PEER REVIEW REPORT ON **HEPTAMALOXYLOGLUCAN** 20 07 2009

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1. Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	Section 1 Open points: ***6*** Points for clarification: ***0*** Data requirements: ***0***			Section 1 Open points: ***0*** Points for clarification: ***0*** Data requirements: ***1***
	Open point: 1.1 The issue of mycotoxin contamination should be considered by a meeting of experts. See reporting table 1(2)	We agree with the RMS evaluation considering stable the apple-derived raw material with regard to the development of fungi responsible for the mycotoxin production (Aw>0.5) and also considering that molecules of MW lower than 250 g/mol are driven out during the 4th step of the manufacturing process (i.e. nanofiltration) Analysis of Patulin carried out on the technical active substance EL101GV and submitted in the dossier (referred as document J and as annex K II 01 08 01 in the Heptamaloxyloglucan submission dossier following annex 1, directive 91/414/EEC, acknowledged by all EC member states and by EFSA the 2nd of July, 2007:" Method of manufacturing of EL101GV") did not show any Patulin occurrence. Alternariol and alternariol monomethyl ether mycotoxins are potentially occurring in apple products at very low levels and are not followed up at a	**RMS (April 09):** RMS agrees with applicant. Open point fulfilled.	PRAPeR 66 (21 – 24 April 2009): Open point fulfilled. Message sent to section 2 (tox). New open point proposed, see below.

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
		regulation level or a peculiar official guideline. A study from the UK food agency only showed 2 samples of alternariol contamination higher than their quantification analysis limit of 3 µg/kg (6.2 and 4.3 µg/kg) among a pool of 300 apple derived product samples (apple juice and so on). Reference of the study: Food Standard Agency – 20 March 2003 – "low levels of mycotoxins in apple juice and apple products" http://www.food.gov.uk/news/newsarchive/2003/mar/apples .		
	New open point 1.7 RMS to summarize the results of batches analysed for Patulin in an Addendum.		**RMS (May 09) : T**he results of Patulin was summarized in an addendum of vol 4. Open point fulfilled.	PRAPeR 66 (21 – 24 April 2009): Open point open. Written procedure Open point fulfilled. The batches are now summarized in the May 2009 addendum to Vol C. No patulin was detected <50 µg/L. However, it was agreed that only having 2 batches was acceptable if the levels found are significantly below the safe level agreed by the tox meeting. This is not the case as the safe level is nearly the same namely 50 µg/Kg, therefore a new data requirement is identified for three additional batches, see below.

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	New data requirement: 1.1 identified by EFSA when writing the conclusion: 3-batch analysis for patulin is required.			Written procedure Data requirement open.
	Open point: 1.2 The meeting of experts should consider the specification, in particular the 20 % of the TGAI that has not been identified. See reporting table 1(3)	We do confirm the technical active substance is a 100% xyloglucan oligosaccharides composition and that the 20% impurities left along with the main product “Heptamaloxyloglucan” are other xyloglucan oligosaccharidic structures, resulting from the enzymatic hydrolysis process (referred as document J and as annex K II 01 10 01 in the Heptamaloxyloglucan submission dossier following annex 1, directive 91/414/EEC, acknowledged by all EC member states and by EFSA the 2nd of July,2007:”impurity characterization EL101GV technical active substance”)	**RMS (April 09):** RMS agrees with applicant. Open point fulfilled.	PRAPeR 66 (21 – 24 April 2009): Open point fulfilled.
	Open point: 1.3 The common name of the active substance should be inserted between the brackets in the title to the table of representative uses. See reporting table 1(6)	The common name *i.e.* "Heptamaloxyloglucan" has been officially proposed to the ISO office on 10/03/2009.	**RMS (April 09):** RMS agrees with applicant. Open point fulfilled. **RMS (May 09) :** This point was corrected in the LOEP revised. Open point fulfilled	PRAPeR 66 (21 – 24 April 2009): Open point open. Written procedure Open point fulfilled. The end points have been amended.
	Open point: 1.4	We do agree with **a > 99%** purity of active substance used in the	**RMS (April 09):** RMS agrees with	PRAPeR 66 (21 – 24 April 2009):

