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Heptamaloxyloglucan

Volume 3 – B.6 (AS)

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

Version History

When	What
09/2020	Initial RAR

The RMS is the author of the Assessment Report. The Assessment Report is based on the validation by the RMS, and the verification during the EFSA peer-review process, of the information submitted by the Applicant in the dossier, including the Applicant's assessments provided in the summary dossier. As a consequence, data and information including assessments and conclusions, validated and verified by the RMS experts, may be taken from the applicant's (summary) dossier and included as such or adapted/modified by the RMS in the Assessment Report. For reasons of efficiency, the Assessment Report should include the information validated/verified by the RMS, without detailing which elements have been taken or modified from the Applicant's assessment. As the Applicant's summary dossier is published, the experts, interested parties, and the public may compare both documents for getting details on which elements of the Applicant's dossier have been validated/verified and which ones have been modified by the RMS. Nevertheless, the views and conclusions of the RMS should always be clearly and transparently reported; the conclusions from the applicant should be included as an Applicant's statement for every single study reported at study level; and the RMS should justify the final assessment for each endpoint in all cases, indicating in a clear way the Applicant's assessment and the RMS reasons for supporting or not the view of the Applicant.

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B.6. TOXICOLOGY AND METABOLISM DATA

B.6.1. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION IN MAMMALS

No new data or assessment is provided by the applicant since the previous evaluation (DAR 2007).

Active substance EL101GV is an oligosaccharide made of 7 glucidic monomer units. There are β-1,4 linkages on the main chain between the two D-glucopyranosyl units and terminal D-glucitol, and α-1,2, β-1,2 and α-1,6 linkages between the various monomer units present in side chains. The latter side chain-monomers are D-xylopyranosyl (α-1,6-linked to D-glucopyranosyl), D-galactopyranosyl (β-1,2-linked to D-xylopyranosyl) and L-fucopyranosyl (α-1,2-linked to D-galactopyranosyl).

Xyloglucan is the principal hemicellulosic component of primary cell walls of dicotyledonous and non-graminaceous monocotyledonous plants. Specific oligosaccharides such as heptamaloxyloglucan can be produced naturally from xyloglucan by partial hydrolysis with cellulose (β-1,4-D-glucanase) and various other enzymes which are present in plants and soil micro-organisms. It has been demonstrated that these specific oligosaccharides accumulate extracellularly in plants and act at very low levels as signalling molecules that participate in cell-cell and wall-nucleus communication (KCA 5.1/01 Buchanan et al., 2000; KCA 5.1/02 Fry et al. 1993, KCA 5.1/03 Hayashi, 1989)

Annex point:	KCA 5.1/01
Report author	Nicholas Carpita et al.
Report year	2000
Report title	The cell wall
Report No	Biochemistry and Molecular Biology of Plants – Chapter 2: The cell wall. Buchanan B.B., Gruissen W., and Jones R.L, Eds.
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

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

2 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).

This review is a wide presentation of the components, the structure, the biosynthesis and cell physiology of cell wall. It describes the function and structure of xyloglucans as an essential component of the plant cell wall.

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Xyloglucans are a class of natural polysaccharides. With cellulose, they are essential components of all plant cell wall. They are a class of cross-linking glycans that coat microfibrils of cellulose and link together to form a network. Xyloglucans are composed of the combination of the following monosaccharides: glucose, galactose, xylose, fucose and arabinose

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Annex point:	KCA 5.1/02
Report author	Fry et al
Report year	1993
Report title	Oligosaccharides as Signals and Substrates in the Plant Cell Wall
Report No	Plant Physiol., Vol. 103 (1993), pp. 1-5
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

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

This review presents the signaling activity of oligosaccharides derived from the fragmentation of plant cell wall polysaccharides. A focus is made on the "elicitors" activity of xyloglucan-derived oligosaccharides with the presentation of several structures (XXFG, XXFGol, GXFG, XLLG, XXLG, XXXG) and associated activities.
Some of these compounds have been found to accumulated in the extracellular space and some experiment data support that they are naturally occurring signalling molecules.
At the nanomolar range of concentration xyloglucan oligosaccharides can modulate plant growth (promotion and inhibition) and morphogenesis.

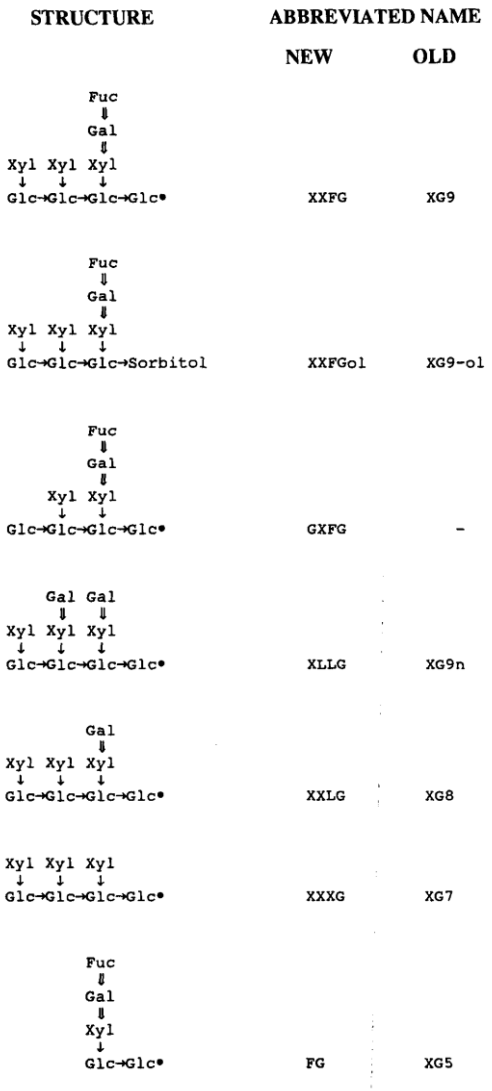


Figure 1. Simplified structures and abbreviated names of xyloglucan oligosaccharides mentioned in the text. In the structures, arrows indicate glycosidic bonds: →, (1→4)-linkage; ↓, (1→6)-linkage; ⇓, (1→2)-linkage; •, reducing terminus. For further details of this revised nomenclature, see Fry et al. (1993).

MATERIALS AND METHODS

Non applicable

RESULTS

Non applicable

CONCLUSION

Assessment and conclusion by applicant:

Xyloglucans oligosaccharides are naturally occurring molecules that can have a signaling activity in plants at the nanomolar range of concentration.

Assessment and conclusion by RMS 2020:

Acceptability/Reliability: This report is considered for supplementary information only.

Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Annex point:	KCA 5.1/03
Report author	Hayashi T
Report year	1989
Report title	XYLOGLUCANS IN THE PRIMARY CELL WALL
Report No	Annu. Rev. Plant Physiol. Plant Mol. Biol. 1989, 40:139-68
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013

[2] 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).

This review is dedicated to xyloglucans. It presents occurrence, structure, biosynthesis, biodegradation, macromolecular organization, and growth regulation activities of xyloglucans.

Xyloglucans are present in the primary and secondary wall of higher plant cells (dicotyledons and monocotymedons). Xyloglucans possess a 1,4-/3-glucan backbone subtitued by glucose / xylose / galactose / fucose (excepted monocotymedons).

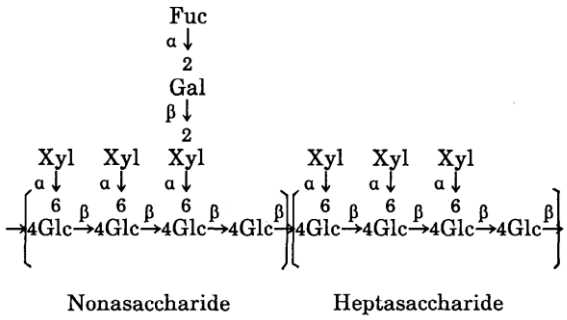


Figure 1 Chemical repeating unit of pea xyloglucan.

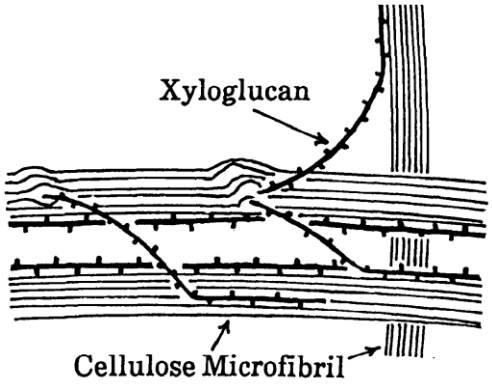


Figure 4 Potential linkages between xyloglucan and cellulose.

One of the main function of Xyloglucans is to contribute to the cross-linking of each cellulose microfibril network. The rigidity of the walls is constrained by xyloglucan networks. Xyloglucan polysaccharide degradation into oligosaccharides and monosaccharide under the action of endogenous endo-1,4-β-glucanases is associated with Auxin-induced cell enlargement.

Xyloglucan oligosaccharides can have an inhibition activity on cell elongation at the 100 nM range.

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Xyloglucans oligosaccharides are naturally occurring molecules generated endogenously by the plant from the enzymatic hydrolysis of xyloglucan polysaccharide. These compounds can be involved in the regulation of plant cell elongation with activities at the 100 nanomolar range of concentration.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

As heptamaloxyloglucan occurs in plants and soil at very low levels, the manufacturing process mimics the natural phenomenons of enzymatic degradation using a polygalacturonase preparation (Pectinex 3XL, food grade specifications) in order to accelerate the rate of natural biochemical process and thus increase heptamaloxyloglucan yields. Moreover this enzyme preparation is commonly used for clarification of apple juice and wine, in order to hydrolyse insoluble polymers into soluble pectins and xyloglucans of lower molecular weights, including heptamaloxyloglucan (see MCA S6).

Expected fate of the unchanged compound:
The unchanged active substance itself cannot be absorbed by passive diffusion because of its low K_{ow} (< 10^{-4} and high molecular weight (> 1000 g/mol)) which excludes spontaneous passage through biological lipid membranes. Facilitated diffusion or active passage of the unchanged active substance will most probably not occur because this substance is absent in animals, and these mechanisms of absorption do not exist in animals for unchanged hemicellulose. After oral intake, a very low fraction is expected to be hydrolyzed by the acid pH of the stomach (varying from 1 to 5) because heptamaloxyloglucan does not present significant degradation at pH of 4-9 (KCA 2.14/01/KCA 7.2.1/01 Abiotic degradation on the technical heptamaloxyloglucan pH dependent hydrolysis (Test C7) - Ricau, H., 2006b 05-905012-003,). A proportion of the active substance will therefore remain unchanged in the gastro-intestinal content. **As the unchanged parent molecule EL101GV is not absorbable, it cannot induce systemic effects.**

B.6.1.1. Absorption, distribution, metabolism and excretion by oral route

The probable fate of heptamaloxyloglucan ingested by mammals is summarised in Figure B.6.1.1-1. In the gastroinstestinal tract, heptamaloxyloglucan can undergo three degradation pathways: acidic hydrolysis, enzymatic hydrolysis and fermentation.

B.6 .1.1.1 Enzymatic hydrolysis in the mouth

The digestion starts in the mouth with the salivary α-amylase. The α-1,2, β-1,2 and α-1,6 linkages of heptamaloxyloglucan will resist digestion by α-amylase which only hydrolyses the α-1,4 (glucose-glucose) bonds of starch (KCA 5.1/04, Wahbeh T.G. and Christie D.L., 2006).

Annex point:	KCA 5.1/04
Report author	Wahbeh T et al.
Report year	2006
Report title	Basic aspects of digestion and absorption
Report No	Chapter 2: Basic aspects of digestion and absorption.
	Pediatric Gastrointestinal and Liver disease, 3rd edition, Hardback edition, 1348 p.
Document No	-
Guidelines followed in study	Not relevant (scientific article)

Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013

[2] 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).

This review presents the process of digestion in human of nutrients including carbohydrates and oligosaccharides. Digestible carbohydrates (lactose, α1,4 and linked α1,6 carbohydrates such as starch amylose and amylopectin, glycogen) are hydrolysed into monosaccharides that are absorbed across the enterocyte membrane in the intestine. Unlike these carbohydrates, hemicellulose (including xyloglucan) are composed of glucose linked by β1,4 bounds, that unlike α1,4 and they are resistant to hydrolases present in human (α-amylase).

Non-digestible carbohydrates are fermented by colonic bacteria leaving short chain fatty acids that are readily absorbed and may account for a minute caloric source in healthy state, in addition to possibly having cellular trophic properties

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Xyloglucans are naturally non-digestible fibers that are fermented by colonic bacteria leaving short chain fatty acids that are readily absorbed and may account for a minute caloric source in healthy state, in addition to possibly having cellular trophic properties.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

B.6 .1.1.2 Acid hydrolysis in the stomach

In the stomach, unchanged heptamaloxyloglucan will be exposed to an acidic environment (pH 2-4). Generally, in acidic environment, the carbohydrates can undergo hydrolysis of their glycosidic bonds. The acid reaction of sugar hydrolysis generally follows kinetics of pseudo first order (KCA 5.1/05, Heyraud et al., 1981). The rate constant of the acid hydrolysis reaction is directly dependant on pH and temperature.

Data point:	KCA 5.1/05
Report author	Heyraud A et al.
Report year	1981
Report title	HYDROLYSIS OF OLIGOSACCHARIDES BY POLYELECTROLYTES
Report No	European polymer journal, Vol.17, pp.181-189, 1981
Document No	-
Guidelines followed in study	Not relevant (scientific article)

Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013
[2] 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).

This study shows the hydrolysis of oligosaccharides into constitutive monosaccharides (glucose) under acid conditions.

MATERIALS AND METHODS

Acid hydrolysis of oligosaccharides (cellobiose, gentiobiose, maltose) and polysaccharides was performed with by 0.20 N sulphuric acid and 0.2 N polystyrene sulphonic acid. The rate of hydrolysis was quantified by HPLC.

RESULTS

The oligosaccharides and polysaccharides are hydrolysed by the two acids and the thermodynamic parameter of the reaction are described.

CONCLUSION

Assessment and conclusion by applicant:
Oligosaccharides and polysaccharides are hydrolysed in extreme acidic condition. The rate of hydrolysis is dependent on pH and temperature.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Annex point:	KCA 5.1/06
Report author	HAVET S.
Report year	2007
Report title	EL101GC Hydrolysis study at pH 2.2 and 50°C during 2 days
Report No	Study No. EL101GV-31012007-01
Document No	-
Guidelines followed in study	Not relevant
Deviations from current test guideline	Not relevant
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013
[2] 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).

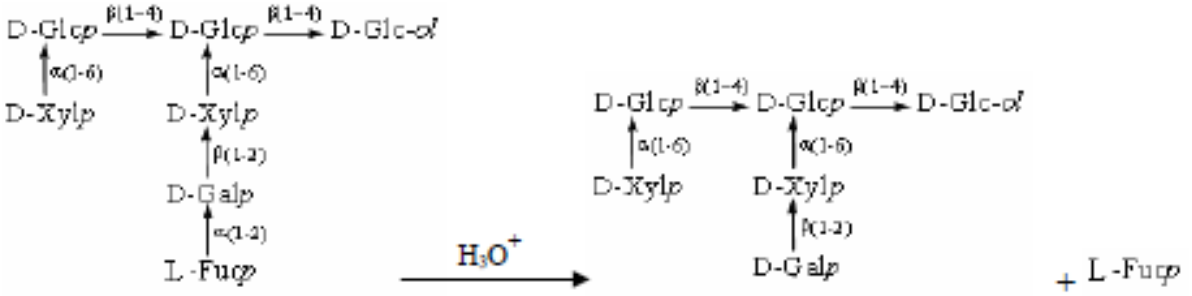
This study estimates the fraction of Heptamaloxyloglucan hydrolyzed at pH 2.2, in abiotic environment, after 2 days with 50°C.

MATERIALS AND METHODS

Heptamaloxyloglucan (88,6% w/w of XFGol) is solubilized at 10 g/L in a buffer at pH 2.2 and the solution is incubated at 50°C for 2 days.
XFGol concentration is determined by HPAEC-PAD.

RESULTS

Under these conditions, XFGol is chemically hydrolyzed at a rate of 4.1 % in 48 hours.
The potential products of hydrolysis are the oligosaccharide of lower polymerization degree (XLGol) and fucose.
This reaction is presented as follows:



In the acidic environment of the stomach, it can be anticipated that heptamaloxyloglucan will be hydrolysed to XLGol and Fucose at least, by rupture of α-1-2) glycosidic bond. So in the stomach, a high proportion of the active substance heptamaloxyloglucan will remain unchanged. Nevertheless, the acidic hydrolysis of heptamaloxyloglucan can produce a small proportion (< 1%) of smaller oligosaccharide fragments (polymerisation degree < 7) and/or monosaccharides (glucose, glucitol, xylose, galactose, fucose).

CONCLUSION

Assessment and conclusion by applicant:
In acid environment, Heptamaloxyloglucan can be hydrolysed in XLGol and Fucose, by rupture of alpha 1-2 glycosidic bond.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

B.6.1.1.3 Enzymatic hydrolysis (in the small intestine by digestive enzymes and the large intestine by microflora)

Heptamaloxyloglucan and the smaller oligosaccharide fragments (polymerisation degree < 7) which can be produced in very low amounts after acidic hydrolysis in the stomach are soluble non digestible complex carbohydrates similar to hemicellulose fibres (KCA 5.1/07, Alvarez E.E. and Sanchez P.G., 2006). They cannot be broken down by human enzymes of the small intestine (amylase, sucrose, maltase, isomaltase, trehalase and lactase) and will be further fermentated in the colon. All the bonds linking the sugars of heptamaloxyloglucan can be hydrolysed by the enzymes of the microflora: β-D-glucoside glucohydrolase, β-D-galactoside galactohydrolase, β-D-galactoside galactohydrolase, α-xylosidase, α-L-fucoside fucohydrolase (KCA 5.1/08, Macfarlane et al., 1998), producing various smaller oligosaccharides and also the monomer units: galactose, glucose, xylose and fucose.
The unfermented unchanged heptamaloxyloglucan and smaller oligosaccharides (polymerisation degree < 7) are eliminated in the faeces.

Annex point:	KCA 5.1/07
Report author	Alvarez E.E. and Sanchez P.G.
Report year	2006
Report title	La fibra dietética - Dietary fibre

Report No	Nutrition Hospitalaria, Vol.21 (supl. 2), pp. 60-71, 2006
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013

[2] 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).

This review presents the process of digestion of dietary fibres, including hemicellulose. They reach the large bowel and are attacked by colonic microflora, yielding short chain fatty acids, hydrogen, carbon dioxide, and methane as fermentation products.

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Hemicellulose are dietary fbres that are digest in the large bowel under the action of colonic microbiota.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Data point:	KCA 5.1/08
Report author	Macfarlane S. et al.
Report year	1998
Report title	Polysaccharide degradation by human intestinal bacteria during growth under multi-substrate limiting conditions in a three-stage continuous culture system
Report No	FEMS Microbiology Ecology, Vol. 26, pp. 231-243, 1998
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013

[2] 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).

The aim of this study is to investigate the process involved in the depolymerization of polysaccharides by mixed populations of intestinal bacteria, particularly in relation to substrate utilisation patterns.

MATERIALS AND METHODS
A three-stage continuous culture model was used which was designed to reproduce in vitro the disparate nutritional and environmental conditions that affect the growth and activities of bacteria growing in the proximal and distal colons. Bacteria populations were identified, and the polysaccharides and glucosidase activities associated with these populations have been investigated. The polysaccharides used in this study were starch, xylan, mucin, inulin, pectin, guar gum.

RESULTS
The polysaccharides in the feed medium were degraded by colonic microorganisms into monosaccharides and oligosaccharides. The following polysaccharidase and glycoside hydrolase activities were measured: amylase, glalactomannase, xylanase, arabinogalactanase, polygalacturonase, α-Glucosidase, α-Galactosidase, β-Galactosidase, α-Fucosidase N-Acetyl-β-glucosaminidase N-Acetyl-β-galactosaminidase, β-Xylosidase, β-Arabinofuranosidase, Neuraminidase. The unfermented oligosaccharides (polymerisation degree < 7) are eliminated in the faeces.

CONCLUSION

Assessment and conclusion by applicant:
Polysaccharides are degraded into polysaccharides and monosaccharides by the colonic microorganisms and unfermented oligosaccharides are are eliminated in the faeces.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Expected fate of metabolites
Galactose, glucose, xylose and fucose
Only monosaccharides can be absorbed in the mammal small intestine (KCA 5.1/04, Wahbeh T.G. and Christie D.L., 2006). The fate of each of the glucidic monomers constituting heptamaloxyloglucan is well known in mammals: galactose, glucose, xylose and fucose are all nutrients found in the normal diet in humans. They possess an energetic value and they belong to the eight monosaccharides essential to glycoconjugate synthesis, by direct incorporation into glycoproteins and glycolipids (KCA 5.1/09-13 Gardiner T., 2000).

Data point:	KCA 5.1/09
Report author	Gardiner T
Report year	2000
Report title	Absorption, Distribution, Metabolism, and Excretion (ADME) of Eight Known Dietary Monosaccharides Required for Glycoprotein Synthesis and Cellular Recognition Processes
Report No	GlycoScience & nutrition., Vol 1 (12), pp. 1-7, 2000
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013

[2] 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).

This review presents the absorption, the distribution, the metabolism and the excretion of mannose, galactose, fucose, xylose, glucose, sialic acid, N-acetylglucosamine. These eight monosaccharides are essentials for the biosynthesis of glycoconjugates. They can be readily absorbed and directly incorporated into glycoproteins and glycolipids that form the receptors for cell-to-cell communication.

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Galactose, fucose, xylose, glucose are dietary essential monosaccharides that can be readily absorbed and directly incorporated into glycoproteins and glycolipids.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Data point:	KCA 5.1/10
Report author	Gardiner T
Report year	2000
Report title	Dietary Fucose: Absorption, Distribution, Metabolism, Excretion (ADME) and Biological Activity
Report No	GlycoScience & nutrition., Vol 1 (6), pp.1-4, 2000
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities1,2	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013
[2] 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).

This review presents the absorption, the distribution, the metabolism, the excretion and biological activity of fucose.

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Fucose can be readily absorbed and used as an energy source and directly incorporated into glycoproteins and glycolipids.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Annex point:	KCA 5.1/11
Report author	Gardiner T
Report year	2000
Report title	Dietary Galactose: Absorption, Distribution, Metabolism, Excretion (ADME) and Biological Activity
Report No	GlycoScience & nutrition., Vol 1 (7), pp.1-4, 2000
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013
[2] 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).

This review presents the absorption, the distribution, the metabolism, the excretion and biological activity of galactose.

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Galactose can be readily absorbed and used as an energy source and directly incorporated into glycoproteins and glycolipids.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Data point:	KCA 5.1/12
Report author	Gardiner T
Report year	2000
Report title	Dietary Glucose: Absorption, Distribution, Metabolism, Excretion (ADME) and Biological Activity

Report No	GlycoScience & nutrition., Vol 1 (18), pp.1-4, 2000
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities[1,2]	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013
[2] 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).

This review presents the absorption, the distribution, the metabolism, the excretion and biological activity of glucose.

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Glucose is readily absorbed and widely distributed throughout the body and used as an energy source. It can directly be incorporated into glycoproteins and glycolipids.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Annex point:	KCA 5.1/13
Report author	Gardiner T
Report year	2000
Report title	Dietary Xylose: Absorption, Distribution, Metabolism, Excretion (ADME) and Biological Activity
Report No	GlycoScience & nutrition., Vol 1 (5), pp.1-2, 2000
Document No	
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities1,2	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013
[2] 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).

This review presents the absorption, the distribution, the metabolism, the excretion and biological activity of Xylose.

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Xylose is naturally readily absorbed and used as an energy source. It can directly be incorporated into glycoproteins and glycolipids. Xylose is considered to be as safe as glucose at dietary levels.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Glucitol
Glucitol, also known as sorbitol, is a sugar alcohol with the same linear structure as the chain form of glucose, but the –CHO (aldehyde) group is replaced with a $–CH_2OH$ group. It is used as an additive in food (agent for anticaking, thickening, texturizing, emulsifying, firming, drying, curing, pickling, flavouring and sweetening) and cosmetic industry (stabilizer in toothpaste and makeup). It is also produced naturally in the body by the reduction of glucose or fructose. It cannot be readily digested by humans, but is degraded by fermentation by the digestive microflora. The limit for appearance of a laxative effect is the consumption of more than 50 grams sorbitol/day (KCA 5.1/14, Ramberg J., 2005).

Annex point:	KCA 5.1/14
Report author	Ramberg J
Report year	2001
Report title	Sorbitol
Report No	GlycoScience. The nutrition science site. Web capture. Date Last modified : 2001
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities1,2	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013
[2] 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).

Sorbitol is a monosaccharide that is found in some foods and that is produced naturally in the body by the reduction of glucose or fructose. Sobitol is degraded by bacteria in the digestive tract. Sorbitol is GRAS (Generally Recognized as safe by the FDA) and may be used as a direct food substance. When added to foods it serves a wide variety of purposes, including as an agent for anticaking, thickening, texturizing, emulsifying, firming, drying,

curing, or pickling. It is also used as a flavoring agent or nutritive sweetener. A daily ingestion of 50 grams of sorbitol is the upper limit to observe a potential laxative effect. For comparison, 340 grams (12 ounces) of prune, pear, and apple juices contain 48, 7.5, and 1.5 grams of sorbitol, respectively.

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

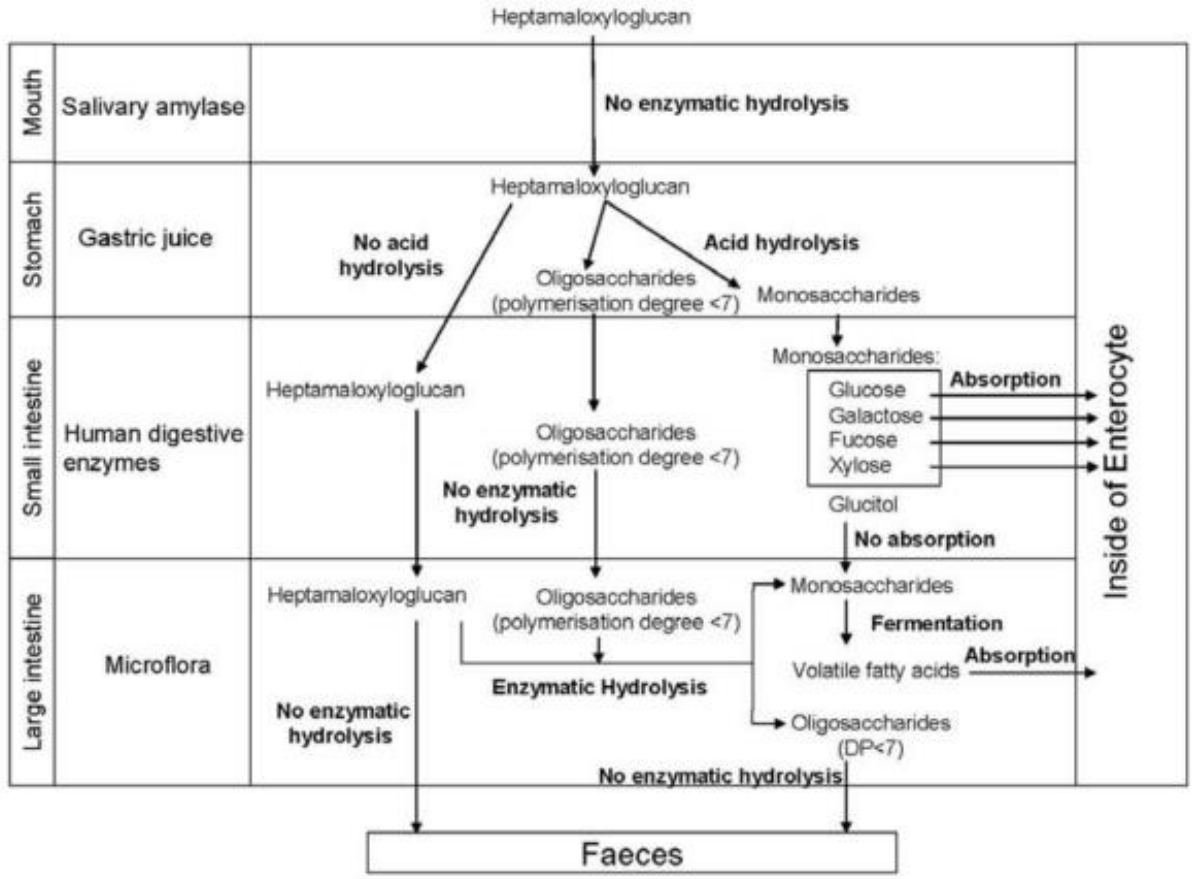
CONCLUSION

Assessment and conclusion by applicant:
Sorbitol is a monosaccharide that is found in some foods and that is produced naturally in the body by the reduction of glucose or fructose. The potential laxative effect of sorbitol could be obsaerved from a daily consumption of 50 gram.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

B.6.1.1.3 Fermentation

An expected metabolic pathway for non-hydrolysed EL101GV is fermentation, producing short-chain fatty acids. This will mainly occur in the colon and/or caecum of monogastric Mammals, and in the rumen of Ruminants, thanks to digestive flora. Short chain fatty acids acetate, propionate and butyrate are also fermentation products of cellulose and more generally glucidic fibres. They do not accumulate as they are subjected to a large variety of enzymatic reactions in humans and animals. They are not toxic except when one at least is produced in large amounts, either because of a bacterial overgrowth or unbalanced alimentation.
In the colon and/or caecum of mammals, further breakdown of the oligosaccharides and monomeric sugars will occur by the microflora leading to short-chain fatty acids and pyruvate. Pyruvate does not appear in the large bowel because it is immediately converted to end-products. Short-chain fatty acids (SCFA) are mainly acetate, propionate and butyrate. End-products include carbon dioxide, hydrogen, and methane which are also fermentation products of cellulose and more generally of glucidic fibres (KCA 5.1/15, Topping and Clifton, 2001; KCA 5.1/04, Wahbeh T.G. and Christie D.L., 2006). SCFA are absorbed at the site of production and transported to the liver via entero-heptatic circulation (KCA 5.1/16, Khattak, 2002). They do not accumulate as they are subjected to a large variety of enzymatic reactions in humans and animals.
They are not toxic except when one at least is produced in large amounts, either because of bacterial overgrowth or unbalanced alimentation. Both situations will not occur with the very small amounts of heptamaloxyloglucan to which humans or animals will be exposed based on the very low application rate (0.05 to 0.5 g a.s./ha on vines). Therefore no toxic metabolite is expected to be produced in the large intestine by fermentation of heptamaloxyloglucan.



Ref : 2007/01/17- AFSSA COMMUNICATION, REF 07-0015

Figure B.6.1.1-1: Probable fate of the heptamaloxyloglucan after oral intake

Annex point:	KCA 5.1/15
Report author	Topping D et al.
Report year	2001
Report title	Short-Chain Fatty Acids and Human Colonic Function: Roles of Resistant Starch and Nonstarch Polysaccharides
Report No	Physioloical Reviews, Vol. 81 (3), pp. 1031-1063, 2001
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities1,2	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013

[2] 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).

This review presents the metabolism of Resistant starch (RS), Nonstarch Polysaccharides (NSP) and non-starch-derived oligosaccharides. RS is the fraction of small intestinal starch digestion that enters in the large bowel. NSP and non-starch-derived oligosaccharides (major components of dietary fibers), also enter the large bowel because they are resistant to digestion by the intrinsic enzymes of the human stomach and small intestine. Human colonic bacteria ferment RS, NSP and non-starch-derived oligosaccharides to short-chain fatty acids (SCFA), mainly acetate, propionate, and butyrate. SCFA stimulate colonic blood flow and fluid and electrolyte uptake. Butyrate is a preferred substrate for colonocytes and appears to promote a normal phenotype in these cells. Fermentation of some RS types favors butyrate production.

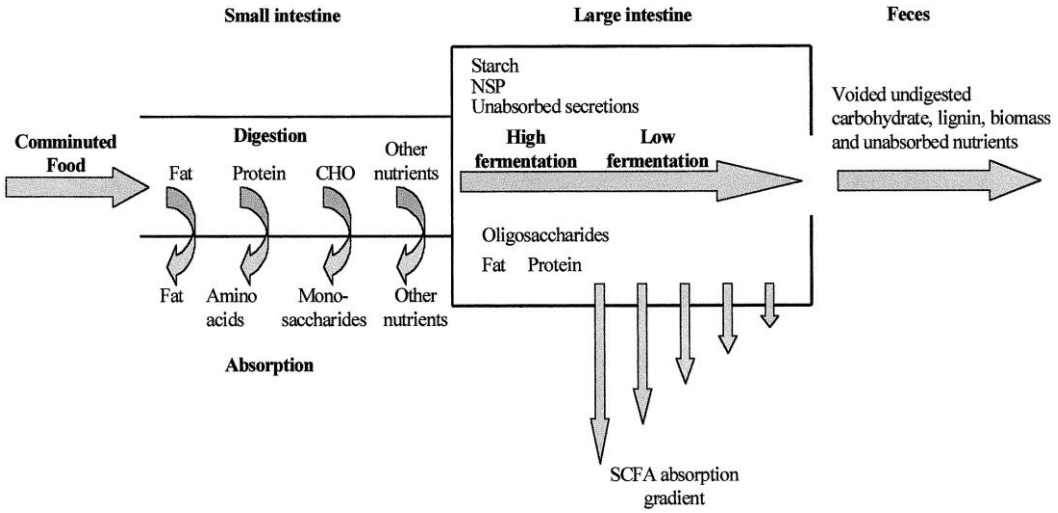


Figure: An overview of the relationship between transit of food through the human gastrointestinal tract and the digestion of nutrients in the small intestine and fermentation in the cecum and colon. In the small intestine, digestion occurs through the action of intrinsic enzymes, and nutrients are absorbed. Food components and endogenous secretions not absorbed (including RS, NSP and non-starch-derived oligosaccharides) in that viscus pass through the ileocecal valve and are fermented. Fermentation is high in the proximal large bowel as is the SCFA production. Absorption of SCFA and of water and minerals (including calcium) is high in this viscus. On passage of the fecal stream, fermentation declines through substrate depletion, and SCFA values fall.

MATERIALS AND METHODS

Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Non-starch-derived oligosaccharides that are resistant to small intestinal digestion enter into the large bowel where they are metabolised by colonic bacteria to short-chain fatty acids (SCFA).

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

Annex point:	KCA 5.1/16
Report author	Khattak MA
Report year	2002
Report title	Physiological effects of dietary complex carbohydrates and its metabolites role in certain diseases
Report No	Pakistan Journal of Nutrition, Vol. 1 (4), pp. 161-168, 2002
Document No	-
Guidelines followed in study	Not relevant (scientific article)
Deviations from current test guideline	Not relevant (scientific article)
Previous evaluation	Yes, previously submitted
GLP/Officially recognised testing facilities1,2	No, not conducted under GLP/Officially recognised testing facilities (scientific article)
Acceptability/Reliability:	Supportive only

[1] See Art.3 of Annex of Regulation No 283/2013 and 284/2013
[2] 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).

