Renewal Assessment Report

Cydia pomonella GV

Volume 1

Rev. 0 - 16 October 2020

Rapporteur Member State: Germany

Co-Rapporteur Member State: The Netherlands

Version history

When	What
16 October 2020	First version submitted to EFSA

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.

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Cydia pomonella GV

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 the renewal assessment report was prepared

1.1.1 Purpose for which the renewal assessment report was prepared

This renewal assessment report has been prepared in accordance with Commission Regulation (EC) No 844/2012 and Guidance Document SANCO/12545/2014 – rev. 2 in order to evaluate the application and the supplementary dossier submitted by the CpGV AIR4 Task Force represented by GAB Consulting GmbH and to allow a decision on the renewal of the approval of the active substance *Cydia pomonella* Granulovirus (CpGV).

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

According to Commission Regulation (EU) No 844/2012 Germany was assigned rapporteur Member State (RMS) and the Netherlands was assigned Co-rapporteur Member State (Co-RMS).

The Co-RMS had comments on the draft RAR, which were incorporated in the assessment before it was sent to EFSA.

1.1.3 EU Regulatory history for use in plant protection products

CpGV was re-evaluated under the 4th stage of the EU review programme of existing active substances according to Council Directive 91/414/EEC with Germany being the designated rapporteur Member State.

Andermatt Biocontrol GmbH and Probis GmbH together as a Task Force, Arysta LifeScience S.A.S. and Sipcam S.p.A. submitted each by November 2005 a dossier for Annex I inclusion of Council Directive 91/414/EEC:

Following a peer review organised by the European Commission CpGV was included in Annex I of Council Directive 91/414/EEC with Commission Directive 2007/6/EC, entering into force on 11 July 2008. According to Regulation (EU) No 540/2011 CpGV is deemed to have been approved under Regulation (EC) No 1107/2009 as well.

The overall conclusions of the evaluation of CpGV, as finalised by the Standing Committee on Plant Health on 7 May 2008, were provided in the Review Report (*Cydia pomonella* Granulovirus (Mexican isolate) SANCO/1548/08 – rev. Final 07 May 2008).
The peer review concluded that only uses as insecticide may be authorised. These conclusions were reached within the framework of the following uses, which were supported by the main data submitters:

- ➔ Control of pomiferous fruit and nut trees against *Cydia pomonella*

In agreement with Article 1 of Regulation (EC) No 844/2012 CpGV AIR4 Task Force submitted an

application to Germany as RMS and the Netherlands as Co-RMS notifying the intention to renew the existing approval of CpGV on 28 April 2016.

A supplementary dossier from CpGV AIR4 Task Force represented by the GAB Consulting GmbH was submitted on 28 October 2016.

1.1.4 Evaluations carried out under other regulatory contexts

The following evaluations are available:

- EFSA (European Food Safety Authority), 2011. Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2011 update). The EFSA journal 2011;9(12):2497.

- EFSA (European Food Safety Authority), 2017. Update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 7: suitability of taxonomic units notified to EFSA until September 2017. EFSA Journal 2018;16(1):5131.

1.2 Applicant information

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

Applicant: CpGV AIR4 Task Force
Consisting of:
Andermatt Biocontrol GmbH
Arysta LifeScience S.A.S
Serbios srl
Represented by APIS Applied Insect Science GmbH
Kurze Straße 3
21682 Stade
Germany

Contact Point: [redacted]

1.2.2 Producer or producers of the active substance

Confidential information, see Volume 4

1.2.3 Information relating to the collective provision of dossiers

The companies Andermatt Biocontrol GmbH, Arysta Life Science S.A.S. and Serbios srl have agreed on the formation of a Task Force in order to submit the dossier for the renewal of approval of the microorganism *Cydia pomonella* Granulovirus (CpGV) as an active substance in compliance with Regu-

lation (EU) No 844/2012 and Regulation (EC) 1107/2009. The Task Force has authorized the companies GAB Consulting GmbH, Ottenbecker Damm 10, 21684 Stade, Germany and GAB Consulting Spain S.L.U, Av Cortes Valencianas, n° 39, 8B, 46015Valencia, Spain to submit the application and the dossier for renewal of approval of the active substance *Cydia pomonella* Granulovirus (CpGV).

1.3 Identity of the micro-organism

1.3.1	**Name and species description, strain characterisation**	*Cydia pomonella* granulovirus (CpGV)
1.3.1.1	**Composition of material used for manufacturing of the formulated product**	
Andermatt Biocontrol GmbH Content of CpGV: 6.0 x 10^{13} granules/L min 6 × 10^{13} granules/L, max 12 × 10^{13} granules/L Arysta LifeScience S.A.S. Minimal CpGV concentration: 2.6 x 10^{13} granules/L Nominal CpGV concentration: 3.2 x 10^{13} granules/L Maximal CpGV concentration: 1.8 x 10^{14} granules/L. Serbios srl No own isolate is produced.		

1.3.1.2 Accession number in culture collection	Andermatt Biocontrol GmbH All isolates are deposited in the German Collection of Microorganisms and Cell Cultures (DSMZ), Inhoffen-straße 7B, D-38124 Braunschweig, Germany. Mexican isolate: Virus accession number: GV-0001 CpGV-V01: Virus accession number: GV-0003 CpGV-V03: Virus accession number: GV-0006 CpGV-V15: Virus accession number: GV-0013 CpGV-V22: Virus accession number: GV-0014 CpGV-V14: Virus accession number: GV-0015 CpGV-V45: Virus accession number: GV-0017 Arysta LifeScience S.A.S. All isolates are deposited in the German Collection of Microorganisms and Cell Cultures (DSMZ), Inhoffen-straße 7B, D-38124 Braunschweig, Germany. Mexican isolate: Virus accession number: GV-0002 CpGV-R5: Virus accession number: GV-0007

1.3.1.3 Scientific name and taxonomic grouping, i.e. family, genus, species, strain, serotype, pathovar or any other denomination relevant to the microorganism

Taxonomy	Organism: *Cydia pomonella* granulovirus (CpGV) Genus: Betabaculovirus Family: Baculoviridae
Indigenous or non-indigenous	*Cydia pomonella* granulovirus is naturally present in the environment.
Wild type	yes
Spontaneous or induced mutant*	No mutant
Genetically modified according to Directive 2001/18/EC*	Not genetically modified
* All known differences between the modified microorganism and the parent wild strain must be provided	

1.3.1.4 Test procedures and criteria used for identification

Isolate identification by Restriction Fragment Analysis (RFLP) or single nucleotide polymorphism (SNP)
Determination of the active ingredient by a standard bioassay with the target pest.

1.3.1.5	**Common name or alternative and superseded names and code names used during the development**	Codling moth granulovirus Granulosis virus of codling moth Apfelwickler-Granulosevirus Apfelwickler-Granulovirus Codling moth granulosis virus Laspeyresia pomonella GV Granulosis of Laspeyresia pomonella Carpocapsa pomonella GV CARPOVIRUSINE granulosis virus Virus de la Granulose du Carpocapse des Pommes et des Poires
1.3.1.6	**Relationship to known pathogens**	See 2.2.1
1.3.1.7	**Method of manufacture (synthesis pathway) of the active substance**	Confidential information, see Vol. 4
1.3.2	**Specification of the material used for manufacturing of formulated products**	Not applicable
1.3.3	**Content of the micro-organism**	Andermatt Biocontrol GmbH Content of CpGV: 6.0 x 10^{13} granules/L Arysta LifeScience S.A.S. Content of CpGV: 3.2 x 10^{13} granules/L Serbios srl No own isolate is produced.
1.3.4	**Identity and content of impurities, additives, contaminating micro-organisms**	
1.3.4.1	Significant impurities	none
1.3.4.2	Relevant impurities	none
1.3.4.3	Additives	none
1.3.4.4	Contaminating	Confidential information, see Vol. 4

	micro-organisms	
1.3.5	**Analytical profile of batches**	Confidential information, see Vol. 4

1.4 Information on the plant protection product

1.4.1	**Applicant**	Arysta LifeScience S.A.S.
1.4.2	**Producer of the plant protection product**	Confidential information, see Vol. 4
1.4.3	**Current, former and proposed trade names and development code numbers**	
Trade Name		CARPOVIRUSINE
Code Number		I1136ab / ARY-0453a-03 (initial EU dossier representative composition) I1136aa / ARY-0453a-04 (actual representative composition)

1.4.4	**Detailed quantitative and qualitative information on the composition of the plant protection product**	
1.4.4.1	Composition of the plant protection product	Confidential information, see Vol. 4
1.4.4.2	Information on the active substances	CpGV Mexican isolate Declared content of CpGV: 1×10^{13} granules/L Content of technical CpGV: 909 g/L (85.33 %) Content of contaminating micro-organism: *Bacillus cereus*: $< 1 \times 10^{7}$ CFU/g
1.4.4.3	Information on safeners, synergists and co-formulants	Confidential information, see Vol. 4
1.4.5	**Type and code of the plant protection product**	Suspensions concentrate (SC)
1.4.6	**Function**	Viral entomopathogen, functioning as a microbiological insecticide.
1.4.7	**Field of use envisaged**	Orcharding and home-gardening
1.4.8	**Effects on harmful organisms**	Very selective contact insecticide, protective – treatment at hatching of larvae, early-instar larvae of coding moth occur on the surface of the fruits and come in contact with the virus before entering into the fruit. After oral intake by the codling moth larvae, the granules are dissolved in the midgut and free virions are released which invade the midgut cells by fusion with the microvilli. After infection of the midgut epithelium, other tissues are invaded, e.g. fat body, epidermis, the tracheal matrix and Malpighian tubules. Although there is no precise description on the mode of action, this polyorganotropic disease most likely is caused by the large multiplication rate of the virus which is only possible by interference with the metabolism of the host cells. Most of the larvae continue to grow and after having reached the fifth stage, not managing to form pupae, turn white in colour until their death. The body of the insect liquefies and the virus is released into the environment where it can infect other codling moth larvae.