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	Temperature of decomposition purity should read >99% in the LoEP. See reporting table 1(10)	Heptamaloxyloglucan temperature decomposition study.	applicant. Open point fulfilled.	Open point open. RMS to amend the list of endpoint accordingly. Written procedure Open point fulfilled. The list of end points has been amended.
	Open point: 1.5 What type of opening is “crimped hermetically”? Please provide more detail. What material is used to seal the opening? See reporting table 1(29)	The 20 ml volume flask (from Wheaton ref. N°223762) made in a borosilicate glass is sealed thanks to a crimping tool (from Wheaton ref. 224323). The tap is a plastic one (chlorobutyl, color grey, Wheaton ref. N°224100-194) that perfectly fits the flask opening. It is surrounded with an aluminium capsule (from Wheaton ref.224193-01) set up thanks to the previously described crimping tool. 	**RMS (April 09):** These explanations are considered acceptable. Open point fulfilled.	PRAPeR 66 (21 – 24 April 2009): Open point fulfilled.
	Open point: 1.6 Meeting of experts should consider the new study on shelf-life. See the addendum 1 (vol3 Annex B2). See reporting table 1(30)	The 2-year shelf-life study that has just been deposited to the dossier highlights stability of the reference preparation. The whole dossier is communicated to the EFSA and to all the EC member states.	**RMS (April 09):** The 2-year shelf life study is considered acceptable. Open point fulfilled.	PRAPeR 66 (21 – 24 April 2009): Open point fulfilled.

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	New open point 1.8 RMS to update the list of end points according to PRAPeR 66. (refer to Discussion table)		**RMS (May 09) :** The LOEP has been revised according to PRAPeR 66. Open point fulfilled	PRAPeR 66 (21 – 24 April 2009): Open point open. Written procedure Open point fulfilled. The list of end points has been amended.
	New open point 1.9 RMS to amend the list of studies relied on with EN method for Patulin.		**RMS (May 09) :** The list of studies relied on was amended in the addendum 1 to vol4 and addendum 1 to vol2. Open point fulfilled.	PRAPeR 66 (21 – 24 April 2009): Open point open. Written procedure Open point fulfilled. The end points have been amended.
	Message to section 2 (mammalian toxicology): Patulin may be present in the technical active ingredient. Please advise on the maximum level of Patulin which can be considered as safe.			Answer: The maximum intake of patulin from food (TMDI) is 0.4 μg/kg bw/d (JECFA, 2000 as confirmed by the SCF). The safe limit should be set as 50 μg/kg (fruit juices, concentrated fruit juices as reconstituted and fruit nectars) according to Commission Regulation No 1881/2006. Therefore, the maximum level of Patulin which can be considered as safe in the technical specification is 50 μg/kg.
	Message from section 2 (mammalian toxicology): Boric acid is produced during the production of the product		**RMS (May 09) :** The content of boric acid was not quantified in the technical active substance. Data required.	Answer : It is highly unlikely that boric acid will be present in the technical material given the HPLC cleanup step there fore no further

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	– does Boric acid appear in the final technical product? This is a repro Cat2 hence concerns were raised by experts.		New data requirement.	data should be required.

2. Mammalian toxicology

<table>
<tr><th>No.</th><th>Column A
Conclusions from the Reporting Table</th><th>Column B
Comments from the notifier / applicant</th><th>Column C
Rapporteur Member State comments on the notifier / applicant comments</th><th>Column D
Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure</th></tr>
<tr><td></td><td>Section 2
Open points: 5
Points for clarification: 0
Data requirements: 1</td><td></td><td></td><td>Section 2
Open points: 0
Points for clarification: 0
Data requirements: 0</td></tr>
<tr><td></td><td>Open point: 2.1
The comparison of the current specification and the batches tested in the mammalian toxicity data package; and the potential toxicological relevance of impurities has to be confirmed by the experts.

