

European Commission



**Combined Draft Renewal Assessment Report prepared according to
Regulation (EC) N° 1107/2009
and
Proposal for Harmonised Classification and Labelling (CLH Report)
according to Regulation (EC) N° 1272/2008**

HEPTAMALOXYLOGLUCAN

Volume 3 – B.2 (AS)

Rapporteur Member State: France
Co-Rapporteur Member State: Spain

Version History

| When | What |
|---------|-------------|
| 2020-09 | Initial RAR |
| | |
| | |
| | |

Introduction

The applicant Elicityl prepared a draft renewal assessment report to support the renewal of inclusion of the active substance Heptamaloxyloglucan.

Heptamaloxyloglucan was included in Annex I of Directive 91/414/EEC under Commission Directive 2010/14/EU, which entered into force on 01 June 2010. According to Regulation (EU) No 540/2011, heptamaloxyloglucan is deemed to have been approved under Regulation (EC) No 1107/2009. An extension of approval has been granted by Regulation (EU) 2017/1527 until 31/05/2021.

The Annex I Inclusion Directive for Heptamaloxyloglucan (2010/14/EU) provides specific provisions under Part B which need to be considered by the applicant in the preparation of their submission and by the MS prior to granting an authorisation:

For the implementation of the uniform principles of Annex VI, the conclusions of the review report on heptamaloxyloglucan (SANCO/10502/09 – final, 27/11/2009), and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 27/11/2009 shall be taken into account.

Heptamaloxyloglucan is included in AIR 4 program (SANTE-2016-10616–rev 9, June 2018). The rapporteur Member State is France and the co-rapporteur Member State is Spain (Commission Implementing Regulation (EU) 2016/183 of 11 February 2016).

The draft renewal assessment report will be prepared according to Commission Regulation No.844/2012.

Table of contents

| | |
|---|-----------|
| B.2. PHYSICAL AND CHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE | 4 |
| B.2.1. MELTING POINT AND BOILING POINT | 4 |
| B.2.2. VAPOUR PRESSURE, VOLATILITY | 4 |
| B.2.3. APPEARANCE (PHYSICAL STATE, COLOUR) | 5 |
| B.2.4. SPECTRA (UV/VIS, IR, NMR, MS), MOLAR EXTINCTION AT RELEVANT WAVELENGTHS, OPTICAL PURITY | 6 |
| B.2.5. SOLUBILITY IN WATER..... | 7 |
| B.2.6. SOLUBILITY IN ORGANIC SOLVENTS..... | 7 |
| B.2.7. PARTITION COEFFICIENT N-OCTANOL/WATER | 8 |
| B.2.8. DISSOCIATION IN WATER..... | 8 |
| B.2.9. FLAMABILITY AND SHELF-HEATING..... | 8 |
| B.2.10. FLASH POINT | 8 |
| B.2.11. EXPLOSIVE PROPERTIES | 9 |
| B.2.12. SURFACE TENSION..... | 9 |
| B.2.13. OXIDISING PROPERTIES | 9 |
| B.2.14. OTHER STUDIES..... | 9 |
| B.2.15. REFERENCES RELIED ON..... | 11 |

B.2. PHYSICAL AND CHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE

| Test or Study Annex Point | Guideline and method | Test material purity and specification | Used methods / Results | Comments (Acceptable / Non acceptable) | GLP | Reference |
|--|----------------------|--|--|---|-----|-----------------------------------|
| B.2.1. MELTING POINT AND BOILING POINT | | | | | | |
| Melting, freezing or solidification point B.2.1/01 | EEC A1 OECD 102 | Batch ref ALD0405, purity >99 % | Melting point was determined by DSC: 172.7 ± 0.5°C. A complementary assay using the Kofler hot bench confirmed the melting point between 170 and 175°C. | Acceptable | Y | Mourgues, L., 2006, 05-905012-001 |
| Boiling point B.2.1/02 | EEC A2. OECD 103 | Batch ref ALD0405, purity >99 % | No boiling point observed up to about 525°C by DSC. | Acceptable | Y | Mourgues, L., 2006, 05-905012-001 |
| Decomposition / Sublimation temperature B.2.1/03 | EEC A1 OECD 102 | Batch ref. ALD0405 purity >99% | An endothermic phenomenon was observed between 281.4 – 305.5°C; this phenomenon may correspond to the test item change started to be observed with the Kofler hot bench from about 240°C upwards. The test item in the form of a white beige powder turned to a clear to dark brown sticky paste as the temperature increased. This sticky paste had a little tendency to blow up. | Acceptable, the active substance decomposes before sublimation. | Y | Mourges l., 2006, 05-905012-001 |
| B.2.2. VAPOUR PRESSURE, VOLATILITY | | | | | | |