Resistant starch, dietary fibres (NSP, non-strarch polysaccharides) and derived-oligosaccharides are not digested in the upper gastrointestinal tract and are fermenter in the large bowel by the action of bacterial. The major NSP are cellulose, hemicellulose, pectins. The fermentation products are mainly short-chain fatty acids (SCFA), methane, hydrogen and carbon dioxide. The SCFA produced from the fermentation are absorbed at site production and transported to the liver via entero-hepatic circulation. SCFA play an important nutritional role.

The process of fermentation involves the hydrolysis by the bacteria of the polymeric substrates to their monomeric units (glucose, galactose, xylose arabinose, fucose, uronic acids) that are fermented via glycolysis to pyruvate and to SCFA (mainly acetate, propionate and butyrate).

MATERIALS AND METHODS
Non applicable

RESULTS
Non applicable

CONCLUSION

Assessment and conclusion by applicant:
Non-starch-derived oligosaccharides that are resistant to small intestinal digestion enter into the large bowel where they are metabolised by colonic bacteria to short-chain fatty acids (SCFA).

Assessment and conclusion by RMS 2020:

Acceptability/Reliability: This report is considered for supplementary information only.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The RMS agrees with the conclusions of the applicant.

B.6.1.1.4 Conclusion

Oral intake of heptamaloxyloglucan will result in animal or human exposure to unchanged parent and widespread and well-known oligosaccharides and glucidic monomers (absorbable glucose, fucose, xylose and galactose; unabsorbable glucitol) and short-chain fatty acids (acetate, propionate, butyrate). As these substances are common natural nutrients and as the large variety of enzymatic reactions in which they are involved excludes any bioaccumulation, no metabolism study was specifically performed with heptamaloxyloglucan. Neither unkown nor toxic metabolites are expected to be produced by heptamaloxyloglucan.

Assessment and conclusion by RMS 2020:
The heptamaloxyloglucan ingested by mammals can undergo three degradation pathways: acidic hydrolysis, enzymatic hydrolysis and fermentation. The digestion starts in the mouth with the salivary α-amylase followed by acidic hydrolysis in the stomach and enzymatic hydrolysis in the small intestine and fermentation by the microflora at the large intestine level. The remaining fraction of non-metabolised or non-hydrolysed heptamaloxyloglucan will be excreted in feces. No toxic metabolites are expected to be produced by heptamaloxyloglucan. Since the ADME properties are based on human data, an *in vitro* comparative metabolism study is not judged necessary.
In conclusion, RMS considers the information presented on heptamaloxyloglucan metabolism as sufficient.

B.6.1.2. Absorption, distribution, metabolism and excretion by other routes

No study was performed because no toxic compound is produced by heptamaloxyloglucan metabolic pathways (see B 6.1).

For dermal absorption, no study was performed. Indeed, K_{ow} of EL101GV is low ($< 10^{-4}$) and molecular weight is high (> 1000 g/mol): the active substance is unable to penetrate through lipophilic membranes, and thus no dermal absorption is possible. This was supported by the absence of adverse effects in an acute dermal toxicity study performed in rats (see B 6.2.2; dermal LD_{50} > 2000 mg/kg b.w.).

For the inhalative route, no study was submitted by the applicant. Due to the active substance physico-chemical properties and its molecular weight inhalative absorption is not expected. The molecular weight is equal to 1078 g/mol, higher than the limit of 1000 g/mol, indicating that the molecule may be too large to be absorbed by the respiratory tract. Therefore, systemic exposure *via* inhalation route is not expected. The vapour pressure is largely below 0.1 Pa indicating the substance is not volatile. The inhalation of vapour is not expected and may be very limited. According to the ECHA guidance (2017), page 51/427: "poorly water- and lipid-soluble particles (*i.e.* log P is *ca.* 0 and water solubility *ca.* 1 mg/L or less) with aerodynamic diameters ≤1 µm have the potential to deposit in the alveolar region of the lung". Therefore, combining the high Log P and the high solubility in water, heptamaloxyloglucan is not expected to readily absorb through the respiratory tract.
Considering all the above information, heptamaloxyloglucan is not expected to penetrate the respiratory tract and to absorb through the respiratory tract epithelium.

Assessment and conclusion by RMS 2020:
For dermal absorption, RMS agrees with the applicant conclusion on the absence of dermal absorption of the active subsantce.

For inhalation absorption, RMS considers that the provided elements do not bring sufficient evidence. Please refer to the section B.6.2.3 acute toxicity by inhalation, i.e. this RMS would consider this concern addressed and that ADME inhalation study can be waived if an acute inhalation toxicity study was provided.

B.6.2. ACUTE TOXICITY

No new study is provided by the applicant compared to previous evaluation (DAR 2007).

B.6.2.1. Oral

Annex Point	KCA 5.2.1/01
Report author	**********
Report year	2006b
Report title	EL101GV: Acute oral toxicity study in the rat: Acute toxic class method Centre de Recherches Biologiques (CERB), Chemin de Montifault, 18800 Baugy, France
Guidelines	OECD N°423
Major deviations from current guideline	None
Previous evaluation	Yes, study already evaluated and accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	Yes
Acceptability/reliability	Yes

MATERIAL AND METHODS:
EL101GV (batch ALP0103, heptamaloxyloglucan content: 96.2% w/w) was administered by the oral route to female Sprague-Dawley rats (8-10 weeks, nulliparous, non-pregnant, body weight ranging 184.1–217.8g at dosing). The test item was administered by oral gavage, as a solution into sterile water, at a constant dose volume of 10 mL/kg. The body weight of each animal was recorded immediately before dosing, and the quantity of test item to be administered was based on the result. The dose-levels of 300 and 2000 mg/kg body weight (b.w.) were tested in the following succesive steps:

- Three females were treated at 300 mg/kg b.w. (step 1), and then the same procedure was repeated on three other females (step 2) in order to confirm the results;
- Then three females were treated at 2000 mg/kg b.w. (step 3), and then the same procedure was repeated on three other females (step 4) in order to confirm the results.

Day of treatment was noted day 1. Mortality was recorded twice daily for a 14-day observation period. Clinical signs were recorded twice on day 1 and daily thereafter. A detailed clinical examination including functional and behavioural tests was carried out on days 1 and 7 on all animals. Individual body weights were measured on days 1, 7, 14 and at the time of sacrifice. On day 15, all animals were sacrificed by exsanguination under anaesthesia. All animals were subjected to gross necropsy and macroscopic examination of the liver, spleen, kidneys, stomach, intestines, gonads and reproductive tract, lungs and heart.

RESULTS:
At each step of the study, all rats survived the two-week observation period.

Table B.6.2.1-1: Mortality among female rats administered a single oral dose of EL101GV on day 1.

Dose-level (mg/kg b.w.)	Mortality	Time of death
300 (step 1)	0/3	-
300 (step 2)	0/3	-
2000 (step 3)	0/3	-
2000 (step 4)	0/3	-

There were no treatment-related clinical signs.

All rats showed the expected body weight gain over the study period.

There were no treatment-related observations in any of the rats at necropsy.

CONCLUSION:
After a single oral administration of EL101GV to female Sprague-Dawley rats at the dose-level of 300 or 2000 mg/kg b.w., there were neither mortalities nor treatment-related clinical signs. Acute oral LD_{50} can be set at 2000 mg/kg b.w. Under the experimental conditions and according to the acute toxic class method (OECD N°423), **EL101GV is in category 5 or unclassified and its acute oral LD_{50} in rats is higher than 5000 mg/kg b.w.**

In accordance with Regulation (EC) No.1272/2008, the active substance must not be classified. No signal word or hazard statement is required.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This study is considered acceptable.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The active substance does not require classification for this toxicological endpoint.

B.6.2.2. Dermal

Annex Point	KCA 5.2.2/01
Report author	*********
Report year	2006a
Report title	EL101GV: Acute dermal toxicity study in the rat (OECD 402) Centre de Recherches Biologiques (CERB), Chemin de Montifault, 18800 Baugy, France
Guidelines	OECD N°402, Method B3 of Commision Directive 92/69/EEC
Major deviations from current guideline	None
Previous evaluation	Yes, study already evaluated and accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	Yes
Acceptability/reliability	Yes

MATERIAL AND METHODS:
EL101GV (batch ALD0204, heptamaloxyloglucan content: 86.1% w/w) was applied to the skin of 5 male and 5 nulliparous, non-pregnant female Sprague-Dawley rats (8-12 weeks, body weight ranging 305-319 g in males and 198-213 g in females at dosing). The test item was applied moistened with sterile water, to the closely clipped skin of the dorsal region of each rat, at a dose-level of 2000 mg/kg b.w. (limit test) . The body weight of each animal was recorded immediately before dosing, and the quantity of test item to be applied was based on the result. The treated site was protected by absorbent gauze, a pad and an adhesive tape and this protection was held in place for 24 h.

Day of treatment was noted day 1. Mortality was recorded twice daily for a 14-day observation period. Clinical signs were recorded twice on day 1 and daily thereafter. Daily cutaneous observations for erythema and oedema were performed using the Draize scheme. A detailed clinical examination including functional and behavioural tests was carried out on days 2 and 7 on all animals. Individual body weights were measured on days 1, 7, 14 and at the time of sacrifice. On day 15, all animals were sacrificed by exsanguination under anaesthesia. All animals were subjected to gross necropsy and liver, spleen, kidneys, stomach, intestines, gonads and reproductive tract, lungs and heart and treated area were examined macroscopically.

RESULTS:
All rats survived the two-week observation period.

Table B.6.2.2-1: Mortality among male and female rats applied a single dermal dose of EL101GV on day 1.

	Males	Females

Dose-level (mg/kg b.w.)	Mortality	Time of death	Mortality	Time of death
2000	0/5	-	0/5	-

There were no clinical signs or dermal reactions.

All rats showed the expected body weight gain over the study period.

There were no treatment-related observations in any of the rats at necropsy.

CONCLUSION:
After a single dermal application of EL101GV to male and female Sprague-Dawley rats at the dose-level of 2000 mg/kg b.w., there were neither mortalities nor treatment-related clinical signs. An acute dermal LD_{50} can be set at 2000 mg/kg b.w. Under the experimental conditions, **the acute dermal LD_{50} of EL101GV in rats is higher than 2000 mg/kg.**

In accordance with Regulation (EC) No.1272/2008, the active substance must not be classified. No signal word or hazard statement is required.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This study is considered acceptable.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The active substance does not require classification for this toxicological endpoint.

B.6.2.3. Inhalation

Assessment and conclusion by applicant:
According to Section 5.2.3 of Part A of the Regulation (EU) No.283/2013, an acute inhalation toxicity study is not relevant for an active substance according to the following criteria:
- the active substance has a vapour pressure > 1×10^{-2} Pa at 20 °C;
- the active substance is a powder containing a significant proportion of particles of a diameter < 50 µm (> 1 % on weight basis);
- the active substance is included in products that are powders or are applied by spraying.
In the present assessment, no study was performed. The active substance doesn't encounter any criteria described above, except the application by spraying. However it appears useless to perform unnecessary testing in mammals.

As already detailed, the active substance heptamaloxyloglucan is an oligosaccharide made of 7 glucidic monomer units. Based on appropriate publications and study reports, it has been demonstrated that heptamaloxyloglucan can be derived naturally from xyloglucan, which is the principal hemicellulosic component of primary cell walls of dicotyledonous and non-graminaceous monocotyledonous plants.
As detailed in B 6.1, oral intake of heptamaloxyloglucan was expected to result in animal or human exposure to unchanged parent and widespread and well-known oligosaccharides and glucidic monomers (absorbable glucose, fucose, xylose and galactose; unabsorbable glucitol) and short-chain fatty acids (acetate, propionate, butyrate). These substances being common natural nutrients and as the large variety of enzymatic reactions in which they are involved excludes any bioaccumulation, there was no expected toxicological concern.
No toxicological concern is expected also *via* inhalation route, especially by taking into account that the human respiratory mucins in the lungs are composed mostly by carbohydrates, also identified in heptamaloxyloglucan (e.g. fucose, galactose …) (KCA 5.2.3/01 Lamblin G. et al., 1992).

Inhalation exposure is related to the deposition of the particles into the respiratory tract and to the respiratory absorption. The location of deposition and then the absorption mainly depend on the physico-chemical properties of the particle. Toxicity data also provide information on potential inhalation absorption and toxicity. Based on these considerations, a qualitative assessment is proposed to demonstrate inhalation exposure and absorption of heptamaloxyloglucan is very limited and therefore inhalation toxicity is not expected.

The table below presents:
- properties to be considered for respiratory deposition and absorption (according to ECHA Guidance on the BPR, Vol. III (Parts B+C), Version 4.0, December 2017),
- information available for the active substance heptamaloxyloglucan,

- consequences for respiratory exposure, deposition and absorption.

Table B 6.2.3-1: Qualitative assessment of respiratory tract absorption

Property	**Consequences**	**Data on heptamaloxyloglucan (source: Doc N2 181130)**	**Influence on exposure, deposition and absorption**
Molecular weight	< 500, favour absorption > 1000, do not favour absorption	1078 g/mol	-
Vapour pressure	> 25 kPa = highly volatile < 0.1 Pa = low volatile	1.1 10^{-11} Pa at °C	-
Log P	-1 < log P < 4 = favourable absorption through the respiratory tract epithelium by passive diffusion. Any lipophilic compound may be taken up by micellar solubilisation but this mechanism may be of particular importance for highly lipophilic compounds (log P >4), particularly those that are poorly soluble in water (≤1 mg/L) that would otherwise be poorly absorbed.	15.96 (pH not relevant)	-
Water solubility	Very hydrophilic substances may be retained within the mucus. Low water solubility, like small particle size enhances penetration to the lower respiratory tract. If the molecular weight is low (<200) the substance may pass through aqueous pores	558 g/L at 20°C	-
Toxicological classification	Dermal corrosion/irritation or sensitisation may impact the epithelium and be favourable for penetration	Not classified	-
Oral toxicity	If signs of systemic toxicity are present in an oral toxicity study or there are other data indicating the potential for absorption following ingestion, the substance will likely be absorbed also when inhaled.	LD_{50} oral, rat > 5000 mg/kg b.w. NOAEL, rat, 28-d study = 1000 mg/kg b.w. (highest dose level tested, no critical effect)	0

-: condition not favourable for respiratory absorption
0: condition that do not affect absorption

The molecular weight is equal to 1078 g/mol, higher than the limit of 1000 g/mol, indicating that the molecule may be too large to be absorbed by the respiratory tract. Therefore, systemic exposure *via* inhalation route is not expected.

The vapour pressure is largely below 0.1 Pa indicating the substance is not volatile. The inhalation of vapour is not expected and may be very limited.

According to the ECHA guidance (2017), page 51/427: "poorly water- and lipid-soluble particles (*i.e.* log P is *ca.* 0 and water solubility *ca.* 1 mg/L or less) with aerodynamic diameters ≤1 µm have the potential to deposit in the alveolar region of the lung". Therefore, combining the high Log P and the high solubility in water, heptamaloxyloglucan is not expected to readily absorb through the respiratory tract.

Regarding toxicity data available, heptamaloxyloglucan is not classified for its toxicological properties and has low acute and repeated oral toxicity with no effect reported on respiratory tract. These aspect represent favourable conditions for a very limited absorption.

Considering all the above information (biological and molecular aspects), heptamaloxyloglucan is not expected to penetrate the respiratory tract and to absorb through the respiratory tract epithelium. Also, no specific local or systemic toxicity *via* inhalation is expected.

Therefore, no study is required for acute toxicity by inhalation route since exposure of humans *via* inhalation is unlikely taking into account the physicochemical properties of the substances and the lack of exposure to aerosols, particles or droplets of inhalable size under normal conditions of use.

The active substance is not expected to present acute toxicity by inhalation exposure.
In accordance with Regulation (EC) No.1272/2008, the active substance must not be classified. No signal word or hazard statement is required.

Assessment and conclusion by RMS 2020:
RMS notes that spraying is the mode of application of the active substance which is a criterion under Regulation No. 283/2013. Section 5.2.3 stipulates *"The acute inhalation toxicity of the active substance shall be reported where any of the following apply: - the active substance has a vapour pressure > 1 × 10–2 Pa at 20 °C; - the active substance is a powder containing a significant proportion of particles of a diameter < 50 μm (> 1 % on weight basis); - the active substance is included in products that are powders or are applied by spraying.".*

There is no evidence submitted by the applicant that the heptamaloxyloglucan is unlikely to trigger inhalation toxicity.
In light of the above remark and lack of ADME data on the inhalation route, RMS considers that the provided elements do not bring sufficient evidence in the applicant's conclusion for inhalation endpoint and this should be substantiated by at least a read across evaluation with a suitable analogue that would have reliable acute inhalation data. If no suitable analogue is found, inhalation route testing is then required. In the absence of read across evaluation or test, a data gap will be considered for this endpoint.

B.6.2.4. Skin irritation

Annex Point	KCA 5.2.4/01
Report author	********
Report year	2006c
Report title	EL101GV: Acute skin irritation study in the rabbit (OECD 404) Centre de Recherches Biologiques (CERB), Chemin de Montifault, 18800 Baugy, France
Guidelines	OECD N°404
Major deviations from current guideline	None
Previous evaluation	Yes, study already evaluated and accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	Yes
Acceptability/reliability	Yes

MATERIAL AND METHODS:
EL101GV (as supplied by the sponsor, batch ALP0103, heptamaloxyloglucan content: 96.2% w/w) was moistened and applied at the dose of 0.5 g to the closely clipped right flank skin of 3 female New Zealand White rabbits (weighing 2.9-3.5 kg). It was placed on a gauze square, protected by a semi-occlusive dressing and kept in contact with the skin for 4 hours. Day of application was noted day 1.

Cutaneous observations for erythema and oedema were performed using the Draize scheme, at 1, 24, 48 and 72 hours after test material removal. Individual body weights were recorded at test initiation and at the end of the study (at 72h).

RESULTS:

There was no mortality. Two of the three rabbits lost weight over the 3-day observation period: -9g and -130g. However, the third rabbit gained 62g weight.

Table B.6.2.4-1: Individual body weight and body weight gain (BWG)

Treatment	Animal number	BW on Day 1 (kg)	BW on Day 4 (kg)	BWG (g)
EL101GV	20040127	3.443	3.313	-130
	20040128	2.892	2.883	-9
	20040129	2.969	3.031	+62

One hour after application, very slight erythema was observed in all three rabbits. This lesion was not observed at the next examinations (24, 48 and 72 h post-treatment). There was no other local reaction to the treatment.

Table B.6.2.4-2: Individual and mean skin irritation scores according to the Draize scheme

Animal	Erythema score			Oedema score		
Female number	1	2	3	1	2	3
1 h	1	1	1	0	0	0
24 h	0	0	0	0	0	0
48 h	0	0	0	0	0	0
72 h	0	0	0	0	0	0
Mean 24-72h	0	0	0	0	0	0

CONCLUSION:
After topical application of EL101GV on the skin of female rabbits for 4 hours under semi-occlusive, only minimal and transient erythema was observed. **In accordance with Regulation (EC) No.1272/2008, the active substance must not be classified. No signal word or hazard statement is required..**

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This study is considered acceptable.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The active substance does not require classification for this toxicological endpoint.

B.6.2.5. Eye irritation

Annex Point	KCA 5.2.5/01
Report author	*********
Report year	2006d
Report title	EL101GV: Acute eye irritation study in the rabbit (OECD 405) Centre de Recherches Biologiques (CERB), Chemin de Montifault, 18800 Baugy, France
Guidelines	OECD N°405
Major deviations from current guideline	None
Previous evaluation	Yes, study already evaluated and accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	Yes
Acceptability/reliability	Yes

MATERIAL AND METHODS:
Three female New Zealand White rabbits (weighing 2.5-3.3 kg) were instilled the test item EL101GV (as supplied by the sponsor, batch ALP0103, heptamaloxyloglucan content: 96.2% w/w) onto the eye.

A first rabbit was treated, and based on the observations, two other rabbits were treated in the same way, as follows: 0.1 g of test item was instilled into the conjunctival sac of each rabbit's left eye and the eyelids were then held closed for ten seconds to prevent loss of test material. The untreated right eye of each rabbit served as a control. The eyes of all rabbits remained unwashed post-treatment. Day of instillation was noted day 1.

Treated eyes were examined and ocular reactions were graded at 1, 24, 48 and 72 hours post-dosing for corneal opacity, iridial lesions and conjunctival reactions (redness, chemosis and discharge). All rabbits were examined for signs of pain. Individual body weights were recorded at test initiation and at 72 hours post-dosing.

RESULTS:
There was no mortality. No pain reactions were noted after treatment. The three rabbits presented the expected weight gain over the 3 days of observation period: +31, +53 and +23g.
One hour after instillation, some blood vessels were hyperhaemic in the treated eye of the three rabbits. This lesion was not observed at the next examinations (24, 48 and 72 h post-treatment). There was no other local reaction to the treatment.

Table 5.2.5/1: Eye irritation score of the left eye of rabbits instilled EL101GV at the dose of 0.1 g into the conjunctival sac.

Clinical signs	Rabbit number		
	1	2	3
Conjunctival redness			
After 1 hr	1	1	1
After 24 hr	0	0	0
After 48 hr	0	0	0
After 72 hr	0	0	0
Group mean score 24-72 hr	**0**		
Conjunctival chemosis			
After 1 hr	0	0	0
After 24 hr	0	0	0
After 48 hr	0	0	0
After 72 hr	0	0	0
Group mean score 24-72 hr	**0**		
Corneal opacity (grade)			
After 1 hr	0	0	0
After 24 hr	0	0	0
After 48 hr	0	0	0
After 72 hr	0	0	0
Group mean score 24-72 hr	**0**		
Corneal opacity (area involved)			
After 1 hr	0	0	0
After 24 hr	0	0	0
After 48 hr	0	0	0
After 72 hr	0	0	0
Group mean score 24-72 hr	**0**		
Iridial inflammation			
After 1 hr	0	0	0
After 24 hr	0	0	0
After 48 hr	0	0	0
After 72 hr	0	0	0
Group mean score 24-72 hr	**0**		

CONCLUSION:
After eye-instillation of EL101GV to female rabbits, minimal and transient conjunctival redness was observed at 1 hour post-treatment as an only reaction. **In accordance with Regulation (EC) No.1272/2008, the active substance must not be classified. No signal word or hazard statement is required.**

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This study is considered acceptable.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The active substance does not require classification for this toxicological endpoint.

B.6.2.6. Skin sensitization

Annex Point	KCA 5.2.6/01
Report author	********
Report year	2006
Report title	EL101GV: Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA) CIT, B.P.563, 27005 Evreux Cedex, France
Guidelines	OECD N°429

Major deviations from current guideline	None
Previous evaluation	Yes, study already evaluated and accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	Yes
Acceptability/reliability	Yes

MATERIAL AND METHODS:

A preliminary test was first performed in order to define the concentrations of test item to be used in the main test. In the main test, twenty-eight female CBA/J mice were allocated to seven groups:

- five treated groups of four animals receiving the test item EL101GV (batch ANN0304, heptamaloxyloglucan content: 78.1% w/w) at the concentration of 1, 2.5, 5, 10 or 25%,
- one negative control group of four animals receiving the vehicle (dimethylformamide = DMF),
- one positive control group of four animals receiving the reference item, α-hexylcinnamaldehyde (HCA), a moderate sensitizer, at the concentration of 25%.

During the induction phase, the test item, vehicle or reference item was applied over the ears (25 µL per ear) for 3 consecutive days (days 1, 2 and 3). After 2 days of resting, the proliferation of lymphocytes in the lymph node draining the application site was measured by incorporation of tritiated methyl thymidine (day 6). The obtained values were used to calculate stimulation indices (SI).

The irritant potential of the test item was assessed in parallel by measurement of ear thickness on days 1, 2, 3 and 6.

RESULTS:

Due to the unsatisfactory solubility of the test item in the first recommended vehicle (acetone/olive oil (4/1, v/v)), dimethylformamide was chosen among the other proposed vehicles. A solution was obtained whatever the proportion.

Consequently, the concentrations selected for the preliminary test were 5, 10, 25 and 50%.

Preliminary test:

Table B6.2.6-1: Results of the preliminary test (ear thickness measurements)

			D1		D2		D3		D4		
Number Animal	Concentration %		Ear Thickness	Local reaction	Ear Thickness	Local reaction	Ear Thickness	Local reaction	Ear Thickness	Local reaction	%
Female 301	50	RE	0.25	0	0.26	0	0.26	0/Su	0.28	0/Su	12.00
Female 301	25	LE	0.25	0	0.25	0	0.26	0	0.26	0	4.00
Female 302	50	RE	0.25	0	0.26	0/Su	0.27	0/Su	0.29	0/Su	16.00
Female 302	25	LE	0.26	0	0.25	0	0.25	0	0.25	0	-3.85
Female 303	10	RE	0.26	0	0.25	0	0.26	0	0.26	0	0.00
Female 303	5	LE	0.26	0	0.27	0	0.27	0	0.26	0	0.00
Female 304	10	RE	0.25	0	0.25	0	0.25	0	0.25	0	0.00
Female 304	5	LE	0.25	0	0.25	0	0.25	0	0.25	0	0.00

RE = right ear
LE = left ear
D = day
0 = no cutaneous reaction
Su = residual test item
% = percentage of ear thickness increase compared to day 1

No cutaneous reactions were observed at the tested concentrations. Only a slight in ear thickness was recorded at the concentration of 50%, showing the slightly irritant potential of the test item at this concentration. The highest concentration retained for the main test was 25% on the basis of the results of the solubility and preliminary assays.

Main test:

Systemic clinical signs and mortality: No mortality and no clinical signs were observed during the study.

Local irritation: No cutaneous reactions and no noteworthy increase in ear thickness were observed in the animals of the treated groups.

Proliferation assay: No noteworthy lymphoproliferation and no dose-response relationship were noted at the tested concentrations, while significant lymphoproliferation was observed with HCA at 25%.

Table B.6.2.6-2: LLNA results for mice exposed to test item EL101GV

Treatment	Concentration (%)	Irritation level	Stimulation Index (SI)
Test item	1	non-irritant	0.65
Test item	2.5	non-irritant	0.91
Test item	5	non-irritant	0.63
Test item	10	non-irritant	0.33
Test item	25	non-irritant	1.19
HCA	25	-	6.84

CONCLUSION:
Under the experimental conditions, the test item EL101GV did not induce delayed contact hypersensitivity in the murine Local Lymph Node Assay. **In accordance with Regulation (EC) No.1272/2008, the active substance must not be classified. No signal word or hazard statement is required.**

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This study is considered acceptable.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The active substance does not require classification for this toxicological endpoint.

B.6.2.7. Phototoxicity

According to Part A of the Regulation (EU) No.283/2013, an acute phototoxicity study and a photomutagenicity study is required under certain conditions.
A phototoxicity study is required when the ultraviolet / visible molar extinction / absorption coefficient of the active substance is higher than 10 L x mol^{-1} x cm^{-1}.
A photomutagenicity study is required when the ultraviolet / visible molar extinction / absorption coefficient of the active substance and its major metabolite is higher than 1000 L x mol^{-1} x cm^{-1}.

The active substance has molar extinction rates comprised in a range from 2.5 to 4.4 L × mol^{-1} × cm^{-1}. Therefore no phototoxicity issue is expected for the active substance. **In accordance with Regulation (EC) No.1272/2008, the active substance must not be classified. No signal word or hazard statement is required.**

Assessment and conclusion by RMS 2020:
Waiving study for phototoxicity and photomutagenicity is considered acceptable and the active substance does not require classification.

B.6.3. SHORT-TERM TOXICITY

B.6.3.1. Oral 28-day study

Annex Point	KCA 5.3.1/01
Report author	*********
Report year	2006
Report title	EL101GV: Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA) CIT, B.P.563, 27005 Evreux Cedex, France
Guidelines	OECD N°407
Major deviations from current guideline	None
Previous evaluation	Yes, study already evaluated and accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	Yes
Acceptability/reliability	Yes

MATERIAL AND METHODS:

1. Study design

At the request of Elicityl SA, the tolerance and any possible systemic toxicity of EL101GV (technical heptamaloxyloglucan batch n°AND0706, purity: 88.6% w/w) was evaluated following daily administration for 28 consecutive days in the rat by the oral route.

The study involved 4 groups of 20 SPF Sprague-Dawley rats (each of 10 males and 10 females), 7 to 8 weeks old and weighing between 222.2 g and 256.9 g for males and between 168.7 g and 195 g for females on the day of randomisation. Animals were purchased from Charles River Laboratories France (Domaine des Oncins - 69592 L'Arbresle Cedex, France).

Groups were as follows:

- group 1: control group dosed with the vehicle (*i.e.* sterile water)
- group 2: EL101GV at a dose of 50 mg/kg b.w.
- group 4: EL101GV at a dose of 200 mg/kg b.w.
- group 5: EL101GV at a dose of 1000 mg/kg b.w.

The amounts of EL101GV are expressed in mg/kg pure heptamaloxyloglucan.

Animals were weighed on the day of randomisation.

EL101GV or the vehicle (*i.e.* sterile water) were administered daily by the oral route in a volume of 10 mL/kg, at approximatively the same time of the day, for 28 consecutive days.

2. Experimental procedure

Body weight assessment, food consumption and full clinical examination were performed once a week. General observations were performed daily, 60 min post-dose (± 30 min). Mortality was recorded twice a day.

Functional and neurobehavioural tests: Functional and neurobehavioural tests and measurement of body temperature were performed before the first dosing and on D28, 60 min post-dose (± 30 min).

Blood and urine sampling: Blood samples for haematology, coagulation parameters, clinical chemistry analysis and urine sample were taken on the day of necropsy, on D29.

Necropsy: All animals surviving at the end of the study were submitted to full necropsy. The following organs were weighed at scheduled necropsy for all animals: adrenals, brain (cerebrum, cerebellum and stem), epididymides, heart, kidneys, liver, spleen, testes, thymus, lymph node (popliteal and sub-maxillary) ovaries and uterus. Paired organs were weighed together. Organs were weighed after dissection of fat and other contiguous tissues.

Only animals at 0 and 1000 mg/kg bw/day were examined for histopathology.

All organs/tissues sampled were fixed and preserved in 4% buffered formalin with the following exception: testes and epididymides were fixed in alcoholic Bouin*0*s fluid (about 4 days), then transferred into ethanol 95%.
The following organs were examined macroscopically: stomach, liver, duodenum, jejunum, ileum (+peyer's patches), caecum, colon, rectum, heart, trachea, lungs incl. bronchi and bronchioles, kidneys, ureters, urinary bladder, testes, epididymides, prostate, seminal vesicles, ovaries, uterus and oviducts, vagina, bone marrow in sternum, Mesenteric lymph node, Sub-maxillary lymph node, Popliteal lymph node, Thymus, Spleen, Adrenals, Thyroids, Brain (cerebrum, cerebellum, and brain stem), Spinal cord (3 levels cervical, thoracic and lumbar), Peripheral nerve (sciatic), gross lesion.

3. Statistical analysis

Results of general observations, full clinical examination, functional and neurobehavioural observations and mortality were expressed as incidence of the various clinical signs within each group.
The effects of EL101GV on the incidence of the various clinical signs were compared with those of the vehicle using a Fisher0s test [2] at each measurement time. Only clinical signs exhibited were tabulated.
Results of body weights are expressed as percentage of variation calculated in relation to predose values.
Homogeneity of predose values was tested by an analysis of variance. The effects of EL101GV on body weight changes from D1 up to D28 were compared with those of the vehicle using an analysis of variance for repeated measurements with a Dunnetts0test [3] in case of significance (P60.05).
Organ weights were expressed as absolute values (g) and relative values (g per 100 g of body weight measured on the day of necropsy and g per 100 g of brain weight).
The effects of EL101GV on organ weights, body temperature and mean clinical pathology results (haematology and blood chemistry) were compared with those of the vehicle using an analysis of variance with a Dunnett0s test [3] in case of significance (P 6 0.05).
The effects of EL101GV on quantitative urinalysis were compared with those of the vehicle using an analysis of variance with a non-parametric Mann-Whitney U test [2] in case of significance (P 6 0.05).

RESULTS:

1. Mortality

EL101GV administered by the oral route at the dose of 50, 200 or 1000 mg/kg did not induce any mortality.

2. Clinical signs

No clinical sign was observed in animals dosed with the vehicle (i.e. sterile water) except one male which had soft faeces on D1. This sign is not regarded as of toxicological relevance.
No clinical sign was observed in animals dosed with EL101GV at 50, 200 or 1000 mg/kg.

3. Body weight

No effect on body weight gain was seen in males and females dosed with EL101GV at 50, 200 or 1000 mg/kg, when compared with the control group.

Table B.6.3.1-1: Effect on body weight of males (mean table in percentage of variation)

Treatment		D-1	D7 (%)	D14 (%)	D21 (%)	D28 (%)
Vehicle	Mean	247.0	21	37	52	61
	SEM	4.4	1	2	3	4
	N	10.0	10	10	10	10
EL101GV 50 mg/kg	Mean	249.1	20	36	50	60
	SEM	3.6	1	2	2	3
	N	10.0	10	10	10	10
	P	NS	NS	NS	NS	NS
EL101GV 200 mg/kg	Mean	242.8	21	37	49	58
	SEM	4.7	1	1	2	3
	N	10.0	10	10	10	10
	P	NS	NS	NS	NS	NS
EL101GV 1000 mg/kg	Mean	239.8	21	39	52	65
	SEM	3.2	1	1	2	2
	N	10.0	10	10	10	10
	P	NS	NS	NS	NS	NS
	Threshold	14.0	7	7	7	7

Table B.6.3.1-2: Effect on body weight of females (mean table in percentage of variation)

Treatment		D-1	D7 (%)	D14 (%)	D21 (%)	D28 (%)
Vehicle	Mean	193.2	11	23	29	35
	SEM	4.0	1	2	2	3
	N	10.0	10	10	10	10
EL101GV 50 mg/kg	Mean	192.9	12	24	30	35
	SEM	5.4	1	2	2	2
	N	10.0	10	10	10	10
	P	NS	NS	NS	NS	NS
EL101GV 200 mg/kg	Mean	190.4	12	26	35	40
	SEM	6.1	3	3	3	3
	N	10.0	10	10	10	10
	P	NS	NS	NS	NS	NS
EL101GV 1000 mg/kg	Mean	194.1	11	25	32	39
	SEM	5.7	2	2	3	3
	N	10.0	10	10	10	10
	P	NS	NS	NS	NS	NS
	Threshold	18.6	8	8	8	8

4. Body temperature

No effect on body temperature was seen in males and females dosed with EL101GV at 50, 200 or 1000 mg/kg when compared with the control group.

5. Food consumption

Under the experimental conditions adopted, no effect on food consumption was seen in animals dosed with EL101GV at 50, 200 or 1000 mg/kg when compared with the control group.

Table B.6.3.1-3: Effect on food consumption of males (mean table)

Treatment		Week 1	Week 2	Week 3	Week 4
Vehicle	Mean	26	28	28	28
	SEM	1	1	1	1
	%		+8	+8	+8
	N	2	2	2	2
EL101GV 50 mg/kg	Mean	27	28	30	30
	SEM	1	0	1	1
	%		+4	+11	+11
	N	2	2	2	2
EL101GV 200 mg/kg	Mean	26	28	27	27
	SEM	1	1	1	1
	%		+8	+4	+4
	N	2	2	2	2
EL101GV 1000 mg/kg	Mean	26	27	27	27
	SEM	2	0	1	1
	%		+4	+4	+4
	N	2	2	2	2

Table B.6.3.1-4: Effect on food consumption of females (mean table)

Treatment		Week 1	Week 2	Week 3	Week 4
Vehicle	Mean	18	20	20	20
	SEM	0	1	1	1
	%		+11	+11	+11
	N	2	2	2	2
EL101GV 50 mg/kg	Mean	19	20	20	21
	SEM	2	1	1	2
	%		+5	+5	+11
	N	2	2	2	2
EL101GV 200 mg/kg	Mean	18	21	21	21
	SEM	1	2	2	2
	%		+17	+17	+17
	N	2	2	2	2
EL101GV 1000 mg/kg	Mean	19	20	20	20
	SEM	2	1	1	1
	%		+5	+5	+5
	N	2	2	2	2

6. Haematology and coagulation parameters

No effect on haematology and coagulation parameters was seen in males and females dosed with EL101GV at 50, 200 or 1000 mg/kg when compared with the control group.