1.4.9	**Applicant**	Andermatt Biocontrol GmbH
1.4.10	**Producer of the plant protection product**	Confidential information, see Vol. 4
1.4.11	**Current, former and proposed trade names and development code numbers**	
Trade Name		MADEX
Code Number		none

1.4.12	**Detailed quantitative and qualitative information on the composition of the plant protection product**	
1.4.12.1	Composition of the plant protection product	Confidential information, see Vol. 4
1.4.12.2	Information on the active substances	CpGV Mexican isolate Declared content of CpGV-M: 3 x 10^{13} granules/L Content of technical active substance: 44.61% w/w, i.e. 513.01 g/L Content of contaminating micro-organism *Bacillus cereus*: < 1 × 10^{7} CFU/g
1.4.12.3	Information on safeners, synergists and co-formulants	Confidential information, see Vol. 4
1.4.13	**Type and code of the plant protection product**	Suspensions concentrate (SC)
1.4.14	**Function**	Viral entomopathogen, functioning as a microbiological insecticide.
1.4.15	**Field of use envisaged**	Orcharding and home-gardening
1.4.16	**Effects on harmful organisms**	very selective contact insecticide, protective – treatment at hatching of larvae, early-instar larvae of coding moth occur on the surface of the fruits and come in contact with the virus before entering into the fruit. After oral intake by the codling moth larvae, the granules are dissolved in the midgut and free virions are released which invade the midgut cells by fusion with the microvilli. After infection of the midgut epithelium, other tissues are invaded, e.g. fat body, epidermis, the tracheal matrix and Malpighian tubules. Although there is no precise description on the mode of action, this polyorganotropic disease most likely is caused by the large multiplication rate of the virus which is only possible by interference with the metabolism of the host cells. Most of the larvae continue to grow and after having reached the fifth stage, not managing to form pupae, turn white in colour until their death. The body of the insect liquefies and the virus is released into the environment where it can infect other codling moth larvae.

1.4.17 Applicant	Andermatt Biocontrol GmbH
1.4.18 Producer of the plant protection product	Confidential information, see Vol. 4
1.4.19 Current, former and proposed trade names and development code numbers	
Trade Name	MADEX-TWIN
Code Number	ABC-V22

1.4.20	**Detailed quantitative and qualitative information on the composition of the plant protection product**	
1.4.20.1	Composition of the plant protection product	Confidential information, see Vol. 4
1.4.20.2	Information on the active substances	Isolate CpGV-V22 Declared content of CpGV-V22: 3 x 10^{13} granules/L Content of technical CpGV-V22: 44.61% w/w, i.e. 513.01 g/L Content of contaminating micro-organism *Bacillus cereus*: < 1 × 10^{7} CFU/g
1.4.20.3	Information on safeners, synergists and co-formulants	Confidential information, see Vol. 4
1.4.21	**Type and code of the plant protection product**	Suspensions concentrate (SC)
1.4.22	**Function**	Viral entomopathogen, functioning as a microbiological insecticide.
1.4.23	**Field of use envisaged**	Orcharding and home-gardening
1.4.24	**Effects on harmful organisms**	Very selective contact insecticide, protective – treatment at hatching of larvae, early-instar larvae of coding moth occur on the surface of the fruits and come in contact with the virus before entering into the fruit. After oral intake by the codling moth larvae, the granules are dissolved in the midgut and free virions are released which invade the midgut cells by fusion with the microvilli. After infection of the midgut epithelium, other tissues are invaded, e.g. fat body, epidermis, the tracheal matrix and Malpighian tubules. Although there is no precise description on the mode of action, this polyorganotropic disease most likely is caused by the large multiplication rate of the virus which is only possible by interference with the metabolism of the host cells. Most of the larvae continue to grow and after having reached the fifth stage, not managing to form pupae, turn white in colour until their death. The body of the insect liquefies and the virus is released into the environment where it can infect other codling moth larvae.

1.4.25	**Applicant**	Serbios Srl
1.4.26	**Producer of the plant protection product**	Confidential information, see Vol. 4
1.4.27	**Current, former and proposed trade names and development code numbers**	
Trade Name		VIRGO
Code Number		SC0018GV

1.4.28	**Detailed quantitative and qualitative information on the composition of the plant protection product**	
1.4.28.1	Composition of the plant protection product	Confidential information, see Vol. 4
1.4.28.2	Information on the active substances	CpGV Mexican isolate Declared content of CpGV: 2 x 10^{13} granules/L Content of technical CpGV: 49.6 g/L (4 % w/w) Content of contaminating micro-organism *Bacillus cereus*: < 1 × 10^{7} CFU/g
1.4.28.3	Information on safeners, synergists and co-formulants	Confidential information, see Vol. 4
1.4.29	**Type and code of the plant protection product**	Suspensions concentrate (SC)
1.4.30	**Function**	Viral entomopathogen, functioning as a microbiological insecticide.
1.4.31	**Field of use envisaged**	Orcharding and home-gardening
1.4.32	**Effects on harmful organisms**	very selective contact insecticide, protective – treatment at hatching of larvae, early-instar larvae of coding moth occur on the surface of the fruits and come in contact with the virus before entering into the fruit. After oral intake by the codling moth larvae, the granules are dissolved in the midgut and free virions are released which invade the midgut cells by fusion with the microvilli. After infection of the midgut epithelium, other tissues are invaded, e.g. fat body, epidermis, the tracheal matrix and Malpighian tubules. Although there is no precise description on the mode of action, this polyorganotropic disease most likely is caused by the large multiplication rate of the virus which is only possible by interference with the metabolism of the host cells. Most of the larvae continue to grow and after having reached the fifth stage, not managing to form pupae, turn white in colour until their death. The body of the insect liquefies and the virus is released into the environment where it can infect other codling moth larvae.

1.5 Detailed uses of the plant protection product

1.5.1 Details of representative uses

GAP rev. 1, date: 2021-January-15

Active Substance:
CARPOVIRUSINE *Cydia pomonella* Granulovirus (CpGV, Mexican isolate)
MADEX *Cydia pomonella* Granulovirus (CpGV, Mexican isolate)
MADEX TWIN *Cydia pomonella* Granulovirus (CpGV-V22)
VIRGO *Cydia pomonella* Granulovirus (CpGV, Mexican isolate)

Crop and/or situation (a)	**Member State or Country**	**Product name**	**F G or I** (b)	**Pests or Group of pests controlled** (c)	**Preparation**		**Application**				**Application rate per treatment**			**PHI (days)** (m)	**Remarks**
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		Application				Application rate per treatment			PHI (days) (m)	Remarks
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
ome fruit (apple, pear, quince, nashi) Stone fruit (peach, apricot) Walnut	*EU*	CARPOVIRUSINE	*F*	Codling moth (*Cydia pomonella*) Oriental fruit moth (*Grapholita molesta*)	*SC*	1×10^{13} GV/L product	Foliar spray (tractor drawn)	BBCH 71-89	*10*	*10 days*	1 l product / ha / application	*1000*	1×10^{13} GV/ha	*1*	The application rate of 1 L/ha corresponds to 0.1 L/hL in 1000 L water/ha or 0.7 L/ha LWA (leaf wall area)
Pome fruit (apple, pear, quince, nashi) Stone fruit (peach, apricot) Walnut	*EU*	CARPOVIRUSINE	*Fn*	Codling moth (*Cydia pomonella*) Oriental fruit moth (*Grapholita molesta*)	*SC*	1×10^{13} GV/L product	Foliar spray (Knapsack sprayer)	BBCH 71-89	*10*	*10 days*	1 l product / ha / application	*1000*	1×10^{13} GV/ha	*1*	Home gardening; Max. tree height: 2 m; The application rate of 1 L/ha corresponds to 0.1 L/hL in 1000 L water/ha or 0.7 L/ha LWA (leaf wall area)
Pome fruit (apple, pear, quince, nashi, *Mespilus*) Walnut	EU	*MADEX*	F	Codling moth (*Cydia pomonella*)	*SC*	3×10^{13} GV/L product	Foliar spray (tractor drawn)	Before first larvae hatch from eggs*[1] (BBCH 71-89)	*10*	*6 days**[2]	0.1 l product / ha / application	*400-1200*	0.3×10^{13} GV/ha	-	The application rate of 0.1 L/ha corresponds to 0.0875 L/ha LWA (leaf wall area)
Pome fruit (apple, pear, quince, nashi) Walnut	EU	*MADEX*	Fn	Codling moth (*Cydia pomonella*)	*SC*	3×10^{13} GV/L product	Foliar spray (Knapsack sprayer)	Before first larvae hatch from eggs*[1] (BBCH 71-89)	*10*	*6 days**[2]	0.1 l product / ha / application	*400-1200*	0.3×10^{13} GV/ha	-	Home gardening Max. tree height: 2 m The application rate of 0.1 L/ha corresponds to 0.0875 L/ha LWA (leaf wall area)

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		Application				Application rate per treatment			PHI (days) (m)	Remarks
					Type (d-f)	Conc. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
Stone fruit (apricot, peach, nectarine, almond, plum)	*EU*	*MADEX TWIN*	F	Oriental fruit moth (*Grapholita molesta*)	*SC*	3×10^{13} GV/L	Foliar spray (tractor drawn)	Before first larvae hatch from eggs (BBCH 71-89)	*12*	*6-8*2*	0.1 l product / ha / application*3	*800*	0.3×10^{13} GV/ha	-	
Stone fruit (apricot, peach, nectarine, almond, plum)	*EU*	*MADEX TWIN*	F n	Oriental fruit moth (*Grapholita molesta*)	*SC*	3×10^{13} GV/L	Foliar spray (Knapsack sprayer)	Before first larvae hatch from eggs (BBCH 71-89)	*12*	*6-8*2*	0.1 l product / ha / application*3	*800*	0.3×10^{13} GV/ha	-	Home gardening
Pome fruit (apple, pear, quince, nashi) Walnut	*EU*	*VIRGO*	F	Codling moth (*Cydia pomonella*)	*SC*	2×10^{13} GV/L product	Foliar spray (tractor drawn)	BBCH 71-87	*6*	*7*	0.75 l product / ha / application	*1500-1700*4*	1.5×10^{13} GV/ha	*3*	Minimum dose rate: 0.5 L/ha; The application rate of 0.75 L/ha corresponds to 0.656 L/ha LWA (leaf wall area).

*1 First treatment 85 degree days after the first warm evening with flight activity. Zero point of development of the codling moth is 10°C.
*2 sunny days, counting 2 partially sunny days as 1 day
*3 This application rate of 0.1 L/ha corresponds to 0.0875 L/ha LWA (leaf wall area).
*4 The lower water volume should be used for lower trees, whereas the highest water amount is recommended for trees with a higher leaf area. In case of very expanded leaf area which requires more than 1500 L water/ha, a higher water volume can be applied, but the maximum rate of 15×10^{12} GV/ha must be respected.

