European Commission

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

GIBBERELLINS (GA4, GA7)

Volume 1

Rapporteur Member State: SLOVENIA
Co-Rapporteur Member State: SLOVAKIA

Version History

When	What
2019/April	Initial DRAR with co-RMS suggestions

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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Level 1

GIBBERELLINS (GA4, GA7)

1 STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1.1 CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED

1.1.1 Purpose for which the draft assessment report was prepared

This renewal assessment report has been prepared in accordance with Commission Regulation (EU) No 844/2012, setting out the provisions necessary for the implementation of the renewal procedure for active substances in order to evaluate the supplementary dossier submitted by European Gibberellin Task Force (Valent Biosciences Corporation (Sumitomo Chemical Agro Europe), Fine Agrochemicals Ltd, Globachem NV) application for EU renewal of the Annex I inclusion of active substance gibberellins (GA4, GA7). The document supplements and updates the corresponding Annex B section of the Draft Assessment Report produced during the first review of gibberellins (2005 - 2011).

Gibberellins ($GA_{4/7}$) have been identified as a presumed low-risk active substance in the Commission working document on the AIR-IV renewal programme (SANTE-2016-10616-rev 8). The EU Gibberellin Task Force (EGTF) proposes that Gibberelin is a low risk active substance according to Regulation (EC) 1107/2009 as amended by Commission Regulation 2017/1432. Based on study results and taking into account all submitted data a classification (Eye Irrit. 2, H319, Aquatic acute 1, H400, Aquatic Chronic 3, H412) is proposed for Gibberellins (GA4/7) according to the criteria of Regulation 1272/2008. A proposal for Classification and Labelling is included within Vol. 1. However, the proposed ecotoxicological classification is not in line with the requirements for low risk substances thus; the criteria for a low risk active substance are not met.

Gibberellins ($GA_{4/7}$) are temporarily included on Annex IV Regulation (EC) No. 396/2005. No new MRLs were proposed.

1.1.2 Arrangements between rapporteur Member State and co-rapporteur Member State

According to Commission Implementing Regulation (EU) 2016/183 Slovenia was designated Rapporteur Member State (RMS) and Slovak Republic assigned as Co-Rapporteur Member State (Co-RMS).
Slovenia, as RMS, evaluated the dossier submitted by the applicant and drafted the Renewal Assessment Report (RAR) for all the sections. RMS sent the RAR (except Volume 3CA_B-6) for comments to the Co-RMS Slovak Republic which commented on it. The draft RAR was revised according to the Slovak Republic comments before of the official sending to EFSA.

1.1.3 EU Regulatory history for use in Plant Protection Products

Gibberellins ($GA_{4/7}$) were included in Annex I to Directive 91/414/EEC on 1 September 2009 pursuant to Article 24b of the Regulation (EC) No 2229/2004 (hereinafter referred to as „the Regulation") and has subsequently been deemed to be approved under Regulation (EC) No 1107/2009, in accordance with Commission Implementing Regulation (EU) No 540/2011, as amended by Commission Implementing Regulation (EU) No 541/201. The expiration date of the approval of Gibberellins ($GA_{4/7}$) is 31 August 2020. According to Review report for the active substance giberelline (SANCO/2614/08 – rev. 3, 1 June 2012), no further confirmatory data were needed.

Fine Agrochemicals Ltd., Globachem and Valent Biosciences Srl. were the sole data submitters of the 1st EU

review. Gibberellins ($GA_{4/7}$) were first evaluated as part of a programme for Existing Active Substances (review 4). Hungary was the designated Rapporteur Member State (RMS) submitted the DAR on Gibberelline to EFSA on August 2006. The peer review was initiated on 12 June 2008 by dispatching the DAR to the notifier and MSs, the DAR was finalised in the meeting of the Standing Committee on 28 October 2008. The Commission referred on 9 March 2012 an updated review report to the Standing Committee on the Food Chain and Animal Health, for examination.

The following documents of the previous evaluation process resulting in the first approval of Gibberelline are considered to provide relevant review information on already accepted data or a reference to where such information and data can be found:

• Review report for the active substance gibberelline (SANCO/2614/08 – rev. 2, 1 June 2012
• Draft Assessment Report (DAR) on Gibberelline, Julay 2006
• Revised Draft Assessment Report (DAR) on Gibberelline, August 2011
• European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance gibberellins (GA_4, GA_7). EFSA Journal 2012;10(1):2502. [50 pp.] doi:10.2903/j.efsa.2012.2502. Available online: www.efsa.europa.eu/efsajournal
•EFSA Peer Review Report on Gibberellins 07 December 2011, including:

- Comments on the assessment report
- Reporting table
- Pesticides peer review meeting reports
- Evaluation table
- Comments on the additional information assessment
- Comments on the draft EFSA conclusion

$GA_{4/7}$ is temporarily included on Annex IV Regulation (EC) No. 396/2005. Applicant and RMS propose that $GA_{4/7}$ should remain on Annex IV Regulation (EC) No. 396/2005. Definition of the residue is therefore not necessary.

1.1.4 Evaluations carried out under other regulatory contexts

According to our knowledge gibberellins are not evaluated under any other regulatory context

1.2 APPLICANT INFORMATION

1.2.1 Name and address of applicant(s) for approval of the active substance

TSGE Consulting Ltd., UK, on behalf of the European Gibberellin Task Force:

- Valent Biosciences Corporation (Sumitomo Chemical Agro Europe)
- Fine Agrochemicals Ltd,
- Globachem NV)

Address: TSGE Consulting Ltd.,
Concordia House,
St James Business Park, Grimbald Crag Court,
Knaresborough, N Yorkshire, HG5 8QB,
UK

EGTF Member	Contact person
Valent BioSciences	[redacted] (Sumitomo Chemical Agro Europe SAS) Parc d'Affaire de Crécy 10A rue de la Voie Lactée FR – 69370 Saint Didier au Mont d'Or Tel: [redacted] Fax: [redacted] [redacted] [redacted] (Valent BioSciences LLC) 870 Technology Way Suite 100 Libertyville IL 60048 Tel: [redacted] Fax: [redacted] [redacted]
Fine Agrochemicals Ltd.	[redacted] Hill End House Whittington Worcester United Kingdom WR5 2RQ Tel: [redacted] Fax: [redacted]
Globachem	[redacted] Brustem Industriepark Lichtenberglaan 2019 3800 Sint-Truiden Belgium Tel: [redacted] Fax: [redacted] [redacted]

1.2.2 Producer or producers of the active substance

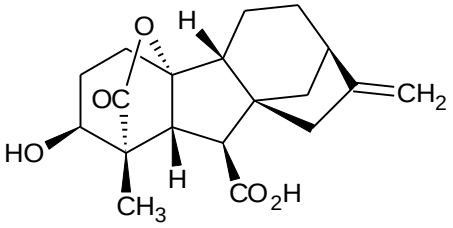
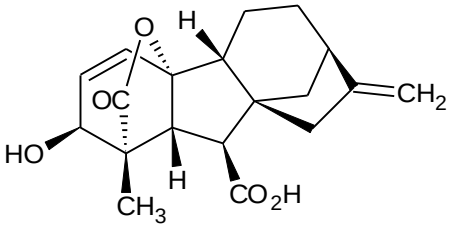
Confidential – Please see Vol.4.

1.2.3 Information relating to the collective provision of dossiers

The dossier was submitted by The European Gibberellins Task Force (EGTF):
-Valent Biosciences Corporation (Sumitomo Chemical Agro Europe)
- Fine Agrochemicals Ltd,
- Globachem NV
Each taskforce member has submitted a separate confidential data Document J for the active substance.
The dossier was prepared by TSG Consulting on behalf of EGTF. For the renewal process the use of only one PPP, Novagib, is supported by EGTF.

1.3 IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1 Common name proposed or ISO-accepted and synonyms	There is no ISO common name for this compound Synonyms are Gibberellins, GA4/7
1.3.2 Chemical name (IUPAC and CA nomenclature)	
IUPAC	GA_4: (3S,3aR,4S,4aR,7R,9aR,9bR,12S)-12-hydroxy-3-methyl-6-methylene-2-oxoperhydro-4a,7-methano-3,9b-propanoazuleno[1,2-b]furan-4-carboxylic acid GA_7: (3S,3aR,4S,4aR,7R,9aR,9bR,12S)-12-hydroxy-3-methyl-6-methylene-2-oxoperhydro-4a,7-methano-9b,3-propenoazuleno[1,2-b]furan-4-carboxylic acid
CA	GA_4: (1α,2β,4aα,4bβ,10β)-2,4a-dihydroxy-1-methyl-8-methylenegibbane-1,10-dicarboxylic acid 1,4a-lactone GA_7: (1α,2β,4aα,4bβ,10β)-2,4a-dihydroxy-1-methyl-8-methylenegibb-3-ene-1,10-dicarboxylic acid 1,4a-lactone
1.3.3 Producer's development code number	EU Gibberellin Task Force: Not applicable
1.3.4 CAS, EEC and CIPAC numbers	
CAS	GA4: 468-44-0 GA7: 510-75-8 GA4/GA7 mixture: 8030-53-3
EEC	GA4: 207-406-9 GA7: 208-117-0
CIPAC	904
1.3.5 Molecular and structural formula, molecular mass	

Molecular formula	GA4 = $C_{19}H_{24}O_5$ GA7 = $C_{19}H_{22}O_5$
Structural formula	GA4  GA7 
Molecular mass	GA4 332.40 g/mol GA7 330.40 g/mol
1.3.6 Method of manufacture (synthesis pathway) of the active substance	CONFIDENTIAL information - data provided separately (Vol.4)
1.3.7 Specification of purity of the active substance in g/kg	1. Fine Agrochemicals Ltd.: GA4: 905-919 g/kg; GA7: 19.5-27 g/kg; **GA4/GA7: min. 924 g/kg** 2. Globachem NV: GA4: 648-653 g/kg; GA7: 248-253 g/kg; **GA4/GA7: min. 885 g/kg** 3. Valent Biosciences Ltd.: GA4: 631-778 g/kg; GA7: 130-288 g/kg; **GA4/GA7: min. 852 g/kg**
1.3.8 Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1 Additives	CONFIDENTIAL information - data provided separately (Vol.4)
1.3.8.2 Significant impurities	CONFIDENTIAL information - data provided separately (Vol.4)

1.3.8.3 Relevant impurities	CONFIDENTIAL information - data provided separately (Vol.4)
1.3.9 Analytical profile of batches	CONFIDENTIAL information - data provided separately (Vol.4)

1.4 INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1 Applicant	Name: EU Gibberellin Task Force (EGTF) represented by TSGE Consulting Ltd, UK Address: TSGE Consulting, Concordia House, St James Business Park, Grimbald Crag Court, Knaresborough, N Yorkshire, HG5 8QB, UK Contact: [redacted] Tel: [redacted] email: [redacted] Alternative contact: [redacted] Address: Fine Agrochemicals Limited, Hill End House, Whittington, Worchester, WORCS. WR5 2RQ Tel: [redacted] E-mail: [redacted]
1.4.2 Producer of the plant protection product	Fine Agrochemicals Ltd Address: Hill End House, Whittington, Worchester, WR5 2RQ, UK
1.4.3 Trade name or proposed trade name and producer's development code number of the plant protection product	Trade name: Novagib Code number: -
1.4.4 Detailed quantitative and qualitative information on the composition of the plant protection product	

<table>
<tr><td>1.4.4.1 Composition of the plant protection product</td><td>
Pure active substance
<table>
<tr><td>content of pure active substance:</td><td>10 g / l</td><td>(1% w / w)</td></tr>
<tr><td>limits :</td><td>8.5-11.5 g/l</td><td>0.85 – 1.15% w/w</td></tr>
</table>
Technical active substance
<table>
<tr><td>content of technical active substance :</td><td>11.1 g / l</td><td>(1.11 % w / w)</td></tr>
<tr><td>limits :</td><td>9.435-12.765 g/l</td><td>(0.9435 – 1.2765% w / w)</td></tr>
</table>
at a minimum purity of the technical active substance of 90%
</td></tr>
<tr><td>1.4.4.2 Information on the active substances</td><td>
<table>
<tr><td>Type</td><td>Name/Code Number</td></tr>
<tr><td>ISO common name</td><td>Gibberellins, GA4/7</td></tr>
<tr><td>CAS No</td><td>GA4: 468-44-0
GA7: 510-75-8
GA4A7 mixture: 8030-53-3</td></tr>
<tr><td>EC No</td><td>GA4: 207-406-9
GA7: 208-117-0</td></tr>
<tr><td>CIPAC No</td><td>904</td></tr>
<tr><td>Salt, ester anion or cation present</td><td>NA</td></tr>
</table>
</td></tr>
<tr><td>1.4.4.3 Information on safeners, synergists and co-formulants</td><td>CONFIDENTIAL information – please see Vol.4</td></tr>
<tr><td>1.4.5 Type and code of the plant protection product</td><td>Type: soluble concentrate (SC)
Product Code: -
Trade name: Novagib</td></tr>
<tr><td>1.4.6 Function</td><td>Plant growth regulator.</td></tr>
</table>

1.4.7 Field of use envisaged	Agriculture, orchards.
1.4.8 Effects on harmful organisms	Not applicable for Novagib. Novagib containing gibberellins (GA4/GA7). Gibberellins (GA4/GA7) is plant growth regulator and does not act against harmful organisms, against weeds, insects, fungi or other pests. The mode of action of gibberellins is complex and the molecular basis of their effect of cell elongation is currently not fully understood. However, it is known that they induce the transcription of genes responsible for cell elongation in plants and upregulate expression of enzymes known to loosen cell wall structures. Increased plasticity of cellular wall structures then enhance cell expansion. The biological activity of different groups of gibberellins varies with plant species. For example, while golden delicious apple russet was significantly reduced by GA_4/GA_7, GA_3 showed no significant effect (Werthheim 1982).

1.5 DETAILED USES OF THE PLANT PROTECTION PRODUCT

Plant protection product Novagib (product code: -) is used outdoors as plant growth regulator in agriculture, in orchards: apples and pears as representative uses for reduction of russet and fruit cracking, improvement of fruit and fruit set quality.

Novagib is applied to :

- apples at 2.5 - 5 g a.s./ha (0.25-0.5 L PPP/ha) by using tractor mounted orchard sprayer and using water volumes of 300 - 1000 l/ha from BBCH 69 – 74 (April – July) up to 4 applications at 7 to 10 day intervals and to
- pears at 6 -12 g a.s./ha (0.6-1.2 L PPP/ha) by using tractor mounted orchard sprayer and using water volumes of 300 - 1000 l/ha from BBCH 62 – 69 (March – May) one or two applications at 3 day interval for pears.

1.5.1 Details of representative uses

Crop and/or situation (a)	Member State	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc of a.i. g/kg (i)	Method kind (f-h)	Growth stage and season (j)	Number min max (k)	Interval between applications (min)	g a.i./hl min max (g/hl)	Water l/ha min max	g a.i./ha min max (*) (g/ha)		
Apple (*Malus domestica* MABS)	EU	Novagib	F	Plant growth regulator. Reduction of russet and cracking, Improvement of fruit quality / skin finish	SL	10	Spraying	From BBCH 69 to BBCH 74 (April-July)	a) 1 b) 4	7 days	a) 0.25-1.66 b) 1-6.64	300-1,000	a) 2.5-5 b) 10-20	n.a.	Dose rate: 25-50 mL PPP /100 L (=0.25-0.5 L PPP/ha)
Pear (*Pyrus communis* PUYCO)	EU	Novagib	F	Plant growth regulator. Fruit set improvement	SL	10	Spraying	BBCH62-BBCH69 (March-May)	a) 1 b) 1	-	a) 1.2-4 b) 1.2-4	300-1,000	a) 12 b) 12	n.a.	Dose rate: 120 mL PPP /100 L (=1.2 L PPP/ha)
Pear (*Pyrus communis* PUYCO)	EU	Novagib	F	Plant growth regulator. Fruit set improvement	SL	10	Spraying	BBCH62-BBCH69 (March-May)	a) 1 b) 2	3 days	a) 0.6-2 b) 1.2-4	300-1,000	a) 6 b) 12	n.a.	Dose rate: 60 mL PPP /100 L (=0.6 L PPP/ha)

(a) For crops, the EU and Codex classification (both) should be taken into account ; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and sucking insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes – GIFAP Technical Monograph N° 2, 1989
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant – type of equipment used must be indicated
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) Any remarks or details about the uses

1.5.2 Further information on representative uses

- *Method of application:* by using tractor mounted orchard sprayer and using water volumes of 300 - 1000 l/ha for apples and pears.

- *Number and timing of applications:*
  - Apples: Up to 4 applications at 7 to 10 day intervals from BBCH 69 – 74 (April – July).
  - Pears: One or two applications at 3 day intervals BBCH 62 – 69 (March – May)

- *Duration of protection:*
No relevant, Novagib is a plant growth regulator.

- *Necessary waiting period or other precautions to avoid phytotoxic effects on succeeding crops:*
Not relevant as apples and pears are permanent crops.

- *Proposed instructions for use:* Propose instructions for use were not provided for the renewal of the active substance. The applicant refers to product label but product label was not included. However, detailed consideration of proposed instructions for use will be fully assessed in the context of subsequent product authorisation process.

1.5.3 Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

No other uses were evaluated except representative ones. Therefore, details of such uses are not relevant.

1.5.4 Overview on authorisations in EU Member States

Plant protection products containing gibberellins (GA4/GA7) are registered in the following Member States:

Country	Formulation	Trade name	A.S. Content	Authorisation holder	Reg. Number	Status of application	Registered uses
Austria	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	3469	Authorised	Apple and pear
Belgium	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	8929P/B	Authorised	Apples and pears
Belgium	SL	Stefagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	9392P/B	Authorised	Apples and pears
Belgium	SL	Perlan	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	8928P/B	Authorised	Apple (including tree and nursery) and pear
Croatia	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	525-091 1457-16-8	Authorised	Apple and pear
Czech Republic	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	5135-0	Authorised	Apples
France	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	9700355	Authorised	Apples
France	SL	Stefagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	2010643	Authorised	Apples
France	SL	Perlan	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	9700357	Authorised	Apple (including tree nursery)
Germany	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	006447-00	Authorised	Apples
Greece	SL	Novagib SL	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	8235	Authorised	Apples and pears
Greece	SL	Perlan	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	8122	Authorised	Apples and pears
Hungary	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	04.2/1345-1/2017. NEBIH	Authorised	Apples and pears

Country	Formulation	Trade name	A.S. Content	Authorisation holder	Reg. Number	Status of application	Registered uses
Italy	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	9696	Authorised	Apples and pears
Italy	SL	Gerlagib LG	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	11185	Authorised	Apples and pears
Italy	SL	Nectar Plus	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	15100	Authorised	Apples and pears
Italy	SL	Nectar	GA4/7, 20 g/L	Fine Agrochemicals Ltd.	10196	Authorised	Apples
Italy	SL	Perlan	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	9695	Authorised	Apple (including tree nursery) and pear
Italy	SL	Progerbalin LG	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	11183	Authorised	Apples and pears
Italy	SL	Profile	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	9550	Authorised	Apples and pears (including tree nurseries)
Italy	SL	Profile Plus	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	16792	Authorised	Apples and pears
Netherlands	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	20120355 ZTG	Authorised	Apples and pears
Netherlands	SL	Floralife Bulb 100	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	15013N	Authorised	Ornamental plant production
Poland	SL	Novagib 010 SL	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	R-32/2016 wu	Authorised	Apples and pears
Portugal	SL	Perlan	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	03868	Provisional	Apples (including nurseries) and pears
Slovenia	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	34330-148/2015/2	Authorised	Apples and pears
Spain	SL	Novagib	GA4/7, 10 g /L	Fine Agrochemicals Ltd.	22.238	Authorised	Apples and pears
Spain	SL	Perlan	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	23.705	Authorised	Apples and pears
UK	SL	Novagib	GA4/7, 10 g	Fine	08954	Authorised	Apples and

Country	Formulation	Trade name	A.S. Content	Authorisation holder	Reg. Number	Status of application	Registered uses
			/L	Agrochemicals Ltd.			pears
UK	SL	Floralife Bulb 100	GA4/7 + 6-BA, 19g/L+19g/L	Fine Agrochemicals Ltd.	17995	Authorised	Ornamental plant production
Austria	SL	Gibb Plus	10 g/L GA4/7	Globachem NV	3279	Authorised	Pome fruits (pear)
Belgium	SL	Gibb Plus	10 g/L GA4/7	Globachem NV	9471P/B	Authorised	Pome fruits (apple, pear and nurseries (apple, pear))
Belgium	SL	Gibb Plus SL	10 g/L GA4/7	Globachem NV	10246P/B	Authorised	Pome fruits (apple)
Belgium	SL	Gibbalin	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	9620P/B	Authorised	Pome fruits (apple, pear, nurseries (apple))
Belgium	SL	Prorex	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	10184/B	Authorised	Pome fruits (apple, pear, nurseries (apple))
Czech Republic	SL	Gibb plus	10 g/L GA4/7	Globachem NV	4856-0	Authorised	Pome fruits (apple)
Germany	SL	Gibb plus	10 g/L GA4/7	Globachem NV	006898-00	Authorised	Pome fruits (pear)
Spain	SL	Folmoxanil	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	24.713	Authorised	Pome fruits (apple and nurseries (apple))
Spain	SL	Gibb plus	10 g/L GA4/7	Globachem NV	24.922	Authorised	Pome fruits (apple)
Spain	SL	Gibbalin	19 g/L GA4/7 + 19 g/L 6-BA	Q-Chem	24.713	Authorised	Pome fruits (apple and nurseries (apple))
Spain	SL	Gibenina	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	24.771	Authorised	Pome fruits (apple and nurseries (apple))
Spain	SL	Keygib	10 g/L GA4/7	Globachem NV	25.125	Authorised	Pome fruits (apple)
Spain	SL	Keygib plus	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	24.400	Authorised	Pome fruits (apple and nurseries (apple))
Finland	SL	Gibb Plus Forest	10 g/L GA4/7	Globachem NV	3330	Authorised	Pines
France	SL	Gibb Plus	10 g/L GA4/7	Globachem NV	2030259	Authorised	Pome fruits (apple)
France	SL	Gibbalin	19 g/L	Globachem	2060079	Authorised	Pome fruits

Country	Formulation	Trade name	A.S. Content	Authorisation holder	Reg. Number	Status of application	Registered uses
			GA4/7 + 19 g/L 6-BA	NV			(apple and nurseries (apple))
Greece	SL	Keygib Max	10 g/L GA4/7	Globachem NV	8263	Authorised	Pome fruits (apple)
Greece	SL	Keygib Plus	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	8183	Authorised	Pome fruits (apple)
Hungary	SL	Gibb Plus	10 g/L GA4/7	Globachem NV	04.2/3508-2/2011	Authorised	Pome fruits (apple)
Ireland	SL	Gibb Plus	10 g/L GA4/7	Globachem NV	5340	Authorised	Pome fruits (apple, pear)
Italy	SL	Agrimix Gold	10 g/L GA4/7	Globachem NV	10889	Authorised	Pome fruits (apple)
Italy	SL	Agrimix Pro	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	10004	Authorised	Pome fruits (apple, pear and nurseries (apple))
Italy	SL	Aramis Plus	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	15502	Authorised	Pome fruits (apple, pear and nurseries (apple))
Italy	SL	Gibb plus	10 g/L GA4/7	Globachem NV	12989	Authorised	Pome fruits (apple, pear)
Italy	SL	Plis	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	12406	Authorised	Pome fruits (apple, pear and nurseries (apple))
Italy	SL	Prorex	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	12857	Authorised	Pome fruits (apple, pear and nurseries (apple))
Luxembourg	SL	Gibb Plus	10 g/L GA4/7	Globachem NV	L01702-101	Authorised	Pome fruits (apple, pear)
Netherlands	SL	Gibb Plus SL	10 g/L GA4/7	Globachem NV	14695N	Authorised	Pome fruits (apple)
Poland	SL	Gibb Plus 11 SL	10 g/L GA4/7	Globachem NV	R-143/2016	Authorised	Pome fruits (apple, pear)
Poland	SL	Gibb Plus	10 g/L GA4/7	Globachem NV	0923	Authorised	Pome fruits (apple)
Poland	SL	Gibbalin	19 g/L GA4/7 + 19 g/L 6-BA	Globachem NV	0924	Authorised	Pome fruits (apple and nurseries (apples))
Sweden	SL	Gibb Plus Forest	10 g/L GA4/7	Globachem NV	5040	Authorised	Pines
UK	SL	GIBB	10 g/L	Globachem	17251	Authorised	Pome fruits

Country	Formulation	Trade name	A.S. Content	Authorisation holder	Reg. Number	Status of application	Registered uses
		Plus	GA4/7	NV			(apple)
Spain	SG	Regulex 10SG	100 g/kg GA4A7 SG	Kenogard SA	24825	Authorised	Apple
Italy	SG	Regulex 10SG, Triumph	100 g/kg GA4A7 SG	Sumitomo Chemical Agro Europe SAS	013063	Authorised	Apple
United Kingdom	SG	Regulex 10SG	100 g/kg GA4A7 SG	Sumitomo Chemical Agro Europe SAS	M17158	Authorised	Apple and pear, and nursery seed production (nothofagus)
Germany	SG	Regulex 10SG	100 g/kg GA4A7 SG	Sumitomo Chemical Agro Europe SAS	006929-00	Authorised	Apple and pear
Austria	SG	Regulex 10SG	100 g/kg GA4A7 SG	Sumitomo Chemical Agro Europe SAS	3400	Authorised	Apple and pear
Poland	SG	Regulex 10SG	100 g/kg GA4A7 SG	Sumitomo Chemical Agro Europe SAS	R-17/2016wu	Authorised	Apple and pear
Netherlands	SG	Regulex 10SG	100 g/kg GA4A7 SG	Sumitomo Chemical Agro Europe SAS	14817N	Authorised	Apple and pear
Belgium	SG	Regulex 10SG	100 g/kg GA4A7 SG	Sumitomo Chemical Agro Europe SAS	7269P/B	Authorised	Apple and pear
France	SG	Regulex 10SG	100 g/kg GA4A7 SG	Sumitomo Chemical Agro Europe SAS	3400	Authorised	Apple and pear
Spain	SL	Promalin	19 g/l GA4A7 and 19 g/l 6-BA SL	Kenogard SA	18210	Authorised	Apple and pear
Slovenia	SL	Promalin	19 g/l GA4A7 and 19 g/l 6-BA SL	Sumitomo Chemical Agro Europe SAS	9448P/B	Authorised	Apple and pear
Italy	SL	Promalin NT, Conquest	19 g/l GA4A7 and 19 g/l 6-BA SL	Sumitomo Chemical Agro Europe SAS	009509	Authorised	Apple and pear
France	SL	Promalin	19 g/l GA4A7 and 19 g/l 6-BA SL	Sumitomo Chemical Agro Europe SAS	8200489	Authorised	Apple and pear

Country	Formulation	Trade name	A.S. Content	Authorisation holder	Reg. Number	Status of application	Registered uses
Greece	SL	Promalin	19 g/l GA4A7 and 19 g/l 6-BA SL	Sumitomo Chemical Agro Europe SAS	8187	Authorised	Apple and pear
Netherlands	SL	Promalin	19 g/l GA4A7 and 19 g/l 6-BA SL	Sumitomo Chemical Agro Europe SAS	15288N	Authorised	Apple and pear
Poland	SL	Promalin	19 g/l GA4A7 and 19 g/l 6-BA SL	Sumitomo Chemical Agro Europe SAS	180/2017	Authorised	Apple and pear

Level 2

GIBBERELLINS (GA4, GA7)

2 SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

Summary of methodology proposed by the applicant for literature review and for all sections

The literature search was performed for both GA3 and GA4/7 at once since the applicant expected that there would be overlap of relevant papers. Only searches in bibliographic databases were undertaken. The public literature search process is documented according to the 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 first public literature search was performed on April 2016 and update on May 2016 due to the finding of too few references for Residues and Toxicology/Human Health. An additional search was carried out in November 2017 due to the extension of the submission date for the renewal dossier. The search period is in line with the requirements of the Commission Implementing Regulation (EU) No 844/2012, as referred in Article 8(5) of Regulation (EC) No 1107/2009.

The search strategies were based on a single concept search. The search was performed combining the terms gibberellic acid or GA3 or gibberellin or GA4/7 or using the belonging CAS Registry numbers and applying them to each of the search terms listed by scientific area (Physical Chemistry, Residues, Toxicology, Environmental fate, Ecotoxicology) the "AND" operator. The summary record retrieved were reported for all the scientific area and searched databases together. The searched databases were Databases BIOSIS, CABA, CAPLUS, MEDLINE and TOXCENTER.

The selection process resulted in three categories of publication:

1. Publications which meet the relevance criteria and are assessed to be reliable which are addressed at the appropriate data points in the relevant Part B Section document of the dossier.
2. Publications which meet the relevance criteria but are assessed to be non -reliable are referenced and a justification for not meeting the reliability criteria provided.
3. Publications not meeting the relevance criteria.

The following relevance criteria were applied:

Data requirement(s) indicated by the correspondent OECD data point number(s)	**Criteria for relevance**
Analytical methods (OECD code: IIA 4)	1. Well described method 2. SANCO/825/00 rev. 8.1.guideline referenced
Toxicological and metabolism studies (OECD code: IIA 5.1 to 5.7)	1. Well-defined test material (including its purity and impurity profile). 2. Relevant test species (to the mammalian toxicological assessment -preferred species are rodents - rats and mice, the dog is the preferred non-rodent species). 3. Number of animals per group sufficient to establish a statistical significance. 4. Several dose levels tested (at least 3), preferably including a negative control, to establish a dose-response. 5. Relevant route of administration in terms of risk assessment (oral, dermal or by inhalation). 6. Description of the observations, examinations, analysis performed, or necropsy. 7. Well described test methodology – appropriate guideline referenced 8. In addition: studies which may be helpful for the interpretation of other studies present in the dossier, but do not fit under a specific toxicological endpoint.

Residues **(OECD code: IIA 6)**	1. Well-defined test material (including its purity and impurity profile). 2. Any information on residues in crops relevant to the EU 3. Well described methodology and results
Fate and behaviour in the environment **(OECD code: IIA 7)**	1. Any information that could affect the environmental parameters, degradation profile or endpoints used in the risk assessment 2. Any environmental monitoring information relevant to the usage pattern. 3. Well defined test material (including its purity and impurity profile). 4. Well described test methodology – appropriate guideline referenced
Ecotoxicological studies **(OECD code: IIA 8)**	1. Well defined test material (including its purity and impurity profile). 2. Relevant test species 3. Number of animals per group sufficient to establish a statistical significance. 4. Several dose levels tested (at least 3), preferably including a negative control, to establish a dose-response. 5. Well described test methodology – appropriate

In the Literature review Report on GA3, there is stated that the reliability assessment for relevant studies was done according to Klimisch *et al.* However, the reliability assessment provided in tables "Reason(s) for not including this study in the dossier« of the Literature Review Report lacks of Klimisch scores (e.g. 1,2,3,4) with description (e.g. not reliable). Thus, it is not entirely clear, how the reliability and relevance assessment of full text publications was done. Some new data requirements were not adequately covered by the literature search (see relevant sections in DRAR Vol 3).

Following an assessment of full-text documents, the applicant included in the dossier 2 publications for risk assessment purpose; both being for section of ecotoxicology. To conclude, the RMS is of the opinion that the applicant should repeat the literature search and more accurately evaluate the outputs.

2.1 IDENTITY

2.1.1 Summary or identity

Data submitted from three members of the GA4/7 Task Force have been evaluated. The three applicants (Fine Agrochemicals Ltd, Globachem and Valent BioSciences) have provided measured data to address several endpoints, including physicochemical properties which are important in the assessment of the potential hazard of the substance. Data from the Agritox database have also been relied on in the dossier. A summary of the data provided and list of waivered endpoints are given below:

1. Status of data provided by Fine Agrochemicals Ltd:

Acceptable data of pure (99% w/w) GA4/7 were provided for: melting point, vapour pressure, Henry's law constant, appearance, IR, NMR, UV-Vis and MS spectra, solubility in water at different pH, solubility in six

different organic solvents, partition coefficient with pH variability, dissociation in water and surface tension. Further acceptable data was provided to address: flammability, explosive and oxidising properties

2. Status of data provided by Globachem:

Acceptable calculations were provided for: melting point, vapour pressure, solubility in water and partition coefficient. An MSDS was considered acceptable for appearance. Acceptable NMR and MS spectra of GA4/7 batches were given. Reasoned expert theoretical statements were provided for explosive and oxidising properties.

3. Status of data provided by Valent BioSciences:

Acceptable data of technical (90.1-92.5% w/w) GA4/7 were provided for: melting/boiling point, vapour pressure, appearance, IR and UV-Vis spectra, water solubility, solubility in six different organic solvents and partition coefficient. Further data on technical GA4/7 were given for: flammability, explosive and oxidising properties. Acceptable data of pure GA4 (97.9% w/w) and GA7 (95-99% w/w) were provided for: IR, NMR and MS spectra. Henry's law constant and dissociation in water were addressed by theoretical calculation.

Reasoned waivers have been submitted for:

- Optical purity
- Spectra of relevant impurities
- Self-heating
- Flash-point
- Self-reacting
- Corrosive to metals

Due to the variation of the GA4:GA7 ratio in the technical active substance (GA4/7) assessed, minor differences were observed among data provided by the three applicants. Despite this, from the data submitted, the following overall conclusions can be drawn:

Gibberellin (GA4/7) is a white, odourless powder with a melting point of 205-231 °C. Thermal decomposition was observed at elevated temperatures (≥210 °C), though GA4 and GA7 have calculated boiling points of around 483 °C. The mean vapour pressure for GA4/7 (99% w/w) at 25 °C was 1 x 10^{-5} Pa. GA4/7 (99% w/w) is moderately soluble in water at pH 4 (141 mg/L) and readily soluble at pH 7 (40 mg/L) and pH 9 (>250 mg/L). GA4/7 (99% w/w) has low to moderate solubility in n-heptane, xylene and dichloroethane (<0.5 to 3380 mg/L), however is readily soluble in pyridine, ethyl acetate, methanol, acetone, propan-2-ol and tetra-hydro-furfuryl alcohol (41 to >250 g/L). The octanol/water partition coefficient for GA4/7 (99% w/w) varies with pH, ranging from -1.23 at pH 10 to 2.47 at pH 4. The dissociation constant (pKa) is 4.35. GA4/7 is not surface active; at a concentration of 114 mg/L and 20 °C it has a surface tension of 64 mN/m. Spectra (IR, NMR and MS) are in agreement with the proposed structure for GA4/7. No relevant impurities have been identified in the technical active substances as manufactured. GA4/7 is not flammable, explosive and oxidising, nor is the substance classified as self-heating, self-reacting or corrosive to metals. The properties indicate that gibberellin (GA4/7) is a low risk active substance with respect to handling, storage and transport

2.2 PHYSICAL AND CHEMICAL PROPERTIES [EQUIVALENT TO SECTION 7 OF THE CLH REPORT TEMPLATE]

2.2.1 Summary of physical and chemical properties of the active substance

Due to the variation of the GA4:GA7 ratio in the technical active substance (GA4/7) assessed, minor differences were observed among data provided by the three applicants. Despite this, from the data submitted, the following overall conclusions can be drawn:
Gibberellin (GA4/7) is a white, odourless powder with a melting point of 205-231 °C. Thermal decomposition was observed at elevated temperatures (≥210 °C), though GA4 and GA7 have calculated boiling points of around 483

°C. The mean vapour pressure for GA4/7 (99% w/w) at 25 °C was 1 x 10-5 Pa. GA4/7 (99% w/w) is moderately soluble in water at pH 4 (141 mg/L) and readily soluble at pH 7 (40 mg/L) and pH 9 (>250 mg/L). GA4/7 (99% w/w) has low to moderate solubility in n-heptane, xylene and dichloroethane (<0.5 to 3380 mg/L), however is readily soluble in pyridine, ethyl acetate, methanol, acetone, propan-2-ol and tetra-hydro-furfuryl alcohol (41 to >250 g/L). The octanol/water partition coefficient for GA4/7 (99% w/w) varies with pH, ranging from 1.23 at pH 10 to 2.47 at pH 4. The dissociation constant (pKa) is 4.35. GA4/7 is not surface active; at a concentration of 114 mg/L and 20 °C it has a surface tension of 64 mN/m. Spectra (IR, NMR and MS) are in agreement with the proposed structure for GA4/7. No relevant impurities have been identified in the technical active substances as manufactured. GA4/7 is not flammable, explosive and oxidising, nor is the substance classified as self-heating, self-reacting or corrosive to metals. The properties indicate that gibberellin (GA4/7) is a low risk active substance with respect to handling, storage and transport.

Table 1: Summary of physicochemical properties of the active substance

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Physical state at 20°C and 101,3 kPa	White, odourless powder at 25 °C Purity: 99% w/w	Comb, 1997 (CA 2.3, DAR: B.2.1.8 FA / IIA 2.4.1)	Visual assessment GLP: Yes
	White, odourless powder at room temperature Purity: 92.5% w/w	Rojas, 1996 (CA 2.3, DAR: B.2.1.7 VA / IIA 2.4.1)	Visual assessment GLP: Yes
Melting/freezing point	205.5-231.0 °C Purity: 99% w/w	Comb, 1997 (CA 2.1, DAR: B.2.1.1 FA / IIA 2.1.1)	EEC A.1, OECD 102 GLP: Yes
	205.6-224.5 °C Purity: 92.5% w/w	Rojas, 1996 (CA 2.1; DAR: B.2.1.1 VA / IIA 2.1.1)	USP 23 for class I (741), OECD 102 GLP: Yes
Boiling point	Boiling point not applicable as decomposition was observed before boiling occurred (at ≥210 °C) Purity: 99% w/w	Comb, 1997 (CA 2.1; DAR: B.2.1.1 FA / IIA 2.1.1)	EEC A.1, OECD 102 GLP: Yes
Relative density	1.27 at 20 °C Purity: 99% w/w	Comb, 1997 (DAR: IIA 2.2)	EEC A.3, OECD 109 GLP: Yes
Vapour pressure	1×10^{-5} Pa at 25 °C (mean) Purity: 99% w/w	Comb, 1997 (CA 2.2; DAR: B.2.1.5 FA / IIA 2.3.1)	EEC A.4, OECD 104 GLP: Yes
	GA4: 0.16 Pa at 22 °C	Purghart, 2000a	EEC A.4,

Property	Value	Reference	Comment (e.g. measured or estimated)
	GA7: 0.067 Pa at 22 °C Purity: 90.8% w/w	(CA 2.2; DAR: B.2.1.5 VA / IIA 2.3.1/01)	OECD 104 GLP: Yes
Surface tension	64 mN/m at 114 mg/L at 20 °C The test substance is not surface active. Purity: 99% w/w	Comb, 1997 (CA 2.12; DAR: B.2.1.24 FA / IIA 2.14)	EEC A.5 GLP: Yes
Water solubility	At 20 °C: Pure water – 127 mg/L pH 4 buffer – 141 mg/L pH 7 buffer – 40 mg/L pH 10 buffer – >250 mg/L Purity: 99% w/w	Comb, 1997 (CA 2.5; DAR: B.2.1.12 FA / IIA 2.6)	EEC A.6, OECD105 GLP: Yes
Partition coefficient n-octanol/water	Log P_{ow} at 20 °C: pH 4 – 2.47 pH 7 – 0.146 pH 10 – -1.23 Purity: 99% w/w	Comb, 1997 (CA 2.7; DAR: B.2.1.14 FA / IIA 2.8)	EEC A.8, OECD 107 GLP: Yes
	Log P_{ow} at 20 °C, without pH control: GA4 = 2.34 GA7 = 2.25 Purity: 90.8% w/w	Purghart, 2000b (CA 2.7; DAR: B.2.1.14 VA / IIA 2.8/01)	EEC A.8, OECD 107 GLP: Yes
Henry's law constant	Henry's law constant = 2.0×10^{-5} Pa m^3 mol^{-1} (20 °C) Purity: 99% w/w	Comb, 1997 (CA 2.7; DAR: B.2.1.14 FA / IIA 2.8)	calculation
Flash point	Not applicable GA4/7 has a melting point of >40 °C.	-	-
Flammability	Not highly flammable Purity: 99% w/w	Comb, 1997 (CA 2.9; DAR: B.2.1.20 FA / IIA 2.11)	EEC A.10 GLP: Yes Only a preliminary test was performed, which is essentially identical to the preferred CLP method: UN Test N.1, Part III, Sub-

Property	Value	Reference	Comment (e.g. measured or estimated)
			section 33.2.1.4.3.1 of the UN-MTC.
	Not highly flammable Purity: 90.8% w/w	Young, 2000 (CA 2.9; DAR: B.2.1.20 VA / IIA 2.11)	EEC A.10 GLP: Yes Only a preliminary test was performed, which is essentially identical to the preferred CLP method: UN Test N.1, Part III, Sub-section 33.2.1.4.3.1 of the UN-MTC.
Explosive properties	Not explosive Purity: 99% w/w	Comb, 1997 (CA 2.11; DAR: B.2.1.23 FA / IIA 2.13)	EEC A.14 GLP: Yes
	Not explosive Purity: 90.8% w/w	Young, 2000 (CA 2.11; DAR: B.2.1.23 VA / IIA 2.13/01)	EEC A.14 GLP: Yes
Self-ignition temperature	Not auto-flammable Purity: 99% w/w	Comb, 1997 (CA 2.9; DAR: B.2.1.21 FA / IIA 2.11.2)	EEC A.16 GLP: Yes
Oxidising properties	Not oxidising Purity: 99% w/w	Comb, 1997 (CA 2.13; DAR: B.2.1.25 FA / IIA 2.15)	EEC A.17 GLP: Yes
	Not oxidising Purity: 90.8% w/w	Young, 2000 (CA 2.13; DAR: B.2.1.25 VA; IIA 2.15/01)	EEC A.17 GLP: Yes
Granulometry	Not relevant	-	-

Property	Value	Reference	Comment (e.g. measured or estimated)
Solubility in organic solvents and identity of relevant degradation products	Not applicable as stability in organic solvents is not considered critical to this substance.	-	-
Dissociation constant	pKa = 4.3 at 23 °C The dissociated species is the corresponding carboxylate anion. Purity: 99% w/w	Comb, 1997 (CA 2.8; DAR: B.2.1.18 FA / IIA 2.9.4)	OECD 112 GLP: Yes
Viscosity	Not applicable as GA4/7 is a solid.	-	-
Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity	The IR, ^{1}H NMR, ^{13}C NMR and MS spectra of GA4/7 support the chemical structure of gibberellins. A methanol solution of GA4/7 absorbed wavelengths at <250 nm. No maxima were observed >210 nm. Molar absorption coefficients (ε) at or above 298 nm were <10 L cm^{-1} mol^{-1}. GA4 and GA7 are enantiomerically pure but given large number of stereogenic centres, analysis in plain polarised light would not confirm optical purity.	Comb, 1997 (CA 2.13; DAR: B.2.1.25 FA / IIA 2.15 Purity: 99% w/w)	OECD 101

2.2.1.1 Evaluation of physical hazards [equivalent to section 8 of the CLH report template]

2.2.1.1.1 Explosives [equivalent to section 8.1 of the CLH report template]

Table 2: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
EEC A.14	Not explosive Purity: 99% w/w	1 (reliable without restriction) Key study Experimental result GLP: Yes	Comb, 1997 (CA 2.11; DAR: B.2.1.23 FA / IIA 2.13)
EEC A.14	Not explosive Purity: 90.8% w/w	1 (reliable without restriction) Key study Experimental result GLP: Yes	Young, 2000 (CA 2.11; DAR: B.2.1.23 VA / IIA 2.13/01)

2.2.1.1.1.1 Short summary and overall relevance of the provided information on explosive properties

In the key experimental studies by Comb (1997) and Young (2004), gibberellin (GA4/7) was tested for explosivity in accordance with EEC Method A.14. As part of the method, the substance was tested for thermal

sensitivity (effect of flame) and mechanical sensitivity (shock and friction). GA4/7 was found to be not explosive. The studies are considered relevant, adequate and reliable without restriction.