See reporting table 2(1)</td><td>The EL101GV technical active substance proposed for the 28d rat short-term toxicity study is representative of the manufacturing process carried out in 2006 with an active substance purity very close to the average specifications determined for Heptamaloxyloglucan. The seven accompanying impurities disclosed in these specifications are all present in this batch intended for that toxicological assay. These impurities have been clearly identified as being other xyloglucan oligosaccharides.</td><td>RMS (April 09): agreed.
Furthermore the purity of the batch used for the Ames test and the skin sensitisation test was 78.2 % which is comparable to the purity grade of > 78 % determined in the 5 batches analyses, therefore it can be anticipated that all impurities were also tested.
<table>
<tr><th>Batch n°</th><th>Purity</th><th>Test</th></tr>
<tr><td rowspan="3">ALP0103</td><td rowspan="3">96.2 %</td><td>Acute oral toxicity</td></tr>
<tr><td>Acute skin irritation</td></tr>
<tr><td>Acute eye irritation</td></tr>
<tr><td>ALD0204</td><td>86.1 %</td><td>Acute percutaneous toxicity</td></tr>
<tr><td>ANN0304</td><td>78.1 %</td><td>Acute skin sensitization</td></tr>
</table></td><td>PRAPeR 69 (4 – 8 May 2009):

Open point fulfilled.

The toxicological batches cover the technical specification.

Message sent to section 1.</td></tr>
</table>

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments			Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
					Mutagenicity in vitro in bacterial cells (Ames's technique)	
			AND0706	87%	Short-term toxicity Oral administration 28-day, Rat	
					Mutagenicity in vitro in mammalian cell (Lymphoma)	
	Data requirement: 2.1 Applicant to submit positive control data for the in vitro Ames assay. See reporting table 2(3)	The information about the experimental data of this assay are disclosed in the report No.FSR-IPL 060207/EL101GV/ELICITY submitted to all different EC Member States and to EFSA in the Heptamaloxyloglucan submission dossier following annex 1, directive 91/414/EEC, the 2nd July 2007	**RMS (April 09):** agreed			PRAPeR 69 (4 – 8 May 2009): Data requirement closed.
	Open point: 2.2 Data waivers on long-term toxicity and carcinogenicity studies to be confirmed at a meeting of experts. See reporting table 2(5)	The following items presented in the Draft Assessment Report support demand of data waivers on long-term toxicity and carcinogenicity studies: • Heptamaloxyloglucan is naturally occurring in the organism (digestion of xyloglucan polysaccharides from plant origin) and in the daily diet (found in food industry products originating from apples , e.g.	**RMS (April 09):** agreed			PRAPeR 69 (4 – 8 May 2009): Open point fulfilled. Data waivers accepted.

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
		apple juice 9.44 mg/L) • The exposure brought by Heptamaloxyloglucan application as a plant protection product at 0.44 g/ha rate (exposure deemed at 1.2 mg/d on an apple juice consumption basis) is lower than the daily exposure of a consumer deemed in a worst case situation at 0.11 mg/d (calculation model presented in the Draft Assessment Report p.155 paragraph B6.10.10).		
	Open point: 2.3 Data waivers on reprotoxicity studies to be confirmed at a meeting of experts. See reporting table 2(6)	The following items presented in the Draft Assessment Report support demand of data waivers on reprotoxicity studies: • Heptamaloxyloglucan is naturally occurring in the organism (digestion of xyloglucan polysaccharides from plant origin) and in the daily diet (found in food industry products originating from apples , e.g. apple juice 9.44 mg/L) • The exposure brought by Heptamaloxyloglucan application as a plant protection product at 0.44 g/ha rate deemed in a worst-case situation at 0.11 mg/d (calculation model presented in the Draft Assessment Report p.155 paragraph B6.10.10) is lower than the daily exposure of a consumer (exposure deemed at 1.2	**RMS (April 09):** agreed	PRAPeR 69 (4 – 8 May 2009): Open point fulfilled. Data waivers accepted.