(a) For crops, the EU and Codex classifications (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)
(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 is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(j) Growth stage range from first to last treatment (BBCH Monograph, Growth Stages of Plants, 1997,

(e) CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide (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	Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application (k) Indicate the minimum and maximum number of applications 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) PHI - minimum pre-harvest interval

1.5.2 Further information on representative uses

Cydia pomonella GV is a viral entomopathogen, functioning as a microbiological insecticide in orchards (professional and amateur gardening). There is development of resistance to CpGV in *C. pomonella* treated broadly with plant protection products based on this baculovirus.

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

Cydia pomonella GV is included in Annex IV of Regulation (EC) No 396/2005. Consequently, no maximum residue levels are set in food and feed. Also no action levels and no residue definitions are proposed or exist for *Cydia pomonella* GV in soil, water and air. Consequently, analytical methods for the determination of residues are not considered necessary.

1.5.4 Overview on authorisations in EU Member States

Cydia pomonella GV containing products are widely authorised in various European countries. For details please refer to documents D-2 of the individual company.

Table 1.5.4-1: Currently registered uses and registrations

Product / Code	CpGV isolate	Crop F/G	Country	Registration number	Product application rate per treatment (max)	Active substance application rate per treatment (max)	Number of treatments per season/crop	Active substance total dose/ha (max)
VIRGO	CpGV-M (Mexican isolate)	Apple, pear, quince, walnut nashi F	Italy	12113 dated 06-08-2004	500 ml/ha	1 × 1013	3	3 × 1013
Carpostop	CpGV-M (Mexican isolate)	Apple, pear, quince, walnut nashi F	Italy	12368 dated 09-12-2004	500 ml/ha	1 × 1013	3	3 × 1013
Carpo 600	CpGV-M (Mexican isolate)	Apple, pear, quince, walnut nashi F	Italy	14523 dated 23-12-2009	600 ml/ha	9.6 × 1012	3	2.88 × 1013
Style	CpGV-M (Mexican isolate)	Apple, pear, quince, walnut nashi F	Italy	16558 dated 05-12-2016	600 ml/ha	9.6 × 1012	3	2.88 × 1013

Product / Code	**CpGV isolate**	**Crop F/G**	**Country**	**Registration number**	**Product application rate per treatment (max)**	**Active substance application rate per treatment (max)**	**Number of treatments per season/crop**	**Active substance total dose/ha (max)**
MADEX	CpGV-M (Mexican isolate)	Pome trees F	France	2060064	0.1 L/ha	3×10^{12} GV/ha	3 treatments per generation	9×10^{12} GV/ha
MADEX 3	CpGV-M (Mexican isolate)	Pome trees F	Germany	4148-00	0.15 L/ha	4.5×10^{12} GV/ha	3 treatments per generation	1.35×10^{12} GV/ha
MADEX SC	CpGV-M (Mexican isolate)	Pome trees F	Greece	1878	0.1 L/ha	3×10^{12} GV/ha	3 treatments per generation	9×10^{12} GV/ha
MADEX	CpGV-M (Mexican isolate)	Apple, pear, quince, nuts, nashi F	Italy	10327	0.08-0.12 L/ha	3.6×10^{12} GV/ha	3 treatments per generation	10.8×10^{12} GV/ha
MADEX 3	CpGV-M (Mexican isolate)	Apple, pear F	Spain	20.038	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX 3	CpGV-M (Mexican isolate)	Apple, pear F	Denmark	404-7	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX	CpGV-M (Mexican isolate)	Apple, pear F	Finnland	3054	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX	CpGV-M (Mexican isolate)	Apple, pear F	Slovakia	11-05-1184	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX	CpGV-M (Mexican isolate)	Apple, pear F	Portugal	0169	0.1 L/ha	3×10^{12} GV/ha	Max 6 treatments per year	1.8×10^{13} GV/ha

Product / Code	CpGV isolate	Crop F/G	Country	Registration number	Product application rate per treatment (max)	Active substance application rate per treatment (max)	Number of treatments per season/crop	Active substance total dose/ha (max)
MADEX	CpGV-M (Mexican isolate)	Pome fruits, walnuts F	Hungary	02.5/1156/7/2009	0.1 L/ha	3×10^{12} GV/ha	Max 8 treatments per year	2.4×10^{13} GV/ha
MADEX 100	CpGV-V01	Pome fruits F	Italy	13859	0.08-0.12 L/ha	3.6×10^{12} GV/ha	n.a.	n.a.
MADEX PLUS	CpGV-V01	Pome fruits F	The Netherlands	13302 N	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX TWIN	CpGV-V22	Pome fruits, stone fruits, walnuts F	France	2140238	0.1 L/A	3×10^{12} GV/ha	Max 9-12 treatments per year	3.6×10^{13} GV/ha
MADEX TWIN	CpGV-V22	Pome fruits, stone fruits F	Bulgaria	01327	0.1 L/A	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADEX TWIN	CpGV-V22	Pome fruits, stone fruits F	Italy	16415	0.1 L/A	3×10^{12} GV/ha	Max 9-12 treatments per year	3.6×10^{13} GV/ha
MADEX TWIN	CpGV-V22	Pome fruits, stone fruits, walnuts F	Spain	ES-00182	0.1 L/A	3×10^{12} GV/ha	Max 9-12 treatments per year	3.6×10^{13} GV/ha
MADEX TWIN	CpGV-V22	Pome fruits F	Austria	Under evaluation	0.1 L/A	3×10^{12} GV/ha	n.a.	n.a.
MADEX TOP	CpGV-V15	Pome fruits F	Greece	14.474	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADEX PRO	CpGV-V15	Pome fruits, walnuts F	France	2130175	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE	CpGV-	Pome	Italy	16221	0.1 L/ha	3×10^{12}	3-4	3 ×

Product / Code	CpGV isolate	Crop F/G	Country	Registration number	Product application rate per treatment (max)	Active substance application rate per treatment (max)	Number of treatments per season/crop	Active substance total dose/ha (max)
X TOP	V15	fruits F				GV/ha	treatments per generation	10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits, walnuts F	Spain	ES-00086	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	Czech Republic	5059-0	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	Austria	3592	0.1 L/ha	3×10^{12} GV/ha	Max. 6 treatments per year	1.8×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	Slovakia	Under evaluation	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	The Netherlands	Under evaluation	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	Bulgaria	01309	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X MAX	CpGV-V03	Apple, pear F	Belgium	10147P/B	0.15 L/ha	4.5×10^{12} GV/ha	3 treatments per generation	2.7×10^{13} GV/ha
MADE X MAX	CpGV-V03	Pome fruits F	Germany	006903-00	0.15 L/ha	4.5×10^{12} GV/ha	Max 10 treatments per year	4.5×10^{13} GV/ha
MADE X MAX	CpGV-V03	Pome fruits F	Poland	R-11/2012 wu	0.15 L/ha	4.5×10^{12} GV/ha	Max 10 treatments per year	4.5×10^{13} GV/ha
MADE X MAX	CpGV-V03	Pome fruits F	Slovenia	34330-50/12/8	0.15 L/ha	4.5×10^{12} GV/ha	Max 10 treatments per year	4.5×10^{13} GV/ha
MADE X MAX	CpGV-V03	Pome fruits	Austria	3316	0.15 L/ha	4.5×10^{12} GV/ha	Max 6 treatments	2.7×10^{13} GV/ha

Product / Code	CpGV isolate	Crop F/G	Country	Registration number	Product application rate per treatment (max)	Active substance application rate per treatment (max)	Number of treatments per season/crop	Active substance total dose/ha (max)
		F					per year	
MADEX	CpGV-M (Mexican isolate)	Pome trees F	France	2060064	0.1 L/ha	3×10^{12} GV/ha	3 treatments per generation	9×10^{12} GV/ha
MADEX 3	CpGV-M (Mexican isolate)	Pome trees F	Germany	4148-00	0.15 L/ha	4.5×10^{12} GV/ha	3 treatments per generation	1.35×10^{12} GV/ha
MADEX SC	CpGV-M (Mexican isolate)	Pome trees F	Greece	1878	0.1 L/ha	3×10^{12} GV/ha	3 treatments per generation	9×10^{12} GV/ha
MADEX	CpGV-M (Mexican isolate)	Apple, pear, quince, nuts, nashi F	Italy	10327	0.08-0.12 L/ha	3.6×10^{12} GV/ha	3 treatments per generation	10.8×10^{12} GV/ha
MADEX 3	CpGV-M (Mexican isolate)	Apple, pear F	Spain	20.038	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX 3	CpGV-M (Mexican isolate)	Apple, pear F	Denmark	404-7	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX	CpGV-M (Mexican isolate)	Apple, pear F	Finnland	3054	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX	CpGV-M (Mexican isolate)	Apple, pear F	Slovakia	11-05-1184	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX	CpGV-M (Mexican isolate)	Apple, pear F	Portugal	0169	0.1 L/ha	3×10^{12} GV/ha	Max 6 treatments per year	1.8×10^{13} GV/ha

Product / Code	CpGV isolate	Crop F/G	Country	Registration number	Product application rate per treatment (max)	Active substance application rate per treatment (max)	Number of treatments per season/crop	Active substance total dose/ha (max)
MADEX	CpGV-M (Mexican isolate)	Pome fruits, walnuts F	Hungary	02.5/1156/7/2009	0.1 L/ha	3×10^{12} GV/ha	Max 8 treatments per year	2.4×10^{13} GV/ha
MADEX 100	CpGV-V01	Pome fruits F	Italy	13859	0.08-0.12 L/ha	3.6×10^{12} GV/ha	n.a.	n.a.
MADEX PLUS	CpGV-V01	Pome fruits F	The Netherlands	13302 N	0.1 L/ha	3×10^{12} GV/ha	n.a.	n.a.
MADEX TWIN	CpGV-V22	Pome fruits, stone fruits, walnuts F	France	2140238	0.1 L/A	3×10^{12} GV/ha	Max 9-12 treatments per year	3.6×10^{13} GV/ha
MADEX TWIN	CpGV-V22	Pome fruits, stone fruits F	Bulgaria	01327	0.1 L/A	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADEX TWIN	CpGV-V22	Pome fruits, stone fruits F	Italy	16415	0.1 L/A	3×10^{12} GV/ha	Max 9-12 treatments per year	3.6×10^{13} GV/ha
MADEX TWIN	CpGV-V22	Pome fruits, stone fruits, walnuts F	Spain	ES-00182	0.1 L/A	3×10^{12} GV/ha	Max 9-12 treatments per year	3.6×10^{13} GV/ha
MADEX TWIN	CpGV-V22	Pome fruits F	Austria	Under evaluation	0.1 L/A	3×10^{12} GV/ha	n.a.	n.a.
MADEX TOP	CpGV-V15	Pome fruits F	Greece	14.474	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADEX PRO	CpGV-V15	Pome fruits, walnuts F	France	2130175	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE	CpGV-	Pome	Italy	16221	0.1 L/ha	3×10^{12}	3-4	3 ×