2.2.1.1.1.2 Comparison with the CLP criteria

2.2.1.1.1.2.1 Study 1: Comb, 1997

Study reference

A.L. Comb, GA4/7 (99% technical): Determination of the Physico-Chemical Properties, Report No. 96/FNA052/1221, 1997 (Key study, 1 – reliable without restriction).

Test type

GLP study (inc. certificate) run in accordance with EEC Method A.14 and meeting the requirements of Commission Regulation (EU) No 283/2013 (formally Commission Directive 91/414/EEC (Annex II)). A Koenen test apparatus was used for determination of sensitivity to heat (flame), a fall hammer for determination of sensitivity to shock and a friction test apparatus for determination of sensitivity to friction.

Test substance

Identity: GA4/7
Purity: 99% w/w
Batch No.: D104

Method

Thermal sensitivity (flame) test:
The test substance was tested as received. Steel tubes were each filled to a level of 60 mm with test substance. The tubes were sealed with 6 mm nozzle plates and placed in the Koenen apparatus. Each tube was heated by four propane burners for up to five minutes. The procedure was repeated three times and then a further three times with a 2 mm nozzle plate.
Mechanical sensitivity (shock) test:
The test substance was sieved (500 μm) prior to testing. A 10 kg weight was released from a height of 0.4 m onto the test assembly containing test material (40 mm^3). The test was performed six times.
Mechanical sensitivity (friction) test:
The test substance was sieved (500 μm) prior to testing. Test substance (10 mm^3) was loaded onto the porcelain plate of the friction apparatus. The plate was placed in a position on the tester and a force of 360 N applied. The test was performed six times.

Results

Thermal sensitivity (flame) test:
Apparatus tubes were recovered unchanged.
Mechanical sensitivity (shock and friction) tests:
No evidence of explosion or decomposition.

Conclusion

GA4/7 was not explosive under the test conditions

2.2.1.1.1.2.2 Study 2: Young, 2000

Study reference

S. Young, Gibberellin A4/A7 Physicochemical Properties, Report No. VLT 013/004024, 2000 (Key study, 1 – reliable without restriction).

Test type

GLP study (inc. certificate) run in accordance with EEC Method A.14 and meeting the requirements of Commission Regulation (EU) No 283/2013 (formally Commission Directive 91/414/EEC (Annex II)). A Koenen

test apparatus was used for determination of sensitivity to heat (flame), a fall hammer for determination of sensitivity to shock and a friction test apparatus for determination of sensitivity to friction.

Test substance
Identity: Gibberellin A4/A7
Purity: 90.8% w/w total GA4/7, 72.5% w/w GA4.
Batch No.: 33263CD00

Method
The test substance was sieved (0.5 mm) and dried prior to testing.
Thermal sensitivity (flame) test:
A steel tube (75 mm x 24 mm) was filled to a level of 60 mm with test substance (*c.a.* 21.0 g). The tube was sealed with a 6 mm orifice plate and placed in the Koenen apparatus. The propane burners (heating rate of 214.3 °C/min) were ignited and allowed to burn for five minutes or until an explosion occurred. This procedure was repeated three times and then a further three times with a 2 mm orifice plate.
Mechanical sensitivity (shock) test:
Test substance (40 mm^3) was added to the die assembly and placed on the anvil in the drop hammer apparatus. A 10 kg weight was released from a height of 0.4 m onto the test sample. The test was performed six times using fresh sample and die assembly each time.
Mechanical sensitivity (friction) test:
Test substance (10 mm^3) was placed on the porcelain plate of the friction apparatus, and the porcelain peg drawn across with a loading of 360 N. The test was performed six times with fresh sample each time.

Results
Thermal sensitivity (flame) test:
No explosion observed and no deformation to any of the apparatus tubes.
Mechanical sensitivity (shock and friction) tests:
No visible or audible reaction observed.

2.2.1.1.1.3 Conclusion on classification and labelling for explosive properties

GA4/7 was not explosive under the test conditions.

2.2.1.1.2 Flammable gases (including chemically unstable gases) [equivalent to section 8.2 of the CLH report template]

Hazard classification not relevant (see 2.2.1.1.2.3).

Table 3: Summary table of studies on flammable gases (including chemically unstable gases)

Method	Results	Remarks	Reference
-	-	-	-

2.2.1.1.2.1 Short summary and overall relevance of the provided information on flammable gases (including chemically unstable gases)

Not necessary (see 2.2.1.1.2.3).

2.2.1.1.2.2 Comparison with the CLP criteria

Not necessary (see 2.2.1.1.2.3).

2.2.1.1.2.3 Conclusion on classification and labelling for flammable gases

GA4/7 does not require classification as a flammable or chemically unstable gas under the CLP Regulation as GA4/7 is a solid.

2.2.1.1.3 Oxidising gases [equivalent to section 8.3 of the CLH report template]

Hazard classification not relevant (see 2.2.1.1.3.3).

Table 4: Summary table of studies on oxidising gases

Method	Results	Remarks	Reference
-	-	-	-

2.2.1.1.3.1 Short summary and overall relevance of the provided information on oxidising gases

Not necessary (see 2.2.1.1.3.3).

2.2.1.1.3.2 Comparison with the CLP criteria

Not necessary (see 2.2.1.1.3.3).

2.2.1.1.3.3 Conclusion on classification and labelling for oxidising gases

GA4/7 does not require classification as an oxidising gas under the CLP Regulation as GA4/7 is a solid.

2.2.1.1.4 Gases under pressure [equivalent to section 8.4 of the CLH report template]

Hazard classification not relevant (see 2.2.1.1.4.3).

Table 5: Summary table of studies on gases under pressure

Method	Results	Remarks	Reference
-	-	-	-

2.2.1.1.4.1 Short summary and overall relevance of the provided information on gases under pressure

Not necessary (see 2.2.1.1.4.3).

2.2.1.1.4.2 Comparison with the CLP criteria

Not necessary (see 2.2.1.1.4.3).

2.2.1.1.4.3 Conclusion on classification and labelling for gases under pressure

GA4/7 does not require classification as a gas under pressure under the CLP Regulation as GA4/7 is a solid.

2.2.1.1.5 Flammable liquids [equivalent to section 8.5 of the CLH report template]

Hazard classification not relevant (see 2.2.1.1.5.3).

Table 6: Summary table of studies on flammable liquids

Method	Results	Remarks	Reference
-	-	-	-

2.2.1.1.5.1 Short summary and overall relevance of the provided information on flammable liquids

Not necessary (see 2.2.1.1.5.3).

2.2.1.1.5.2 Comparison with the CLP criteria

Not necessary (see 2.2.1.1.5.3).

2.2.1.1.5.3 Conclusion on classification and labelling for flammable liquids

GA4/7 does not require classification as a flammable liquid under the CLP Regulation as GA4/7 is a solid.

2.2.1.1.6 Flammable solids [equivalent to section 8.6 of the CLH report template]

Table 7: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
EEC A.10	Not highly flammable Purity: 99% w/w	1 (reliable without restriction) Key study Experimental result GLP: Yes	Comb, 1997 (CA 2.9; DAR: B.2.1.20 FA / IIA 2.11)
EEC A.10	Not highly flammable Purity: 90.8% w/w	1 (reliable without restriction) Key study Experimental result GLP: Yes	Young, 2000 (CA 2.9; DAR: B.2.1.20 VA / IIA 2.11)

2.2.1.1.6.1 Short summary and overall relevance of the provided information on flammable solids

In the key experimental studies by Comb (1997) and Young (2004), gibberellin (GA4/7), a white powder, was tested for flammability in accordance with EEC Method A.10. In both studies, GA4/7 melted but did not ignite and so was concluded to be not highly flammable under the test conditions. The studies are considered relevant, adequate and reliable without restriction.

2.2.1.1.6.2 Comparison with the CLP criteria

According to the Regulation (EC) No 1272/2008 (CLP), a flammable solid is "*readily combustible, or may cause or contribute to fire through friction. Readily combustible solids are powdered, granular, or pasty substances or mixtures which are dangerous if they can be easily ignited by brief contact with an ignition source, such as a burning match, and if the flame spreads rapidly.*" (Annex I, Part 2, Section 2.7.1.1).
The substance should be tested for flammability in accordance with the test method N.1 described in Part III, sub-section 33.2.1, of the UN RTDG MTC. A flammable solid is classified as either Category 1 (Danger), Category 2 (Warning) or Not Classified based on the results of a preliminary screening test and burning rate test:

Category	**Criteria**	
	For substances or mixtures other than metal powders	*For metal powders*
1	The screening test is positive and the burning time is <45s / burning rate is >2.2 mm/s and the wetted zone does not stop the fire.	The screening test is positive and the burning time is <5 min.
2	The screening test is positive and the burning time is <45s / burning rate is >2.2 mm/s and the wetted zone does stop the fire.	The screening test is positive and the burning time is ≤10 min and >5 min.
Not Classified	Screening test is negative or the screening test is positive and the burning time is >45s / burning rate is <2.2 mm/s.	The screening test is negative or the screening test is positive and the burning time is >10 min.

If in the preliminary screening test the substance does not ignite and propagate combustion either by burning with flame or smouldering, it is not necessary to perform the complete burning rate test. In this case, the substance is not considered a readily combustible or highly flammable solid.
GA4/7 was tested for flammability (Comb, 1997 and Young, 2000) using EEC Method A.10. The test method EEC A.10 is considered sufficiently similar to the guideline test method N.1 in Part III, sub-section 33.2.1 of the UN RTDG MTC to be used for classification of the substance under CLP. The Commission Communication 2013/C 95/01 requires either EEC Method A.10 (flammable solids) or Test N.1 of the UN RTDG MTC (Part III, sub section 33.2.1) to determine flammability of the (solid) active substance.
Both experimental studies concluded that GA4/7 was not highly flammable under the test conditions: GA4/7 melted but failed to ignite during the preliminary screening tests and so the full burning rate test was not required.

2.2.1.1.6.3 Conclusion on classification and labelling for flammable solids

The flammability of GA4/7 was determined following the procedures specified in EEC Method A.10 and was found to be not highly flammable. GA4/7 should not therefore be classified under this CLP endpoint.

2.2.1.1.7 Self-reactive substances [equivalent to section 8.7 of the CLH report template]

Hazard classification not necessary (see 2.2.1.1.7.2 and 2.2.1.1.7.3).

Table 8: Summary table of studies on self-reactivity

Method	Results	Remarks	Reference
-	-	-	-

2.2.1.1.7.1 Short summary and overall relevance of the provided information on self-reactive substances

Not necessary (see 2.2.1.1.7.2 and 2.2.1.1.7.3).

2.2.1.1.7.2 Comparison with the CLP criteria

The CLP Regulation defines self-reactive substances or mixtures as "*thermally unstable liquid or solid substances or mixtures liable to undergo a strongly exothermic decomposition even without participation of oxygen (air)"* (Annex I, Part 2, Section 2.8.1.1) and "*liable to detonate, to deflagrate rapidly or to show a violent effect when heated under confinement"* (Annex I, Part 2, Section 2.8.1.2). These definitions exclude substances and mixtures classified as explosives, organic peroxides or oxidising.

Self-reactive substances and mixtures are classified into one of seven categories: Types A (most hazardous) through to G (least hazardous) in accordance with test series A to H (Part II) of the UN RTDG MTC. Specific criteria for each category are outlined in the CLP Regulation.

However, the classification procedures for self-reactive substances and mixtures need not be applied if there are no chemical groups present in the molecule associated with self-reactive (Table 12) or explosive (Table 10) properties.

Table 1: Examples of chemical groups indicating self-reactive properties in organic materials (Table A6.2 in Appendix 6 of the UN RTDG MTC)

Structural Feature	Examples
Mutually reactive groups	Aminonitriles, haloanilines, organic salts of oxidising acids
S=O	Sulphonyl halides, sulphonyl cyanides, sulphonyl hydrazides
P-O	Phosphites
Strained rings	Epoxides, aziridines
Unsaturation	Olefins, cyanates

Additionally, ECHA guidance (Guidance on the Application of the CLP Criteria, Version 5.0, July 2017) lists the following examples of self-reactive moieties:

- Aliphatic azo compounds (-C-N=N-C-)
- Organic azides (-C-N_3)
- Diazonium salts (-$CN_2^+Z^-$)
- N-nitroso compounds (-N-N=O)

- Aromatic sulfohydrasides (-SO_2-NH-NH_2).

These lists are not exhaustive and substances with other reactive groups, combination of groups and some mixtures of substances may display similar properties whilst not containing these groups.

A theoretical evaluation of the chemical structure of GA4/7 confirms that the substance does contain any chemical groups associated with explosivity (Table 10). Although, the structure does contains olefins (alkenes), which might suggest self-reactive behaviour (Table 12). However, GA4/7 is considered a thermally stable solid (see 8.1, 8.6 and 8.10) that would not be expected to be susceptible to rapid, exothermic chemical reaction. Furthermore, gibberellin is a naturally occurring plant hormone, where, experience in handling and manufacture of the substance has shown no indication of self-reactive properties. Therefore, GA4/7 is not expected to possess self-reactive properties and so the classification procedure for self-reactive substances need not be applied.

2.2.1.1.7.3 Conclusion on classification and labelling for self-reactive substances

There is sufficient information available to propose that GA4/7 is not a self-reactive solid without the need for testing and application of the classification procedure. GA4/7 is not proposed for classification under the endpoints of: explosives (see 8.1), flammable solids (see 8.6) or self-heating substances (see 8.10). Therefore, GA4/7 is considered to be thermally stable and unlikely to undergo rapid, exothermic chemical reaction. GA4/7 is also a naturally occurring plant hormone, where, experience in handling and manufacture of the substance has shown no indication of self-reactive properties. GA4/7 should not therefore be classified as a self-reactive substance under CLP.

2.2.1.1.8 Pyrophoric liquids [equivalent to section 8.8 of the CLH report template]

Hazard classification not relevant (see 2.2.1.1.8.3).

Table 9: Summary table of studies on pyrophoric liquids

Method	Results	Remarks	Reference
-	-	-	-

2.2.1.1.8.1 Short summary and overall relevance of the provided information on pyrophoric liquids

Not necessary (see 2.2.1.1.8.3).

2.2.1.1.8.2 Comparison with the CLP criteria

Not necessary (see 2.2.1.1.8.3).

2.2.1.1.8.3 Conclusion on classification and labelling for pyrophoric liquids

GA4/7 does not require classification as a pyrophoric liquid under the CLP Regulation as GA4/7 is a solid.

2.2.1.1.9 Pyrophoric solids [equivalent to section 8.9 of the CLH report template]

Table 10: Summary table of studies on pyrophoric solids

Table 10: Summary table of studies on pyrophoric solids

Method	Results	Remarks	Reference
EEC A.16	Not auto-flammable. GA4/7 does not self-ignite before melting (206-231 °C). Purity: 99% w/w	1 (reliable without restriction) Key study Experimental result GLP: Yes	Comb, 1997 (CA 2.9; DAR: B.2.1.21 FA / IIA 2.11.2)

2.2.1.1.9.1 Short summary and overall relevance of the provided information on pyrophoric solids

In the key experimental study by Comb (1997), the relative self-ignition temperature of gibberellins (GA4/7) was measured according to EEC Method A.16. GA4/7 did not self-ignite before melting (206-231 °C). The study is relevant to understand the thermal stability of GA4/7, and in turn determine whether the substance displays pyrophoric behaviour. The study is accurate and reliable without restriction.

2.2.1.1.9.2 Comparison with the CLP criteria

The CLP Regulation defines a pyrophoric solid as "*a solid substance or mixture which, even in small quantities, is liable to ignite within five minutes after coming into contact with air*" (Annex I, Part 2, Section 2.10.1.). In other words, the self-ignition temperature for a pyrophoric substance or mixture is lower than room (ambient) temperature.
Pyrophoric solids are classified into a single category (Category 1) if results of test N.2 described in Part III, sub-section 33.3.1.4, of the UN RTDG MTC show that the solid ignites within five minutes of coming into contact with air.
The classification procedure for pyrophoric solids need not be applied when experience in manufacture or handling shows that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the substance is known to be stable at room temperature for prolonged periods of time (days)).
GA4/7 does not have a self-ignition temperature lower than room (ambient) temperature and in fact does not self-ignite below its melting point of 206-231 °C (Comb, 1997). GA4/7 is not auto-flammable. As such, the classification procedure for pyrophoric solids need not be applied to GA4/7.

2.2.1.1.9.3 Conclusion on classification and labelling for pyrophoric solids

There is sufficient data available to propose that GA4/7 is not a pyrophoric solid without the need for testing in accordance with guideline test method N.2 of the UN RTDG MTC. GA4/7 is not auto-flammable according to EEC Method A.16 and does not have a self-ignition temperature below 206-231 °C (Comb, 1997). Experience in handling the active substance therefore shows that GA4/7 does not ignite spontaneously on coming into contact with air at ambient temperatures. In conclusion, GA4/7 should not be classified as a pyrophoric solid under CLP.

2.2.1.1.10 Self-heating substances [equivalent to section 8.10 of the CLH report template]

Table 11: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
EEC A.16	Not auto-flammable. GA4/7 does not self-ignite before melting (206-231 °C). Purity: 99% w/w	1 (reliable without restriction) Key study	Comb, 1997 (CA 2.9; DAR: B.2.1.21 FA / IIA 2.11.2)

Method	Results	Remarks	Reference
		Experimental result GLP: Yes	

2.2.1.1.10.1 Short summary and overall relevance of the provided information on self-heating substances

In the key experimental study by Comb (1997), the relative self-ignition temperature of gibberellins (GA4/7) was measured according to EEC Method A.16. GA4/7 did not self-ignite before melting (206-231 °C). The study is relevant to understand the thermal stability of GA4/7, and in turn determine whether the substance displays self-heating behaviour. The study is accurate and reliable without restriction.

2.2.1.1.10.2 Comparison with the CLP criteria

The CLP Regulation (Regulation (EC) No 1272/2008) defines self-heating substances and mixtures in the following terms:

- "*A liquid or solid substance or mixture, other than a pyrophoric liquid or solid, which by reaction with air and without energy supply, is liable to self-heat; […] it will ignite only when in large amounts (kilograms) and after long periods of time (hours or days)*" (Annex I, Part 2, Section 2.11.1.1).
- "*A process where the gradual reaction of that substance or mixture with oxygen (in the air) generates heat. If the rate of heat production exceeds the rate of heat loss, then the temperature of the substance or mixture will rise which, after an induction time, may lead to self-ignition and combustion.*" (Annex I, Part 2, Section 2.11.1.2).

The phenomenon of self-heating can occur only where a large surface of substance or mixture is in contact with air or oxygen (for example, piles of powders, crystals, splinters, any other rough surface etc.).
In order to be classified under CLP, the substance should be tested for self-heating properties using test method N.4 described in Part III, sub-section 33.3.1.6 of the UN RTDG MTC. A positive result is obtained if spontaneous ignition occurs or if the temperature of the sample exceeds the oven temperature by 60 °C during the 24 hour testing period. For positive results, the CLP Regulation has defined two categories (1 and 2), where specific criteria for each category is outlined in the CLP Regulation. If a negative result is obtained, the material is not classified under this endpoint.
The classification procedure for self-heating substances or mixtures need not be applied if the results of a screening test (e.g. The Grewer Oven test or The Bulk Powder Screening test) can be adequately correlated with the classification test and an appropriate safety margin is applied.

Although not tested for self-heating properties under the guideline test method, there is data available to propose that GA4/7 does not possess self-heating properties and so the classification procedure for self-heating substances need not be applied. GA4/7 does not self-ignite before melting (206-231 °C) and is not considered auto-flammable (Comb, 1997). GA4/7 is not explosive (see 8.1), flammable (see 8.6) or oxidising (see 8.13). Experience in handling of GA4/7 therefore supports the fact that the substance is thermally stable and so is unlikely to possess self-heating properties. Furthermore, GA4/7 is a naturally occurring plant hormone that features no chemically unstable functional groups that could lead to an exothermic reaction with the oxygen in the air.

2.2.1.1.10.3 Conclusion on classification and labelling for self-heating substances

There is sufficient data available to propose that GA4/7 is not a self-heating solid without the need for testing in accordance with guideline test method N.4 of the UN RTDG MTC. Gibberellin (GA4/7) is considered thermally stable:

- GA4/7 does not self-ignite before melting (206-231 °C) and is not auto-flammable (Comb, 1997)

- No explosion or deformation to any of the apparatus steel tubes were observed as part of the Koenen test to determine thermal sensitivity (see 8.1);
- GA4/7 melted but failed to ignite during the preliminary screening test for flammability (potential ignition of GA4/7 by flame, see 8.6);

GA4/7 is also mechanically (shock and friction) stable (see 8.1) and non-oxidising (see 8.13). In conclusion, GA4/7 should not be considered for classification under this CLP endpoint.

2.2.1.1.11 Substances which in contact with water emit flammable gases [equivalent to section 8.11 of the CLH report template]

Hazard classification not necessary (see 2.2.1.1.11.2 and 2.2.1.1.3).

Table 12: Summary table of studies on substances which in contact with water emit flammable gases

Method	Results	Remarks	Reference
-	-	-	-

2.2.1.1.11.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

Not necessary (see 2.2.1.1.11.2 and 2.2.1.1.3).

2.2.1.1.11.2 Comparison with the CLP criteria

to "*solid or liquid substances or mixtures which, by interaction with water, are liable to become spontaneously flammable or to give off flammable gases in dangerous quantities.*" (Annex I, Part 2, Section 2.12.1.)

Substances which in contact with water emit flammable gases are tested using test method N.5 of the UN RTDG MTC (Part III, sub-section 33.4.1.4) and are classified under this endpoint as either Category 1 (most hazardous), Category 2 or Category 3 (least hazardous) if spontaneous ignition is observed at any stage of the test procedure.

However, the classification procedure need not be applied if:

- the chemical structure of the substance or mixture does not contain metals or metalloids, or;
- experience in handling and use shows that the substance or mixture does not react with water, e.g. the substance is manufactured with water or washed with water, or;
- the substance or mixture is known to be soluble in water to form a stable mixture.

A theoretical evaluation of the chemical structure of gibberellin (GA4/7) confirms that the substance does not contain metals or metalloids. The classification procedure of GA4/7 for this hazard class is therefore not necessary.

2.2.1.1.11.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

Classification of GA4/7 under this CLP endpoint does not need to be applied as the chemical structure of GA4/7 does not contain metals or metalloids.

2.2.1.1.12 Oxidising liquids [equivalent to section 8.12 of the CLH report template]

Hazard classification not relevant (see 2.2.1.1.12.3).

Table 13: Summary table of studies on oxidising liquids

Method	Results	Remarks	Reference
-	-	-	-

2.2.1.1.12.1 Short summary and overall relevance of the provided information on oxidising liquids

Not necessary (see 2.2.1.1.12.3).

2.2.1.1.12.2 Comparison with the CLP criteria

Not necessary (see 2.2.1.1.12.3).

2.2.1.1.12.3 Conclusion on classification and labelling for oxidising liquids

Gibberellin (GA4/7) does not require classification as an oxidising liquid under the CLP Regulation as GA4/7 is a solid.

2.2.1.1.13 Oxidising solids [equivalent to section 8.13 of the CLH report template]

Table 14: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
EEC A.17	Not oxidising Purity: 99% w/w	1 (reliable without restriction) Key study Experimental result GLP: Yes	Comb, 1997 (CA 2.13; DAR: B.2.1.25 FA / IIA 2.15)
EEC A.17	Not oxidising Purity: 90.8% w/w	1 (reliable without restriction) Key study Experimental result GLP: Yes	Young, 2000 (CA 2.13; DAR: B.2.1.25 VA; IIA 2.15/01)

2.2.1.1.13.1 Short summary and overall relevance of the provided information on oxidising solids

In the key experimental studies by Comb (1997) and Young (2000), the oxidising properties of gibberellin (GA4/7) were tested in accordance with EEC Method A.17. GA4/7 was found to be not oxidising under the test conditions. The studies are considered relevant, adequate and reliable without restriction.

2.2.1.1.13.2 Comparison with the CLP criteria

According to the CLP Regulation, an oxidising solid is a "*solid substance or mixture which, while in itself is not necessarily combustible, may, generally by yielding oxygen, cause, or contribute to, the combustion of other material*." (Annex I, Part 2, Section 2.14.1.)

Oxidising solids are classified under this endpoint as either Category 1 (most hazardous), Category 2 or Category 3 (least hazardous) using method O.1 of the UN RTDG MTC (Part III, sub-section 34.4.1).

Although, the classification procedure for this hazard class need not be applied if:

- the substance or mixture does not contain oxygen, fluorine or chlorine; or
- the substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen.

A theoretical evaluation of the chemical structure of GA4/7 confirms that the substance does contain oxygen atoms; however these elements are chemically bonded only to carbon or hydrogen. The classification procedure for this hazard class is therefore not necessary. Additionally the oxidising properties of GA4/7 were experimentally determined (Comb, 1997 and Young, 2000). GA4/7 was found to be not oxidising.

2.2.1.1.13.3 Conclusion on classification and labelling for oxidising solids

The classification procedure under this endpoint does not need to be applied as the chemical structure of GA4/7 contains oxygen atoms that are bonded only to carbon or hydrogen. Additionally, the oxidising properties of GA4/7 were experimentally determined using EEC Method A.17. GA4/7 was found to be not oxidising. GA4/7 should not be classified as an oxidising solid under CLP.

2.2.1.1.14 Organic peroxides [equivalent to section 8.14 of the CLH report template]

Not necessary (see 2.2.1.1.14.2 and 2.2.1.1.14.3).

Table 15: Summary table of studies on organic peroxides

Method	Results	Remarks	Reference
-	-	-	-

2.2.1.1.14.1 Short summary and overall relevance of the provided information on organic peroxides

Not necessary (see 2.2.1.1.14.2 and 2.2.1.1.14.3).

2.2.1.1.14.2 Comparison with the CLP criteria

The hazard class of organic peroxides is assigned purely on chemical structure. According to the CLP Regulation, organic peroxides are defined as "*liquid or solid organic substances which contain the bivalent -O-O- structure and may be considered derivatives of hydrogen peroxide, where one or both of the hydrogen atoms have been replaced by organic radicals.*" (Annex I, Part 2, Section 2.15.1.1.)

If assigned, organic peroxides are classified into one of seven categories using the test series (Part II) described in the UN RTDG MTC: Types A (most hazardous) through to G (least hazardous). Classification depends on the detonation, deflagration and thermal explosion properties of the substance; response to heating under confinement; explosive power and the concentration and the type of diluent added to desensitise the organic peroxide.

A theoretical evaluation of the chemical structure of GA4/7 confirms that the substance does contain the bivalent -O-O- structure. The classification procedure for this hazard class is therefore not necessary.

2.2.1.1.14.3 Conclusion on classification and labelling for organic peroxides

Classification of GA4/7 under this endpoint does not need to be applied as the chemical structure of GA4/7 does not contain the bivalent -O-O- structure and so is not regarded as an organic peroxide.

2.2.1.1.15 Corrosive to metals [equivalent to section 8.15 of the CLH report template]

Table 16: Summary table of studies on the hazard class corrosive to metals

Method	Results	Remarks	Reference
EEC A.1, OECD 102	205.5-231.0 °C Purity: 99% w/w	1 (reliable without restriction) Key study Experimental result GLP: Yes	Comb, 1997 (CA 2.1, DAR: B.2.1.1 FA / IIA 2.1.1)
USP 23 for class I (741), OECD 102	205.6-224.5 °C Purity: 92.5% w/w	1 (reliable without restriction) Key study Experimental result GLP: Yes	Rojas, 1996 (CA 2.1; DAR: B.2.1.1 VA / IIA 2.1.1)

2.2.1.1.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

In the two key experimental studies, the melting point of gibberellin (GA4/7) was within the range 205.5-231.0 °C in accordance with OECD Method 102 (Comb, 1997 and Rojas, 1996). The studies are relevant to understand the thermal stability of GA4/7 and in turn support whether the substance should be classified under this endpoint. The studies are accurate and reliable without restriction.

2.2.1.1.15.2 Comparison with the CLP criteria

According to the CLP Regulation, "*a substance or a mixture that is corrosive to metals means a substance or a mixture which by chemical action will materially damage, or even destroy, metals*." (Annex I, Part 2, Section 2.16.1.)

Materials considered under this endpoint should be tested using method C.1 of the UN RTDG MTC (Part III, sub-section 37.4). If test results show that the corrosion rate on either steel or aluminium surfaces exceeds 6.25 mm/yr at a test temperature of 55 °C when tested on both materials, test substances/mixtures are classified as Category 1. Otherwise, the substance/mixture is not classified under this endpoint. The test is only applicable to liquids and solids that may become liquid during transport, i.e. by melting due to an increase in temperature or by dissolution in water, following exposure of the solid to e.g. atmospheric moisture or unintentional contact with water. The corrosive properties of a preparation are influenced by the nature of the material and/or the pH (for a liquid).

GA4/7 has a melting point range of 205.5-231.0 °C (Comb, 1997 and Rojas, 1996) so is therefore considered thermally stable and not likely to become liquid during transport through melting. Although gibberellin contains an acidic (COOH) functional group, the material is not expected to corrode metal at the rate required for classification. Previous manufacture and handing experience has also given no indication that GA4/7 is corrosive to metals. In addition there is currently no accepted test method to determine this property of solids. The CLP criteria for the hazard class of corrosive to metals need not therefore be applied to GA4/7.

2.2.1.1.15.3 Conclusion on classification and labelling for corrosive to metals

The CLP endpoint corrosive to metals is associated with substances or mixtures with a low melting point (<55 °C) and extreme pHs. Chemical characteristics associated with this property include acidic or basic functional groups and halogens. The test applies to liquids and solids that may become liquid during transport, although, there is currently no accepted test method to measure this property of solids.

GA4/7 has a high melting point range 205.5-231.0 °C (OECD method 112; Comb, 1997 and Rojas, 1996) so is considered thermally stable and not likely to become liquid during transport through melting. Previous manufacture and handing experience has given no indication that GA4/7 is corrosive to metals and so the material is not expected to corrode metal at the rate required for classification. GA4/7 should not therefore be classified under this CLP endpoint.

2.2.2 Summary of physical and chemical properties of the plant protection product

Novagib is a clear, colourless liquid with an odour similar to a heavy alcohol. The product is not explosive, oxidising or flammable: Novagib has a flash point of 86 °C at atmospheric pressure. As a 1% w/v solution, Novagib has a pH of 4.11. The formulation has a relative density of 1.04, kinematic viscosities of 57.8 and 20.3 mm^2/s (at 20 and 40 °C, respectively) and an aqueous surface tension of 71.5 mN/m (0.25 and 0.002% v/v, 20 °C) and so is not surface active. Accelerated storage stability data (two weeks at 54 °C) and long-term storage stability data (two years at ambient temperature) on Novagib in commercial packaging were considered acceptable as no significant changes were noted in the following physical properties: persistence of foaming, pH, acidity, dilution stability, packaging stability and weight following storage. Dilution stability and persistent foaming were within acceptable FAO guidelines. Novagib is not considered for classification as self-heating, self-reacting or corrosive to metals. The properties indicate that Novagib is low risk with respect to handling, storage and transport.

2.3 DATA ON APPLICATION AND EFFICACY

Plant protection product Novagib is used outdoors as plant growth regulator in agriculture, in orchards: apples and pears as representative uses for reduction of russet and fruit cracking, improvement of fruit and fruit set quality.

Novagib containing gibberellins (GA4/GA7) at a concentration of 10 g/L.Gibberellins (GA4/GA7) is plant growth regulator and does not act against harmful organisms, against weeds, insects, fungi or other pests.
The mode of action of gibberellins is complex and the molecular basis of their effect of cell elongation is currently not fully understood. However, it is known that they induce the transcription of genes responsible for cell elongation in plants and upregulate expression of enzymes known to loosen cell wall structures. Increased plasticity of cellular wall structures then enhance cell expansion. The biological activity of different groups of gibberellins varies with plant species. For example, while golden delicious apple russet was significantly reduced by GA_4/GA_7, GA_3 showed no significant effect (Werthheim 1982).

Novagib is applied to apples at 2.5 - 5 g a.s./ha (0.25-0.5 L PPP/ha) up to 4 applications at 7 to 10 day intervals from BBCH 69 – 74 (April – July) and to pears at 6 -12 g a.s./ha (0.6-1.2 L PPP/ha) one or two applications at 3 day interval from BBCH 62 – 69 (March – May) using tractor mounted orchard sprayer and using water volumes of 300 - 1000 l/ha.

2.3.1 Summary of effectiveness

No effectiveness data were provided for the renewal of the active substance. Detailed consideration of efficacy will be fully assessed in the context of subsequent product authorisation process when a full biological assessment dossier will be required.

2.3.2 Summary of information on the development of resistance

No data were provided for the renewal of the active substance. Detailed consideration of information on the development of resistance will be fully assessed in the context of subsequent product authorisation process when a full biological assessment dossier will be required. Gibberellins (GA4/GA7) is plant growth regulator and does not act against weeds, insects, fungi or other pests and therefore occurrence of resistance is not relevant. However, based on the function of gibberellins (GA4/GA7) as plant growth regulator, there is no expectation of resistance in treated crops.

2.3.3 Summary of adverse effects on treated crops

No data were provided for the renewal of the active substance. Detailed consideration of adverse effects on treated crops will be fully assessed in the context of subsequent product authorisation process when a full biological assessment dossier will be required.

2.3.4 Summary of observations on other undesirable or unintended side-effects

No data were provided for the renewal of the active substance. Detailed consideration of observations on other undesirable or unintended side-effects will be fully assessed in the context of subsequent product authorisation process when a full biological assessment dossier will be required.

2.4 FURTHER INFORMATION

2.4.1 Summary of methods and precautions concerning handling, storage, transport or fire

Handling:
Ensure adequate ventilation. Keep in a cool, dry, well ventilated place. Keep away from food, drink and animal feedstuffs. The usual precautions for handling chemicals should be observed. Use good personal hygiene practices. Wash thoroughly after use. Wear suitable protective clothing and gloves.
In case of fire use foam, carbon dioxide or dry agent. Large volumes my penetrate soil and contaminate groundwater. Seek expert advice for removal and disposal of all contaminated materials and wastes. Wear chemical protection suit and positive-pressure breathing apparatus.

2.4.2 Summary of procedures for destruction or decontamination

Do not discharge into drains or the environment, dispose to an authorised waste collection point. Incineration by an approved method could be considered. Do not reuse any empty containers.

2.4.3 Summary of emergency measures in case of an accident

Wear protective clothing. Do not allow to enter public sewers and watercourses. Contain spillage by any means possible. If contamination of drainage systems or water courses is unavoidable, immediately inform appropriate

authorities. Absorb spillage in suitable inert material. Place in sealable container. Remove contaminated material to safe location for subsequent disposal.

2.5 METHODS OF ANALYSIS

2.5.1 Methods used for the generation of pre-authorisation data

2.5.1.1 Analysis of the active substance as manufactured

Validated methods of analysis have been submitted for the determination of the active substance GA4/7 (gibberellin) in the technical material. The methods rely on high performance liquid chromatography coupled with either UV detection (HPLC-UV) at 204 nm or 210 nm or a combination of a diode array detector and mass spectrometer (HPLC/MS/DAD) run over 190 to 500 nm. The methods were considered acceptable.

2.5.1.2 Formulation analysis

Two validated methods for the analysis of GA4/7 in the plant protection product, Novagib, were submitted and considered acceptable. The first method, detecting amounts of GA4 as a representation of total GA4/7 contents, uses HPLC-UV at 210 nm. The second method, detecting both GA4 and GA7, relies on HPLC-UV at 206 nm.

2.5.1.3 Methods for Risk Assessment

A method for the determination of GA4/7 in soil, in support of environmental fate studies, is presented in the dossier. Soil samples were fortified with GA4 and GA7 (in acetonitrile) then extracted twice with acetonitrile:water mixture (80:20, v/v); the final extraction occurring at 55 °C via microwave. Concentrations of GA4/7 were quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The method was validated in German standard soil LUFA 2.1, 2.2, 2.3 and 6S. The LOQ was 0.0018 mg/kg for GA4 and 0.0009 mg/kg for GA7. No new risk assessment methods in water, sediment or air in support of environmental fate studies were required as part of the renewal of approval of GA4/7.

No new methods in soil or water in support of efficacy studies were required as part of the renewal of approval of GA4/7.

No new methods in body fluids and tissues or air in support of toxicological and exposure studies have been submitted as part of the renewal of approval of GA4/7.

Two residue trials, on apples and pears, are presented in this dossier that were previously evaluated and accepted as part of the original EU review for GA4/7. A brief summary of the method and validation data within these studies is also included in this dossier. Samples were extracted by macerating in the presence of methanol, filtered and diluted with 0.1% formic acid:water. The filtrate was purified by reverse phase C18 SPE cartridge clean-up and eluted with acetonitrile. Extracts were concentrated to <0.25 mL prior to dilution with acetonitrile:water:formic acid (30:69.9:0.1, v/v/v). Levels of GA4/7 were quantified by LC-MS/MS. The LOQ of the method was 0.05 mg/kg.

A freezer storage stability study, which was not previously evaluated at EU level as part of the original review for GA4/7, is presented in this dossier. The study uses the same analytical method as was used in the two residue studies described above to quantify levels of GA4/7 in pome fruit. The method was considered acceptable as part of the original EU review for GA4/7 and so is assumed to still be considered acceptable at renewal to support the stability study.

