.87
		3.50	-7.21	-5.19	-4.67	-5.71
		4.00	-6.83	-4.92	-4.44	-5.41
		4.50	-6.38	-4.53	-4.07	-5
		5.00	-5.88	-4.06	-3.62	-4.53
		5.50	-5.34	-3.57	-3.14	-4.03
		6.00	-4.73	-3.06	-2.64	-3.5
		6.50	-4	-2.51	-2.12	-2.91
		7.00	-3.16	-1.9	-1.58	-2.25
		7.50	-2.25	-1.22	-0.97	-1.51
		8.00	-1.31	-0.43	-0.24	-0.68
		8.50	-0.35	0.44	0.59	0.22
		9.00	0.56	1.32	1.46	1.11
		9.50	1.37	2.12	2.24	1.91
		10.00	2.01	2.76	2.88	2.55
		10.50	2.49	3.24	3.36	3.03
		11.00	2.8	3.55	3.67	3.34
		11.50	2.96	3.71	3.83	3.5
		12.00	3.03	3.77	3.9	3.56
		12.50	3.05	3.79	3.92	3.59
		13.00	3.05	3.8	3.92	3.59
		13.50	3.06	3.8	3.93	3.6
		14.00	3.06	3.8	3.93	3.6
Structure (incl. pka values)	[redacted]					

Table 29: Comparison of the various LogP and LogD results for [redacted]

Component	Log P	LogD				
		pH	VG	KLOP	PHYS	WEIGHTED
[redacted]	VG: 3.01 KLOP: 3.73 PHYS: 3.78 Log P Log D pH VG KLOP PHYS WEIGHTED Weighted: 3.51 logD at pI VG: -0.24 KLOP: 1.10 PHYS: 1.45 Weighted: 0.77	0.00	-7.85	-5.78	-5.11	-6.25
		0.50	-7.83	-5.74	-5.07	-6.22
		1.00	-7.76	-5.65	-4.95	-6.12
		1.50	-7.62	-5.46	-4.75	-5.95
		2.00	-7.43	-5.25	-4.51	-5.74
		2.50	-7.26	-5.08	-4.34	-5.57
		3.00	-7.08	-4.95	-4.22	-5.43
		3.50	-6.81	-4.79	-4.09	-5.24
		4.00	-6.43	-4.51	-3.84	-4.94
		4.50	-5.97	-4.12	-3.47	-4.53
		5.00	-5.48	-3.65	-3.02	-4.06
		5.50	-4.95	-3.16	-2.54	-3.56
		6.00	-4.37	-2.65	-2.05	-3.04
		6.50	-3.71	-2.1	-1.55	-2.48
		7.00	-3.01	-1.53	-1.06	-1.89
		7.50	-2.37	-0.97	-0.56	-1.32
		8.00	-1.81	-0.44	-0.07	-0.78
		8.50	-1.3	0.06	0.42	-0.28
		9.00	-0.84	0.51	0.86	0.18
		9.50	-0.47	0.88	1.23	0.54
		10.00	-0.24	1.1	1.45	0.77
		10.50	-0.18	1.14	1.49	0.81
		11.00	-0.27	1.02	1.36	0.69
		11.50	-0.43	0.77	1.09	0.46
		12.00	-0.57	0.52	0.78	0.22
		12.50	-0.63	0.35	0.56	0.08
		13.00	-0.66	0.28	0.44	0.01
		13.50	-0.67	0.25	0.4	-0.01
		14.00	-0.67	0.24	0.38	-0.02
Structure (incl. pka values)	[redacted]					