Product / Code	CpGV isolate	Crop F/G	Country	Registration number	Product application rate per treatment (max)	Active substance application rate per treatment (max)	Number of treatments per season/crop	Active substance total dose/ha (max)
X TOP	V15	fruits F				GV/ha	treatments per generation	10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits, walnuts F	Spain	ES-00086	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	Czech Republic	5059-0	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	Austria	3592	0.1 L/ha	3×10^{12} GV/ha	Max. 6 treatments per year	1.8×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	Slovakia	Under evaluation	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	The Netherlands	Under evaluation	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X TOP	CpGV-V15	Pome fruits F	Bulgaria	01309	0.1 L/ha	3×10^{12} GV/ha	Max 10 treatments per year	3×10^{13} GV/ha
MADE X MAX	CpGV-V03	Apple, pear F	Belgium	10147P/B	0.15 L/ha	4.5×10^{12} GV/ha	3 treatments per generation	2.7×10^{13} GV/ha
MADE X MAX	CpGV-V03	Pome fruits F	Germany	006903-00	0.15 L/ha	4.5×10^{12} GV/ha	Max 10 treatments per year	4.5×10^{13} GV/ha
MADE X MAX	CpGV-V03	Pome fruits F	Poland	R-11/2012 wu	0.15 L/ha	4.5×10^{12} GV/ha	Max 10 treatments per year	4.5×10^{13} GV/ha
MADE X MAX	CpGV-V03	Pome fruits F	Slovenia	34330-50/12/8	0.15 L/ha	4.5×10^{12} GV/ha	Max 10 treatments per year	4.5×10^{13} GV/ha
MADE X MAX	CpGV-V03	Pome fruits	Austria	3316	0.15 L/ha	4.5×10^{12} GV/ha	Max 6 treatments	2.7×10^{13} GV/ha

Product / Code	**CpGV isolate**	**Crop F/G**	**Country**	**Registration number**	**Product application rate per treatment (max)**	**Active substance application rate per treatment (max)**	**Number of treatments per season/crop**	**Active substance total dose/ha (max)**
		F					per year	
CARPOVIRUSINE 2000 / I1136aa	CpGV-M (Mexican isolate)	Pome fruits, Stone fruits, Walnut F	FR	9800076	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE GARDEN / I1136aa	CpGV-M (Mexican isolate)	Pome fruits, Stone fruits, Walnut F	FR	2150851	0.1 mL/m^2	1×10^{9} GV/m^2	10 / 10	10×10^{9} GV/m^2
CARPOVIRUSINE 2000 J / I1136aa	CpGV-M (Mexican isolate)	Pome fruits, Stone fruits, Walnut F	FR	2160620	0.1 mL/m^2	1×10^{9} GV/m^2	10 / 10	10×10^{9} GV/m^2
CARPOVIRUSINA / I1136aa	CpGV-M (Mexican isolate)	Pome fruits, Stone fruits, *Walnut* F	ES	20.010	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE PLUS / I1136aa	CpGV-M (Mexican isolate)	Pome fruits, Stone fruits, Walnut F	IT	10952	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE 2000 SC / I1136aa	CpGV-M (Mexican isolate)	Pome fruits, Stone fruits, Walnut F	GR	14545	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE / I1136aa	CpGV-M (Mexican isolate)	*Pome fruits, Stone fruits, Walnut F*	*PT*	*In evaluation*	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV / ha
CARPOVIR	CpGV-M	Pome fruits	CZ	4706-1	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13}

Product / Code	CpGV isolate	Crop F/G	Country	Registration number	Product application rate per treatment (max)	Active substance application rate per treatment (max)	Number of treatments per season/crop	Active substance total dose/ha (max)
USINE / I1136aa	(Mexican isolate)	F						GV / ha
CARPOVIR USINE / I1136aa	CpGV-M (Mexican isolate)	Pome fruits F	HU	02.5/11051-1/2010	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV / ha
CARPOVIR USINE SUPER SC / I1136aa	CpGV-M (Mexican isolate)	Pome fruits F	PL	R-12/2006	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV / ha
CARPOVIR USINE / I1136aa	CpGV-M (Mexican isolate)	Pome fruits F	SI	34330-1/2012/5	1 L/ha	1×10^{13} GV/ha	3 / 3	3×10^{13} GV / ha
CARPOVIR USINE / I1136aa	CpGV-M (Mexican isolate)	Pome fruits F	BE	8615P/B	1 L/ha (0.7 L/ha of leaf wall area)	1×10^{13} GV/ha	10 / 10	10×10^{13} GV / ha
CARPOVIR USINE PLUS / I1136aa	CpGV-M (Mexican isolate)	Pome fruits F	NL	11819 N	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV / ha
CARPOVIR USINE / I1136aa	CpGV-M (Mexican isolate)	Pome fruits F	RO	2792	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV / ha
CARPOVIR USINE / I1136aa	CpGV-M (Mexican isolate)	Pome fruits F	DE	ZV1 007135-00/00	1 L/ha (0.5 L/ha and m crown height)	1×10^{13} GV/ha	10 / 10	10×10^{13} GV / ha
CARPOVIR	CpGV-M	Pome fruits	AT	2570	1 L/ha	1×10^{13} GV/ha	6 / 6	6×10^{13}

Product / Code	**CpGV isolate**	**Crop F/G**	**Country**	**Registration number**	**Product application rate per treatment (max)**	**Active substance application rate per treatment (max)**	**Number of treatments per season/crop**	**Active substance total dose/ha (max)**
USINE / I1136aa	(Mexican isolate)	F						GV / ha
CARPOVIR USINE / I1136aa	CpGV-M (Mexican isolate)	Pome fruits F	UK	MAPP 15243	1 L/ha	1×10^{13} GV/ha	3 / 3	3×10^{13} GV / ha
CARPOVIR USINE / I1136aa	CpGV-M (Mexican isolate)	Pome fruits F	SK	12-05-1291	1 L/ha	1×10^{13} GV/ha	3 / 3	3×10^{13} GV / ha
CARPOVIR USINE / I1136aa	CpGV-M (Mexican isolate)	*Pome fruits, Stone fruits, Walnut F*	*BG*	*under evaluation*	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIR USINE EVO2 / I1137aa	CpGV-R5	Pome fruits, *Stone fruits*, *Plums,* Walnut F	FR	2120081	1 L/ha	1×10^{13} GV/ha	3 / 3	10×10^{13} GV/ha
CARPOVIR USINE EVO2 / I1137aa	CpGV-R5	Pome fruits, *Stone fruits*, *Plums,* Walnut F	ES	25.820	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIR USINE EVO2 / I1137aa	CpGV-R5	Pome fruits, *Stone fruits*, *Plums,* Walnut F	IT	15598	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIR USINE EVO2 / I1137a	CpGV-R5	Pome fruits, *Stone fruits*, *Plums,*	GR	14414	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha

Product / Code	**CpGV isolate**	**Crop F/G**	**Country**	**Registration number**	**Product application rate per treatment (max)**	**Active substance application rate per treatment (max)**	**Number of treatments per season/crop**	**Active substance total dose/ha (max)**
a		Walnut F						
CARPOVIRUSINE EVO2 / I1137aa	CpGV-R5	Pome fruits, *Stone fruits*, *Plums,* Walnut F	HR	UP/I-320-20/13-01/96	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE EVO2 / I1137aa	CpGV-R5	*Pome fruits, Stone fruits, Plums, Walnut F*	*PT*	*under evaluation*	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE EVO2 / I1137ab	CpGV-R5	Pome fruits F	DE	ZV1 007748-00/00	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE EVO2 / I1137ab	CpGV-R5	Pome fruits F	UK	MAPP 17565	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE EVO2 / I1137ab	CpGV-R5	Pome fruits F	NL	15051 N	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE EVO2 / I1137ab	CpGV-R5	*Pome fruits F*	*AT*	*under evaluation*	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha
CARPOVIRUSINE EVO2 / I1137ab	CpGV-R5	*Pome fruits F*	*BE*	*under evaluation*	1 L/ha	1×10^{13} GV/ha	10 / 10	10×10^{13} GV/ha

Level 2

Cydia pomonella GV

2 Summary of active substance hazard and of product risk assessment

2.1 Identity

Virus
Cydia pomonella Granulovirus is naturally present in the environment. It is no mutant and not genetically modified. For the first inclusion of CpGV only the Mexican isolate was evaluated. Several additional isolates were evaluated according to the "Guidance Document SANCO/0253/2008 on the assessment of new isolates of baculovirus species already included in Annex I of Council Directive 91/414" and added to Appendix III of the Review Report.
Two new isolates, CpGV-V14 and CpGV-V45, were evaluated for the renewal. For CpGV-V14 a 5-batch analysis for *Salmonella* according to the requirements in SANCO/12116/2012 is missing. For CpGV-V45 clarification regarding the content of the virus in technical active is required. For CpGV-M from Arysta a 5-batch analysis with respect to the content of CpGV in technical microbial active not older than 5 years is missing.

Plant protection products

CARPOVIRUSINE

CARPOVIRUSINE is a suspension concentrate (SC) microbial plant protection product. The CFU content of the product is 1×10^{13} granules/L. The content of technical CpGV as manufactured is 909 g/L.

While RMS was still evaluating the dossier the member state NL prepared a draft equivalence report for the strains CpGV-M and CpGV-R5 (March 2019). The production process for CpGV has been altered in comparison to the RAR leading to a higher content of CpGV in the technical concentrate. The studies and information provided for assessment of the equivalence should also be provided to RMS so that it can be described in a revised RAR. Additionally, the composition of the product Carpovirusine should be revised by the applicant taking the higher content of CpGV in the technical concentrate into account.