A further pre-registration validated method for the determination of GA4 and GA7 residues in pears, used in support of an additional freezer storage stability study, is presented in this dossier. Pre-homogenised, frozen

samples of pears were fortified with GA4/7, extracted with Milli-Q water, pH adjusted (to pH 2), re-extracted with ethyl acetate and then evaporated to dryness. Residues were dissolved in methanol, filtered and levels of GA4/7 quantified by LC-MS/MS. The LOQ of the method, equivalent to the lowest fortified level, for GA4 and GA7 was 0.02 mg/kg. The LOD for GA4 is 0.004 mg/kg and for GA7 is 0.003 mg/kg.

A series of published articles from literature focussing on the natural background levels of gibberellins have been reviewed as part of the renewal of approval for GA4/7. There is evidence to suggest that there is no significant difference between naturally occurring levels of GA4/7 and levels arising from the use of GA4/7 as a plant protection product. For this reason, it would not be possible to enforce MRLs for GA4/7 in any edible foodstuffs including food of plant and animal origin. Therefore, despite having presented methods for the detection of GA4/7 in food of plant and animal origin for the purposes of risk assessment within this dossier, such methods are not necessary.

A validated method to determine GA4/7 levels in Elendt M4 test medium in support of an ecotoxicology study (21-day semi-static reproduction with *daphnia magna*) is presented. Samples of the test medium were fortified with of GA4/7 (in methanol and water) before concentrations of GA4/7 were quantified by LC-MS/MS. The LOQ was 0.022 mg/L, equivalent to the lowest fortified level. Validated methods analysing GA4/7 in Diet C formulation (as part of a larval toxicity test) and in 50% (w/v) aqueous sugar solution (as part of a chronic oral toxicity test) are also presented. Concentrations of GA4/7 in fortified samples were quantified by ultra-performance liquid chromatography (UPLC) with UV detection at 205 nm. The LOQs for GA4/7, equivalent to the lowest fortification levels analysed, were 0.208 mg/mL (in Diet C formulation) and 9 µg/g (in 50% (w/v) aqueous sugar solution). The LODs were 0.0932 µg/mL (Diet C) and 0.0332 µg/mL (sugar solution). A validated method for the determination of GA3 in freshwater is also used as read-across for GA4/7. A validated method to determine GA4/7 levels in acidified EPA medium is presented in support of an ecotoxicology study (growth inhibition limit test with *Navicula pelliculos*). Samples of GA4/7 in EPA medium were analysed by LC-MS/MS. The LOQs for GA4 and GA7 were 153 and 1.8 µ/L (respectively). Quantifier and qualifier ion transitions were monitored and validated for both GA4 and GA7. A method for determination of GA4/7 in aqueous spray solution containing isopropyl alcohol presented to support a phytotoxicity evaluation study was validated in accordance with SANCO/3029/99 rev.4. The method relied on HPLC-UV at 204 nm with quantification by an external bracketing standard solution. No new methods in sediment or soil in support of ecotoxicological studies have been submitted as part of the renewal of approval of GA4/7.

No new physico-chemical studies have been submitted as part of the renewal of approval of GA4/7.

2.5.2 Methods for post control and monitoring purposes

Plants and plant products

Gibberellin (GA4/7) occurs naturally in many plant species, with detected residue levels close to background levels. Furthermore, no residue definition in plants for monitoring and enforcement has been set for GA4/7 and no MRLs are proposed. Monitoring methods for the detection of GA4/7 in plants and plant products are therefore not required. Nevertheless, a validated method (previously evaluated in the DAR) is presented for the determination of GA4/7 in pome fruit that is suitable for monitoring GA4/7 residues in crops with high water content. GA4/7 was extracted from crops by mixing samples of fruit with acetone and buffer solution at pH 7. The extract was purified by liquid/liquid partitioning with ethyl acetate followed by HPLC (normal phase). Concentrations of GA4/7 were quantified by HPLC with UV detection (206 nm). The method was independently validated using tandem mass spectrometric detection. The LOQ for the monitoring method is 0.05 mg/kg, equivalent to the lowest fortified level in the independent validation study.

Food of animal origin

Gibberellins are a family of naturally occurring plant hormones which are widespread in plants and fungi. There is no significant difference between naturally occurring levels and levels arising from the use of GA4/7 as a plant protection product. No MRLs are proposed nor is there a residue definition for monitoring and enforcement in

animals (EFSA Conclusion, 2012). As such, monitoring methods for the determination of GA4/7 residues in or on food and feed of animal origin are not required.

Soil

During the 2008 EU review, analytical methods for analysis of soil samples were not considered necessary (DAR). However, the 2012 EFSA Conclusion (EFSA Journal 2012; 10(1); 2502) identified methods of analysis for soil as a data gap. A new monitoring method for the detection of GA4/7 in soil is presented in this dossier. Soil samples (fortified and non-fortified) were extracted with water:methanol:formic acid mixture and then made to volume with the same solution. Levels of GA4/7 were quantified by LC-MS/MS with four ion transitions monitored (quantification: 331→243 and 329→223 m/z; confirmation: 331→225 and 329→241 m/z). The method was validated in sandy soil and clay soil. The LOQ for GA4/7 in both soil matrices was 0.01 mg/kg.

Water

Validated methods for the determination of GA4/7 in surface and drinking water that were previously evaluated during the 2008 EU review and presented in the DAR are still considered suitable for monitoring and enforcement purposes of GA4/7 residues in water. Such methods have been summarised in this dossier. The LOQs were 10 and 0.11 µg/L for determination of GA4/7 in drinking and surface water (respectively). The analytical method has been validated by an independent laboratory for the determination of GA4/7 in drinking water. The LOQ for GA4/7 was 0.1 µg/L. This was equivalent to 0.06 µg/L for GA4 and 0.03 µg/L for GA7, after correcting for GA4 and GA7 purities in the test substance.

Air

Gibberellin (GA4/7) is a non-volatile, low risk active substance. Exposure from proposed uses will not cause any significant environmental exposure above that from the natural occurrence of gibberellins in plants. Therefore, monitoring methods for analysis of air samples are not necessary.

Body fluids and Tissues

Gibberellin (GA4/7) is a non-volatile, non-toxic active substance. Exposure from proposed uses will not cause any significant environmental exposure above that from the natural occurrence of gibberellins in plants. Therefore, monitoring methods for analysis of body fluids and tissue samples are not necessary.

2.6 EFFECTS ON HUMAN AND ANIMAL HEALTH

More details on toxicological studies performed are presented in Volume 3CA, section B.6.

2.6.1 Summary of absorption, distribution, metabolism and excretion in mammals *[equivalent to section 9 of the CLH report template]*

Table 17: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
OECD 417 (1984) Rat, Sprague-Dawley, 5/sex and 12/sex for depletion kinetics in tissues Doses tested: Low dose (LD): 65 mg/kg bw/day, High dose (HD): 1000 mg/kg bw/day Purity: 90.8% % (GA4/7 Lot/Batch: D33263CD00 Acceptable.	Absorption: 40% (♀), 18% (♂) (based on urinary excretion within 248 h in bale cannulated rats. Widely distributed (highest levels in kidney and liver). No evidence of accumulation. Rapid and extensive excretion (approximately 96%) within 24h; mainly via urine (18 – 39%), faeces (3 – 12%) and bile (56-73%). Metabolism involved Hydroxylation and glucuronide conjugation of parent compounds and hydroxyls. C_{max} (µg eq/g): 5.3-7.9 (LD) C_{max} (µg eq/g): 141-154 (HD) T_{max} (h): 1(LD), 2(HD) LD: First $T_{1/2}$ (h): 1.1 - 1.8 and Second $T_{1/2}$ (h): 5-6 HD: $T_{1/2}$ (h): 4 AUC(µg*h/g): 26.5-29.8 (LD) AUC(µg*h/g): 1223-1648 (HD)	Radiolabelled material: [^{14}C] Gibberellin A4 and A7 (ratio between 70:30 and 75:25)	[redacted] (2000)

2.6.1.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

The studies followed OECD 417 (1984) and GLP principles. The study design complies with the latest version of the guideline OECD 417 (2010). Nevertheless, the identification of metabolites according to paragraph 42 of OECD417 (2010) has not been carried out (only HPLC analyses were performed with no additional spectroscopic analyses).

Rats were dosed with a single dose of 1000 mg/kg or 65 mg/kg of GA4. Continuous exposure was studied by dosing the rats for 14 day with "non-radioactive" 1000 mg/kg GA4 followed by the final dosing with radioactive GA4 (equivalent to 65 mg/kg GA4). Pharmacokinetic behaviour of GA4 and GA7 was compared at the low dose of [14C]-GA4 and [14C]-GA7. No significant differences in blood kinetic and ADME parameters were observed thus, further studies were carried out using [14C]-GA4 as GA4 compared to GA7 represents a higher proportion in the GA4/GA7 technical material. Radioactive recovery was adequate.

The absorption and excretion of GA4 in rats following oral administration was found to be rapid, with wide distribution (major part of radioactivity observed in liver, kidney and plasm). Due to possible first pass effect, the oral absorption was estimated at 40% in females and 18% in males based on urinary excretion at 48 hours, with no evidence for accumulation (98% of the recovered radioactivity was excreted via urine, faces and bile within 48 hours). Biliary excretion was the major route at low doses but a shift to urinary excretion occurred at high doses,

particularly in females, implying a saturation of some part of the biliary route. Bile-cannulation experiments also demonstrated that at low doses the major part of the faecal radioactivity was excreted via the biliary route. At 168 hours after administration of the low dose, the majority of tissue residues (except liver and kidneys for females and liver and blood for males) were below the limit of quantification. At the high dose, all tissue levels at 168 hours were above the limit of quantification. The tissue distribution and route of excretion correlate well to the target organs identified in the short-term studies (liver and kidney), and in the reproductive toxicity study (kidney). Metabolism involved hydroxylation and glucuronic acid conjugation at various positions on the molecule. Dose and sex depended differences were observed in the metabolite profiles.

Evidence of rapid absorption and wide distribution following oral dosing could be of relevance to the interpretation of studies of *in vivo* genotoxicity (e.g. mouse micronucleus assay) if radioactivity residues would be also available in bones.

2.6.2 Summary of acute toxicity

2.6.2.1 Acute toxicity - oral route [equivalent to section 10.1 of the CLH report template]

Table 18: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 401 Acceptable	Rat, Sprague-Dawley, 5/sex	GA4/7 Purity: 99.0% (GA4>90%) Lot/Batch: D105	5000 mg/kg bw (single dose)	>5000 mg/kg bw	[redacted] (1997)
EPA 81-1; equivalent to OECD 401 Acceptable	Rat, Sprague-Dawley, 5/sex	GA4/7 Purity: 90.0% Lot/Batch: 16-213-CD	5000 mg/kg bw (single dose)	>5000 mg/kg bw	[redacted] (1988)

Table 19: Summary table of human data on acute oral toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

Table 20: Summary table of other studies relevant for acute oral toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

The two studies on acute oral toxicity were submitted during the previous EU review of GA4/7. The studies followed the OECD TG 401 (1987) and GLP principles. OECD TG 401 was deleted in December 2002. Since then, OECD TG 420/423/425 for the evaluation of the acute toxicity potential of test items are used in order to minimize the number of animals. The purity of the a.s.in the first study was defined as >90% w/w (GA4). No information on the a.s. purity was found in the second study, however from the oral prenatal developmental study [redacted], 1989) and acute inhalation study ([redacted] (1988)) done using the same batch it can be assumed, that the purity was 90% w/w GA4/7. The LD_{50} endpoint derived by the older guideline is still adequate and can be used for classification purposes according to CLP Regulation (EC) No 1272/2008. The acute oral LD_{50} value for fasted rats (males, females, combined) was > 5000 mg/kg bw in all the presented studies

See RAR, Vol. 3, section B6.2.1 for details.

2.6.2.1.2 Comparison with the CLP criteria regarding acute oral toxicity

According to the CLP criteria, classification for acute oral toxicity is required for substances with acute oral LD_{50} values of >300 but ≤2000 mg/kg bw (Category 4); >50 but ≤300 mg/kg bw (Category 3); >5 but ≤50 mg/kg bw (Category 2); ≤5 mg/kg bw (Category 1).

The acute oral LD_{50} value for rats (males, females, combined) was > 5000 mg/kg bw in all the presented studies. As LD_{50} being > 2000 mg/kg bw, no classification regarding acute oral toxicity is required for GA.

2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity

No classification regarding acute oral toxicity is required for GA4/7 according to criteria laid down in Regulation (EC) No 1272/2008; the test substance is not subject to labelling requirements.

2.6.2.2 Acute toxicity - dermal route [equivalent to section 10.2 of the CLH report template]

Table 21: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
OECD 402 Acceptable	Rat, Sprague-Dawley, 5/sex	GA4/7 Purity: 99.0% (GA4>90%) Lot/Batch: D105	2000 mg/kg bw (single dose)	>2000 mg/kg bw	[redacted] (1997
US EPA 81-2; equivalent to OECD 402 Acceptable	Rabbit, New Zealand White, 5/sex	GA4/7 Purity: 90.0% Lot/Batch: 16-213-CD	2000 mg/kg bw (single dose)	>2000 mg/kg bw	[redacted] (1989)

Table 22: Summary table of human data on acute dermal toxicity

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

Table 23: Summary table of other studies relevant for acute dermal toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

The two studies on acute dermal toxicity (one on rat and one on rabbits) were submitted during the previous EU review of GA4/7. The studies are acceptable. The studies followed the OECD 402 (1987) or guideline equivalent to OECD 402 and GLP principles. A new version of OECD 402 was adopted in November 2017 in order to minimize the number of animals needed for the conduction of acute derma toxicity study if the waving of the study is not possible. According to Commission Regulation (EU) No 283/2013 (Annex, Point 5.2.2.) the acute dermal toxicity study could be waived due to oral LD_{50} being more than 2000 mg/kg bw, thus leading to no classification according to CLP Regulation (EC) No 1272/2008. However, the LD_{50} endpoint derived by the older guideline is still adequate and can be used for classification purposes according to CLP Regulation (EC) No 1272/2008. The acute dermal LD_{50} value for rats and rabbits (males, females, combined) was > 2000 mg/kg bw in all the presented studies.

See RAR, Vol. 3, section B6.2.2 for details.

2.6.2.2.2 Comparison with the CLP criteria regarding acute dermal toxicity

According to the CLP criteria, classification for acute dermal toxicity is required for substances with acute dermal LD50 values of >1000 but ≤2000 mg/kg bw (Category 4); >200 but ≤1000 mg/kg bw (Category 3); >50 but ≤200 mg/kg bw (Category 2); ≤50 mg/kg bw (Category 1).

The acute dermal LD_{50} value for rats and rabbits (males, females, combined) was > 2000 mg/kg bw in all the presented studies.

2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

No classification regarding acute dermal toxicity is required for GA4/7 according to criteria laid down in Regulation (EC) No 1272/2008; the test substance is not subject to labelling requirements.

2.6.2.3 Acute toxicity - inhalation route [equivalent to section 10.3 of the CLH report template]

Table 24: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
OECD 403 Acceptable (Recalculation of	Rat, Sprague-Dawley, 5/sex	GA4/7 Purity: 99.0%	5.44 mg/L (MAC) 4 hour, nose only	>5.44 mg/L	[redacted] (1997) [redacted]

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
the concentration to MMAD 4.0 µm)		(GA4>90%) Lot/Batch: D105	MMAD 4.4 µm; GSD 3.36 µm		
US EPA 152-12; comparable to OECD 403 Supportive (MMAD > 4 µm)	Rat, Sprague-Dawley, 5/sex	GA4/7 Purity: 90.0% Lot/Batch: 16-213-CD	2.98 mg/L (MAC) 4-hour, whole body MMAD 5.83 µm, GSD 1.67 µm	>2.98 mg/L	[redacted] (1988) [redacted]

Table 25: Summary table of human data on acute inhalation toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

Table 26: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

The two studies on acute inhalation toxicity were submitted during the previous EU review of GA4/7. The studies followed guidelines equivalent to OECD 403 and GLP principles. The nose-only exposure was used in the first study and in the second one the whole-body exposure. The concentrations tested in the studies were the maximum attainable concentrations. No major deviations has been observed in the first study compared to the OECD 403 (2009). The MMAD in the first study was >4 µm with SD >3 µm, thus exceeding the maximum MMAD and SD recommended in the current guideline OECD 403. However, a recalculations was done, giving an estimated exposure concentration for a MMAD of 4.0 µm 5.12 mg/L. The study is considered acceptable. In the second study, the MMAD was 5.83 µm at estimated exposure of 2.98 mg/L. No particle size distribution data were presented. In the second study the body weight observations are lacking for day 3. The study is considered to be of limited acceptability, and is used for supplementary information.

See RAR, Vol. 3, section B6.2.3 for details.

2.6.2.3.2 Comparison with the CLP criteria regarding acute inhalation toxicity

According to the CLP criteria, classification for acute inhalation toxicity is required for dusts with acute inhalation LC50 values of >1.0 but ≤5.0 mg/L (Category 4); >0.5 but ≤1.0 mg/L (Category 3); >0.05 but ≤0.5 mg/L (Category 2); ≤0.05 mg/L (Category 1).

The acute inhalation LC_{50} for rats (males, females, combined) is > 5 mg/L air 4h (nose only).

2.6.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

No classification regarding acute inhalation toxicity is required for GA4/7 according to criteria laid down in Regulation (EC) No 1272/2008; the test substance is not subject to labelling requirements.

2.6.2.4 Skin corrosion/irritation [equivalent to section 10.4 of the CLH report template]

Table 27: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Results** **- Observations and time point of onset[2]** **- Mean scores/animal** **- Reversibility**	**Reference**
OECD 404 acceptable	Rabbit (NZW); 6 males	GA4/7 Purity: 99.0% (GA4>90%) Lot/Batch: D105	0.5 g (moistened); 4 hours, semi-occlusive	No signs of irritation observed at observation times of 1, 24, 48 or 72 hours: mean scores of 0.0 for erythema and oedema at all time points. No signs of toxicity or ill health were noted in any rabbit during the observation period.	[redacted] (1997) [redacted]
US EPA 81-5; comparable to OECD 404 acceptable	Rabbit (NZW); 3/sex	GA4/7 Purity: 90.0% Lot/Batch: 16-213-CD	0.5 g (moistened); 4 hours, semi-occlusive	No signs of irritation observed at observation times of 0.5, 24, 48 or 72 hours: mean scores of 0.0 for erythema and oedema at all time points. No signs of toxicity or ill health were noted in any rabbit during the observation period	[redacted] (1988) [redacted]

Table 28: Summary table of human data on skin corrosion/irritation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

Table 29: Summary table of other studies relevant for skin corrosion/irritation

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

2.6.2.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

The two studies on skin irritation were submitted during the previous EU review of GA4/7. The studies followed the OECD 404 (1981) or a guideline equivalent to it and GLP principles. The reported studies` deviations when

compared to the latest version of the OECD 404 (2015) do not affect the outcome of the tests. Thus, the studies are found acceptable for hazard classification.

GA4/7 did not irritate skin of treated rabbits.

See RAR, Vol. 3, section B6.2.4 for details.

2.6.2.4.2 Comparison with the CLP criteria regarding skin corrosion/irritation

Skin corrosion is described (Annex I: 3.2.1.1 of the CLP Regulation) as the production of irreversible damage to the skin following the application of a test substance for up to 4 hours. Skin irritation is defined as the production of reversible damage to the skin following the application of a test substance for up to 4 hours. Classification of a substance for skin irritation (Category 2) is required on the basis of an animal study showing a mean (24-72 hours) value of between 2.3-4.0 for erythema/eschar or oedema. Classification is also required for inflammation that persists to the end of the observation period (normally 14 days).
Studies performed in the rabbit with gibberellins show no dermal reactions following a 4-hour exposure. Gibberellins (GA4/7) do not therefore require classification for skin corrosion or skin irritation according to the CLP Regulation.

2.6.2.4.3 Conclusion on classification and labelling for skin corrosion/irritation

No classification regarding skin irritation is required for GA4/7 according to criteria of Regulation 1272/2008.

2.6.2.5 Serious eye damage/eye irritation [equivalent to section 10.5 of the CLH report template]

Table 30: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels duration of exposure**	**Results** **- Observations and time point of onset[2]** **- Mean scores/animal** **- Reversibility**	**Reference**
OECD 405	Rabbit (NZW); 6	GA4/7 Purity: 99.0% (GA4>90%) Lot/Batch: D105	0.1 mL; unwashed	Mean (24-72h) scores: Animal #1: cornea (0.00), iris (0.00), erythema (1.33), chemosis (0.67) Animal #2: cornea (0.00), iris (0.00), erythema (1.33), chemosis (1.00) Animal #3: cornea (0.00), iris (0.00), erythema (1.00), chemosis (0.67) Animal #4: cornea (0.00), iris (0.00), erythema (0.67), chemosis (0.33) Animal #5: cornea (0.00), iris (0.00), erythema (1.00), chemosis (0.67) Animal #6: cornea (0.00), iris (0.00), erythema (1.33), chemosis (0.67) All reactions reversed within 72 h (Animals #2-5) or 96h (Animal #1)	[redacted] (1997) [redacted]
US EPA 81-4; comparable	Rabbit (NZW); 6	GA4/7 Purity: 90.0%	0.1 mL (60 mg); unwashed	Mean (24-72h) scores: Animal #1: cornea (0.00), iris (0.33), erythema (1.67), chemosis (1.33)	[redacted] (1988) [redacted]

to OECD 405		Lot/Batch: 16-213-CD		Animal #2: cornea (0.00), iris (0.00), erythema (2.00), chemosis (1.00) Animal #3: cornea (0.00), iris (0.33), erythema (2.33), chemosis (1.33) Animal #4: cornea (0.00), iris (0.00), erythema (2.00), chemosis (1.33) Animal #5: cornea (0.33), iris (0.00), erythema (2.00), chemosis (1.00) Animal #6: cornea (0.00), iris (0.00), erythema (1.67), chemosis (1.00) All reactions reversed within 168h (all animals).	

Table 31: Summary table of human data on serious eye damage/eye irritation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

Table 32: Summary table of other studies relevant for serious eye damage/eye irritation

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

2.6.2.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

The two studies on eye irritation were submitted during the previous EU review of GA4/7. The purity of the tested material in the second study was not stated, however, it is assumed to be 90.0% GA4/7 based on the information from some other study reports where the same batch was tested. The studies followed the OECD 405 (1981) or a guideline equivalent to it and principles of GLP. The studies` deviations already noted by the applicant, even compared to the latest version of the OECD 405 (2017), do not affect the outcome of the tests. The studies are acceptable.

GA4/7 moderately irritated eyes of treated rabbits, as indicated by conjunctival redness and chemosis observed in all the studies. Based on the mean scores at 24, 48 and 72 hours, conjunctival redness of grade ≥2 was observed in 4/6 rabbits. Thus, gibberellins (GA4/7) needs to be classification as Eye Irrit. 2, H319 according to criteria of Regulation 1272/2008.

2.6.2.5.2 Comparison with the CLP criteria regarding serious eye damage/eye irritation

Serious eye damage (CLP Category 1) is defined as the production of tissue damage in the eye, or serious physical decay of vision, following application of a substance to the anterior surface of the eye, which is not fully reversible within 21 days of application (Annex I: 3.3.1.1). Classification in Category 1 is required for substances producing (in at least in one animal) effects on the cornea, iris or conjunctivae that are not expected to reverse or

have not fully reversed within the observation period (normally 21 days). Classification is also required where mean (24-72 hour) scores of ≥3 for corneal opacity or >1 for iritis are attained.

Serious eye irritation (CLP Category 2) is defined as the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application (Annex I: 3.3.1.1). Classification in Category 2 is required for substances producing mean (24-72 hour) scores of ≥1 for corneal opacity, ≥1 for iritis, ≥2 for conjunctival erythema and/or ≥2 for chemosis.

Furthermore, for studies performed in six rabbits, the following specific guidance applies:

Classification in Category 1 is required if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or) at least 4 out of 6 rabbits show a mean score per animal of ≥3 for corneal opacity and/or >1.5 for iritis.

Classification in Category 2 is required if at least 4 out of 6 rabbits show a mean score of ≥1 for corneal opacity, and/or ≥1 for iritis, and/or ≥2 for conjunctival erythema and/or ≥2 for chemosis, and which fully reverse within an observation period of normally 21 days.

The studies available for gibberellin do not indicate any potential for serious eye damage but show mild to moderate eye irritation at early time points. Based on the mean scores at 24, 48 and 72 hours [redacted] 1988), conjunctival redness of grade ≥2 was observed in 4/6 rabbits. Therefore, triggering classification in Category 2.

2.6.2.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Gibberellins (GA4/7) needs to be classification as Eye Irrit. 2, H319 according to criteria of Regulation 1272/2008

2.6.2.6 Respiratory sensitisation [equivalent to section 10.6 of the CLH report template]

Table 33: Summary table of animal studies on respiratory sensitisation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels, duration of exposure**	**Results**	**Reference**
No data available	-	-	-	-	-

Table 34: Summary table of human data on respiratory sensitisation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

Table 35: Summary table of other studies relevant for respiratory sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.2.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No repeated dose inhalation studies or other relevant animal data are available. The data from medical surveillance shows there is no evidence in humans that GA3 can lead to specific respiratory hypersensitivity.

See RAR, vol. 3, section B 6.9 for details.

2.6.2.6.2 Comparison with the CLP criteria regarding respiratory sensitisation

A respiratory sensitiser is described as a substance that will lead to hypersensitivity of the airways following inhalation (Annex I: 3.4.1.1 of the CLP Regulation). Respiratory sensitisers are allocated into Category 1A (strong sensitisers) or Category 1B (other sensitisers), based on a weight of evidence from reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals. Substances are classified as Category 1 respiratory sensitisers where data are not sufficient for sub-categorisation, if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity, or if there are positive results from an appropriate animal test. Substances are classified as Category 1A respiratory sensitisers where there is evidence of a high frequency of occurrence in humans, or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests. Substances are classified as Category 1B respiratory sensitisers where there is evidence of a low to moderate frequency of occurrence in humans, or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests.

There are no animal data. The data from medical surveillance shows there is no evidence in humans that GA4/7 can lead to specific respiratory hypersensitivity. In the absence of relevant human or non-human data, gibberellins (GA4/7) are not classified as a respiratory sensitiser.

2.6.2.6.3 Conclusion on classification and labelling for respiratory sensitisation

In the absence of any data, gibberellins (GA4/7) do not require classification for respiratory sensitisation according to the CLP Regulation

2.6.2.7 Skin sensitisation [equivalent to section 10.7 of the CLH report template]

Table 36: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
US EPA 81-6 OECD 406	Guinea pig, Dunkin-	GA4/7 Purity:	2.5% (intradermal	Slight irritation was observed at the induction phase in control and test animals, no dermal reactions were observed in control and test	[redacted] (1997) [redacted]

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
(Maximisation). Acceptable	Hartley: 20 test / 10 control	99.0% (GA4>90%) Lot/Batch: D105	induction) 70% (topical induction) 35%, 70% (topical challenge)	animals after challenge phase. No evidence of sensitisation.	[redacted]
US EPA 81-6; comparable to OECD 406 (Maximisation). No data on: positive control, dermal reactions after induction Supportive	Guinea pig, Dunkin-Hartley: 20 test / 10 control	GA4/7 Purity: 90.0% Lot/Batch: 16-213-CD	1% (intradermal induction) 75% (topical induction) 30%, 75% (topical challenge)	No information of dermal reactions after induction No dermal reactions were observed in control and test animals after challenge phase. No evidence of sensitisation	[redacted] (1988) [redacted]
Comparable to OECD 406 (Maximisation). Acceptable	Guinea pig. Dunkin: 20 test / 10 control	GA4/7 (purity 90.2%) Lot/Batch:not stated	50% (topical induction) 3%, 10%, 30%, 75% (topical challenge)	No information of dermal reactions after induction Following challenge with 30%, erythema was reported in 6/20 test animals. No reactions were seen following a second challenge with 3%, 10% or 75%	[redacted] (1994) [redacted]

Table 37: Summary table of human data on skin sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

Table 38: Summary table of other studies relevant for skin sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.2.7.1 Short summary and overall relevance of the provided information on skin sensitisation

Three studies were submitted, all using the M&K method. The studies followed OECD 406 (1992) or guideline comparable to OECD 406 and principles of GLP. The GA4// purity in three experiments was > 90 %. All three

studies encountered minor deviations as not reporting numerical values of dermal effects seen after induction. However, the first study is judged to be the most reliable. The effects after induction were described as slight irritation, slight erythema and necrosis in groups of control and test animals. No signs of skin irritation were observed after the challenging. Summary of positive control data were reported and judged to be adequate. In the second study no information is given on the skin reactions after induction and no data on positive control were reported or mentioned in the study report. Thus, the second study is considered as supportive. In the third study no information is given on the skin reactions after induction. Summary of positive control data were reported and judged to be adequate. After challenging, 30% animals exhibited skin reaction in the tested mid group (30%). However, no skin reactions were observed at the highest (75%) and lowest (10%) tested concertation, thus the study results are judged equivocal.
Based on the all evaluated data for skin sensitisation no classification is required regarding skin sensitization according to criteria laid down in Regulation 1272/2008 as amended.

2.6.2.7.2 Comparison with the CLP criteria regarding skin sensitisation

A skin sensitiser is defined as a substance that will lead to an allergic response following skin contact (Annex 1: 3.4.1.2 of the CLP Regulation). Skin sensitisers are allocated into Category 1A (strong sensitisers) or Category 1B (other sensitisers), based on a weight of evidence from reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals.

Substances are classified as Category 1 skin sensitisers where data are not sufficient for sub-categorisation, if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or if there are positive results from an appropriate animal test.

Substances are classified as Category 1A skin sensitisers where there is evidence of a high frequency of occurrence in humans and/or a high potency in animals. For the Maximisation study, substances are allocated to Category 1A where a response of ≥30% is seen at intradermal induction concentrations of ≤0.1%; or where a response of ≥60% is seen at intradermal induction concentrations of >0.1% to ≤1%.

Substances are classified as Category 1B skin sensitisers where there is evidence of a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals. For the Maximisation study, substances are allocated to Category 1B where a response of ≥30% to <60% is seen at intradermal induction concentrations of >0.1% to ≤1%; or where a response of ≥30% is seen at intradermal induction concentrations of >1%.

Since no reliable positive reactions were seen in the three studies and there is no human data, gibberellins (GA4/7) are not classified as a skin sensitiser according to the CLP Criteria.

2.6.2.7.3 Conclusion on classification and labelling for skin sensitisation

Based on the all evaluated data for skin sensitisation no classification is required regarding skin sensitization according to criteria laid down in Regulation 1272/2008 as amended.

2.6.2.8 Phototoxicity

Table 39: Summary table of studies on phototoxicity

Method, guideline, deviations if any	**Test substance**	**Dose levels duration of exposure**	**Results**	**Reference**
OECD 432	Gibberellic Acid	Balb/c 3T3 cells;	Not phototoxic	Gerbeix, C.

(2004)	A4/A7Purity: 90.16% Lot/Batch: 1000048922	clone A31 UV-A / +UV-A (main test): 0, 263.34, 318.64, 385.55, 466.51, 564.48, 683.02, 826.45, 1000 µg/mL	The visible molar absorption coefficient of GA4/7 is below 10 $L \times mol^{-1} \times cm^{-1}$ in methanol at wavelength ≥ 286 nm, consequently criteria laid down in the Commission Regulation (EU) No 283/2013 for the performance of the phototoxicity study are not met.	(2018) 45159 TIP

Table 40: Summary table of human data on phototoxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

Table 41: Summary table of other studies relevant for phototoxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.2.9 Aspiration hazard [equivalent to section 10.13 of the CLH report template]

Table 42: Summary table of evidence for aspiration hazard

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.2.9.1 Short summary and overall relevance of the provided information on aspiration hazard

No data are available.

2.6.2.9.2 Comparison with the CLP criteria regarding aspiration hazard

GA4/7 is not a low viscosity hydrocarbon or chlorinated hydrocarbon liquid and does not therefore meet the criteria for classification for aspiration hazard.

2.6.2.9.3 Conclusion on classification and labelling for aspiration hazard

GA4/7 is not classified for aspiration hazard according to the CLP criteria.

2.6.2.10Specific target organ toxicity-single exposure (STOT SE) [equivalent to section 10.11 of the CLH report template]

Table 43: Summary table of animal studies on STOT SE (specific target organ toxicity-single exposure)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
No studies specific for STOT SE are available	-	-	-

Table 44: Summary table of human data on STOT SE (specific target organ toxicity-single exposure)

Type of data/report	**Test substance**	**Route of exposure Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

Table 45: Summary table of other studies relevant for STOT SE (specific target organ toxicity-single exposure)

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

2.6.2.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure (STOT SE)

Classification with STOT SE is appropriate for substances showing clear evidence of toxicity to a specific organ following a single exposure, especially where this is seen in the absence of lethality. Specific target organ toxicity (single exposure) is defined as specific, non-lethal target organ toxicity arising from a single exposure (Section 3.8.1.1 of Annex I of the CLP Regulation). All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed, are included in this category. Relevant data for gibberellins (GA4/7) are limited to the acute oral, dermal and inhalation toxicity studies discussed in Section 2.6.2, above.
Refer also to RAR Volume 3CA, section B.6.2 and 6.7.

2.6.2.10.2 Comparison with the CLP criteria regarding STOT SE (specific target organ toxicity-single exposure)

Classification in STOT SE Category 1 is required for substances that have produced significant toxicity in humans or which, on the basis of studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following a single exposure. Substances are classified in Category 1 on the basis of reliable and good quality evidence from human cases, or observations from animal studies in which significant and/or severe effects of relevance to human health are seen at generally low exposure levels. Exposure levels

relevant to classification in Category 1 are defined (Annex I: 3.8.2.1.9.3 of the CLP Regulation) as ≤300 mg/kg bw (oral route, rat); ≤1000 mg/kg bw (dermal route, rat) and ≤1 mg/L (inhalation route, rat, dust). In the absence of human data and in the absence of any effects (clinical signs or pathology) considered to constitute significant or severe effects in the acute oral, dermal or inhalation toxicity studies, classification of gibberellin in Category 1 for STOT SE is not required.

Classification in STOT SE Category 2 is required for substances showing significant toxic effects of relevance to humans, in studies in experimental animals and at generally moderate exposure levels.

In the absence of any effects (clinical signs or pathology) considered to constitute significant or severe effects in the acute oral, dermal or inhalation toxicity studies, classification of gibberellin in Category 2 for STOT SE is not required.

2.6.2.10.3 Conclusion on classification and labelling for STOT SE (specific target organ toxicity-single exposure)

Gibberellins (GA4/7) do not require classification for STOT SE (Category 1 or 2) according to the CLP Regulation based on the available data.

2.6.3 Summary of repeated dose toxicity (short-term and long-term toxicity) [section 10.12 of the CLH report]

2.6.3.1 Specific target organ toxicity-repeated exposure (STOT RE) [equivalent to section 10.12 of the CLH report template]

Table 46: Summary table of animal studies on repeated dose toxicity (short-term and long-term toxicity) STOT RE (specific target organ toxicity - repeated exposure)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**

EPA 82-1; comparable to OECD 408 (1981)* Sprague-Dawley rat (10/sex/group) Acceptable with limitations	GA4/7 Purity: 85.5% Lot/Batch: 21-018-CD 0, 1000, 10000, 50000 (on day 15 25000) ppm (diet); 90 days Equivalent to: 0, 50, 500, 1250 mg/kg bw/day	NOAEL: 10000 ppm (500 mg/kg bw/day) LOAEL: 25000 ppm (1250 mg/kg bw/day) Target: Kidney, liver The highest dose level was reduced from 50000 to 25000 ppm from Day 15 of treatment after adverse effects were apparent. <u>1250 mg/kg bw/day:</u> ↓ bodyweight gain, ↓ food consumption, a single mortality (with clinical signs of reaction to treatment (hunched posture, bloody crust around nose and thin, rough haircoat), changes in clinical chemistry parameters, macroscopic and microscopic changes in the kidneys: chronic inflammation (♂: 8/10, ♀: 4/10), cortical fibrosis (♂: 9/10, ♀: 7/10), tubular dilation (♂: 10/10, ♀: 2/10), ↑relative kidney weight (♂:15%), ↓ absolute kidney weight (♀: 10%). Liver effects were limited to hepatocyte vacuolation (♂: 8/10, ♀: 2/10) and degeneration (♂:3/10).	[redacted] (1990) [redacted]
EPA 870.3150, 409 (1998) beagle dogs (4/sex) no measurements of ornithine decarboxylase (ODC) and no histopathological examination of: bonne marrow, Payers' patches were not specifically mentioned, testes included epididymis. Acceptable with limitations	GA4/7 Purity: 90% (GA4=73.1%) Lot/Batch: 57-601-CD 0, 330, 720, 1100 mg/kg bw/d capsule	NOAEL: 720 mg/kg bw/day LOAEL: 1100 mg/kg bw/day Target: Kidney, liver <u>1100 mg/kg bw/day:</u> ↓ bodyweight gain, ↓ food consumption, The ↑ in adjusted kidney weight show a dose response both in males and females and: ♂: 11%, ♀: stat. sign. 24%. Stat. signif. ↑ in absolute (25% ↑) and adjusted (35% ↑) liver weight in ♂ with a dose response.	[redacted] (2001) [redacted]

*no conduction of sensory activity, grip strength and motor activity assessments, omission of urinalysis (optionally), they did not weight: epididymis, prostate + seminal vesicles with coagulating glands, uterus, thymus, spleen, heart, pituitary gland and thyroid gland; the histopathology was not performed for: male mammary glands, coagulating glands, and vaginal smear; payers patches were not specifically mentioned; no analyses of serum/plasma hormones (T4, T3, TSH, FSH, LH, oestradiol, testosterone) and HDL, LDL and no sperm measures (cauda epididymis sperm reserves, sperm motility, sperm morphology) according Annex B of OECD 408 were done

Table 47: Summary table of human data on repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of data/report	**Test substance**	**Route of exposure Relevant information about the study (as applicable)**	**Observations**	**Reference**

No data available	-	-	-	-

Table 48: Summary table of other studies relevant for repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.3.1.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure (short-term and long-term toxicity)

The 90-day dietary study in rat was done according to a guidance comparable to an old version of OECD 408 (1981) and follows principles of GLP. The latest version of OECD 408 (2018) was updated to add endocrine-sensitive endpoints which are not included in this study. A NOAEL of 500 mg/kg bw/day, is based on bodyweight effects, kidney and liver pathology at the highest dose level of 1250 mg/kg bw/day. Kidney and liver effects (increased organ weight) have been also observed in a 90-day study on dogs. The study was done according to the latest version of OECD 409 (1998) and follows principles of GLP. The study encountered some deviations which are described in the table above. No death occurred during the study. Small thymus weights were noted in 3/4 ♂ at 1100 mg/kg bw/day which coincided with thymus atrophy found in the same males. The finding was attributed to be a secondary effect of stress and also associated with significant body weight deficits. Haematological and urinalyses parameters were considered to be unaffected by the treatment. Clinical chemistry parameters did not show relevant effects which could be attributed to the treatment. The increase in adjusted kidney weight show a dose response both in males and females and when compared to the control at 1100 mg/kg bw/day being: ♂: 11%, ♀: stat. sign. 24%. Increase in absolute and adjusted liver weight in males show a dose response and is statistically significant at the 1100 mg/kg bw/day (25% ↑ absolute liver weight, 35% ↑adjusted liver weight). Histopathological liver and kidney effects were found only in 1 male and 1 female, respectively

Table 49: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days [if adequate, otherwise please delete]

Study reference	Effective dose (mg/kg/day)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
No data available	-	-	-	-

2.6.3.1.2 Comparison with the CLP criteria regarding STOT RE (specific target organ toxicity-repeated exposure)

Specific target organ toxicity (repeated exposure) is defined in the CLP Regulation (Annex I, 3.9.1.1) as specific, target organ toxicity arising from repeated exposure to a substance. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included in this definition. The adverse health effects relevant for STOT RE classification include consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or haematology of the organism and these

changes are relevant for human health. With respect to animal data, Annex 1, Section 3.9.2.5 of the CLP Regulation notes that the standard animal studies in rats or mice that provide this information are 28-day, 90-day or lifetime studies that include haematological, clinical chemistry and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Data from repeat dose studies performed in other species may also be used, if available and other long-term exposure studies such as carcinogenicity, neurotoxicity or reproductive toxicity may also provide evidence of specific target organ toxicity that could be used in the assessment of STOT RE classification.

Substances are classified in STOT RE Category 1 based on evidence of significant toxicity in humans or where there is evidence from studies in experimental animals that they can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. For classification in Category 1, either reliable good quality human data (evidence from human cases or epidemiological studies) or animal data (observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were observed at generally low exposure concentrations) is required. Annex I, Section 3.9.2.9.6 of the CLP Regulation provides a 'guidance value' of ≤10 mg/kg bw/day from a 90-day rat study to assist in Category 1 classification.