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
		mg/d on an apple juice consumption basis).		
	Open point: 2.4 Reference values (ADI, ARfD and AOEL) to be agreed on at a meeting of experts. See reporting table 2(9)	We agree with the proposals done by the RMS in the Draft Assessment Report: o ADI non relevant o ARfD non relevant o AOEL 1 mg/kg b.w./d	**RMS (April 09):** no comment	PRAPeR 69 (4 – 8 May 2009): Open point fulfilled. ADI, AOEL, ARfD not required.
	Open point: 2.5 Operator, worker and bystander exposure to be confirmed at a meeting of experts. See reporting table 2(10)	We agree with the Draft Assessment Report suggested by the RMS related to a weak exposure of 12.79 µg/kg b.w./d representing 1.28 % of the proposed AOEL. This value is lower than consumer exposure through its daily diet (example of apple juice: 1.2 mg/d, *i.e.* for an average adult of 70 kg, 17 µg/kg b.w. / d)	**RMS (April 09):** agreed	PRAPeR 69 (4 – 8 May 2009): Open point fulfilled. Exposure estimates not required.
	Message from section 1 (phys-chem): Patulin may be present in the technical active ingredient. Please advise on maximum level of Patulin which can be considered as safe.			PRAPeR 69 (4 – 8 May 2009): Answer: The maximum intake of patulin from food (TMDI) is 0.4 µg/kg bw/d (JECFA, 2000 as confirmed by the SCF). The safe limit should be set as 50 µg/kg (fruit juices, concentrated fruit juices as reconstituted and fruit nectars) according to Commission Regulation No 1881/2006. Therefore, the maximum level of Patulin

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
				which can be considered as safe in the technical specification is 50 μg/kg.
	Message to section 1 (Phys-chem): Boric acid is produced during the production of the product – does Boric acid appear in the final technical product? This is a repro Cat2 hence concerns were raised by experts.			Message sent to section 1.

3. Residues

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	Section 3 Open points: ***0*** Points for clarification: ***0*** Data requirements: ***0***	-	-	

4. Environmental fate and behaviour

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	Section 4 Open points: ***5*** Points for clarification: ***0*** Data requirements: ***0***			Section 4 Open points: ***1*** Points for clarification: ***0*** Data requirements: ***0***
	Open point: 4.1 RMS to consider if they might wish to provide any argumentation why a Koc of 20 L/kg might be appropriate for use in a leaching assessment. See reporting table 4(1)	The active substance is fully part of soil constituents and that is why it is impossible to assess any weak exogenous contribution with regard to an endogenous quantity and therefore, a Koc. Even making an unrealistic worst-case Koc with a value of Zero, and a DT_{50} of 13.3 days in PELMO3.3.2 model, gives 80th percentile estimations lower than 0,015 µg/L or in other words well below the limit fixed at 0.1 µg / L. The risk will be even lower with a more realistic Koc set at 20 L/kg as proposed by the RMS.	**RMS (April 2009):** It is agreed that the Koc value is not really sustained. This value was chosen by expert judgement as a conservative (worst case) value for risk assessment in the first version of the DAR. In the corrigendum 1 to the DAR we propose that due to the absence of MRL and ADI there is no need for a calculated PECgw and thus no need to determine a Koc. No data was reported in the LoEP. Moreover heptamaloxyloglucan is not considered to enter in the definition of residue. Heptamaloxyloglucan is a stimulator of plant defence natural mechanisms and is not toxic at all for Human and the environment. In other words, the 0.1µg/L limit is not considered to apply in this particular case.	PRAPeR 67 (20 -24 April.2009): Open point fulfilled.
	Open point: 4.2 Member state experts to discuss and conclude if the results of the available ready	We agree with the RMS proposal to determine DT_{50} at 13.3 days. This fixed value calculated from the results of the ready biodegradability study is considered from our point of view as a	**RMS (April 2009):** The use of ready biodegradability to estimate a credible soil degradation rate was not the purpose of the	PRAPeR 67 (20 -24 April.2009): Open point fulfilled.