MADEX

MADEX is a suspension concentrate (SC) microbial plant protection product containing a nominal content of 3×10^{13} granules/L corresponding to 44.61% (w/w) of CpGV Mexican isolate (virus accession number: GV-0001). The active ingredient has to be standardised by bioassays and not by weight. The composition of the product Madex has been corrected (see Vol. 4 Andermatt).

Sufficient number of batch analyses are missing for *Bacillus cereus.*

MADEX TWIN

MADEX TWIN contains the same components as MADEX, with the only exception that another virus isolated is used (CpGV-V22, virus accession number: GV-0014). The two isolates can be distinguished by molecular genetic methods or by their infectivity towards some *C. pomonella* populations which are resistant to the isolate CpGV-M used in MADEX, but susceptible to the isolated CpGV-V22 used in MADEX TWIN. All other product components are identical.

The CpGV aqueous virus slurry has a content of the active ingredient CpGV of 3.0×10^{13} granules/L.

MADEX/MADEX TWIN
Safety data sheets for two co-formulants are missing.

VIRGO

VIRGO is a suspension concentrate (SC) microbial plant protection products containing a nominal content of 2 x 10^{13} granules/L corresponding to 4% (w/w) of CpGV Mexican isolate.

Sufficient number of batch analyses are missing for contaminating micro-organisms including *Bacillus cereus*. Clarification is needed regarding the content of CpGV in the product VIRGO.

Content of contaminating micro-organism *Bacillus cereus*
For all products the content of contaminating micro-organism *Bacillus cereus* shall be $< 1 \times 10^7$ CFU/g.

2.2 Biological properties

2.2.1 Summary of biological properties of the active substance

Origin and natural occurrence

Cydia pomonella Granulovirus (CpGV) belongs to the group of baculoviruses. Baculoviruses are ubiquitous in the environment, their prevalence depending on the frequency of occurrence of their arthropod hosts (OECD, 2002). Their geographic distribution usually corresponds to the distribution of their hosts. Baculoviruses and CpGV in particular have been used for decades as plant protection products to control diverse pest insects.

The CpGV-M isolate which is commonly used for the control of the codling moth *C. pomonella* in different European countries and in the US was originally isolated in 1963 from diseased insects on apple and pear trees found in Mexico (near Valle de Allende, Chihuahua; OECD, 2002 and references therein). The Mexican isolate (CpGV-M) is genetically heterogeneous. It consists of a mixture of similar genotypes, which differ in the presence or absence of insertions or deletions or by point mutations. Genetically homogenous strains are very difficult to obtain and even not desired to account for variations in host susceptibility.

As other CpGV isolates, CpGV-V14 is infective to *C. pomonella* and to some extend to *Cryptophlebia leucotreta*, but is in contrast to other isolates not infective to the closely related tortricid species *Grapholita molesta.* The isolate does not have any phenotypic characteristics differing from the typical description of the species. It differs from CpGV-M in the ability to break the resistance of *C. pomonella* populations that are resistant to CpGV-M and other CpGV-M like isolates. The new isolate CpGV-V14 does not contain genetic modifications.

The isolate CpGV-V15 has been isolated from *C. pomonella* larvae and does not have any characteristics differing from the typical description of the species (Kessler, 2010a). CpGV-V15 differs from CpGV-M only in the ability to break the resistance of *C. pomonella* populations that are resistant to CpGV-M (Jehle and Eberle, 2009a).

The new isolate CpGV-V22 was obtained from infested *C. pomonella* (Kessler, 2010b). Genetically, CpGV-V22 is closely related to CpGV-M and belongs to the same genome type as CpGV-M (Jehle and Eberle, 2009b). In contrast to CpGV-M and other CpGV isolates, CpGV-V22 is infective to larvae of the oriental fruit moth, *Grapholita molesta* (Tortricidae). Otherwise, CpGV-V22 does not have any other characteristics differing from the typical description of the species and the representative isolate CpGV-M.

As other CpGV isolates, the new isolate CpGV-V45 is infective to *C. pomonella* and *Grapholita molesta.* The isolate does not have any phenotypic characteristics differing from the typical description of the species. It differs from CpGV-M in the ability to break the resistance of *C. pomonella* populations that are resistant to CpGV-M and other CpGV-M like isolates. The new isolate CpGV-V45 does not contain genetic modifications.

The new isolate CpGV-V03 has been "conventionally" selected and does not have any characteristics differing from the typical description of the species. CpGV-V03 differs from CpGV-M only in the ability to break the resistance of *C. pomonella* populations that are resistant to CpGV-M.

The new isolate CpGV-V01 (CpGV-Madex Plus) was selected from the CpGV-M isolate used in MADEX (Kessler, 2008a; Jehle, 2006). CpGV-V01 shows high efficacy against *C. pomonella* populations who are resistant against CpGV-M, comparable to the efficacy of the original MADEX against susceptible *C. pomonella*. The efficacy of CpGV-V01 and CpGV-M against susceptible populations is similar.

The isolate CpGV-R5 was obtained by selection on *C. pomonella* larvae that are highly resistant against the Mexican isolate CpGV-M. CpGV-R5 is able to overcome resistance in *C. pomonella* populations that are resistant to CpGV-M.

Target organisms

The target organism of all CpGV isolates is the codling moth *Cydia pomonella*. The target organisms of the new isolate CpGV-R5 of Arysta LifeScience S.A.S, as well as of the new isolates CpGV-V22 and CpGV-V45 of Andermatt Biocontrol AG is also the oriental fruit moth, *Grapholita molesta*.

Mode of action

The mode of action of CpGV is a bi-phasic infection process of the larval stages of *C. pomonella* and *G. molesta*. After oral ingestion of viral occlusion bodies, the virus replicates in the midgut cells (primary infection) and then infection is spread via non-occluded viruses to other body tissues (secondary infection) leading to the insect's death. The body of the insect liquefies and the virus is released into the environment where it can infect other codling moth larvae. The incubation period is independent of the dose of virus consumed by the insect. The various larval stages of the codling moth show different susceptibility: first-instar larvae are more sensitive to infection, and the tolerance increases with age until reaching its maximum at the fourth stage. Some of the larvae with late infection continue to grow but, after having reached the fifth stage, do not manage to form pupae.

Host specificity range and effects on species other than the target harmful organism

Baculoviruses have been found only in arthropods, particularly in members of Lepidoptera (mainly), Hymenoptera (few) and Diptera (very few). No member of this family is known to infest vertebrates (for more details, see section 2.6) or plants. Granuloviruses are reported only from lepidopteran hosts, however, their host range is mostly restricted to a single species (OECD, 2002). CpGV is restricted in its infectivity to very few hosts of the tortricid family of the Lepidoptera. CpGV acts highly specific against larvae of the codling moth *Cydia pomonella* and some isolates can infest the oriental fruit moth *Grapholita molesta* or the plum fruit moth *Grapholita funebrana*. Besides, cross transmission experiments have also revealed alternative tortricid hosts like the pea moth *Laspeyresia nigricana* (= *Cydia nigricana*) and the European pine shoot moth *Rhyacionia buoliana* (Gröner, 1986 and references therein) as well as the false codling moth *Cryptophlebia leucotreta* (Fritsch *et al.*, 1990).

Development stages/life cycle of the micro-organism

The natural route of infection is the peroral ingestion of viral occlusion bodies by larvae. In the alkaline environment of the midgut (pH > 9.5), the occlusion bodies dissolve rapidly and occlusion-derived virions (ODV's) are released (Evans and Harrap, 1982; OECD, 2002). The ODV's pass through the peritrophic membrane (PM), a proteinaceous-chitinaceous layer which is secreted by the midgut cells to protect the midgut epithelium from direct contact with ingested material. After attachment to the microvilli of the midgut epithelium, the nucleocapsids enter the cell lumen either via fusion of the virion envelope with the epithelial membrane or by viropexis. The nucleocapsids are transported, most likely under involvement of the cellular microtubular structures, to the nucleus and become uncoated at the nuclear pore or within the nucleus where the viral DNA is released and DNA expression and replication is initiated (OECD, 2002). Initial replication produces non-occluded virus

particles to hasten the invasion of the host insect (Copping, 1998). By exocytosis the newly formed virions get to the hemolymph and from there into various tissues of the organism. In the cells of the fat body, hypodermis, Malpighian tubules and tracheal matrix, free virus rods, with and without developmental membrane, partly encapsulated rods and capsules have been observed (Bilimoria, 1986). After cell lysis a large number of occluded CpGV will be set free which are able to infest new hosts.

The occlusion body protects the virion and makes it quite stable at moderate and low temperatures, in soil and water, and resistant to various chemicals. Because of their resistance to environmental conditions occlusion bodies will retain their infectivity for long periods, for example 20 years stored as dry powders or in flame-sealed glass tubes (Evans and Harrap, 1982 and references therein). Viruses stored as intact occlusion bodies may retain activity for several years in storage in the dark at 4°C (Jaques, 1977 and references therein) whereas virions in hemolymph or released from occlusion bodies retain activity for much shorter periods.

Infectiveness, dispersal and colonisation ability

Effects of sunlight
Sunlight is considered the most important factor contributing to the inactivation of viral occlusion bodies. Huber (1982) showed that *Cydia pomonella* GV applied to apple leaves in the field exhibited a half-life of 15 sunshine hours. Steineke (2004) calculated the half-life of CpGV in apple orchards to around 52.2 sunlight hours.

There is considerable evidence that it is the ultraviolet portion of sunlight that inactivates CpGV and other insect viruses (Krieg *et al.*, (1981). However, short-wave UV light (254 nm) has a considerably higher germicidal effect than long-wave UV light (285-380 nm).

It is generally well known that most of the CpGV applied with a treatment is inactivated rather quickly by UV-irradiation with a half-life of about two days (Kienzle *et al.*, 2003 and references therein). Thus, frequent treatments are believed to be inevitable for CpGV. However, at least two studies showed, that a small part of the CpGV persists for much longer time in the orchard (Kienzle *et al.*, 2003 and references therein). Laboratory findings indicate that the UV-inactivation of CpGV curve is bi-shaped. This means, that most of the CpGV (about 99%) is inactivated very fast, a small part, however, is subjected to a much lower inactivation (Kienzle *et al.*, 2003 and references therein).