Table B.6.3.1-4: Effect on haematology and coagulation parameters of males (mean values)

Treatment		WBC	NEUT	EOSI	LYMP	RBC	HGB	HCT
Vehicle	Mean	9.3	1.61	0.09	7.54	8.58	16.0	49
	SEM	0.4	0.25	0.04	0.32	0.11	0.2	1
	N	10	10	10	10	10	10	10
EL101GV	Mean	9.6	1.18	0.05	8.37	8.49	15.9	48
50 mg/kg	SEM	0.7	0.19	0.02	0.67	0.25	0.2	1
	N	10	10	10	10	10	10	10
	%	+3	-27	-44	+11	-1	-1	-2
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	10.0	1.22	0.09	8.67	8.61	16.3	50
200 mg/kg	SEM	0.6	0.14	0.03	0.56	0.15	0.2	1
	N	10	10	10	10	10	10	10
	%	+8	-24	0	+15	0	+2	+2
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	9.9	1.40	0.08	8.45	7.75	15.8	50
1000 mg/kg	SEM	0.8	0.14	0.03	0.70	0.79	0.2	1
	N	10	10	10	10	10	10	10
	%	+6	-13	-11	+12	-10	-1	+2
	P	NS	NS	NS	NS	NS	NS	NS
	Threshold	2.3	0.64	0.10	2.02	1.47	0.8	4

Treatment		MCV	MCH	MCHC	THR	PT	APTT
Vehicle	Mean	57	18.6	32.7	1024	15.17	18.8
	SEM	0	0.2	0.1	42	0.21	0.7
	N	10	10	10	10	10	10
EL101GV	Mean	56	18.9	33.6	927	15.12	17.8
50 mg/kg	SEM	0	0.5	0.9	57	0.21	0.7
	N	10	10	10	10	10	10
	%	-2	+2	+3	-9	0	-5
	P	NS	NS	NS	NS	NS	NS
EL101GV	Mean	58	19.0	32.9	929	14.59	16.6
200 mg/kg	SEM	1	0.1	0.1	77	0.12	0.3
	N	10	10	10	10	10	10
	%	+2	+2	+1	-9	-4	-12
	P	NS	NS	NS	NS	NS	NS
EL101GV	Mean	57	18.2	31.8	1002	14.67	17.1
1000 mg/kg	SEM	0	0.5	0.8	73	0.23	0.6
	N	10	10	10	10	10	10
	%	0	-2	-3	-2	-3	-9
	P	NS	NS	NS	NS	NS	NS
	Threshold	1	1.3	2.1	220	0.68	2.0

Table B.6.3.1-5: Effect on haematology and coagulation parameters of females (mean values)

Treatment		WBC	NEUT	EOSI	LYMP	RBC	HGB	HCT
Vehicle	Mean	5.8	0.53	0.07	5.18	7.94	15.1	45
	SEM	0.5	0.11	0.03	0.48	0.08	0.1	0
	N	10	10	10	10	10	10	10
EL101GV	Mean	5.5	0.61	0.06	4.88	7.69	14.6	44
50 mg/kg	SEM	0.3	0.10	0.01	0.31	0.30	0.4	2
	N	10	10	10	10	10	10	10
	%	-5	+15	-14	-6	-3	-3	-2
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	6.2	0.60	0.04	5.53	8.25	15.5	47
200 mg/kg	SEM	0.7	0.05	0.02	0.71	0.13	0.2	1
	N	10	10	10	10	10	10	10
	%	+7	+13	-43	+7	+4	+3	+4
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	6.6	0.59	0.08	5.90	8.11	15.1	46
1000 mg/kg	SEM	0.6	0.11	0.02	0.58	0.11	0.2	0
	N	10	10	10	10	10	10	10
	%	+14	+11	+14	+14	+2	0	+2
	P	NS	NS	NS	NS	NS	NS	NS
	Threshold	1.9	0.34	0.07	1.87	0.62	0.9	3

Treatment		MCV	MCH	MCHC	THR	PT	APTT
Vehicle	Mean	57	19.0	33.3	911	15.87	16.2
	SEM	0	0.2	0.2	49	0.47	0.4
	N	10	10	10	10	10	10
EL101GV	Mean	57	19.1	33.8	806	17.20	17.2
50 mg/kg	SEM	1	0.3	0.7	95	1.40	0.7
	N	10	10	10	10	10	10
	%	0	+1	+2	-12	+8	+6
	P	NS	NS	NS	NS	NS	NS
EL101GV	Mean	56	18.7	33.2	857	15.75	17.4
200 mg/kg	SEM	0	0.2	0.1	57	0.43	1.1
	N	10	10	10	10	10	10
	%	-2	-2	0	-6	-1	+7
	P	NS	NS	NS	NS	NS	NS
EL101GV	Mean	57	18.6	32.9	956	16.36	17.1
1000 mg/kg	SEM	1	0.1	0.2	49	1.03	1.7
	N	10	10	10	10	10	10
	%	0	-2	-1	+5	+3	+6
	P	NS	NS	NS	NS	NS	NS
	Threshold	2	0.8	1.2	226	3.21	3.8

7. Clinical chemistry

No effect on clinical chemistry parameters was seen in males and females dosed with EL101GV at 50, 200 or 1000 mg/kg when compared with the control group.

Table B.6.3.1-5: Effect on clinical chemistry of males (mean values)

Treatment		ALT	ALB	AST	CHOL	CL	CREA	GLU	K
Vehicle	Mean	24	31.3	64	1.88	105	35	5.21	4.2
	SEM	2	0.4	3	0.08	0	1	0.25	0.1
	N	10	10	10	10	10	10	10	10
EL101GV	Mean	22	31.2	60	1.94	105	34	5.42	4.2
50 mg/kg	SEM	2	0.3	4	0.14	0	1	0.15	0.2
	N	10	10	10	10	10	10	10	10
	%	-8	0	-6	+3	0	-3	+4	0
	P	NS	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	21	31.1	68	1.76	105	37	5.39	4.2
200 mg/kg	SEM	2	0.4	7	0.09	0	2	0.32	0.2
	N	10	10	10	10	10	10	10	10
	%	-13	-1	+6	-6	0	+6	+3	0
	P	NS	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	20	30.5	71	1.69	104	35	5.18	4.1
1000 mg/kg	SEM	1	0.5	8	0.10	0	1	0.21	0.1
	N	10	10	10	10	10	10	10	10
	%	-17	-3	+11	-10	-1	0	-1	-2
	P	NS	NS	NS	NS	NS	NS	NS	NS
	Threshold	6	1.4	21	0.37	1	4	0.84	0.5

Treatment		NA	ALP	PROT	UREA	CREU	KU	NAU
Vehicle	Mean	144	153	64	4.9	5234	83.2	44
	SEM	1	5	1	0.1	196	3.4	6
	N	10	10	10	10	9	9	9
EL101GV	Mean	144	159	65	5.0	5012	74.8	63
50 mg/kg	SEM	0	6	1	0.3	495	8.8	16
	N	10	10	10	10	9	9	9
	%	0	+4	+2	+2	-4	-10	+43
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	144	157	67	5.1	5334	83.2	45
200 mg/kg	SEM	0	5	1	0.1	295	3.1	5
	N	10	10	10	10	9	9	9
	%	0	+3	+5	+4	+2	0	+2
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	143	167	63	5.0	5360	78.1	66
1000 mg/kg	SEM	0	7	1	0.2	239	9.3	20
	N	10	10	10	10	10	10	10
	%	-1	+9	-2	+2	+2	-6	+50
	P	NS	NS	NS	NS	NS	NS	NS
	Threshold	2	20	3	0.7	1139	24.6	47

Table B.6.3.1-6: Effect on clinical chemistry of females (mean values)

Treatment		ALT	ALB	AST	CHOL	CL	CREA	GLU	K
Vehicle	Mean	18	31.0	76	2.48	107	39	5.13	4.1
	SEM	1	0.5	6	0.17	0	2	0.13	0.2
	N	10	10	10	10	10	10	10	10
EL101GV	Mean	22	30.9	75	2.24	107	41	5.63	3.9
50 mg/kg	SEM	3	0.4	6	0.12	1	1	0.24	0.2
	N	10	10	10	10	10	10	10	10
	%	+22	0	-1	-10	0	+5	+10	-5
	P	NS	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	19	31.8	68	2.17	106	40	5.20	3.9
200 mg/kg	SEM	1	0.6	6	0.13	0	2	0.14	0.1
	N	10	10	10	10	10	10	10	10
	%	+6	+3	-11	-13	-1	+3	+1	-5
	P	NS	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	18	31.4	62	2.09	106	39	5.56	3.9
1000 mg/kg	SEM	1	0.7	4	0.10	0	2	0.18	0.1
	N	10	10	10	10	10	10	10	10
	%	0	+1	-18	-16	-1	0	+8	-5
	P	NS	NS	NS	NS	NS	NS	NS	NS
	Threshold	6	2.0	20	0.46	2	6	0.61	0.6

Treatment		NA	ALP	PROT	UREA	CREU	KU	NAU
Vehicle	Mean	144	97	63	5.9	6501	71.9	50
	SEM	0	8	1	0.3	759	4.8	5
	N	10	10	10	10	8	8	8
EL101GV	Mean	144	112	62	6.3	5806	76.6	48
50 mg/kg	SEM	1	9	1	0.2	311	5.4	5
	N	10	10	10	10	8	8	8
	%	0	+15	-2	+7	-11	+7	-4
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	144	109	63	6.2	6153	73.0	49
200 mg/kg	SEM	1	5	1	0.2	757	4.9	1
	N	10	10	10	10	9	9	9
	%	0	+12	0	+5	-5	+2	-2
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	143	88	62	6.1	5238	66.5	52
1000 mg/kg	SEM	1	3	1	0.3	424	6.3	4
	N	10	10	10	10	10	10	10
	%	-1	-9	-2	+3	-19	-8	+4
	P	NS	NS	NS	NS	NS	NS	NS
	Threshold	2	23	3	0.9	2049	19.1	15

8. Urinalysis

No effect on urinary volume was seen in males and females dosed with EL101GV at 50, 200 or 1000 mg/kg when compared to the control group. No effect on urinary osmolality was seen in males and females dosed with EL101GV at 50 or 200 mg/kg when compared to the control group. A statistically significant decrease in urinary osmolality of males (-8%) and females (-15%) dosed with EL101GV at 1000 mg/kg was seen when compared with the control group. Since this change is slight and not correlated to any other change, this is not regarded as of toxicological relevance.

Table B.6.3.1-7: Effect on urinary volume of males (median values)

Treatment		D29
Vehicle	Median	16
	N	9
EL101GV	Median	14
50 mg/kg	N	9
	P	NS
EL101GV	Median	17
200 mg/kg	N	9
	P	NS
EL101GV	Median	16
1000 mg/kg	N	9
	P	NS

Table B.6.3.1-8: Effect on urinary volume of females (median values)

Treatment		D29
Vehicle	Median	10
	N	8
EL101GV	Median	10
50 mg/kg	N	9
	P	NS
EL101GV	Median	9
200 mg/kg	N	9
	P	NS
EL101GV	Median	11
1000 mg/kg	N	10
	P	NS

Table B.6.3.1-9: Effect on urinary osmolarity of males (median values)

Treatment		D29
Vehicle	Median	548
	N	9
EL101GV	Median	502
50 mg/kg	N	9
	P	NS
EL101GV	Median	512
200 mg/kg	N	9
	P	NS
EL101GV	Median	504
1000 mg/kg	N	10
	P	*

Table B.6.3.1-10: Effect on urinary osmolarity of females (median values)

Treatment		D29
Vehicle	Median	696
	N	8
EL101GV	Median	720
50 mg/kg	N	9
	P	NS
EL101GV	Median	644
200 mg/kg	N	9
	P	NS
EL101GV	Median	589
1000 mg/kg	N	10
	P	*

9. Organ weights

No effect on organ weights was seen in animals treated with EL101GV at 50, 200 or 1000 mg/kg when compared with the control group.

Table B.6.3.1-11: Absolute organ weights of males (mean values)

Treatment		body weight (g)	liver (g)	heart (g)	kidneys (g)	testes (g)	epididymides (g)	sub-maxillary lymph nodes (g)
Vehicle	Mean	352	11.82	1.418	2.869	3.51	1.23	0.0979
	SEM	6	0.31	0.029	0.060	0.11	0.04	0.0083
	N	10	10.00	10.000	10.000	10.00	10.00	10.0000
EL101GV 50 mg/kg	Mean	358	11.96	1.434	2.892	3.62	1.28	0.0917
	SEM	9	0.31	0.070	0.079	0.09	0.04	0.0060
	N	10	10.00	10.000	10.000	10.00	10.00	10.0000
	%	+2	+1	+1	+1	+3	+4	-6
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV 200 mg/kg	Mean	342	11.40	1.342	2.726	3.47	1.23	0.1066
	SEM	8	0.42	0.023	0.101	0.09	0.03	0.0190
	N	10	10.00	10.000	10.000	10.00	10.00	10.0000
	%	-3	-4	-5	-5	-1	0	+9
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV 1000 mg/kg	Mean	352	11.67	1.484	2.765	3.54	1.23	0.0959
	SEM	8	0.40	0.050	0.067	0.08	0.02	0.0094
	N	10	10.00	10.000	10.000	10.00	10.00	10.0000
	%	0	-1	+5	-4	+1	0	-2
	P	NS	NS	NS	NS	NS	NS	NS
	Threshold	26	1.26	0.162	0.272	0.33	0.11	0.0409

Treatment		popliteal lymph nodes (g)	thymus (g)	spleen (g)	adrenals (g)	brain (g)
Vehicle	Mean	0.0366	0.706	0.807	0.0744	2.226
	SEM	0.0037	0.046	0.028	0.0037	0.025
	N	9.0000	10.000	10.000	10.0000	10.000
EL101GV 50 mg/kg	Mean	0.0375	0.751	0.814	0.0669	2.182
	SEM	0.0046	0.045	0.029	0.0053	0.037
	N	10.0000	10.000	10.000	10.0000	10.000
	%	+2	+6	+1	-10	-2
	P	NS	NS	NS	NS	NS
EL101GV 200 mg/kg	Mean	0.0381	0.652	0.802	0.0662	2.185
	SEM	0.0047	0.035	0.044	0.0035	0.025
	N	10.0000	10.000	10.000	10.0000	10.000
	%	+4	-8	-1	-11	-2
	P	NS	NS	NS	NS	NS
EL101GV 1000 mg/kg	Mean	0.0424	0.683	0.796	0.0759	2.221
	SEM	0.0060	0.022	0.028	0.0030	0.023
	N	10.0000	10.000	10.000	10.0000	10.000
	%	+16	-3	-1	+2	0
	P	NS	NS	NS	NS	NS
	Threshold	0.0172	0.132	0.114	0.0137	0.096

Table B.6.3.1-12: Absolute organ weights of females (mean values)

Treatment		body weight (g)	liver (g)	heart (g)	kidneys (g)	ovaries (g)	uterus (g)	sub-maxillary lymph nodes (g)
Vehicle	Mean	235	7.62	0.964	1.745	0.1112	0.577	0.0470
	SEM	1	0.28	0.022	0.047	0.0049	0.043	0.0027
	N	10	10.00	10.000	10.000	10.0000	10.000	10.0000
EL101GV	Mean	233	7.44	0.981	1.779	0.1094	0.660	0.0519
50 mg/kg	SEM	4	0.32	0.022	0.049	0.0053	0.060	0.0045
	N	10	10.00	10.000	10.000	10.0000	10.000	10.0000
	%	-1	-2	+2	+2	-2	+14	+10
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	241	7.58	1.005	1.829	0.1216	0.621	0.0571
200 mg/kg	SEM	6	0.19	0.018	0.036	0.0031	0.050	0.0034
	N	10	10.00	10.000	10.000	10.0000	10.000	10.0000
	%	+3	-1	+4	+5	+9	+8	+21
	P	NS	NS	NS	NS	NS	NS	NS
EL101GV	Mean	239	7.71	1.023	1.841	0.1246	0.687	0.0530
1000 mg/kg	SEM	5	0.19	0.015	0.036	0.0073	0.051	0.0031
	N	10	10.00	10.000	10.000	10.0000	10.000	10.0000
	%	+2	+1	+6	+6	+12	+19	+13
	P	NS	NS	NS	NS	NS	NS	NS
	Threshold	17	0.87	0.067	0.148	0.0186	0.178	0.0121

Treatment		popliteal lymph nodes (g)	thymus (g)	spleen (g)	adrenals (g)	brain (g)
Vehicle	Mean	0.0308	0.552	0.626	0.0849	2.097
	SEM	0.0037	0.028	0.022	0.0027	0.023
	N	10.0000	10.000	10.000	10.0000	10.000
EL101GV	Mean	0.0298	0.471	0.619	0.0941	2.085
50 mg/kg	SEM	0.0022	0.023	0.046	0.0042	0.028
	N	10.0000	10.000	10.000	10.0000	10.000
	%	-3	-15	-1	+11	-1
	P	NS	NS	NS	NS	NS
EL101GV	Mean	0.0308	0.511	0.597	0.0861	2.161
200 mg/kg	SEM	0.0023	0.030	0.018	0.0026	0.028
	N	10.0000	10.000	10.000	10.0000	10.000
	%	0	-7	-5	+1	+3
	P	NS	NS	NS	NS	NS
EL101GV	Mean	0.0270	0.535	0.626	0.0884	2.064
1000 mg/kg	SEM	0.0018	0.034	0.014	0.0016	0.025
	N	10.0000	10.000	10.000	10.0000	10.000
	%	-12	-3	0	+4	-2
	P	NS	NS	NS	NS	NS
	Threshold	0.0089	0.100	0.097	0.0102	0.091

10. Histopathology

Only animals at 0 and 1000 mg/kg bw/day were examined.

There was a single female rat treated at 1000 mg/kg (group 4) that had an erosion (mild in degree) in the glandular stomach. This had been observed at the necropsy examination. Such a change at this incidence could not be ascribed to treatment.

The occasional lesions present were examples of commonplace usual lesions in the tissues of adult laboratory rats. The incidence and degree were usual and none was associated with treatment.

There were no treatment-related lesions in rats treated with EL101GV 1000 mg/kg.

Table B.6.3.1-13: Incidence of non-neoplasic microscopic findings

	MALES		**FEMALES**	
Group	**Vehicle**	**EL101GV 1000 mg/kg/b.w.**	**Vehicle**	**EL101GV 1000 mg/kg/b.w.**
Number of animals	**10**	**10**	**10**	**10**
Heart ventricule				
Focal myocarditis	1	1	0	0
Kidneys				

Cortical interstitial lymphocytic infiltration	0	0	0	1
Liver				
Mononuclear cell infiltration	0	0	1	1
Lungs				
Pneumonitis	2	2	0	0
Lymph nodes, popliteal				
Plasmacytic hyperplasia	0	1	0	0
Lymph nodes, submaxillary				
Lymphoid hyperplasia	0	1	0	0
Stomach glandular				
Erosion	0	0	0	1
Thymus				
Petechial haemorrhage	0	1	0	0
Ureters				
One only	1	1	0	0
Urinary bladder				
Perivascular lymphocytosis	0	0	0	1
Uterus horns				
Physiological dilatation	-	-	2	3
Vagina				
Squamous keratinized epithlium	-	-	1	1
Mucinous epithelium	-	-	1	4

In conclusion, treatment with EL101GV 1000 mg/kg resulted in no systemic toxicity.

CONCLUSION:
In a 28-day toxicity study, EL101GV was administered to male and female Sprague-Dawley rats by gavage at dose levels of 50, 200 or 1000 mg/kg bw/day (expressed in pure heptamaloxyloglucan).
There was no compound related effect on mortality, clinical signs, body weight, food consumption, haematology, clinical chemistry, urinalysis and organ weights. There were no treatment-related lesions in rats dosed with heptamaloxyloglucan at 1000 mg/kg at the histopathological examination.
The oral NOAEL is above 1000 mg/kg b.w./day for heptamaloxyloglucan expressed in pure heptamaloxyloglucan.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This study is considered acceptable.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. The NOAEL for this endpoint is considered to be >1000 mg/kg b.w./day.

B.6.3.2. Other routes

No short-term dermal study was performed. Indeed, K_{ow} of EL101GV is $< 10^{-4}$: the active substance is unable to penetrate through lipophilic membranes, and thus no dermal absorption is possible. Furthermore, there were no adverse effects in an acute dermal toxicity study performed in rats (see 5.2.2; dermal LD_{50} > 2000 mg/kg b.w.).
No short-term inhalation study was performed as no acute inhalation study was required (see B 6.2.3).

Assessment and conclusion by RMS 2020:
No short term dermal or inhalation studies were submitted by the applicant.

B.6.3.3. Oral 90- day study

As demonstrated under B 6.1, oral intake of EL101GV will result in animal or human exposure to unchanged parent, and wide-spread and well-known oligosaccharides, glucidic monomers (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate). None of these compounds is toxic. This was confirmed in an acute toxicity study with EL101GV in rats: female Sprague-Dawley rats treated at the dose-level of 300 or 2000 mg/kg b.w. presented no adverse effect concerning survival, clinical signs, weight gain or *post-mortem* gross necropsy (LD_{50} > 2000 mg/kg b.w.).

These data were confirmed with the results from a 28–day oral study in rats with a NOAEL higher than 1000 mg/kg b.w./day and for which no compound related effect was observed on mortality, clinical signs, body weight, food consumption, haematology, clinical chemistry, urinalysis and organ weights.

As demonstrated under B 6.1 there is no bioaccumulation potential as the unchanged molecule is not absorbed in the digestive tract, and as all metabolites are glucids or short-chain fatty acids which are involved in a large variety of metabolic pathways present in animals.

Furthermore, a xyloglucan from tamarind seed, made of D-glucose, D-xylose and D-galactose (molar ratios: 3:2:1 exactly as in EL101GV) and therefore very similar to EL101GV, was tested in a 13-week oral study in mice preliminary to a carcinogenicity study (KCA 5.3.2./01 (KCA 5.5/05), Sano M, Miyata E, Tamano S, Hagiwara A, Ito N, Shirai T. Lack of carcinogenicity of tamarind seed polysaccharide in B6C3F1 mice. *Food Chem Toxicol.* 1996;34(5):463-7). Groups of 10 male and 10 female animals were given diets containing 0, 0.625, 1.25, 2.5 and 5% of tamarind seed polysaccharide for 13 weeks. There were no adverse effects in any treated group concerning any parameter or observation (mortality, clinical signs, weight data, food and water intake, haematology and biochemistry, gross pathology, weights of brain, heart, liver, spleen, kidneys, adrenals, testes/ovaries, and microscopic examination of weighed organs, lymph nodes, bone marrow, thymus, pituitary, thyroids, parathyroids, trachea, lungs, tongue, salivary glands, oesophagus, stomach, duodenum, jejunum, ileum, caecum, colon, rectum, pancreas, gall bladder, urinary bladder, prostate, seminal vesicle, mammary gland, uterus, vagina, femur, sternum, skin and subcutis, eyes, Harder glands, spinal cord and gross lesions) except for statistically, but minimally lower protein levels in all groups of treated males compared to controls. These results demonstrated that tamarind seed polysaccharide had no short-term toxicity in B6C3F1 mice of either sex. This supports the expected lack of short-term toxicity of EL101GV in mice.

Assessment and conclusion by RMS 2020:
No 90-day study has been conducted on heptamaloxyloglucan.
The 90 day mice study was conducted with tamarind an analogue of the active substance, read across based on tamarind seed polysaccharide is not considered acceptable due to very high molecular weight of ca. 650000 Da for this polysaccharide i.e., ca. 650-fold Heptamaloxyloglucan molecular weight which is 1078 Da.
However, the oral 90-day study is not considered necessary based on:
- Results from a 28–day oral study in rats (no compound related effect was observed on mortality, clinical signs, body weight, food consumption, haematology, clinical chemistry, urinalysis and organ weights (NOAEL higher than 1000 mg/kg b.w./day) and
- No evidence of bioaccumulation potential as the unchanged molecule is not absorbed in the digestive tract, and as all metabolites are glucids or short-chain fatty acids which are involved in a large variety of metabolic pathways present in animals.

B.6.4. GENOTOXICITY

No new study is provided by the applicant since the previous evaluation (DAR 2007).

According to the EFSA scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Journal 2011;9(9):2379), genotoxic potential must be assessed according to a step-wise approach with as a first step a basic battery of *in vitro* test with the two following *in vitro* tests fulfilling the basic requirements to cover the three genetic endpoints (gene mutations and both structural and numerical chromosome aberrations):
- a bacterial reverse mutation test (OECD TG 471), and

- an *in vitro* mammalian cell micronucleus test (OECD TG 487).
Also, EFSA guidance proposes to consider any other relevant knowledge on the substance such as physico-chemical properties to develop a test strategy.

As already explained, the active substance heptamaloxyloglucan is an oligosaccharide made of 7 glucidic monomer units. As detailed in Point B 6.1, the absorbable metabolites of heptamaloxyloglucan are monosaccharides (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate). They are naturally present in metabolic pathways of animals and humans and are all known to be devoid of toxicity except when ingested in very large quantities. Furthermore, these compounds are also produced by degradation of oligosaccharides from vegetal food items or xyloglucans present in apples (from which heptamaloxyloglucan is prepared), so the metabolites of heptamaloxyloglucan are necessarily already present in human and animal diet independently of vine treatment with the plant protection product. Therefore, there is no expected toxicological concern for heptamaloxyloglucan or absorbable metabolites. This absence of toxicological effects is demonstrated in acute toxicity studies (B 6.2), short-term toxicity studies (B 6.3.1) and long-term toxicity and carcinogenicity studies (B 6.5).
Regarding specifically oligosaccharide genotoxicity, some studies conclude in the absence of genotoxic effect:
- The genotoxicity of GOS (composed of common nutrients (*e.g.*, oligosaccharides galactose, lactose, glucose, minerals) such as some absorbable metabolites of the active substance heptamaloxyloglucan) has been evaluated in several studies including the bacterial reverse mutation assay, mammalian chromosomal aberration test, and *in vivo* micronucleus assay in mice and the outcome for all investigations has consistently demonstrated that GOS are not genotoxic.[1]
- the genotoxicity of fucose, one of the absorbable metabolite of the active substance heptamaloxyloglucan, was assessed in a series of *in vitro* genotoxicity/mutagenicity tests. It was concluded l-Fucose was non-genotoxic[2].

Consequently, taking into account the natural occurrence of the parent active substance heptamaloxyloglucan, its ADME profile in mammals (metabolites are naturally present in mammalian metabolic pathways and available toxicological data on the substance, metabolites and analogues, no concern is expected about the toxicological properties of the heptamaloxyloglucan generally and on genotoxicity more specifically.
Hence there is no bioaccumulation potential as the unchanged molecule is not absorbed in the digestive tract, and as all metabolites are glucids or short-chain fatty acids which are involved in a large variety of metabolic pathways present in animals.

Therefore, taking into account all these considerations, the following test strategy is proposed and considered as sufficient to answer on the expected absence of genotoxic potential of the active substance heptamaloxyloglucan:
- *in vitro* test for gene mutations in bacteria (OECD 471);
- supportive data on mutagenicity in bacteria;
- *in vitro* gene mutation test in mammalian cells (OECD 476).

B.6.4.1. In vitro studies

MUTAGENESIS IN BACTERIAL CELLS

Annex Point	KCA 5.4.1/01
Report author	Le Curieux F,
Report year	2006
Report title	Bacterial test on Salmonella typhimurium His- (5 strains) using B.N. Ames's technique with EL101GV Institut Pasteur de Lille, Genetic Toxicology Laboratory, Lille, France
Guidelines	OECD N°471
Major deviations from current guideline	None

[1] GRAS Exemption Claim for Galacto-oligosaccharides. Nestlé Nutrition, 2015. https://www.fda.gov/media/98650/download
[2] Sharon S.H. and al. Safety evaluation of the human-identical milk monosaccharide, l-fucose. Regulatory Toxicology and pharmacology, Vol 72, June 2015.

Previous evaluation	Yes, study already evaluated and accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	Yes
Acceptability/reliability	Yes

MATERIAL AND METHODS:

Strains used: TA 1535, TA1537, TA98, TA100, TA102
Preliminary test of toxic activity: Carried out on 5 strains – Incubation period: 48 hours
Sterility test: Normal
Mutagenicity test: Carried out both with and without metabolic activation using hepatic microsomes from rat livers induced by Aroclor 1254 –
Incubation period: 48 hours
Number of assays: 2 (the second assay with metabolic activation was performed according to pre-incubation method)
Limiting factor for maximum dose: Maximum dose according to OECD procedures
Test substance: Heptamaloxyloglucan (EL101GV)
Batch n°: AND0706
Purity: 88.6% w/w

Table B.6.4.1-6-1: Doses used in main test (expressed as µg/plate pure heptamaloxyloglucan)

Without S9 mix

Strain	TA1535		TA1537		TA98		TA100		TA102	
Assay	1	2	1	2	1	2	1	2	1	2
Doses µg/plate	0	0	0	0	0	0	0	0	0	0
	-	-	-	-	-	-	-	-	5	-
	-	-	-	-	-	-	-	-	15	-
	50	50	50	50	50	50	50	50	50	50
	150	150	150	150	150	150	150	150	150	150
	500	500	500	500	500	500	500	500	500	500
	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000

With S9 mix

Strain	TA1535		TA1537		TA98		TA100		TA102	
Assay	1	2*	1	2*	1	2*	1	2*	1	2*
Doses µg/plate	0	0	0	0	0	0	0	0	0	0
	50	50	50	50	50	50	50	50	50	50
	150	150	150	150	150	150	150	150	150	150
	500	500	500	500	500	500	500	500	500	500
	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000

* with pre-incubation

RESULTS:

1. **Toxic activitiy**

Toxicity assay

The results of the test for toxic activity are summarized in Table B.6.4.1-2.
The microscopic observation of the background lawn did not reveal any toxicity in all strains tested with or without metabolic activation. However, a clear decrease in the number of revertants was observed without metabolic activation, at the three highest doses tested of 500, 1500 and 5000 µg/plate in strain TA102.
Under these conditions, the dose of 5000 µg/plate was retained as the maximum dose tested in the first mutagenicity assay, both with and without metabolic activation. Taking into account the decrease in the number

of revertants noted in strain TA102 without metabolic activation, further doses were added, i.e. 15 and 5 µg/plate in this strain.

First mutagenicity assays
No toxicity was noted during the first mutagenicity assay either with or without metabolic activation. Under these conditions, the highest dose of 5000 µg/plate was kept for the second mutagenicity assay both with and without metabolic activation.

Table B.6.4.1-2: Toxic activity results

Compound : EL101GV **Solvent : Distilled water**

Strain	dose* µg/plate	without S9-mix			with S9-mix		
		T	P	Revertants/ plate	T	P	Revertants/ plate
TA 1535	0	-	-	15	-	-	5
	50	-	-	8	-	-	13
	150	-	-	5	-	-	15
	500	-	-	15	-	-	6
	1500	-	-	3	-	-	5
	5000	-	-	11	-	-	11
TA 1537	0	-	-	1	-	-	4
	50	-	-	1	-	-	2
	150	-	-	2	-	-	5
	500	-	-	4	-	-	5
	1500	-	-	3	-	-	3
	5000	-	-	2	-	-	3
TA 98	0	-	-	12	-	-	28
	50	-	-	21	-	-	22
	150	-	-	17	-	-	27
	500	-	-	26	-	-	24
	1500	-	-	20	-	-	19
	5000	-	-	21	-	-	23
TA 100	0	-	-	77	-	-	79
	50	-	-	66	-	-	95
	150	-	-	61	-	-	74
	500	-	-	58	-	-	80
	1500	-	-	59	-	-	93
	5000	-	-	57	-	-	68
TA 102	0	-	-	150	-	-	244
	50	-	-	154	-	-	373
	150	-	-	135	-	-	323
	500	-	-	45	-	-	330
	1500	-	-	17	-	-	384
	5000	-	-	11	-	-	404

* expressed as µg/plate heptamaloxyloglucan
T=Toxicity
(- non toxic; + slightly toxic; ++ moderately toxic; +++ strongly toxic; N no bacterial growth)
P = Precipitate
(- absence; + slight precipitate; ++ moderate precipitate; +++ important precipitate hindering scoring)

2. Mutagenicity assays

Concurrently to the main assays, tests were carried out on reference mutagenic compounds in order to show the sensitivity of the strains tested and the efficiency of the metabolic activation system. A statistically significant increase in the number of revertants was observed in the presence of positive reference substances. The values observed were within the limits of
historical controls. The frequency of spontaneous revertants (solvent control) was within the limits generally observed under our experimental conditions. The validity criteria for the test were fulfilled.

The summary of results of the test are given in Tables B 6.4.1-3 and 6.4.1-4. In two independent assays performed either with or without metabolic activation (the second assay with S9-mix was performed according to the pre-

incubation protocol), no biologically significant increase in the mean number of revertants was noted in the five *Salmonella typhimurium* strains tested in the presence of **EL101GV**.
During the first assay without metabolic activation, statistically significant increases in the number of revertants were observed on the whole range of doses tested, i.e. from 5000 to 50 µg/plate, in strain TA100; nevertheless, the biological threshold for a positive response set at 2 for this dose, was not reached (induction ratios from 1.3 to 1.4). Furthermore, these effects were neither dose-related nor reproducible; indeed, the second assay was clearly negative. Therefore, this increase could not be attributed to a mutagenic effect.