| Test or Study Annex Point | Guideline and method | Test material purity and specification | Used methods / Results | Comments (Acceptable / Non acceptable) | GLP | Reference |
|--|---|--|---|--|---|--|
| Vapour pressure B.2.2/01 | Estimation by Quantitative Structure-Activity Relationships (QSAR) using EPIWIN (v3.12) | NA | Vapour pressure has been calculated from melting point measured (172.7°C). Calculated vapour pressure : 1.1×10^{-11} Pa | Not acceptable, as no detail on the validity of EPIWIN (v3.12) to the estimation of the vapour pressure of the active substance has been provided. Vapour pressure should be measured. The applicant argued that an experimental test would require a high amount of pure active substance. Considering its high molecular weight (1079 g/mol), the vapour pressure of the active substance can however be considered $<10^{-5}$ Pa. | N | Fort, S., Ambrosi, D., 2006 ASC 05/24 |
| Volatility (Henry's Law constant) B.2.2/02 | Estimation by QSAR / Henry v3.10 | NA | Henry's law constant $= 0.24 \times 10^{-13}$. Pa/mol. m ³ | Not acceptable : as the value of vapour pressure has not been considered acceptable, the value for Henry's law constant cannot be considered accurate. | N | Fort, S., Ambrosi, D., 2006 ASC 05/24 |
| B.2.3. APPEARANCE (PHYSICAL STATE, COLOUR) | | | | | | |
| Physical state and colour B.2.3/01 | Visual examination | Batch ref. AND0205, purity 87.0% | Heptamaloxyloglucan is described as a highly expanded white beige freeze dried cake. | Acceptable. The physical state of pure active substance should also have been reported, however considering the nature of impurities the same aspect is expected for the pure active substance. | N (quality assurance report was not signed) | Tieche, A., 2006b 05-905012-005 |

| Test or Study Annex Point | Guideline and method | Test material purity and specification | Used methods / Results | Comments (Acceptable / Non acceptable) | GLP | Reference | | | | | | | | | | | | | | | | |
|--|----------------------|--|---|--|-----|--|-----|-----------------|-----|-----|-----|-----------------|-------|-------|-------|--|-----|-----|-----|---|---|---------------------------------------|
| B.2.4. SPECTRA (UV/VIS, IR, NMR, MS), MOLAR EXTINCTION AT RELEVANT WAVELENGTHS, OPTICAL PURITY | | | | | | | | | | | | | | | | | | | | | | |
| Ultraviolet/visible (UV/VIS) B.2.4/01 | OECD 101 | Batch ref ALD0405, purity >99 % | <p>The UV/visible spectra were taken between 195 nm and 800nm at pH 5, 7 and 9.</p> <p>The molecular absorption coefficient of the highest absorption peak is:</p> <table><tr><td></td><td>pH5</td><td>pH7</td><td>pH9</td></tr><tr><td>Wavelength (nm)</td><td>285</td><td>288</td><td>292</td></tr><tr><td>Absorbance (μA)</td><td>0.044</td><td>0.038</td><td>0.025</td></tr><tr><td>ε (L.mol⁻¹.cm⁻¹)</td><td>4.4</td><td>3.8</td><td>2.5</td></tr></table> <p>No absorbance with ε > 10L/mol/cm at wavelength >290 nm</p> | | pH5 | pH7 | pH9 | Wavelength (nm) | 285 | 288 | 292 | Absorbance (μA) | 0.044 | 0.038 | 0.025 | ε (L.mol ⁻¹ .cm ⁻¹) | 4.4 | 3.8 | 2.5 | Acceptable, the active substance shows no absorbance at wavelengths >290 nm | Y | Mourgues, L. 2006 05-905012-001 |
| | pH5 | pH7 | pH9 | | | | | | | | | | | | | | | | | | | |
| Wavelength (nm) | 285 | 288 | 292 | | | | | | | | | | | | | | | | | | | |
| Absorbance (μA) | 0.044 | 0.038 | 0.025 | | | | | | | | | | | | | | | | | | | |
| ε (L.mol ⁻¹ .cm ⁻¹) | 4.4 | 3.8 | 2.5 | | | | | | | | | | | | | | | | | | | |
| Infrared (IR) B.2.4/02 | OECD 101 | Batch ref ALD0405, purity >99 % | <p>IR spectra are given, and are consistent with the structure of heptamaloxylglucan.</p> <p>Wavelength (cm⁻¹) : 3409 (elongation O-H), 2894 (elongation C-H), 1645 and 1424 (elongation O-C-O), 1050 (elongation C-O)</p> | Acceptable | N | Havet, S. 2006 EL101GV-160106-01 | | | | | | | | | | | | | | | | |
| Nuclear magnetic resonance (NMR) B.2.4/03 | OECD 101 | Batch ref ALD0405, purity >99 % | <p>H-NMR spectra are given, and are consistent with the structure of heptamaloxylglucan.</p> <p>Characteristic chemical shift (ppm): 5.15 (H1, Fuc 2) ; 4.95 (H1, Xyl 2) ; 4.80 (H1, Xyl</p> | Acceptable | N | Havet, S. 2006 EL101GV-160106-01 | | | | | | | | | | | | | | | | |