Substances are classified in STOT RE Category 2 based on evidence from studies in experimental animals that they can be presumed to have the potential to be harmful to human health following repeated exposure. For classification in Category 2, animal data (observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were observed at generally moderate exposure concentrations) is required. Annex I, Section 3.9.2.9.7 of the CLP Regulation provides a 'guidance value' of 10-100 mg/kg bw/d from a 90-day rat study to assist in Category 2 classification.

2.6.3.1.3 Conclusion on classification and labelling for STOT RE (specific target organ toxicity-repeated exposure)

The available data demonstrate very low repeated dose oral toxicity for gibberellins, with limited effects of treatment observed at dose levels below the limit dose of 1000 mg/kg bw/d. NOAELs of 500 and 650 mg/kg bw/d, respectively, are reported for 90-day studies in the rat and dog. Classification for STOT RE is therefore not required.

2.6.4 Summary of genotoxicity / germ cell mutagenicity [equivalent to section 10.8 of the CLH report template]

Table 50: Summary table of genotoxicity/germ cell mutagenicity tests *in vitro*

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
OECD 471 (1983) strain to detect cross-linking mutagens was not included Supportive	GA4/7 Purity: 99.0% (GA4>90%) Lot/Batch: D105	Tested concentrations +/- S9: 0, 50, 150, 500, 1500, 5000 µg/plate *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100 S9 mix from Aroclor 1254-induced rat liver	Negative for the strains tested. No cytotoxicity observed and no material precipitation reported. No evidence of mutagenicity (*S. typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100)	May K (1997) 96/FNA024/0935
OECD 471 (1983)	GA4/7	Tested concentrations +/- S9:	Negative for the strains tested.	Lawlor TE (1988) T8201.501014

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
strain to detect cross-linking mutagens was not included Supportive	Purity: 90.0% Lot/Batch: 16-213-CD	0, 667, 1000, 3333, 6667 and 10000 µg/plate *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100 S9 mix from Aroclor 1254-induced rat liver	No cytotoxicity observed and no material precipitation reported. No evidence of mutagenicity (*S. typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100)	
OECD 473 (1983) Only 200 cells/dose scored, HCD for positive control not reported Acceptable	GA4/7 Purity: 99.0% (GA4>90%) Lot/Batch: D105	Tested concentrations: -S9: 187.5, 375, 750, 1000, 1500, 2000, 2500, 3000 and 4000 µg/mL +S9: 312.5, 625, 1250, 2500, 3000, 3500 and 4000 µg/mL Cultured human lymphocytes	Not clearly positive. Evidence of clastogenicity in the absence and presence of metabolic activation.	Kitching JD (1997) FNA 25/962243
US EPA 84-2 OECD 473 (1983) EC B10 Only 200 cells/dose scored, HCD for positive and negative control not reported Acceptable	GA4/7 Purity: 87.3% Lot/Batch: 21-018-CD	Tested concentrations +/- S9: 262, 655, 1310, 1970 and 2620 µg/mL CHO cells	Not clearly positive. Evidence of clastogenicity at 1970 and 2620 µg/mL (-S9) Possible influence of cytotoxicity, results not repeatable.	Murli H (1994) 15393-0-437Z
OECD 476 (1984) Similar to OECD 490 (2016) Only 2 concentrations without precipitate, no sizing of colonies, Supportive	GA4/7 Purity: 99.0% (GA4>90%) Lot/Batch: D105	Tested concentrations up to 3000 µg/mL (-/+S9) L5178Y cells	Not clearly negative. IMF<GEF Acceptance criteria for the negative and positive control are not fulfilled.	Lloyd JM (1997) 96/FNA026/0944
US EPA, equivalent to	GA4/7 Purity:	Tested concentrations up to 1570 µg/mL (-S9); 1530 µg/mL (+S9);	Not clearly negative.	Cifone MA (1994) HWA 15693-0-431

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations /Results	Reference
OECD 476 (1984) Similar to OECD 490 (2016) No sizing of colonies, Acceptable	87.3% Lot/Batch: 21-018-CD	L5178Y cells	No evidence of mutagenicity (IMF<GEF), no excessive cytotoxicity observed and no precipitation of the material reported. Acceptance criteria for the negative (trial 2 and 3) and positive control (trial 2) are not fulfilled.	
Equivalent to OECD 482 (deleted) Supportive	GA4/7 Purity: 90.0% Lot/Batch: 16-213-CD	Tested concentrations 0.5-1000 µg/mL Cultured primary rat hepatocytes	No evidence of unscheduled DNA synthesis (UDS), assessed by autoradiography, excessive cytotoxicity at the top concentration.	Curren RD (1988) T8201.380009

Table 51: Summary table of genotoxicity/mutagenicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	Test substance	Relevant information about the study (as applicable)	Observations/Results	Reference
OECD 474 (1997) bone marrow exposure not demonstrated Supportive	GA4/7 Purity: not stated Lot/Batch: 287450001	CD-1 mice (5/sex). Dose levels 0, 500, 1000, 2000 mg/kg bw (oral gavage); single dose. Sacrifice at 24 hours (all groups) and at 48 hours (0 and 2000 mg/kg bw).	Not clearly negative. No mortality. Signs of toxicity (transient hunched posture) at 1200 mg/kg bw. No evidence of bone marrow toxicity. No biologically or statistically significant increase in the frequency of MPCEs at any dose level at either 24 or 48 hours after the treatment compared to the vehicle control.	[redacted] (1988) [redacted]
in-house design, comparable to OECD 474 (1983) only half number of PCE/dose were scored Acceptable with limitations.	GA4/7 Purity: 90.0% Lot/Batch: 16-213-CD	ICR mice (5/sex). Dose levels 0, 120, 600, 1200 mg/kg bw (intraperitoneal injection). Sacrifice at 24, 48 and 72 hours.	Negative. No mortality. Signs of toxicity in one male at 500 mg/kg bw. A 18-25% decrease in the PCE: total erythrocytes ratio was seen at 24 hours at 1200 mg/kg bw. There was no increase in the proportion of MNPCEs in any of the dose groups at any time point.	[redacted] (1988) [redacted]

Table 52: Summary table of human data relevant for genotoxicity / germ cell mutagenicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.4.1 Short summary and overall relevance of the provided information on genotoxicity / germ cell mutagenicity

Gibberellins (GA4/7) have been tested for DNA damage, gene mutation and chromosomal aberration in 7 studies *in vitro*. Two studies of bacterial reverse mutation (Ames tests) report negative results in the absence and presence of metabolic activation; studies are not fully compliant with the current (1997) version of the guideline (OECD 471) as a bacterial strain capable of detecting cross-linking mutagens was not included. Two studies of chromosomal aberration (one in cultured human lymphocytes, one in CHO cells) are available and report positive results in the absence of metabolic activation. No evidence of mutagenicity is reported in two studies of mammalian cell (forward) mutation (mouse lymphoma) assays. Negative results are also reported in a study of unscheduled DNA synthesis (UDS) in cultured primary rat hepatocytes. All the presented in *vitro* studies have some limitations and the results are quoted as "not clearly negative" or not "clearly positive".
The genotoxicity of gibberellin has also been investigated in studies *in vivo*. Two mouse bone marrow micronucleus assays using oral gavage and intraperitoneal injection report negative results. The study using gavage dosing (at dose levels up to the limit dose) did not report clear evidence of systemic toxicity or bone marrow toxicity. Target tissue exposure in the study using intraperitoneal injection can be assumed, and this study reports evidence of bone marrow exposure (decrease in the PCE: total erythrocytes) and of systemic toxicity at the highest dose level (stated to be 80% of the LD50). Nevertheless, only half number of PCE/dose were scored when compared to the latest version of OECD 474 and the intraperitoneal exposure is not considered as the most relevant exposure for pesticides. As acceptability criteria of OECD 474 (2016) were not fulfilled in either of the *in vivo* studies, the results for both studies were considered "not clearly negative".

Gibberellin was consistently negative in studies of gene mutation in bacterial and mammalian cells *in vitro*, despite testing results should be considered as not clearly negative/ positives due to not fulfilling the acceptance criteria according to the latest guidelines. Overall, evidence show the GA4/7 is probably not genotoxic as positive results for clastogenicity reported in studies *in vitro* are not replicated in the acceptable *in vivo* study on Micronucleus.

Refer also to RAR Volume 3CA, section B.6.4.

2.6.4.2 Comparison with the CLP criteria regarding genotoxicity / germ cell mutagenicity

Annex I Section 3.5.1.1 of the CLP Regulation defines mutation as a permanent change in the amount or structure of the genetic material in a cell. The term mutation applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications. The term 'mutagenic' and 'mutagen' are used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms. This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests *in vitro* and in mammalian somatic and germ cells *in vivo* are also considered in classifying substances within this hazard class.

Classification for mutagenicity in Category 1 is appropriate for substances known to induce heritable mutations (Category 1A) or for substances regarded as if they induce heritable mutations in the germ cells of humans (Category 1B).

Classification in Category 1A is based on positive evidence from human epidemiological studies.

Classification in Category 1B is based on positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with evidence that the substance has potential to cause mutations to germ cells; or positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny.

Classification for mutagenicity in Category 2 is appropriate for substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. Classification in Category 2 is based on positive evidence obtained from somatic cell mutagenicity tests in mammals and/or in some cases from somatic cell mutagenicity tests in mammals and supporting data from *in vitro* experiments.

Positive results for clastogenicity reported in studies *in vitro* are not replicated in the acceptable *in vivo* study on Micronucleus.

2.6.4.3 Conclusion on classification and labelling for genotoxicity / germ cell mutagenicity

On the basis of the available data, classification for germ cell mutagenicity is not required for gibberellin according to the CLP Regulation.

2.6.5 Summary of long-term toxicity and carcinogenicity [equivalent to section 10.9 of the CLH report template]

Table 53: Summary table of animal studies on long-term toxicity and carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
No data available	-	-	-

Table 54: Summary table of human data on long-term toxicity and carcinogenicity

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

Table 55: Summary table of other studies relevant for long-term toxicity and carcinogenicity

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

2.6.5.1 Short summary and overall relevance of the provided information on long-term toxicity and carcinogenicity

2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity

Annex I Section 3.6.1.1 of the CLP Regulation defines a carcinogen as a substance which induces cancer or increases its incidence. Substances which have induced benign and malignant tumours in well-performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans. Carcinogenic substances are allocated to Category 1 (known or presumed human carcinogens) or Category 2 (suspected human carcinogens).
A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. Substances known to have carcinogenic potential in humans (based largely on human evidence) are classified in Category 1A. Substances presumed to have carcinogenic potential for humans (based largely on animal evidence) are classified in Category 1B. A substance is classified in Category 1 for carcinogenicity on the basis of human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B.

Table 56: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
-	-	-	-	-	-	-	-	-

2.6.5.3 Conclusion on classification and labelling for carcinogenicity

In the absence of any data, gibberellin does not require classification for classification according to Regulation (EC) No 1272/2008.

2.6.6 Summary of reproductive toxicity [equivalent to section 10.10 of the CLH report template]

2.6.6.1 Adverse effects on sexual function and fertility – generational studies [equivalent to section 10.10.1 of the CLH report template]

Table 57: Summary table of animal studies on adverse effects on sexual function and fertility – generational studies

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for sexual function and fertility, parents) - target tissue/organ - critical effects at the LOAEL	Reference
OECD 416 (1993)	Gibberellins (GA4/7) Purity:	NOAEL reproductive: 1000 mg/kg bw/day, LOAEL reproductive: not defined	[redacted], (2001) [redacted]

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results** **- NOAEL/LOAEL (for sexual function and fertility, parents)** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Sprague-Dawley rats (30/sex/group) weight of paired organs was not reported individually, thyroid of parenteral animals was not weighted, histopathology of vagina, uterus with cervix, ovaries, one testis, one epididymis, seminal vesicles, prostate and coagulating gland in only 1/3 of control and high dose parenteral animals, Acceptable with limitations	90.8% w/w (GA4/7), 72.5% w/w (GA4) Lot/Batch: 33263CD00 0, 300, 600, 1000 mg/kg bw/day (dietary)	NOAEL parents: 300 mg/kg bw/day, LOAEL parents: 600 mg/kg bw/day NOAEL offspring: 600 mg/kg bw/day, LOAEL offspring: 1000 mg/kg bw/day 1000 mg/kg bw/day: Parents: ↓ bw gain, ↑ in incidence and severity of microscopic pathological findings in kidneys: nephropathy, urothelial medullary papilla hyperplasia, tubular epithelium medullary hyperplasia, tubular dilatation, medullary basophilic interstitium and medullary fibroplasia and (♀: F0, F1). Offspring: ↓ bw, ↓bw gain ↓ spleen weight (F1, F2), ↓ abs. thymus weight (F2) 600 mg/kg bw/day: ↑ in incidence of microscopic pathological findings in kidneys (♀: F0, F1)	

Table 58: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

Table 59: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

2.6.6.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility – generational studies

The study follows OECD 416 and principles of GLP. The study is acceptable with limitations.
In the study, there were no treatment related mortalities and/or clinical findings observed for both generations (F0, F1) of parenteral animals. In all dose levels in both generations no treatment related effects were observed on: reproductive performance, precoital interval, regularity and duration of oestrus cycle, gestation length and spermatogenic endpoints (testicular and epididymal sperm numbers, sperm production rate, sperm motility and/or the percentage of morphologically normal sperm). In the 600 and 1000 mg/kg as/day group of F0 and F1 females, an increase in incidence and severity in microscopic pathological findings in kidneys were observed and thus, considered to be treatment related.
The mean live litter size, mean number of pups born and sex ratio at birth were unaffected by the treatment in both the F1 and F2 litters. There were no treatment-related effects on general physical condition or viability of pups in either generation. A decrease in the body weight compared to control was observed in males and females at PND 21 in the first and second generation at 1000 mg/kg bw/day. Thus, the effect was considered treatment related. There were no necropsy remarkable findings for pups found dead during the postnatal period. Mean absolute spleen weights for F1 offspring, males and females, were significantly reduced at 1000 mg/kg bw/day when compared to the control group, 19.4% and 17.8 %, respectively. The same effect was also observed in the second generation thus, the reductions were considered to be treatment related. In the F2 generation, mean absolute and relative spleen weights were significantly reduced in males (22%) and females (25%) of the 1000 mg/kg bw/day group. Additionally, mean absolute thymus weights were reduced in F2 males (significantly, 16%) and females (11%). Necropsy of the pups showed no treatment-related findings. Landmarks of sexual maturation (balanopreputial separation and vaginal patency) in the F1 generation were not affected adversely in the treated groups.

The study does not report any effects on sexual function or fertility at dose levels of up to 1000 mg/kg bw/day.

See the RAR Volume 3CA Section B.6.6.2 for details.

2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility

The definition of reproductive toxicity in the CLP Regulation includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring.
The critical study for gibberellin is the GLP- and guideline-compliant two-generation reproductive toxicity study in the rat ([redacted] 2001); this study does not show any effects of treatment on sexual function or fertility at dietary concentrations of up to 1000 mg/kg bw/day.

No classification is proposed with respect to sexual function and fertility.

2.6.6.2 Adverse effects on development [equivalent to section 10.10.4 of the CLH report template]

Table 60: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ - critical effects at the LOAEL**	**Reference**
OECD 414 (1981)	Gibberellins (GA4/7)	NOAEL maternal = 300 mg/kg bw/day,	[redacted] (1989)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL (for parent, offspring and for developmental effects) - target tissue/organ - critical effects at the LOAEL	Reference
NZW rabbit (18 dams/group) dosing only at the organogenesis, less than 20 dams/group with implantation sites at necropsy , limitation in results interpretation at 1000 mg/kg bw/day due to high mortality of dams Acceptable with limitations	Purity: 90% w/w (GA4/7) 0, 100, 300, 1000 mg/kg bw/d (gavage); GD 7-19	LOAEL maternal = 1000 mg/kg bw/day NOAEL developmental: ≥ 300 mg/kg bw/d LOAEL developmental: not defined. 1000 mg/kg bw/day: Dams: ↑ mortality (14/18), clinical signs (prostration, hypoactivity, unsteady gait, stained urogenital region, voiding no or few faeces), abortions, ↓ body weight gain and ↓ food consumption There were no treatment-related external, visceral or skeletal abnormalities on offspring.	[redacted]

Table 61: Summary table of human data on adverse effects on development

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

Table 62: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.6.2.1 Short summary and overall relevance of the provided information on adverse effects on development

The study follows GLP and is comparable to the OECD 414 (1981) as the dosing was performed in the period of organogenesis (day 7 to Day 19). According to the newer version, the tested chemical should be administered at least from implantation to one day prior to the day of scheduled humane killing. In this study only 18 females/group instead of 20 dams/group with implantation sites at necropsy (required by the current OECD 414) were used. The study is acceptable with imitations. In the study, the mid dose amounted to 14 pregnant females at the scheduled sacrifice, and the high dose group to only 4 survived pregnant rats. Due to high mortality rate at the

highest dose can be used for setting the NOAEL/LOAEL only with limitation e.g. effects seen till the death of females on day 17. The mid dose, 300 mg/kg bw/day with only 13 pregnant females is also questionable; however, the number of live foetuses doesn't significantly differ from those found in other two groups, thus this group was considered in the setting of NOAEL / LOAEL. The effects observed in foetuses lack of statistical significance and dose response when compared between groups 0-300 mg/kg bw/day. Reproductive parameters 0-300 mg/kg bw/day were not significantly affected by the treatment.

Based on the study results, the proposed maternal NOAEL for rabbits is 300 mg/kg bw/day, based on maternal mortality, clinical signs, abortions, reduced body weight gain and food consumption at 1000 mg/kg bw/day. The proposed development NOAEL for rabbits is ≥ 300 mg/kg bw/day as no treatment related effects have been observed at 300 mg/kg bw/day. Due to high mortality rate of dams, findings at 1000 mg/kg bw/day were not considered reliable.

See the RAR Volume 3CA Section B.6.6.2 for details.

2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development

Adverse effects on development of the offspring includes any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or post-natally, to the time of sexual maturation.

The critical study for gibberellins GA4/7 is the GLP-compliant and guideline-comparable study of developmental toxicity in the rabbit ([redacted] 1989). The study do not show treatment related effect on development at dose levels of up to 300 mg/kg bw/day.

No classification is proposed with respect to developmental toxicity.

2.6.6.3 Adverse effects on or via lactation [equivalent to section 10.10.7 of the CLH report template]

Table 63: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations[1] if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL**	**Reference**
No specific studies are available	-	-	-

Table 64: Summary table of human data on effects on or via lactation

Type o data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No data available	-	-	-	-

Table 65: Summary table of other studies relevant for effects on or via lactation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available	-	-	-	-

2.6.6.3.1 Short summary and overall relevance of the provided information on effects on or via lactation

The only study potentially providing evidence of effects on or via lactation is the GLP- and guideline-compliant two-generation reproductive toxicity study in the rat ([redacted], 2001), which is discussed in detail in Section 10.10.1. This study reports effects on offspring at the highest dose level of 1000 mg/kg bw/day. Offspring viability and growth were unaffected by treatment, with the exception of slightly lower pup weights and weight gain at 1000 mg/kg bw/d. Findings are associated with and likely to be secondary to maternal toxicity and do not represent a lactation-mediated effect.

2.6.6.3.2 Comparison with the CLP criteria regarding effects on or via lactation

There are no results of the two-generation study in rats indicating adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk. Studies with gibberellin do not therefore provide any evidence of effects on or via lactation.

2.6.6.4 Conclusion on classification and labelling for reproductive toxicity

There is no evidence for any effects on sexual function or fertility, on or via lactation. No developmental toxicity was seen to the limit dose 300 mg/kg bw/day. Gibberellins (GA4/7) are therefore not classified for reproductive toxicity according to Regulation (EC) No 1272/2008

2.6.7 Summary of neurotoxicity

No data are available and none are required. Regulation 283/2012 specifies that neurotoxicity studies shall be performed for active substances with structures that are similar or related to those capable of inducing neurotoxicity or delayed polyneuropathy, and for active substances which induce specific indications of potential neurotoxicity, neurological signs or neuropathological lesions in toxicity studies at dose levels not associated with marked general toxicity. Gibberellins GA4/7 does not possess structural alerts for neurotoxicity; it is not an organophosphate or carbamate, and no potential for neurotoxicity was observed in the available toxicology studies *in vivo*. In addition, gibberellins GA4/7 is a normal component of the human diet due to its presence in fruit and vegetables, therefore studies to investigate neurotoxicity or delayed polyneuropathy are not considered necessary and are not proposed.

Table 66: Summary table of animal studies on neurotoxicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL**	**Reference**
No specific studies are available	-	-	-

2.6.8 Summary of other toxicological studies

2.6.8.1 Toxicity studies of metabolites and impurities

No additional toxicological studies on metabolites and impurities were submitted. The toxicological properties of the impurities were evaluated in the confidential part of the DRAR (DAR 22_Volume 4)

2.6.8.2 Supplementary studies on the active substance

In the provided 2-generational study on rats, there were some slight effects noted on the organs of the immune system. At the dose of 1000 mg/kg bw/day in the 2-generational study on rats a treatment -related reduction in spleen weight (F1, F2) and thymus weight (F2) was observed in pups of both sexes. No macroscopical changes in spleen and thymus were identified in parenteral animals and pups. In such cases, histopathology as defined by the guidance is not required and thus, was not performed. Additionally. no clinical and haematological parameters are investigated in the 2-generational studies which could provide additional information.

Decrease in thymus weight and atrophy of thymus was found in 3/4 male dogs in the group 1000 mg/kg bw/day in the 90 -day study. Thymus is an organ that is sensitive to the effects of stress, general toxicity and aging. No dose-response effect was observed. The finding was attributed by the study author to be a secondary effect of stress. According to the » EFSA supporting publication 2015:EN-782« thymus atrophy was frequently associated with significant body weight deficits which is also the case in this study. There were also no treatment-related changes in haematological and clinical chemistry parameters. No relevant effects on spleen, thymus, lymph nodes, adrenals and WBC were observed in a 90 day rat study.

The effects on spleen and thymus were considered treatment-related only at the highest dose tested, 1000 mg/kg bw/day an thus covered with the toxicological risk assessment. Additionally, chronic dietary exposure to GA4/7 is extremely low (see Vol1, Point 2.7.9.), thus no additional studies on immunotoxicity are foreseen.

See the RAR Volume 3CA Section B.6. for details.

2.6.9 Summary of medical data and information

Manufacturing plant personnel are monitored annually. Medical exams are performed annually or every 3 years dependent upon role, and include spirometry, complete blood count and blood chemistry. No adverse reactions have been documented or reported and there have been no medical surveillance abnormalities to date (approximately 30 years).

See RAR Volume 3CA Section B.6.9 for details.

2.6.10 Toxicological end points for risk assessment (reference values)

Table 67: Overview of relevant studies for derivation of reference values for risk assessment

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Sprague-Dawley rat	EPA 82-1; comparable to OECD 408 (1981) 90 days, diet, 0, 1000, 10000, 50000 (on day 15 25000) ppm Equivalent to: 0, 50, 500, 1250 mg/kg bw/day	GA4/7 Purity: 85.5% Lot/Batch: 21-018-CD	↓ bodyweight gain, ↓ food consumption, a single mortality (with clinical signs of reaction to treatment (hunched posture, bloody crust around nose and thin, rough haircoat), changes in clinical chemistry macroscopic and microscopic changes in the kidneys: chronic inflammation (♂: 8/10, ♀: 4/10), cortical fibrosis (♂: 9/10, ♀: 7/10), tubular dilation (♂: 10/10, ♀: 2/10), ↑relative kidney weight (♂:15%), ↓ absolute kidney weight (♀: 10%). Liver effects were limited to hepatocyte vacuolation (♂: 8/10, ♀: 2/10) and degeneration (♂:3/10).	10000 ppm (500 mg/kg bw/day)	25000 ppm (1250 mg/kg bw/day)	2.6.3.1
beagle dogs (4/sex)	EPA 870.3150, 409 (1998), 90 days, capsule 0, 330, 720, 1100 mg/kg bw/day	GA4/7 Purity: 90% (GA4=73.1%) Lot/Batch: 57-601-CD	↓ bodyweight gain, ↓ food consumption, The ↑ in adjusted kidney weight show a dose response both in males and females and: ♂: 11%, ♀: stat. sign.	720 mg/kg bw/day	1100 mg/kg bw/day	2.6.3.1

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
			24%. Stat. signif. ↑ in absolute (25% ↑) and adjusted (35% ↑) liver weight in ♂ with a dose response.			
Sprague-Dawley rats	Two-generation reproduction study (diet) 0, 300, 600, 1000 mg/kg bw/day (dietary)	Gibberellins (GA4/7) Purity: 90.8% w/w (GA4/7) 72.5% w/w (GA4)	1000 mg/kg bw/day: Parents: ↓ bw gain, ↑ in incidence and severity of microscopic pathological findings in kidneys: nephropathy, urothelial medullary papilla hyperplasia, tubular epithelium medullary hyperplasia, tubular dilatation, medullary basophilic interstitium and medullary fibroplasia and (♀: F0, F1). Offspring: ↓ bw, ↓bw gain ↓ spleen weight (F1, F2), ↓ thymus weight (F2) 600 mg/kg bw/day: ↑ in incidence of microscopic pathological findings in kidneys (♀: F0, F1)	reproductive: 1000 mg/kg bw/day parenteral: 300 mg/kg bw/day offspring: 600 mg/kg bw/day,	reproductive: not defined parenteral: 600 mg/kg bw/day offspring: 1000 mg/kg bw/day	2.6.6.1
NZW rabbit	0, 100, 300, 1000 mg/kg bw/d (gavage); GD 7-19	Gibberellins (GA4/7) Purity: 90% w/w (GA4/7)	1000 mg/kg bw/day: Dams: ↑ mortality (14/18), clinical signs (prostration, hypoactivity, unsteady gait, stained urogenital region, voiding no or few faeces), abortions, ↓ body weight gain and ↓ food consumption	maternal = 300 mg/kg bw/day, maternal = 1000 mg/kg bw/day	maternal = 1000 mg/kg bw/day developmental: not defined.	2.6.6.2

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
			There were no treatment-related external, visceral or skeletal abnormalities on offspring.			

2.6.10.1Toxicological end point for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake)

As no long-term toxicity studies were submitted by the applicant the ADI is set based on the findings in short term toxicity studies. The ADI set during the previous evaluation is reconfirmed and is based on the NOAEL of 300 mg/kg bw/day from the multigeneration toxicity study by applying the standard safety factor of 100 and an additional safety factor of 10 due to use of a short term toxicity study and to general database weakness. ADI is 0.3 mg/kg bw/day.

2.6.10.2Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

GA4/7 is not acutely toxic if swallowed; it is not a neurotoxic compound, and it does not show developmental toxicity after oral administration., thus ARfD is not warranted. The setting of the ARfD was discussed during the PPR 88 where come to the conclusion, that based on the toxicological profile of GA4/7 it is not justified to set an ARfD.

2.6.10.3Toxicological end point for assessment of occupational, bystander and residents risks – AOEL (acceptable operator exposure level)

The AOEL set during the previous evaluation is reconfirmed and is based on the NOAEL of 300 mg/kg bw/day from the multigeneration toxicity study by applying the standard safety factor of 100 and an additional safety factor of 3 due to the missing of a developmental toxicity study in rats and corrected for 18% oral absorption. AOEL is 0.18 mg/kg bw/day.

2.6.10.4Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL (acute acceptable operator exposure level)

Since no acute effects were observed in toxicological studies with GA4/7 and no ARfD is needed to be set for this substance, no AAOEL is proposed for GA4/7.

2.6.11 Summary of product exposure and risk assessment

The representative formulation is “Novagib” containing 10 g/L pure gibberellins (GA4/7) and is formulated as soluble concentrate (SC). The formulation is a plant growth regulator used on apples and pears. Novagib was one of the representative formulations considered during the EU review of the active substance. Studies were performed with ‘GA4/7 10 g/L formulation’, which is identical to ‘Novagib’. The PPP has low acute oral, dermal and inhalation toxicity, it is not irritating to skin and is not a skin sensitiser. It is slightly irritating to the eyes. Based on these data, classification according to Regulation (EC) No 1272/2008 is not required. No studies on dermal absorption were provided, consequently default values according to the. 50% dermal absorption is used for both, the product concentrate (and spray dilution).

Estimates of potential operator, bystander/resident and worker exposure have been undertaken for GA4// using the list of intended uses summarised below.

Table 1.6.11.-1: Summary of criticalusepatterns(i.e.worst case)

Crop	Application Equipment	Application Rate (kg a.s./ha)	Minimum Water Volume (L/ha)	Maximum Number of Applications	Interval Between Applications
Apple	Tractor-mounted sprayer (spray directed upwards and outwards), Manual - knapsack	0.005	300	4	7 days
Pear	Tractor-mounted sprayer (spray directed upwards and outwards) Manual - knapsack	0.012	300	1	N/A

2.6.11.1Estimation of operator exposure

Operator exposure was assessed using the EFSA Calculator (AOEM) according to the EFSA Guidance on the assessment of operators, workers, residents and bystanders in risk assessment for plant protection products (EFSA Journal 2014; 12(10):3874). Estimates of potential operator exposure during tractor mounted application to apples and pears were made without PPE, for operators wearing work wear during mixing/loading and application and also with PPE when using a hand-held (knapsack) application

The results are summarised in the table below.

Table 2.6.11.1-1: Estimated operator exposure

Model data	Level of PPE	Total absorbed dose (mg/kg bw/d)	% of systemic AOEL
Tractor mounted spray application outdoors to pome fruit (upwards spraying) *Application rate 0.012 kg a.s./ha*			
Spray application (AOEM**;** 75th percentile) 10 ha/day 60 kg operator	Work wear (arms, body and legs covered) M/L and A	0.01283	7.13
Manual knapsack application outdoors to pome fruit (upwards spraying) *Application rate 0.012 kg a.s./ha*			
Spray application (AOEM**;** 75th percentile) 1 ha/day 60 kg operator	Work wear (arms, body and legs covered) M/L and A	0.38331	212.95
	Work wear (arms, body and legs covered), FP2, P2 and similar, gloves M/L and A	0.37741	209.67

According to the model calculations, operator exposure is acceptable without the use of PPE for application to pome fruit using a tractor mounted sprayer (spray directed upwards). Operator exposure is not acceptable for application to pome fruit using a knapsack sprayer, even with the use of PPE (gloves and respiratory protection FP2, P2 during mixing/loading and application).

2.6.11.2 Estimation of bystander and resident exposure

According to the EFSA Guidance (EFSA Journal 2014; 12(10):3874); no bystander risk assessment is required for plant protection products that do not have significant acute toxicity or the potential to exert toxic effects after a single exposure. Exposure in this case will be determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days. Therefore, exposure assessments for residents also cover bystander exposure. As Novagib is not acutely toxic an estimation of bystander exposure is not required. Resident exposure to GA4/7 was assessed using the EFSA Calculator. The Calculator estimates exposure for four exposure pathways; drift, vapour, deposits and re-entry (75th percentile). The sum (mean) of all pathways is also provided.

The results are summarised in the table below.

Table 2.6.11.2-1: Estimated resident exposure

Model data		**Total absorbed dose (mg/kg bw/d)**	**% of systemic AOEL**
Tractor mounted spray application outdoors to pome fruit (pear) *Interval between treatments: Not applicable*			
Number of applications and application rate		1 x 0.012 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.0028	1,54%
	Vapour (75th perc.)	0.0161	8,92%
	Deposits (75th perc.)	0.0001	0.05%
	Re-entry (75th perc.)	0.0010	0.56%
	Sum (mean)	0.0187	10.41%
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0015	0.86%
	Vapour (75th perc.)	0.0035	1.92%
	Deposits (75th perc.)	0.0000	0.02%
	Re-entry (75th perc.)	0.0006	0.31%
	Sum (mean)	0.0049	2.74%
Tractor mounted spray application outdoors to pome fruit (pear *Interval between treatments: 7 days*			
Number of applications and application rate		4 x 0.005 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.0012	0.64%
	Vapour (75th perc.)	0.0161	8.92%
	Deposits (75th perc.)	0.0001	0.07%
	Re-entry (75th perc.)	0.0013	0.75%

	Sum (mean)	0.0180	9.98%
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0006	0.36%
	Vapour (75th perc.)	0.0035	1.92%
	Deposits (75th perc.)	0.0001	0.03%
	Re-entry (75th perc.)	0.0007	0.42%
	Sum (mean)	0.0045	2.50%

According to the model calculations, there is no unacceptable risk for the child or adult resident (and bystander) following application of Novagib to pome fruit using a tractor mounted sprayer.

2.6.11.3 Estimation of worker exposure

Re-entry workers may enter crops previously treated with Novagib to carry out tasks such as pruning and hand harvesting of pome fruit. Worker re-entry exposure was estimated using the EFSA Calculator; the following parameters were used in the calculation. Usage information is summarised in Table 2.6.11-1.

The results are summarised in the table below.

Table 2.6.11.3-1: Estimated worker exposure

Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/d)**	**% of systemic AOEL**
Tractor mounted spray application outdoors to apples			
Number of applications and application rate		4 x 0.005 kg a.s./ha	
Body weight: 60 kg Work rate: 8 h/day	Potential TC: 22500 cm^2/person/h	0.0718	39.87%
	Work wear (arms, body and legs covered) TC: 4500 cm^2/person/h	0.0144	7.97%

According to the model calculations, there is no unacceptable risk for the worker performing work on pome fruits previously treated with Novagib. As a standard rule, it is recommended that treated crops should not be re-entered before spray deposits have completely dried.

See also RAR Volume 3CP Section B.6.4 for details.

2.7 RESIDUE

In studies R A9206 and AD/6258/VB (evaluated in RAR) stability of $GA_{4/7}$ at < -18°C in apples and pears was proven for 30 months.

2.7.1 Summary of storage stability of residues

In studies R A9206 and AD/6258/VB (evaluated in RAR) stability of $GA_{4/7}$ at < -18°C in apples and pears was proven for 30 months.

2.7.2 Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

Study 22-1-02.PMET (evaluated in DAR and RAR), which is scientific paper it was shown that GA_4 and GA_7 are widespread in plants including many common varieties of fruits, vegetables and cereals. This study also contains information on the metabolism of gibberellins in plants and it can be concluded that the metabolism of gibberellins GA_4 in plants primarily involves conjugation with glucose to form 3-O-glucosides and glucosyl esters. Hydroxylation at the 13-C position also occurs and results in the formation of GA_1 from which the GA_4-13-O-glucoside is then subsequently formed. Hydroxylation at the 2-carbon position was also reported giving rise to the gibberellins GA_8 and GA_{34}, with subsequent glucose conjugation possible. Gibberellin GA_2 was also tentatively observed as a further hydroxylation product. Similarly from GA_7 metabolites like GA_7-3-O-glucoside are formed.

Studies on metabolism and distribution of GA_4/GA_7 in poultry, pigs and ruminants are not necessary, since it is not possible to distinguish GA_4/GA_7 in products of animal origin, resulting from consumption of naturally occurring residues, from those resulting from the use of plant growth regulators. Moreover, pome fruit is not a feeding stuff for poultry and pigs. Besides residues of $GA_{4/7}$ in apples were below the LOQ of 0.05 mg/kg in all supervised residue trials (see B 7.3.), which means that the trigger value 0.004 mg/kg bw/day in the diet of lactating ruminants will not be exceed. Therefore, metabolism data in poultry, ruminants and pigs are not necessary.

2.7.3 Definition of the residue

$GA_{4/7}$ is temporarily included on Annex IV Regulation (EC) No. 396/2005. Applicant and RMS propose that $GA_{4/7}$ should remain on Annex IV Regulation (EC) No. 396/2005. Definition of the residue is therefore not necessary.

2.7.4 Summary of residue trials in plants and identification of critical GAP

$GA_{4/7}$ is authorized in apples and pears only. Within this dossier, residue data are provided for the representative uses supporting the renewal of approval. The solo SC formulation Novagib has been selected as the representative formulation.

Treated apples
GAP is presented in Table 2.7.4.1-1.

Table 2.7.4.1-1: Critical GAP on apples for $GA_{4/7}$ in the EU

Crop	EU residues zone	Application					PHI (days)
		Max. no.	Interval (days)	Max. rate (kg a.s./ha)	Spray Volume (L/ha)	Growth stage (BBCH)	
Apples	North and south	4	7	0.005	300-1000	69 to 74	n/a

Seven acceptable field trials were available conducted in Northern (2) and Southern (5) EU at GAP 4 x 14-17 g a.s./ha, BBCH 72-74, (Studies AF/6256/VB, AF/6989/VB). Residues were <0.05 mg/kg in all trials. Proposed GAP can be authorized.

Untreated apples
GA_4 has been identified in 54 plant species, 7 fungi and 3 bacteria species. In plants GA_4 was found mainly in seeds, leaves, shoots, buds, fruits and pollen.

GA_7 has been identified in 14 plant species and 1 fungus species. In plants GA_7 was found mainly in seeds, leaves, shoots and pollen.

In scientific papers natural background concentration of GA_4 in apples was up to 0.00017 mg/kg and natural background concentration of GA_7 up to 0.000004 mg/kg.

We can conclude that the use of $GA_{4/7}$ as a plant protection product results in residue levels similar to the natural levels in plants.

Treated pears
GAP is presented in Table 2.7.4.3-1.

Table 2.7.4.3-1: Critical GAP on pears for $GA_{4/7}$ in the EU

Crop	EU residues zone	Application					PHI (days)
		Max. no.	Interval (days)	Max. rate (kg a.s./ha)	Spray Volume (L/ha)	Growth stage (BBCH)	
Pears	North and south	2	3	0.006	300-1000	62 to 69	n/a
Pears	North and south	1	n/a	0.012	300-1000	62 to 69	n/a

Four acceptable field trials were available conducted in Northern (2) and Southern (2) EU at GAP 2 x 14-16 g a.s./ha, BBCH 64-68, (Studies AF/6256/VB, AF/6989/VB). Residues were <0.05 mg/kg in all trials. Proposed GAPs can be authorized.

Untreated pears
GA_4 has been identified in 54 plant species, 7 fungi and 3 bacteria species. In plants GA_4 was found mainly in seeds, leaves, shoots, buds, fruits and pollen.

GA_7 has been identified in 14 plant species and 1 fungus species. In plants GA_7 was found mainly in seeds, leaves, shoots and pollen.

In scientific papers natural background concentration of GAs in pears was up to 0.06 mg/kg.

We can conclude that the use of $GA_{4/7}$ as a plant protection product results in residue levels similar to the natural levels in plants.

2.7.5 Summary of feeding studies in poultry, ruminants, pigs and fish

$GA_{4/7}$ occurs naturally in apples and pears at similar level than in treated apples and pears therefore it would be impossible to distinguish between natural background and $GA_{4/7}$ originating from treatment with PPP. Moreover

apples and pears are not feed to poultry, pigs and fish. Besides residues of $GA_{4/7}$ in apples were below the LOQ of 0.05 mg/kg in all supervised residue trials (see B 7.3.), which means that the trigger value 0.004 mg/kg bw/day in the diet of lactating ruminants will not be exceed. Therefore studies on poultry, ruminants, pigs and fish are not required.

2.7.6 Summary of effects of processing

Residues in treated apples and pears were <LOQ (<0.05 mg/kg). Therefore studies are not required.

2.7.7 Summary of residues in rotational crops

No studies are required since orchards are permanent crops.

2.7.8 Summary of other studies

The potential of residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom was considered. In 17 honey samples from China GA_4 and GA_7 concentration was analysed. In all samples GA_7 was not detected (limit of detection was 0.0000185 mg/kg) and content of GA_4 was up to 0.0005822 mg/kg; indicating that transfer from pollen (where $GA_{4/7}$ is naturally present) to honey is minimal and limited.

2.7.9 Estimation of the potential and actual exposure through diet and other sources

The toxicological endpoints used in the risk assessments, the ADI and ARfD for the active substance $GA_{4/7}$ is summarized in the table below.

Table 2.7.9-1: Toxicological endpoints – $GA_{4/7}$

Endpoint	Value	Study	Safety factor	Reference
Acceptable Daily Intake (ADI)	0.3 mg/kg bw/d	Rat multigeneration	1000	SANCO/2614/08 – rev. 1- Review Report 2012 EFSA Journal 2012;10(1):2502
Acute Reference Dose (ARfD)	Not allocated - not necessary			

TMDI calculation

The summary of the calculation using the EFSA model rev 2.0 is presented in Table 2.7.9-2. Input values were LOQ of analytical method (0.05 mg/kg) for all plant and animal matrices. For the assessment, an ADI of 0.3 mg/kg bw/day was used. According to the EFSA model, the TMDI has been simultaneously calculated for adults, children, toddlers and infants (different age groups), vegetarian and elderly in different EU countries.

With the current EFSA model, the chronic risk assessment ranges from 0.2 to 1.3% of the ADI. The diet with the highest TMDI is "FR toddler" with 1.3% of the ADI. For this diet, the highest contributors are products of animal origin with 0.7% of the ADI. The diet with the second highest TMDI is "UK infant" with 1.2% of the ADI, in which also products of animal origin are the major contributors with 0.7% of the ADI.