Forms of irradiation other than UV and a part of the visible spectrum appear to have little effect on insect viruses (Jaques, 1977 and references therein).

Effects of temperature
Virus suspensions or dried powders remain generally active for long periods if they are kept at low temperatures. Suspensions of *Cydia pomonella* GV stored at 5-8°C did not lose any activity during more than two years of storage. Multiple freeze-thawing of granuloviruses does not cause a significant loss of activity (Jaques, 1977 and references therein) indicating that repeated freezing and thawing of a virus in the field environment would not affect its activity appreciably.

Several studies indicate that baculoviruses withstand temperatures up to about 40°C in the field for at least short periods (Jaques, 1977 and references therein). However, exposure to higher temperatures causes inactivation. Results of several studies show that a 10-minute exposure to temperatures of 70-80°C would be expected to inactivate an insect virus. The CpGV formulation Granupom becomes biologically unstable and loses its efficacy if stored at temperatures above 54°C for more than 14 days (Gröner *et al.*, 1990).

Effects of humidity
Several studies indicate that humidity does not show a direct influence on viral stability (Jaques, 1977 and references therein). However, there may be an indirect influence by affecting chemical action on the virus and by increasing the inactivation rate by sunlight.

Effects of substrate
Naturally, virus deposits on leaves/fruits on the inside of the foliage canopy are more protected than those of the periphery. Certain substances have negative impacts on the stability of viruses. Leaf exudates may produce alkaline layers of pH up to 10.1 and high concentrations of metallic ions (Jaques, 1977 and references therein; Evans and Harrap, 1982 and references therein). However, these observations do not exist for CpGV on fruit trees.

Baculoviruses may persist in soil for longer periods. However, the pH of the soil may affect persistence of viruses (Jaques, 1977 and references therein): the lower the pH, the more rapidly the virus is inactivated (Thomas *et al.*, 1973).

While it is known that most viruses in intact occlusion bodies are reasonable stable in aqueous suspension, little is known of their persistence in natural aquatic environment. It is supposed that the pH and the salt concentration of the water influence their stability.

Dispersal routes
Dispersal of baculoviruses in general includes small animals and birds (their faeces are able to contain infective viruses), predators, wind blow of dry soil and rain splash at canopy edges. Knowledge of the importance of such mechanisms is scant (Evans and Harrap, 1982).

Relationships to known plant or animal or human pathogens

Known baculoviruses have been exclusively isolated from arthropods (OECD, 2002) and not from other animals, humans or plants. CpGV as well as all other baculoviruses are not related to any known plant, animal (other than arthropods) or human pathogen.

Genetic stability and factors affecting it

The Mexican CpGV isolate is genetically stable over several investigated intervals as profound genetic mutations became not evident within nine years (Harvey and Volkman, 1983) and within five years of continuous propagation (Croizier, 2001). Furthermore, the isolates used in the products Carpovirusine, Madex, and Virgo did not change genetically compared to the originally described Mexican isolate CpGV-M (Croizier, 1996; Biache, 1998; Croizier, 2001; Jehle, 2006).

Horizontal gene transfer
In very rare cases CpGV may exchange DNA with the host genome as is typical for many if not all viruses during evolutionary time. This is concluded from phylogenetic analyses of different baculovirus genes, which suggest that some of them were acquired from the host's genome, others from bacteria or other viruses (Hughes and Friedmann, 2003, Herniou et al., 2001) during millions of years. There is also direct evidence for the potential transfer of host DNA sequences to several baculoviruses (OECD, 2002). Intensive screening for CpGV mutants after applying specific infection and selection procedures resulted in the isolation of two CpGV isolates carrying host transposable elements in their genome (Jehle *et al.*, 1995, Jehle *et al.*, 1998). However, it was demonstrated that these mutants were effectively out-competed by the wildtype CpGV-M (Mexican isolate) and would not be able to establish in a mixture together with CpGV-M (Arends *et al.*, 2005).

Recently it was shown that multiple copies of two transposable elements of the cabbage looper (*Trichoplusia ni*) transposed *in vivo* into genomes of the baculovirus *Autographa californica multiple nucleopolyhedovirus* (AcMNPV) during caterpillar infections (Gilbert *et al.*, 2014). The authors demonstrated that both transposable elements underwent recent horizontal transfer between several sympatric moth species (*T. ni*, *Manduca sexta*, *Helicoverpa spp.*) showing different degrees of susceptibility to AcMNPV.

Gilbert *et al.* (2016) studied the influx of genetic material from hosts to virus populations and calculated that on average 4.8% of baculoviruses harbor at least one moth sequence. However, it was also found that no insertion of moth DNA was maintained in any viral population after 10 successive infection cycles. Yet, Gilbert *et al.* (2016) found that at least 21 of the moth transposable elements integrat-

ed into viral genomes underwent repeated horizontal transfers between various insect species, including some lepidopterans susceptible to baculoviruses. These results identify host DNA influx as a potent source of genetic diversity in viral populations. They also support a role for baculoviruses as vectors of DNA horizontal transfer between insects.

In conclusion, genetic exchange of virus sequences with other organisms is a natural occurring process and does also occur between baculoviruses and their hosts. Horizontal transfer of genes and transposable elements has been occuring frequently within baculoviruses and indicates a role for baculoviruses as vectors of horizontal DNA transfer between insects. Though it cannot be excluded that a single virus may contain host DNA sequences, the recorded stability of the CpGV genome provides clear evidence that these mutants are extremely seldom and do not establish during the production process (Jehle, 2007).

Information on the production of metabolites (especially toxins)

Viruses have no metabolism of their own and are therefore not able to produce secondary metabolites.

Antibiotics and other anti-microbial agents

Not applicable to viruses as they are (i) not metabolically active and, therefore, do not produce antimicrobial substances, and are (ii) not sensitive to antibiotics or other antimicrobial drugs and, accordingly, cannot become resistant to these substances or spread resistance.

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

CARPOVIRUSINE

CARPOVIRUSINE ARY-0453a-04 is a suspension concentrate and visually consists of a free flowing homogeneous liquid with bright red colour. There are some suspended solids observed in the formulation but no signs of separation or sedimentation are observed. It presents a pH around 5 to 6. The formulation is not explosive or oxidising and no flash point can be determined due to the properties of the test item (boiling and decomposition of the test item was observed at approx. 100ºC). The auto ignition temperature is 505ºC

The activity of the formulation expressed as LD_{50} remained stable when stored at -18 ºC over the testing period from beginning of the experiment until 24 months and when stored at 4°C ± 4 °C over the testing period from beginning of the experiment until 12 months.

The concentration in aerobic mesophilic flora is stable throughout the storage duration at -18°C, 4°C or 25°C. The concentration in *Bacillus cereus* slightly decreases after one month of storage at 25°C and after 12 months of storage at -18°C or 4°C.

All studies have been performed in accordance with the current requirements and the results are deemed to be acceptable. The relevant physical, chemical and technical properties are adequate for a suspension concentrate.

Two storage stability tests are currently ongoing and should be provided when finalised. For storage studies on biological stability information on packing material is missing.

MADEX and MADEX TWIN

MADEX is a grey-brown and odourless suspension concentrate which is not explosive, oxidising or flammable. Its pH is within the neutral range. No loss of efficacy is noted when MADEX is stored at – 18 °C for six years. The technical properties of MADEX indicate that no particular problems are to be expected when it is used as recommended.

Before and after storage the LD_{50} of the test item is not significantly lower than that of the reference item. Therefore, the test item is considered to be stable when stored for 42 months at 5ºC.

Physical, chemical and technical properties were determined for the plant protection product MADEX. MADEX contains the same components as MADEX TWIN, with the only exception that another virus isolate is used. The two isolates can only be distinguished by molecular genetic methods or by their infectivity towards some *C. pomonella* populations which are resistant to the isolate CpGV-M used in MADEX, but susceptible to the isolate CpGV-V22 used in MADEX TWIN. All other product components are identical. Therefore, physical-chemical and technical properties are identical between MADEX and MADEX TWIN.

For MADEX storage stability tests regarding physical and chemical properties and the growth of contaminating micro-organism are missing. For viscosity data are missing.

VIRGO

VIRGO is a dark blue suspension concentrate of characteristic smell which is not explosive, oxidising or flammable. Its pH is within the neutral range. Physical conditions are not changed when stored at 0°C for seven days and when stored for 4 weeks at 40°C. The technical properties of VIRGO indicate that no particular problems are to be expected when it is used as recommended.

For Virgo storage stability test regarding the growth of contaminating micro-organism is missing. For storage stability studies information on packing material is missing.

2.3 Data on application and efficacy

According to the intended uses listed in documents D-1 of the individual formulated products, *Cydia pomonella* GV is used in pome fruit (apple, pear, quince, nashi, *Mespilus*), stone fruit (peach, apricot, nectarine, almond, plum) and walnut against the codling moth (*Cydia pomonella*) and the oriental Fruit moth (*Grapholita molesta*).

2.3.1 Summary of effectiveness

According to SANCO/12545/2014 rev. 2, efficacy data, i.e., Document MMP 6, is not required for renewal of active substances.

2.3.2 Summary of information on the development of resistance

Since no new data was submitted for this chapter within the renewal process of the active substance existing data have to be used.
Moreover, no additional references were identified during the peer-reviewed literature search to address this data point.
However, the already presented data fulfils the existing data requirements.

Generally, viruses cannot produce antimicrobial substances because they are not metabolically active.
However possible viral resistance to virucidal or virustatic drugs cannot be excluded. In addition transmission of that such resistance from one virus species to another one has not been proven so far.

In the last years, several cases of reduced efficacy of CpGV-M formulations for the control of *Cydia pomonella* were reported. All over Europe 38 resistant populations of *C. pomonella* have been found. However, resistant populations are not abundant and occurred solely in orchards, were CpGV has been applied as the only plant protection product against *C. pomonella* for years. In laboratory experiments, LD50-values differed by a factor of 1000 between resistant and susceptible laboratory and field strains. In the presence of the virus, resistance could be increased when compared to the initial orchard population. Therefore, further use of CpGV-M or even increased virus rates as a response of the farmer to reduced efficacy of the CpGV-M treatment are likely to lead to an enforcement of resistance

in the *C. pomonella* population.
To counteract the resistance, the use of various virus isolates is recommended. The risk of development of resistance is classified as moderate.