| Test or Study Annex Point | Guideline and method | Test material purity and specification | Used methods / Results | Comments (Acceptable / Non acceptable) | GLP | Reference |
|--|--|--|--|--|-----|--|
| | | | 3) ; 4.50 (H1, Glc 2 and Gal 2) ; 4.35 (H1, Glc 3) ; 4.30 (H5, Fuc 2) ; 1.10 (Me, Fuc 2). | | | |
| Mass spectra (MS) B.2.4/04 | OECD 101 | Batch ref ALD0405, purity >99 % | Mass spectra are given, and are consistent with the structure of heptamalaxyloglucan. MALDI-TOF : m/z = 1101.35 (M+Na), 1117.36 (M+K) Electrospray (for fragment identification) | Acceptable | N | Havet, S. 2006 EL101GV- 160106-01 |
| Spectra for impurities B.2.4/05 | | | Technical substance contains no impurities of toxicological or environmental significance. | Acceptable, Patulin is considered a relevant impurity, however it is not detected in the technical material. Detection methods for patulin are available in the literature. | N | Havet, S. 2006 EL101GV- 160106-01 |
| B.2.5. SOLUBILITY IN WATER | | | | | | |
| Solubility in water B.2.5/01 | In house method equivalent to EEC A.6 (shake flask method) | Batch ref. AND0205, purity 87.0% | Hydrosolubility of heptamalaxyloglucan has been determined at 20°C: 558 g/L (mean of three values). | Acceptable, although water solubility should have been determined on pure active substance, the result shows that water solubility of pure heptamalaxyloglucan > 500 g/L | Y | Ricau, H., 2006a 05-905012- 002 |
| B.2.6. SOLUBILITY IN ORGANIC SOLVENTS | | | | | | |
| Solubility in organic solvents B.2.6/01 | In house method equivalent to EEC A.6 (shake flask method) | Batch ref. AND0205, purity 87.0% | The solubility of heptamalaxyloglucan was determined in the following solvents at 20°C (in mg/L) : n-heptane: 1 p-xylene: <1 1,2-dichloroethane: 15 methanol: 10000 | Acceptable | Y | Ricau, H., 2006a 05-905012- 002 |