The ADI utilization does not exceed the ADI when using LOQ values. Thus, no unacceptable long-term exposure of

consumers was identified.

Table 2.7.9-2: $GA_{4/7}$ TMDI calculation based on LOQ input values

Gibberellin (GA4/7)			
Status of the active substance:		Code no.	
LOQ (mg/kg bw):	0,05	proposed LOQ:	
Toxicological end points			
ADI (mg/kg bw/day):	**0,3**	ARfD (mg/kg bw):	
Source of ADI:	**EFSA**	Source of ARfD:	
Year of evaluation:	**2012**	Year of evaluation:	

Prepare workbook for refined calculations

Undo refined calculations

Explain choice of toxicological reference values.

The risk assessment has been performed on the basis of the MRLs collected from Member States in April 2006. For each pesticide/commodity the highest national MRL was identified (proposed temporary MRL = pTMRL).
The pTMRLs have been submitted to EFSA in September 2006.

Chronic risk assessment

TMDI (range) in % of ADI minimum - maximum	
0	1
No of diets exceeding ADI:	---

Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)
1,3	FR toddler	0,7	PRODUCTS OF ANIMAL ORIGIN	0,3	VEGETABLES	0,2	FRUIT (FRESH OR FROZEN)	1,3
1,2	UK Infant	0,7	PRODUCTS OF ANIMAL ORIGIN	0,2	SUGAR PLANTS	0,1	VEGETABLES	1,2
1,1	UK Toddler	0,4	PRODUCTS OF ANIMAL ORIGIN	0,4	SUGAR PLANTS	0,1	FRUIT (FRESH OR FROZEN)	1,1
1,1	NL child	0,5	PRODUCTS OF ANIMAL ORIGIN	0,2	FRUIT (FRESH OR FROZEN)	0,2	VEGETABLES	1,1
1,1	FR infant	0,5	PRODUCTS OF ANIMAL ORIGIN	0,3	VEGETABLES	0,3	FRUIT (FRESH OR FROZEN)	1,1
1,0	DE child	0,4	PRODUCTS OF ANIMAL ORIGIN	0,4	FRUIT (FRESH OR FROZEN)	0,1	VEGETABLES	1,0
0,8	WHO Cluster diet B	0,2	VEGETABLES	0,2	CEREALS	0,1	FRUIT (FRESH OR FROZEN)	0,8
0,7	DK child	0,4	PRODUCTS OF ANIMAL ORIGIN	0,2	CEREALS	0,1	VEGETABLES	0,7
0,6	SE general population 90th percentile	0,3	PRODUCTS OF ANIMAL ORIGIN	0,2	VEGETABLES	0,1	FRUIT (FRESH OR FROZEN)	0,6
0,6	ES child	0,3	PRODUCTS OF ANIMAL ORIGIN	0,1	FRUIT (FRESH OR FROZEN)	0,1	CEREALS	0,6
0,6	IE adult	0,2	FRUIT (FRESH OR FROZEN)	0,2	VEGETABLES	0,1	CEREALS	0,6
0,5	WHO cluster diet E	0,2	VEGETABLES	0,1	PRODUCTS OF ANIMAL ORIGIN	0,1	CEREALS	0,5
0,5	WHO cluster diet D	0,2	VEGETABLES	0,1	CEREALS	0,1	PRODUCTS OF ANIMAL ORIGIN	0,5
0,4	WHO regional European diet	0,2	PRODUCTS OF ANIMAL ORIGIN	0,2	VEGETABLES	0,1	CEREALS	0,4
0,4	WHO Cluster diet F	0,1	PRODUCTS OF ANIMAL ORIGIN	0,1	VEGETABLES	0,1	CEREALS	0,4
0,4	NL general	0,1	PRODUCTS OF ANIMAL ORIGIN	0,1	VEGETABLES	0,1	FRUIT (FRESH OR FROZEN)	0,4
0,3	ES adult	0,1	PRODUCTS OF ANIMAL ORIGIN	0,1	FRUIT (FRESH OR FROZEN)	0,1	VEGETABLES	0,3
0,3	UK vegetarian	0,1	SUGAR PLANTS	0,1	VEGETABLES	0,1	PRODUCTS OF ANIMAL ORIGIN	0,3
0,3	FR all population	0,1	FRUIT (FRESH OR FROZEN)	0,1	PRODUCTS OF ANIMAL ORIGIN	0,1	VEGETABLES	0,3
0,3	PT General population	0,1	FRUIT (FRESH OR FROZEN)	0,1	VEGETABLES	0,1	CEREALS	0,3
0,3	UK Adult	0,1	PRODUCTS OF ANIMAL ORIGIN	0,1	SUGAR PLANTS	0,1	VEGETABLES	0,3
0,3	DK adult	0,1	PRODUCTS OF ANIMAL ORIGIN	0,1	VEGETABLES	0,1	FRUIT (FRESH OR FROZEN)	0,3
0,3	IT kids/toddler	0,1	CEREALS	0,1	VEGETABLES	0,1	FRUIT (FRESH OR FROZEN)	0,3
0,3	LT adult	0,1	PRODUCTS OF ANIMAL ORIGIN	0,1	VEGETABLES	0,0	CEREALS	0,3
0,2	FI adult	0,1	PRODUCTS OF ANIMAL ORIGIN	0,0	VEGETABLES	0,0	FRUIT (FRESH OR FROZEN)	0,2
0,2	IT adult	0,1	CEREALS	0,1	VEGETABLES	0,0	FRUIT (FRESH OR FROZEN)	0,2
0,2	PL general population	0,1	VEGETABLES	0,1	FRUIT (FRESH OR FROZEN)	0,0	PULSES, DRY	0,2

Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.
A long-term intake of residues of Gibberellin (GA4/7) is unlikely to present a public health concern.

2.7.10 Proposed MRLs and compliance with existing MRLs

$GA_{4/7}$ is temporarily included on Annex IV Regulation (EC) No. 396/2005. Applicant and RMS propose that $GA_{4/7}$ should remain on Annex IV Regulation (EC) No. 396/2005. Therefore, no compliance is possible with existing MRLs and no new MRLs are proposed.

2.7.11 Proposed import tolerances and compliance with existing import tolerances

Import tolerances do not exist. No new import tolerances are proposed.

2.8 FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1 Summary of fate and behaviour in soil

The route and rate of aerobic degradation of the individual components gibberellins GA4 and gibberellins GA7 of the active substance gibberellins GA4/7 was investigated in four soil types (ranging from loamy sand to clay loam) of varying origin in the dark under laboratory conditions at a temperature of 20°C and moisture content of 100% pF 2. The individual components gibberellins GA4 and gibberellins GA7 degrade extensively in soil. Numerous degradation products were observed but not fully identified. Ultimate degradation led to the formation of un-extracted soil residues and mineralisation to carbon dioxide.

For both gibberellins GA4 and gibberellins GA7 the best-fit persistence half-lives were <2 days in all soil types (and a conservative protective value of 2 days is used for PEC generation). The DT_{50} and DT_{90} values are summarised in Table 2.8.1-1. The available data clearly indicate that the active substance gibberellins GA4/7 and its individual components gibberellins GA4 and gibberellins GA7 are not persistent in soil. Therefore, in accordance with Regulation (EC) No. 1272/2008, gibberellins GA4/7 fulfils the criteria for consideration as a low-risk active substance in this regard.

Table 2.8.1-1: DT50 of gibberellins GA4 and gibberellins GA7 (FOCUS persistence endpoints)

Soil	Kinetic Model	Degradation rate (days)		Chi2err (%)
		DT50	DT90	
gibberellins GA4				
(conducted at 20°C and pF 2 moisture content)				
Speyer 5M	SFO	0.171	0.568	3.188
Speyer 2.2	SFO	0.347	1.153	20.75
Brierlow	SFO	0.392	1.303	18.61
South Witham	SFO	0.104	0.346	28.78
(conducted at 20°C and 45% MWHC)				
Soil LUFA 2.1	SFO	1.542	5.083	7.2
Soil LUFA 2.2	DFOP	1.125	12.583	7.2
Soil LUFA 2.3	FOMC	1.000	5.333	14.7
Soil LUFA 6S	SFO	1.083	3.625	5.6
gibberellins GA7				
(conducted at 20°C and pF 2 moisture content)				
Speyer 5M	SFO	0.060	0.200	13.57
Speyer 2.2	SFO	0.064	0.212	13.20
Brierlow	SFO	0.132	0.440	16.67
South Witham	SFO	0.011	0.036	1.005
(conducted at 20°C and 45% MWHC)				
Soil LUFA 2.1	SFO	0.500	1.625	11.2
Soil LUFA 2.2	DFOP	0.292	0.917	12.2
Soil LUFA 2.3	FOMC	0.167	0.583	5.2
Soil LUFA 6S	SFO	0.583	1.917	11.3

The degradation of the active substance gibberellins GA4/7 in soil under anaerobic conditions has not been investigated as anaerobic conditions are not relevant for uses of the representative formulation.

The molar absorbance coefficients of the individual components gibberellins GA4 and gibberellins GA7 are <10 L/mol/cm at or above wavelength 298 nm and therefore the trigger value of 10 L/mol/cm is not exceeded i.e.

soil photolysis is not expected to contribute significantly to the environmental degradation of the active substance due to low light absorbance.
The soil sorption properties of the individual components of the active substance gibberellins GA4/7, gibberellins GA4 and gibberellins GA7 were investigated in four soils (UK origin) with a range of characteristics (pH 3.8 to 7.4, %OC 0.8 to 5.2) at five concentrations (0.05 – 5 µg/mL) using the batch equilibrium technique with a soil to solution ratio of 1:1 w/v and a 3 hr equilibration time. The sorption parameters determined were Kf (0.19 - 1.32 mL/g), Koc 4 - 165 mL/g and 1/n (0.9611 - 0.9706) for gibberellins GA4 and Kf (0.22 - 1.33 mL/g), Koc (4 - 166 mL/g) and 1/n (0.9802 - 1.0464) for gibberellins GA7.

2.8.2 Summary of fate and behaviour in water and sediment [equivalent to section 11.1 of the CLH report template]

The active substance gibberellins GA4/7, comprises two components i.e. gibberellins GA4 and gibberellins GA7. The degradation of the active substance in aquatic systems was investigated by conducting studies on the individual components, where necessary.
Gibberellins GA4 was stable to hydrolysis at pH 4, 7 and 9 (i.e. half-life values of > 1 year at 20°C). Gibberellins GA7 was stable to hydrolysis at pH 7 but was hydrolysed at pH 4 and pH 9 at 50°C. However, the rate of hydrolysis at 20°C is expected to be slow. Degradation products were not identified, but may include the diol derivative of gibberellins GA7 following hydroxylation at the double bond position in the gibberellins GA7 unsaturated ring. Potential degradation products are not considered to be of any environmental concern and are not considered further.
The molar absorption coefficients of gibberellins GA4 and gibberellins GA7 are <10 L/mol/cm and therefore a measurement of the photolytic half-life and quantum yield is not required. Nevertheless, the rate of photolysis of gibberellins GA4 and gibberellins GA7 in aqueous buffer solutions at pH 5, 7 and 9 was investigated using artificial sunlight. The photochemical degradation of combined gibberellins GA4 and gibberellins GA7 was slow with a half-life in the range of 104 to 267 days. The photo-degradation of gibberellins GA4 and gibberellins GA7 measured separately was 101 to 163 days and 57 to 145 days, respectively. Photolysis of gibberellins GA4 and gibberellins GA7 can therefore be regarded as a slow process and not a significant route of degradation in the environment.
The active substance gibberellins GA4/7 was determined to be readily biodegradable in a modified Sturm test (OECD 301B). However, a second study, which was also conducted using the carbon dioxide evolution (Modified Sturm) test, provided a conflicting result (i.e. not readily biodegradable). It is therefore concluded that the active substance gibberellins GA4/7 cannot be reliably classified as being readily biodegradable. However, on the basis of the degree of biodegradation observed in the non-positive test (in conjunction with the rapid and extensive microbial degradation and ultimate complete mineralisation via other natural components observed in the soil and aquatic metabolism studies), it is concluded that the active substance gibberellins GA4/7 can be considered inherently biodegradable.
Degradation of the active substance gibberellins GA4/7 in aquatic systems (pelagic water and water/sediments systems) was assessed by read across to studies conducted using the structurally related active substance gibberellins GA3. On this basis degradation of the active substance gibberellins GA4/7 in these systems is assumed to proceed via isomerisation and/or opening of the lactone ring to form metabolites which are not likely to be environmentally important and would also be formed by degradation of naturally occurring gibberellins GA4 and gibberellins GA7.
The available data indicate that gibberellins GA4/7 and its individual components gibberellins GA4 and gibberellins GA7 are not persistent in pelagic water or water-sediment systems. Therefore, in accordance with Regulation (EC) No. 1272/2008, gibberellins GA4/7 fulfils the criteria for consideration as a low-risk active substance in this regard.

2.8.2.1 Rapid degradability of organic substances

Table 68: Summary of relevant information on rapid degradability

Method	Results*	Key or Supportive study	Remarks	Reference
Modified Sturm test	Mean cumulative CO_2 production by mixtures containing gibberellins GA_4 and GA_7 was equivalent to 21% of the theoritical value after 13 days, 65% of the theoritical value after 19 days and 77% by the end of the test on day 29. Based on graphic estimation the evolved CO_2 was 10% on the day of 10 of test. Gibberellins GA_4 and GA_7 are readily biodegradable under the conditions of the test and do not have an inhibitory effect on microbial activity in the test medium.	Barnes, S., P., (2005), Gibberellins GA4/7, Assessment of Ready Biodegradability	None. The study was considered acceptable.	Vol3CA 8.2.2.2, page 66
Modified Sturm test	Gibberellins GA4/7 technical failed to meet the requirements for a pass in this test (≥60% degradation relative to $ThCO_2$) with a maximum 6% recorded on day 14. The result shows that gibberellins GA4/7 cannot be classified as readily biodegradable on the basis of this test. The reference substance was degraded by 85 and 137% of its TCO_2 in the absence and presence of gibberellins GA4/7, respectively after 29 days. The results confirm the suitability of the test medium and show that gibberellins GA4/7 had no inhibitory effect on microbial activity in the test medium.	Drake, R., M., (2009), Gibberellins GA4/7, Assessment of Ready Biodegradability	None. The study was considered acceptable.	Vol3CA 8.2.2.2, page 69

** data on full mineralization should be reported*

2.8.2.1.1 Ready biodegradability

On the basis of the conflicting results of the two ready biodegradability studies (Barnes 2005 and Drake 2009), it is concluded that the active substance gibberellins GA4/7 cannot be reliably classified as readily biodegradable. However, on the basis of the degree of biodegradation observed in the non-positive test (in conjunction with the rapid and extensive microbial degradation and ultimate complete mineralisation via other natural components observed in the soil and water/sediment studies), it is concluded that the active substance gibberellins GA4/7 can be considered as inherently biodegradable.

2.8.2.1.2 BOD5/COD

No data were presented by applicant.

2.8.2.2 Other convincing scientific evidence

No data were presented by applicant.

2.8.2.2.1 Aquatic simulation tests

No data were presented by applicant.

2.8.2.2.2 Field investigations and monitoring data (if relevant for C&L)

No data were presented by applicant.

2.8.2.2.3 Inherent and enhanced ready biodegradability tests

No data were presented by applicant.

2.8.2.2.4 Soil and sediment degradation data

Please see section 2.8.1 and 2.8.2. of this document.

2.8.2.2.5 Hydrolysis

Please see section 2.8.2 of this document.

2.8.2.2.6 Photochemical degradation

Please, see section 2.8.2 of this document.

2.8.2.2.7 Other / Weight of evidence

No further data were presented by applicant.

2.8.3 Summary of fate and behaviour in air

Based on vapour pressure values of 0.160 and 0.067 Pa (22°C) for the components gibberellins GA4 and gibberellins GA7, respectively, the components are potentially volatile from plant and soil surfaces. However, no volatility of the individual components gibberellins GA4 or gibberellins GA7 was observed in any of the environmental fate studies and therefore volatility under the conditions of use is not expected. Furthermore, the estimated photochemical oxidative degradation half-lives in air of the components gibberellins GA4 and gibberellins GA7 (calculated using the Atkinson equation), are 1.67 and 0.99 hours, respectively (EFSA LoEP). Therefore, these components will not persist in the atmosphere, if present.

2.8.3.1 Hazardous to the ozone layer

Applicant presented no data. Not applicable.

2.8.3.2 Hazardous to the ozone layer

Table 69: Summary table of studies on hazards to the ozone layer

Method	Results	Remarks	Reference
-	-	-	-

Applicant presented no data. Not applicable.

2.8.3.2.1 Short summary and overall relevance of the provided information on hazards to the ozone layer

Applicant presented no data. Not applicable.

2.8.3.2.2 Comparison with the CLP criteria

Applicant presented no data. Not applicable.

2.8.3.2.3 Conclusion on classification and labelling for hazardous to the ozone layer

Applicant presented no data. Not applicable.

2.8.4 Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

No monitoring studies for the active substance gibberellins GA4/7 are available.

2.8.5 Definition of the residues in the environment requiring further assessment

Based on the information provided in the dossier under previous points, the following residue definitions for risk assessment are proposed for soil, groundwater, surface water, sediment and air:

The residue definition for risk assessment in soil is based on the following studies:

- Studies investigating aerobic soil degradation found the following major components:
  - 7.1.1.1/01 - gibberellins GA4 and gibberellins GA7 only (although several major (>10% AR) metabolites were observed these are considered to be of no environmental concern due to the natural occurrence of the active substance)
  - 7.1.2.1.1/01 – gibberellins GA4 and gibberellins GA7 only
- Residue definition for risk assessment in soil: gibberellins GA4 and gibberellins GA7 only

The residue definition for risk assessment in groundwater is based on the residue definition for soil:

- Residue definition for risk assessment in groundwater: gibberellins GA4 and gibberellins GA7 only (although several major (>10% AR) metabolites were observed these are considered to be of no

environmental concern due to the natural occurrence of the active substance)

The residue definition for risk assessment in surface water and sediment is based on the following studies:

- Studies investigating hydrolysis found the following major components:
  - 7.2.1.1/01 - gibberellins GA4 and gibberellins GA7 only
- Studies investigating direct aqueous photolysis found the following major components:
  - 7.2.1.2/01 - gibberellins GA4 and gibberellins GA7 only
- Studies investigating degradation in pelagic water systems found the following major components:
  - 7.2.2.2/01 - gibberellins GA4 and gibberellins GA7 only, based on a study conducted using gibberellins GA3 (although significant metabolites were observed these were considered to be of no environmental concern due to the natural occurrence of the active substance)
- Studies investigating degradation in water/sediment systems found the following major components:
  - 7.2.2.3/01 – For surface water gibberellins GA4 and gibberellins GA7 only, based on a study conducted using gibberellins GA3 (although significant metabolites were observed these were considered to be of no environmental concern due to the natural occurrence of the active substance). For sediment gibberellins GA4 and gibberellins GA7 only
- Residue definition for risk assessment in surface water and sediment: For surface water gibberellins GA4 and gibberellins GA7 only. For sediment gibberellins GA4 and gibberellins GA7 only (although several major (>10% AR) metabolites were observed these are considered to be of no environmental concern due to the natural occurrence of the active substance).

The residue definition in air for risk assessment is based on vapour pressure values of 0.160 and 0.067 Pa (22°C) for the components gibberellins GA4 and gibberellins GA7, respectively. Although potentially volatile from plant and soil surfaces, the components were not observed to be volatile in any of the environmental fate studies. Therefore volatility under the conditions of use is not expected. Furthermore, the estimated photochemical oxidative degradation half-lives in air of the components gibberellins GA4 and gibberellins GA7 (calculated using the Atkinson equation), are 1.67 and 0.99 hours, respectively (EFSA LoEP, page 39/50). Therefore, these components will not persist in the atmosphere, if present.

- Residue definition in air for risk assessment: gibberellins GA4 and gibberellins GA7 only

Definition of the residue for monitoring

Based on the information considered for the definition of the residue for risk assessment, the persistence and relative toxicity of the components involved and the general natural occurrence of the components and their degradation products, the following residue definitions for monitoring purposes are proposed for soil, groundwater, surface water, sediment and air.

The residue definition for monitoring purposes in soil is gibberellins GA4 and gibberellins GA7 only (as above).

The residue definition for monitoring purposes in groundwater is gibberellins GA4 and gibberellins GA7 only (as above).

The residue definition for monitoring purposes in surface water is gibberellins GA4 and gibberellins GA7 only (as above).

The residue definition for monitoring purposes in sediment is gibberellins GA4 and gibberellins GA7 only (as above).

The residue definition for monitoring purposes in air is gibberellins GA4 and gibberellins GA7 only (as above).

2.8.6 Summary of exposure calculations and product assessment

PREDICTED ENVIRONMENTAL CONCENTRATIONS IN SOIL (PECs)

Use of the formulated product 'Novagib' can potentially lead to amounts reaching soil, therefore the predicted environmental concentration in soil (PECsoil) of the formulated product 'Novagib', the individual components gibberellins GA4 and gibberellins GA7 in the active substance and any associated significant metabolites is considered. 'Novagib' is a soluble concentrate formulation containing the active substance gibberellins GA4/7 (10 g/L).

The critical Good Agricultural Practice (GAP) for 'Novagib' is presented in Document D1, with relevant agronomic parameters summarised in Table 2.8.6-1

Table 2.8.6-1: GAP for 'Novagib'

Treatment details			Application timing	Crop Inter-ception[1]	Effective treatment rate (g a.s./ha)
Crop	**No.**	**Rate**			
Apple	4 (7 d min interval)	5 g a.s./ha (0.5 L/ha)	GS 69-74	60	4 x 2.0
			1-Apr (earliest)	50	4 x 2.5
Pear	1	12 g a.s./ha (1.2 L/ha)	GS 62-69	60	1 x 4.8
			1-Apr (earliest)	50	1 x 6.0
Pear	2 (3 d min interval)	6 g a.s./ha (0.6 L/ha)	GS 62-69	60	2 x 2.4
			1-Apr (earliest)	50	2 x 3.0

(1) EFSA 2014. EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain $DegT_{50}$ values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014;12(5):3662, 37 pp., doi:10.2903/j.efsa.2014.3662.

Based on the GAP parameters specified in Table2.8.6-1, the predicted environmental concentration of the formulated product 'Novagib' and the two components of the active substance and any associated metabolite(s) in soil are determined as follows:

The predicted environmental concentration in soil (PECs) was calculated based upon the maximum proposed use rate following the recommendations of the FOCUS Soils Group (FOCUS 1997[1]). Calculations assume any of the applied active substance reaching the soil surface is distributed uniformly to a depth of 5 cm (with no mechanical incorporation). The bulk density of soil is assumed to be 1.5 g/cm^3.

The initial predicted environmental concentration in soil of the formulated product 'Novagib' is presented in Table 2.8.6-2. Since the formulation components other than the active substance are assumed to dissipate rapidly in the environment, it is only necessary to consider the initial concentration for 'Novagib'. As a worst-case, it is assumed that the annual application rate is applied on a single occasion i.e. no dissipation of the formulation is considered between applications.

[1] FOCUS (1997). Soil persistence models and EU registration. European Commission Document 7617/VI/96.

Table 2.8.6-2: Worst-case initial PECsoil for intact formulation 'Novagib' needed for risk assessment

Crop	Formulation application rate	Application timing	Crop interception	Soil concentration (mg 'Novagib'/kg dw soil)
Apple	4 x 0.5 L/ ha 'Novagib' (equivalent to 4 x 520 g 'Novagib'/ha[1])	GS 69-74	60	1.11
		1-Apr (earliest)	50	1.39
Pear	1 x 1.2 L/ ha 'Novagib' (equivalent to 1 x 1248 g 'Novagib'/ha[1])	GS 62-69	60	0.67
		1-Apr (earliest)	50	0.83
Pear	2 x 0.6 L/ ha 'Novagib' (equivalent to 2 x 624 g 'Novagib'/ha[1])	GS 62-69	60	0.67
		1-Apr (earliest)	50	0.83

(1) Based on a formulation relative density of 1.04 g/ml.

The maximum potential initial concentration of the intact formulated product 'Novagib' in soil following application is 1.39 mg/kg (dw soil).

The fate and behaviour of the active substance and any associated metabolites in soil is investigated in Document M-CA, Section 8, under Points CA 8.1.1 and CA 8.1.2 and summarised under Point CA 8.1.2.3. The definition of the residue for risk assessment (soil) is defined under Point CA 8.6. The active substance gibberellins GA4/7 contains two components (gibberellins GA4 and gibberellins GA7). Degradation of gibberellins GA4 and gibberellins GA7 in soil under aerobic conditions leads to the formation of numerous degradation products, however, due to the natural occurrence of the active substance these metabolites are considered to be of no environmental concern and have not been considered further.

The active substance gibberellins GA4/7 consists of two components gibberellins GA4 and gibberellins GA7. In the representative formulation 'Novagib' the two components are present in a certain ratio (see confidential section), however, in order to take into account other possible ratios of the two components and to provide a conservative assessment, PECsoil are calculated assuming 100% content of both gibberellins GA4 and gibberellins GA7.

The actual initial predicted environmental concentrations in soil (PECsoil) for gibberellins GA4/7 are provided in Table 2.8.6-3 assuming, as a worst-case, a single application at the annual application rate i.e. no degradation of the active substance is considered between applications. Short and long term actual and time weighted average PEC values are not required for the risk assessment and have therefore not been calculated.

Table 2.8.6-3: Worst-case initial PECsoil for the active substance gibberellins GA4/7 following treatment with 'Novagib'

Crop	Application details				Initial concentration in soil (mg a.s./kg soil dw) gibberellins GA4/7
	Actual rate (g a.s./ha)	Timing	Crop interception (%)	Effective rate (g a.s./ha)	
Apple	4 x 5 (7 d minimum interval)	GS 69-74	60	4 x 2	0.0107
		1-Apr (earliest)	50	4 x 2.5	0.0133
Pear	1 x 12 g a.s./ha	GS 62-69	60	1 x 4.8	0.0064
		1-Apr (earliest)	50	1 x 6.0	0.0080
Pear	2 x 6 g a.s./ha (3 d minimum interval)	GS 62-69	60	2 x 2.4	0.0064
		1-Apr (earliest)	50	2 x 3.0	0.0080

Following treatment with 'Novagib' according to the supported GAP, the maximum potential initial residue in soil of the active substance gibberellins GA4/7 is 0.0133 mg/kg dw (soil mixing depth 5 cm).

PREDICTED ENVIRONMENTAL CONCENTRATIONS IN GROUND WATER (PEC_{GW})

The predicted environmental concentration in groundwater (PECgw) of the active substance gibberellins GA4/7 and any associated metabolites following use of the formulated product 'Novagib' has been addressed in accordance with the recommendations of the FOCUS groundwater working group (FOCUS 2000[2], 2014a[3] and 2014b[4]) using the FOCUS PEARL (FOCUS version 4.4.4) and FOCUS PELMO (FOCUS version 5.5.3) models. Simulations were also conducted using the FOCUS MACRO model (FOCUS version 5.5.4), with the Châteaudun scenario. Since the formulation components other than the active substance are assumed to dissipate rapidly in the environment, the predicted environmental concentration in groundwater (PECgw) of the formulated product 'Novagib' is not calculated.

The supported GAP is presented with relevant agronomic parameters being summarised in Table 2.8.6-1. Based on the proposed application timings, the dates selected at each scenario location for the modelling simulations are presented in Table 2.8.6-4.

Application dates were chosen using the AppDate utility (ver 2.03 SE, 2 Jun 2017) using the earliest specified growth stage within the recommended application window. In addition, to cover potential early applications i.e. as early as 1-April, additional application dates were also considered.

[2] FOCUS (2000): FOCUS groundwater scenarios in the EU review of active substances. Report of the FOCUS groundwater scenarios workgroup, EC Document Reference Sanco/321/2000 rev. 2.

[3] FOCUS (2014a). Generic Guidance for Tier 1 FOCUS Ground Water Assessments. Version: 2.2, May 2014.

[4] FOCUS (2014b) "Assessing Potential for Movement of Active Substances and their Metabolites to Ground Water in the EU" Report of the FOCUS Ground Water Work Group, EC Document Reference Sanco/13144/2010 version 3, 613 pp.

Table 2.8.6-4: Summary of modelled application dates and timings for groundwater simulations

Treatment pattern and actual application timings	Scenario	Default FOCUS dates for leaf emergence/harvest	Modelled application date (relative to emergence/harvest date)	
			Main	Earliest
Apple 4 x 5 g a.s./ha (7 day minimum interval)	Châteaudun (C)	1-Apr/1-Oct	7-Jul (97/-86 d), 14-Jul, 21-Jul, 28-Jul[1]	1-Apr, 8-Apr, 15-Apr, 22-Apr[4]
	Hamburg (H)	15-Apr/30-Oct	3-Jun (49/-149 d), 10-Jun, 17-Jun, 24-Jun	
	Jokioinen (J)	10-May/15-Oct	7-Jul (58/-100 d), 14-Jul, 21-Jul, 28-Jul	
	Kremsmünster (K)	15-Apr/30-Oct	3-Jun (49/-149 d), 10-Jun, 17-Jun, 24-Jun	
	Okehampton (N)	25-Mar/15-Sep	13-Jul (110/-64 d), 20-Jul, 27-Jul, 3-Aug	
	Piacenza (P)	1-Apr/1-Nov	16-Jul (106/-108 d), 23-Jul, 30-Jul, 6-Aug	
	Porto (O)	15-Mar/31-Oct	6-Aug (144/-86 d), 13-Aug, 20-Aug, 27-Aug	
	Sevilla (S)	15-Mar/15-Oct	11-Jul (118/-96 d), 18-Jul, 25-Jul, 1-Aug	
	Thiva (T)	15-Mar/20-Oct	2-Aug (140/-79 d), 9-Aug, 16-Aug, 23-Aug	
	Application timing and equivalent application rate		GS 69-74 (i.e. 60% crop interception). Effective application rate 4 x 2.0 g a.s./ha	1st Apr earliest (i.e. 50% crop interception). Effective application rate 4 x 2.5 g a.s./ha
Notes: Pome fruit (apples) was used as the crop type in the FOCUS modelling. Treatments were assumed to be conducted every year and made to the soil surface. Absolute application dates were used within the models.				
Pear 1 x 12 g a.s./ha	Châteaudun (C)	1-Apr/1-Oct	8-Jun (68/-115 d)[2]	1-Apr[5]
	Hamburg (H)	15-Apr/30-Oct	19-May (34/-164 d)	
	Jokioinen (J)	10-May/15-Oct	4-Jun (25/-133 d)	
	Kremsmünster (K)	15-Apr/30-Oct	19-May (34/-164 d)	
	Okehampton (N)	25-Mar/15-Sep	21-Jun (88/-86 d)	
	Piacenza (P)	1-Apr/1-Nov	10-Jun (70/-144 d)	
	Porto (O)	15-Mar/31-Oct	8-Jul (115/-115 d)	

Treatment pattern and actual application timings	Scenario	Default FOCUS dates for leaf emergence/harvest	Modelled application date (relative to emergence/harvest date)	
			Main	Earliest
	Sevilla (S)	15-Mar/15-Oct	9-Jun (86/-128 d)	
	Thiva (T)	15-Mar/20-Oct	7-Jul (114/-105 d)	
	Application timing and equivalent application rate		GS 62-69 (i.e. 60% crop interception). Effective application rate 1 x 4.8 g a.s./ha	1st Apr earliest (i.e. 50% crop interception). Effective application rate 1 x 6.0 g a.s./ha
Notes: Pome fruit (apples) was used as the crop type in the FOCUS modelling, as a surrogate for pear. Treatments were assumed to be conducted every year and made to the soil surface. Absolute application dates were used within the models.				
Pear 2 x 6 g a.s./ha, (3 day minimum interval)	Châteaudun (C)	1-Apr/1-Oct	8-Jun (68/-115 d), 11-Jun[3]	1-Apr, 4-Apr[6]
	Hamburg (H)	15-Apr/30-Oct	19-May (34/-164 d), 22-May	
	Jokioinen (J)	10-May/15-Oct	4-Jun (25/-133 d), 7-Jun	
	Kremsmünster (K)	15-Apr/30-Oct	19-May (34/-164 d), 22-May	
	Okehampton (N)	25-Mar/15-Sep	21-Jun (88/-86 d), 24-Jun	
	Piacenza (P)	1-Apr/1-Nov	10-Jun (70/-144 d), 13-Jun	
	Porto (O)	15-Mar/31-Oct	8-Jul (115/-115 d), 11-Jul	
	Sevilla (S)	15-Mar/15-Oct	9-Jun (86/-128 d), 12-Jun	
	Thiva (T)	15-Mar/20-Oct	7-Jul (114/-105 d), 10-Jul	
	Application timing and equivalent application rate		GS 62-69 (i.e. 60% crop interception). Effective application rate 2 x 2.4 g a.s./ha	1st Apr earliest (i.e. 50% crop interception). Effective application rate 2 x 3.0 g a.s./ha
Notes: Pome fruit (apples) was used as the crop type in the FOCUS modelling, as a surrogate for pear. Treatments were assumed to be conducted every year and made to the soil surface. Absolute application dates were used within the models.				

(1) Julian dates for MACRO simulations: 188, 195, 202 and 209.
(2) Julian dates for MACRO simulations: 159
(3) Julian dates for MACRO simulations: 159 and 162
(4) Julian dates for MACRO simulations: 91, 98, 105 and 112.
(5) Julian dates for MACCO simulations: 91
(6) Julian dates for MACRO simulations: 91 and 94

The active substance gibberellins GA4/7 contains two components (gibberellins GA4 and gibberellins GA7). Degradation of gibberellins GA4 and gibberellins GA7 in soil under aerobic conditions leads to the formation of

numerous degradation products, however, due to the natural occurrence of the active substance these metabolites are not considered to be of any environmental concern and have not been considered further.
As the ratio of gibberellins GA4 and gibberellins GA7 in the active substance can vary between sources, for the determination of PECs of the active substance the approach adopted as a precautionary worst-case has been to consider alternate situations where the active substance is 100% gibberellins GA4 and separately 100% gibberellins GA7.

FOCUS PEARL (ver 4.4.4)
The modelling parameters used for the simulations conducted using the FOCUS PEARL model are presented in Table 2.8.6-5.

Table 2.8.6-5: Summary of input parameters for determination of worst-case PECgw for components gibberellins GA4 and gibberellins GA7 following treatment with 'Novagib' using PEARL 4.4.4

Parameter	Input parameters		Remarks
	gibberellins GA4	**gibberellins GA7**	
General parameters			
Chemical name	(3*S*,3a*R*,4*S*,4a*R*,7*R*,9a*R*,9b*R*,12*S*)-12-hydroxy-3-methyl-6-methylene-2-oxoperhydro-4a,7-methano-3,9b-propanoazuleno[1,2-*b*]furan-4-carboxylic acid (IUPAC)	(3*S*,3a*R*,4*S*,4a*R*,7*R*,9a*R*,9b*R*,12*S*)-12-hydroxy-3-methyl-6-methylene-2-oxoperhydro-4a,7-methano-9b,3-propenoazuleno[1,2-*b*]furan-4-carboxylic acid (IUPAC)	For structure see Appendix 1
Molecular weight (g/mol)	332.40	330.40	See appendix 1
Vapour pressure (Pa)	0	0	Worst-case
Molar enthalpy of vaporization (kJ/mol)	95	95	FOCUS recommendation
Water solubility (mg/L)	340 (20°C)	340 (20°C)	See Doc CA, Section 2, Point CA 2.5. (Note a value of 340 mg/L was used to be consistent with the agreed parameter specified in the existing EFSA LoEP (p37/50).
Molar enthalpy of dissolution (kJ/mol)	27	27	FOCUS recommendation
Freundlich Sorption parameters			
Sorption option	Kom, pH independent	Kom, pH independent	FOCUS recommendation
Soil adsorption coefficient, Kfoc (ml/g) at 20°C	4 (worst-case, pH dependant, n=4)	4 (worst-case, pH dependant, n=4)	See Doc CA, Section 7, Point 8.1.2
Kfom (ml/g) at 20°C	2.3	2.3	Determined from Kfoc divided by 1.724
Molar enthalpy of sorption (kJ/mol)	0	0	FOCUS recommendation
Reference concentration in liquid phase (mg/L)	1	1	FOCUS recommendation

Parameter	Input parameters		Remarks
	gibberellins GA4	**gibberellins GA7**	
Freundlich exponent 1/n (-)	0.97 (average n=4)	1.01 (average n=4)	See CA, Section 8, Point 8.1.2
Desorption rate coefficient (d^{-1})	0	0	FOCUS recommendation
Factor relating CofFreNeq and CofFreEql (-)	0	0	FOCUS recommendation
Transformation parameters			
DT_{50} in soil (days)	2 (worst-case)[1]	2 (worst-case) [1]	See Doc CA, Section 8, Point 8.1.2
Temperature correction function: - reference temperature (°C) - optimum moisture conditions (pF 2 or wetter) - Liquid content in incubation experiment (kg/kg) - exponent for the effect of liquid (-) - molar activation energy (kJ/mol)	 20 selected 1 0.7 65.4	 20 selected 1 0.7 65.4	FOCUS recommendations
Diffusion parameters			
Reference temperature for diffusion (C)	20	20	FOCUS recommendation
Diffusion coefficient in water (m^2/d)	4.3×10^{-5}	4.3×10^{-5}	FOCUS recommendation
Diffusion coefficient in air (m^2/d)	0.43 (20°C)	0.43 (20°C)	FOCUS recommendation
Crop parameters			
Wash off factor (m^{-1})	0.0001	0.0001	FOCUS recommendation
Canopy process option	Lumped	Lumped	FOCUS recommendation
Half life at crop surface (d)	1000000	1000000	FOCUS recommendation
Plant uptake factor	0	0	Worst-case
Transformation scheme			
Transformation pathway	Parent > sink	Parent > sink	PEARL option
Application data			
Kind of Application	To soil surface	To soil surface	PEARL option
Mode of application	Every year	Every year	FOCUS recommendation
Application rate (kg/ha)	see Table in CP		-
Application depth (cm)	0	0	FOCUS recommendation

(1) The DT_{50} values reported in Document M-CA, Section 8, are based on FOCUS procedures for the determination of persistence endpoints i.e. best fit DT_{50} values. For modelling parameters DT_{50} values based on FOCUS procedures for the determination of modelling endpoints are required. In the absence of properly determined FOCUS modelling DT_{50} values, a protective worst-case value of 2 days was selected.

The parameters specified in Table 2.8.6-5 were used in conjunction with the application dates and agronomic parameters specified in Table 2.8.6-4. The resulting predicted 80th percentile annual average concentrations of each component of the active substance in groundwater are summarised in Table 2.8.6-6.

Table 2.8.6-6: Worst-case PECgw for components gibberellins GA4 and gibberellins GA7 following treatment with 'Novagib' using PEARL 4.4.4

Scenario	80th percentile annual average concentration (µg/L)			
	gibberellins GA4		gibberellins GA7	
	Main appln	Earliest appln	Main appln	Earliest appln
Apple 4 x 5 g a.s./ha (7 day minimum interval)				
Châteaudun (C)	<0.001	<0.001	<0.001	<0.001
Hamburg (H)	<0.001	<0.001	<0.001	<0.001
Jokioinen (J)	<0.001	<0.001	<0.001	<0.001
Kremsmünster (K)	<0.001	<0.001	<0.001	<0.001
Okehampton (N)	<0.001	<0.001	<0.001	<0.001
Piacenza (P)	<0.001	<0.001	<0.001	<0.001
Porto (O)	<0.001	<0.001	<0.001	<0.001
Sevilla (S)	<0.001	<0.001	<0.001	<0.001
Thiva (T)	<0.001	<0.001	<0.001	<0.001
Pear 1 x 12 g a.s./ha				
Châteaudun (C)	<0.001	<0.001	<0.001	<0.001
Hamburg (H)	<0.001	<0.001	<0.001	<0.001
Jokioinen (J)	<0.001	<0.001	<0.001	<0.001
Kremsmünster (K)	<0.001	<0.001	<0.001	<0.001
Okehampton (N)	<0.001	<0.001	<0.001	<0.001
Piacenza (P)	<0.001	<0.001	<0.001	<0.001
Porto (O)	<0.001	<0.001	<0.001	<0.001
Sevilla (S)	<0.001	<0.001	<0.001	<0.001
Thiva (T)	<0.001	<0.001	<0.001	<0.001
Pear 2 x 6 g a.s./ha (3 day minimum interval)				
Châteaudun (C)	<0.001	<0.001	<0.001	<0.001
Hamburg (H)	<0.001	<0.001	<0.001	<0.001
Jokioinen (J)	<0.001	<0.001	<0.001	<0.001
Kremsmünster (K)	<0.001	<0.001	<0.001	<0.001
Okehampton (N)	<0.001	<0.001	<0.001	<0.001
Piacenza (P)	<0.001	<0.001	<0.001	<0.001
Porto (O)	<0.001	<0.001	<0.001	<0.001
Sevilla (S)	<0.001	<0.001	<0.001	<0.001
Thiva (T)	<0.001	<0.001	<0.001	<0.001

Using the FOCUS methodology, the 80th percentile PECgw values for the two components gibberellins GA4 and gibberellins GA7 in the active substance gibberellins GA4/7 in groundwater were generated assuming repeated annual applications at the maximum seasonal treatment rate for the crops supported in the GAP. Annual average concentrations were calculated as the cumulative annual chemical flux divided by the cumulative annual water recharge volume at 1 m depth. The predicted concentration is a conservative estimate of what may actually be expected in groundwater used for drinking water, as soil pore water at one-meter depth is not a likely source of drinking water.