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Dissociation Constant** It is not technically feasible to experimentally determine the dissociation constants of Ampholyt 20 due to the material being a mixture of a number of soluble components. It should also be noted that OECD guideline number 112 only applies to active substances if the water solubility cannot be measured. The components making up Ampholyt 20 are assumed to be ionised in the environmental pH range (4 – 9) based on the presence of acidic (pKa ~ 4) and basic (pKa ~ 10) functional groups in the respective structures. The applicants assumption is confirmed by the applicant by the provision of pKa values for the indivdual components of Ampholyt 20 using QSAR (generated by MarvinSketch) See Table 1 below. The following observations can be made regarding the QSAR generated pKa values: (1) Structure class "1" - R-NH-C3H6-NH2: These substances represent propylene diamine molecules of varying chain length; they cannot dissociate, instead they are protonated under physiological and environmental conditions due to their high PK value of 10.8. (2) Structure classes 2-5: These groups of molecules contain not only amine, but also carboxyl groups. As such, they may contain both protonated (cationic) as well as dissociated (anionic) structures at environmental or physiologically relevant pH. (3) The „minor constituents" included in Ampholyt 20 contain eith amine or carboxyl groups, or both and therefore may contain both protonated (cationic) as well as dissociated (anionic) structures at environmental or physiologically relevant pH. Overall, based on the above mentioned properties, dissociation is not relevant under practical conditions, since at neutral, environmental and physiological pH conditions, >90% of the consituenst should be in the ionic form.
Results and discussion	The applicant has provided QSAR generated pKa values for the individual components in Ampholyt 20 because it technically not possible to provide an experimental pKa value for Ampholyt 20.
Conclusion	The QSAR generated pKa data suggests that the individual components included in Ampholyt 20 will be ionised and cationic under relevant pH conditions.
Reliability	2 – It is not technically feasible to experiremnatlly determine the dissociation constant for Ampholyt 20, however the applicant has provided QSAR pKa values for each constituent of Ampholyt 20.
Acceptability	Acceptable
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Table 1: QSAR-calculated pKa values for the components of Ampholyt 20

Structure (incl. pka values)	pka values
[redacted]	-NH-: 10.80 -NH_2: 8.44
[redacted]	-NH-: 10.80 -NH_2: 8.44
[redacted]	-NH-: 10.80 -NH_2: 8.44
[redacted]	-NH-: 10.80 -NH_2: 8.44
[redacted]	-NH-: 10.79 -NH_2: 8.90 -OH: 2.07
[redacted]	-NH-: 10.79 -NH_2: 8.90 -OH: 2.07
[redacted]	-NH-: 10.79 -NH_2: 8.90 -OH: 2.07
[redacted]	-NH-: 10.79 -NH_2: 8.90 -OH: 2.07
[redacted]	-NH-: 10.90 -NH-: 8.67 -OH: 2.14
[redacted]	-NH-: 10.90 -NH-: 8.67 -OH: 2.14
[redacted]	-NH-: 10.90 -NH-: 8.67 -OH: 2.14
[redacted]	-NH-: 10.90 -NH-: 8.67 -OH: 2.14
[redacted]	-NH-: 10.68 -N-: 6.37 -OH: 3.54 -OH: 2.81
[redacted]	-NH-: 10.68 -N-: 6.37 -OH: 3.54 -OH: 2.81
[redacted]	-NH-: 10.68 -N-: 6.37 -OH: 3.54 -OH: 2.81
[redacted]	-NH-: 10.68 -N-: 6.37 -OH: 3.54 -OH: 2.81
[redacted]	-N-: 10.98 -OH: 1.38 -NH-: 8.67 -OH: 2.13

Structure (incl. pka values)	pka values
[redacted]	-N-: 10.98 -OH: 1.38 -NH-: 8.67 -OH: 2.13
[redacted]	-N-: 10.98 -OH: 1.38 -NH-: 8.67 -OH: 2.13
[redacted]	-N-: 10.98 -OH: 1.38 -NH-: 8.67 -OH: 2.13
[redacted]	-NH2: 10.21
[redacted]	-NH2: 10.21
[redacted]	-NH2: 9.49 -NH2: 10.89 -N-: 7.05
[redacted]	-NH: 29.72 -NH: 10.97 -N-:7.06 -OH:2.07