Table B.6.4.1-3: Mutagenicity assay 1 results

COMPOUND: **EL101GV** Solven: **Distilled water**

	TA 1535		TA 1537		TA 98		TA 100		TA102	
	DOSE* µg/plate	revertants /plate	DOSE µg/plate	revertants /plate	DOSE µg/plate	revertants /plate	DOSE µg/plate	revertants /plate	DOSE µg/plate	revertants /plate
Positive control	(a)	**350.0**	(a)	**1144.0**	(a)	**550.0**	(a)	**405.3**	(a)	**1296.0**
	-	-	-	-	-	-	-	-	0	**223.7**
TEST COMPOUND	-	-	-	-	-	-	-	-	5	**235.0**
	0	**14.0**	0	**4.0**	0	**17.5**	0	**75.5**	15	**246.3**
without	50	**11.7**	50	**2.7**	50	**17.7**	50	**106.0**	50	**252.0**
S9-mix	150	**8.0**	150	**2.3**	150	**17.3**	150	**96.7**	150	**244.0**
	500	**7.7**	500	**2.3**	500	**17.0**	500	**102.3**	500	**245.0**
	1500	**7.7**	1500	**2.7**	1500	**24.0**	1500	**98.0**	1500	**267.3**
	5000	**14.0**	5000	**2.3**	5000	**19.3**	5000	**106.7**	5000	**278.3**
Positive control	(b)	**319.3**	(b)	**177.3**	(b)	**1376.0**	(b)	**1602.7**	(b)	**1730.7**
	0	**8.7**	0	**4.3**	0	**19.0**	0	**97.0**	0	**305.5**
TEST COMPOUND	50	**8.0**	50	**5.0**	50	**23.7**	50	**94.3**	50	**226.0**
with	150	**13.3**	150	**6.0**	150	**19.0**	150	**98.7**	150	**301.3**
S9-mix	500	**8.3**	500	**5.3**	500	**23.3**	500	**94.0**	500	**303.0**
without	1500	**9.7**	1500	**4.7**	1500	**23.0**	1500	**99.0**	1500	**309.3**
pre-incubation	5000	**8.7**	5000	**6.7**	5000	**20.3**	5000	**97.7**	5000	**225.3**

* expressed as µg/plate heptamaloxyloglucan
Reference positive compounds (µg/plate):
(a) TA1535 and TA100 : Sodium azide 1 ; TA1537 : 9-amino-acridine 50 ; TA98 : 2-nitrofluorene 2
TA102: Mitomycin C 0.125
(b) TA1535, TA1537, TA98, TA100 : 2-anthramine 2 ; TA102: benzo(a)pyrene 2

Table B.6.4.1-4: Mutagenicity assay 2 results

COMPOUND: EL101GV Solvent: **Distilled water**

	TA 1535		TA 1537		TA 98		TA 100		TA102	
	DOSE* µg/plate	revertants /plate	DOSE µg/plate	revertants /plate	DOSE µg/plate	revertants /plate	DOSE µg/plate	revertants /plate	DOSE µg/plate	revertants /plate
Positive control	(a)	**299.7**	(a)	**538.7**	(a)	**1039.3**	(a)	**508.0**	(a)	**1706.7**
	0	**8.8**	0	**4.2**	0	**17.2**	0	**128.3**	0	**307.2**
TEST COMPOUND	50	**8.7**	50	**4.0**	50	**16.3**	50	**149.0**	50	**365.7**
	150	**7.0**	150	**4.7**	150	**16.0**	150	**131.3**	150	**418.0**
without	500	**6.7**	500	**3.3**	500	**15.0**	500	**138.3**	500	**364.0**
S9-mix	1500	**9.3**	1500	**2.0**	1500	**15.3**	1500	**131.0**	1500	**402.0**
	5000	**12.7**	5000	**3.7**	5000	**16.3**	5000	**129.3**	5000	**410.7**
Positive control	(b)	**280.0**	(b)	**271.3**	(b)	**2320.0**	(b)	**3125.3**	(b)	**1695.3**
	0	**5.8**	0	**3.3**	0	**15.2**	0	**92.7**	0	**294.7**
TEST COMPOUND	50	**5.7**	50	**2.7**	50	**18.3**	50	**77.3**	50	**330.0**
with	150	**5.0**	150	**4.0**	150	**18.7**	150	**78.3**	150	**349.3**
S9-mix	500	**8.3**	500	**2.7**	500	**20.7**	500	**73.3**	500	**348.0**
with	1500	**7.3**	1500	**2.3**	1500	**24.7**	1500	**78.3**	1500	**377.7**
pre-incubation	5000	**6.3**	5000	**4.0**	5000	**25.3**	5000	**75.7**	5000	**383.3**

* expressed as µg/plate heptamaloxyloglucan

Reference positive compounds (µg/plate):

(a) TA1535 and TA100 : Sodium azide 1 ; TA1537 : 9-amino-acridine 50 ; TA98 : 2-nitrofluorene 2
TA102: Mitomycin C 0.125

(b) TA1535, TA1537, TA98, TA100 : 2-anthramine 1 ; TA102: benzo(a)pyrene 2

CONCLUSION:

Under the experimental conditions, the test item EL101GV induced no mutagenic activity in the five Salmonella typhimurium strains tested with or without metabolic activation, in two independent assays.

Supportive data on mutagenicity in bacteria

Heptamaloxyloglucanis prepared from, and naturally present in, vegetal cell walls of apple fruits. Therefore, *Escherichia coli* and *Salmonella typhimurium* bacteria can be naturally exposed to heptamaloxyloglucan, as to any oligosaccharide. As demonstrated under B 6.1, bacteria and notably *Escherichia coli* and *Salmonella typhimurium* possess the enzymes necessary to the degradation of EL101GV. Therefore, the active substance will not reach the genetic material in its unchanged form. Furthermore, xyloglucans were demonstrated to inhibit the mutagenic activity of 1-nitropyrene on *Salmonella typhimurium* (KCA 5.4.1/02, Hensel A, Meier K: Pectins and xyloglucans exhibit antimutagenic activities against nitroaromatic compounds. *Planta Med.* 1999, 65(5): 395-399). In this study, mutagenesis inhibition rates were dose-dependent. Considering all these arguments, heptamaloxyloglucanis not expected to have any mutagenic potential. Moreover, as heptamaloxyloglucan does not enter cells due to its low K_{ow} ($< 10^{-4}$) and high molecular weight (> 1000 g/mol), any mutagenic potential would not be relevant to animals or humans.

Biotransformation of heptamaloxyloglucan by enzymatic systems of bacteria will produce smaller oligosaccharides, glucidic monomers (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate) as demonstrated under B 6.1. Thus biotransformation of heptamaloxyloglucan is similar to the natural process of decay, and to digestion of glucidic fibres by flora present in the rumen of Ruminants or the caecum of horses for example. The metabolites of heptamaloxyloglucan are therefore natural compounds with no expected mutagenic potential, and these glucids or fatty acids are not comparable with any known mutagen.

Therefore, heptamaloxyloglucan is not expected to cause gene mutation in bacterial cells and no study was performed.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This study is considered acceptable.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. Agreed with conclusion i.e., no mutagenicity shown.

MUTAGENESIS IN MAMMALIAN CELLS

Annex Point	KCA 5.4.1/03
Report author	Nesslany F,
Report year	2006
Report title	Mutation assay at the TK locus in L5178Y Mouse lymphoma cells using a microtiter cloning technique (Trifluorothymidine Resistance) carried out with EL101GV Institut Pasteur de Lille, Genetic Toxicology Laboratory, Lille, France Study N° FSR-IPL 060230 / EL101GV / Elicityl
Guidelines	OECD N°476
Major deviations from current guideline	None
Previous evaluation	Yes, study already evaluated and accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	Yes
Acceptability/reliability	Yes

MATERIAL AND METHODS:
Cell strain: L5178Y mouse lymphoma cells
Type of mutation study: TK Locus (Trifluorothymidine Resistance)
Test substance: Heptamaloxyloglucan (EL101GV)
Batch n°: AND0706
Purity: 88.6% w/w

Toxicity test
Treatment duration:
- Without S9-mix : 3 hours (short treatment)
  24 hours (continuous treatment)
- With S9-mix : 3 hours

Concentrations tested of **EL101GV** in µg/mL of Heptamaloxyloglucan:
- Without S9-mix : 5000 – 2500 – 1250 – 625 – 312.5 – 156.25 – 78.12
- With S9-mix : 5000 – 2500 – 1250 – 625 – 312.5 – 156.25 – 78.12

Mutagenicity test
It was carried out both without and with metabolic activation using hepatic microsomes from rat livers induced by Aroclor1254 (S9-mix).
Treatment duration:
- Without S9-mix : 3 hours (short treatment)
  24 hours (continuous treatment)
- With S9-mix : 3 hours

Concentrations tested of **EL101GV** in µg/mL of Heptamaloxyloglucan:
- Without S9 mix : 5000 – 2500 – 1250 – 625 (assay 1: 3-hour treatment)
  5000 – 2500 – 1250 – 625 (assay 2: 24-hour treatment)
- With S9 mix : 5000 – 2500 – 1250 – 625 (assay 1)

5000 – 2500 – 1250 – 625 (assay 2)

Solvent : Distilled water (Fresenius, batch UCV 161/2)

Positive controls:
- Without S9-mix : methyl methanesulfonate 10 µg/mL (3-h treatment)
  methyl methanesulfonate 2 µg/mL (24-h treatment)
- With S9-mix : cyclophosphamide, 2 µg/mL

Expression time : 2 days after treatment
Number of assays : 2
Number of replicate cultures : 2 per dose

Factor limiting the maximum concentration tested: none

RESULTS:

1. Cytotoxic activitiy

In cytotoxicity assay

The results of the cytotoxicity assays with and without metabolic activation are summarized in Table 5.4.1/5.
Without metabolic activation in the 3-hour and 24-hour treatments, at the maximum concentration tested of 5000 µg/mL, the test compound **EL101GV** did not reveal any cytotoxicity in L5178Y cells with 101 and 98.8 % adjusted RTG in the 3-hour and 24-hour treatments, respectively (Tables 1, 6 and 10). Under these conditions, the concentration of 5000 µg/mL was retained as the maximum concentration for the mutagenicity test without S9-mix.
With metabolic activation, no cytotoxicity was observed at the highest concentration tested of 5000 µg/mL with 87.9% adjusted RTG. Under these conditions, 5000 µg/mL was retained as the top concentration for the mutagenicity test with metabolic activation.

In mutagenicity assays

As no cytotoxic activity was observed in the first mutagenicity assay without metabolic activation in the 3-hour treatment, with an adjusted RTG of 104.6 % at the highest concentration studied of 5000 µg/mL, the top concentration was kept at 5000 µg/mL in the second mutagenicity assay following the 24-hour continuous treatment, using the same range of concentrations, *i.e.* 5000 – 2500 – 1250 – 625 µg/mL.
In the case of the treatment with metabolic activation, the test compound induced no cytotoxicicty during the first assay, with an adjusted RTG of 94.6 % at the highest concentration studied of 5000 µg/mL.
Under these conditions, the top concentration was the same as in the first mutagenicity assay, *i.e.* 5000 µg/mL.
No cytotoxic activity was induced in the second mutagenicity assay following the 24-hour continuous treatment without metabolic activation and in the assay with metabolic activation with 94.6 and 91% of adjusted RTG, respectively.

Table B.6.4.1-5: Results on cytotoxicity assays with and without metabolic activation

Cytotoxicity assay without S9-mix 3-h treatment	Conc. µg/mL	Plating efficiency at T0 PE_0 (%)	Relative survival at T0 RS_0 (%)	Plating efficiency at T2 PE2 (%)	Relative survival at T2 RS2 (%)	% RSG	% adjusted RTG
Solvent control	0	111.98	100	**116.02**	100	***100.0***	**100.0**
EL101GV	**78.12**	138.31	123.5	**93.52**	80.6	***103.4***	**72.0**
	156.25	101.24	90.4	**106.38**	91.7	***94.5***	**93.1**
	312.5	94.99	84.8	**118.14**	101.8	***89.5***	**101.7**
	625	96.50	86.2	**118.14**	101.8	***111.8***	**119.4**
	1250	104.62	93.4	**108.20**	93.3	***111.5***	**79.9**
	2500	102.91	91.9	**141.36**	121.8	***103.8***	**115.7**
	5000	102.91	91.9	**144.57**	124.6	***97.6***	**101.0**

Cytotoxicity assay without S9-mix 24-h treatment	Conc. µg/mL	Plating efficiency at T0 PE_0 (%)	Relative survival at T0 RS_0 (%)	Plating efficiency at T2 PE2 (%)	Relative survival at T2 RS2 (%)	% RSG	% adjusted RTG
Solvent control	0	151.52	100	**151.52**	100	***100.0***	**100.0**
EL101GV	**78.12**	178.73	118.0	**135.40**	89.4	***120.4***	**87.7**
	156.25	116.02	76.6	**106.38**	70.2	***107.0***	**95.8**
	312.5	106.38	70.2	**118.14**	78.0	***112.8***	**107.8**
	625	108.20	71.4	**110.06**	72.6	***125.3***	**102.8**
	1250	135.40	89.4	**113.97**	75.2	***127.2***	**98.2**
	2500	79.28	52.3	**93.52**	61.7	***111.4***	**79.1**
	5000	85.35	56.3	**113.97**	75.2	***123.0***	**98.8**

Cytotoxicity assay with S9-mix 3-h treatment	Conc. µg/mL	Plating efficiency at T0 PE_0 (%)	Relative survival at T0 RS_0 (%)	Plating efficiency at T2 PE2 (%)	Relative survival at T2 RS2 (%)	% RSG	% adjusted RTG
Solvent control	0	135.40	100	**155.31**	100	***100.0***	**100.0**
EL101GV	**78.12**	135.40	100.0	**155.31**	100.0	***100.7***	**91.3**
	156.25	101.24	74.8	**168.28**	108.4	***100.6***	**112.8**
	312.5	116.02	85.7	**127.41**	82.0	***119.5***	**97.2**
	625	118.14	87.2	**135.40**	87.2	***119.8***	**108.8**
	1250	129.97	96.0	**147.95**	95.3	***118.5***	**102.9**
	2500	129.97	96.0	**147.95**	95.3	***112.9***	**107.6**
	5000	102.91	76.0	**129.97**	83.7	***102.1***	**87.9**

2. Mutagenicity assays

Concurrently to the main assays, tests were carried out with reference mutagenic compounds (methyl methanesulfonate in the absence of metabolic activation and cyclophosphamide in the presence of metabolic activation via S9-mix). A significant increase in the number of mutants was observed in the presence of reference positive substances and the values observed were within the limits of historical controls.
Regarding the results obtained with the negative solvent controls, they were comparable with those usually obtained in the laboratory, except in the 24-hour treatment without metabolic activation, with a mutation frequency of 125.9 *vs.* 122 for the highest value already seen in the historical data.
Nevertheless, this is only a slight deviation that affected neither the quality nor the integrity of the study. The acceptance criteria for the results were considered as fulfilled.
The summaries of test results are given in Tables B 6.4.1-6 to 6.4.1-9.
In two independent assays using 3-hour and 24-hour treatments without metabolic activation and in two separate assays with metabolic activation using a 3-hour treatment, neither statistically nor biologically significant increase in the mutation frequency of total induced mutants (small and large colonies) or in the number and in the mutation frequency of small colonies was noted at any concentration tested in the presence of **EL101GV**.

In the 3-hour treatment with metabolic activation, a trend to an increase in the number and in the mutation frequency of total induced mutants (small and large colonies) was observed during the second assay, with induction ratios ranging from 1.4 to 0.9. Nevertheless, these increases were neither statistically nor biologically significant. Indeed, the induced mutation frequency at the highest concentration tested of 5000 µg/mL (129.4 – 93.5 = 35.9 x 10^{-6} mutants) did not rise above the global evaluation factor set at 126 x 10^{-6} mutants for a biologically positive response. Hence, this trend to an increase had no meaning in terms of genotoxic activity.

Table B.6.4.1-6: Results of assays 1 and 2 without metabolic activation

ASSAY 1	Concentrations in µg/mL					
	0	*625*	*1250*	*2500*	*5000*	MMS 10
	Adjusted RTG (Relative total growth)					
WITHOUT S9	100.0	117.2	126.6	131.2	104.6	87.3
3-Hour treatment	MUTATION FREQUENCY X10^{-6} cells					
	71.8	68.4	75.1	62.6	76.8	459.4
MEAN INDUCTION RATIO	-	*1.0*	*1.0*	*0.9*	*1.1*	*6.4*
Statistical significance (Dunnett's test)		NS	NS	NS	NS	<0.05

ASSAY 2	Concentrations in µg/mL					
	0	*625*	*1250*	*2500*	*5000*	MMS 2
	Adjusted RTG (Relative total growth)					
WITHOUT S9	100.0	107.3	113.7	111.2	94.6	65.6
24-Hour treatment	MUTATION FREQUENCY X10^{-6} cells					
	125.9	100.3	111.5	105.6	116.2	905.2
MEAN INDUCTION RATIO	-	*0.8*	*0.9*	*0.8*	*0.9*	*7.2*
Statistical significance (Dunnett's test)		NS	NS	NS	NS	<0.05

$$\text{Induction ratio} = \frac{\text{Mutation frequency (treated)}}{\text{Mutation frequency (control)}}$$

N.S.: Not statistically significant (with α = 0.05 critical value)

Table B.6.4.1-7: Results of assays 1 and 2 with metabolic activation

ASSAY 1	Concentrations in µg/mL					
	0	625	1250	2500	5000	CPA 2
WITH S9	Adjusted RTG (Relative total growth)					
	100.0	82.8	90.3	97.7	94.6	67.4
3 Hour-treatment	MUTATION FREQUENCY X10^{-6} cells					
	88.0	123.6	125.4	111.5	110.3	749.3
INDUCTION RATIO	-	1.4	1.4	1.3	1.3	8.5
Statistical significance (Dunnett's test)		NS	NS	NS	NS	*
ASSAY 2	Concentrations in µg/mL					
	0	625	1250	2500	5000	CPA 2
WITH S9	Adjusted RTG (Relative total growth)					
	100.0	96.0	78.0	89.8	91.0	89.7
3-Hour treatment	MUTATION FREQUENCY X10^{-6} cells					
	93.5	86.4	101.1	126.7	129.4	406.5
MEAN INDUCTION RATIO	-	0.9	1.1	1.4	1.4	4.3
Statistical significance (Dunnett's test)		NS	NS	NS	NS	*

*: *Because of heterogenicity between the two cultures, statistical analysis could not be assessed.*

$$\text{Induction ratio} = \frac{\text{Mutation frequency (treated)}}{\text{Mutation frequency (control)}}$$

N.S.: Not statistically significant (with α =0.05 critical value)

Table B.6.4.1-8: Number and mutation frequency of small colonies in assays 1 and 2 without metabolic activation

ASSAY 1 WITHOUT S9 3-Hour treatment	Concentrations in µg/mL					
	0	625	1250	2500	5000	MMS 10
Mean number of Small Colonies	35.5	40	37.5	32	38.5	157.5
Mutation Frequency	42.6	41.9	45.9	34.5	50.1	273.5
Mean induction ratio	-	1.0	1.1	0.8	1.2	6.4
Statistical significance (Dunnett's test)		NS	NS	NS	NS	<0.05

ASSAY 2 WITHOUT S9 24-Hour treatment	Concentrations in µg/mL					
	0	625	1250	2500	5000	MMS 2
Mean number of Small Colonies	58	51	64.5	67.5	60.5	196.5
Mutation Frequency	83.5	62.5	78.5	78.1	78.6	452.1
Mean induction ratio	-	0.7	0.9	0.9	0.9	5.4
Statistical significance (Dunnett's test)		NS	NS	NS	NS	<0.05

Table B.6.4.1-9: Number and mutation frequency of small colonies in assays 1 and 2 with metabolic activation

ASSAY 1 WITH S9 3-Hour treatment	Concentrations in µg/mL					
	0	625.0	1250	2500	5000	CPA 2
Mean number of Small Colonies	59	80	79	73	66	202
Mutation Frequency	62.2	97.1	93.9	82.7	80.5	380.8
Mean induction ratio	-	1.6	1.5	1.3	1.3	6.1
Statistical significance (Dunnett's test)		NS	NS	NS	NS	*

ASSAY 2 WITH S9 3-Hour treatment	Concentrations in µg/mL					
	0	625	1250	2500	5000	CPA 2
Mean number of Small Colonies	44.5	40.5	39.5	52	53	147
Mutation Frequency	64.3	54.2	72.5	83.3	86.4	293.4
Mean induction ratio	-	0.8	1.1	1.3	1.3	4.6
Statistical significance (Dunnett's test)		NS	NS	NS	NS	<0.05

N.S.: Not statistically significant (with α =0.05 critical value)

*: *Because of heterogenicity between the two cultures, statistical analysis could not be assessed.*

CONCLUSION:
Under these experimental conditions, the test item EL101GV induced no mutagenic activity in presence or in absence of metabolic activation being demonstrated at the TK locus in L5178Y mouse lymphoma cell culture.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This study is considered acceptable.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation. Heptamaloxylogucan is not not mutagenic with or without metabolic activitation.

IN VITRO CYTOGENETIC TESTS

For the reasons described above, heptamaloxyloglucan is an absorbable compound degradable into molecules naturally present in mammalian metabolic pathways. Also, according to the physico-chemical properties and already toxicological data available, no concern is expected about the toxicological properties of the heptamaloxyloglucan generally and on genotoxicity more specifically.

Therefore, as no mutagenicity activity is demonstrated in the submitted studies and as the genotoxicity of GOS was evaluated, particularly with *in vivo* micronucleus assay in mice, demonstrating the absence of effects[3], the active substance heptamaloxyloglucan is not expected to cause clastogenic or aneugenic effects.

No further study was deem necessary.

DNA DAMAGE AND REPAIR

For the reasons mentioned before, heptamaloxyloglucan is an absorbable compound degradable into molecules naturally present in mammalian metabolic pathways.

Therefore, heptamaloxyloglucan is not expected to induce damage to the DNA and no study was performed.

Assessment and conclusion by RMS 2020:

[3] GRAS Exemption Claim for Galacto-oligosaccharides. Nestlé Nutrition, 2015. https://www.fda.gov/media/98650/download

Two out of three required *in vitro* tests have been provided (Regulation 283/2013). No clastogenicity test has been submitted. However, a read across approach with suitable analogue(s) having chromosomal aberration *in vitro* data and or micronucleus *in vitro* data would be acceptable given the nature and physico-chemical properties of the active substance. In absence of a *in vitro* test or read across data, a data gap is considered.

B.6.4.2. In vivo studies in somatic cells

In unchanged form, heptamaloxyloglucan is not able to enter host cells of humans or animals because of its low K_{ow} ($< 10^{-4}$) and high molecular weight (> 1000 g/mol), and can therefore not have any activity these cells. The only possible activity would be directed towards digestive flora, to which it will not be mutagen as demonstrated under B 6.4.1. Furthermore heptamaloxyloglucan is prepared from, and naturally present in, apple fruit which is part of human and animal diet.

As it is unabsorbed by the digestive tract, ingested heptamaloxyloglucan will be partly biotransformed by enzymatic systems of digestive flora, producing smaller oligosaccharides, glucidic monomers (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate) as demonstrated under B 6.1. All these molecules, except for oligosaccharides, are able to enter mammalian cells, notably enterocytes. However these compounds are naturally present in metabolic pathways of mammals and especially those involved in digestion. They have no expected mutagenic potential and are not comparable with any known mutagen.

Therefore no *in vivo* test was performed with heptamaloxyloglucan in somatic cells.

Assessment and conclusion by RMS 2020:
One *in vivo* test is usually expected when three *in vitro* tests are negative (Regulation 283/2013). Waiving *in vivo tests* would be acceptable if three *in vitro* tests were available. However given the nature of the active substance and the absence of accumulation in mammals and lack of toxicity in the 28 rat study the *in vivo* test with heptamaloxyloglucan in somatic cells is considered not necessary.

B.6.4.3. In vivo studies in germ cells

No *in vivo* test on germ cells was performed with heptamaloxyloglucan, for the reasons mentioned under B 6.4.2. Furthermore, as heptamaloxyloglucan and its metabolites cannot be genotoxic to somatic cells, investigations on genotoxicity to germ cells are not required.

Assessment and conclusion by RMS 2020:
Waiving *in vivo tests* would be acceptable if three *in vitro* tests were available. However given the nature of the active substance and the absence of accumulation in mammals and lack of toxicity in the 28 rat study the *in vivo* test with heptamaloxyloglucan in germ cells is considered not necessary.

B.6.5. LONG-TERM TOXICITY AND CARCINOGENESIS

No new study is provided by the applicant compared to previous evaluation (DAR 2007).

Heptamaloxyloglucan, cannot penetrate lipophilic membranes ($K_{ow} < 10^{-4}$ and high molecular weight (> 1000 g/mol) and thus not enter any host cell in animals and humans. The absence of toxicity was confirmed:
- in acute oral and dermal toxicity studies in rats, with acute NOAELs of 2000 mg/kg b.w. in both studies;
- in short-term toxicity study (28-day oral in rats) with a NOAEL higher than 1000 mg/kg b.w./day.

Therefore, no chronic toxicity or carcinogenic potential is expected for xyloglucan EL101GV, in unchanged form.

The absorbable metabolites of heptamaloxyloglucan are monosaccharides (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate) which are naturally present in metabolic pathways of animals and humans. Furthermore, these compounds are also produced by degradation of oligosaccharides from vegetal food items or xyloglucans present in apples (from which heptamaloxyloglucan is prepared). The very small amounts to which animals and humans may be exposed following use of heptamaloxyloglucan are therefore not expected to induce development of chronic toxicity or carcinogenesis.

Several publications confirm the unexpected effects on chronic toxicity and carcinogenicity of heptamaloxyloglucan.

PUBLICATIONS TO EVALUATE CHRONIC TOXICITY AND CARCINOGENICITY AT 2 YEARS IN THE RAT AND 18 MONTHS IN THE MOUSE PERFORMED WITH TAMARIND SEEDS:

1. KCA 5.5/01; 2 years oral study in rats

Annex Point	KCA 5.5/01
Report author	Iida M, Matsunaga Y, Matsuoka N *et al*.
Report year	1978
Report title	Two years feeding toxicity study of tamarind seed polysaccharide in rats. *Journal of Toxicological Sciences.* 1978; 3:163-192).
Guidelines	None
Major deviations from current guideline	Not applicable
Previous evaluation	Yes, study already evaluated and not accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	No
Acceptability/reliability	Supportive

This study demonstrated that a xyloglucan from tamarind seed, made of D-glucose, D-xylose and D-galactose (molar ratios: 3:2:1 as in heptamaloxyloglucan) and therefore very similar to heptamaloxyloglucan, was not carcinogenic or toxic when fed to male and female rats at the dietary levels of 4%, 8% and 12% for two years.

Study acceptance:
DAR has concluded that this study was performed with a xyloglucan extracted from tamarind seed, which is constituted of D-glucose, D-xylose and D-galactose in a molar ration (3:2:1) similar to heptamaloxyloglucan, but whose molecular weight is much higher (650 000 compared to 1078 for heptamaloxyloglucan); moreover the English abstract only is available. This study cannot be accepted for bridging with heptamaloxyloglucan; it might only support the indication that heptamaloxyloglucan has a very low potential for chronic toxicity.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
A two year rat study was conducted with tamarind an analogue of the active substance. As already stated in Section B.6.3.2, read across based on tamarind seed polysaccharide is not considered acceptable due to very high molecular weight of ca. 650000 Da for this polysaccharide i.e., ca. 650-fold Heptamaloxyloglucan molecular weight which is 1078 Da. Reading across or extrapolating to heptamaloxyloglucan is therefore not accepted.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation.

2. KCA 5.5/05; 18 months oral study in mice

Annex Point	KCA 5.5/05
Report author	Sano M, Miyata E, Tamano S, Hagiwara A, Ito N, Shirai T.
Report year	1996
Report title	Lack of carcinogenicity of tamarind seed polysaccharide in B6C3F1 mice. *Food Chem Toxicol.* 1996;34(5):463-7
Guidelines	None
Major deviations from current guideline	Not applicable
Previous evaluation	Yes, study already evaluated and not accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	No
Acceptability/reliability	Supportive

Additionally, a xyloglucan from tamarind seed, made of D-glucose, D-xylose and D-galactose (molar ratios: 3:2:1) and therefore very similar to EL101GV, was tested in a 18-month oral carcinogenicity study in mice). Groups of 50 male and 50 female animals were given diets containing 0, 1.25 and 5% of tamarind seed polysaccharide for 18 months. There were no adverse effects in any treated group concerning any parameter or observation (mortality, clinical signs, weight data, food and water intake, haematology, gross pathology, weights of brain, heart, liver, spleen, kidneys, adrenals, testes/ovaries, and microscopic examination of weighed organs, lymph nodes, bone marrow, thymus, pituitary, thyroids, parathyroids, trachea, lungs, tongue, salivary glands, oesophagus, stomach, duodenum, jejunum, ileum, caecum, colon, rectum, pancreas, gall bladder, urinary bladder, prostate, seminal vesicle, mammary gland, uterus, vagina, femur, sternum, skin and subcutis, eyes, Harder glands, spinal cord and gross lesions) except for a moderate and progressive body weight retardation in both groups of treated females. This effect was however not dose-related and of minimal amplitude: 10.1 and 7.2% lower weight, at 1.25 and 5% respectively, compared to controls; furthermore, it was described as a prevention of obesity. Treatment had no influence on neoplasia development. These results demonstrated that tamarind seed polysaccharide had no long-term toxicity and was not carcinogenic in B6C3F1 mice of either sex. This supports the expected lack of long-term toxicity and carcinogenicity of heptamaloxyloglucan in mice.

Study acceptance:
DAR has concluded that this study was performed with a xyloglucan extracted from tamarind seed, which is constituted of D-glucose, D-xylose and D-galactose in a molar ration (3:2:1) similar to heptamaloxyloglucan, but whose molecular weight is much higher (650 000 compared to 1078 for heptamaloxyloglucan); the published report only is available. This study cannot be accepted for bridging with heptamaloxyloglucan; it might only support the indication that heptamaloxyloglucan has a very low potential for chronic toxicity.

Assessment and conclusion by RMS 2020:
Acceptability/Reliability: This report is considered for supplementary information only.
An 18-month oral carcinogenicity study was conducted with tamarind an analogue of the active substance in mice. The study is not considered acceptable due to very high molecular weight of ca. 650000 Da for this polysaccharide which is 650-fold higher than Heptamaloxyloglucan molecular weight of 1078 Da. Reading across or extrapolating to heptamaloxyloglucan is therefore not accepted.
Outcome and conclusion of the study: No change from the previous peer-reviewed evaluation.

PUBLICATIONS TO EVALUATE THE ANTI-TUMOUR ACTIVITY OF POLYSACCHARIDE FRACTIONS EXTRACTED FROM CHINESE MUSHROOM:

1. KCA 5.5/02; Antitumor protein-containing polysaccharides from a Chinese mushroom

Annex Point	KCA 5.5/02
Report author	Zhuang C, Mizuno T, Shimada A *et al.*
Report year	1993
Report title	Antitumor protein-containing polysaccharides from a Chinese mushroom Fengweigu or Houbitake, Pleurotus sajor-caju (Fr.) Sings. *Biosci Biotechnol Biochem.* 1993;57(6): 901-6
Guidelines	Not applicable
Major deviations from current guideline	Not applicable
Previous evaluation	Yes, study already evaluated and not accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	No
Acceptability/reliability	Supportive

A purified, water-soluble protein-bound xyloglucan (named fraction Fi_0-a) was extracted from fruiting bodies of *Pleurotus pulmonarius* a medicinal Chinese fungus also known as *Pleurotus sajor-caju*). It was made at 76% (w/w; remaining part is the proteic fraction) of a xyloglucan consisting in Man:Gal:Xyl:Glc = 2:12:42:42 (molar ratios), which is therefore comparable with EL101GV except for presence of mannose (Man) and absence of fucose. This proteo-xyloglucan was demonstrated to have a marked anti-tumoral activity on Sarcoma 180 implanted in mice: 85% tumour inhibition ratio at 3 weeks. In the same study, those *Pleurotus pulmonarius* oligosaccharides which

did not contain mannose also presented a markled antitumoral activity, so the latter was not attributable to mannose.
A very large number of other oligosaccharides naturally produced by fungi were demonstrated to have anti-tumoral activities. It is notably the case for several compounds related to, or comparable with the xyloglucan EL101GV: xyloglucans of *Grifola frondosa* and *Polyporus confluens*, xylogalactoglucans of *Inonotus obliquus*, galactoxyloglucans of *Hericium erinaceus* and fucogalactans of *Sarcadon aspratus* (all listed in the same review: KCA 5.5/03, Wasser SP. Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. *Appl Microbiol Biotechnol*. 2002;60(3): 258-74 – available under http:фунго.рф/upload/files/_wasser_polysaccharide.pdf), and also various protein-bound polysaccharides of *Tricholoma giganteum* containing glucose, xylose, galactose, with or without mannose (KCA 5.5/04, Mizuno T, Kinoshita T, Zhuang C, Ito H, Mayuzumi Y. Antitumor-active heteroglycans from niohshimeji mushroom, *Tricholoma giganteum*. *Biosci Biotechnol Biochem.* 1995;59(4):568-71).
Combining all these data strongly suggests that EL101GV, a xyloglucan made of a glucose backbone (as in each of the compounds mentioned in the last three paragraphs, except for fucogalactans) and galactose, xylose and fucose will be devoid of carcinogenic potential, and may even present an antitumoral activity. Therefore, no long-term study was performed on rats with EL101GV.

2. KCA 5.5/03; Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides

Annex Point	KCA 5.5/03
Report author	Wasser SP.
Report year	2002
Report title	Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. *Appl Microbiol Biotechnol*. 2002;60(3): 258-74
Guidelines	Not applicable
Major deviations from current guideline	Not applicable
Previous evaluation	Yes, study already evaluated and not accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	No
Acceptability/reliability	Supportive

Basidiomycetes mushrooms contain biologically active polysaccharides in fruit bodies, cultured mycelium, culture broth. Data on mushroom polysaccharides have been collected from 651 species and 7 infraspecific taxa from 182 genera of higher Hetero- and Homobasidiomycetes. These polysaccharides are of different chemical composition, with most belonging to the group of β-glucans; these have β-(1→3) linkages in the main chain of the glucan and additional β-(1→6) branch points that are needed for their antitumor action. The antitumor polysaccharides from various mushrooms are characterized by their molecular weight, degree of branching, and higher (tertiary) structure.
High molecular weight glucans appear to be more effective than those of low molecular weight. Chemical modification is often carried out to improve the antitumor activity of polysaccharides and their clinical qualities (mostly water solubility). The main procedures used for chemical improvement are: Smith degradation (oxydo-reducto-hydrolysis), formolysis, and carboxymethylation. Most of the clinical evidence for antitumor activity comes from the commercial polysaccharides lentinan, PSK (krestin), and schizophyllan, but polysaccharides of some other promising medicinal mushroom species also show good results. Their activity is especially beneficial in clinics when used in conjunction with chemotherapy. Mushroom polysaccharides prevent oncogenesis, show direct antitumor activity against various allogeneic and syngeneic tumors, and prevent tumor metastasis. Polysaccharides from mushrooms do not attack cancer cells directly, but produce their antitumor effects by activating different immune responses in the host. The antitumor action of polysaccharides requires an intact T-cell component; their activity is mediated through a thymus-dependent immune mechanism. Practical application is dependent not only on biological properties, but also on biotechnological availability.

3. KCA 5.5/04; Antitumor-active heteroglycans from *niohshimeji* mushroom, *Tricholoma giganteum*

Annex Point	KCA 5.5/04

Report author	Mizuno T, Kinoshita T, Zhuang C, Ito H, Mayuzumi Y.
Report year	1995
Report title	Antitumor-active heteroglycans from niohshimeji mushroom, *Tricholoma giganteum*. *Biosci Biotechnol Biochem.* 1995;59(4):568-71
Guidelines	Not applicable
Major deviations from current guideline	Not applicable
Previous evaluation	Yes, study already evaluated and not accepted for the first EU approval review (DAR, 2007)
GLP/Officially recognised testing facilities	No
Acceptability/reliability	Supportive

Water-soluble polysaccharide FI and water-insoluble polysaccharides FII, FIll-1, and FIII-2 were obtained from fruiting bodies of *Tricholoma giganteum*. Polysaccharides were further fractionated by ion-exchange chromatography, gel filtration, and affinity chromatography. The 24 polysaccharide fractions obtained were examined for their antitumor effect on Sarcoma 180 implanted in mice. The following antitumor-active polysaccharides were identified: Flo-a, a mixture of α-D-glucan and xyloglucomannan with an average molecular weight of 1.6 × 106; FA-1, a β-D-glucan containing 1% protein and with a molecular weight of 4.0 × 104; FII-1, a (1 → 3)-β-D-glucan containing 7.8% protein, with a molecular weight of 5.2 × 104; FIII-1-b, a protein–polysaccharide complex (ratio, 37.5: 62.5, w/w), with a molecular weight of 6.8 × 104 and with xylose, galactose, mannose, and glucose in the polysaccharide moiety (proportions of 8.9: 14.9: 29.3: 46.9 by weight), and FIII-2-a, b, and c, three (1 → 6)-β-D-glucosyl-branched (1 → 3)-β-D-glucans with a molecular weight from 2.6 × 105 to 4.1 × 105 and containing small amounts of xylose and galactose and 3.5–8.3% protein

General conclusion by RMS 2020:
The literature referenced long-term studies in rats and mice were considered supportive since they were conducted with similar analogue polysaccharides but with much higher molecular weights or different glucidic structure. Hence the read across to heptamaloxyloglucan could not be considered acceptable.