In reasonable worst-case scenarios using the FOCUS PEARL model, the annual average concentrations of the two components gibberellins GA4 and gibberellins GA7 in the active substance gibberellins GA4/7 in soil pore water at one-meter depth following use of 'Novagib' in pome fruit were all significantly less than 0.1 µg/L.

FOCUS PELMO (ver 5.5.3)

Simulations were also conducted using the FOCUS PELMO model as per current requirements. The modelling parameters used for the simulations conducted using the FOCUS PELMO model are presented in Table 2.8.6-7.

Table 2.8.6-7: **Summary of input parameters for determination of worst-case PECgw for components gibberellins GA4 and gibberellins GA7 following treatment with 'Novagib' using PELMO 5.5.3**

Parameter	Input parameters		Remarks
	gibberellins GA4	**gibberellins GA7**	
General parameters			
Chemical name	(3*S*,3a*R*,4*S*,4a*R*,7*R*,9a*R*,9b*R*,12*S*)-12-hydroxy-3-methyl-6-methylene-2-oxoperhydro-4a,7-methano-3,9b-propanoazuleno[1,2-*b*]furan-4-carboxylic acid (IUPAC)	(3*S*,3a*R*,4*S*,4a*R*,7*R*,9a*R*,9b*R*,12*S*)-12-hydroxy-3-methyl-6-methylene-2-oxoperhydro-4a,7-methano-9b,3-propenoazuleno[1,2-*b*]furan-4-carboxylic acid (IUPAC)	For structure see Appendix 1
Molecular weight (g/mol)	332.40	330.40	See appendix 1
Application data			
Kind of Application	Soil Application	Soil Application	FOCUS option
Mode of application	Every year	Every year	FOCUS recommendation
Application rate (kg/ha)	see Table CP 9.2.4.1-1		-
Application depth (cm)	0	0	FOCUS recommendation
Plant uptake factor	0	0	Worst-case
Volatilisation and Soil Photolysis Data			
Henry's Law Constant	Calculated option	Calculated option	FOCUS recommendation
Vapour Pressure (Pa)	0 (20°C) 0 (30°C)	0 (20°C) 0 (30°C)	Worst-case
Aqueous Solubility (mg/L)	340 (20°C) (680, 30°C)	340 (20°C)	See Doc CA, Section 8, Point 8.1.2. (Note a value 340 mg/L was used to be consistent with the agreed parameter specified in the existing EFSA LoEP.
Soil Photolysis Rate (1/d)	0 (worst-case)	0 (worst-case)	FOCUS recommendation
Reference Radiation (W/m^2)	500	500	FOCUS recommendation
Sorption Data			
Soil adsorption coefficient, Kfoc (ml/g), 20°C	4 (worst-case, pH dependant, n=4)	4 (worst-case, pH dependant, n=4)	See Doc M-CA, Section 8, Point 8.1.2
Freundlich exponent 1/n (-)	0.97 (average n=4)	1.01 (average n=4)	See Doc M-CA, Section 8, Point 8.1.2
Limit for Freundlich (µg/L)	1×10^{-20}	1×10^{-20}	FOCUS recommendation
Annual increase (%)	0	0	FOCUS recommendation
Equilibrium constant for DOC (L/kg)	0	0	FOCUS recommendation
Increase of sorption when soil is air dried (-)	1	1	FOCUS recommendation

Parameter	Input parameters		Remarks
	gibberellins GA4	**gibberellins GA7**	
pH-dependent sorption option	Not selected	Not selected	PELMO option
Kinetic sorption option	Not selected	Not selected	PELMO option
Depth Dependent Sorption and Transformation Data (Focus Tier 2)	Standard values (Tier 1) selected	Standard values (Tier 1) selected	PELMO option
Degradation in the liquid phase only	Not selected	Not selected	PELMO option
Transformation Scheme			
DT_{50} in soil (days)	2 (worst-case)[2]	2 (worst-case)[2]	See Doc CA, Section 8,
Rate correction in soil	Individual, correction with Q_{10} = 2.58	Individual, correction with Q_{10} = 2.58	FOCUS recommendation
Transformation pathway	Parent > sink (ff=1)	Parent > sink (ff=1)	PELMO option

(1) The vapour pressure value for 30°C was determined using the value at 20°C and the PELMO default of x2.
(2) The DT_{50} values reported in Document M-CA, Section 8 are based on FOCUS procedures for the determination of persistence endpoints i.e. best fit DT_{50} values. For modelling parameters DT_{50} values based on FOCUS procedures for the determination of modelling endpoints are required. In the absence of properly determined FOCUS modelling DT_{50} values, a protective worst-case value of 2 days was selected.

The parameters specified in Table 2.8.6-7 were used in conjunction with the application dates and agronomic parameters specified. The resulting predicted 80th percentile annual average concentrations of each component of the active substance in groundwater are summarised in Table 2.8.6-8.

Table 2.8.6-8: Worst-case PECgw for components gibberellins GA4 and gibberellins GA7 following treatment with 'Novagib' using PELMO 5.5.3

Scenario	80th percentile annual average concentration (µg/L)			
	gibberellins GA4		**gibberellins GA7**	
	Main appln	**Earliest appln**	**Main appln**	**Earliest appln**
Apple 4 x 5 g a.s./ha (7 day minimum interval)				
Châteaudun (C)	<0.001	<0.001	<0.001	<0.001
Hamburg (H)	<0.001	<0.001	<0.001	<0.001
Jokioinen (J)	<0.001	<0.001	<0.001	<0.001
Kremsmünster (K)	<0.001	<0.001	<0.001	<0.001
Okehampton (N)	<0.001	<0.001	<0.001	<0.001
Piacenza (P)	<0.001	<0.001	<0.001	<0.001
Porto (O)	<0.001	<0.001	<0.001	<0.001
Sevilla (S)	<0.001	<0.001	<0.001	<0.001
Thiva (T)	<0.001	<0.001	<0.001	<0.001
Pear 1 x 12 g a.s./ha				
Châteaudun (C)	<0.001	<0.001	<0.001	<0.001
Hamburg (H)	<0.001	<0.001	<0.001	<0.001
Jokioinen (J)	<0.001	<0.001	<0.001	<0.001
Kremsmünster (K)	<0.001	<0.001	<0.001	<0.001
Okehampton (N)	<0.001	<0.001	<0.001	<0.001
Piacenza (P)	<0.001	<0.001	<0.001	<0.001
Porto (O)	<0.001	<0.001	<0.001	<0.001
Sevilla (S)	<0.001	<0.001	<0.001	<0.001
Thiva (T)	<0.001	<0.001	<0.001	<0.001

Scenario	80th percentile annual average concentration (µg/L)			
	gibberellins GA4		gibberellins GA7	
	Main appln	Earliest appln	Main appln	Earliest appln
Pear 2 x 6 g a.s./ha (3 day minimum interval)				
Châteaudun (C)	<0.001	<0.001	<0.001	<0.001
Hamburg (H)	<0.001	<0.001	<0.001	<0.001
Jokioinen (J)	<0.001	<0.001	<0.001	<0.001
Kremsmünster (K)	<0.001	<0.001	<0.001	<0.001
Okehampton (N)	<0.001	<0.001	<0.001	<0.001
Piacenza (P)	<0.001	<0.001	<0.001	<0.001
Porto (O)	<0.001	<0.001	<0.001	<0.001
Sevilla (S)	<0.001	<0.001	<0.001	<0.001
Thiva (T)	<0.001	<0.001	<0.001	<0.001

In reasonable worst-case scenarios using the PELMO model, the annual average concentrations of the two components gibberellins GA4 and gibberellins GA7 in the active substance gibberellins GA4/7 in soil pore water at one-meter depth following use of 'Novagib' in pome fruit were all significantly less than 0.1 µg/L.

FOCUS MACRO (ver 5.5.4)

Simulations were also conducted using the FOCUS MACRO model as per current requirements. The modelling parameters used for the simulations conducted using the FOCUS MACRO model are presented in Table 2.8.6-9.

Table 2.8.6-9: Summary of input parameters for determination of worst-case PECgw for components gibberellins GA4 and gibberellins GA7 following treatment with 'Novagib' using MACRO 5.5.4

Parameter	Input parameters		Remarks
	gibberellins GA4	gibberellins GA7	
General parameters			
Molecular weight (g/mol)	332.40	330.40	See appendix 1
Vapour Pressure (Pa)	0	0	Worst-case
Sorption parameters			
Soil adsorption coefficient, Kfoc (ml/g), 20°C	4 (worst-case, pH dependant, n=4)	4 (worst-case, pH dependant, n=4)	See Doc CA, Section 8, Point 8.1.2
Kfom (ml/g) at 20°C	2.3	2.3	Determined from Kfoc divided by 1.724
Freundlich exponent 1/n (-)	0.97 (average n=4)	1.01 (average n=4)	See Doc CA, Section 8, Point CA 8.1.2
Transformation parameters			
DT_{50} in soil (days)	2 (worst-case)[1]	2 (worst-case)[1]	See Doc CA, Section 8
Exponent for temperature response	0.0948		FOCUS recommendations
Exponent for moisture response	0.49		
Crop parameters			
Plant uptake factor	0		Worst-case

Parameter	Input parameters		Remarks
	gibberellins GA4	gibberellins GA7	
Transformation scheme			
Transformation pathway	Parent > sink (ff=1)	Parent > sink (ff=1)	Model option
Application data			
Kind of Application	To soil surface		Model option
Mode of application	Every year		Model option
Application rate (kg/ha)	see Table in CP		-
Application depth (cm)	0		FOCUS recommendation

(1) The DT_{50} values reported in Document M-CA, Section 8, are based on FOCUS procedures for the determination of persistence endpoints i.e. best fit DT_{50} values. For modelling parameters DT_{50} values based on FOCUS procedures for the determination of modelling endpoints are required. In the absence of properly determined FOCUS modelling DT_{50} values, a protective worst-case value of 2 days was selected.

The parameters specified in Table 2.8.6-9 were used in conjunction with the application dates and agronomic parameters specified. The resulting predicted 80th percentile annual average concentrations of each component of the active substance in groundwater are summarised in Table 2.8.6-10.

Table 2.8.6-10: Worst-case PECgw for components gibberellins GA4 and gibberellins GA7 following treatment with 'Novagib' using MACRO 5.5.4

Scenario	80th percentile annual average concentration (µg/L)			
	gibberellins GA4		gibberellins GA7	
	Main appln	Earliest appln	Main appln	Earliest appln
4 x 5 g a.s./ha (7 day minimum interval)				
Châteaudun (C)	<0.001	<0.001	<0.001	<0.001
1 x 12 g a.s./ha				
Châteaudun (C)	<0.001	<0.001	<0.001	<0.001
2 x 6 g a.s./ha (3 day minimum interval)				
Châteaudun (C)	<0.001	<0.001	<0.001	<0.001

In reasonable worst-case scenarios using the MACRO model, the annual average concentrations of the two components gibberellins GA4 and gibberellins GA7 in the active substance gibberellins GA4/7 in soil pore water at one-meter depth following use of 'Novagib' in pome fruit were all significantly less than 0.1 µg/L.
In all cases, the predicted concentrations of gibberellins GA4 and gibberellins GA7 in groundwater are <0.1 µg/L.
In accordance with Regulation (EC) No. 1272/2008, the active substance gibberellins GA4/7 therefore fulfils the criteria for consideration as a low-risk active substance in this regard.

PREDICTED CONCENTRATIONS IN SURFACE WATER (PECsw) AND SEDIMENT (PECsed)

The predicted environmental concentration of the formulated product 'Novagib' and the two components gibberellins GA4 and gibberellins GA7 in the active substance gibberellins GA4/7 and any significant components in surface water (PECsw) is determined using the standardised recommendations of the FOCUS working group on surface water scenarios (FOCUS 2001[5] and 2015[6]). The FOCUS Surface Water Modelling Working Group described a step by step modelling procedure for the calculation of PECsw in which the estimation of pesticide surface water and sediment concentrations is conducted using a tiered approach that introduces increasing levels of realism into the modelling assessment.
The initial predicted environmental concentration in surface water of the formulated product 'Novagib' is presented in Table 2.8.6-11. Since the formulation components other than the active substance are assumed to

[5] FOCUS (2001): "FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC". Report of the FOCUS Working Group on Surface Water Scenarios, EC Document Reference SANCO/4802/2001-rev.2. 245 pp.
[6] FOCUS (2015). Generic guidance for FOCUS surface water scenarios, ver 1.4, May 2015.

dissipate rapidly in the environment, it is only necessary to consider the initial concentration for the formulated product.

The FOCUS spray drift calculator (model v.1 12-Apr-2001) was used to determine the maximum potential concentration of the intact formulation in surface water via spray drift. As a worst-case situation for the intact formulation, it is assumed that the total annual application rate is applied on a single occasion i.e. number of applications = 1.

Table 2.8.6-11: Worst-case initial PECsw for intact formulation 'Novagib' needed for risk assessment

Crop	Formulation application rate	Application timing	PECsw (µg 'Novagib' /L)[1] at default distance		
			Water body type Ditch	Water body type Pond	Water body type Stream
Apple	4 x 0.5 L/ ha 'Novagib' (equivalent to 4 x 520 g 'Novagib'/ha[1])	GS 69-74	163.6	9.838	149.6
Pear	1 x 1.2 L/ ha 'Novagib' (equivalent to 1 x 1248 g 'Novagib'/ha[1])	GS 62-69	98.17	5.903	89.78
Pear	2 x 0.6 L/ ha 'Novagib' (equivalent to 2 x 624 g 'Novagib'/ha[1])	GS 62-69	98.17	5.903	89.78

(1) Using FOCUS drift calculator (v.1) and the crop scenario pome/stone fruit early applications (as a worst-case).
(2) Based on a formulation relative density of 1.04 g/ml.

The maximum initial concentration of the formulated product 'Novagib' in surface water following application is 163.6 µg 'Novagib'/L (worst-case assumptions, no mitigation).

Exposure of surface water can occur directly *via* spray drift or *via* soil drainage and run-off, therefore the fate and behaviour of the active substance in soil and aquatic systems is considered.

The fate and behaviour of the active substance and any associated metabolites in soil is investigated in Document CA, Section 8. The definition of the residue for risk assessment (soil) is defined too. The active substance gibberellins GA4/7 contains two components (gibberellins GA4 and gibberellins GA7). Degradation of gibberellins GA4 and gibberellins GA7 in soil leads to the formation of numerous degradation products. However, due to the natural occurrence of the active substance these metabolites are not considered to be of environmental concern and have not been considered further.

The fate and behaviour of the active substance and associated metabolites in aquatic systems is investigated in Document CA, Section 8 too. The degradation of gibberellins GA4 and gibberellins GA7 in aquatic systems is expected to be rapid and complete with the formation of numerous degradation products. However, due to the natural occurrence of the active substance these metabolites are not considered to be of environmental concern and are not considered further.

As the ratio of gibberellins GA4 and gibberellins GA7 in the active substance can vary between sources, for the determination of PECs of the active substance the approach adopted as a precautionary worst-case has been to consider alternate situations where the active substance is 100% gibberellins GA4 and separately 100% gibberellins GA7.

The supported GAP is presented in Document D1, with relevant agronomic parameters being summarised in Table 2.8.6-11.

FOCUS Steps 1 and 2

Worst-case precautionary predicted environmental concentrations in surface water of the two components (gibberellins GA4 and gibberellins GA7) in the active substance following treatment with 'Novagib' have been calculated using the procedures recommended by the FOCUS Working group on surface water scenarios according to Step 1 and Step 2, using the FOCUS Steps 1 & 2 calculator (ver 3.2).

Table 2.8.6-12: Summary of key agronomic input parameters used for FOCUS Step 1 and 2 calculations

Run no.	FOCUS Step	Location[2]	Application details			Crop inter-ception[1]	Crop type
			Timing[2,3]	No. of applns (interval)	Appln rate (g a.s./ha)		
38c1t1	1-2	S EU	Mar-May	4 x (7 d)	5	average (i.e. 40%)	Pome fruit, early
38c1t2	1-2	S EU	Mar-May	1 x (n.a.)	12	average (i.e. 40%)	Pome fruit, early
38c1t3	1-2	S EU	Mar-May	2 x (3 d)	6	average (i.e. 40%)	Pome fruit, early

(1) The crop interception values chosen within the constraints of the FOCUS drift calculator were selected to be as consistent as possible (without being preferential) with the worst-case application timings specified in Table 8.5-1.
(2) Only the worst-case location/application timing combination was considered.
(3) The worst-case timing range takes into account all the application timings specified in Document D1 and Table 8.5-1.

Chemical parameters used for the two components (gibberellins GA4 and gibberellins GA7) of the active substance are presented in Table 2.8.6-13.

Table 2.8.6-13: Summary of key chemical input parameters used for FOCUS Step 1 and 2 calculations

Endpoint	Parameter value used		Comments
	gibberellins GA4 (component code[1] 38c1)	**gibberellins GA7 (component code[1] 38c2)**	
Physico-chemical parameters			
Water solubility (mg/L)	340	340	See Doc CA, Section 3, Point CA 2.5. (Note a value of 340 mg/L was used to be consistent with the agreed parameter specified in the existing EFSA LoEP (p35/50).
Environmental behaviour			
DT_{50} in soil (days)	2 (worst-case)	2 (worst-case)	See Doc CA, Section 8, (Note based on the persistence DT_{50} values, a worst-case modelling DT_{50} of 2 days was assumed)
Soil adsorption coefficient, Kfoc (ml/g)	4 (worst-case, pH dependant, n=4)	4 (worst-case, pH dependant, n=4)	See Doc CA, Section 8,
Half-life water (days, 20ºC)	1000	1000	worst-case default (precautionary)
Half-life sediment (days, 20ºC)	1000	1000	worst-case default (precautionary)
Half-life sediment/water system (days, 20ºC)	1000	1000	worst-case default (precautionary)

(1) Used in modelling files

Using the agronomic information supplied in Table 2.8.6-12 and the endpoints and chemical parameters specified in Table 2.8.6-13, the maximum predicted environmental concentrations of the two components in the active substance (gibberellins GA4 and gibberellins GA7) according to FOCUS Steps 1-2 calculations are presented in Table 2.8.6-14. Short and long term actual and time weighted average PEC values are not required for the risk assessment (see Ecotox part) and have therefore not been calculated.

Table 2.8.6-14: FOCUS Step 1 and Step 2 PECsw (µg/L) and PECsed (µg/kg) of components gibberellins GA4 and gibberellins GA7 following treatment with 'Novagib'

Step	Crop	Application details (g a.s./ha)	EU Region and season of application	Predicted environmental concentration	
				Initial PECsw (µg/L)	Max. PECsed (µg/kg dw)
gibberellins GA4 and gibberellins GA7					
1	Pome fruit	4 x 5	n.a.	8.58	0.343
2			S EU Mar-May	1.66 (0.583)[1]	0.066 (0.023)[1]
1	Pome fruit	1 x 12	n.a.	5.15	0.206
2			S EU Mar-May	1.40 (-)	0.056 (-)
1	Pome fruit	2 x 6	n.a.	5.15	0.206
2			S EU Mar-May	1.18 (0.700)[1]	0.047 (0.028)[1]

(1) Values in brackets are the corresponding PEC resulting from a single application.
Following use of 'Novagib' according to the representative GAP, the maximum potential concentrations in surface water and sediment of the two components gibberellins GA4 and gibberellins GA7 according to FOCUS Step 2 calculations are 1.66 µg/L and 0.066 dw µg/kg.

On the basis of the aquatic risk assessment, no further refinements are necessary.

2.9 EFFECTS ON NON-TARGET SPECIES

The representative formulations for the previous inclusion of gibberellins (GA4/GA7) in Annex I were Regulex 10 SG, a soluble granule formulation containing 10% w/w gibberellins GA4/GA7, Novagib and GibbPlus, both soluble concentrate formulation containing 10 g/L GA4/GA7. Current representative formulation is Novagib, a soluble concentrate formulation containing 10 g/L GA4/GA7. New studies have been conducted with Novagib and new endpoints are available for formulation toxicity. New study is available for active substance toxicity to address data gap for chronic risk to aquatic invertebrates identified in previous peer review (EFSA Journal 2012; 10(1):2502). Read across principle is used in chronic risk assessment for fish. It is based on gibberellic acid GA3 chronic toxicity data, which was submitted to address a data gap identified in previous peer review (EFSA Journal 2012; 10(1):2502). Formulation toxicity data is available to address the data gap regarding the risk of active substance to aquatic plants.

2.9.1 Summary of effects on birds and other terrestrial vertebrates

No data are available assessing the toxicity of gibberellins GA4/GA7 to birds. However, on the basis of the similarities between gibberellic acid (GA3) and GA4/GA7, and the high margin of safety obtained with the risk assessment for GA3, the toxicity data for GA3 is considered acceptable to address the risk to GA4/GA7. A low acute toxicity (LD_{50} >2000 mg/kg bw) to birds is concluded based on an acute oral toxicity test with GA3 in the bobwhite quail (*Colinus virginianus*). No studies on the reproductive toxicity of GA3 to birds are available, but short-term dietary toxicity studies to birds showed low toxicity (NOEL = 1376 mg/kg bw/d). As a protective worst-case, the long-term NOEL for GA4/GA7 for birds has been assumed to be 100-fold lower than the NOEL for short-term toxicity in GA3 in order to assess the long-term risk. Given that the NOEL for short-term toxicity was found to equate to the highest dose rate tested in each study, this is considered to be an acceptable approach.

Table 2.9.1-1: Endpoints and effect values relevant for the risk assessment for birds

Species	Substance	Exposure system	Results	Reference
Colinus virginianus Bobwhite quail	GA3	Oral Acute	**LD_{50} > 2000 mg/kg bw**	CA 8.1.1.1/03
Colinus virginianus Bobwhite quail	GA3	Dietary Short-term	LDD_{50} > 1376 mg/kg bw/d **NOEL = 1376 mg/kg bw/d**	CA 8.1.1.2/01

Endpoints in bold are used in the risk assessment

A low acute oral toxicity (LD_{50} >5000 mg/kg bw) to mammals is concluded based on rat studies with GA4/GA7 and the formulation GA4/GA7 10 g/L (identical to the representative formulation, Novagib). A two-generation dietary reproductive toxicity study with GA4/GA7 also demonstrated a low reproductive toxicity (NOAEL = 300 mg/kg bw/d).

Table 2.9.1-2: Endpoints and effect values relevant for the risk assessment for mammals

Species	Substance	Exposure System	Results	Reference
Rat	GA4/GA7	Oral Acute	**LD_{50} >5000 mg/kg bw**	CA 5.2.1/02
Rat	GA4/GA7	Dietary Two-generation reproductive	**NOAEL = 300 mg/kg bw/d**	CA 5.6.1/01
Rat	GA4/GA7 10 g/L formulation (identical to Novagib)	Oral Acute	LD_{50} >5000 mg/kg bw	CP 7.1.1/01

Endpoints in bold are used in the risk assessment

2.9.2 Summary of effects on aquatic organisms [section 11.5 of the CLH report]

Based on standard toxicity studies, the acute toxicity (LC_{50}) to fish of gibberellins GA4/GA7 and Novagib is >100 mg a.s./L and >9700 mg product/L, respectively. A new fish early life stage (ELS) toxicity test with gibberellic acid GA3 is available with fathead minnow, *Pimephales promelas* (NOEC = 11 mg a.s./L), which is considered appropriate for the risk assessment of GA4/GA7 based on the similarities between GA3 and GA4/GA7, as well as the high margin of safety obtained in the risk assessment. The acute toxicity (EC_{50}) to *Daphnia magna* of GA4/GA7 and Novagib is >100 mg a.s./L and >9700 mg product/L, respectively, whilst the reproductive toxicity of GA4/GA7 is concluded with a NOEC of 3.00 mg a.s./L. E_rC_{50} values were determined in algal studies with GA4/GA7 (*Pseudokirchneriella* >100 mg a.s./L; *Navicula* >91.35 mg a.s./L) and Novagib (*Desmodesmus* 6080 mg product/L, equivalent to 60 mg a.s./L), as well as aquatic macrophyte studies with Novagib (*Lemna* >100 mg product/L, equivalent to >0.96 mg a.s./L). A study with Novagib was also conducted with *Myriophyllum* and gave an endpoint <100 mg product/L, equivalent to <0.95 mg a.s./L. The studies on aquatic macrophytes are not sufficient to address the risk to aquatic macrophytes and a data gap has been concluded.

Table 2.9.2- 1 : Endpoints and effect values relevant for the acute risk assessment for aquatic organisms

Species	Substance	Exposure System	Results	Reference
Oncorhynchus mykiss	GA4/GA7	96 h, ss	**LC_{50} >100 mg a.s./L $_{nom}$**	CA 8.2.1/01
Oncorhynchus mykiss	Novagib	96 h, s	**96 h LC_{50} >9700 mg product/L, equivalent to > 100 mg a.s./L $_{nom}$**	CP 10.2.1/01
Pimephales promelas	GA3	33 d, f, (ELS)	**NOEC = 11 mg a.s./L $_{mm}$**	CA 8.2.2.1/01
Daphnia magna	GA4/GA7	48 h, s	**EC_{50} >100 mg a.s./L $_{nom}$**	CA 8.2.4.1/01
Daphnia magna	Novagib	48 h, s	**48 h EC_{50} >9700 mg product/L,** equivalent to > 100 mg a.s./L $_{nom}$	CP 10.2.1/02
Daphnia magna	GA4/GA7	21 d, ss	**NOEC = 3.00 mg a.s./L $_{nom}$**	CA 8.2.5.1/01
Pseudokirchneriella subcapitata	GA4/GA7	72 h, s	E_rC_{50} >100 mg a.s./L $_{nom}$ E_bC_{50} >100 mg a.s./L $_{nom}$	CA 8.2.6.1/01
Navicula pelliculosa	GA4/GA7	72 h, s	E_rC_{50} >91.35 mg a.s./L $_{nom}$	CA 8.2.6.2/01
Desmodesmus subspicatus	Novagib	72 h, s	**E_rC_{50} = 6080 mg product/L, equivalent to 60 mg a.s./L $_{nom}$** E_yC_{50} = 6384 mg product/L, equivalent to 63 mg a.s./L $_{nom}$	CP 10.2.1/03
Lemna minor	Novagib	7 d, ss	**E_rC_{50} > 100 mg product/L, equivalent to > 0.96 mg a.s./L $_{nom}$** E_yC_{50} > 100 mg product/L, equivalent to > 0.96 mg a.s./L $_{nom}$	CP 10.2.1/04
Myriophyllum spicatum	Novagib	14 d, ss	**E_rC_{50} < 100 mg product/L, equivalent to < 0.95 mg a.s./L $_{nom}$** E_yC_{50} < 100 mg product/L, equivalent to < 0.95 mg a.s./L $_{nom}$	CP 10.2.1/05
Higher-tier studies (micro- or mesocosm studies)				
Not required				

s: static; ss: semi-static; f: flow-through; nom: based on nominal concentrations; mm: based on mean measured concentrations; im: based on initial measured concentrations
Endpoints in bold are used in the risk assessment

2.9.2.1 Bioaccumulation [equivalent to section 11.4 of the CLH report template]

Table 70: Summary of relevant information on bioaccumulation

Method	Species	Results	Key or Supportive study	Remarks	Reference
Partition coefficient n-octanol/water (log K_{ow}) (OECD 107)	The measured log K_{ow} of GA4 is 2.34 and of GA7 is 2.25 at 20 °C, without pH control.	Purghart (2000b)	Partition coefficient n-octanol/water (log K_{ow}) (OECD 107)	The measured log K_{ow} of GA4 is 2.34 and of GA7 is 2.25 at 20 °C, without pH control.	Purghart (2000b)
Calculation	The estimated	Ville (2005)	Calculation	The estimated	Ville (2005)

(EPIWIN)	log K_{ow} of GA4 is 1.76 and of GA7 is 1.55.		(EPIWIN)	log K_{ow} of GA4 is 1.76 and of GA7 is 1.55.	

2.9.2.1.1 Estimated bioaccumulation

The estimated log K_{ow} values, calculated using EPIWIN, are as follows: GA4 log K_{ow} = 1.76; GA7 log K_{ow} = 1.55 (Ville, 2005).

2.9.2.1.2 Measured partition coefficient and bioaccumulation test data

Following OECD 107 guidelines in accordance with GLP, the octanol-water partition coefficients of GA4 and GA7 were determined in a study carried out at 22 °C without pH control. Log K_{ow} of GA4 was 2.34 and log K_{ow} of GA7 was 2.25 (Purghart, 2000b). The measured log K_{ow} values are below the cut-off value of log K_{ow} ≥4 for classification as bioaccumulative. The bioconcentration potential of GA4/7 may therefore be considered to be negligible and GA4/7 is unlikely to bioaccumulate in aquatic or terrestrial food chains.
The data are relevant and adequate for classification purposes. **Data used for classification: GA4 log K_{ow} = 2.34. GA7 log K_{ow} = 2.25.**

2.9.2.2 Acute aquatic hazard [equivalent to section 11.5 of the CLH report template]

Table 71: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results[1]	Key or Supportive study	Remarks	Reference
Semi-static acute toxicity, freshwater OECD 203 (1992), US EPA OPPTS draft 850.1075	*Oncorhynchus mykiss*	GA4/7	96 h (semi-static) LC_{50} >100 mg a.s./L (nominal)	Reliable. Key study (critical endpoint)	[redacted] (2004a)	Semi-static acute toxicity, freshwater OECD 203 (1992), US EPA OPPTS draft 850.1075
Static acute toxicity, freshwater OECD 202 (1984)	*Daphnia magna*	GA4/7	48 h (static) EC_{50} > 100 mg a.s./L (nominal)	Reliable. Key study (critical endpoint)	Sayers, L.E. (2004b)	Static acute toxicity, freshwater OECD 202 (1984)
Static algal inhibition test, freshwater OECD 201 (1984)	*Pseudokirchneriella subcapitata*	GA4/7	96 h (static) E_rC_{50} >100 mg a.s./L (nominal) NOEC = 100 mg a.s./L	Reliable. Supporting study.	Gries, T. (2000). Reassessment of validity by Collison, E. (2017)	Static algal inhibition test, freshwater OECD 201 (1984)
Static algal inhibition test, freshwater OECD 201 (2011)	*Navicula pelliculosa*	GA4/7	72 h (static) E_rC_{50} >91.35 mg a.s./L (nominal) NOEC = 91.35 mg	Reliable. Supporting study.	Mantilacci, S. (2017)	Static algal inhibition test, freshwater OECD 201 (2011)

			a.s./L			
Static algal inhibition test, freshwater OECD 201 (2006)	*Desmodesmus subspicatus*	Novagib (10 g GA4/7/L)	72 h (static) E_rC_{50} = 60 mg a.s./L (nominal) NOEC = 32 mg a.s./L	Reliable. Supporting study.	Vryenhoef, H. and Mullee, D. M. (2010)	Static algal inhibition test, freshwater OECD 201 (2006)
Semi-static aquatic plant inhibition test, freshwater OECD 221 (2006)	*Lemna minor*	Novagib (10 g GA4/7/L)	7 d (semi-static) E_rC_{50} > 0.96 mg a.s./L (nominal) NOEC = 0.96 mg a.s./L	Reliable. Supporting study.	Scheerbaum, D. (2012)	Semi-static aquatic plant inhibition test, freshwater OECD 221 (2006)
Static aquatic plant inhibition test, freshwater Draft OECD guideline 2 December 2013	*Myriophyllum spicatum*	Novagib (10 g GA4/7/L)	14 d (static) E_rC_{50} <0.95 mg a.s./L (nominal) NOEC<0.95 mg a.s./L	Not sufficient. Key study (critical endpoint) DATA GAP	Hermes, H. & Wydra, V. (2014)	Static aquatic plant inhibition test, freshwater Draft OECD guideline 2 December 2013

2.9.2.2.1 Acute (short-term) toxicity to fish

An acute toxicity study with *Oncorhynchus mykiss* has been assessed according to accepted guidelines and to GLP.

Following OECD 203 (1992) and US EPA guidelines, rainbow trout were exposed to GA4/GA7 over a period of 96 hours at the following nominal concentrations under semi-static conditions: 0 (control), 6.3, 13, 25, 50 and 100 mg a.s./L. Dissolution of the test substance without the need for solvents was achieved by stirring, combined with ultrasonification. The mean measured concentrations were 0 (control), 5.7, 12, 25, 47 and 96 mg a.s./L and all measured concentrations in the samples taken ranged from 90 to 100% so results were based on nominal concentrations. Environmental parameters (temperature, pH, total hardness, dissolved oxygen and photoperiod) remained within acceptable limits throughout the test. There were no adverse effects among fish of the control or treated groups throughout the test. The 96 h (semi-static) LC_{50} was >100 mg a.s./L (nominal) ([redacted], 2004a).

The data are relevant and adequate for classification purposes. **Data used for classification: fish 96 h LC_{50} >100 mg a.s./L** (i.e. the lowest LC_{50} value obtained).

2.9.2.2.2 Acute (short-term) toxicity to aquatic invertebrates

An acute toxicity study with *Daphnia magna* has been assessed according to accepted guidelines and to GLP.

Following OECD 202 (1984) guidelines, *Daphnia magna* were exposed to GA4/GA7 over a period of 48 hours at the following nominal concentrations under static conditions: 0 (control), 6.3, 13, 25, 50 and 100 mg a.s./L. Dissolution of the test substance without the need for solvents was achieved by stirring, combined with ultrasonification. The mean measured concentrations were 0, 5.6, 11, 23, 48 and 97 mg a.s./L. Environmental parameters (temperature, pH, total hardness, dissolved oxygen and photoperiod) remained within acceptable limits throughout the test. There were no adverse effects among daphnids of the control or treated groups throughout the test. The 48 h (static) EC_{50} was > 100 mg a.s./L (nominal) (Sayers, 2004b).

The data are relevant and adequate for classification purposes. **Data used for classification: aquatic invertebrates 48 h EC_{50} >100 mg a.s./L** (i.e. the lowest EC_{50} value obtained).

2.9.2.2.3 Acute (short-term) toxicity to algae or aquatic plants

Three algal growth studies with *Pseudokirchneriella subcapitata, Desmodesmus subspicatus* and *Navicula pelliculosa* have been assessed according to accepted guidelines and to GLP. Two studies on aquatic plants have also been assessed.

Following OECD 201 (1984) guidelines, *Pseudokirchneriella subcapitata* cells were exposed to GA4/GA7 over a period of 96 hours in a limit test at 100 mg a.s./L under static conditions. A nutrient medium control and a solvent control containing 100 µL dimethylformamide/L were also tested. The measured GA4 and GA7 concentrations at test initiation ranged from 102.5 to 104.6% of nominals and were reduced to 97.9 and 71.3% of nominals, respectively, after 96 hours. The pH values of the control and solvent control cultures increased from 8.0 and 7.91 at 0 hours to 9.81 and 9.86 at 96 hours, respectively. From 0 to 96 hours there was a decrease in pH from 7.92 to 5.68 in the 100 mg/L test culture. Retrospective calculations of the validity criteria according to the updated (2011) OECD 201 guideline demonstrated that all validity criteria were met (Collison, 2017). There were no observed effects of growth inhibition in any of the control or test cultures. The no observed effect concentration (NOEC) was 100 mg a.s./L (nominal). The 96 h (static) E_rC_{50} was >100 mg a.s./L (nominal) (Gries, 2000).

Following OECD 201 (2011) guidelines, *Navicula pelliculosa* cells were exposed to GA4/GA7 over a period of 72 hours in a limit test at 91.35 mg a.s./L under static conditions. The measured GA4 and GA7 concentrations throughout the study period were within ±20% of nominals and results were therefore based on nominal concentrations. There were no observed effects of growth inhibition in any of the control or test cultures. The 72 h NOEC was 91.35 mg a.s./L (nominal). The 72 h (static) E_rC_{50} was 91.35 mg a.s./L (nominal) (Mantilacci, 2017).

Following OECD 201 (2006) guidelines, *Desmodesmus subspicatus* cells were exposed to the formulation Novagib (10 g GA4/7/L) over a period of 72 hours at the following nominal concentrations under static conditions: 0 (control), 1.0, 3.2, 10, 32 and 100 mg a.s./L. The measured concentrations ranged between 85 and 100% of nominals for all samples at test start and test end and results were therefore based on nominal concentrations. The 72 h NOEC was 32 mg a.s./L. The 72 h (static) E_rC_{50} was 60 mg a.s./L (nominal) (Vryenhoef and Mullee, 2010).

Following OECD 221 (2006) guidelines, *Lemna minor* fronds were exposed to the formulation Novagib (10 g GA4/7/L) over a period of 7 days in a limit test at 100 mg product/L, equivalent to 0.96 mg a.s./L, under semi-static conditions. The measured concentrations in the fresh and old media were 106-109% and 105-113% of nominals, respectively and results were therefore based on nominal concentrations. There were no observed effects of growth inhibition in any of the control or test cultures. The 7 d NOEC was 0.96 mg a.s./L, the highest concentration tested. The 7 d (semi-static) E_rC_{50} was > 0.96 mg a.s./L (nominal), the highest concentration tested (Scheerbaum, 2012).

Following draft OECD guidelines (2013), *Myriophyllum spicatum* shoots were exposed to the formulation Novagib (10 g GA4/7/L) over a period of 14 days in a limit test at 100 mg product/L, equivalent to 0.95 mg a.s./L, under static conditions. The measured concentrations in all samples at test start and test end ranged between 94% to 104% of nominals and results were therefore based on nominal concentrations. The results of this study show that gibberellins GA4/GA7 causes an increase in yield and growth rate based on shoot length. The 14 d (static) E_rC_{50} was therefore determined to be <0.95 mg a.s./L (nominal), the highest concentration tested. The NOEC was <0.95 mg a.s./L, the highest concentration tested (Hermes and Wydra, 2014). The data are not adequate for classification purposes. The study is not sufficient to address the risk of gibberellins GA4/GA7 to aquatic plants. A study with appropriate dose-response design is needed to determine toxicity of GA4/GA7 to aquatic plants. The RMS therefore concludes a data gap for adequate data to address effects of GA4/GA7 on aquatic plants..

2.9.2.2.4 Acute (short-term) toxicity to other aquatic organisms

No other studies are considered relevant for the classification and labelling of GA4/GA7.

2.9.2.3 Long-term aquatic hazard [equivalent to section 11.6 of the CLH report template]

Table 72: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results	Relevant study	Remarks	Reference
Early life-stage toxicity, freshwater, flow-through OECD 210 (2013)	*Pimephales promelas*	GA3	33 d NOEC (flow-through) = 11 mg GA4/7/L (mean measured)	Reliable. Key study (critical endpoint)	[redacted] S.P. (2016)	Early life-stage toxicity, freshwater, flow-through OECD 210 (2013)
Semi-static reproduction test, freshwater, OECD 211 (2012)	*Daphnia magna*	GA4/7	21 d NOEC (semi-static) = 3.00 mg a.s./L (nominal)	Reliable. Key study (critical endpoint)	Juckeland, D. (2014)	Semi-static reproduction test, freshwater, OECD 211 (2012)

2.9.2.3.1 Chronic toxicity to fish

Given the low acute toxicity of GA4/GA7 to fish (*Oncorhynchus mykiss* 96 h LC_{50} >100 mg a.s./L) and the fact that GA4 and GA7 are naturally occurring compounds, low chronic toxicity to fish is expected. No data on the reproductive toxicity of GA4/GA7 to fish are available, but a reproductive toxicity test with gibberellic acid GA3 is considered appropriate to predict the toxicity of GA4/GA7 given the similarities between GA3 and GA4/GA7. Following OECD 210 (2013) guidelines, fathead minnows were exposed to GA3 over a period of 33 days (a 5-day hatching period plus a 28-day post-hatch growth period) at the following nominal concentrations under flow-through conditions: 0 (control), 0.63, 1.3, 2.5, 5.0 and 10 mg a.s./L. A solvent control (0.1 mL/L HPLC-grade dimethylformamide) was also tested. When the measured concentrations of test solution samples collected on Days 0, 7, 14, 21, 28 and 33 of the test were averaged for each treatment group, the mean measured test concentrations were 0.64, 1.3, 2.7, 5.2 and 11 mg a.s./L, which represented 102, 100, 108, 104 and 110% of nominal concentrations, respectively. The results of the study were based on the mean measured concentrations. There were no statistically significant treatment-related effects on hatching success or survival at concentrations ≤11 mg a.s./L. There were no biologically meaningful reductions in total length, wet weight or dry weight at concentrations ≤11 mg GA3/L. The 33 d NOEC (flow-through) was 11 mg GA3/L (mean measured) [redacted], 2016).