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	biodegradability study on heptamaloxyloglucan can be used to estimate a credible soil degradation rate for use in a leaching estimate. See reporting table 4(1)	worst case. Indeed, it is calculated taking into account a full mineralization of Heptamaloxyloglucan into CO_2. If we refer to the real DT_{50} (disclosed in the study: "An assessment of the ready biodegradability" undertaken by ELICITYL and presented in the Heptamaloxyloglucan submission dossier following annex 1, directive 91/414/EEC, the 2nd July 2007), DT_{50} is shorter than 40 hours including the lag phase (selection and development phases).	proposed soil DT50. It was used in the first version of the DAR to estimate the PEC groundwater only as indicative. This value was not part of the proposed list of endpoint. Moreover we considered that "the fate and behaviour of heptamaloxyloglucan in soil and possible assimilation and degradation by soil micro- and macro-organisms are well described" (see B.8.1.2.4. Conclusion on route and rate of degradation).	
	Open point: 4.3 Member state experts to discuss and conclude if the case made by the applicant regarding the potential for groundwater contamination as reported in the DAR on page 205 to Vol. 3 is sufficient to conclude groundwater contamination >0.1 µg/L is unlikely. See reporting table 4(1)	Taking extremely disadvantageous parameters, a DT_{50} fixed at 13.3 days and a Koc equal to zero, there are no risks for groundwater contamination.	**RMS (April 2009):** See answer to open point 4(1)	PRAPeR 67 (20 -24 April.2009): Open point fulfilled.
	Open point: 4.4 Member state competent authorities to consider if they would wish to request their	A Decision to class Heptamaloxyloglucan as a pesticide for a determination of drinking water limit fixed at 0.1 µg/L recovers from	**RMS (April 2009):** As heptamoloxyloglucan acts as a stimulator of plant defence natural mechanisms, it was not considered to	PRAPeR 67 (20 -24 April.2009): Open point open.

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	risk managers to consult legal advice, so they will be able to provide a view to the working group legislation whether the drinking water limit of 0.1 µg/L would or would not apply to heptamaloxyloglucan (the active substance)? Note: EFSA understands that whether 0.1 µg/L applies has nothing to do with whether an MRL or ADI is defined, i.e. if there might be any risk. The only issue is whether heptamaloxyloglucan is a 'pesticide' according to the definition in Council Directive 98/83/EC. See reporting table 4(2)	the expertises of the EC comity. Whether this limit fixed at 0.1 µg/L should be kept, risk modelling presented in the DAR by the RMS show that it will be esteemed.	have detrimental "biocide" effects and that it was not considered to have detrimental effects in any sections of the Draft Assessment Report, the RMS considered that the limit of 0.1 µg/L is not relevant in this particular case. **RMS (May 2009):** this open point should be addressed to the legislation group	Written procedure Open point open.
	Open point: 4.5 EFSA to refer to the more conservative FOCUSsw and sed step 1 calculations included in corrigendum 1 to the DAR (January 2009) in its conclusion.	We agree with the last model calculation from the RMS Focus step 1, which in extremely disadvantageous cases (Koc is zero and DT_{50} is 1000 days) give an exposure lower than 0.6 µg/L.	**RMS (April 2009):** noted, no action made by the RMS. **RMS (May 2009):** this point was related to an action to be done by EFSA	PRAPeR 67 (20 -24 April.2009): Open point open. Written procedure Open point fulfilled. The reference in the EFSA conclusion is to the PECsw and sed in the corrigendum

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	See reporting table 4(3)			1 of the DAR.
	New open point 4.6 RMS to amend the residue definition for further assessment in line with the conclusions of the PRAPeR 67 meeting: Residue definition: parent heptamaloxyglucan for all compartments		**RMS (May 2009):** The residue definition was already defined as heptamaloxyloglucan in the List of Endpoint and the B.8.	PRAPeR 67 (20 -24 April.2009): Open point open. Written procedure Open point fulfilled. The RMS had appropriately updated the LoEP as requested.

5. Ecotoxicology

No.	Column A Conclusions from the Reporting Table	Column B Comments from the notifier / applicant	Column C Rapporteur Member State comments on the notifier / applicant comments	Column D Recommendations of the PRAPeR Expert Meeting / Conclusions from the written procedure
	Section 5 Open points: ***0*** Points for clarification: ***0*** Data requirements: ***0***	-	-	