Similarly, the three publications on the anti-tumour activity of polysaccharide fractions extracted from chinese mushroom are considered as supportive. Furthermore, polysaccharide fractions obtained over the breakdown pathway from fungi used in these studies have much higher molecular weight than heptamaloxyloglucan and slightly different glucidic monomers structure. Reading across or extrapolating to heptamaloxyloglucan is therefore not accepted.

However, given the active substance nature, physico-chemical properties and low potential for accumulation in mammals, no mutagenic effect in the two in vitro mutagenic studies and the absence of adverse effects in a 28-day rat study, the active substance is not expected to present concerns for long-term toxicity and carcinogenicity. Tests for both endpoints are considered not necessary.

B.6.6. REPRODUCTIVE TOXICITY

No new study is provided by the applicant compared to previous evaluation (DAR 2007).

B.6.6.1. Generational studies

Heptamaloxyloglucan cannot penetrate lipophilic membranes ($K_{ow} < 10^{-4}$, solubility > 500 g/L, high molecular weight (> 1000 g/mol)) and thus not enter any host cell in animals and humans. The absence of toxicity was confirmed in acute oral and dermal toxicity studies in rats, with acute NOAELs of 2000 mg/kg b.w. in both studies. Therefore, no systemic toxicity to breeding or pregnant animals is expected for heptamaloxyloglucan, in unchanged form.
The absorbable metabolites of heptamaloxyloglucan are monosaccharides (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate) which are naturally present in metabolic pathways of animals and humans. Furthermore, these compounds are also produced by degradation of oligosaccharides from

vegetal food items or xyloglucans present in apples (from which heptamaloxyloglucan is prepared), so heptamaloxyloglucan and its metabolites are already present in human and animal diet independently of vine treatment with the plant protection product. The very small additional amounts to which animals and humans may be exposed following use of heptamaloxyloglucan are therefore not expected to induce toxicity towards reproduction. Furthermore, no oligo- or monosaccharide is known to be toxic towards reproduction.
As heptamaloxyloglucan is not expected to have any adverse effect on reproduction, no multigeneration study was performed.

B.6.6.2. Developmental toxicity studies

For the reasons mentioned in B.6.6.1, and as no oligo- or monosaccharide is known to be a teratogen or embryotoxic substance, heptamaloxyloglucan is not expected to have any adverse effect on development.
Therefore, no developmental toxicity study was performed in rats or rabbits.

Assessment and conclusion by RMS 2020:
RMS agrees with applicant's conclusion. Heptamaloxyloglucan is not expected to have adverse effects on reproduction or to be teratogenic.

B.6.7. NEUROTOXICITY

No new study is provided by the applicant compared to previous evaluation (DAR 2007).

B.6.7.1. Neurotoxicity studies in rodents

The chemical structure of heptamaloxyloglucan is not structurally related to neurotoxicants and therefore, no studies were performed to assess a delayed neurotoxicity.

Heptamaloxyloglucan cannot penetrate lipophilic membranes ($K_{ow} < 10^{-4}$, solubility > 500 g/L, high molecular weight (> 1000 g/mol)) and thus not enter any host cell in animals and humans. Therefore the crossing of the blood-brain barrier is unlikely. The absence of toxicity and notably of any neurotoxic effect was confirmed in acute oral and dermal toxicity studies in rats, with acute NOAELs of 2000 mg/kg b.w. in both studies. Therefore, no acute, delayed or chronic neurotoxicity is expected for heptamaloxyloglucan.

The absorbable metabolites of heptamaloxyloglucan are monosaccharides (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate) which are naturally present in metabolic pathways of animals and humans. Furthermore, these compounds are also produced by degradation of oligosaccharides from vegetal food items or xyloglucans present in apples (from which heptamaloxyloglucan is prepared), so heptamaloxyloglucan and its metabolites are already naturally present in human and animal diets independently of vine treatment with the plant protection product. The very small additional amounts to which animals and humans may be exposed following use of heptamaloxyloglucan are therefore not expected to induce development of acute, delayed or chronic neurotoxicity.

Furthermore, no oligosaccharide or glucidic monomer is known to be neurotoxic. Therefore, no neurotoxicity study was performed with heptamaloxyloglucan.

Assessment and conclusion by RMS 2020:
No study is deemed necessary since heptamaloxyloglucan is not similar or related to structures involved in neurotoxicity.

B.6.7.2. Delayed polyneuropathy studies

For the same reasons presented before (B 6.7.1.) no delayed polyneuropathy studies was performed with heptamaloxyloglucan.

Assessment and conclusion by RMS 2020:
No study is deemed necessary since heptamaloxyloglucan is not similar or related to structures able to induce delayed neurotoxicity.

B.6.8. OTHER TOXICOLOGICAL STUDIES

B.6.8.1. Toxicity studies on metabolites and relevant impurities

As demonstrated under B 6.1, the absorbable metabolites of heptamaloxyloglucan are monosaccharides (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate). They are naturally present in metabolic pathways of animals and humans and are all known to be devoid of toxicity except when ingested in very large quantities. Furthermore, these compounds are also produced by degradation of oligosaccharides from vegetal food items or xyloglucans present in apples (from which heptamaloxyloglucan is prepared), so the metabolites of heptamaloxyloglucan are necessarily already present in human and animal diet independently of vine treatment with the plant protection product. The very small additional amounts to which animals and humans may be exposed following use of heptamaloxyloglucan are therefore not expected to have any effect.
Therefore, no study was performed concerning the toxicity of heptamaloxyloglucan metabolites.

Assessment and conclusion by RMS 2020:
The metabolites of heptamaloxyloglucan are monosaccharides (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate) are already found in human and animal diet and no toxicity is expected. Hence no study is deemed necessary,

B.6.8.2. Supplementary studies on the active substance

As no specific risk is expected from oligo/monosaccharides, no additional study was performed.

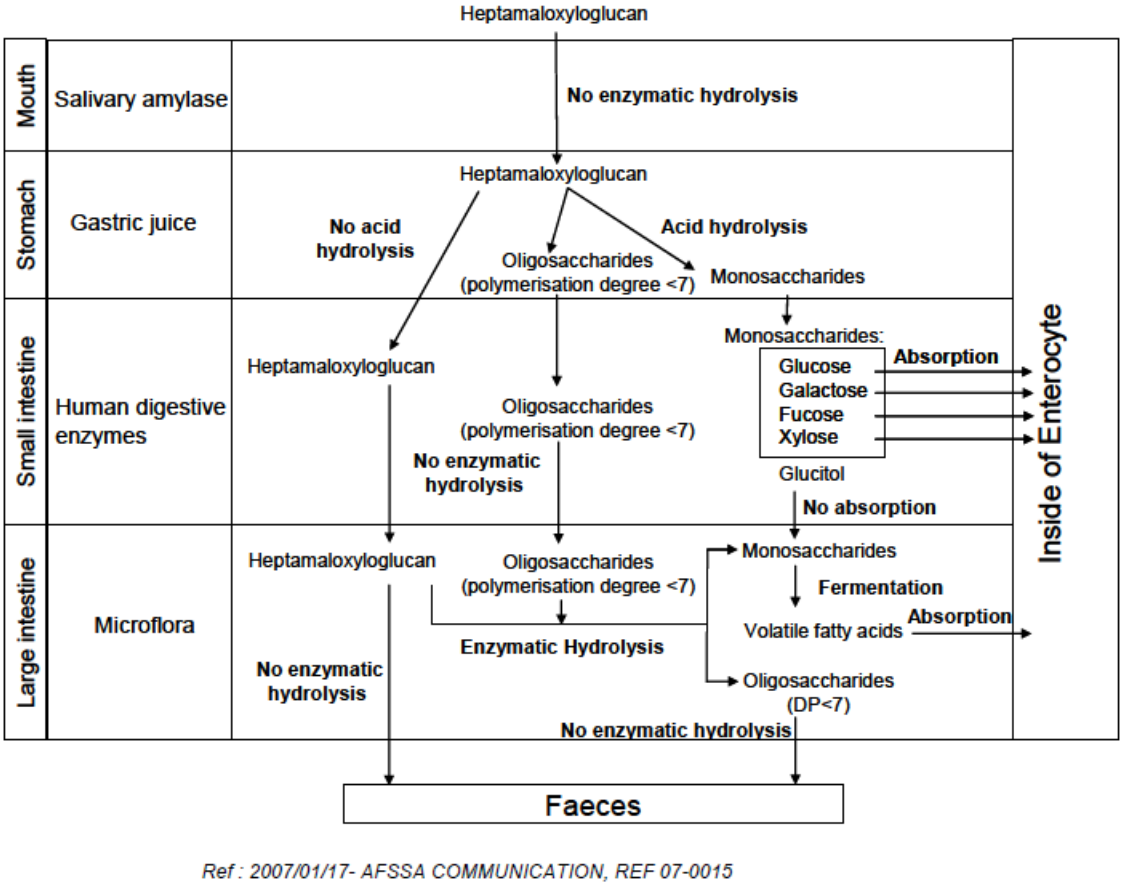
B.6.8.3. Studies on endocrine disruption

Heptamaloxyloglucan cannot penetrate lipophilic membranes (Kow < 10-4, solubility > 500 g/L, high molecular weight (> 1000 g/mol)) and thus not enter any host cell in animals and humans. Especially, crossing of the blood-brain barrier is impossible. As demonstrated under B 6.1, the absorbable metabolites of heptamaloxyloglucan are monosaccharides (glucose, fucose, xylose and galactose) and short-chain fatty acids (acetate, propionate and butyrate). They are naturally present in metabolic pathways of animals and humans and are all known to be devoid of toxicity except when ingested in very large quantities. Furthermore, these compounds are also produced by degradation of oligosaccharides from vegetal food items or xyloglucans present in apples (from which heptamaloxyloglucan is prepared), so the metabolites of heptamaloxyloglucan are necessarily already present in human and animal diet independently of vine treatment with the plant protection product.
Neither xyloglucan nor heptamaloxyloglucan metabolites are recognized as substance with established or potential endocrine disrupting activity. None are described in the "Suspected" Endocrine Disruptors List in EU.
See: http://ec.europa.eu/environment/chemicals/endocrine/strategy/index_en.htm. [Annex 15 - List of 66 Category 1 substances with categorisation high, medium or low exposure concern, and Annex 15: 564 chemicals that had been suggested by various organisations or in published papers or reports as being suspected EDs)]
Moreover the EDGD Appendix-E1 (KCA 5.8.3/01) has been completed with the available data from the Repeated dose 28-day oral toxicity study in rodents concluding to the absence of ED effects.
Therefore, no study was performed concerning the endocrine disturbing properties of heptamaloxyloglucan metabolites.
The active substance heptamaloxyloglucan is an oligosaccharide made of 7 glucidic monomer units. There are β-1,4 linkages on the main chain between the two D-glucopyranosyl units and terminal D-glucitol, and α-1,2, β-1,2 and α-1,6 linkages between the various monomer units present in side chains. The latter side chain-monomers are D-xylopyranosyl (α-1,6-linked to D-glucopyranosyl), D-galactopyranosyl (β-1,2-linked to D-xylopyranosyl) and L-fucopyranosyl (α-1,2-linked to D-galactopyranosyl).

Based on appropriate publications and study reports it has been demonstrated that heptamaloxyloglucan can be derived naturally from xyloglucan, which is the principal hemicellulosic component of primary cell walls of

dicotyledonous and non-graminaceous monocotyledonous plants. This production may occur by partial hydrolysis with cellulose (β-1,4-D-glucanase) and various other enzymes which are present in plants and soil micro-organisms. It has been showed that these specific oligosaccharides accumulate extracellularly in plants and act at very low levels as signalling molecules that participate in cell-cell and wall-nucleus communication. Consequently the active substance heptamaloxyloglucan occurs naturally in plants and soil at very low levels leading to a residual exposure for humans and environment.

As detailed in B 6.1.1, the following metabolic pathway has been proposed for heptamaloxyloglucan.



Ref : 2007/01/17- AFSSA COMMUNICATION, REF 07-0015

Figure B 6.8.3-1: Probable fate of the heptamaloxyloglucan after oral intake

It was concluded that oral intake of heptamaloxyloglucan was expected to result in animal or human exposure to unchanged parent and widespread and well-known oligosaccharides and glucidic monomers (absorbable glucose, fucose, xylose and galactose; unabsorbable glucitol) and short-chain fatty acids (acetate, propionate, butyrate).
These substances being common natural nutrients and as the large variety of enzymatic reactions in which they are involved excludes any bioaccumulation, there was no expected toxicological concern.

Consequently, taking into account the natural occurrence of the parent and its ADME profile in mammals, no concern is expected about the toxicological properties of the heptamaloxyloglucan generally and on the EDs properties more specifically.
Hence there is no bioaccumulation potential as the unchanged molecule is not absorbed in the digestive tract, and as all metabolites are glucids or short-chain fatty acids which are involved in a large variety of metabolic pathways present in animals.

This absence of toxicological effects has been demonstrated:

- in the short-term toxicity studies (B 6.3.1)
  (1) Oral 28-day study in rats treated by gavage at dose levels of 50, 200 or 1000 mg/kg b.w./day (expressed in pure heptamaloxyloglucan). The study was conducted according to OECD 407 (1995); relevant endocrine organs weighed and examined histologically included testes, epididymides,

prostate, seminal vesicles, ovaries, uterus and oviducts, vagina, thymus, adrenals and thymus. There was no compound related effect on mortality, clinical signs, body weight, food consumption, haematology, clinical chemistry, urinalysis and organ weights. There were no treatment-related lesions in rats dosed with heptamaloxyloglucan at 1000 mg/kg at the histopathological examination.

(2) As well in a supportive study, read-across using xyloglucan from tamarind seed was proposed. This compound was made of D-glucose, D-xylose and D-galactose (molar ratios: 3:2:1 exactly as in heptamaloxyloglucan) and therefore very similar to heptamaloxyloglucan. Tested in a 13-week oral study in mice (preliminary to a carcinogenicity study), there were no adverse effects in any treated group concerning any parameter or observation (mortality, clinical signs, weight data, food and water intake, haematology and biochemistry, gross pathology, weights of brain, heart, liver, spleen, kidneys, adrenals, testes/ovaries, and microscopic examination of weighed organs, lymph nodes, bone marrow, thymus, pituitary, thyroids, parathyroids, trachea, lungs, tongue, salivary glands, oesophagus, stomach, duodenum, jejunum, ileum, caecum, colon, rectum, pancreas, gall bladder, urinary bladder, prostate, seminal vesicle, mammary gland, uterus, vagina, femur, sternum, skin and subcutis, eyes, Harder glands, spinal cord and gross lesions) except for statistically, but minimally lower protein levels in all groups of treated males compared to controls. These results demonstrated that tamarind seed polysaccharide had no short-term toxicity in mice of either sex, supporting the expected lack of short-term toxicity of heptamaloxyloglucan in mice.

- In the Long-term toxicity and carcinogenicity (B 6.5)

(1) In a supportive study (Two years feeding toxicity in rats), read-across using xyloglucan from tamarind seed was proposed. This compound was made of D-glucose, D-xylose and D-galactose (molar ratios: 3:2:1 as in heptamaloxyloglucan). Despite RMS didn't support the bridging at the occasion of the first submission, it was accepted that heptamaloxyloglucan had a very low potential for chronic toxicity.

(2) As well in other supportive study, read-across using purified, water-soluble protein-bound xyloglucan (extracted from fruiting bodies of *Pleurotus pulmonarius* a medicinal Chinese fungus also known as *Pleurotus sajor-caju*) was proposed. This compound was made at 76% (w/w; remaining part is the proteic fraction) of a xyloglucan consisting in Man:Gal:Xyl:Glc = 2:12:42:42 (molar ratios), which is therefore comparable with heptamaloxyloglucan except for presence of mannose (Man) and absence of fucose. Therefore it was suggested that heptamaloxyloglucan is devoided of carcinogenic potential, and may even present an antitumoral activity.

(3) In a supportive study (18-month oral toxicity in mice), read-across using xyloglucan from tamarind seed was proposed. This compound was made of D-glucose, D-xylose and D-galactose (molar ratios: 3:2:1) and therefore very similar to heptamaloxyloglucan. Tested in a 18-month oral study in mice, there were no adverse effects in any treated group concerning any parameter or observation (mortality, clinical signs, weight data, food and water intake, haematology, gross pathology, weights of brain, heart, liver, spleen, kidneys, adrenals, testes/ovaries, and microscopic examination of weighed organs, lymph nodes, bone marrow, thymus, pituitary, thyroids, parathyroids, trachea, lungs, tongue, salivary glands, oesophagus, stomach, duodenum, jejunum, ileum, caecum, colon, rectum, pancreas, gall bladder, urinary bladder, prostate, seminal vesicle, mammary gland, uterus, vagina, femur, sternum, skin and subcutis, eyes, Harder glands, spinal cord and gross lesions) except for a moderate and progressive body weight retardation in both groups of treated females. This effect was however not dose-related and of minimal amplitude: 10.1 and 7.2% lower weight, at 1.25 and 5% respectively, compared to controls; furthermore, it was described as a prevention of obesity. Treatment had no influence on neoplasia development. These results demonstrated that tamarind seed polysaccharide had no long-term toxicity and was not carcinogenic in B6C3F1 mice of either sex. This supported the expected lack of long-term toxicity and carcinogenicity of heptamaloxyloglucan in mice.

Taking into account the oligosaccharidic nature of the active substance and this absence of toxicological effects, in order to avoid unnecessary experiments in mammals, no further experimental investigations have been made on reproductive and neurotoxicity studies.

Using the EFSA Guidance for the identification of endocrine disruptors, by gathering all relevant information, after assessing their relevance and reliability, it is concluded that heptamaloyloglucan does not possess endocrine disrupting properties and therefore will not result in any "change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences". No EATS-mediated adversity has been observed or is expected with the oligosaccharidic active substance heptamaloyloglucan.

Assessment and conclusion by RMS 2020:
Physico-chemical properties and ADME information demonstrate that no bioaccumulation potential relates to heptamaloxyloglucan as the unchanged molecule is not absorbed in the digestive tract, and all metabolites are glucids or short-chain fatty acids which are involved in a large variety of physiological metabolic pathways occurring in mammals.

The potential endocrine activity has not been investigated as per the new guidance Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009.

Two *in vivo* short-term toxicity studies providing data on adverse effects on endocrine endpoints are available:

- The oral 28-day study in rat was performed with heptamaloxyloglucan treated by gavage at dose levels of 50, 200 or 1000 mg/kg b.w./day. In this study, relevant endocrine organs were weighed and examined histologically included testes, epididymides, prostate, seminal vesicles, ovaries, uterus and oviducts, vagina, thymus, adrenals. There was no toxicological effect observed of heptamaloxyloglucan.
- The oral 90-day study in mice was performed with tamarind seed. The results demonstrate that tamarind seed had no short-term toxicity.. However, even if the glucidic monomers structure of tamarind seed is similar to heptamaloxylogucan, the bridging is not considered acceptable based on the molecular weight difference (650,000 versus 1,078 g/mol for tamarind and heptamaloxyloglucan respectively).

The long-term toxicity and carcinogenicity studies provided are considered as supportive studies performed with tamarind seed or protein-bound xyloglucan. The bridging between tamarind seed and heptamaloxyloglucan based on the molecular weight difference could not be considered acceptable. Similarly the bridging between protein-bound xyloglucan and heptamaloxyloglucan is not supported based on the glucidic monomers structure.

No EATS mediated adversity has been observed but data are considered limited.

There is no indication of EATS mediated adversity of heptamaloxyloglucan observed in the oral 28-day study, which falls under level 4 of the OECD Conceptual Framework (CF) for endocrine disruptors. Considering its physico-chemical properties, lack of toxicity in the 28 day rat study and no potential for accumulation, no further investigation on the endocrine disrupting properties is considered necessary.

B.6.9. MEDICAL DATA AND INFORMATION

B.6.9.1. Medical surveillance on manufacturing plant personnel and monitoring studies

No data was available. As demonstrated in all previous sections, no toxicity is expected from heptamaloxyloglucan and its metabolites, which are oligo- and monosaccharides.

B.6.9.2. Data collected on humans

No data collected.

B.6.9.3. Direct observation

No event to be reported during the development, the production and the use of heptamaloxyloglucan.

B.6.9.4. Epidemiological studies

No data was available. As implied by the definition of the active substance, and by the biotransformations it will undergo (see B6.1), heptamaloxyloglucan and its metabolites (oligosaccharides, glucose, fucose, xylose, galactose, acetate, propionate and butyrate) can naturally be found during digestion of untreated apples. They are physiologically part of vegetal cell walls or produced by their biotransformation. The very small additional amounts to which animals and humans may be exposed following use of heptamaloxyloglucan are negligible compared to natural exposure to each of these compounds, especially regarding the low application rate of

heptamaloxyloglucan: 0.05-0.5 g/ha on vines. Furthermore, due to the ubiquity of these compounds, residues from heptamaloxyloglucan-application on vines would not be distinguishable from their natural equivalents.

Therefore, a study of exposure to heptamaloxyloglucan was neither necessary nor possible.

B.6.9.5. Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical test

No clinical case or poisoning incident occurred with heptamaloxyloglucan during any phase of development, production or use of the active substance.
As no poisoning occurred with heptamaloxyloglucan, diagnosis methods, signs and clinical tests are not known.
Besides, determination of active substance or metabolites in biological fluids is not relevant for heptamaloxyloglucan. Indeed, the active substance cannot enter cells (including enterocytes) or skin because of its low K_{ow} ($< 10^{-4}$, solubility > 500 g/L, high molecular weight (> 1000 g/mol)) and can be found in apples. Its metabolites (oligosaccharides, glucose, fucose, xylose, galactose, acetate, propionate and butyrate) can naturally be found during digestion of apples and are part of many other physiological metabolic pathways, and most of them are physiologically present in blood. Therefore, compounds resulting from heptamaloxyloglucan-contamination would not be distinguishable from their natural equivalents in biological fluids.

Not known as heptamaloxyloglucan and its metabolites are not toxic (see B.6.2) and as no poisoning occurred with heptamaloxyloglucan.

B.6.9.6. Proposed treatment: first aid measures, antidotes, medical treatment

Not applicable as heptamaloxyloglucan and its metabolites are not toxic (see B 6.2).

Assessment and conclusion by RMS 2020:
No clinical case or poisoning incident has been reported with heptamaloxyloglucan during any phase of development, production or use of the active substance.

B.6.10. 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 5.1/01 (KCA 6.2.1/01)	Buchanan B.B., Gruissen W., and Jones R.L.	2000	Biochemistry and Molecular Biology of Plants Public literature (book) GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/02	Fry S. and al.	1993	Oligosaccharides as signals and substrates in the plant cell wall. Plant Physiol., Vol. 103 (1993), pp. 1-5 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/03	Hayashi T.	1989	Xyloglucans in the primary cell wall Annu. Rev. Plant Physiol. Plant Mol. Biol. 1989, 40:139-68 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/04	Wahbe T.G. and Christie D.L.	2006	Chapter 2: Basic aspects of digestion and absorption. Pediatric Gstrointestinal and Liver disease, 3rd edition, Hardback edition, 1348 p., 2006 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/05	Heyraud A., Rinaudo M.	1981	Hydrolysis of oligosaccharides by polyelectrolytes. European polymer journal, Vol.17, pp.181-189, 1981 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)

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 5.1/06	Havet S.	2007	EL101GC Hydrolysis study at pH 2.2 and 50°C during 2 days Elicityl SA, 38920 Crolles, France Study No. EL101GV-31012007-01 No GLP Unpublished	N	N	-	-	Y (DAR, 2007)
KCA 5.1/07	Alvarez E.E. and Sanchez P.G.	2006	Dietary fibre Nutrition Hospitalaria, Vol.21 (supl. 2), pp. 60-71, 2006 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/08	Macfarlane S. et al.	1998	Polysaccharide degradation by human intestinal bacteria during growth under multi-substrate limiting conditions in a three-stage continuous culture systems FEMS Microbiology Ecology, Vol. 26, pp. 231-243, 1998 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/09	Gardiner T.	2000a	Absorption, distribution, metabolism and excretion (ADME) of eight known dietary monosaccharides required for glycoprotein synthesis and cellular recognition processes. GlycoScience & nutrition., Vol 1 (12), pp. 1-7, 2000 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)

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 5.1/10	Gardiner T.	2000b	Dietary fucose: Absorption, distribution, metabolism and excretion (ADME) and biological activity. GlycoScience & nutrition., Vol 1 (6), pp.1-4, 2000 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/11	Gardiner T.	2000c	Dietary galactose: Absorption, distribution, metabolism and excretion (ADME) and biological activity. GlycoScience & nutrition., Vol 1 (7), pp.1-4, 2000 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/12	Gardiner T.	2000d	Dietary glucose: Absorption, distribution, metabolism and excretion (ADME) and biological activity. GlycoScience & nutrition., Vol 1 (18), pp.1-4, 2000 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/13	Gardiner T.	2000e	Dietary xylose: Absorption, distribution, metabolism and excretion (ADME) and biological activity. GlycoScience & nutrition., Vol 1 (5), pp.1-2, 2000 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/14	Ramberg J.	2005	Sorbitol GlycoScience. The nutrition science site. Web capture. Date Last modified : 2001 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)

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 5.1/15	Topping D.L. and Clifton P.M.	2001	Short-chain fatty acids and human colonic function : roles of resistant starch and nonstarch polysaccharides Physioloical Reviews, Vol. 81 (3), pp. 1031-1063, 2001 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.1/16	Kattak M.M.A.	2002	Physiological effects of dietary complex carbohydrates and its metabolites in certain diseases Pakistan Journal of Nutrition, Vol. 1 (4), pp. 161-168, 2002 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.2.1/01	********.	2006b	Acute oral toxicity in the rat : Acute toxicity class method (OECD 423) CERB Study 20030812ST GLP Unpublished	Y	N	-	Elicityl	Y (DAR, 2007)
KCA 5.2.2/01	*********	2006a	Acute dermal toxicity in the rat (OECD 402) CERB Study 20050508STC GLP Unpublished	Y	N	-	Elicityl	Y (DAR, 2007)
KCA 5.2.3/01	Lamblin G. et al.	1992	Human respiratory mucins. *Eur Resplr J 199~. 5, 247-268* GLP non relevant (Public literature) Published	N	N	-	Elicityl	N
KCA 5.2.4/01	**********	2006c	Acute skin irritation in the rabbit (OEC404) CERB Study 200401148STC GLP Unpublished	Y	N	-	Elicityl	Y (DAR, 2007)

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 5.2.5/01	********	2006d	Acute eyes irritation in the rabbit (OEC405) CERB Study 200401147STC GLP Unpublished	Y	N	-	Elicityl	Y (DAR, 2007)
KCA 5.2.6/01	********	2006	Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA) CIT Study 31168 TSS GLP Unpublished	Y	N	-	Elicityl	Y (DAR, 2007)
KCA 5.3.1/01	**********.	2006	EL101GV Repeated dose 28-day toxicity study in the rat by the oral route Centre de Recherches Biologiques (CERB) 20060118TRB GLP Unpublished	Y	N	-	Elicityl	Y (DAR, 2007)
KCA 5.3.2/01 (KCA 5.5/05)	Sano M, Miyata E, Tamano S, Hagiwara A, Ito N, Shirai T.	1996	Lack of carcinogenicity of tamarind seed polysaccharide in B6C3F1 mice. *Food Chem Toxicol.* 1996;34(5):463-7 GLP non relevant (Public literature) Published	Y	N	-	Elicityl	Y (DAR, 2007)
KCA 5.4.1/01	Le Curieux F.	2006	Bacterial test on Salmonella typhimurium His- (5 strains) using B.N. Ames's technique with EL101GV FSR-IPL 030207 / EL101GV / Elicityl GLP Unpublished	N	N	-	Elicityl	Y (DAR, 2007)

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 5.4.1/02	Hensel A, Meier K.	1999	Pectins and xyloglucans exhibit antimutagenic activities against nitroaromatic compounds. *Planta Med.* 1999, 65(5): 395-399 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.4.1/03	Nesslany F.	2006	Mutation assay at the TK locus in L5178Y Mouse lymphoma cells using a microtiter cloning technique (Trifluorothymidine Resistance) carried out with EL101GV GLP Unpublished	N	N	-	Elicityl	Y (DAR, 2007)
KCA 5.5/01	Iida M, Matsunaga Y, Matsuoka N *et al*.	1978	Two years feeding toxicity study of tamarind seed polysaccharide in rats. *Journal of Toxicological Sciences.* 1978; 3:163-192 GLP non relevant (Public literature) Published	Y	N	-	-	Y (DAR, 2007)
KCA 5.5/02	Zhuang C, Mizuno T, Shimada A *et al*.	1993	Antitumor protein-containing polysaccharides from a Chinese mushroom Fengweigu or Houbitake, Pleurotus sajor-caju (Fr.) Sings. *Biosci Biotechnol Biochem.* 1993;57(6): 901-6 GLP non relevant (Public literature) Published	Y	N	-	-	Y (DAR, 2007)
KCA 5.5/03	Wasser SP.	2002	Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. *Appl Microbiol Biotechnol*. 2002;60(3): 258-74 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)

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 5.5/04	Mizuno T, Kinoshita T, Zhuang C, Ito H, Mayuzumi Y.	1995	Antitumor-active heteroglycans from niohshimeji mushroom, *Tricholoma giganteum*. *Biosci Biotechnol Biochem.* 1995;59(4):568-71 GLP non relevant (Public literature) Published	N	N	-	-	Y (DAR, 2007)
KCA 5.8.3/01	Guillot A.L.	2020	EDGD_Appendix-E1_hexamaloxyloglucan_EDdata_v1 GLP non relevant Non published	Y	N	-	Elicityl	N

[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).

References cited in Vol. 3. B.6 (AS) but not submitted:

- Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009.
- Regulation (EU) No.283/2013
- Guidance by OECD on the review of the GLP
- ECHA Guidance on the BPR, Vol. III (Parts B+C), Version 4.0, December 2017)
- Regulation (EC) No.1272/2008
- Genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Journal 2011;9(9):2379
- Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances (EFSA 2019)
- Doc SANCO 12592 rev.2 March 19.

B.6.10.1. Bibliographic database selection

Aim is to find scientific peer-reviewed open literature, as required by Article 8(5) of Regulation (EC) No 1107/2009 on the placing of plant protection products on the market, on Heptamaloxyloglucan and its relevant metabolites dealing with toxicological and toxicokinetic studies, residues, fate and behavior in the environment and ecotoxicological studies which are published within the last ten years from various data sources.
EFSA and AGES agreed that it is sufficient to use only one bibliographic database. PubMed is a free search engine which has over 23 million records going back to 1966 and a database of citations and abstracts for biomedical literature from MEDLINE and additional life science journals. However in order to scan a broad spectrum of research, other various database have also been consulted at the occasion of this literature data review.
Therefore the following databases have been consulted to complete the scientific peer-reviewed open literature on Heptamaloxyloglucan and its relevant metabolites:
1. Pubmed, 2. ScienceDirect, 3. Europe PMC, 4. Agricola

The search was analyzed manually for each relevant reference without using dedicated software. Any removal of ambiguity or de-duplication was done manually based on the literature unique ID (e.g., PMID) or title of the literatures.

B.6.10.2. Search strategy

The main parameters that allow the characterization of the literature search are listed below. Trade names were not considered in the literature search as they are covered by the search on Heptamaloxyloglucan: any trade name should be found without reference to the active substance.

B.6.10.2.1. Date span of the literature search

The search identified scientific peer-reviewed open literatures published in last 10 years (≥ 2008).

B.6.10.2.2. Databases used in the literature review

The literature review has been performed using a broad collection of relevant databases for the literature search (see Table CA 9.11/01).

Table CA 9.11/01: List of databases for the literature search of Heptamaloxyloglucan

Database	Date of the Latest Database Update Included in the Search
1. Pubmed	2018/09
2. ScienceDirect	2018/09
3. Europe PMC	2018/09
4. Agricola	2018/09

Justifications for choosing these databases as literature sources are detailed in Appendix II (see Section CA 9.6.2).

B.6.10.2.3. Search terms for the literature review

The following Table CA 9.11/02 presents the General Search terms and Section Specific Search terms for the database search on Heptamaloxyloglucan. The information used for screening the selected databases to identify all relevant publications consists of common names, as far as available.
The General Search terms are intended to cover all data requirements whereas the Section Specific Search terms are keywords dedicated to their respective sections (Toxicology, Residues, Ecotoxicology, Fate and Environment).
Active substance EL101GV is an oligosaccharide made of 7 glucidic monomer units. There are β-1,4 linkages on the main chain between the two D-glucopyranosyl units and terminal D-glucitol, and α-1,2, β -1,2 and α -1,6 linkages between the various monomer units present in side chains. The latter side chain-monomers are D-xylopyranosyl (α -1,6-linked to D-glucopyranosyl), D-galactopyranosyl (β-1,2-linked to D-xylopyranosyl) and L-fucopyranosyl (α -1,2-linked to D-galactopyranosyl). Therefore these terms have been used for the literature search.