The data are relevant and adequate for classification purposes. **Data used for classification: fish 33 d NOEC = 11 mg a.s./L** (based on read-across from GA3).

2.9.2.3.2 Chronic toxicity to aquatic invertebrates

A reproductive toxicity test with *Daphnia magna* has been assessed according to accepted guidelines and to GLP. Following OECD 211 (2013) guidelines, *Daphnia magna* were exposed to GA4/GA7 over a period of 21 days at the following nominal concentrations under semi-static conditions: 0 (control), 0.111, 0.333, 1.00, 3.00 and 9.00 mg a.s./L. The measured test concentrations of GA4/GA7 in the test solutions remained within a range of 87 to 104 % of nominal values in the freshly prepared test solutions at the start of the test and at each renewal and

within a range of 91 to 107 % of nominal in the spent solutions at each renewal and at the end of the test (after 21 days). Therefore, the results for GA4/GA7 are based on the nominal concentrations. A 10% reduction in reproductive output (number of living offspring) relative to the control was observed at the highest concentration tested (9 mg a.s./L), but no significant effects were observed at all other tested concentrations. The 21 d NOEC (semi-static) was 3.00 mg a.s./L (nominal) (Juckeland, 2014).

The data are relevant and adequate for classification purposes. **Data used for classification: aquatic invertebrates 21 d NOEC = 3.00 mg a.s./L.**

2.9.2.3.3 Chronic toxicity to algae or aquatic plants

See section 2.9.2.2.3.

The data are not adequate for classification purposes. A study with appropriate dose-response design is needed to determine toxicity of GA4/GA7 to aquatic plants. The RMS therefore concludes a data gap for adequate data to address effects of GA4/GA7 on aquatic plants.

2.9.2.3.4 Chronic toxicity to other aquatic organisms

No other studies are considered relevant for the classification and labelling of GA4/GA7.

2.9.2.4 Comparison with the CLP criteria

2.9.2.4.1 Acute aquatic hazard

Table 73: Summary of information on acute aquatic toxicity relevant for classification

Method	Species	Test material	Results	Remarks	Reference
Semi-static acute toxicity, freshwater OECD 203 (1992), US EPA OPPTS draft 850.1075	*Oncorhynchus mykiss*	GA4/7	96 h (semi-static) LC_{50} >100 mg a.s./L (nominal)	Reliable. Key study (critical endpoint)	[redacted] (2004a)
Static acute toxicity, freshwater OECD 202 (1984)	*Daphnia magna*	GA4/7	48 h (static) EC_{50} > 100 mg a.s./L (nominal)	Reliable. Key study (critical endpoint)	Sayers, L.E. (2004b)
Static aquatic plant inhibition test, freshwater Draft OECD guideline 2 December 2013	*Myriophyllum spicatum*	Novagib (10 g GA4/7/L)	14 d (static) E_rC_{50} <0.95 mg a.s./L (nominal)	Not sufficient. Key study (critical endpoint) DATA GAP	Hermes, H. & Wydra, V. (2014)

The relevant data for acute aquatic hazard classification purposes under CLP Regulation (EC) 1272/2008 are as follows:

Fish 96 h LC_{50} >100 mg a.s./L (i.e. the lowest LC_{50} value obtained).

Aquatic invertebrates 48 h EC_{50} >100 mg a.s./L (i.e. the lowest EC_{50} value obtained).

Aquatic macrophytes 14 d E_rC_{50} <0.95 mg a.s./L (based on the highest concentration tested in the study).

The M-factor is 1.

According to Table 4.1.0(a) of Annex I of Regulation (EC) 1272/2008, a substance is considered to fall into category Aquatic Acute 1 if any species within the three trophic levels (fish, invertebrates and algae or other aquatic plants) tested in the framework of acute (short-term) toxicity tests shows a $LC_{50}/EC_{50} \leq 1$ mg/L. The E_rC_{50} endpoint for *Myriophyllum spicatum* is <0.95 mg a.s./L. **According to CLP criteria Aquatic Acute 1 classification is proposed for gibberellins GA4/GA7.**

2.9.2.4.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Table 74: Summary of information on long-term aquatic toxicity relevant for classification

Method	Species	Test material	Results[1]	Remarks	Reference
Early life-stage toxicity, freshwater, flow-through OECD 210 (2013)	*Pimephales promelas*	GA3	33 d NOEC (flow-through) = 11 mg GA4/7/L (mean measured)	Reliable. Key study (critical endpoint)	[redacted] (2016)
Semi-static reproduction test, freshwater, OECD 211 (2012)	*Daphnia magna*	GA4/7	21 d NOEC (semi-static) = 3.00 mg a.s./L (nominal)	Reliable. Key study (critical endpoint)	Juckeland, D. (2014)
Static aquatic plant inhibition test, freshwater Draft OECD guideline 2 December 2013	*Myriophyllum spicatum*	Novagib (10 g GA4/7/L)	14 d (static) NOEC<0.95 mg a.s./L	Not sufficient. Key study (critical endpoint) DATA GAP	Hermes, H. & Wydra, V. (2014)

2.9.2.5 Conclusion on classification and labelling for environmental hazards

Bioaccumulation: The measured log K_{ow} values of 2.34 and 2.25 for GA4 and GA7, respectively, are below the cut-off value of log $K_{ow} \geq 4$ for classification as bioaccumulative according to Regulation (EC) 1272/2008.

Degradation: Gibberellins GA4/GA7 cannot be reliably classified as readily biodegradable under the conditions of the Modified Sturm Test and significant hydrolysis or photolysis of gibberellins GA4/GA7 and its individual components gibberellins GA4 and gibberellins GA7 at environmentally relevant temperature and pH is not expected. However, gibberellins GA4/GA7 is demonstrated to be rapidly and extensively degraded in water-sediment systems (through read across to a water-sediment study conducted with the structurally related active substance gibberellic acid GA3), and both gibberellins GA4 and gibberellins GA7 are demonstrated to be rapidly and extensively degraded in soil, with calculated DT_{50} values considerably below 16 days. Based on the weight of evidence, gibberellins GA4/GA7 and its individual components gibberellins GA4 and gibberellins GA7 are therefore rapidly degradable according to CLP criteria.

Chronic toxicity: The relevant data for long-term aquatic hazard classification purposes under CLP Regulation (EC) 1272/2008 are as follows:

Fish 33 d NOEC = 11 mg a.s./L (based on read-across from GA3).

Aquatic invertebrates 21 d NOEC = 3.00 mg a.s./L.

Macrophyte NOEC < 0.95 mg a.s./L (based on the highest concentration tested in the study).

Assessment of M-factor is not relevant.

According to Table 4.1.0(b)(ii) of Annex I of Regulation (EC) 1272/2008, a rapidly degradable substance is considered to fall into category Aquatic Chronic 3 if any species within the three trophic levels (fish, invertebrates and algae or other aquatic plants) tested in the framework of chronic toxicity tests shows a NOEC/EC_x ≤1 mg/L. The NOEC endpoint for *Myriophyllum spicatum* is given as <0.95 mg a.s./L. **According to CLP criteria Aquatic Chronic 3 classification is proposed for gibberellins GA4/GA7.**

2.9.2.6 Conclusion on classification and labelling for environmental hazards

CLASSIFICATION
Acute aquatic hazard classification: Aquatic acute 1, H400
Long-term aquatic hazard classification: Aquatic Chronic 3, H412

LABELLING
H410 – Very toxic to aquatic life with long lasting effects.
WARNING
GHS019
P273, P391, P501

2.9.3 Summary of effects on arthropods

A low acute toxicity to adult honey bees is concluded based on standard acute oral and contact toxicity tests with GA4/GA7 (oral LD_{50} >87 µg a.s./bee; contact LD_{50} >100 µg a.s./bee). A low chronic toxicity to adult honey bees (LDD_{50} >5.644 µg a.s./bee/day) and a low toxicity to honey bee larvae (72 h, single exposure, LD_{50} >100 µg a.s./larva) were also observed with standard laboratory tests on GA4/GA7.

Table 2.9.3-1: Endpoints and effect values relevant for the risk assessment for bees

Species	**Substance**	**Exposure System**	**Results**	**Reference**
Apis mellifera	GA4/GA7	Acute oral, 48 h	**LD_{50} >87 µg a.s./bee**	CA 8.3.1.1/01
Apis mellifera	GA4/GA7	Acute contact, 48 h	**LD_{50} >100 µg a.s./bee**	CA 8.3.1.1/02
Apis mellifera	GA4/GA7	Chronic oral, 10 days	LC_{50} >150 mg a.s./kg diet LDD_{50} >5.644 µg a.s./bee/day	CA 8.3.1.2/01
Apis mellifera	GA4/GA7	Larval, single exposure, 72 h	LD_{50} >100 µg a.s./larva	CA 8.3.1.3/01
Higher-tier studies (tunnel test, field studies)				
Not required				

Endpoints in bold are used in the risk assessment

GA4/GA7 and Novagib were also shown to have low toxicity to non-target arthropods other than bees. Standard glass plate laboratory tests concluded LR_{50} values of >40 g a.s./ha for both *Aphidius rhopalosiphi* and *Typhlodromus pyri* exposed to GA4/7. In line with this, a new study on *Typhlodromus pyri* concluded an LR_{50} of >80 L Novagib/ha (equivalent to >800 g a.s./ha).

Table 2.9.3-2: Endpoints and effect values relevant for the risk assessment for non-target arthropods other than bees

Species	Substance	Exposure System	Results	Reference
Aphidius rhopalosiphi (adults)	GA4/GA7	Laboratory test glass plates (2D)	**LR_{50} > 40 g a.s./ha**	CA 8.3.2/01
Typhlodromus pyri (protonymphs)	GA4/GA7	Laboratory test glass plates (2D)	**LR_{50} > 40 g a.s/ha**	CA 8.3.2/02
Typhlodromus pyri (protonymphs)	Novagib	Laboratory test glass plates (2D)	LR_{50} > 80 L product/ha, equivalent to > 800 g a.s./ha	CP 10.3.2.1/01
Field or semi-field tests				
Not required				

Endpoints in bold are used in the risk assessment

2.9.4 Summary of effects on non-target soil meso- and macrofauna

A low chronic toxicity to earthworms ($NOEC_{corr}$ = 125 mg a.s./kg dw) is concluded based on a standard reproductive toxicity test with the active substance, GA3. Read across between GA3 and GA4/GA7 is considered acceptable based on the similarities between GA3 and GA4/GA7 and the high margin of safety obtained in the risk assessment.

No further data on effects on other soil meso- and macrofauna are available, but no concerns were raised for effects on leaf-dwelling non-target arthropods (see 2.9.3). Furthermore, the springtail Folsomia candida is an omnivorous, free-living soil organism. Springtails do not directly engage in the decomposition of organic matter, but contribute to it indirectly through the fragmentation of organic matter. They commonly consume fungal hyphae and spores, but also have been found to consume plant material and pollen, animal remains, colloidal materials, minerals and bacteria. Through their feeding on organic matter, Folsomia are naturally exposed to GA4/7, especially through their feeding on fungal hyphae that actively produce gibberellins. *Hypoaspis aculeifer* is a soil dwelling mite that feeds on small arthropods and nematodes, including bulb mites, springtails, thrips pupae and fungus gnats. Thus Hypoaspis feed on arthropods which feed on plants. In the soil, mites will come into direct contact with natural sources of GA4/GA7 and other gibberellins through plant roots, falling leaves, etc.

Table 2.9.4-1: Endpoints and effect values relevant for the risk assessment of non-target soil meso- and macrofauna

Species	Substance	Exposure System	Results	Reference
Eisenia fetida	GA4/GA7	Acute 14 d	14 d LC_{50} > 1250 mg a.s./kg dw soil LC_{50corr} > 625 mg a.s./kg dw soil	CA 8.4.1/01
Eisenia fetida	Novagib	Acute 14 d	14 d LC_{50} > 96 mg a.s./kg dw soil **LC_{50corr} > 48 mg a.s./kg dw soil**	CP 10.4.1.1/01
Eisenia fetida	GA3	Mixed into substrate	NOEC = 250 mg GA3/kg dw	CA 8.4.1/02

Species	Substance	Exposure System	Results	Reference
		56 d, chronic 10 % peat content	**$NOEC_{corr}$* = 125 mg GA3/kg dw**	

Endpoints in bold are used in the risk assessment

* Corrected value derived by dividing the endpoint by a factor of 2 in accordance with the EPPO earthworm scheme 2002 as GA4 and GA7 have log Pow values >2

2.9.5 Summary of effects on soil nitrogen transformation

In a standard soil nitrogen mineralisation study with GA4/GA7, no effects of >25% compared to the control were observed on soil microbial activity up to a maximum tested concentration of 0.13 mg a.s./kg soil, after 28 days.

Table 2.9.5-1: Endpoints and effect values relevant for the risk assessment for soil microorganisms

Endpoint	Substance	Exposure System	Results	Reference
N-mineralisation	GA4/GA7	28 d, aerobic soil type	**< 15 % at 28 d at 0.013 and 0.13 mg/kg dw soil**	CA 8.5/01

Endpoints in bold are used in the risk assessment

2.9.6 Summary of effects on terrestrial non-target higher plants

Standard seedling emergence and vegetative vigour studies are available testing effects of GA4/GA7 and Novagib, respectively. No significant reduction in cropped shoot weight was observed in any of the ten plant species used the seedling emergence study and the ER_{50} value was consequently >222 g a.s./ha, the highest rate applied. In the vegetative vigour study, an ER_{50} of >34.8 g a.s./ha was determined based on effects on plant weight for *Lactuca sativa*, the most sensitive species tested.

Table 2.9.6-1: Endpoints and effect values relevant for the risk assessment of terrestrial non-target higher plants

Species	Substance	Exposure system	Results	Reference
10 species, including *Lactuca sativa* (lettuce)	GA4/GA7	21 d Seedling emergence	[1)] ER_{50} emergence > 222 g a.s./ha **[2)] ER_{50} plant weight > 222 g a.s./ha**	CA 8.6.2/01
Lactuca sativa (Lettuce)	Novagib	21 d Vegetative vigour	[1)] ER_{50} plant weight > 100 g a.s./ha **[2)] ER_{50} plant height = 34.8 g a.s./ha**	CP 10.6.2/01

Endpoints in bold are used in the risk assessment

2.9.7 Summary of effects on other terrestrial organisms (flora and fauna)

No further data are available or considered necessary.

2.9.8 Summary of effects on biological methods for sewage treatment

An activated sludge respiration inhibition test for GA4/GA7 found a 3 h EC_{50} value of >100 mg a.s./L, the highest dose tested.

Test type/organism	end point
Activated sludge	3-hour EC_{50} > 100 mg/L (nominal) NOEC = 100 mg a.s./L

2.9.9 Summary of product exposure and risk assessment

For the proposed use of Novagib 10g/L SL in apple and pear an acceptable risk at the first tier without the need for specific risk mitigation measures was concluded in the following areas of the ecotoxicological risk assessment: birds, mammals, bees, non-target arthropods other than bees, soil meso- and macro-fauna, microorganisms, non-target terrestrial plants, biological methods for sewage treatment and other terrestrial organisms.
No acceptable risk could be concluded for aquatic organisms. Low risk was concluded for fish, aquatic invertebrates and algae. Risk assessment based on toxicity data for *Myriophillum spicatum* (E_rC_{50} <100000 µg/L, corresponding to <950µg a.s./L) shows potentially unacceptable risk to aquatic macrophytes. The ratio PEC/RAC is > 0.016 in FOCUS Step 3 and could therefore be above 1. The risk to rooted aquatic macrophyts cannot be excluded. A further dose-response study needs to be performed to determine toxicity endpoint for *Myriophillum spicatum* and to finalize the risk assessment to aquatic macrophytes.

2.9.9.1 Summary of product exposure and risk assessment for birds

Acute and chronic risk assessment for exposure via diet
The risk assessment was conducted in accordance with EFSA/2009/1438.

All calculations are presented in DRAR Vol.3 Novagib B.9.2.

Table.2.9.9.1-1: Screening assessment of the acute and long-term/reproductive risk for birds due to the use of Novagib in apples and pears

Intended use	**Apples and pears**				
Active substance/product	GA4/GA7/ Novagib				
Application rate (kg/ha)	1 x 0.012 BBCH 62-74				
Acute toxicity (mg/kg bw)	> 2000				
TER criterion	10				
Crop scenario Growth stage	**Indicator/generic focal species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_a**
Orchards (all growth stages- screening step)	Small insectivorous bird	46.8	1	0.562	> 3651
Reprod. toxicity (mg/kg bw/d)	13.76*				
TER criterion	5				
Crop scenario Growth stage	**Indicator/generic focal species**	**SV_m**	**MAF_m × TWA**	**DDD_m (mg/kg bw/d)**	**TER_{lt}**
Orchards (all growth stages- screening step)	Small insectivorous bird	18.2	1 x 0.53	0.116	119

SV: shortcut value; MAF: multiple application factor; TWA: time-weighted average factor; DDD: daily dietary dose; TER: toxicity to exposure ratio. TER values shown in bold fall below the relevant trigger.

* As a protective worst-case, the long-term NOEL for birds has been assumed to be 100-fold lower than the NOEC for short-term toxicity. Given that the NOEL for short-term toxicity was found to equate to the highest dose rate tested in the study, this is considered to be an acceptable approach.

The TERa and TERlt values are above the relevant triggers (10 and 5, respectively) for all relevant growth stages in apples and pears at the first tier. In the absence of long-term toxicity data for birds the long-term risk assessment was based on a worst-case toxicity value assuming the long-term NOEL to be 100-fold lower than the NOEL for short-term toxicity in GA3. Given that the NOEL for short-term toxicity was found to equate to the highest dose rate tested in the study, this is considered to be an acceptable approach. An acceptable long-term risk is concluded even under this worst-case assumption and further studies on sub-chronic and reproductive toxicity to birds and the associated expenditure of vertebrate test animals are therefore not justified. Furthermore, GA4/GA7 is ubiquitous in the tissues of plants and therefore represents a habitual component of the diet in herbivorous birds and insectivorous birds that feed upon herbivorous arthropod prey. As GA4/GA7 is a natural dietary component of birds it is expected that the long-term toxicity value is indeed higher than 13.76 mg a.s./kg bw/d.

Risk assessment for exposure via drinking water

Due to the characteristics of the puddle exposure scenario in connection with the standard assumptions for water uptake by animals, no specific calculations of exposure and TER are necessary when the ratio of effective application rate (in g/ha) to relevant endpoint (in mg/kg bw/d) does not exceed 50 in the case of less sorptive substances (Koc < 500 L/kg) or 3000 in the case of more sorptive substances (Koc ≥ 500 L/kg). With a K(f)oc of 0.5747 L/kg, GA4/GA7 belongs to the group of less sorptive substances.

Effective application rate (g/ha)	=	12		
Acute toxicity (mg/kg bw)	=	>2000	quotient =	<0.006
Reprod. toxicity (mg/kg bw/d)	=	13.76*	quotient =	0.872

* As a protective worst-case, the long-term NOEL for birds has been assumed to be 100-fold lower than the NOEC for short-term toxicity. Given that the NOEL for short-term toxicity was found to equate to the highest dose rate tested in the study, this is considered to be an acceptable approach.

The quotients are well below the trigger of 50 and therefore no further assessment is considered necessary to address the risk to birds due to exposure to GA4/GA7 via contaminated drinking water in puddles.

Risk assessment for Bioaccumulation and Secondary Poisoning

The log P_{ow} values of GA4 and GA7 are 2.34 and 2.25, respectively (EFSA Journal 2012;10(1):2502) and thus do not exceed the trigger value of 3. A risk assessment for effects due to secondary poisoning is not required.

An acceptable risk to birds is concluded at the first tier following the proposed use of Novagib in apples and pears, without the need for specific risk mitigation measures.

2.9.9.2 Summary of product exposure and risk assessment for mammals

The risk assessment was conducted in accordance with EFSA/2009/1438.

All calculations are presented in DRAR Vol.3 Novagib B.9.2.

Table.2.9.9.2-1: Screening assessment of the acute and long-term/reproductive risk for mammals due to the use of Novagib in apples and pears

Intended use	**Apples and pears**				
Active substance/product	GA4/GA7/ Novagib				
Application rate (kg/ha)	1 x 0.012 BBCH 62-74				
Acute toxicity (mg/kg bw)	> 5000				
TER criterion	10				
Crop scenario Growth stage	**Indicator/generic focal species**	**SV_{90}**	**MAF_{90}**	**DDD_{90} (mg/kg bw/d)**	**TER_a**
Orchards (all growth stages- screening step)	Small herbivorous mammal	136.4	1	1.64	> 3049
Reprod. toxicity (mg/kg bw/d)	300				
TER criterion	5				
Crop scenario Growth stage	**Indicator/generic focal species**	**SV_m**	**MAF_m × TWA**	**DDD_m (mg/kg bw/d)**	**TER_{lt}**
Orchards (all growth stages- screening step)	Small herbivorous mammal	72.3	1 x 0.53	0.460	652

SV: shortcut value; MAF: multiple application factor; TWA: time-weighted average factor; DDD: daily dietary dose; TER: toxicity to exposure ratio. TER values shown in bold fall below the relevant trigger.

The TERa and TERlt values are well above the relevant triggers (10 and 5, respectively) for all relevant growth stages in apples and pears, concluding an acceptable acute and long-term risk to mammals following the proposed use of Novagib in apples and pears. Furthermore, GA4/GA7 is ubiquitous in the tissues of plants and therefore represents a habitual component of the diet in herbivorous mammals.

Risk assessment for exposure via drinking water

Due to the characteristics of the exposure scenario in connection with the standard assumptions for water uptake by animals, no specific calculations of exposure and TER are necessary when the ratio of effective application rate (in g/ha) to relevant endpoint (in mg/kg bw/d) does not exceed 50 in the case of less sorptive substances (Koc < 500 L/kg) or 3000 in the case of more sorptive substances (Koc ≥ 500 L/kg). With a K(f)oc of 0.5747 L/kg, GA4/GA7 belongs to the group of less sorptive substances.

Effective application rate (g/ha)	=	12		
Acute toxicity (mg/kg bw)	=	>5000	quotient =	<0.0024
Reprod. toxicity (mg/kg bw/d)	=	300	quotient =	0.04

The quotients are well below the trigger of 50 and therefore no further assessment is considered necessary to address the risk to mammals due to exposure to GA4/GA7 via contaminated drinking water.

Risk assessment for Bioaccumulation and Secondary Poisoning

The log P_{ow} values of GA4 and GA7 are 2.34 and 2.25, respectively (EFSA Journal 2012;10(1):2502) and thus do not exceed the trigger value of 3. A risk assessment for effects due to secondary poisoning is not required.

An acceptable risk to mammals is concluded at the first tier following the proposed use of Novagib in apples and pears, without the need for specific risk mitigation measures.

2.9.9.3 Summary of product exposure and risk assessment for aquatic organisms

The risk assessment was conducted in accordance with the recommendations of the "Guidance document on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters in the context of Regulation (EC) No 1107/2009", as provided by the Commission Services (SANTE-2015-00080, 15 January 2015).

All calculations are presented in DRAR Vol.3 Novagib B.9.3.

The relevant global maximum FOCUS PEC_{SW} values for risk assessments covering the proposed use pattern are provided in DRAR Vol.3 Novagib B.8.

Table.2.9.9.3-1: Aquatic organisms: acceptability of risk (PEC/RAC < 1) for GA4/GA7 for each organism group based on FOCUS Steps 1 and 2 calculations for the use of Novagib in apples and pears

Group		**Fish acute**	**Fish prolonged**	**Inverteb. acute**	**Inverteb. prolonged**	**Algae**	**Macrophytes**	**Macrophytes**
Test species		***Oncorhynchus mykiss***	***Pimephales promelas***	***Daphnia magna***	***Daphnia magna***	***Desmodesmus subspicatus***	***Lemna minor***	***Myriophyllum spicatum***
Endpoint (µg/L)		LC_{50} >100000	NOEC 11000	EC_{50} >100000	NOEC 3000	E_rC_{50} 60000	E_rC_{50}/E_yC_{50} >960	E_rC_{50}/E_yC_{50} <950
AF		100	10	100	10	10	10	10
RAC (µg/L)		>1000	1100	>1000	300	6000	>96	<95
FOCUS Scenario	**PEC $_{gl-max}$ (µg/L)**							
Step 1								
	8.58	<0.009	0.008	<0.009	0.029	0.001	<0.089	**>0.090**
Step 2								
S-Europe	1.66	<0.002	0.002	<0.002	0.006	<0.001	<0.017	**>0.018**

AF: Assessment factor; PEC: Predicted environmental concentration; RAC: Regulatory acceptable concentration; PEC/RAC ratios above the relevant trigger of 1 are shown in bold

For the intended uses of Novagib, calculated PEC/RAC ratios indicate an acceptable risk for the most sensitive group of aquatic organisms, that is aquatic plants, based on *Lemna minor* endpoint E_rC_{50} of >960 µg/L in connection with an assessment factor of 10 in FOCUS Steps 1-2 scenarios. Risk assessment based on toxicity data for *Myriophyllum spicatum* (E_rC_{50} <950 µg/L) shows potentially unacceptable risk. The ratio PEC/RAC is > 0.018 in FOCUS Step 2 and could therefore be above 1. The risk to rooted aquatic macrophytes cannot be excluded. A further dose-response study needs to be performed to determine toxicity endpoint for *Myriophillum spicatum* and to finalize the risk assessment.

No acceptable risk to aquatic organisms can be concluded following the proposed use of Novagib in apples and pears. Further data are considered necessary to show acceptable risk. A data gap has been identified.

2.9.9.4 Summary of product exposure and risk assessment for bees

The evaluation of the acute risk for bees was performed in accordance with the recommendations of the "Guidance Document on Terrestrial Ecotoxicology", as provided by the Commission Services (SANCO/10329/2002 rev.2 (final), October 17, 2002). The draft EFSA bee guidance document (EFSA Journal 2013;11(7):3295) has not yet been formally agreed and noted.

All calculations are presented in DRAR Vol.3 Novagib B.9.6.

Table.2.9.9.4-1: First-tier assessment of the risk for bees due to the use of Novagib in apples and pears

Intended use	Apples and pears		
Active substance	GA4/GA7		
Application rate (g/ha)	1 x12		
Test design	**LD_{50} (lab.) (µg/bee)**	**Single application rate (g/ha)**	**Q_{HO}, Q_{HC} criterion: $Q_H \leq 50$**
Oral toxicity	>87	12	<0.14
Contact toxicity	>100		<0.12

Q_{HO}, Q_{HC}: Hazard quotients for oral and contact exposure. Q_H values shown in bold breach the relevant trigger.

The acute oral and contact hazard quotients are below the trigger of 50, indicating an acceptable risk to bees following the proposed use of Novagib in apples and pears.

A formal risk assessment is not conducted for the chronic risk to honey bee adults and larvae as no agreed risk assessment scheme is available at the time of submission. Nevertheless, no further studies or risk assessments are considered necessary as the available data demonstrate a low chronic toxicity to adults and a low toxicity to larvae for GA4/GA7. Furthermore, GA4/GA7 is ubiquitous in the tissues of plants and therefore bees are likely naturally exposed to gibberellins when foraging for nectar, pollen, propolis and other botanical sources.

An acceptable risk to bees is concluded at the first tier following the proposed use of Novagib in apples and pears, without the need for specific risk mitigation measures.

2.9.9.5 Summary of product exposure and risk assessment for Non-target arthropods other than bees

The evaluation of the risk for non-target arthropods was performed in accordance with the recommendations of the "Guidance Document on Terrestrial Ecotoxicology", as provided by the Commission Services (SANCO/10329/2002 rev.2 (final), October 17, 2002), and in consideration of the recommendations of the guidance document ESCORT 2.

All calculations are presented in DRAR Vol.3 Novagib B.9.6.

Table.2.9.9.5-1: First-tier assessment of the in-field risk for non-target arthropods due to the use of Novagib in apples and pears

Intended use	**Apples and pears**		
Active substance/product	GA4/GA7/ Novagib		
Application rate (g/ha)	4 x 5 (minimum interval 7 days) BBCH 62-74		
MAF	2.7 (based on ESCORT II guidance for 4 applications, and a default dissipation DT_{50}: Spray interval of 2.3:1)		
Test species Tier I	**LR_{50} (lab.) (g/ha)**	**$PER_{in\text{-}field}$ (g/ha)***	**$HQ_{in\text{-}field}$ criterion: HQ ≤ 2**
Typhlodromus pyri	> 40	13.5	< 0.338
Aphidius rhopalosiphi	> 40		<0.338

MAF: Multiple application factor; PER: Predicted environmental rate; HQ: Hazard quotient; Criteria values shown in bold breach the relevant trigger.

* $PER_{in\text{-}field}$ = Application rate × MAF

The in-field hazard quotients ($HQ_{in\text{-}field}$) are well below the trigger of 2 for both standard indicator species, concluding an acceptable in-field risk to non-target arthropods following the proposed use of Novagib in apples and pears.

Table.2.9.9.5-2: First-tier assessment of the off-field risk for non-target arthropods due to the use of Novagib in apples and pears

Intended use	**Apples and pears**					
Active substance/product	GA4/GA7/ Novagib					
Application rate (g/ha)	1 x 12 BBCH 62-74					
MAF	1.0					
Test species Tier I	**LR_{50} (lab.) (g/ha)**	**Drift factor**	**VDF**	**CF**	**$PER_{off\text{-}field}$ (g/ha)***	**$HQ_{off\text{-}field}$ criterion: HQ ≤ 2**
Typhlodromus pyri	> 40	15.73 (based on late fruit crops, ESCORT II)	10	10	1.89	< 0.047
Aphidius rhopalosiphi	> 40					< 0.047

MAF: Multiple application factor; PER: Predicted environmental rate; HQ: Hazard quotient; VDF: Vegetation Distribution Factor; CF: Correction Factor; Criteria values shown in bold breach the relevant trigger.

* $PER_{off\text{-}field}$ = [Application rate x MAF x (drift factor/VDF)]/CF

The off-field hazard quotients ($HQ_{off\text{-}field}$) are well below the trigger of 2 for both standard indicator species, concluding an acceptable off-field risk to non-target arthropods following the proposed use of Novagib in apples and pears.

An acceptable risk to non-target arthropods is concluded at the first tier following the proposed use of Novagib in apples and pears, without the need for specific risk mitigation measures.

2.9.9.6 Summary of product exposure and risk assessment for non-target soil meso- and macrofauna

The evaluation of the risk for earthworms was performed in accordance with the recommendations of the "Guidance Document on Terrestrial Ecotoxicology", as provided by the Commission Services (SANCO/10329/2002 rev 2 (final), October 17, 2002).

All calculations are presented in DRAR Vol.3 Novagib B.9.8.

The relevant PEC_{soil} for risk assessments covering the proposed use pattern are taken from DRAR Vol.3 Novagib B.8.

Table.2.9.9.6-1: First-tier assessment of the acute and chronic risk for earthworms due to the use of Novagib in apples and pears

Intended use	Apples and pears		
Acute effects on earthworms			
Product/active substance	**LC_{50} (mg/kg dw)**	**PEC_{soil} (mg/kg dw)**	**TER_a (criterion TER ≥ 10)**
Novagib	>48	0.0133[a]	>3609
Chronic effects on earthworms			
Product/active substance	**NOEC (mg/kg dw)**	**PEC_{soil} (mg/kg dw)**	**TER_{lt} (criterion TER ≥ 5)**
GA4/GA7	125	0.0133[a]	9398

[a] Worst case PEC based on critical use pattern of 4 x 5 g a.s./ha (7 d minimum interval).
TER values shown in bold fall below the relevant trigger.

The acute and long-term TER values are well above the relevant triggers of 10 and 5 respectively. An acceptable risk to earthworms is concluded at the first tier following the proposed use of Novagib in apples and pears, without the need for specific risk mitigation measures.

2.9.9.7 Summary of product exposure and risk assessment for soil microorganisms

The evaluation of the risk for soil microorganisms was performed in accordance with the recommendations of the "Guidance Document on Terrestrial Ecotoxicology", as provided by the Commission Services (SANCO/10329/2002 rev 2 (final), October 17, 2002).

All calculations are presented in DRAR Vol.3 Novagib B.9.10.

The relevant PEC_{soil} for risk assessments covering the proposed use pattern are taken from DRAR Vol.3 Novagib B.8.

Table.2.9.9.7-1: Assessment of the risk for effects on soil micro-organisms due to the use of Novagib in apples and pears

Intended use	Apples and pears		
N-mineralisation			
Product/active substance	**Max. conc. with effects ≤ 25 % (mg a.s./kg dw)**	**PEC_{soil} (mg/kg dw)**	**Risk acceptable?**
GA4/GA7	0.13 (at 28 d)	0.0133	yes

The results of the active substance study showed no effects of >25% compared to the control (trigger value according to SANCO/10329/2002) on soil microbial activity up to a maximum tested concentration of 0.13 mg a.s./kg soil, after 28 days. As the maximum tested concentration is much higher than the maximum initial PEC from the proposed use of Novagib, an acceptable risk to soil microbial activity is concluded. Furthermore, GAs are naturally produced by bacteria and fungi and given that the degradation rates of GA4 and GA7 in soil are rapid, it

is considered that there will be no significant carry over of residues between applications and that there will be no long-term risk to microbial activity.

An acceptable risk to soil microorganisms is concluded following the proposed use of Novagib in apples and pears, without the need for specific risk mitigation measures.

2.9.9.8 Summary of product exposure and risk assessment for terrestrial non-target plants

The risk assessment is based on the "Guidance Document on Terrestrial Ecotoxicology", (SANCO/10329/2002 rev.2 final, 2002). It is restricted to off-field situations, as non-target plants are non-crop plants located outside the treated area.

All calculations are presented in DRAR Vol.3 Novagib B.9.12.

Table.2.9.9.8-1: Assessment of the risk for non-target plants due to the use of Novagib in apples and pears

Intended use	Apples and pears			
Active substance/product	GA4/GA7/ Novagib			
Application rate (g/ha)	1 x 12 BBCH 55-75			
Test species	**ER_{50} (g/ha)**	**Drift rate**	**$PER_{off\text{-}field}$ (g/ha)**	**TER criterion: TER ≥ 5**
10 species (seedling emergence)	>222	15.73*	1.89	>117
Lettuce (vegetative vigour)	34.8	15.73*	1.89	18.4

PER: Predicted environmental rate; TER: toxicity to exposure ratio. TER values shown in bold fall below the relevant trigger.
*Drift rate for late fruit crops at 3 m (Rautmann et al. 2001)

The TER values are above the trigger of 5 for all ten species tested in the seedling emergence study (ER_{50} endpoints all >222 g GA4/7/ha) and the most sensitive species (*Lactuca sativa*) tested in the vegetative vigour study performed with Novagib.

An acceptable risk to non-target plants is concluded at the first tier following the proposed use of Novagib in apples and pears, without the need for specific risk mitigation measures.

2.10 ENDOCRINE DISRUPTING PROPERTIES

2.10.1 ED assessment for humans

This evaluation comprises an assessment of the available literature data and an assessment of the toxicological studies according to the ECHA/EFSA guidance document (Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009, EFSA Journal 2018;16(6)5311), utilising Appendix E1 and the corresponding sub-guidance document for completion of the Excel spreadsheet. The Excel spreadsheet is provided separately.

Endocrine disrupting properties of gibberellins (GA4/7) were not sufficiently investigated in the provided literature search. The additionally provided in vitro mechanistic studies were assessed to be used for supportive information due to deviations from the current relevant guidelines.
After gathering and analysing all the available information provided, the RMS came to the conclusion that:

For the EATS modalities, although adversity was not observed, the dataset was not sufficient for both adversity and endocrine activity. Therefore, further data need to be generated before a conclusion on whether the ED criteria are met for the EATS-modalities can be drawn.
The following testing is proposed:

Based on scenario 2a (iii), the endocrine activity was not sufficiently investigated for the EAS-modalities:

- E modality: There is not ToxCast ER model neither Uterotrophic assay (OECD TG 440)
- A modality: There is no Hershberger Assay (OECD TG 441)
- S modality: There is no Steroidogenesis Assay (OECD TG 456)

Therefore, according to the guidance, additional information should be generated (Scenario 2a(iii)). Level 3 studies are required for E modality i.e. OECD TG 440 and A modality i.e. OECD TG 441, and Level 2 study for S modality i.e. OECD TG 456.

- If the above studies are negative, the scenario 2a(ii) applies and ED criteria are not met.
- If endocrine activity is observed, the scenario 2a(i) applies and further data will be needed to support the MoA analysis, i.e. extended one-generation study (OECD TG 443, Level 5).

As there are no specific studies which can be additionally submitted to cover the endocrine activity of the thyroid gland. The RMS is of the opinion that according to the data provided, no final conclusions can be reached regarding the thyroid mediated adversity and endocrine activity. In case of a negative conclusion about EAS modalities, a combined chronic toxicity and carcinogenicity study (OECD 451-3) and extended one-generation reproductive toxicity study (OECD 443) are proposed.

In the Tables below the lines of evidence for T and EAS modalities for are presented as they have been compiled by RMS.

For a more detailed assessment details please, refer to Vol 3 CA Section B.6.8.3

Table 2.10.1.-1 Lines of evidence for adverse effects and endocrine activity related to T-modality

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
2	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	13	Weeks	Oral	1100	mg/kg bw/day	Change	1/2 dogs was treated with steroids.	not reliable result	Isolated effects upon adrenals in one dog study, brain weight in one rat study and litter parameters in one rabbit study were related to generalised systemic toxicity at the high dose level only and were unrelated to ED mediated effects. Due to high mortality rate of dams in the rabbit study the two reproductive effects	Overall. No evidence for T-adversity - Datased not sufficientl y invenstigat ed
1		Brain weight	Rat	13	Weeks	Oral	25000	ppm	Increase	Effect seen at discontinuation of treatment and persisted following 4-week recovery period;	Not necessarily indicative of a treatment - related effect and instead may be indicative of adaptation to general toxicity and preservation of key organ functions		
4		Number of live births	Rabbit	13	Days	Oral	1000	mg/kg bw/day	Decrease	not reliable result	Due to high mortality rate of dams at the top dose in the rabbit study the two reproductive		

4		Post implantation loss	Rabbit	13	Days	Oral	1000	mg/kg bw/day	Increase	not reliable result	effects are not reliable	are not reliable	
1	Target organ toxicity	Kidney histopathology	Rat	13	Weeks	Oral	25000	ppm	Change	chronic inflammation that tended to be more severe and more prevalent in males; severity in both sexes tended to be reduced following 4-week recovery period.	Treatment related findings in organ weight and histopathology are indicative of potentially adaptive changes and generalised systemic toxicity unrelated to endocrine-mediated activity. Effects upon primary lymphoid tissues (eg thymus and spleen) could be indicative of stress secondary to general systemic toxicity.	Sufficient evidence of systemic toxicity kidney (dog, rat), liver (rat) and spleen (rat), possible effect on thymus toxicity (dog)	
1			Rat	13	Weeks	Oral	25000	ppm	Change	Rough surface (more prevalent in females) or depressed foci/areas in the cortex (more prevalent in males); changes were largely unresolved following 4-week recovery period.			