2.3.3 Summary of adverse effects on treated crops

Due to their highly specific mode of action, baculoviruses are generally non-toxic to plants. This is also true for *Cydia pomonella granulovirus*. The virus does not penetrate into the plant tissue and is inactivated relatively rapidly on the plant surface by UV light without any interaction with the plant itself. Therefore, it is not supposed to affect the quantity or quality of the yield e.g. 'taint'.

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

No symptoms of phytotoxicity were reported. Furthermore, the active substance. Due to the selectivity of *Cydia pomonella granulovirus* relevant beneficial organisms are not at risk.

2.4 Further information

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

Acceptable information has been provided, including safety data sheets for CpGV and the plant protection products. See Volume 3 MA and MP, Section B.4.

2.4.2 Summary of procedures for destruction or decontamination

Acceptable information has been provided, including safety data sheets for CpGV and the plant protection products. See Volume 3 MA and MP, Section B.4.

2.4.3 Summary of emergency measures in case of an accident

Acceptable information has been provided, including safety data sheets for CpGV and the plant protection products. See Volume 3 MA and MP, Section B.4.

2.5 Analytical methods

Identification/distinction of/between CpGV isolates is carried out by Restriction Fragment Analysis (RFLP) or the analysis of single nucleotide polymorphisms (SNP).

Granules of CpGV can be counted under the microscope but for the determination of CpGV in the representative formulations a standard bioassay with the target pest is used. The method was already provided and accepted during first approval of CpGV. However, validation data are missing for the determination of CpGV in terms of granules/L or a description is missing how the content in terms of granules/L is derived from the bioassay tests.

For microbial contaminant screenings according to SANCO/12116/2012-rev.0 including quantification of *B. cereus* standard microbiological methods (EN ISO) are used which are considered validated as such.

Residue analytical methods for *Cydia pomonella* GV in food or feed, in environmental matrices such as water, air, soil and body fluids and tissues are not considered necessary because neither residue definitions nor maximum residue levels or other action levels are proposed or exist.

However, studies have been submitted by the applicant to report method validation for the determination of *Cydia pomonella* GV in plant matrices, water samples, and soil samples. Because such methods are not required they have not been evaluated in detail.

2.6 Impact on human and animal health

2.6.1 Effects having relevance to human and animal health arising from exposure to the virus or to impurities, additives, or contaminating micro-organisms contained in the material used for manufacturing of formulated products

Preface on general approach:
For this re-evaluation of CpGV to support its further approval in the EU, the Volume 1 of the previous DAR (Germany, 2007, ASB2010-10675) has been completely revised even though the conclusions remained virtually the same. Like in the previous health risk assessment of CpGV, reference is still made quite frequently to data obtained with other baculovirus species, belonging either also to the genus *Granulovirus* (GV) or, even more often, to the genus *Nucleopolyhedrovirus* (NPV). This approach is considered scientifically sound and the information obtained with other baculoviruses generally applicable to CpGV because of the close relationships within the family *Baculoviridae*. Baculoviruses are large, enveloped and in its infective forms rod-shaped viruses. Their genome consists of double-stranded, circular DNA. They all form "occlusion bodies" (OB, sometimes, the synonymous term "inclusion body/bodies" still in use) to protect the virus against damaging environmental conditions and, thus, to allow the virions to remain viable for many years. Historically, in particular the differences regarding these OB, resulted in grouping them into either NPV or GV (Benz, 1986, ASB2018-879). Despite many similarities, remarkable differences between these two groups do exist and must not be ignored (see
). However, it must be emphasised that the matrix protein of GV, granulin, is genetically and serologically closely related to the NPV matrix protein polyhedron. This similarity is considered more important for risk assessment than, e.g., the number of nucleocapsides, since proteins in general affect the infectivity and immunogenicity of viruses much more.

Table 2.6-1: Differences between NPV and GV with possible impact on health effects, collected from textbooks of virology

Table Criteria	NPV	GV
Viral protein	Polyhedrin	Granulin
Shape of the crystalline protein matrix	Polyhedral	Ovicylindral
Size of occlusion bodies (OB)	0.15 – 15 µm	0.13 – 0.5 µm
Number of virion per OB	One or several	One
Nature of virions in OB	Single nucleocapsid (S) or multiple nucleocapsids (M) within a single viral envelope	Single nucleocapsid (S)
Size of complete genome (nucleotides)	90,000 – 165,000	100,000 – 180,000

Nonetheless, because of the apparent differences, studies with CpGV or its formulations or published data obtained with this virus species, if available for a certain endpoint, is mainly relied on and given higher regulatory weight. In these cases, information on other baculoviruses is included in Volume 3 as additional or supportive evidence, but is not mentioned in Volume 1 any longer. With the exemption that only data of NPV is available for a certain endpoint, direct reference to information obtained with NPV is made to use it as some kind of "surrogate".

Basic information:
Viruses are obligate intracellular parasites, *i.e.,* they can only multiply inside living cells. Therefore, the first-line consideration on their safe use for plant protection purposes should address the ability of a certain virus species or strain to infect other organisms than the target species that is intended to be controlled. For baculoviruses in general, it is broadly assumed that they are highly specific to certain arthropod (mainly insect) species and cannot infect vertebrates, including humans (e.g., Heimpel and Buchanan, 1967, TOX2003-1143; Ignoffo, 1973, TOX9750934; Krieg, 1976, BWS2003-90; or Burges et al., 1980, TOX2006-1679). More recent literature searches performed by the RMS (see Volume 3, B.6.3) as well as by the applicant Arysta Life Science SAS (Anon., 2016, ASB2017-11923) or, on behalf of EFSA but for other purposes, by Hackl et al. (2015, ASB2015-4072) confirmed this previous knowledge. A review by Hackl et al. (2015, ASB2015-4072) that was conducted on behalf of EFSA, although for other purposes, came to the same conclusion.
It must be acknowledged that the major part of testing on the host range and of infectivity and pathogenicity to vertebrates was done with NPV. However, limited published data is also available for CpGV itself to demonstrate at least that it did not affect the health of mice and Guinea pigs after feeding, inhalation or injection (Gröner et al., 1978, TOX2003-1154). This previous information was confirmed by the outcome of the few regulatory studies that have been performed and submitted to support the approval of CpGV for plant protection purposes (see below). It is also supported by the occupational health surveillance of people who were involved in research and development as well as in manufacturing, formulation and partly also spraying of microbiological pest control products (MPCP) containing CpGV (see Volume 3, B.6.1.1.2). No indications of adverse effects on humans have been revealed so far.

It is a controversial issue if the contact with baculoviruses may result in some seroconversion or other immunological reactions in humans or animals (Huang et al., 1977, cited by Burges et al., 1980, TOX2006-1679; Döller and Gröner, 1981, TOX2003-1166; Anon., 1982, TOX2003-1156). A serological response to CpGV itself was reported to have occurred in trapped woodmice (*Apodemus sylvaticus*) in which antibodies were detected as early as four days after spraying (Bailey and Hunter Fujita, 1987, TOX2003-1171). Döller (1981, TOX2003-1168) had found evidence of an unspecific interaction of CpGV matrix protein globulin with human and other mammalian (horse, cattle, sheep, and pig) immunoglobulins *in vitro*. In contrast, no antibodies to CpGV were detected in serum of mouse pups of which the mothers had been treated prior to mating (Döller and Huber, 1983, TOX2003-1169). It must be emphasised that a serological response is not adverse *per se* but rather indicative of an adequate reaction of a healthy organism to an antigen. As an occasional finding, it is considered proof of exposure but does not suggest an actual infection.

Along with their experimentally proven non-infectivity to vertebrates *in vivo*, baculoviruses were also found not capable of infecting vertebrate cells in culture (Ignoffo and Refajko, 1972, TOX2003-1161; Röder and Pünter, 1977, TOX2003-1162). Likewise, they did not activate endogenous retroviruses (Schmidt and Erfle, 1982, TOX2003-1163). This information was confirmed later in an unpublished study for CpGV itself since it was shown that at least to different isolates of this virus did not replicate in the human diploid cell line W138 and no transcription of any viral genes was observed (Winstanley, 2000, TOX2006-2290).
These findings do not prove that NPV or GV could not penetrate vertebrate cells, but there is convincing evidence that they do not persist and replicate there. Baculoviruses, including CpGV, under *in vitro* conditions at least, were detected in the cytoplasm and even in the nucleus of different types of vertebrate cells including such of human origin (Tjia et al., 1983, TOX2003-1159; Volkman and Goldsmith, 1983, ASB2018-885; Gröner et al., 1984, TOX2003-1160; Winstanley, 2000, TOX2006-

2290). However, no persistence of the virus and no replication were observed in any of these studies and rapid clearance from the vertebrate cells was common. The narrow host range and the non-infectivity of baculoviruses to vertebrates and their cells is likely to have a genetic background and seems to be due mainly to the presence of certain promoters occurring only is some insect species (Gronowski et al., 1999, TOX2006-1043; Mitchell and Friesen, 2012, ASB2018-28). At least in susceptible (insect) cells, low temperature may also contribute to the maintenance of a productive infection that is terminated when temperatures go higher (Winstanley and Crook, 1993, ASB2017-15579).

Even though being not infective, some immuno-stimulating effects of baculoviruses other than CpGV have been shown in human and murine cell lines as well as *in vivo* in mice (Gronowski et al., 1999, TOX2006-1043; Abe et al., 2003, ASB2018-888; Hervas-Stubbs et al., 2007, ASB2018-891; Molinari et al., 2010, ASB2017-11929; Wang et al., 2015, ASB2017-11930). This information has no impact on the risk assessment of CpGV as an active ingredient in plant protection product since (a) the applied amount of virus in these experiments was rather high and mostly artificial routes such as the intravenous or intraperitoneal were used for route of exposure; and (b) the effects observed so far were all beneficial since they resulted in stimulation of interferon production and provided some protection from otherwise fatal infection with other, pathogenic viruses.
The general safety of baculoviruses for vertebrates including humans was confirmed by OECD (2002, TOX2006-1036) as well as by EFSA's biohazard panel (EFSA, 2012, ASB2014-3917). This latter conclusion is also supported by the wide and apparently safe use of baculoviruses as vectors for gene transfer into mammalian (including human) cells for "genetic engineering" purposes, just because they may enter the cell but not replicate there (e.g., Sandig et al., 1996, TOX2006-2293; Chiang et al., 2006, ASB2018-890; Kitayima et al., 2006, ASB2018-892). Nonetheless, it must be acknowledged that all these experiments have been carried out with baculoviruses other than CpGV. Further reassuring is the long history of application of baculoviruses for insect control in plant protection, dating back at least to the 1930iers, according to other sources even to the end of the 19th century (Krieg, 1976, BWS2003-90; Benz, 1986, ASB2018-879; Huber, 1986, ASB2018-1330; Kalawate, 2014, ASB2017-16166). No reports on adverse effects of such applications to humans could be retrieved from the medical literature.