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Solubility in organic solvents, including the effect of temperature on solubility** The active substance is soluble in methanol and essentially insoluble/not readily soluble in apolar solvents like n-heptane.
Results and discussion	No further data required
Conclusion	No further data required
Reliability	1
Acceptability	Acceptable
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Thermal stability, identity of relevant breakdown products** A DSC analysis study concluded that the dry active substance started to decompose at *ca.* 140°C. The applicant has made the following statment in relation to the identity of decomposition products: „In the absence of oxygen the following decomposition products would be expected– 1. Decarboxylation with formation of CO_2. 2. Cleavage of N-C- bonds releasing amines and fatty acids. 3. Additional heating would be expected to create NH_3, CH_4 and carbon residues. In the presence of oxygen, decomposition should take place at a lower temperature and lead to CO_2, H_2O and N-oxides“.
Results and discussion	The active substance decomposes at *ca.* 140°C. The applicants' statement in relation to the anticipated decomposition products is acceptable.
Conclusion	The active substance decomposes at *ca.* 140°C.
Reliability	1
Acceptability	Acceptable.
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Flammability and auto-flammability** The test substance used in the flammability study should have been technical material as manufactured. However, since the dry technical material was not considered to be flammable and the technical material as manufactured is made up of *ca.* 80% w/w water, then it can be stated with certainty that the technical material as manufactured will not classify as being flammable or highly flammable.
Results and discussion	No further data required
Conclusion	No further data required
Reliability	1
Acceptability	Acceptable
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Flash point** The flash point should have been determined using the technical material as manufactured (liquid). However, since the technical material as manufactured is made up of *ca.* 80% w/w water, then it can be stated with certainty that the technical material as manufactured will not classify as being flammable or highly flammable.
Results and discussion	No further data required
Conclusion	No further data required
Reliability	1
Acceptability	Acceptable
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**X – Viscosity** The technical material as manufactured is a liquid (*ca.* 80% water). The applicant provided the following viscosity study: *Reference: ‚Ampholyt 20 – Kinematic Viscosity OECD 114', [redacted], July 2007.* The kinematic vsocosity was determined at 20 and 40°C using a capillary viscometer according to OECD 114. The kinematioc viscosity at 20°C was reported as 7.409 mm^2/s. The kinematioc viscosity at 40°C was reported as 4.516mm^2/s.
Results and discussion	The kinematioc viscosity at 20oC was reported as 7.409 mm2/s. The kinematioc viscosity at 40oC was reported as 4.516mm2/s. The Kinematic viscosity of technical Ampholyt 20 is dependent on temperature.
Conclusion	The Kinematic viscosity of technical Ampholyt 20 is dependent on temperature.
Reliability	1
Acceptability	Acceptable
Remarks	No further data required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

	Evaluation by Competent Authorities
	Evaluation by Rapporteur Member State
Date	09/08/13
Materials and Methods	**Corrosivity to metals** The applicant also provided a corrosivity to metals study in order to determine whether Ampholyt 20 would classify as being corrosive to metals under the CLP Regulation. Reference: *Corrosion Test (05/1984): TEGO 2000. Goldschmidt Home Care.* The tests were performed at 25°C over 14 days reflecting the use conditions of Ampholyt 20 in the dairy industry.
Results and discussion	The CLP classification criteria (test temperature and storage period) are not covered by the method presented by the applicant. The CLP Regulation sets out the criteria for the recommended corrosive to metals UN test method – A Category 1 Classification is applied if the corrosion rate on either steel or aluminium surfaces exceeds 6,25 mm per year at a test temperature of 55 °C when tested on both materials. The specimen to be used for the test shall be made of the following materials: (a) for the purposes of testing steel, steel types — S235JR+CR (1.0037 resp.St 37-2), — S275J2G3+CR (1.0144 resp.St 44-3), ISO 3574 as amended, Unified Numbering System (UNS) G 10200, or SAE 1020; (b) for the purposes of testing aluminium: non-clad types 7075-T6 or AZ5GU-T6.
Conclusion	The study can be used as supporting information. The applicant should provide a new corrosivity to metals study in order to confirm their proposal of not classifying from a phys.chem. point of view under the CLP Regulation. The results of this analysis should be provided to the RMS at least 6 months before the date of entry into force.
Reliability	3
Acceptability	Not acceptable
Remarks	A new corrosivity to metals study is required.
	Comments from
Date	*Give date of the comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*