Table CA 9.11/02: List of Search terms for the database search

Heptamaloxyloglucan	
Common names / ISO name	Heptamaloxyloglucan
General Search terms:	In all fields: Heptamaloxyloglucan - Oligoxyloglucan - Heteroglycan – Xyloglucan Only in title: Saccharide - Oligosaccharide - Monosaccharide - Sorbitol - Xylose Glucopyranosyl - Glucopyranose - Glucitol - Xylopyranosyl - Xylopyranose Galactopyranosyl - Galactopyranose - Fucopyranosyl – Fucopyranose
Section Specific Search terms:	See Section CA 9.6.3 Appendix III

B.6.10.3. Search results

A total of 17 611 summary records was retrieved before removing duplicates, divided as:

Table CA 9.11/03: List of publications after first search and compilation of all databases

Database	Specific Search terms	First search
1_Pubmed Hepta-sorbi	In abstract: Heptamaloxyloglucan OR Oligoxyloglucan OR Heteroglycan OR Xyloglucan OR In title: Saccharide OR Oligosaccharide OR Monosaccharide OR Sorbitol AND 01/01/2008 – 23/10/2018	2 731

Database	Specific Search terms	First search
2_Pubmed glucitolxylose	In title: Xylose OR Glucitol AND 01/01/2008 – 23/09/2018	1 136
3_Pubmed Pyran	In title Glucopyranosyl OR Glucopyranose OR Xylopyranosyl OR Xylopyranose OR Galactopyranosyl OR Galactopyranose OR Fucopyranosyl OR Fucopyranose AND 01/01/2008 – 07/09/2018	352
4_ScienceDirect Xyloglyca	In title, abstract, or author-specified keywords Heptamaloxyloglucan OR Oligoxyloglucan OR Heteroglycan OR Xyloglucan AND 2008-2018	368
5_ScienceDirect Sacch	In title Saccharide OR Oligosaccharide OR Monosaccharide OR Sorbitol OR Xylose OR Glucopyranosyl OR Glucopyranose OR Glucitol AND 2008-2018	3 032
6_ScienceDirect pyran	In title Xylopyranosyl OR Xylopyranose OR Galactopyranosyl OR Galactopyranose OR Fucopyranosyl OR Fucopyranose AND 2008-2018	56
7_EuropePMChepta	(ABSTRACT:"oligoxyloglucan" OR ABSTRACT:"heptamaloxyloglucan" OR ABSTRACT:"heteroglycan" OR ABSTRACT:"xyloglucan" OR TITLE:"saccharide" OR TITLE:"oligosaccharide" OR TITLE:"monosaccharide") AND (SRC:"AGR" OR SRC:"CTX" OR SRC:"PAT" OR SRC:"PPR" OR SRC:"MED")[4] AND (FIRST_PDATE:[2008-01-01 TO 2018-09-24])	2 949

[4] AND Sources: Agricola (USDA/NAL), CiteXplore records, Patents, Preprint records, PubMed/MEDLINE (NKM)

Database	Specific Search terms	First search
8_EuropePMCxylose	(TITLE:"sorbitol" OR TITLE:"xylose" OR TITLE:"glucopyranosyl" OR TITLE:"glucopyranose" OR TITLE:"glucitol" OR TITLE:"xylopyranosyl" OR TITLE:"xylopyranose" OR TITLE:"galactopyranosyl" OR TITLE:"galactopyranose" OR TITLE:"fucopyranosyl" OR TITLE:"fucopyranose") AND (FIRST_PDATE:[2008-01-01 TO 2018-09-24])	2 136
9_NAL hept	In any field: Heptamaloxyloglucan Oligoxyloglucan Heteroglycan Xyloglucan In title: Saccharide Oligosaccharide Monosaccharide Sorbitol (search done 09/2018)	23
10_NAL pyran	In title Xylose glucitol Glucopyranosyl Glucopyranose Xylopyranosyl Xylopyranose Galactopyranosyl Galactopyranose Fucopyranosyl Fucopyranose (search done 09/2018)	12
11_NAL articles hepta	In any field: Heptamaloxyloglucan Oligoxyloglucan Heteroglycan Xyloglucan (search done 09/2018)	1 073
12_NAL articles sacc	In title: Saccharide Oligosaccharide Monosaccharide Sorbitol glucitol (search done 09/2018)	1 986
13_NAL articles pyran	In title Xylose Glucopyranosyl Glucopyranose Xylopyranosyl Xylopyranose Galactopyranosyl Galactopyranose Fucopyranosyl Fucopyranose (search done 09/2018)	1 757
Total	**(Total search in Excel sheet KCA 9.3/01)**	**17 611**

All references have been compiled by the applicant under an Excel sheet referenced KCA 9.3/01.

The total of publications before removing duplicates was summarised in the Table below:

Table CA 9.11/04: List of publications after removing of too old literature (before 2007)

	Heptamaloxyloglucan
Total number of publications retrieved (with duplicates) (global search results)	17 611
Total number of too old publications (Before 2008 in Excel sheet KCA 9.3/01)	2 670
Total number of publications retrieved removing too old literature	**14 941**

After removing duplicates, the total number of publications is presented below:

Table CA 9.11/05: List of publications after removing duplicates/triplicates

	Heptamaloxyloglucan
Total number of publications retrieved removing too old literature	14 941
Total removed publications (duplicates/triplicates – Duplicate title in Excel sheet KCA 9.3/01)	8 977
Total number of publications retrieved after removing of duplicates	**5 964**

B.6.10.4. Evaluation

The evaluation of the search results was performed according to the EFSA Guidance Document[5] and following the workflow described in Appendix I (see Section CA 9.6.1).

[5] Guidance of EFSA, Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009, EFSA Journal 2011;9(2):2092

The numbering of the Tables in the following corresponds to the numbering system of the EFSA Guidance Document. The criteria for the relevance assessments are described in Appendix IV (see Section CA 9.6.4).

B.6.10.4.1. Rapid assessment on the literature review

A rapid assessment based on the reading of the titles allows performing a first selection.
The number of obviously irrelevant publications appears in Table CA 9.11/06, documenting the study selection process.

Table CA 9.11/06: List of publications after rapid assessment

	HEPTAMALOXYLOGLUCAN			
Study selection process	Toxicology	Residues	Fate	Ecotoxicology
Number of publications excluded after rapid assessment for relevance according to title (not relevant according to title in Excel sheet KCA 9.3/01)	5 731			
Number of publications further assessed in detail (possible relevant literature for at least one section according to title – Relevant according to title in Excel sheet KCA 9.3/01) Table CA 9.4.2/06	**233**			

B.6.10.4.2. Detailed assessment on the literature review

Those publications, which have passed the rapid assessment, have been evaluated based on abstract and full text versions for each section. The criteria for the relevance assessments are described in Appendix IV (see Section CA 9.6.4).

Table CA 9.4.2/01: Results of the study selection process

	Study selection process	Toxicology
Assessment according to title in Excel sheet KCA 9.3/01	Number of possible relevant publications (title relevant for at least one section) Table CA 9.4.2/06 ("yes")	82
Assessment "section" in Excel sheet KCA 9.3/01	Number of publications further assessed according to abstract for respective section (possible relevant literature for this section) Table CA 9.4.2/06 ("yes")	82
	Number of publications excluded according to irrelevance of abstract for respective section (excluded literature for this section) Table CA 9.4.2/05	82

	Number of publications further assessed according to full-text for respective section (possible relevant literature for this section) Table CA 9.4.2/04 + Table CA 9.4.2/02	0
	Number of publications excluded according to irrelevance of full-text for respective section (excluded literature for this section) Table CA 9.4.2/04	0
	Number of publications not excluded for relevance after detailed assessment (i.e. relevant publications) (included literature) Table CA 9.4.2/02 (Table CA 9.4.2/03)	0

The results of the detailed assessment are shown in KCA 9.3/01 (Excel sheet) and in Tables CA 9.4.2/02 to CA 9.4.2/06.

Relevant literature:
No relevant literature according to abstract:
In Table CA 9.4.2/05: Report of studies relevant according to title but excluded after detailed assessment of abstract (C)

In Table CA 9.4.2/06 is presented the study selection process: publications include according to relevance of title for at least one section ("yes")

Table CA 9.4.2/05: Report of studies relevant according to title but excluded after detailed assessment of abstract

Author(s)	Year	Title	Source	Reason for not including in dossier
Battaglia, M.	2017	Assessment of a Registered Dietitian Administered Fermentable Oligosaccharide Disaccharide, Monosaccharide, and Polyol Elimination Diet Experience	Journal of the Academy of Nutrition and Dietetics	No relevance from toxicological point of view
Bouaziz, Fatma; Ben Romdhane, Molka; Boisset Helbert, Claire; Buon, Laurine; Bhiri, Fatma; Bardaa, Sana; Driss, Dorra; Koubaa, Mohamed; Fakhfakh, Akram; Sahnoun, Zouhair; Kallel, Fatma; Zghal, Najiba; Ellouz Chaabouni, Semia	2014	Healing efficiency of oligosaccharides generated from almond gum (Prunus amygdalus) on dermal wounds of adult rats	Journal of Tissue Viability 23(3):98-108.	Not interest concerning the toxicological data requirements for active substances per se
Bozkurt, M.; Bintas, E.; Kirkan, S.; Aksit, H.; Kucukyilmaz, K.; Erbas, G.; Cabuk, M.; Aksit, D.; Parin, U.; Ege, G.; Kocer, B.; Seyrek, K.; Tuzun, A. E.	2016	Comparative evaluation of dietary supplementation with mannan oligosaccharide and oregano essential oil in forced molted and fully fed laying hens between 82 and 106 weeks of age	Poult Sci 95 2576-2591	No relevance from toxicological point of view

Cao, Wenlei; Aghajanian, Haig K.; Haig-Ladewig, Lisa A.; Gerton, George L.	2008	Sorbitol can fuel mouse sperm motility and protein tyrosine phosphorylation via sorbitol dehydrogenase	Developmental Biology 80(1): 124–133	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view AND Structural non relevance from sorbitol (single sugar alcohol in comparison to heptamaloxyloglucan being non-digestible oligosaccharide)
Cardoso, F. S.; Araujo-Lima, C. F.; Aiub, C. A.; Felzenszwalb, I.	2016	Exposure to sorbitol during lactation causes metabolic alterations and genotoxic effects in rat offspring	Toxicol Lett 260:36-45.	Structural non relevance from sorbitol (single sugar alcohol in comparison to heptamaloxyloglucan being non-digestible oligosaccharide)
Chen, B. R.; Du, L. J.; He, H. Q.; Kim, J. J.; Zhao, Y.; Zhang, Y. W.; Luo, L.; Dai, N.	2017	Fructo-oligosaccharide intensifies visceral hypersensitivity and intestinal inflammation in a stress-induced irritable bowel syndrome mouse model	World J Gastroenterol 23(47):8321-8333	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Chen, H. L.; Wang, C. H.; Kuo, Y. W.; Tsai, C. H.	2011	Antioxidative and hepatoprotective effects of fructo-oligosaccharide in d-galactose-treated Balb/cJ mice	Br J Nutr 105(6):805-9	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view

Chen, Hua; Li-jun, Liu; Jian-jun, Zhu; Bo, Xu; Rui, Li	2010	Chemical composition analysis of soybean oligosaccharides and its effect on ATPase activities in hyperlipidemic rats	International Journal of Biological Macromolecules 46(2):229-31	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view
Chen, Hua; Liu, Li-jun; Zhu, Jian-jun; Xu, Bo; Li, Rui	2010	Effect of soybean oligosaccharides on blood lipid, glucose levels and antioxidant enzymes activity in high fat rats	Food Chemistry Vol 119 (4) Pages 1633-1636	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view AND Extracted from soybean
Chiu, Chen-Yuan; Hsu, Wei-Hsiang; Liu, Hui-Kang; Liu, Shing-Hwa; Lin, Yun-Lian	2018	Prepared Rehmanniae Radix oligosaccharide regulates postprandial and diabetic blood glucose in mice	Journal of Functional Foods Vol 41 Pages 210-215	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Christensen, E. G.; Licht, T. R.; Leser, T. D.; Bahl, M. I.	2014	Dietary xylo-oligosaccharide stimulates intestinal bifidobacteria and lactobacilli but has limited effect on intestinal integrity in rats	BMC Res Notes 7:660	No relevance from toxicological point of view
Cloetens, Lieselotte; Swennen, Katrien; De Preter, Vicky; Broekaert, Willem F.; Courtin, Christophe M.; Delcour, Jan A.; Rutgeerts, Paul; Verbeke, Kristin	2008	Effect of arabinoxylo-oligosaccharides on proximal gastrointestinal motility and digestion in healthy volunteers	e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism Vol 3(5) pages e220-e225	No relevance from toxicological point of view

Costa, G. T.; Abreu, G. C.; Guimaraes, A. B.; Vasconcelos, P. R.; Guimaraes, S. B.	2015	Fructo-oligosaccharide effects on serum cholesterol levels. An overview	Acta Cir Bras Vol. 30(5) Pages 366-70	Not interest concerning the toxicological data requirements for active substances per se
Costa, G. T.; Guimaraes, S. B.; Sampaio, H. A.	2012	Fructo-oligosaccharide effects on blood glucose: an overview	Acta Cir Bras Vol 27(3) Pages 279-82	Not interest concerning the toxicological data requirements for active substances per se
Cuesta Triana, F. M.; Villazon Gonzalez, F.; Sanz Paris, A.; Ramos-Clemente Romero, J. I.; Palacio Abizanda, J. E.; Sanz Barriuso, R.	2017	The effects of a high-protein, high-calorie, fiber- and fructo-oligosaccharide-enriched enteral formula on nutritional status, bowel habits and tolerance: Safety and Effectiveness of Enteral Nutrition in elderly Spanish patients (SENS Study)	Nutr Hosp Vol 34(5) Pages 1267-1274	Not interest concerning the toxicological data requirements for active substances per se
de Godoy, M. R.; Knapp, B. K.; Bauer, L. L.; Swanson, K. S.; Fahey, G. C., Jr.	2013	Blending of soluble corn fiber with pullulan, sorbitol, or fructose attenuates glycemic and insulinemic responses in the dog and affects hydrolytic digestion in vitro	J Anim Sci Vol 91(8) Pages 3796-806	No relevance from toxicological point of view
de Kivit, S.; Saeland, E.; Kraneveld, A. D.; van Kooyk, Y.; Garssen, J.; Willemsen, L. E. M.	2011	Dietary non-digestible oligosaccharide-induced galectin-9 correlates with protection against allergic symptoms	European Journal of Pharmacology Vol 668, suppl.1, page e14	No relevance from toxicological point of view
Duan, X. D.; Chen, D. W.; Zheng, P.; Tian, G.; Wang, J. P.; Mao, X. B.; Yu, J.; He, J.; Li, B.; Huang, Z. Q.; Ao, Z. G.; Yu, B.	2016	Effects of dietary mannan oligosaccharide supplementation on performance and immune response of sows and their offspring	Animal Feed Science and Technology 218, C, 17-25	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view AND Extracted from mushrooms

Félix, A. P.; Rivera, N. L. M.; Sabchuk, T. T.; Lima, D. C.; Oliveira, S. G.; Maiorka, A.	2013	The effect of soy oligosaccharide extraction on diet digestibility, faecal characteristics, and intestinal gas production in dogs	Animal feed science and technology Vol 184 Pages 86-93	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view AND Extracted from soy
Forsatkar, Mohammad Navid; Nematollahi, Mohammad Ali; Rafiee, Gholamreza; Farahmand, Hamid; Martínez-Rodríguez, Gonzalo	2017	Effects of prebiotic mannan oligosaccharide on the growth, survival, and anxiety-like behaviors of zebrafish (Danio rerio)	Journal of applied aquaculture Vol 29(2) Pages 183-196	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND Extracted from mushrooms
Fraile, B.; Alcover, J.; Royuela, M.; Rodriguez, D.; Chaves, C.; Palacios, R.; Pique, N.	2017	Xyloglucan, hibiscus and propolis for the prevention of urinary tract infections: results of in vitro studies	Future Microbiol 2:721-731	Not interest concerning the toxicological data requirements for active substances per se
Frias, Rafael; Steiner, Jorg M.; Williams, David A.; Sankari, Satu; Westermarck, Elias	2012	Urinary recovery of orally administered chromium 51–labeled EDTA, lactulose, rhamnose, d-xylose, 3-O-methyl-d-glucose, and sucrose in healthy adult male Beagles	American journal of veterinary research 73(5) 654-8.	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Fujiwara, Reiko; Takemura, Naoki; Watanabe, Jun; Sonoyama, Kei	2010	Maternal consumption of fructo-oligosaccharide diminishes the severity of skin inflammation in offspring of NC/Nga mice	British journal of nutrition Vol 103(4), pages 530-538	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se

Garssen, J.; Hogenkamp, A.; van Vlies, N.; Thijssen, S.; Dingjan, G. M.; Knipping, K.; Knippels, L.	2012	Effects Of Short-chain Galacto- And Long-chain Fructo-oligosaccharides On Systemic And Local Immune Status During Pregnancy	Journal of Allergy and Clinical Immunology	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view
Gelsinger, S. L.; Pino, F.; Jones, C. M.; Gehman, A. M.; Heinrichs, A. J.	2016	Effects of a dietary organic mineral program including mannan oligosaccharides for pregnant cattle and their calves on calf health and performance	The Professional Animal Scientist Vol 32, Issue 2 Pages 205-213	No relevance from toxicological point of view
Ghasemian, M.; Jahanian, R.	2016	Dietary mannan-oligosaccharides supplementation could affect performance, immunocompetence, serum lipid metabolites, intestinal bacterial populations, and ileal nutrient digestibility in aged laying hens	Animal Feed Science and Technology	No relevance from toxicological point of view
Giannenas, I.; Doukas, D.; Karamoutsios, A.; Tzora, A.; Bonos, E.; Skoufos, I.; Tsinas, A.; Christaki, E.; Tontis, D.; Florou-Paneri, P.	2016	Effects of Enterococcus faecium, mannan oligosaccharide, benzoic acid and their mixture on growth performance, intestinal microbiota, intestinal morphology and blood lymphocyte subpopulations of fattening pigs	Animal Feed Science and Technology Vol 220 Pages 159-167	No relevance from toxicological point of view
Gnessi, L.; Bacarea, V.; Marusteri, M.; Pique, N.	2015	Xyloglucan for the treatment of acute diarrhea: results of a randomized, controlled, open-label, parallel group, multicentre, national clinical trial	BMC Gastroenterol	No relevance from toxicological point of view (medical device)
Gómez-Fernández, José; Gómez-Izquierdo, Emilio; Tomás, Cristina; Mocé, Eva; de Mercado, Eduardo	2012	Effect of different monosaccharides and disaccharides on boar sperm quality after cryopreservation	Animal Reproduction Science	No relevance from toxicological point of view

Gomez-Verduzco, G.; Cortes-Cuevas, A.; Lopez-Coello, C.; Avila-Gonzalez, E.; Nava, G. M.	2009	Dietary supplementation of mannan-oligosaccharide enhances neonatal immune responses in chickens during natural exposure to Eimeria spp	Acta Vet Scand Vol 51, Pages 11	No relevance from toxicological point of view
Greenhill, C.	2012	Pediatrics: An oligosaccharide can prevent necrotizing enterocolitis in rats	Nat Rev Gastroenterol Hepatol	Not interest concerning the toxicological data requirements for active substances per se
Hadri, Zouheyr; Rasoamanana, Rojo; Fromentin, Gilles; Azzout-Marniche, Dalila; Even, Patrick C.; Gaudichon, Claire; Darcel, Nicolas; Bouras, Abdelkader Dilmi; Tomé, Daniel; Chaumontet, Catherine	2017	Fructo-oligosaccharides reduce energy intake but do not affect adiposity in rats fed a low-fat diet but increase energy intake and reduce fat mass in rats fed a high-fat diet	Physiology & Behavior	Not interest concerning the toxicological data requirements for active substances per se
Heinrichs, A. J.; Heinrichs, B. S.; Jones, C. M.	2013	Fecal and saliva IgA secretion when feeding a concentrated mannan oligosaccharide to neonatal dairy calves	The Professional Animal Scientist	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Hill, T. M.; Bateman, H. G.; Aldrich, J. M.; Schlotterbeck, R. L.	2008	Oligosaccharides for Dairy Calves	The Professional Animal Scientist	Not interest concerning the toxicological data requirements for active substances per se
Hodoniczky, Jason; Morris, Carol A.; Rae, Anne L.	2012	Oral and intestinal digestion of oligosaccharides as potential sweeteners: A systematic evaluation	Food Chemistry	Not interest concerning the toxicological data requirements for active substances per se
Hogenkamp, A.; de Kivit, S.; Knippels, L. M. J.; Garssen, J.; van Esch, B. C. A. M.	2012	Desensization Of Hen'S Egg Sensitized Mice As A Result Of Dietary (therapeutic) Intervention With A Specific Mixture Of Non-digestible Oligosaccharides	Journal of Allergy and Clinical Immunology	No relevance from toxicological point of view

Hogenkamp, A.; Thijssen, S.; van Vlies, N.; Knippels, L. M. J.; Garssen, J.	2015	Maternal dietary supplementation with specific non-digestible oligosaccharides during pregnancy in mice leads to reduced allergic asthma symptoms in their offspring	Journal of Reproductive Immunology	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Hogenkamp, A.; van Esch, E. C. A. M.; Knippels, L. M. J.; Garssen, J.	2014	Supplementation of ovalbumin-sensitized mice with specific non-digestible oligosaccharides during pregnancy or lactation leads to desensitization in their offspring	PharmaNutrition	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND Extracted from milk
Hogenkamp, A.; van Vlies, N.; Thijssen, S.; Dingjan, G.; Knipping, K.; Garssen, J.; Knippels, L.	2012	Effects of short-chain galacto- and long-chain fructo-oligosaccharides on systemic and local immune status during pregnancy	Journal of Reproductive Immunology	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view
Ivakhnenko, Olena S.; Nyankovskyy, Serhiy L.	2013	Effect of the specific infant formula mixture of oligosaccharides on local immunity and development of allergic and infectious disease in young children: randomized study	Pediatria Polska	No relevance from toxicological point of view
Jiao, L. F.; Song, Z. H.; Ke, Y. L.; Xiao, K.; Hu, C. H.; Shi, B.	2014	Cello-oligosaccharide influences intestinal microflora, mucosal architecture and nutrient transport in weaned pigs	Animal Feed Science and Technology	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view AND Extracted from cellulose

Juśkiewicz, Jerzy; Milala, Joanna; Jurgoński, Adam; Król, Bogusław; Zduńczyk, Zenon	2011	Consumption of polyphenol concentrate with dietary fructo-oligosaccharides enhances cecal metabolism of quercetin glycosides in rats	Nutrition	No relevance from toxicological point of view
Kang, Min-Gyung; Lee, Hee Jae; Cho, Jae-Young; Kim, Kanghwa; Yang, Soo Jin; Kim, Doman	2016	Anti-inflammatory effects of sucrose-derived oligosaccharides produced by a constitutive mutant L. mesenteroides B-512FMCM dextransucrase in high fat diet-fed mice	Biochemical and Biophysical Research Communications	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view
Li, Tuoping; Li, Suhong; Du, Lijuan; Wang, Na; Guo, Mei; Zhang, Junwei; Yan, Fenwen; Zhang, Huili	2010	Effects of haw pectic oligosaccharide on lipid metabolism and oxidative stress in experimental hyperlipidemia mice induced by high-fat diet	Food chemistry	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Li, Wenfeng; Zhang, Ruijun; Guo, Jianjun; Shao, Hongjun; Yang, Xingbin	2016	Protective effect of R. glutinosa oligosaccharides against high l-carnitine diet-induced endothelial dysfunction and hepatic injury in mice	International Journal of Biological Macromolecules	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view
Lim, E.; Lim, J. Y.; Shin, J. H.; Seok, P. R.; Jung, S.; Yoo, S. H.; Kim, Y.	2015	D-Xylose suppresses adipogenesis and regulates lipid metabolism genes in high-fat diet-induced obese mice	Nutr Res Vol 35, Issue 7, Pages 626-36	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se

Lin, T.; Zhang, J. Y.; Diao, Y. F.; Kang, J. W.; Jin, D. I.	2015	Effects of sorbitol on porcine oocyte maturation and embryo development in vitro	Zygote	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Linneen, S. K.; Mourer, G. L.; Sparks, J. D.; Jennings, J. S.; Goad, C. L.; Lalman, D. L.	2014	Effects of mannan oligosaccharide on beef-cow performance and passive immunity transfer to calves	The Professional Animal Scientist Vol 30, Issue 3, Pages 311-317	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Mahajan, Hitendra S.; Gundare, Sadanand A.	2014	Preparation, characterization and pulmonary pharmacokinetics of xyloglucan microspheres as dry powder inhalation	Carbohydrate polymers	Not interest concerning the toxicological data requirements for active substances per se
Mirzapour, ; x, ; Rezaee, S. S.; Farhangi, M.; Rafiee, G.	2017	Combined effects of dietary mannan‐ and fructo‐oligosaccharide on growth indices, body composition, intestinal bacterial flora and digestive enzymes activity of regal peacock (Aulonocara stuartgranti)	Aquaculture nutrition	No relevance from toxicological point of view
Niele, N.; Westerbeek, E. A. M.; van Zwol, A.; Lafeber, H. N.; van Elburg, R. M.	2011	Effect of enteral supplementation of neutral and acidic oligosaccharides in preterm infants on allergic diseases during the first year of life	European Journal of Pharmacology	No relevance from toxicological point of view
Niethamer, Terren K.; Yardeni, Tal; Leoyklang, Petcharat; Ciccone, Carla; Astiz-Martinez, Adrian; Jacobs, Katherine; Dorward, Heidi M.; Zerfas, Patricia M.; Gahl, William A.; Huizing, Marjan	2012	Oral monosaccharide therapies to reverse renal and muscle hyposialylation in a mouse model of GNE myopathy	Molecular genetics and metabolism	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se

Nobre, Clarisse; Cerqueira, Miguel Ângelo; Rodrigues, Lígia Raquel; Vicente, António Augusto; Teixeira, José António	2015	Chapter 19 - Production and Extraction of Polysaccharides and Oligosaccharides and Their Use as New Food Additives	Elsevier	No relevant information from toxicological point of view
Nochta, I.; Tuboly, T.; Halas, V.; Babinszky, L.	2009	Effect of different levels of mannan-oligosaccharide supplementation on some immunological variables in weaned piglets	Journal of animal physiology and animal nutrition Vol 93, Issue 4, Pages 496-504	No relevance from toxicological point of view
Nochta, I.; Halas, V.; Tossenberger, J.; Babinszky, L.	2010	Effect of different levels of mannan‐oligosaccharide supplementation on the apparent ileal digestibility of nutrients, N‐balance and growth performance of weaned piglets	Journal of animal physiology and animal nutrition Vol 94, Issue 6, Pages 747-756	No relevance from toxicological point of view
Noss, I.; Doekes, G.; Thorne, P. S.; Heederik, D. J.; Wouters, I. M.	2013	Comparison of the potency of a variety of beta-glucans to induce cytokine production in human whole blood	Innate Immun	No relevance from toxicological point of view
Panknin, Hardy-Thorsten; Trautmann, Matthias	2014	[Prebiotic oligosaccharides: regular administration in premature infants improves intestinal flora]	Kinderkrankenschwester : Organ der Sektion Kinderkrankenpflege	No relevance from toxicological point of view
Petersen, A.; Bergstrom, A.; Andersen, J. B.; Hansen, M.; Lahtinen, S. J.; Wilcks, A.; Licht, T. R.	2010	Analysis of the intestinal microbiota of oligosaccharide fed mice exhibiting reduced resistance to Salmonella infection	Benef Microbes	No relevance from toxicological point of view
Plesea Condratovici, C.; Bacarea, V.; Pique, N.	2016	Xyloglucan for the Treatment of Acute Gastroenteritis in Children: Results of a Randomized, Controlled, Clinical Trial	Gastroenterol Res Pract	No relevance from toxicological point of view (medical device)

Smith, Daniel L., Jr.; Nagy, Tim R.; Wilson, Landon S.; Dong, Shengli; Barnes, Stephen; Allison, David B.	2010	The Effect of Mannan Oligosaccharide Supplementation on Body Weight Gain and Fat Accrual in C57Bl/6J Mice	Obesity	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view AND Extracted from mushrooms
Soh, Jian Yi; Huang, Chiung-Hui; Chiang, Wen Chin; Llanora, Genevieve; Lee, Alison Joanne; Loh, Wenyin; Lin Chin, Cherlyn Yue; Jia Tay, Victoria Yu; Chan, Yiong Huak; Delsing, Dianne; Lee, Bee-Wah	2015	Allergy to Galacto-Oligosaccharides in an Atopic Population in Singapore	Journal of Allergy and Clinical Immunology	Not relevant sinxe its a milk extract presented as syrup and powder forms
Sparkman, O. David; Penton, Zelda E.; Kitson, Fulton G.	2011	Chapter 35 - Sugars (Monosaccharides)	Academic Press Pages 407-410	No relevance from toxicological point of view
Stick, Robert V.; Williams, Spencer J.	2009	Chapter 6 - Monosaccharide Metabolism	Elsevier	No relevance from toxicological point of view
Stick, Robert V.; Williams, Spencer J.	2009	Chapter 9 - Disaccharides, Oligosaccharides and Polysaccharides	Elsevier Pages 321-341	No relevance from toxicological point of view

Szklany, K.; De Theije, C. G. M.; De Waard, C.; Van Staveren, N. G.; Van Wageningen, T. A.; Wu, J.; Verdouw, M.; Van Limpt, K.; Wopereis, H.; Groenink, L.; Oozeer, R.; Garssen, J.; Knippels, L. M. J.; Kraneveld, A. D.	2016	P.1.c.008 - Effect of early life supplementation of non-digestible oligosaccharides on brain development and behaviour in healthy mice	European Neuropsychopharmacology	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Tusi, Solaleh Khoramian; Khalaj, Leila; Ashabi, Ghorbangol; Kiaei, Mahmoud; Khodagholi, Fariba	2011	Alginate oligosaccharide protects against endoplasmic reticulum- and mitochondrial-mediated apoptotic cell death and oxidative stress	Biomaterials	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view
US-EPA	2014	D-glucopyranose, oligomeric, decyl octyl glycosides; exemption from the requirement of a tolerance	Focus on Surfactants	No relevance from toxicological point of view
Valpotic, H.; Zura Zaja, I.; Samardzija, M.; Habrun, B.; Ostovic, M.; Duricic, D.; Macesic, N.; Mikulec, Z.; Kocila, P.; Sobiech, P.; Valpotic, I.; Vince, S.	2018	Dietary supplementation with mannan oligosaccharide and clinoptilolite modulates innate and adaptive immune parameters of weaned pigs	Pol J Vet Sci	No relevance from toxicological point of view

van Vlies, N.; Hogenkamp, A.; Thijssen, S.; Dingjan, G. M.; Knipping, K.; Garssen, J.; Knippels, L. M. J.	2012	Effects of short-chain galacto- and long-chain fructo-oligosaccharides on systemic and local immune status during pregnancy	Journal of Reproductive Immunology 94(2):161-8.	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view
Vanis, Lora; Hausken, Trygve; Gentilcore, Diana; Rigda, Rachael S.; Rayner, Christopher K.; Feinle-Bisset, Christine; Horowitz, Michael; Jones, Karen L.	2011	Comparative effects of glucose and xylose on blood pressure, gastric emptying and incretin hormones in healthy older subjects	British journal of nutrition 105(11):1644-51.	No relevance from toxicological point of view
Wakao, Norimitsu; Imagama, Shiro; Zhang, Haoquian; Tauchi, Ryoji; Muramoto, Akio; Natori, Takamitsu; Takeshita, Sawako; Ishiguro, Naoki; Matsuyama, Yukihiro; Kadomatsu, Kenji	2011	Hyaluronan oligosaccharides promote functional recovery after spinal cord injury in rats	Neuroscience Letters	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Wan, Jin; Zhang, Jiao; Chen, Daiwen; Yu, Bing; He, Jun	2017	Effects of alginate oligosaccharide on the growth performance, antioxidant capacity and intestinal digestion-absorption function in weaned pigs	Animal Feed Science and Technology	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view

Wang, Jing; Sun, Baoguo; Cao, Yanping; Tian, Yuan	2009	Protection of wheat bran feruloyl oligosaccharides against free radical-induced oxidative damage in normal human erythrocytes	Food and Chemical Toxicology	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view
Wang, Jing; Sun, Baoguo; Cao, Yanping; Wang, Chengtao	2010	Wheat bran feruloyl oligosaccharides enhance the antioxidant activity of rat plasma	Food Chemistry	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view AND Extracted from wheat
Wang, Yan; Guo, Qingbin; Douglas Goff, H.; LaPointe, Gisèle	2018	Oligosaccharides: Structure, Function and Application	Elsevier Title: Reference Module in Food Science 31	Not interest concerning the toxicological data requirements for active substances per se
Wang, Yu; Zeng, Tao; Wang, Shu-e; Wang, Wei; Wang, Qian; Yu, Hong-Xia	2010	Fructo-oligosaccharides enhance the mineral absorption and counteract the adverse effects of phytic acid in mice	Nutrition	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Watanabe, M.; Kokubo, Y.; Higashiyama, A.; Ono, Y.; Miyamoto, Y.; Okamura, T.	2011	Serum 1,5-anhydro-d-glucitol levels predict first-ever cardiovascular disease: An 11-year population-based Cohort study in Japan, the Suita study	Atherosclerosis	Not interest concerning the toxicological data requirements for active substances per se

Yeh, S. L.; Wu, T. C.; Chan, S. T.; Hong, M. J.; Chen, H. L.	2014	Fructo-oligosaccharide attenuates the production of pro-inflammatory cytokines and the activation of JNK/Jun pathway in the lungs of D-galactose-treated Balb/cJ mice	Eur J Nutr	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se
Yen, C. H.; Wang, C. H.; Wu, W. T.; Chen, H. L.	2017	Fructo-oligosaccharide improved brain beta-amyloid, beta-secretase, cognitive function, and plasma antioxidant levels in D-galactose-treated Balb/cJ mice	Nutr Neurosci	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND Test items non-relevant
Zabotina, O. A.	2012	Xyloglucan and its biosynthesis	Front Plant Sci Vol 3, Pages 134	Not interest concerning the toxicological data requirements for active substances per se
Zhang, Ruxue; Zhou, Jun; Li, Maoxing; Ma, Haigang; Qiu, Jianguo; Luo, Xiaohong; Jia, Zhengping	2014	Ameliorating effect and potential mechanism of Rehmannia glutinosa oligosaccharides on the impaired glucose metabolism in chronic stress rats fed with high-fat diet	Phytomedicine	Highly specific mechanistic information which is not requested by the toxicological data requirements for active substances per se AND No relevance from toxicological point of view
Zhou, Xiao-Li; Kong, Xiang-Feng; Lian, Guo-Qi; Blachier, Francois; Geng, Mei-Mei; Yin, Yu-Long	2014	Dietary supplementation with soybean oligosaccharides increases short-chain fatty acids but decreases protein-derived catabolites in the intestinal luminal content of weaned Huanjiang mini-piglets	Nutrition Research	No relevance from toxicological point of view

Table CA 9.4.2/06: Study selection process: publications inclued according to relevance of title for at least one section ("yes")