| Test or Study Annex Point | Guideline and method | Test material purity and specification | Used methods / Results | Comments (Acceptable / Non acceptable) | GLP | Reference |
|---|--------------------------------|--|---|---|-----|---|
| | | | acetone: 3 ethyl acetate: 1 n-octanol: 19 | | | |
| B.2.7. PARTITION COEFFICIENT N-OCTANOL/WATER | | | | | | |
| Partition coefficient n-octanol/water B.2.7/01 | QSAR estimation (KOWWIN v1.67) | - | A preliminary estimation of log P _{ow} based on the solubilities of heptamaloxyloglucan in water and n-octanol gave a result of ~-4.4, therefore no validated method can be used. A QSAR estimation using KOWWIN gave a value of log P _{ow} = -15.96. | Not acceptable, the slow-stirring method is applicable (OECD TM 123) Considering the solubility profile of heptamaloxyloglucan, however, it can be considered that log P _{ow} < 0 | N | Fort, S., Ambrosi, D., 2006 ASC 05/24 |
| B.2.8. DISSOCIATION IN WATER | | | | | | |
| Dissociation constant B.2.8/01 | | | No study required as the active substance does not dissociate. | Acceptable, the structure of the active substance shows no labile hydrogen atom. | | |
| B.2.9. FLAMABILITY AND SHELF-HEATING | | | | | | |
| Flammability B.2.9/01 | Reasoning | | Based on a literature survey, it is concluded that no flammability test should be required. | Acceptable. Oligosaccharides are well-known to be combustible, but are not classified as flammable according to CLP regulation. | N | Burosse, V., Ambrosi, D., 2006 ASC 05/23 |
| Self heating B.2.9/02 | Reasoning | | Based on a literature survey, it is concluded that the substance is not self-heating. | Acceptable, neither the active substance nor its impurities bear chemical functionalities that could bring self-heating properties. | N | Burosse, V., Ambrosi, D., 2006 ASC 05/23 |
| B.2.10. FLASH POINT | | | | | | |
| Flash point | | | Not applicable to solids. | - | | |

| Test or Study Annex Point | Guideline and method | Test material purity and specification | Used methods / Results | Comments (Acceptable / Non acceptable) | GLP | Reference |
|-------------------------------------|----------------------|--|---|--|-----|---|
| B.2.10/01 | | | | | | |
| B.2.11. EXPLOSIVE PROPERTIES | | | | | | |
| Explosive properties B.2.11/01 | Reasoning | - | Based on a literature survey, structural formula and oxygen balance, it is concluded that no explosive test should be required. However, as a potential risk of dust explosion cannot be excluded due to its physical form (combustible fine particles), heptamaloxyloglucan attracts the precautionary statement P271. | Acceptable, the active substance is not explosive. | N | Burosse, V., Ambrosi, D., 2006 ASC 05/23 |
| B.2.12. SURFACE TENSION | | | | | | |
| Surface tension B.2.12/01 | EEC A.5 | Batch ref. AND0205, purity >87.0% | Surface tension of heptamaloxyloglucan at 1 g/L in demineralised water was determined in triplicate at 20°C using the ring method : mean value = 72.6 mN/m | The surface tension must be measured on pure active substance, however considering the structure of the impurities, this result can be considered acceptable. Heptamaloxyloglucan is not a surface active substance. | Y | Tieche, A., 2006a 05-905012-004 |
| B.2.13. OXIDISING PROPERTIES | | | | | | |
| Oxidizing properties B.2.13/01 | Reasoning | - | Based on structural formula and oxygen balance, no oxidising properties test should be required. | Acceptable, the active substance does not have oxidising functionalities nor oxidising properties. | N | Burosse, V., Ambrosi, D., 2006 ASC 05/23 |
| B.2.14. OTHER STUDIES | | | | | | |
| | EEC C.7 | Batch ref. AND0205, purity >87.0% | During the study of the abiotic degradation of the technical heptamaloxyloglucan, it was | Acceptable, the rate of degradation is not affected by pH in the 5-9 range. | Y | Ricau, H., 2006c |

| Test or Study Annex Point | Guideline and method | Test material purity and specification | Used methods / Results | Comments (Acceptable / Non acceptable) | GLP | Reference |
|---------------------------|----------------------|--|--|--|-----|---------------|
| | | | shown that at pH 5, pH 7 and pH 9 no significant hydrolysis occurs | | | 05-905012-003 |

Summary and Conclusions

Heptamaloxyloglucan (technical material EL101GV) belongs to the chemical family of oligosaccharides. It is described as a highly expanded white beige odourless freeze dried cake, that melts at 173°C and has low potential for volatilization. The solubility in water is very high (> 500 g/L), and from low to moderate in various solvents but very high in methanol (10 g/L). Its partition coefficient is very low (calculation based on solubilities in octanol and water gave log P ~ - 4.4, estimation by KOWWIN gave log P ~ -16), indicating that it has very low possibility to bioaccumulate. Heptamaloxyloglucan is hydrolytically stable, and as its UV spectrum showed no absorption at wavelength >290 nm no photodegradation is expected.