3			Rat	5	Months	Oral	600	mg/kg bw/day	Increase	DR increases in the incidence and severity of nephropathy, medullary tubular dilatation, medullary fibroplasia, medullary basophilic interstitium and medullary tubule hyperplasia. Medullary papillary urothelial hyperplasia also apparently observed.			
3			Rat	5	Months	Oral	600	mg/kg bw/day	Increase				
3			Rat	5	Months	Oral	600	mg/kg bw/day	Increase				
1		Kidney weight	Rat	13	Weeks	Oral	25000	ppm	Decrease	stst. Sign. relative in males, not stat. Sig. Absolute in females			
1			Rat	13	Weeks	Oral	25000	ppm	Increase				
2			Dog	13	Weeks	Oral	1100	mg/kg bw/day	Increase	stst. Sign. relative			
3			Rat	5	Months	Oral	1000	mg/kg bw/day	Decrease	stst. Sign. Abolute (males)			

1		Liver histopathology	Rat	13	Weeks	Oral	25000	ppm	Change	epatocellular vacuolization (high incidence, slight to moderate severity) and hepatocellular degeneration (some evidence) were largely resolved following 4-week recovery period			
1		Liver weight	Rat	13	Weeks	Oral	25000	ppm	Decrease	not consistnet effect between males and females			
1			Rat	13	Weeks	Oral	25000	ppm	Increase				
2			Dog	13	Weeks	Oral	1100	mg/kg bw/day	Increase	stst. Sign. Relative, absolute			
3		Spleen weight	Rat	Unknown. Animals exposed from conception.	Months	Oral	1000	mg/kg bw/day	Decrease	observed in F1 and F2 pups			
2		Thymus histopathology	Dog	13	Weeks	Oral	1100	mg/kg bw/day	Change	atrophy, 3/4 males, reported to be a result of stress			
2		Thymus weight	Dog	13	Weeks	Oral	1100	mg/kg bw/day	Decrease	obsreved as small (males)			
3			Rat	Unknown. Animals exposed from conception.	Months	Oral	1000	mg/kg bw/day	Decrease	stat. Signif absolute, F2 offspring males			

1	Systemic toxicity	Clincial chemistry	Rat	13	Weeks	Oral	25000	ppm	Change	Effect noted alongside several other signs of generalised toxicity not indicative of an ED effect	Treatment related findings such as reduced bodyweight, occasional alterations in food intake, haematological or clinical chemistry parameters, clinical signs etc. are considered a consequence of general systemic toxicity and were unrelated to endocrine mediated activity.		
1			Rat	13	Weeks	Oral	25000	ppm	Change				
1		Body weight	Rat	13	Weeks	Oral	50000	ppm	Decrease				
2			Dog	13	Weeks	Oral	1100	mg/kg bw/day	Decrease				
3			Rat	5	Months	Oral	1000	mg/kg bw/day	Decrease				
3			Rat	5	Months	Oral	600	mg/kg bw/day	Decrease				
3			Rat	5	Months	Oral	1000	mg/kg bw/day	Decrease				
3			Rat	Unknown. Animals exposed from conception.	Months	Oral	1000	mg/kg bw/day	Decrease				
4			Rabbit	13	Days	Oral	1000	mg/kg bw/day	Decrease				
1		Clinical chemistry and haematology	Rat	13	Weeks	Oral	25000	ppm	Change				
1		Clinical signs	Rat	13	Weeks	Oral	25000	ppm	Change				
1			Rat	13	Weeks	Oral	50000	ppm	Change				
2			Dog	13	Weeks	Oral	1100	mg/kg bw/day	Change				
4			Rabbit	13	Days	Oral	300	mg/kg bw/day	Increase				
1		Food consumption	Rat	13	Weeks	Oral	50000	ppm	Decrease				
2			Dog	13	Weeks	Oral	1100	mg/kg bw/day	Decrease				
3			Rat	5	Months	Oral	1000	mg/kg bw/day	Increase				
1		Mortality	Rat	13	Weeks	Oral	25000	ppm	Decrease				
4			Rabbit	13	Days	Oral	100	mg/kg bw/day	Increase				

Table 2.10.1-2: Lines of evidence for adverse effects and endocrine activity related to EAS-modalities

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
5	In vitro mechanistic	Androgen receptor	Human	40	Hours	Uptake from the medium	>10000	other	No effect	No effect	NO ER and AR mediated (ant)agonistic activity. Supporting information. The study was assessed as not reliable.	Overall not sufficient to show absence of endocrine activity.	A
5		Estrogen receptor	Human	40	Hours	Uptake from the medium	>10000	other	No effect	No effect			E
1	EATS-mediated	Ovary weight	Rat	13	Weeks	Oral	25000	ppm	Increase	Effect noted at top dose only at which there was clear evidence of generalised toxicity, significant decrease in body weight)	Ovary and testis related weights were affected in one study at a very high dose level, were not replicated and are likely to be secondary to generalised toxicity at this treatment level.	Overall not sufficient to show absence of endocrine activity.	Overall. No evidence for EAS-adversity - Datased not sufficientl y invenstiga ted
1		Testis weight	Rat	13	Weeks	Oral	25000	ppm	Increase				

2		Adrenals histopathology	Dog	13	Weeks	Oral	1100	mg/kg bw/day	Change	1/2 dogs was treated with steroids.	not reliable result		
1	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	13	Weeks	Oral	25000	ppm	Increase	Effect seen at discontinuation of treatment and persisted following 4-week recovery period;	Not necessarily indicative of a treatment -related effect and instead may be indicative of adaptation to general toxicity and preservation of key organ functions	Isolated effects upon adrenals in one dog study, brain weight in one rat study and litter parameters in one rabbit study were related to generalised systemic toxicity at the high dose level only and were unrelated to ED mediated effects. Due to high mortality rate of dams in the rabbit study the two reproductive effects are not reliable	
4		Number of live births	Rabbit	13	Days	Oral	1000	mg/kg bw/day	Decrease	not reliable result	Due to high mortality rate of dams at the top dose in the rabbit study the two reproductive effects are not reliable		
4		Post implantation loss	Rabbit	13	Days	Oral	1000	mg/kg bw/day	Increase	not reliable result			
1	Target organ toxicity	Kidney histopathology	Rat	13	Weeks	Oral	25000	ppm	Change	chronic inflammation that tended to be more severe and more	Treatment related findings in organ weight and histopathology are	Sufficient evidence of systemic	

										prevalent in males; severity in both sexes tended to be reduced following 4-week recovery period.	indicative of potentially adaptive changes and generalised systemic toxicity unrelated to endocrine-mediated activity. Effects upon primary lymphoid tissues (eg thymus and spleen) could be indicative of stress secondary to general systemic toxicity.	toxicity kidney (dog, rat), liver (rat) and spleen (rat), possible effect on thymus toxicity (dog)	
1			Rat	13	Weeks	Oral	25000	ppm	Change	Rough surface (more prevalent in females) or depressed foci/areas in the cortex (more prevalent in males); changes were largely unresolved following 4-week recovery period.			
3			Rat	5	Months	Oral	600	mg/kg bw/day	Increase	DR increases in the incidence and severity of nephropathy, medullary tubular dilatation, medullary fibroplasia, medullary basophilic interstitium and medullary tubule hyperplasia. Medullary papillary urothelial hyperplasia also apparently observed.			
3			Rat	5	Months	Oral	600	mg/kg bw/day	Increase				
3			Rat	5	Months	Oral	600	mg/kg bw/day	Increase				
1		Kidney weight	Rat	13	Weeks	Oral	25000	ppm	Decrease	stst. Sign. relative in males, not stat. Sig. Absolute in females			
1			Rat	13	Weeks	Oral	25000	ppm	Increase				
2			Dog	13	Weeks	Oral	1100	mg/kg bw/day	Increase	stst. Sign. relative			
3			Rat	5	Months	Oral	1000	mg/kg bw/day	Decrease	stst. Sign. Abolute (males)			

1		Liver histopathology	Rat	13	Weeks	Oral	25000	ppm	Change	epatocellular vacuolization (high incidence, slight to moderate severity) and hepatocellular degeneration (some evidence) were largely resolved following 4-week recovery period			
1		Liver weight	Rat	13	Weeks	Oral	25000	ppm	Decrease	not consistnet effect between males and females			
1			Rat	13	Weeks	Oral	25000	ppm	Increase				
2			Dog	13	Weeks	Oral	1100	mg/kg bw/day	Increase	stst. Sign. Relative, absolute			
3		Spleen weight	Rat	Unknown. Animals exposed from conception.	Months	Oral	1000	mg/kg bw/day	Decrease	observed in F1 and F2 pups			
2		Thymus histopathology	Dog	13	Weeks	Oral	1100	mg/kg bw/day	Change	atrophy, 3/4 males, reported to be a result of stress			
2		Thymus weight	Dog	13	Weeks	Oral	1100	mg/kg bw/day	Decrease	obsreved as small (males)			
3			Rat	Unknown. Animals exposed from conception.	Months	Oral	1000	mg/kg bw/day	Decrease	stat. Signif absolute, F2 offspring males			
1	Systemic toxicity	Clincial chemistry	Rat	13	Weeks	Oral	25000	ppm	Change	Effect noted alongside several other signs of generalised toxicity not indicative of an ED effect	Treatment related findings such as reduced bodyweight, occasional alterations in food intake, haematological or clinical chemistry parameters, clinical signs		
1			Rat	13	Weeks	Oral	25000	ppm	Change				
1		Body weight	Rat	13	Weeks	Oral	50000	ppm	Decrease				
2			Dog	13	Weeks	Oral	1100	mg/kg bw/da	Decrease				

								y		etc. are considered a consequence of general systemic toxicity and were unrelated to endocrine mediated activity.		
3			Rat	5	Months	Oral	1000	mg/kg bw/day	Decrease			
3			Rat	5	Months	Oral	600	mg/kg bw/day	Decrease			
3			Rat	5	Months	Oral	1000	mg/kg bw/day	Decrease			
3			Rat	Unknown. Animals exposed from conception.	Months	Oral	1000	mg/kg bw/day	Decrease			
4			Rabbit	13	Days	Oral	1000	mg/kg bw/day	Decrease			
1		Clinical chemistry and haematology	Rat	13	Weeks	Oral	25000	ppm	Change			
1		Clinical signs	Rat	13	Weeks	Oral	25000	ppm	Change			
1			Rat	13	Weeks	Oral	50000	ppm	Change			
2			Dog	13	Weeks	Oral	1100	mg/kg bw/day	Change			
4			Rabbit	13	Days	Oral	300	mg/kg bw/day	Increase			
1		Food consumption	Rat	13	Weeks	Oral	50000	ppm	Decrease			
2			Dog	13	Weeks	Oral	1100	mg/kg bw/day	Decrease			
3			Rat	5	Months	Oral	1000	mg/kg bw/day	Increase			
1		Mortality	Rat	13	Weeks	Oral	25000	ppm	Decrease			
4			Rabbit	13	Days	Oral	100	mg/kg bw/day	Increase			

2.10.2 ED assessment for non-target organisms

Assessment of endocrine disrupting properties of gibberellins GA4/GA7 regarding mammals as non-target organisms

The EFSA/ECHA guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (EFSA Journal 2018;16(6):5311) foresees a gradual approach to identification of endocrine disrupting properties of active substances. It is recommended to strive for a conclusion on the ED properties with regard to humans and in parallel, using the same database, to strive for a conclusion on mammals as non-target organisms. If the substance under investigation is found to be ED for humans, the assessment need not continue. This is because it is sufficient that the substance meets the ED criteria in one taxonomic group in order to conclude that a substance meets the ED criteria for all non-target organisms. If the substance under investigation is not ED for humans, the population relevance of the observed adverse effects needs to be assessed in order to conclude on ED properties with regard to mammals as non-target organisms. In order to conclude on the ED properties of gibberellins GA4/GA7 with regard to humans new data need to be generated (see Vol 3 CA Section B.6.8.3, toxicological assessment). Until a conclusion is made regarding humans the assessment of the ED properties of gibberellins GA4/GA7 with regard to mammals as non-target organisms cannot proceed. For assessment of endocrine disrupting properties of gibberellins GA4/GA7 regarding mammals as non-target organisms please refert to Vol 3 CA Section B.9.1.5.

Assessment of endocrine disrupting properties of gibberellins GA4/GA7 regarding fish, amphibians, birds, reptiles and other non-target organisms

Where the evidence available indicates that the ED criteria are not met for mammals as non-target organisms, the assessment for non-target organisms should proceed by considering fish and amphibians, because these are the taxa where standardised test methods and knowledge on how to interpret the results are available. Information on other taxa (e.g. birds and reptiles) should be considered if available.

In the case of gibberellins GA4/GA7 no relevant information for birds and reptiles is available, therefore no assessment of endocrine disrupting properties in regard to these species was performed.

Some data regarding fish are available, therefore the RMS assessed the ED properties of gibberellins GA4/GA7 regarding fish. One *in vitro* study is available (Saito K (2008), UKT-0038), which RMS considers to be unreliable and is suggested to be used as supporting information. Additionally one guideline study with gibberellic acid (GA3) is available; Fish early life stage toxicity test (OECD 210). The study does not provide any EATS-mediated parameters, *in vivo* mechanistic parameters or *in vitro* mechanistic parameters. The study provides information on Sensitive to but not diagnostic of EATS parameters. Based on structural similarities between GA3 and GA4/GA7 read across approach is acceptable. Based on the available evidence from standard studies for non-target organisms, the EATS-modalities are not considered sufficiently investigated in fish. The dataset is not sufficient to assess the ED properties of gibberellins GA4/GA7. According to the assessment strategy of the guidance for the identification of endocrine disruptors (ECHA, EFSA 2018), a tiered assessment strategy should be followed. In the case of gibberellins GA4/GA7, level 2 and level 3 tests would be required to complete the current data package:

1. A study in line with the OECD 455 (estrogen receptor transactivation)
2. A study in line with the OECD 458 (androgen receptor transactivation)
3. A study in line with the OECD 456 (steroidogenesis)
4. A study in line with the OECD TG 231 (AMA)
5. A study in line with the OECD TG 229 (FSTRA)

These tests investigate potential EATS-mediated endocrine activity. If all tests are negative, this shows that gibberellins GA4/GA7 have no ED properties. However, if these tests show a positive result for at least one modality, additional testing might be needed in order to further investigate the adversity.

In order to be able to conclude whether the approval criteria on the endocrine disruption potential in line with Commission Regulation (EU) 2018/605[7] are met for gibberellins GA4/GA7, the applicant should complete the data package within a period not exceeding 30 months. However, the decision whether or not to request the listed studies is dependent on the conclusion on the ED properties with regard to humans and mammals as non-target organisms. If gibberellins GA4/GA7 are identified as ED for humans, new studies on fish and amphibians do not need to be performed in order to avoid unnecessary vertebrate testing. For detailed assessment of endocrine disrupting properties of gibberellins GA4/GA7 regarding fish, amphibians, birds, reptiles and other non-target organisms please refer to Vol 3 CA Section B.9.2.4. In tables Table 2.10.2- 1 and Table 2.10.2- 2 below the lines of evidence for EAS and T modalities for non-target organisms are presented as they have been compiled by RMS.

[7] Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. OJ L 101, 20.4.2018, p. 33–36.

Table 2.10.2- 1 : Lines of evidence for EAS modalities for non-target organisms

	Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
Integrated LoE for endocrine activirty	5	In vitro mechanistic	Androgen receptor	Human	40	Hours	Uptake from the medium	>10000	other	No effect	No effect	Supporting information. The study was assessed as not reliable.	Overall not sufficient to show absence of endocrine activity.	A
	5	In vitro mechanistic	Estrogen receptor	Human	40	Hours	Uptake from the medium	>10000	other	No effect	No effect	Supporting information. The study was assessed as not reliable.		E
LoE for general toxicity	6	Sensitive to, but not diagnostic of, EATS	Behaviour (fish)	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.	Overall indicates absence of general toxicity. Considered not sufficient to show absence of adversity.	N
	6	Sensitive to, but not diagnostic of, EATS	Body weight (fish)	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.		N
	6	Sensitive to, but not diagnostic of, EATS	Embryo time-to-hatch	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.		N
	6	Sensitive to, but not diagnostic of, EATS	Length (fish)	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.		N

	6	Sensitive to, but not diagnostic of, EATS	Survival of embryos	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.		N
	6	Systemic toxicity	Survival (fish)	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.		N

Table 2.10.2- 2 : Lines of evidence for T modality for non-target organisms

	Study ID Matrix	**Effect classification**	**Effect target**	**Species**	**Duration of exposure**	**Duration unit**	**Route of administration**	**Lowest Effect dose**	**Dose unit**	**Effect direction**	**Observed effect (positive and negative)**	**Assessment of each line of evidence**	**Assessment on the integrated line of evidence**	**Modality**
LoE for general toxicity	6	Sensitive to, but not diagnostic of, EATS	Behaviour (fish)	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.	Overall indicates absence of general toxicity. Considered not sufficient to show absence of adversity.	N
	6	Sensitive to, but not diagnostic of, EATS	Body weight (fish)	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.		N
	6	Sensitive to, but not diagnostic of, EATS	Embryo time-to-hatch	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.		N

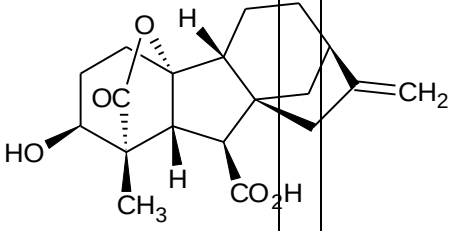
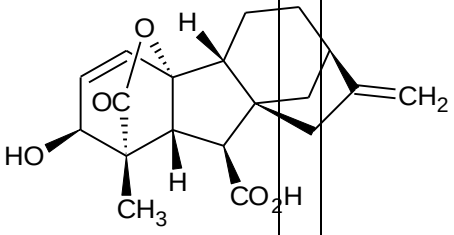
	6	Sensitive to, but not diagnostic of, EATS	Length (fish)	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.	N
	6	Sensitive to, but not diagnostic of, EATS	Survival of embryos	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.	N
	6	Systemic toxicity	Survival (fish)	Fathead minnow	33	days	Uptake from water	>11	mg/L water	No effect	No effect	Not sufficient. No effects observed, but only one study performed, only one species.	N

2.11 PROPOSED HARMONISED CLASSIFICATION AND LABELLING ACCORDING TO THE CLP CRITERIA *[SECTIONS 1-6 OF THE CLH REPORT]*

2.11.1 Identity of the substance [section 1 of the CLH report]

2.11.1.1Name and other identifiers of the substance

Table 75: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	GA_4: (3S,3aR,4S,4aR,7R,9aR,9bR,12S)-12-hydroxy-3-methyl-6-methylene-2-oxoperhydro-4a,7-methano-3,9b-propanoazuleno[1,2-b]furan-4-carboxylic acid GA_7: (3S,3aR,4S,4aR,7R,9aR,9bR,12S)-12-hydroxy-3-methyl-6-methylene-2-oxoperhydro-4a,7-methano-9b,3-propenoazuleno[1,2-b]furan-4-carboxylic acid
Other names (usual name, trade name, abbreviation)	Gibberellin(s), GA4/7, $GA_{4/7,}$ GA4/GA7
ISO common name (if available and appropriate)	There is no ISO common name for this compound Synonyms are Gibberellins, GA4/7
EC number (if available and appropriate)	GA4: 207-406-9 GA7: 208-117-0
EC name (if available and appropriate)	
CAS number (if available)	GA4: 468-44-0 GA7: 510-75-8 GA4/GA7 mixture: 8030-53-3
Other identity code (if available)	
Molecular formula	GA4 = $C_{19}H_{24}O_5$ GA7 = $C_{19}H_{22}O_5$
Structural formula	GA4  GA7 
SMILES notation (if available)	
Molecular weight or molecular weight range	GA4 332.40 g/mol GA7 330.40 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	/
Description of the manufacturing process and identity of the source (for UVCB substances only)	Confidential information

Degree of purity (%) (if relevant for the entry in Annex VI)	1. Fine Agrochemicals Ltd.:	GA4: 905-919 g/kg GA7: 19.5-27 g/kg **GA4/GA7: min. 924 g/kg**
	2. Globachem NV:	GA4: 648-653 g/kg GA7: 248-253 g/kg **GA4/GA7: min. 885 g/kg**
	3. Valent Biosciences Ltd.:	GA4: 631-778 g/kg GA7: 130-288 g/kg **GA4/GA7: min. 852 g/kg**

2.11.1.2Composition of the substance

Table 76: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Not applicable			

Table 77: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
Not relevant				

Table 78: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
Not relevant					

Table 79: Test substances (non-confidential information)

Identification of test substance	**Purity**	**Impurities and additives (identity, %, classification if available)**	**Other information**	**The study(ies) in which the test substance is used**
Not relevant				

2.11.2 Proposed harmonized classification and labelling

2.11.2.1Proposed harmonised classification and labelling according to the CLP criteria

Table 80: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	None	None	None	None	None	None	None	None	-	-	No current Annex VI entry
Dossier submitters proposal		Gibberellins (GA_4 GA_7)	None	8030-53-3 (GA_4A_7 mixture)	Eye Irrit. 2 Aquatic acute 1 Aquatic Chronic 3	H319 H400 H412	GHS07 GHS09 Warning	H319 H410	-	M = 1 (acute)	-
Resulting Annex VI entry if agreed by RAC and COM		Gibberellins (GA_4 GA_7)	None	8030-53-3 (GA_4A_7 mixture)	Eye Irrit. 2 Aquatic acute 1 Aquatic Chronic 3	H319 H400 H412	GHS07 GHS09 Warning	H319 H410	-	M = 1 (acute)	-

2.11.2.2Additional hazard statements / labelling

None.

Table 81: Reason for not proposing harmonised classification and status under CLH public consultation

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Explosives	Data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Hazard class not applicable	Yes
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Hazard class not applicable	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Data conclusive but not sufficient for classification	Yes
Self-reactive substances	Hazard class not applicable	Yes
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Data conclusive but not sufficient for classification	Yes
Self-heating substances	Data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	Hazard class not applicable	Yes
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Data conclusive but not sufficient for classification	Yes
Organic peroxides	Hazard class not applicable	Yes
Corrosive to metals	Data conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Data conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	Data conclusive and sufficient for classification	Yes
Respiratory sensitisation	Data lacking	Yes
Skin sensitisation	Data conclusive but not sufficient for classification	Yes
Germ cell mutagenicity	Data conclusive but not sufficient for classification	Yes
Carcinogenicity	Data lacking	No
Reproductive toxicity	Data conclusive but not sufficient for classification	Yes

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Specific target organ toxicity-single exposure	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-repeated exposure	Data conclusive but not sufficient for classification	Yes
Aspiration hazard	hazard class not applicable	No
Hazardous to the aquatic environment	Harmonised classification proposed	Yes
Hazardous to the ozone layer	Data conclusive but not sufficient for classification	Yes

2.11.3 History of the previous classification and labelling

Gibberellins (GA4, GA7) have not previously been classified according to Dangerous Substance Directive 67/548/EEC or according to Regulation 1272/2008. No classification was proposed during the previous peer review process. Searching the CLH inventory on 15.1.2019, for each GA_4 and GA_7 one notifications is listed, two with the proposal of Skin Sens. 1, H317.

2.11.4 Identified uses

Gibberellins (GA4/GA7) are used as a plant growth regulator. Please, refer also to section (2.3).

2.11.5 Data sources

The data were submitted in the context of renewal of pesticide active substances under Regulation no. 1107/2009 concerning the placing of plant protection products on the market. The data was evaluated in the Draft Renewal Assessment Report for gibberellins (DRAR) Vol. 1-4.

2.12 RELEVANCE OF METABOLITES IN GROUNDWATER

The route and rate of aerobic degradation of the individual components gibberellins GA4 and gibberellins GA7 of the active substance gibberellins GA4/7 was investigated in four soil types (ranging from loamy sand to clay loam) of varying origin in the dark under laboratory conditions at a temperature of 20°C and moisture content of 100% pF 2. The individual components gibberellins GA4 and gibberellins GA7 degraded rapidly and extensively in soil resulting in the formation of numerous degradation products. For gibberellins GA4, up to eight degradation components accounting for >10% AR were observed. Maximum levels were in the range 11.6 to 45.7% AR after 0.25 to 2 days following treatment. By 30 days, maximum levels had declined to ≤5.2% AR. For gibberellins GA7, up to nine degradation components accounting for >10% AR were observed. Maximum levels were in the range 10.2 to 54.3% AR after 0.25 to 2 days following treatment. By 30 days, maximum levels had declined to ≤6.2% AR. Attempts were made to characterise the degradation components but due to their transient nature and fluctuating levels, this proved inconclusive. Ultimate degradation led to the formation of un-extracted soil residues and mineralisation to carbon dioxide.

The individual components gibberellins GA4 and gibberellins GA7 of the active substance gibberellins GA4/7 degraded rapidly and extensively in soil resulting in the formation of numerous degradation products. Due to their transient nature and fluctuating levels, attempts to identify these degradation products proved inconclusive.

Although several major metabolites of gibberellins GA4 and gibberellins GA7 were observed in soil, these are considered to be of no environmental concern due to the natural occurrence of the active substance and have therefore not been considered further.

2.12.1 STEP 1: Exclusion of degradation products of no concern

The active substance gibberellins GA4/7 contains two components (gibberellins GA4 and gibberellins GA7). Degradation of gibberellins GA4 and gibberellins GA7 in soil under aerobic conditions leads to the formation of numerous degradation products. However, due to the natural occurrence of the active substance, these metabolites are not considered to be of any environmental concern and have not been considered further

2.12.2 STEP 2: Quantification of potential groundwater contamination

Not required.

2.12.3 STEP 3: Hazard assessment – identification of relevant metabolites

Not required.

2.12.3.1STEP 3, Stage 1: screening for biological activity

Not required.

2.12.3.2STEP 3, Stage 2: screening for genotoxicity

Not required.

2.12.3.3STEP 3, Stage 3: screening for toxicity

Not required.

2.12.4 STEP 4: Exposure assessment – threshold of concern approach

Not required.

2.12.5 STEP 5: Refined risk assessment

Not required.

2.12.6 Overall conclusion

Degradation of the individual components gibberellins GA4 and gibberellins GA7 of the active substance gibberellins GA4/7 in soil under aerobic conditions leads to the formation of numerous degradation products. However, due to the natural occurrence of the active substance, these metabolites are not considered to be of any

environmental concern. Further consideration of their relevance in groundwater in accordance with the guidance document on the assessment of the relevance of metabolites in groundwater (SANCO/221/2000-rev.10 final 25 February 2003)[8] is therefore not required.

2.13 CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

The active substance gibberelline is not a mixture of isomers. Therefore, no information is presented or required

2.13.1 Identity and physical chemical properties

Not required.

2.13.2 Methods of analysis

Not required.

2.13.3 Mammalian toxicity

Not required.

2.13.4 Operator, Worker, Bystander and Resident exposure

Not required.

2.13.5 Residues and Consumer risk assessment

Not required.

2.13.6 Environmental fate

Not required.

2.13.7 Ecotoxicology

The ecotoxicologically relevant compound (animals and plants, and environment) is the parent compound, Gibberellins GA4/GA7, therefore consideration of isomers in the risk assessment is not required

2.14 RESIDUE DEFINITIONS

[8] Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC SANCO/221/200-rev.10-final 25 February 2003)

2.14.1 Definition of residues for exposure/risk assessment

Food of plant origin: none

Food of animal origin: none

Soil: GA4, GA7

Groundwater: GA4, GA7

Surface water: GA4, GA7

Sediment: GA4, GA7

Air: GA4, GA7

2.14.2 Definition of residues for monitoring

Food of plant origin: none

Food of animal origin: none

Soil: GA4, GA7

Groundwater: GA4, GA7

Surface water: GA4, GA7

Sediment: GA4, GA7

Air: GA4, GA7

Level 3

GIBBERELLINS (GA4, GA7)

3 PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1 BACKGROUND TO THE PROPOSED DECISION

3.1.1 Proposal on acceptability against the decision making criteria – Article 4 and annex II of regulation (EC) No 1107/2009

3.1.1.1 Article 4

		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	X		Gibberellins in Novagib hasve been assessed for uses *on apples and pears.*

3.1.1.2 Submission of further information

		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.	X		The risk assessment for aquatic organisms could not be finalized. A study with appropriate dose-response design is needed to determine toxicity of GA4/GA7 to aquatic plants *Myriophyllum spicatum* and to finalize the risk assessment.

3.1.1.3 Restrictions on approval				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.		X	
3.1.1.4 Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	X		
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.	X		Chronic exposure was calculated using LOQs as input values and ADI 0.3 mg/kg bw/d. With the current EFSA model PRIMo rev. 2, the chronic risk assessment ranges from 0.2 to 1.3% of the ADI. Thus, no unacceptable long-term exposure of consumers was identified. Since no ARfD was allocated, acute risk assessment was not calculated.

	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.			
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	X		Please see details under Level 2 point 2.3. EFFICACY: This summary applies to only one representative uses for plant protection product
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	X		Please see details under level 2 point 2.11.
Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	X		Please see details under level 1 point 1.3 and corresponding confidential Volume 4.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	X		No FAO specification
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted	X		No FAO specification
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which	X		Validated methods of analysis have been submitted for the determination of the gibberellins in the technical material as manufactured. Methods relied on high performance liquid chromatography coupled with UV detection

	are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.			(HPLC-UV) or a diode array detector (HPLC-DAD). The methods were considered acceptable. Please see details under level 2 point 2.5.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	X		Appropriate and accurately validated analytical methods for determination of GA4, GA7 residues were submitted. Please see details under level 2 point 2.5.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		The evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.
Impact on human health				
Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	X		The AOEL is based on the NOAEL of 300 mg/kg bw/day from the multigeneration toxicity study by applying the standard safety factor of 100 and an additional safety factor of 3 due to the missing of a developmental toxicity study in rats and corrected for 18% oral absorption. AOEL is 0.18 mg/kg bw/day. ARfD is not warranted The ADI is based on the NOAEL of 300 mg/kg bw/day from the multigeneration toxicity study by applying the standard safety factor of 100 and an additional safety factor of 10 due to use of a short term toxicity study and to general database weakness. ADI is 0.3 mg/kg bw/day. Please see details under Level 2 point 2.6.10.
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data		X	GA4/7 are not known to induce heritable mutations (Cat 1A) or to be regarded as if it induces heritable mutations (Cat 1B) in the germ cells of

	requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**			humans. Neither is it considered possible that GA3 may induce heritable mutations (Cat 2) in the germ cells of humans on the basis of negative results in in vitro and in vivo studies. Please see details under Level 2 point 2.6.4.
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**		X	No data provided.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.	-	-	
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of		X	According to the provided studies no classification regarding reproductive and developmental effects is proposed. Please see details under Level 2 point 2.6.6.

	Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**			
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			The evaluation on negligible exposure of GA4/7 is not necessary as GA4/7 is not proposed to be classified as toxic to reproduction category 1A or 1B.
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE ~~classified or proposed for classification~~ identified as having endocrine disrupting properties** in accordance with the provisions of point 3.6.5 in Annex II of Regulation (EC) No 1107/2009 ~~1272/2008, as carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties~~		x	Nor sufficiently investigated See Point 2.10.
~~ii)~~	~~It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **toxic for reproduction category 2 and** in addition the RMS considers the substance **has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties~~		~~x~~	~~*[Insert brief overall summary of consideration of toxic effects on endocrine organs here. Cross refer to level 2 as necessary]*~~ ~~*[If yes – cross refer to classification section and go to iii) immediately below.]*~~
ii~~i~~)	Linked to ~~either i) or ii) immediately~~ above identification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans			Inconclusive risk assessment on ED.

	and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Fate and behaviour in the environment				
Persistent organic pollutant (POP)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		X	The criterion for persistence (P) is not fullfield. The criterion for bioaccumulation is not fulfield. The criterion for long range transport is not fullfield. Please see details under level 2 point 2.8.
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		X	The criterion for persistence (P) is not fullfield. The criterion for bioaccumulation is not fulfield. The criterion for long range transport is not fullfield. Please see details under level 2 point 2.8.
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		X	The criterion for persistence (P) is not fullfield. The criterion for bioaccumulation is not fulfield. Please see details under level 2 point 2.8.
Ecotoxicology				
		Yes	No	
i	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or		X	The risk to birds, mammals, bees, other non-target arthropods, soil organisms, micro-organisms, methods for sewage treatment and non-target plants is acceptable following the proposed use of Novagib 10g/L SL in apples and pears. The risk assessment for aquatic organisms could not be finalized.

	synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.			
ii	It is considered that, ~~on the basis of the assessment of Community or internationally agreed test guidelines,~~ the substance **SHOULD BE identified as having endocrine disrupting properties** ~~**HAS** endocrine disrupting properties~~ that may cause adverse effects on non-target organisms in accordance with the provisions of point 3.8.2 in Annex II of Regulation (EC) No 1107/2009.			No decision can be made regarding endocrine disrupting properties of gibberellins GA4/GA7. Based on the available evidence from standard studies for non-target organisms, the EATS-modalities are not considered sufficiently investigated. The dataset is not sufficient to assess the ED properties of gibberellins GA4/GA7. Studies in line with guidelines OECD 455, OECD 458, OECD 456, OECD 231, OECD 229 are needed to conclude the assessment of endocrine disrupting properties of gibberellins GA4/GA7.
iii	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.	X		Applies to all uses.
iv	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	X		The acute oral and contact risk to bees is acceptable following the proposed use of Novagib 10g/L SL in apples and pears.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement	X		RESIDUES : Since $GA_{4/7}$ is naturally present in plants and background levels in apples and pears are similar to residue levels in treated apples and

	purposes.			pears residue definition is not required.
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		Please see details under level 2 point 2.8.6.

3.1.2 Proposal – Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution			

3.1.3 Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** If the active substance is not a micro-organism, in particular it is considered that: (a) the substance **should NOT be classified or proposed for classification** in accordance to Regulation (EC) No 1272/2008 as any of the following: — carcinogenic category 1A, 1B or 2, — mutagenic category 1A, 1B or 2, — toxic to reproduction category 1A, 1B or 2, — skin sensitiser category 1, — serious damage to eye category 1, — respiratory sensitiser category 1, — acute toxicity category 1, 2 or 3, — specific Target Organ Toxicant, category 1 or 2, — toxic to aquatic life of acute and chronic category 1 on the basis of appropriate standard tests, — explosive, — skin corrosive, category 1A, 1B or 1C; (b) it has **not been identified as priority substance under Directive 2000/60/EC**; (c) it is **not deemed to be an endocrine disruptor** in accordance to		X	The substance is proposed for classification Aquatic Acute 1 and Aquatic Chronic 3, based on active substance toxicity to aquatic macrophytes (*Myriophyllum spicatum*, LC_{50}<0.95 mg as/L, NOEC<0.95 mg a.s./L*).* Due to insufficient data set, no decision can be made regarding endocrine disrupting properties of gibberellins GA4/GA7.

	Annex II of Regulation (EC) No 1107/2009; (d) it **has no neurotoxic or immunotoxic effects**; (e) it **is not persistent** (half-life in soil is more than 60 days) or its **bio-concentration factor is lower than 100**. (f) it is a **semiochemical** and verifies points (a) to (d). Paragraph (e) doesn't apply to naturally occurring active substances. If the active substance is a micro-organism, in particular it is considered that at strain level the micro-organism has not demonstrated multiple resistance to anti-microbials used in human or veterinary medicine. If the active substance is a baculovirus, in particular it has not demonstrated adverse effects on non-target insects.			

3.1.4 List of studies to be generated, still ongoing or available but not peer reviewed

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1 Identity of the active substance or formulation				
/				
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
/				
3.1.4.3 Data on uses and efficacy				
/				
3.1.4.4 Data on handling, storage, transport, packaging and labelling				
/				

3.1.4.5 Methods of analysis				
/				
3.1.4.6 Toxicology and metabolism				
<u>RMS Proposal: ED properties of GA4/7:</u> -Output data from the ToxCast ER Bioactivity Model or Uterotrophic bioassay in rodents (OECD TG 440), -Hershberger bioassay in rats (OECD TG 441) -H295R steroidogenesis assay (OECD TG 456) and the aromatase assay (human recombinant OPPTS 890.1200) Conditionally: -Combined chronic toxicity and carcinogenicity study (OECD 451-3) -Extended one-eneration reproductive toxicity study (OECD 443)	All uses	x		
3.1.4.7 Residue data				
/				
3.1.4.8 Environmental fate and behaviour				

/				
3.1.4.9 Ecotoxicology				
Risk assessment of aquatic macrophytes could not be finalized. The submitted study on *Myriophyllum spicatum* was designed as a limit-test and does not give a definitive endpoint, but rather a value less than the tested concentration (<0.95 mg a.s./L). A study with appropriate dose-response design is needed to determine toxicity of GA4/GA7 to aquatic plants and to finalize the risk assessment.	All uses	x		
Assessment of endocrine disrupting properties regarding non-target organisms could not be finalized. Based on the available evidence from standard studies for non-target organisms, the EATS-modalities are not considered sufficiently investigated. The dataset is not sufficient to assess the ED properties of gibberellins GA4/GA7. Studies in line with guidelines OECD 455, OECD 458, OECD 456, OECD 231, OECD 229 are needed to conclude the assessment of endocrine disrupting properties of gibberellins GA4/GA7. If all tests are negative, this shows that gibberellins GA4/GA7 have no ED properties. However, if these tests show a positive result for at least one modality, additional testing might be needed in order to further investigate the adversity.	All uses	x		

3.1.5 Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	**Relevance in relation to representative use(s)**
RESIDUES: None	
EFFICACY: None	
FATE: None	
ECOTOX: 1. Risk to aquatic macrophytes. 2. Assessment of endocrine disrupting properties regarding non-target organisms.	All uses.
TOX: 3. Assessment of endocrine disrupting properties regarding mammals. 4. The Identity of batches used in the toxicological studies is not defined (only purity stated)	
PHYSCHEM: None	
ANALYTICAL METHODS: None	

3.1.6 Critical areas of concern

An issue is listed as a critical area of concern:
(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is

necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	**Relevance in relation to representative use(s)**
RESIDUES: None	
EFFICACY: None	
FATE: None	
ECOTOX: 5. Risk to aquatic macrophytes.	All uses.
TOX: None.	
PHYSCHEM: None	

3.1.7 Overview table of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)
All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use	Apples all uses	Pears all uses

Operator risk	Risk identified		
	Assessment not finalised	X[3]	X[3]
Worker risk	Risk identified		
	Assessment not finalised	X[3]	X[3]
Bystander risk	Risk identified		
	Assessment not finalised	X[3]	X[3]
Consumer risk	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial vertebrates	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised		
Risk to aquatic organisms	Risk identified	X[5]	X[5]
	Assessment not finalised	X[1,2]	X[1,2]
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached		
	Parametric value of 10µg/L[(a)] breached		
	Assessment not finalised		
Comments/Remarks			

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.
(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

3.1.8 Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	**Justification**

RESIDUES : None	
EFFICACY: None	
TOX: None	
FATE: None	
ECOTOX: None.	
PHYSCHEM: None	
ANALYTICAL METHODS: None	

3.1.9 Critical issues on which the Co RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	**Opinion of Co-RMS**	**Opinion of RMS**
RESIDUES : None		
EFFICACY: None		
FATE: None		
ECOTOX: None.		
TOX: DRAR not sent to the coRMS		

PHYSCHEM: None		
ANALYTICAL METHODS: None		

3.2 PROPOSED DECISION

RESIDUES: Yes., FATE: Yes. ECOTOX: Yes., PHYSCHEM, ANALYTICAL METHODS: Yes

It is proposed that:

[redacted]

3.3 RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPROVAL OR AUTHORISATION(S), AS APPROPRIATE

3.3.1 Particular conditions proposed to be taken into account to manage the risks identified

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

3.4 APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

General

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

Section identity, physical chemical and analytical methods

Section physico chemical properties

Guidance document on the interpretation of the transitional measures for the data requirements for chemical active substances and plant protection products according to regulation (EU) No 283/2013 and regulation (EU) No 284/2013 (SANTE/11509 /2013– rev. 5.2)

Guidance document for the generation of data on the physical, chemical and technical properties of plant protection products under regulation (EC) No. 1107/2009 of the eu parliament and council on placing plant protection products on the market.

Guidance on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008

Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (SANCO/2012/11251 rev. 4).

Section analytical methods

Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414. (SANCO/3029/99 rev.4).

Guidance document on pesticide residue analytical methods (SANCO/825/00 rev. 8.1).

Guidance document on analytical quality control and method validation procedures for pesticides residues analysis in food and feed (SANTE/11945/2015).

Guidelines for validation of analytical methods for non-agricultural pesticide active ingredients and products (SANCO/3030/99 rev.4.)

Section Data on application and efficacy

Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 Appendix II (SANCO/2012/11251).

Section Toxicology

Guidance on dermal absorption. EFSA Journal 2017;15(6):4873, 60 pp

Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, EFSA Journal 2014;12(10):3874

Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, SANTE-10832-2015 rev. 1.7, 24 January 2017

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(6):5311, 135 pp.

Section Residue and consumer risk assessment

Guidance document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) 283/2013 and Regulation (EU) No 284/2013 (SANCO/10181/2013– rev. 2, May 2013)

Section fate and behavior in environment

None.

Section ecotoxicology

Guidance Document on Risk Assessment for Birds and Mammals (EFSA Journal 2009; 7(12): 1438

Guidance document on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters in the context of Regulation (EC) No 1107/2009

Guidance Document on Terrestrial Ecotoxicology, as provided by the Commission Services (SANCO/10329/2002 rev.2 (final), October 17, 2002)

Guidance document on Regulatory Testing and Risk Assessment Procedures for Plant Protection Products with Non-target Arthropods, from the ESCORT 2 workshop, 2000

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(6):5311, 135 pp.

3.5 REFERENCE LIST

Section identity, physical chemical and analytical methods
None.

Section data on application and efficacy
None.

Section toxicology

Section residue and consumer risk assessment

None.

Section fate and behavior in environment

None.

Section ecotoxicology
None.

3.6 ANNEX 1 -APPENDIX E

Excel spreadsheets containing data used for assessment of endocrine disrupting properties is submitted separately.