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
	2014	D-glucopyranose, oligomeric, decyl octyl glycosides; exemption from the requirement of a tolerance	Focus on Surfactants 2014 5	yes	yes	-	-
	2016	Fructose and sorbitol	Elsevier 460-461	-	-	yes	yes
Agbogbo, Frank K.; Coward-Kelly, Guillermo	2008	Cellulosic ethanol production using the naturally occurring xylose-fermenting yeast, Pichia stipitis	Biotechnology letters 30 1515-1524	-	-	-	yes
Aguayo, María Francisca; Ampuero, Diego; Mandujano, Patricio; Parada, Roberto; Muñoz, Rodrigo; Gallart, Marta; Altabella, Teresa; Cabrera, Ricardo; Stange, Claudia; Handford, Michael	2013	Sorbitol dehydrogenase is a cytosolic protein required for sorbitol metabolism in Arabidopsis thaliana	Plant science 205-206 63-75	-	yes	-	-
Ait Lahmidi, N.; Courty, P. E.; Brule, D.; Chatagnier, O.; Arnould, C.; Doidy, J.; Berta, G.; Lingua, G.; Wipf, D.; Bonneau, L.	2016	Sugar exchanges in arbuscular mycorrhiza: RiMST5 and RiMST6, two novel Rhizophagus irregularis monosaccharide transporters, are involved in both sugar uptake from the soil and from the plant partner	Plant Physiol Biochem 107 354-363	-	-	yes	-
Akter, Mst Nahid; Sutriana, Amalia; Talpur, Allah Dad; Hashim, Roshada	2016	Dietary supplementation with mannan oligosaccharide influences growth, digestive enzymes, gut morphology, and microbiota in juvenile striped catfish, Pangasianodon hypophthalmus	Aquaculture international 24 127-144	-	-	-	yes
Ali, Syed Raffic; Ambasankar, Kondusamy; Praveena, Ezhil; Nandakumar, Sambasivam; Syamadayal, Jagabatula	2017	Effect of dietary mannan oligosaccharide on growth, body composition, haematology and biochemical parameters of Asian seabass (Lates calcarifer)	Aquaculture research 48 899-908	-	-	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Andres-Barranco, S.; Vico, J. P.; Grillo, M. J.; Mainar-Jaime, R. C.	2015	Reduction of subclinical Salmonella infection in fattening pigs after dietary supplementation with a ss-galactomannan oligosaccharide	J Appl Microbiol 118 284-94	-	-	-	yes
Andrews, Simi Rose; Sahu, Narottam P.; Pal, Asim K.; Kumar, Shivendra	2009	Haematological modulation and growth of Labeo rohita fingerlings: effect of dietary mannan oligosaccharide, yeast extract, protein hydrolysate and chlorella	Aquaculture research 41 61-69	-	-	-	yes
Aprea, E.; Charles, M.; Endrizzi, I.; Laura Corollaro, M.; Betta, E.; Biasioli, F.; Gasperi, F.	2017	Sweet taste in apple: the role of sorbitol, individual sugars, organic acids and volatile compounds	Sci Rep 7 44950	-	yes	-	-
Attia, Mohamed; Stepper, Judith; Davies, Gideon J.; Brumer, Harry	2016	Functional and structural characterization of a potent GH74 endo‐xyloglucanase from the soil saprophyte Cellvibrio japonicus unravels the first step of xyloglucan degradation	FEBS journal 283 1701-1719	-	-	yes	-
Balthazar, C. F.; Silva, H. L. A.; Vieira, A. H.; Neto, R. P. C.; Cappato, L. P.; Coimbra, P. T.; Moraes, J.; Andrade, M. M.; Calado, V. M. A.; Granato, D.; Freitas, M. Q.; Tavares, M. I. B.; Raices, R. S. L.; Silva, M. C.; Cruz, A. G.	2017	Assessing the effects of different prebiotic dietary oligosaccharides in sheep milk ice cream	Food Research International 91 38-46	-	yes	-	-
Basu, Santanu; Shivhare, U. S.	2013	Rheological, Textural, Microstructural, and Sensory Properties of Sorbitol-Substituted Mango Jam	Food and bioprocess technology 6 1401-1413	-	yes	-	-
Basu, Santanu; Shivhare, U. S.; Singh, T. V.; Beniwal, V. S.	2011	Rheological, textural and spectral characteristics of sorbitol substituted mango jam	Journal of food engineering 105 503-512	-	yes	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Battaglia, M.	2017	Assessment of a Registered Dietitian Administered Fermentable Oligosaccharide Disaccharide, Monosaccharide, and Polyol Elimination Diet Experience	Journal of the Academy of Nutrition and Dietetics 117 A17	yes	yes	-	yes
Bonos, Eleftherios; Christaki, Efterpi; Abrahim, Amin; Soultos, Nikolaos; Florou-Paneri, Panagiota	2011	The influence of mannan oligosaccharides, acidifiers and their combination on caecal microflora of Japanese quail (Coturnix japonica)	Anaerobe 17 436-439	-	-	-	yes
Bouaziz, Fatma; Ben Romdhane, Molka; Boisset Helbert, Claire; Buon, Laurine; Bhiri, Fatma; Bardaa, Sana; Driss, Dorra; Koubaa, Mohamed; Fakhfakh, Akram; Sahnoun, Zouhair; Kallel, Fatma; Zghal, Najiba; Ellouz Chaabouni, Semia	2014	Healing efficiency of oligosaccharides generated from almond gum (Prunus amygdalus) on dermal wounds of adult rats	Journal of Tissue Viability 23 98-108	yes	-	-	-
Bouaziz, Fatma; Helbert, Claire Boisset; Romdhane, Molka Ben; Koubaa, Mohamed; Bhiri, Fatma; Kallel, Fatma; Chaari, Fatma; Driss, Dorra; Buon, Laurine; Chaabouni, Semia Ellouz	2015	Structural data and biological properties of almond gum oligosaccharide: Application to beef meat preservation	International journal of biological macromolecules 72 472-479	-	yes	-	-
Bozkurt, M.; Bintas, E.; Kirkan, S.; Aksit, H.; Kucukyilmaz, K.; Erbas, G.; Cabuk, M.; Aksit, D.; Parin, U.; Ege, G.; Kocer, B.; Seyrek, K.; Tuzun, A. E.	2016	Comparative evaluation of dietary supplementation with mannan oligosaccharide and oregano essential oil in forced molted and fully fed laying hens between 82 and 106 weeks of age	Poult Sci 95 2576-2591	yes	yes	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Bozkurt, M.; Küçükyilmaz, K.; Çatli, A. U.; Çinar, M.	2008	Growth Performance and Slaughter Characteristics of Broiler Chickens Fed with Antibiotic, Mannan Oligosaccharide and Dextran Oligosaccharide Supplemented Diets	International journal of poultry science 7 969-977	-	yes	-	yes
Bozkurt, M.; Kucukyilmaz, K.; Catli, A. U.; Cinar, M.; Bintas, E.; Coven, F.	2012	Performance, egg quality, and immune response of laying hens fed diets supplemented with mannan-oligosaccharide or an essential oil mixture under moderate and hot environmental conditions	Poult Sci 91 1379-86	-	yes	-	yes
Buckeridge, M. S.	2010	Seed cell wall storage polysaccharides: models to understand cell wall biosynthesis and degradation	Plant Physiol 154 1017-23	-	-	yes	-
Cabrera, J. C.; Wégria, G.; Onderwater, R. C. A.; González, G.; Nápoles, M. C.; Falcón-Rodríguez, A. B.; Costales, D.; Rogers, H. J.; Diosdado, E.; González, S.; Cabrera, G.; González, L.; Wattiez, R.	2012	Practical use of oligosaccharins in agriculture	Acta horticulturae 195-212	-	-	-	yes
Cao, Wenlei; Aghajanian, Haig K.; Haig-Ladewig, Lisa A.; Gerton, George L.	2008	Sorbitol can fuel mouse sperm motility and protein tyrosine phosphorylation via sorbitol dehydrogenase	Developmental Biology 319 551-552	yes	-	-	-
Cardoso, F. S.; Araujo-Lima, C. F.; Aiub, C. A.; Felzenszwalb, I.	2016	Exposure to sorbitol during lactation causes metabolic alterations and genotoxic effects in rat offspring	Toxicol Lett 260 36-45	yes	-	-	-
Chen, B. R.; Du, L. J.; He, H. Q.; Kim, J. J.; Zhao, Y.; Zhang, Y. W.; Luo, L.; Dai, N.	2017	Fructo-oligosaccharide intensifies visceral hypersensitivity and intestinal inflammation in a stress-induced irritable bowel syndrome mouse model	World J Gastroenterol 23 8321-8333	yes	-	-	-
Chen, H. L.; Wang, C. H.; Kuo, Y. W.; Tsai, C. H.	2011	Antioxidative and hepatoprotective effects of fructo-oligosaccharide in d-galactose-treated Balb/cJ mice	Br J Nutr 105 805-9	yes	-	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Chen, Hua; Li-jun, Liu; Jian-jun, Zhu; Bo, Xu; Rui, Li	2010	Chemical composition analysis of soybean oligosaccharides and its effect on ATPase activities in hyperlipidemic rats	International Journal of Biological Macromolecules 46 229-231	yes	-	-	-
Chen, Hua; Liu, Li-jun; Zhu, Jian-jun; Xu, Bo; Li, Rui	2010	Effect of soybean oligosaccharides on blood lipid, glucose levels and antioxidant enzymes activity in high fat rats	Food Chemistry 119 1633-1636	yes	-	-	-
Cheng, Jun; Song, Wenlu; Xia, Ao; Su, Huibo; Zhou, Junhu; Cen, Kefa	2012	Sequential generation of hydrogen and methane from xylose by two-stage anaerobic fermentation	International Journal of Hydrogen Energy 37 13323-13329	-	-	yes	-
Chiu, Chen-Yuan; Hsu, Wei-Hsiang; Liu, Hui-Kang; Liu, Shing-Hwa; Lin, Yun-Lian	2018	Prepared Rehmanniae Radix oligosaccharide regulates postprandial and diabetic blood glucose in mice	Journal of Functional Foods 41 210-215	yes	-	-	-
Christensen, E. G.; Licht, T. R.; Leser, T. D.; Bahl, M. I.	2014	Dietary xylo-oligosaccharide stimulates intestinal bifidobacteria and lactobacilli but has limited effect on intestinal integrity in rats	BMC Res Notes 7 660	yes	-	-	-
Cloetens, Lieselotte; Swennen, Katrien; De Preter, Vicky; Broekaert, Willem F.; Courtin, Christophe M.; Delcour, Jan A.; Rutgeerts, Paul; Verbeke, Kristin	2008	Effect of arabinoxylo-oligosaccharides on proximal gastrointestinal motility and digestion in healthy volunteers	e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism 3 e220-e225	yes	-	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Combo, Agnan Marie Michel; Aguedo, Mario; Quiévy, Nicolas; Danthine, Sabine; Goffin, Dorothée; Jacquet, Nicolas; Blecker, Christophe; Devaux, Jacques; Paquot, Michel	2013	Characterization of sugar beet pectic-derived oligosaccharides obtained by enzymatic hydrolysis	International Journal of Biological Macromolecules 52 148-156	-	-	yes	-
Constantin, Julian Gelman; Schneider, Matthias; Corti, Horacio R.	2016	Glass Transition Temperature of Saccharide Aqueous Solutions Estimated with the Free Volume/Percolation Model	Journal of physical chemistry 120 5047-5055	-	-	yes	-
Costa, G. T.; Abreu, G. C.; Guimaraes, A. B.; Vasconcelos, P. R.; Guimaraes, S. B.	2015	Fructo-oligosaccharide effects on serum cholesterol levels. An overview	Acta Cir Bras 30 366-70	yes	-	-	-
Costa, G. T.; Guimaraes, S. B.; Sampaio, H. A.	2012	Fructo-oligosaccharide effects on blood glucose: an overview	Acta Cir Bras 27 279-82	yes	-	-	-
Courtois, Josiane	2009	Oligosaccharides from land plants and algae: production and applications in therapeutics and biotechnology	Current Opinion in Microbiology 12 261-273	-	-	-	yes
Cuesta Triana, F. M.; Villazon Gonzalez, F.; Sanz Paris, A.; Ramos-Clemente Romero, J. I.; Palacio Abizanda, J. E.; Sanz Barriuso, R.	2017	The effects of a high-protein, high-calorie, fiber- and fructo-oligosaccharide-enriched enteral formula on nutritional status, bowel habits and tolerance: Safety and Effectiveness of Enteral Nutrition in elderly Spanish patients (SENS Study)	Nutr Hosp 34 1267-1274	yes	-	-	-
Daniels, Carly L.; Merrifield, Daniel L.; Boothroyd, Dominic P.; Davies, Simon J.; Factor, Jan R.; Arnold, Katie E.	2010	Effect of dietary Bacillus spp. and mannan oligosaccharides (MOS) on European lobster (Homarus gammarus L.) larvae growth performance, gut morphology and gut microbiota	Aquaculture 304 49-57	-	-	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
de Godoy, M. R.; Knapp, B. K.; Bauer, L. L.; Swanson, K. S.; Fahey, G. C., Jr.	2013	Blending of soluble corn fiber with pullulan, sorbitol, or fructose attenuates glycemic and insulinemic responses in the dog and affects hydrolytic digestion in vitro	J Anim Sci 91 3796-806	yes	-	-	-
de Kivit, S.; Saeland, E.; Kraneveld, A. D.; van Kooyk, Y.; Garssen, J.; Willemsen, L. E. M.	2011	Dietary non-digestible oligosaccharide-induced galectin-9 correlates with protection against allergic symptoms	European Journal of Pharmacology 668 e14	yes	-	-	-
Dimitroglou, Arkadios; Davies, Simon J.; Sweetman, John; Divanach, Pascal; Chatzifotis, Stavros	2010	Dietary supplementation of mannan oligosaccharide on white sea bream (Diplodus sargus L.) larvae: effects on development, gut morphology and salinity tolerance	Aquaculture research 41 e245-e251	-	-	-	yes
Dimitroglou, Arkadios; Merrifield, Daniel Lee; Spring, Peter; Sweetman, John; Moate, Roy; Davies, Simon John	2010	Effects of mannan oligosaccharide (MOS) supplementation on growth performance, feed utilisation, intestinal histology and gut microbiota of gilthead sea bream (Sparus aurata)	Aquaculture 300 182-188	-	-	-	yes
Do Huu, Hoang; Jones, Clive M.	2014	Effects of dietary mannan oligosaccharide supplementation on juvenile spiny lobster Panulirus homarus (Palinuridae)	Aquaculture 432 258-264	-	-	-	yes
Duan, X. D.; Chen, D. W.; Zheng, P.; Tian, G.; Wang, J. P.; Mao, X. B.; Yu, J.; He, J.; Li, B.; Huang, Z. Q.; Ao, Z. G.; Yu, B.	2016	Effects of dietary mannan oligosaccharide supplementation on performance and immune response of sows and their offspring	Animal Feed Science and Technology 218 17-25	yes	-	-	yes
Félix, A. P.; Rivera, N. L. M.; Sabchuk, T. T.; Lima, D. C.; Oliveira, S. G.; Maiorka, A.	2013	The effect of soy oligosaccharide extraction on diet digestibility, faecal characteristics, and intestinal gas production in dogs	Animal feed science and technology 184 86-93	yes	-	-	-
Fettke, Joerg; Malinova, Irina; Eckermann, Nora; Steup, Martin	2009	Cytosolic heteroglycans in photoautotrophic and in heterotrophic plant cells	Phytochemistry 70 696-702	-	-	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Filip, Miuța; Vlassa, Mihaela; Coman, Virginia; Halmagyi, Adela	2016	Simultaneous determination of glucose, fructose, sucrose and sorbitol in the leaf and fruit peel of different apple cultivars by the HPLC–RI optimized method	Food Chemistry 199 653-659	-	-	-	yes
Forgo, Peter; Kiss, Attila; Korózs, Marietta; Rapi, Sándor	2013	Thermal degradation and consequent fragmentation of widely applied oligosaccharides	Microchemical Journal 107 37-46	-	yes	yes	-
Forsatkar, Mohammad Navid; Nematollahi, Mohammad Ali; Rafiee, Gholamreza; Farahmand, Hamid; Martínez-Rodríguez, Gonzalo	2017	Effects of prebiotic mannan oligosaccharide on the growth, survival, and anxiety-like behaviors of zebrafish (Danio rerio)	Journal of applied aquaculture 29 183-196	yes	-	-	yes
Fraile, B.; Alcover, J.; Royuela, M.; Rodriguez, D.; Chaves, C.; Palacios, R.; Pique, N.	2017	Xyloglucan, hibiscus and propolis for the prevention of urinary tract infections: results of in vitro studies	Future Microbiol 12 721-731	yes	-	-	-
Frias, Rafael; Steiner, Jorg M.; Williams, David A.; Sankari, Satu; Westermarck, Elias	2012	Urinary recovery of orally administered chromium 51–labeled EDTA, lactulose, rhamnose, d-xylose, 3-O-methyl-d-glucose, and sucrose in healthy adult male Beagles	American journal of veterinary research 73 654-658	yes	-	-	-
Fujiwara, Reiko; Takemura, Naoki; Watanabe, Jun; Sonoyama, Kei	2010	Maternal consumption of fructo-oligosaccharide diminishes the severity of skin inflammation in offspring of NC/Nga mice	British journal of nutrition 103 530-538	yes	-	-	-
Galloway, Andrew F.; Pedersen, Martin J.; Merry, Beverley; Marcus, Susan E.; Blacker, Joshua; Benning, Liane G.; Field, Katie J.; Knox, J. Paul	2017	Xyloglucan is released by plants and promotes soil particle aggregation	new phytologist 217 1128-1136	-	-	yes	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Galvão, Alessandro Cazonatto; da Silva Robazza, Weber; Arce, Pedro Felipe; Mocelin, Adriane; Paludo, Ananda Regina	2017	Experimental study and thermodynamic modeling of xylitol and sorbitol solubility in mixtures of methanol and ethanol at different temperatures	Journal of Molecular Liquids 248 509-514	-	-	yes	-
Garssen, J.; Hogenkamp, A.; van Vlies, N.; Thijssen, S.; Dingjan, G. M.; Knipping, K.; Knippels, L.	2012	Effects Of Short-chain Galacto- And Long-chain Fructo-oligosaccharides On Systemic And Local Immune Status During Pregnancy	Journal of Allergy and Clinical Immunology 129 AB215	yes	-	-	-
Geigerová, Martina; Bunešová, Věra; Vlková, Eva; Salmonová, Hana; Rada, Vojtěch	2017	Selection of prebiotic oligosaccharides suitable for synbiotic use in calves	Animal Feed Science and Technology 229 73-78	-	-	-	yes
Gelsinger, S. L.; Pino, F.; Jones, C. M.; Gehman, A. M.; Heinrichs, A. J.	2016	Effects of a dietary organic mineral program including mannan oligosaccharides for pregnant cattle and their calves on calf health and performance	The Professional Animal Scientist 32 205-213	yes	-	-	yes
Geraylou, Zahra; Souffreau, Caroline; Rurangwa, Eugene; De Meester, Luc; Courtin, Christophe M.; Delcour, Jan A.; Buyse, Johan; Ollevier, Frans	2013	Effects of dietary arabinoxylan-oligosaccharides (AXOS) and endogenous probiotics on the growth performance, non-specific immunity and gut microbiota of juvenile Siberian sturgeon (Acipenser baerii)	Fish & Shellfish Immunology 35 766-775	-	-	-	yes
Geraylou, Zahra; Souffreau, Caroline; Rurangwa, Eugene; D'Hondt, Sofie; Callewaert, Lien; Courtin, Christophe M.; Delcour, Jan A.; Buyse, Johan; Ollevier, Frans	2012	Effects of arabinoxylan-oligosaccharides (AXOS) on juvenile Siberian sturgeon (Acipenser baerii) performance, immune responses and gastrointestinal microbial community	Fish & Shellfish Immunology 33 718-724	-	-	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Ghasemian, M.; Jahanian, R.	2016	Dietary mannan-oligosaccharides supplementation could affect performance, immunocompetence, serum lipid metabolites, intestinal bacterial populations, and ileal nutrient digestibility in aged laying hens	Animal Feed Science and Technology 213 81-89	yes	-	-	yes
Giannenas, I.; Doukas, D.; Karamoutsios, A.; Tzora, A.; Bonos, E.; Skoufos, I.; Tsinas, A.; Christaki, E.; Tontis, D.; Florou-Paneri, P.	2016	Effects of Enterococcus faecium, mannan oligosaccharide, benzoic acid and their mixture on growth performance, intestinal microbiota, intestinal morphology and blood lymphocyte subpopulations of fattening pigs	Animal Feed Science and Technology 220 159-167	yes	-	-	yes
Gnessi, L.; Bacarea, V.; Marusteri, M.; Pique, N.	2015	Xyloglucan for the treatment of acute diarrhea: results of a randomized, controlled, open-label, parallel group, multicentre, national clinical trial	BMC Gastroenterol 15 153	yes	-	-	-
Gómez, Belén; Gullón, Beatriz; Yáñez, Remedios; Schols, Henk; Alonso, José L.	2016	Prebiotic potential of pectins and pectic oligosaccharides derived from lemon peel wastes and sugar beet pulp: A comparative evaluation	Journal of Functional Foods 20 108-121	-	-	-	yes
Gómez-Fernández, José; Gómez-Izquierdo, Emilio; Tomás, Cristina; Mocé, Eva; de Mercado, Eduardo	2012	Effect of different monosaccharides and disaccharides on boar sperm quality after cryopreservation	Animal Reproduction Science 133 109-116	yes	-	-	-
Gomez-Verduzco, G.; Cortes-Cuevas, A.; Lopez-Coello, C.; Avila-Gonzalez, E.; Nava, G. M.	2009	Dietary supplementation of mannan-oligosaccharide enhances neonatal immune responses in chickens during natural exposure to Eimeria spp	Acta Vet Scand 51 11	yes	-	-	yes
Greenhill, C.	2012	Pediatrics: An oligosaccharide can prevent necrotizing enterocolitis in rats	Nat Rev Gastroenterol Hepatol 9 66	yes	-	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Gu, Hao; Lu, Man; Zhang, Zhiping; Xu, Jinjin; Cao, Wenhua; Miao, Minmin	2018	Metabolic process of raffinose family oligosaccharides during cold stress and recovery in cucumber leaves	Journal of Plant Physiology 224-225 112-120	-	-	-	yes
H. Najdegerami, Ebrahim; Tokmachi, Amir; Bakhshi, Farideh	2017	Evaluating the Effects of Dietary Prebiotic Mixture of Mannan Oligosaccharide and Poly‐ (Sb‐ (BHydroxybutyrate on the Growth Performance, Immunity, and Survival of Rainbow Trout, Oncorhynchus mykiss (Walbaum 1792), Fingerlings	Journal of the World Aquaculture Society 48 415-425	-	-	-	yes
Hadri, Zouheyr; Rasoamanana, Rojo; Fromentin, Gilles; Azzout-Marniche, Dalila; Even, Patrick C.; Gaudichon, Claire; Darcel, Nicolas; Bouras, Abdelkader Dilmi; Tomé, Daniel; Chaumontet, Catherine	2017	Fructo-oligosaccharides reduce energy intake but do not affect adiposity in rats fed a low-fat diet but increase energy intake and reduce fat mass in rats fed a high-fat diet	Physiology & Behavior 182 114-120	yes	-	-	-
Hajiaghapour, M.; Rezaeipour, V.	2018	Comparison of two herbal essential oils, probiotic, and mannan-oligosaccharides on egg production, hatchability, serum metabolites, intestinal morphology, and microbiota activity of quail breeders	Livestock Science 210 93-98	-	-	-	yes
Harcus, D.; Dignard, D.; Lepine, G.; Askew, C.; Raymond, M.; Whiteway, M.; Wu, C.	2013	Comparative xylose metabolism among the Ascomycetes C. albicans, S. stipitis and S. cerevisiae	PLoS One 8 e80733	-	-	-	yes
Heinrichs, A. J.; Heinrichs, B. S.; Jones, C. M.	2013	Fecal and saliva IgA secretion when feeding a concentrated mannan oligosaccharide to neonatal dairy calves	The Professional Animal Scientist 29 457-462	yes	-	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Hill, T. M.; Bateman, H. G.; Aldrich, J. M.; Schlotterbeck, R. L.	2008	Oligosaccharides for Dairy Calves	The Professional Animal Scientist 24 460-464	yes	yes	-	yes
Hodoniczky, Jason; Morris, Carol A.; Rae, Anne L.	2012	Oral and intestinal digestion of oligosaccharides as potential sweeteners: A systematic evaluation	Food Chemistry 132 1951-1958	yes	yes	-	-
Hogenkamp, A.; de Kivit, S.; Knippels, L. M. J.; Garssen, J.; van Esch, B. C. A. M.	2012	Desensization Of Hen'S Egg Sensitized Mice As A Result Of Dietary (therapeutic) Intervention With A Specific Mixture Of Non-digestible Oligosaccharides	Journal of Allergy and Clinical Immunology 129 AB175	yes	-	-	-
Hogenkamp, A.; Thijssen, S.; van Vlies, N.; Knippels, L. M. J.; Garssen, J.	2015	Maternal dietary supplementation with specific non-digestible oligosaccharides during pregnancy in mice leads to reduced allergic asthma symptoms in their offspring	Journal of Reproductive Immunology 111 26	yes	-	-	-
Hogenkamp, A.; van Esch, E. C. A. M.; Knippels, L. M. J.; Garssen, J.	2014	Supplementation of ovalbumin-sensitized mice with specific non-digestible oligosaccharides during pregnancy or lactation leads to desensitization in their offspring	PharmaNutrition 2 105-106	yes	-	-	-
Hogenkamp, A.; van Vlies, N.; Thijssen, S.; Dingjan, G.; Knipping, K.; Garssen, J.; Knippels, L.	2012	Effects of short-chain galacto- and long-chain fructo-oligosaccharides on systemic and local immune status during pregnancy	Journal of Reproductive Immunology 94 48	yes	-	-	-
Hoseinifar, S. H.; Soleimani, N.; Ringo, E.	2014	Effects of dietary fructo-oligosaccharide supplementation on the growth performance, haemato-immunological parameters, gut microbiota and stress resistance of common carp (Cyprinus carpio) fry	Br J Nutr 112 1296-302	-	-	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Hou, X.	2012	Anaerobic xylose fermentation by Spathaspora passalidarum	Applied microbiology and biotechnology 94 205-214	-	-	yes	-
Hsieh, Y. S.; Harris, P. J.	2012	Structures of xyloglucans in primary cell walls of gymnosperms, monilophytes (ferns sensu lato) and lycophytes	Phytochemistry 79 87-101	-	-	-	yes
Hsieh, Y. S.; Harris, P. J.	2009	Xyloglucans of monocotyledons have diverse structures	Mol Plant 2 943-65	-	-	-	yes
Ivakhnenko, Olena S.; Nyankovskyy, Serhiy L.	2013	Effect of the specific infant formula mixture of oligosaccharides on local immunity and development of allergic and infectious disease in young children: randomized study	Pediatria Polska 88 398-404	yes	-	-	-
Jahani-Moghadam, M.; Amanlou, H.; Nikkhah, A.	2009	Metabolic and productive response to ruminal protein degradability in early lactation cows fed untreated or xylose-treated soybean meal-based diets	Journal of animal physiology and animal nutrition 93 777-786	-	yes	-	-
Jiao, L. F.; Song, Z. H.; Ke, Y. L.; Xiao, K.; Hu, C. H.; Shi, B.	2014	Cello-oligosaccharide influences intestinal microflora, mucosal architecture and nutrient transport in weaned pigs	Animal Feed Science and Technology 195 85-91	yes	-	-	-
Joe Shaw, A.; Jenney, Francis E.; Adams, Michael W. W.; Lynd, Lee R.	2008	End-product pathways in the xylose fermenting bacterium, Thermoanaerobacterium saccharolyticum	Enzyme and Microbial Technology 42 453-458	-	-	yes	-
Jovanovic-Malinovska, Ruzica; Kuzmanova, Slobodanka; Winkelhausen, Eleonora	2015	Application of ultrasound for enhanced extraction of prebiotic oligosaccharides from selected fruits and vegetables	Ultrasonics Sonochemistry 22 446-453	-	yes	-	yes

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Jovanovic-Malinovska, Ruzica; Kuzmanova, Slobodanka; Winkelhausen, Eleonora	2014	Oligosaccharide Profile in Fruits and Vegetables as Sources of Prebiotics and Functional Foods	International journal of food properties 17 949-965	-	yes	-	yes
Juśkiewicz, Jerzy; Milala, Joanna; Jurgoński, Adam; Król, Bogusław; Zduńczyk, Zenon	2011	Consumption of polyphenol concentrate with dietary fructo-oligosaccharides enhances cecal metabolism of quercetin glycosides in rats	Nutrition 27 351-357	yes	-	-	-
Kang, Min-Gyung; Lee, Hee Jae; Cho, Jae-Young; Kim, Kanghwa; Yang, Soo Jin; Kim, Doman	2016	Anti-inflammatory effects of sucrose-derived oligosaccharides produced by a constitutive mutant L. mesenteroides B-512FMCM dextransucrase in high fat diet-fed mice	Biochemical and Biophysical Research Communications 477 350-355	yes	-	-	-
Kartal, O.; Mahlow, S.; Skupin, A.; Ebenhoh, O.	2011	Carbohydrate-active enzymes exemplify entropic principles in metabolism	Mol Syst Biol 7 542	-	yes	-	-
Kirilin, Alexey; Wärnå, Johan; Tokarev, Anton; Murzin, Dmitry Yu	2014	Kinetic Modeling of Sorbitol Aqueous-Phase Reforming over Pt/Al2O3	Industrial & Engineering Chemistry Research 53 4580-4588	-	yes	-	-
Kleintop, Adrienne E.; Echeverria, Dimas; Brick, Leslie A.; Thompson, Henry J.; Brick, Mark A.	2013	Adaptation of the AOAC 2011.25 Integrated Total Dietary Fiber Assay To Determine the Dietary Fiber and Oligosaccharide Content of Dry Edible Beans	Journal of agricultural and food chemistry 61 9719-9726	-	yes	-	-
Kollárová, Karin; Kamenická, Viktória; Vatehová, Zuzana; Lišková, Desana	2018	Impact of galactoglucomannan oligosaccharides and Cd stress on maize root growth parameters, morphology, and structure	Journal of Plant Physiology 222 59-66	-	-	-	yes
Kollárová, Karin; Richterová, Danica; Slováková, Ľudmila; Henselová, Mária; Capek, Peter; Lišková, Desana	2009	Impact of galactoglucomannan oligosaccharides on elongation growth in intact mung bean plants	Plant Science 177 324-330	-	-	-	yes