The active substance is not expected to dissociate, and has an estimated photochemical oxidative degradation half-time of 16.6 min. Based on literature, structural formula and oxygen balance, it is concluded that EL101GV is not flammable, not explosive and does not possess oxidizing properties. However, as a potential risk of dust explosion cannot be excluded due to the physical form of EL101GV (combustible fine particles), the precautionary statement P271 is proposed.

B.2.15. REFERENCES RELIED ON

| Data Point | Author(s) | Year | Title Report No. Document No. Source (where different from company) GLP/ Officially recognised testing facilities ^{2,3} Published or not | Vertebrate study Y/N | Data protection claimed Y/N | Justification if data protection is claimed | Owner | Previously used ¹ Y/N If yes, for which data point? |
|-------------------------|------------------------|------|---|----------------------|-----------------------------|---|----------|--|
| KCA 2.1/01 (KCA 2.4/01) | Mourgues, L. | 2006 | Melting point, boiling point (DSC method) and UV/Visible spectrum of pure heptamaloxyloglucan Defitraces report N°05-905012-001 GLP: Yes Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.2/01 | Fort S. and Ambrosi D. | 2006 | Physico-chemical, environmental and ecotoxicological properties of the active substance heptamaloxyloglucan ASC report N°05/24 GLP: No Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.3/01 | Tieche, A. | 2006 | Accelerated storage procedure for 14 days at 54±2°C and physico-chemical tests after the storage procedure on the preparation PEL101GV Defitraces report N°05-905012-005 GLP: Yes Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.4/01 (KCA 2.1/01) | Mourgues, L. | 2006 | Melting point, boiling point (DSC method) and UV/Visible spectrum of pure heptamaloxyloglucan Defitraces report N°05-905012-001 GLP: Yes Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.4/02 | Havet, S. | 2006 | SPECTROSCOPY STUDY Elicityl report EL101GV-160106-01 GLP: No Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.5/01 (KCA 2.6/01) | Ricau, H. | 2006 | Determination of the solubility on the technical Heptamaloxyloglucan in water and organic solvents | N | N | - | Elicityl | Y, in DAR 2007 |

| | | | | | | | | |
|---|--------------------------------------|------|---|---|---|---|----------|-------------------|
| | | | Defitraces Report N°05-905012-002 GLP: Yes Published: No | | | | | |
| KCA 2.6/01 (KCA 2.5/01) | Ricau, H. | 2006 | Determination of the solubility on the technical Heptamaloxyloglucan in water and organic solvents Defitraces Report N°05-905012-002 GLP: Yes Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.9/01 (KCA 2.11/01) (KCA 2.13/01) | Burosse, V. and and Ambrosi D. | 2006 | Literature survey on flammability, explosive properties, oxidizing properties of the active substance heptamaloxyloglucan ASC report N°06/02 GLP: No Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.11/01 (KCA 2.9/01) (KCA 2.13/01) | Burosse, V. and and Ambrosi D. | 2006 | Literature survey on flammability, explosive properties, oxidizing properties of the active substance heptamaloxyloglucan ASC report N°06/02 GLP: No Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.12/01 | Tieche, A. | 2006 | Physico-chemical tests on the preparation PEL101GV Defitraces report N°05-905012-004 GLP: Yes Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.13/01 (KCA 2.9/01) (KCA 2.11/01) | Burosse, V. and and Ambrosi D. | 2006 | Literature survey on flammability, explosive properties, oxidizing properties of the active substance heptamaloxyloglucan ASC report N°06/02 GLP: No Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| KCA 2.14/01 | Ricau, H. | 2006 | Abiotic degradation on the technical Heptamaloxyloglucan pH dependent hydrolysis (Test C7) Defitraces Addendum to report N°05- 905012-003 GLP: Yes Published: No | N | N | - | Elicityl | Y, in DAR 2007 |
| | | | | | | | | |

¹ In order to facilitate the compilation of the final list of the tests and studies relied upon and the corresponding data protection, indicate whether the study was used in the previous DAR/RAR or, when the information is available, whether the study was already submitted in the framework of national authorisations.

² See Art.3 of Annex of Regulation No 283/2013 and 284/2013

³ The RMS shall check that the GLP statement has been properly signed in the study report, that the study results are properly reported in accordance with GLP standards and following the relevant guidance by OECD on the review of the GLP status of non-clinical safety data (currently under development).