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Kučerová, Danica; Kollárová, Karin; Zelko, Ivan; Vatehová, Zuzana; Lišková, Desana	2014	Galactoglucomannan oligosaccharides alleviate cadmium stress in Arabidopsis	Journal of Plant Physiology 171 518-524	-	-	-	yes
Kumar, Vineet; Naudiyal, Meenakshi; Dubey, Pallavi	2017	Acidic and Neutral Monosaccharide Analysis of Cold Water Soluble Polysaccharide from Hippophae salicifolia D. Don Leaves	Journal of Biologically Active Products from Nature 7 27-33	-	-	-	yes
Lagaert, S.; Belien, T.; Volckaert, G.	2009	Plant cell walls: Protecting the barrier from degradation by microbial enzymes	Semin Cell Dev Biol 20 1064-73	-	yes	-	-
Lange, M.; Lee, H.; Dallas, D.; Le Parc, A.; de Moura Bell, J. M. L. N.; Barile, D.	2014	Determining Functional Properties and Sources of Recently Identified Bioactive Food Components: Oligosaccharides, Glycolipids, Glycoproteins, and Peptides	Academic Press 441-461	-	-	-	yes
Lans, Alexa M.; Frelka, John C.; Paluri, Sravanti; Vodovotz, Yael	2018	Physical properties and sensory analysis of galacto-oligosaccharide glassy confections	LWT 96 499-506	-	yes	-	-
Le Gall, H.; Philippe, F.; Domon, J. M.; Gillet, F.; Pelloux, J.; Rayon, C.	2015	Cell Wall Metabolism in Response to Abiotic Stress	Plants (Basel) 4 112-66	-	-	yes	yes
Lee, F. J.; Rusch, D. B.; Stewart, F. J.; Mattila, H. R.; Newton, I. L.	2015	Saccharide breakdown and fermentation by the honey bee gut microbiome	Environ Microbiol 17 796-815	-	-	-	yes
Li, Pei-jun; Xia, Jin-lan; Nie, Zhen-yuan; Shan, Yang	2016	Pectic oligosaccharides hydrolyzed from orange peel by fungal multi-enzyme complexes and their prebiotic and antibacterial potentials	LWT - Food Science and Technology 69 203-210	-	yes	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Li, Tuoping; Li, Suhong; Du, Lijuan; Wang, Na; Guo, Mei; Zhang, Junwei; Yan, Fenwen; Zhang, Huili	2010	Effects of haw pectic oligosaccharide on lipid metabolism and oxidative stress in experimental hyperlipidemia mice induced by high-fat diet	Food chemistry 121 1010-1013	yes	-	-	-
Li, Wenfeng; Zhang, Ruijun; Guo, Jianjun; Shao, Hongjun; Yang, Xingbin	2016	Protective effect of R. glutinosa oligosaccharides against high l-carnitine diet-induced endothelial dysfunction and hepatic injury in mice	International Journal of Biological Macromolecules 85 285-293	yes	-	-	-
Li, Zongjun; Bai, Hanxun; Zheng, Lixin; Jiang, Huai; Cui, Huiying; Cao, Yangchun; Yao, Junhu	2018	Bioactive polysaccharides and oligosaccharides as possible feed additives to manipulate rumen fermentation in Rusitec fermenters	International Journal of Biological Macromolecules 109 1088-1094	-	-	-	yes
Lim, E.; Lim, J. Y.; Shin, J. H.; Seok, P. R.; Jung, S.; Yoo, S. H.; Kim, Y.	2015	D-Xylose suppresses adipogenesis and regulates lipid metabolism genes in high-fat diet-induced obese mice	Nutr Res 35 626-36	yes	-	-	yes
Lin, T.; Zhang, J. Y.; Diao, Y. F.; Kang, J. W.; Jin, D. I.	2015	Effects of sorbitol on porcine oocyte maturation and embryo development in vitro	Zygote 23 297-306	yes	-	-	-
Linneen, S. K.; Mourer, G. L.; Sparks, J. D.; Jennings, J. S.; Goad, C. L.; Lalman, D. L.	2014	Effects of mannan oligosaccharide on beef-cow performance and passive immunity transfer to calves	The Professional Animal Scientist 30 311-317	yes	-	-	yes
Lioret, Pascal	2011	Food product, useful as madeleines, financiers and muffins, comprises a paste comprising egg, and a cereal product, where the paste further comprises a first polyol sweetener and a second sweetener such as glycerin and/or sorbitol	ST MICHEL HOLDING	-	yes	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Liu, Zhiqian; Rochfort, Simone	2015	Identification and quantitative analysis of oligosaccharides in wheat flour using LC–MS	Journal of Cereal Science 63 128-133	-	yes	-	-
Lucyszyn, Neoli; Lubambo, Adriana F.; Ono, Lucy; Jó, Tatiane A.; de Souza, Clayton F.; Sierakowski, Maria Rita	2011	Chemical, physico-chemical and cytotoxicity characterisation of xyloglucan from Guibourtia hymenifolia (Moric.) J. Leonard seeds	Food hydrocolloids 25 1242-1250	-	yes	-	yes
Luzardo-Ocampo, I.; Campos-Vega, R.; Gaytán-Martínez, M.; Preciado-Ortiz, R.; Mendoza, S.; Loarca-Piña, G.	2017	Bioaccessibility and antioxidant activity of free phenolic compounds and oligosaccharides from corn (Zea mays L.) and common bean (Phaseolus vulgaris L.) chips during in vitro gastrointestinal digestion and simulated colonic fermentation	Food Research International 100 304-311	-	-	-	yes
Mahajan, Hitendra S.; Gundare, Sadanand A.	2014	Preparation, characterization and pulmonary pharmacokinetics of xyloglucan microspheres as dry powder inhalation	Carbohydrate polymers 102 529-536	yes	-	-	-
Maki, K. C.; Gibson, G. R.; Dickmann, R. S.; Kendall, C. W.; Chen, C. Y.; Costabile, A.; Comelli, E. M.; McKay, D. L.; Almeida, N. G.; Jenkins, D.; Zello, G. A.; Blumberg, J. B.	2012	Digestive and physiologic effects of a wheat bran extract, arabino-xylan-oligosaccharide, in breakfast cereal	Nutrition 28 1115-21	-	yes	-	-
Manisseri, Chithra; Gudipati, Muralikrishna	2010	Bioactive xylo-oligosaccharides from wheat bran soluble polysaccharides	LWT - Food Science and Technology 43 421-430	-	yes	-	-
Mao, X.; Xiao, X.; Chen, D.; Yu, B.; He, J.; Chen, H.; Xiao, X.; Luo, J.; Luo, Y.; Tian, G.; Wang, J.	2017	Dietary apple pectic oligosaccharide improves gut barrier function of rotavirus-challenged weaned pigs by increasing antioxidant capacity of enterocytes	Oncotarget 8 92420-92430	-	-	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Martinez, M.; Gullon, B.; Yanez, R.; Alonso, J. L.; Parajo, J. C.	2009	Direct enzymatic production of oligosaccharide mixtures from sugar beet pulp: experimental evaluation and mathematical modeling	J Agric Food Chem 57 5510-7	-	yes	-	-
Martinov, Jelena; Krstić, Miodrag; Spasić, Snežana; Miletić, Srdjan; Stefanović-Kojić, Jovana; Nikolić-Kokić, Aleksandra; Blagojević, Duško; Spasojević, Ivan; Spasić, Mihajlo B.	2017	Apple pectin-derived oligosaccharides produce carbon dioxide radical anion in Fenton reaction and prevent growth of Escherichia coli and Staphylococcus aureus	Food Research International 100 132-136	-	yes	-	-
Mateo, Soledad; Puentes, Juan G.; Sánchez, Sebastián; Moya, Alberto J.	2013	Oligosaccharides and monomeric carbohydrates production from olive tree pruning biomass	Carbohydrate Polymers 93 416-423	-	yes	-	-
Matusek, A.; Merész, P.; Le, T. K. D.; Örsi, F.	2011	Fructo-oligosaccharide degradation in apple pulp matrix	Acta alimentaria 40 182-193	-	yes	-	-
Meijnen, J. P.; de Winde, J. H.; Ruijssenaars, H. J.	2009	Establishment of oxidative D-xylose metabolism in Pseudomonas putida S12	Appl Environ Microbiol 75 2784-91	-	-	yes	-
Meinert, L.; Schafer, A.; Bjergegaard, C.; Aaslyng, M. D.; Bredie, W. L.	2009	Comparison of glucose, glucose 6-phosphate, ribose, and mannose as flavour precursors in pork; the effect of monosaccharide addition on flavour generation	Meat Sci 81 419-25	-	yes	-	-
Mendes, Joana A. S.; Prozil, Sónia O.; Evtuguin, Dmitry V.; Lopes, Luísa P. Cruz	2013	Towards comprehensive utilization of winemaking residues: Characterization of grape skins from red grape pomaces of variety Touriga Nacional	Industrial crops and products 43 25-32	-	yes	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Mirzapour, ; x, ; Rezaee, S. S.; Farhangi, M.; Rafiee, G.	2017	Combined effects of dietary mannan‐ and fructo‐oligosaccharide on growth indices, body composition, intestinal bacterial flora and digestive enzymes activity of regal peacock (Aulonocara stuartgranti)	Aquaculture nutrition 23 629-636	yes	-	-	yes
Moon, Jin Seok; Shin, So Yeon; Choi, Hye Sun; Joo, Wooha; Cho, Seung Kee; Li, Ling; Kang, Jung-Hyun; Kim, Tae-Jip; Han, Nam Soo	2015	In vitro digestion and fermentation properties of linear sugar-beet arabinan and its oligosaccharides	Carbohydrate Polymers 131 50-56	-	yes	-	-
Morgan, Natalie K.; Keerqin, Chake; Wallace, Andrew; Wu, Shu-Biao; Choct, Mingan	2018	Effect of arabinoxylo-oligosaccharides and arabinoxylans on net energy and nutrient utilization in broilers	Animal Nutrition	-	yes	-	yes
Morris, Cécile; Morris, Gordon A.	2012	The effect of inulin and fructo-oligosaccharide supplementation on the textural, rheological and sensory properties of bread and their role in weight management: A review	Food chemistry 133 237-248	-	yes	-	-
Morrison, S. J.; Dawson, S.; Carson, A. F.	2010	The effects of mannan oligosaccharide and Streptococcus faecium addition to milk replacer on calf health and performance	Livestock Science 131 292-296	-	yes	-	-
Mouro, Adriane; Cadete, Raquel M.; Santos, Renata O.; Rosa, Carlos A.; Stambuk, Boris U.	2014	Xylose and cellobiose fermentation by yeasts isolated from the Brazilian biodiversity	BMC proceedings 8 P202-P202	-	-	yes	-
Niele, N.; Westerbeek, E. A. M.; van Zwol, A.; Lafeber, H. N.; van Elburg, R. M.	2011	Effect of enteral supplementation of neutral and acidic oligosaccharides in preterm infants on allergic diseases during the first year of life	European Journal of Pharmacology 668 e14	yes	-	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Niethamer, Terren K.; Yardeni, Tal; Leoyklang, Petcharat; Ciccone, Carla; Astiz-Martinez, Adrian; Jacobs, Katherine; Dorward, Heidi M.; Zerfas, Patricia M.; Gahl, William A.; Huizing, Marjan	2012	Oral monosaccharide therapies to reverse renal and muscle hyposialylation in a mouse model of GNE myopathy	Molecular genetics and metabolism 107 748-755	yes	-	-	-
Nishinari, K.; Takemasa, M.; Yamatoya, K.; Shirakawa, M.	2009	19 - Xyloglucan	Woodhead Publishing 535-566	-	yes	yes	yes
Nobre, Clarisse; Cerqueira, Miguel Ângelo; Rodrigues, Lígia Raquel; Vicente, António Augusto; Teixeira, José António	2015	Chapter 19 - Production and Extraction of Polysaccharides and Oligosaccharides and Their Use as New Food Additives	Elsevier 653-679	yes	yes	-	-
Nochta, I.; Halas, V.; Tossenberger, J.; Babinszky, L.	2010	Effect of different levels of mannan‐oligosaccharide supplementation on the apparent ileal digestibility of nutrients, N‐balance and growth performance of weaned piglets	Journal of animal physiology and animal nutrition 94 747-756	yes	-	-	yes
Nochta, I.; Tuboly, T.; Halas, V.; Babinszky, L.	2009	Effect of different levels of mannan-oligosaccharide supplementation on some immunological variables in weaned piglets	Journal of animal physiology and animal nutrition 93 496-504	yes	-	-	yes
Nodeh, H.; Mansoori, B.; Rahbari, S.; Modirsanei, M.; Aparnak, P.	2008	Assessing the effect of diclazuril on the intestinal absorptive capacity of broilers infected with experimental coccidiosis, using d-xylose absorption test	Journal of veterinary pharmacology and therapeutics 31 265-267	-	-	-	yes

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Noss, I.; Doekes, G.; Thorne, P. S.; Heederik, D. J.; Wouters, I. M.	2013	Comparison of the potency of a variety of beta-glucans to induce cytokine production in human whole blood	Innate Immun 19 10-Sep	yes	-	-	-
Nugroho, Rudy Agung; Fotedar, Ravi	2014	Comparing the effects of dietary selenium and mannan oligosaccharide supplementation on the growth, immune function, and antioxidant enzyme activity in the cultured marron Cherax cainii (Austin, 2002)	Aquaculture international 22 585-596	-	-	-	yes
Ohkawa, W.; Moriya, S.; Kanahama, K.; Kanayama, Y.	2008	Re-evaluation of sorbitol metabolism in fruit from Rosaceae trees	Acta horticulturae 159-166	-	yes	-	-
Okada, Hideki; Fukushi, Eri; Yamamori, Akira; Kawazoe, Naoki; Onodera, Shuichi; Kawabata, Jun; Shiomi, Norio	2010	Novel fructopyranose oligosaccharides isolated from fermented beverage of plant extract	Carbohydrate Research 345 414-418	-	yes	-	-
Panknin, Hardy-Thorsten; Trautmann, Matthias	2014	[Prebiotic oligosaccharides: regular administration in premature infants improves intestinal flora]	Kinderkrankenschwester : Organ der Sektion Kinderkrankenpflege 33 33-34	yes	-	-	-
Pantophlet, A. J.; Gilbert, M. S.; van den Borne, J. J. G. C.; Gerrits, W. J. J.; Priebe, M. G.; Vonk, R. J.	2016	Insulin sensitivity in calves decreases substantially during the first 3 months of life and is unaffected by weaning or fructo-oligosaccharide supplementation	Journal of Dairy Science 99 7602-7611	-	-	-	yes
Pareyt, Bram; Goovaerts, Marijke; Broekaert, Willem F.; Delcour, Jan A.	2011	Arabinoxylan oligosaccharides (AXOS) as a potential sucrose replacer in sugar-snap cookies	LWT - Food Science and Technology 44 725-728	-	yes	-	-
Park, Eunhye; Yang, Hyojik; Kim, Yangsun; Kim, Jeongkwon	2012	Analysis of oligosaccharides in beer using MALDI-TOF-MS	Food Chemistry 134 1658-1664	-	yes	-	-

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Park, M. H.	2016	Sucrose delays senescence and preserves functional compounds in Asparagus officinalis L	Biochem Biophys Res Commun 480 241-247	-	yes	-	yes
Pattanayak, Manabendra; Samanta, Surajit; Maity, Prasenjit; Manna, Dilip K.; Sen, Ipsita K.; Nandi, Ashis K.; Panda, Bibhash C.; Chattopadhyay, Sourav; Roy, Somenath; Sahoo, Atish K.; Gupta, Nibha; Islam, Syed S.	2017	Polysaccharide of an edible truffle Tuber rufum: Structural studies and effects on human lymphocytes	International journal of biological macromolecules 95 1037-1048	-	yes	-	-
Pena, M. J.; Darvill, A. G.; Eberhard, S.; York, W. S.; O'Neill, M. A.	2008	Moss and liverwort xyloglucans contain galacturonic acid and are structurally distinct from the xyloglucans synthesized by hornworts and vascular plants	Glycobiology 18 891-904	-	yes	-	yes
Peng, B.; Huang, S.; Liu, T.; Geng, A.	2015	Bacterial xylose isomerases from the mammal gut Bacteroidetes cluster function in Saccharomyces cerevisiae for effective xylose fermentation	Microb Cell Fact 14 70	-	-	-	yes
Pepe-Ranney, C.; Campbell, A. N.; Koechli, C. N.; Berthrong, S.; Buckley, D. H.	2016	Unearthing the Ecology of Soil Microorganisms Using a High Resolution DNA-SIP Approach to Explore Cellulose and Xylose Metabolism in Soil	Front Microbiol 7 703	-	-	yes	yes
Petersen, A.; Bergstrom, A.; Andersen, J. B.; Hansen, M.; Lahtinen, S. J.; Wilcks, A.; Licht, T. R.	2010	Analysis of the intestinal microbiota of oligosaccharide fed mice exhibiting reduced resistance to Salmonella infection	Benef Microbes 1 271-81	yes	-	-	-
Plesea Condratovici, C.; Bacarea, V.; Pique, N.	2016	Xyloglucan for the Treatment of Acute Gastroenteritis in Children: Results of a Randomized, Controlled, Clinical Trial	Gastroenterol Res Pract 2016 6874207	yes	-	-	-

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Procentese, Alessandra; Raganati, Francesca; Olivieri, Giuseppe; Russo, Maria Elena; Salatino, Piero; Marzocchella, Antonio	2015	Continuous xylose fermentation by Clostridium acetobutylicum – Assessment of solventogenic kinetics	Bioresource Technology 192 142-148	-	-	yes	-
Pustjens, A. M.; de Vries, S.; Schols, H. A.; Gruppen, H.; Gerrits, W. J.; Kabel, M. A.	2014	Understanding carbohydrate structures fermented or resistant to fermentation in broilers fed rapeseed (Brassica napus) meal to evaluate the effect of acid treatment and enzyme addition	Poult Sci 93 926-34	-	yes	-	-
Qian, Li; Zhou, Yan; Teng, Zhaolin; Du, Chun-Ling; Tian, Changrong	2014	Preparation and antibacterial activity of oligosaccharides derived from dandelion	International Journal of Biological Macromolecules 64 392-394	-	-	-	yes
Qian, Zhi-Gang; Jiang, Long-Fa	2014	Preparation and antibacterial activity of the oligosaccharides derived from Rhizoma Phragmites	Carbohydrate Polymers 111 356-358	-	-	-	yes
Ratnayake, R. M.; Sims, I. M.; Newman, R. H.; Melton, L. D.	2011	Effects of cooking on the cell walls (dietary fiber) of 'Scarlet Warren' winter squash (Cucurbita maxima) studied by polysaccharide linkage analysis and solid-state (13)C NMR	J Agric Food Chem 59 7186-93	-	yes	-	-
Razeghi Mansour, M.; Akrami, R.; Ghobadi, S. H.; Amani Denji, K.; Ezatrahimi, N.; Gharaei, A.	2012	Effect of dietary mannan oligosaccharide (MOS) on growth performance, survival, body composition, and some hematological parameters in giant sturgeon juvenile (Huso huso Linnaeus, 1754)	Fish physiology and biochemistry 38 829-835	-	-	-	yes
Ren, Nanqi; Cao, Guangli; Wang, Aijie; Lee, Duu-Jong; Guo, Wanqian; Zhu, Yuhong	2008	Dark fermentation of xylose and glucose mix using isolated Thermoanaerobacterium thermosaccharolyticum W16	International Journal of Hydrogen Energy 33 6124-6132	-	-	yes	-

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Rivero, F.; Torrecillas, S.; Caballero, M. J.; Makol, A.; Izquierdo, M. S.; Montero, D.	2016	Combined effects of dietary mannan oligosaccharides and Pediococcus acidilactici and their combination in low fish meal and fish oil diets for European sea bass, Dicentrarchus labrax, juveniles	Fish & Shellfish Immunology 53 69	-	-	-	yes
Rondeau, Pierangelo; Gambier, François; Jolibert, Franck; Brosse, Nicolas	2013	Compositions and chemical variability of grape pomaces from French vineyard	Industrial Crops and Products 43 251-254	-	yes	-	-
Ruiz, Encarnación; Gullón, Beatriz; Moura, Patrícia; Carvalheiro, Florbela; Eibes, Gemma; Cara, Cristóbal; Castro, Eulogio	2017	Bifidobacterial growth stimulation by oligosaccharides generated from olive tree pruning biomass	Carbohydrate Polymers 169 149-156	-	-	-	yes
Rushdi, Ahmed I.; Oros, Daniel R.; Al-Mutlaq, Khalid F.; He, Ding; Medeiros, Patricia M.; Simoneit, Bernd R. T.	2016	Lipid, sterol and saccharide sources and dynamics in surface soils during an annual cycle in a temperate climate region	Applied Geochemistry 66 Jan-13	-	-	yes	-
Sack, E. L.; van der Wielen, P. W.; van der Kooij, D.	2011	Flavobacterium johnsoniae as a model organism for characterizing biopolymer utilization in oligotrophic freshwater environments	Appl Environ Microbiol 77 6931-8	-	-	yes	-
Safari, Omid; Shahsavani, Davar; Paolucci, Marina; Atash, Masoomeh Mehraban Sang	2014	Single or combined effects of fructo- and mannan oligosaccharide supplements on the growth performance, nutrient digestibility, immune responses and stress resistance of juvenile narrow clawed crayfish, Astacus leptodactylus leptodactylus Eschscholtz, 1823	Aquaculture 432 192-203	-	-	-	yes
Salmon, L.; Edwards, S. A.	2015	The effects of dietary fructo-oligosaccharide addition on boar taint compounds and performance in heavy slaughter weight boars and gilts	Animal Feed Science and Technology 207 130-139	-	-	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Sampedro, J.; Valdivia, E. R.; Fraga, P.; Iglesias, N.; Revilla, G.; Zarra, I.	2017	Soluble and Membrane-Bound beta-Glucosidases Are Involved in Trimming the Xyloglucan Backbone	Plant Physiol 173 1017-1030	-	yes	-	-
Sancho, Renata A. Soriano; Souza, Jane Delane R. P.; de Lima, Fabíola Aliaga; Pastore, Glaucia Maria	2017	Evaluation of oligosaccharide profiles in selected cooked tubers and roots subjected to in vitro digestion	LWT - Food Science and Technology 76 270-277	-	yes	-	-
Sang, H. M.; Fotedar, R.; Filer, K.	2011	Effects of dietary mannan oligosaccharide on the survival, growth, immunity and digestive enzyme activity of freshwater crayfish, Cherax destructor Clark (1936)	Aquaculture nutrition 17 e629-e635	-	-	-	yes
Sang, H. M.; Kien, N. T.; Thanh Thuy, N. T.	2014	Effects of dietary mannan oligosaccharide on growth, survival, physiological, immunological and gut morphological conditions of black tiger prawn (Penaeus monodon Fabricius 1798)	Aquaculture nutrition 20 341-348	-	-	-	yes
Sang, H. M.; Ky le, T.; Fotedar, R.	2009	Dietary supplementation of mannan oligosaccharide improves the immune responses and survival of marron, Cherax tenuimanus (Smith, 1912) when challenged with different stressors	Fish Shellfish Immunol 27 341-8	-	-	-	yes
Sang, Huynh Minh; Fotedar, Ravi	2010	Prebiotic mannan oligosaccharide diet improves health status of the digestive system of marron, Cherax tenuimanus (Smith 1912)	Journal of applied aquaculture 22 240-250	-	-	-	yes
Sang, Huynh Minh; Fotedar, Ravi; Filer, Keith	2011	Effects of Dietary Mannan Oligosaccharide on Survival, Growth, Physiological Condition, and Immunological Responses of Marron, Cherax tenuimanus (Smith 1912)	Journal of the World Aquaculture Society 42 230-241	-	-	-	yes
Sidiras, Dimitris; Batzias, Fragiskos; Ranjan, Rajiv; Tsapatsis, Michael	2011	Simulation and optimization of batch autohydrolysis of wheat straw to monosaccharides and oligosaccharides	Bioresource Technology 102 10486-10492	-	yes	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Singh, Ramkrishna D.; Banerjee, Jhumur; Arora, Amit	2015	Prebiotic potential of oligosaccharides: A focus on xylan derived oligosaccharides	Bioactive Carbohydrates and Dietary Fibre 5 19-30	-	-	-	yes
Smith, Daniel L., Jr.; Nagy, Tim R.; Wilson, Landon S.; Dong, Shengli; Barnes, Stephen; Allison, David B.	2010	The Effect of Mannan Oligosaccharide Supplementation on Body Weight Gain and Fat Accrual in C57Bl/6J Mice	Obesity 18 995-999	yes	-	-	-
Soh, Jian Yi; Huang, Chiung-Hui; Chiang, Wen Chin; Llanora, Genevieve; Lee, Alison Joanne; Loh, Wenyin; Lin Chin, Cherlyn Yue; Jia Tay, Victoria Yu; Chan, Yiong Huak; Delsing, Dianne; Lee, Bee-Wah	2015	Allergy to Galacto-Oligosaccharides in an Atopic Population in Singapore	Journal of Allergy and Clinical Immunology 135 AB252	yes	-	-	-
Sparkman, O. David; Penton, Zelda E.; Kitson, Fulton G.	2011	Chapter 35 - Sugars (Monosaccharides)	Academic Press 407-410	yes	yes	yes	yes
Stick, Robert V.; Williams, Spencer J.	2009	Chapter 6 - Monosaccharide Metabolism	Elsevier 225-251	yes	yes	yes	-
Stick, Robert V.; Williams, Spencer J.	2009	Chapter 9 - Disaccharides, Oligosaccharides and Polysaccharides	Elsevier 321-341	yes	yes	yes	yes
Suo, Hai-qing; Lu, Lin; Xu, Guo-hui; Xiao, Lin; Chen, Xiao-gang; Xia, Rui-rui; Zhang, Li-yang; Luo, Xu-gang	2015	Effectiveness of dietary xylo-oligosaccharides for broilers fed a conventional corn-soybean meal diet	Journal of Integrative Agriculture 14 2050-2057	-	yes	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Szklany, K.; De Theije, C. G. M.; De Waard, C.; Van Staveren, N. G.; Van Wageningen, T. A.; Wu, J.; Verdouw, M.; Van Limpt, K.; Wopereis, H.; Groenink, L.; Oozeer, R.; Garssen, J.; Knippels, L. M. J.; Kraneveld, A. D.	2016	P.1.c.008 - Effect of early life supplementation of non-digestible oligosaccharides on brain development and behaviour in healthy mice	European Neuropsychopharmacology 26 S191	yes	-	-	yes
Takada, T.; Sato, R.; Kikuta, S.	2017	A mannitol/sorbitol receptor stimulates dietary intake in Tribolium castaneum	PLoS One 12 e0186420	-	-	-	yes
Takahashi, Machiko; Yamamoto, Ryoichi; Sakurai, Naoki; Nakano, Yuki; Takeda, Takumi	2015	Fungal hemicellulose-degrading enzymes cause physical property changes concomitant with solubilization of cell wall polysaccharides	Planta 241 359-370	-	yes	yes	-
Tani, Tatsunori; Taguchi, Hisataka; Akamatsu, Takashi	2017	Analysis of metabolisms and transports of xylitol using xylose- and xylitol-assimilating Saccharomyces cerevisiae	Journal of bioscience and bioengineering	-	-	yes	-
Temudo, M. F.; Mato, T.; Kleerebezem, R.; van Loosdrecht, M. C.	2008	Xylose anaerobic conversion by open-mixed cultures	Appl Microbiol Biotechnol 82 231-9	-	-	yes	-
Torrecillas, S.; Rivero-Ramírez, F.; Izquierdo, M. S.; Caballero, M. J.; Makol, A.; Suarez-Bregua, P.; Fernández-Montero, A.; Rotllant, J.; Montero, D.	2018	Feeding European sea bass (Dicentrarchus labrax) juveniles with a functional synbiotic additive (mannan oligosaccharides and Pediococcus acidilactici): An effective tool to reduce low fishmeal and fish oil gut health effects?	Fish & Shellfish Immunology 81 Oct-20	-	-	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Torrecillas, Silvia; Makol, Alex; Benítez-Santana, Tibiábin; Caballero, María José; Montero, Daniel; Sweetman, John; Izquierdo, Marisol	2011	Reduced gut bacterial translocation in European sea bass (Dicentrarchus labrax) fed mannan oligosaccharides (MOS)	Fish & Shellfish Immunology 30 674-681	-	-	-	yes
Torrecillas, Silvia; Montero, Daniel; Caballero, Maria José; Robaina, Lidia; Zamorano, Maria Jesús; Sweetman, John; Izquierdo, Marisol	2015	Effects of dietary concentrated mannan oligosaccharides supplementation on growth, gut mucosal immune system and liver lipid metabolism of European sea bass (Dicentrarchus labrax) juveniles	Fish & Shellfish Immunology 42 508-516	-	-	-	yes
Torrecillas, Silvia; Montero, Daniel; Izquierdo, Marisol	2014	Improved health and growth of fish fed mannan oligosaccharides: Potential mode of action	Fish & Shellfish Immunology 36 525-544	-	yes	-	yes
Tuoping, L. I.; Suhong, L. I.; Na, Wang; Mei, G. U. O.	2009	Oligosaccharide probiotics		-	-	-	yes
Tusi, Solaleh Khoramian; Khalaj, Leila; Ashabi, Ghorbangol; Kiaei, Mahmoud; Khodagholi, Fariba	2011	Alginate oligosaccharide protects against endoplasmic reticulum- and mitochondrial-mediated apoptotic cell death and oxidative stress	Biomaterials 32 5438-5458	yes	-	-	-
Valinhas, R. V.; Pantoja, L. A.; Maia, A. C. F.; Miguel, Mgcp; Vanzela, Apfc; Nelson, D. L.; Santos, A. S.	2018	Xylose fermentation to ethanol by new Galactomyces geotrichum and Candida akabanensis strains	PeerJ 6 e4673	-	-	yes	-
Valpotic, H.; Zura Zaja, I.; Samardzija, M.; Habrun, B.; Ostovic, M.; Duricic, D.; Macesic, N.; Mikulec, Z.; Kocila, P.; Sobiech, P.; Valpotic, I.; Vince, S.	2018	Dietary supplementation with mannan oligosaccharide and clinoptilolite modulates innate and adaptive immune parameters of weaned pigs	Pol J Vet Sci 21 83-93	yes	-	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
van Vlies, N.; Hogenkamp, A.; Thijssen, S.; Dingjan, G. M.; Knipping, K.; Garssen, J.; Knippels, L. M. J.	2012	Effects of short-chain galacto- and long-chain fructo-oligosaccharides on systemic and local immune status during pregnancy	Journal of Reproductive Immunology 94 161-168	yes	-	-	-
Vanis, Lora; Hausken, Trygve; Gentilcore, Diana; Rigda, Rachael S.; Rayner, Christopher K.; Feinle-Bisset, Christine; Horowitz, Michael; Jones, Karen L.	2011	Comparative effects of glucose and xylose on blood pressure, gastric emptying and incretin hormones in healthy older subjects	British journal of nutrition 105 1644-1651	yes	-	-	-
Vargas, Fátima; Domínguez, Elena; Vila, Carlos; Rodríguez, Alejandro; Garrote, Gil	2015	Agricultural residue valorization using a hydrothermal process for second generation bioethanol and oligosaccharides production	Bioresource Technology 191 263-270	-	yes	-	-
Veras, H. C. T.; Parachin, N. S.; Almeida, J. R. M.	2017	Comparative assessment of fermentative capacity of different xylose-consuming yeasts	Microb Cell Fact 16 153	-	-	yes	yes
Wakao, Norimitsu; Imagama, Shiro; Zhang, Haoquian; Tauchi, Ryoji; Muramoto, Akio; Natori, Takamitsu; Takeshita, Sawako; Ishiguro, Naoki; Matsuyama, Yukihiro; Kadomatsu, Kenji	2011	Hyaluronan oligosaccharides promote functional recovery after spinal cord injury in rats	Neuroscience Letters 488 299-304	yes	-	-	-
Wan, Jin; Zhang, Jiao; Chen, Daiwen; Yu, Bing; He, Jun	2017	Effects of alginate oligosaccharide on the growth performance, antioxidant capacity and intestinal digestion-absorption function in weaned pigs	Animal Feed Science and Technology 234 118-127	yes	-	-	-
Wang, Jing; Sun, Baoguo; Cao, Yanping; Tian, Yuan	2009	Protection of wheat bran feruloyl oligosaccharides against free radical-induced oxidative damage in normal human erythrocytes	Food and Chemical Toxicology 47 1591-1599	yes	-	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Wang, Jing; Sun, Baoguo; Cao, Yanping; Wang, Chengtao	2010	Wheat bran feruloyl oligosaccharides enhance the antioxidant activity of rat plasma	Food Chemistry 123 472-476	yes	-	-	-
Wang, Yan; Guo, Qingbin; Douglas Goff, H.; LaPointe, Gisèle	2018	Oligosaccharides: Structure, Function and Application	Elsevier	yes	yes	yes	yes
Wang, Yu; Zeng, Tao; Wang, Shu-e; Wang, Wei; Wang, Qian; Yu, Hong-Xia	2010	Fructo-oligosaccharides enhance the mineral absorption and counteract the adverse effects of phytic acid in mice	Nutrition 26 305-311	yes	-	-	-
Wasserstrom, L.; Portugal-Nunes, D.; Almqvist, H.; Sandstrom, A. G.; Liden, G.; Gorwa-Grauslund, M. F.	2018	Exploring D-xylose oxidation in Saccharomyces cerevisiae through the Weimberg pathway	AMB Express 8 33	-	-	yes	-
Watanabe, M.; Kokubo, Y.; Higashiyama, A.; Ono, Y.; Miyamoto, Y.; Okamura, T.	2011	Serum 1,5-anhydro-d-glucitol levels predict first-ever cardiovascular disease: An 11-year population-based Cohort study in Japan, the Suita study	Atherosclerosis 216 477-483	yes	-	-	-
Werner, Kajsa; Pommer, Linda; Broström, Markus	2014	Thermal decomposition of hemicelluloses	Journal of Analytical and Applied Pyrolysis 110 130-137	-	-	yes	-
Wicklund, Rachel; Harrison Michael, D.; King, Christopher; Hoffman Andrew, J.; Schwenk, Michelle; Napier, Lori; Nehmer, Warren	2008	Edible composition comprising a slowly digestible or digestion resistant oligosaccharide composition	TATE & LYLE INGREDIENTS	-	yes	-	-
Willems, Jamie L.; Low, Nicholas H.	2012	Major Carbohydrate, Polyol, and Oligosaccharide Profiles of Agave Syrup. Application of this Data to Authenticity Analysis	Journal of agricultural and food chemistry 60 8745&#x2013 8754	-	yes	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Wu, Sheng-Jun	2014	Preparation and antioxidant activity of the oligosaccharides derived from Laminaria japonica	Carbohydrate Polymers 106 22-24	-	-	-	yes
Wu, Shengjun; Huang, Xiaolian	2017	Preparation and antioxidant activities of oligosaccharides from Crassostrea gigas	Food Chemistry 216 243-246	-	-	-	yes
Xia, Zhenqiang	2015	Preparation of the oligosaccharides derived from Flammulina velutipes and their antioxidant activities	Carbohydrate Polymers 118 41-43	-	-	-	yes
Xu, H.; Xiong, A. S.; Zhao, W.; Tian, Y. S.; Peng, R. H.; Chen, J. M.; Yao, Q. H.	2011	Characterization of a glucose-, xylose-, sucrose-, and D-galactose-stimulated beta-glucosidase from the alkalophilic bacterium Bacillus halodurans C-125	Curr Microbiol 62 833-9	-	-	-	yes
Yao, Xing-Cun; Cao, Yan; Wu, Sheng-Jun	2013	Antioxidant activity and antibacterial activity of peach gum derived oligosaccharides	International Journal of Biological Macromolecules 62 01-Mar	-	-	-	yes
Ye, J. D.; Wang, K.; Li, F. D.; Sun, Y. Z.	2011	Single or combined effects of fructo- and mannan oligosaccharide supplements and Bacillus clausii on the growth, feed utilization, body composition, digestive enzyme activity, innate immune response and lipid metabolism of the Japanese flounder Paralichthys olivaceus	Aquaculture nutrition 17 e902-e911	-	-	-	yes
Yeh, S. L.; Wu, T. C.; Chan, S. T.; Hong, M. J.; Chen, H. L.	2014	Fructo-oligosaccharide attenuates the production of pro-inflammatory cytokines and the activation of JNK/Jun pathway in the lungs of D-galactose-treated Balb/cJ mice	Eur J Nutr 53 449-56	yes	-	-	-

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Yen, C. H.; Wang, C. H.; Wu, W. T.; Chen, H. L.	2017	Fructo-oligosaccharide improved brain beta-amyloid, beta-secretase, cognitive function, and plasma antioxidant levels in D-galactose-treated Balb/cJ mice	Nutr Neurosci 20 228-237	yes	-	-	-
Young, O. A.; Cummings, T. L.	2008	Effect of Xylose on Sheepmeat Flavors in Casserole-Style Cooking	Journal of food science an official publication of the Institute of Food Technologists 73 S308-S313	-	yes	-	-
Yuan, L.; Li, W.; Huo, Q.; Du, C.; Wang, Z.; Yi, B.; Wang, M.	2018	Effects of xylo-oligosaccharide and flavomycin on the immune function of broiler chickens	PeerJ 6 e4435	-	-	-	yes
Zabotina, O. A.	2012	Xyloglucan and its biosynthesis	Front Plant Sci 3 134	yes	yes	yes	yes
Zerillo, M. M.; Adhikari, B. N.; Hamilton, J. P.; Buell, C. R.; Levesque, C. A.; Tisserat, N.	2013	Carbohydrate-active enzymes in pythium and their role in plant cell wall and storage polysaccharide degradation	PLoS One 8 e72572	-	yes	-	yes
Zhang, Jian; Liu, Yongjian; Tian, Lixia; Yang, Huijun; Liang, Guiying; Xu, Donghui	2012	Effects of dietary mannan oligosaccharide on growth performance, gut morphology and stress tolerance of juvenile Pacific white shrimp, Litopenaeus vannamei	Fish and Shellfish Immunology 33 1027-1032	-	-	-	yes
Zhang, Ruxue; Zhou, Jun; Li, Maoxing; Ma, Haigang; Qiu, Jianguo; Luo, Xiaohong; Jia, Zhengping	2014	Ameliorating effect and potential mechanism of Rehmannia glutinosa oligosaccharides on the impaired glucose metabolism in chronic stress rats fed with high-fat diet	Phytomedicine 21 607-614	yes	-	-	-
Zhang, Shanshan; Hu, Haijuan; Wang, Lufeng; Liu, Fengxia; Pan, Siyi	2018	Preparation and prebiotic potential of pectin oligosaccharides obtained from citrus peel pectin	Food Chemistry 244 232-237	-	yes	-	yes

Author(s)	Year	Title	Source	Toxicology	Residues	Environment	Ecotoxicology
Zhang, Y.	2008	Étude des interactions entre oligosaccharides impliqués dans l'adhésion cellulaire. Exemple du trisaccharide Lewisx	Annales Pharmaceutiques Françaises 66 319-324	-	-	yes	-
Zhang, Zesheng; Lei, Mengmeng; Liu, Rui; Gao, Yunfeng; Xu, Mengying; Zhang, Min	2015	Evaluation of Alliin, Saccharide Contents and Antioxidant Activities of Black Garlic during Thermal Processing	Journal of food biochemistry 39 39-47	-	yes	-	-
Zhang, Zongying; Wang, Nan; Jiang, Shenghui; Xu, Haifeng; Wang, Yicheng; Wang, Chuanzeng; Li, Min; Liu, Jingxuan; Qu, Changzhi; Liu, Wen; Wu, Shujing; Chen, Xiaoliu; Chen, Xuesen	2017	Analysis of the Xyloglucan Endotransglucosylase/Hydrolase Gene Family during Apple Fruit Ripening and Softening	Journal of agricultural and food chemistry 65 429-434	-	yes	-	-
Zhao, X.; Moates, G. K.; Wellner, N.; Collins, S. R.; Coleman, M. J.; Waldron, K. W.	2014	Chemical characterisation and analysis of the cell wall polysaccharides of duckweed (Lemna minor)	Carbohydr Polym 111 410-8	-	-	-	yes
Zhi, Wenbiao; Hu, Yonghong; Yang, Wenge; Kai, Yumei; Cao, Zheng	2013	Measurement and correlation of solubility of d-sorbitol in different solvents	Journal of Molecular Liquids 187 201-205	-	-	yes	-
Zhou, Da-Nian; Zhang, Bao; Chen, Bo; Chen, Han-Qing	2017	Effects of oligosaccharides on pasting, thermal and rheological properties of sweet potato starch	Food Chemistry 230 516-523	-	yes	-	-
Zhou, Xiao-Li; Kong, Xiang-Feng; Lian, Guo-Qi; Blachier, Francois; Geng, Mei-Mei; Yin, Yu-Long	2014	Dietary supplementation with soybean oligosaccharides increases short-chain fatty acids but decreases protein-derived catabolites in the intestinal luminal content of weaned Huanjiang mini-piglets	Nutrition Research 34 780-788	yes	-	-	yes

B.6.10.5. Conclusion

In the frame of this literature search for the active substance Heptamaloxyloglucan, 5 964 references were identified and evaluated for their potential relevances for the data requirements “Toxicological and metabolism studies”, “Residues”, “Fate and behaviour in the environment” and “Ecotoxicological studies”, respectively.
In conclusion, the search did not identify any literatures relevant to the data requirements "Toxicological and metabolism studies".