The general assumption of safety is further supported by the very few valid, guideline-compliant acute studies with CpGV as summarised in Table 2.6-2 and reported in detail in Volume 3, B.6.1.2.2.

Summary of Tier I studies:
Few (unpublished) studies were performed with CpGV on behalf of the manufacturers, mostly following specific EPA guidelines for the testing of micro-organisms. The valid (i.e., fully acceptable or at least supplementary) acute studies are compiled in Table 2.6-2, along with a further study from open literature. Additional experimental data obtained with baculoviruses other than CpGV is reported in Volume 3 of this RAR (B.6.1.2.2) but was not included in Volume 1 since its regulatory value for risk assessment of CpGV is rather limited and the quality of these studies was often poor when compared to today's standards. However, it can be roughly summarised that no evidence of adverse effects was obtained in these experiments.

Table 2.6-2: Acute studies for infectivity, pathogenicity and toxicity with CpGV or with formulations containing this virus (i.e., product studies)

Endpoint and test system	Test item	Dose/Concentration	Results	Reference
Acute oral, CD rat	*Cydia pomonella* Granulovirus	1.015 x 10^8 G/animal	No effects, LD_{50}>1.015 x 10^8 G/animal	[redacted] 2005 (unpublished), TOX2006-1680
Acute oral, SD rat	*Cydia pomonella* Granulovirus in the formulation CARPOVIRUSINE	5000 mg/kg bw (virus particle number not given)	No mortality but transient clinical signs and little pathological changes,	[redacted] 1991 (unpublished)*, TOX2006-2287

Endpoint and test system	Test item	Dose/Concentration	Results	Reference
			LD_{50}>5000 mg (product)/kg bw	
Acute oral, NMRI mouse	*Cydia pomonella* Granulovirus (CpGV)	5 x 10^{11} G/animal	No effects, LD_{50}>5 x 10^{11} G/animal	Gröner et al., 1978 (published)*, TOX2003-1154
Acute inhalation, CD rat	*Cydia pomonella* Granulovirus in the formulation VIRGO	5.10 ± 0.20 mg VIRGO/L air (nominal concentration 2 x 10^{13} G/L)	No effects, LC_{50}>2 x 10^{13} G/L	[redacted] 2005 (unpublished), TOX2006-1054
Acute, intraperitoneal, CD rat	*Cydia pomonella* Granulovirus	1.015 x 10^{7} G/animal	No effects, LD_{50}>1.015 x 10^{7} G/animal	[redacted] 2005 (unpublished), TOX2006-1055

G CpGV granules, *supplementary study

On balance, all these studies unequivocally demonstrated a very low acute pathogenicity and/or toxicity of CpGV by the oral, inhalative and intraperitoneal routes. There was no evidence of infectivity in any study because there were no adverse effects observed during the post-observation period. Even though clearance of the virus from the body was not investigated, virus replication is considered extremely unlikely, based on what is known on baculoviruses in general (see above). Co-formulants in the product Carpovirusine may have caused some weak effects, but not mortality, in the animals receiving a very high dose.

In the health risk assessment of micro-organisms as active ingredients in PPP, sensitisation is always of concern. In case of CpGV (even though not being a micro-organism), allergic reactions might occur because of sensitising properties either of viral envelope proteins, of proteins from the insect larvae on which the virus is propagated or of co-formulants in the commercial products. It is neither technically feasible nor would it make any sense to test the purified virus for sensitisation. In line with that, the available valid studies ([redacted] 1991, TOX2006-2285; [redacted] 2005, TOX2006-1050) have been performed with commercial products and, therefore, are reported and evaluated in the product safety sections in Volumes 1 and 3 of this RAR. Anyway, the commercial products must be labelled as follows: 'Micro-organisms may have the potential to provoke sensitising reactions'.

It must be acknowledged that genotoxicity of CpGV was not investigated according to current standards and data requirements. At least, the virus proved negative in non-guideline studies with regard to cytogenetic changes (chromosome aberrations) and sister chromatid exchange. In these experiments, CpGV was not clastogenic following either single oral application of 1.5 x 10^{12} granules/animal or feeding of 1.6 x 10^{10} granules/animal over 3 months to male Chinese hamsters (Reimann and Miltenburger, 1982, TOX2006-2676; Reimann, 1984, TOX2003-1158). Absence of chromosome aberration in bone marrow smears of NMRI mice after single or multiple doses of CpGV had been reported already before by Gröner et al. (1978, TOX2003-1154) but experimental details were not given. Based on the much more recent and valid cell culture study by Winstanley (2000, TOX2006-2290) and the broad knowledge on virus-cell interactions of baculoviruses in general (see above), the available information, although scarce, is considered sufficient to exclude a genotoxic potential of CpGV.

The very few available studies in which either mice (Gröner et al., 1978, TOX2003-1154) or Chinese hamsters (Reimann, 1984, TOX2003-1158) were exposed to CpGV for ca 3 months did not reveal adverse effects. Unfortunately, these studies do not comply with any guideline and cannot be relied on. For the following reasons, this is not a data gap:
Short-term testing of micro-organisms is needed only if triggered by specific considerations or by results of the acute studies. This rule should be applicable to viruses, too. In case of CpGV, based on the absence of infectivity, pathogenicity and toxicity in the single dose studies and on the general familiarity with baculoviruses, there is apparently no need for such studies.

"Viruses lack the capacity to make energy or substrates, cannot make their own proteins, and cannot replicate there genome independently of the host cell." This general statement (cited here from Murray, P.R.; Rosenthal, K.S. and Pfaller, M.A.: "Medical Microbiology", Fifth Edition, 2005, Elsevier, Philadelphia/USA; Chapter 6 "Viral Classification, Structure, and Replication", page 47) may be found, in other words but with the same meaning, in many standard textbooks of virology. Because of its nature as a virus, CpGV does not produce any metabolite or toxin by itself. Virus proteins (including enzymes which might be, at least theoretically, also of health concern) are synthesised by in infected cells only. In case of CpGV, this synthesis is confined to the very narrow host range. Baculovirus (at least NPV) proteins could induce immunostimulating effects in vertebrate cells or even in animals (e.g., Gronowski et al., 1999, TOX2006-1043), but there is no evidence so far that they were toxic.

Tier II studies:
Gröner (1986, TOX2003-1179) reported that a dose of 2 x 10^{10} CpGV granules was not irritating neither to the skin nor to the eyes of Guinea pigs. Obviously, no guideline was followed and, in addition, these irritation studies are usually performed in rabbits. Taking into account also the absence of any details, these data is not reliable. The same holds true for a combined reproduction and developmental study with CpGV in mice (Döller and Huber, 1983, TOX2003-1169) in which no adverse effects were observed but the number of treated animals was too low for meaningful conclusions. However, because of the reasoning above, higher tier data for CpGV is not warranted and, thus, the low quality of these studies is not of concern.

To conclude, application of CpGV in plant protection products may be reasonably considered to be of low risk to human or animal health. There is no need and no basis to derive reference doses.

Risk Assessment concerning the contamination of CpGV-based plant protection products with *Bacillus cereus*

Introduction
Bacillus cereus is a ubiquitous micro-organism that can be found mainly in soil but also, *e.g.,* in water or in a wide range of foodstuffs. Contamination of CpGV formulations with *B. cereus* has been observed to occur frequently, due to the fact that it may be part of the intestinal flora of *Cydia pomonella* larvae. Because of propagation of the virus on these larvae, it is unlikely that such a contamination can be completely avoided. In line with that, *B. cereus* was detected in all representative formulations which were evaluated now on EU level to decide on further approval of CpGV, even though consistently at concentrations below 10^6 (in all formulations except one that was below 10^7) at colony forming units (CFU) per g. Details are given in the respective Volumes 4. Current EU and OECD recommendations (EU/SANCO, 2012, ASB2019-4942; OECD, 2011, ASB2019-4945) would even allow a maximum concentration of up to 10^7 CFU/g in the formulated product.

Nonetheless, since *B. cereus* is known to cause food intoxications in humans, risk assessment with regard to human health is needed. Like for chemicals, microbial risks may be defined as a function of hazard (*i.e.,* the pathogenic potential and virulence of the microbial agent) and exposure.

Pathogenic properties of *B. cereus* and infectious dose
B. cereus is a gram-positive micro-organism of the genus *Bacillus* which also comprises, among others, the highly pathogenic *B. anthracis* as well as, e.g., the species *B. thuringiensis* that is widely used in plant protection. Because of spore formation, *B. cereus* has a high tenacity and can survive in the environment for a long time. The pathogenic mode of action is mainly by formation of toxins either in the target organism and/or in contaminated food. The genes coding for the different toxins are located on plasmids (OECD, 2011, ASB2019-4945; EFSA, 2016, ASB2016-9771; see also textbooks of microbiology).

Depending on the predominating toxin, two different clinical courses of food poisoning by *B. cereus* can be distinguished.
On one hand, with an incubation time of 30 minutes to 8 hours, vomiting is caused by the emetic neu-

rotoxin cereulide that is produced by *B. cereus* in food. For this toxin, 8-10 µg/kg bw have been reported to be the minimal effect dose in humans and amounts of 2-6 µg/g food were detected when outbreaks were investigated. In rare cases, deaths have occurred and were due then to liver or heart failure. Another severe clinical symptom may be rhabdomyolysis.
On the other hand, 8 – 16 hours following ingestion, diarrhoea, often accompanied by abdominal pain, can develop. These symptoms are caused either by a non-haemolytic enterotoxin or by a haemolysin or both (Al-Joudi, 2007, ASB2019-4970; Ankolekar and Labbé, 2009, ASB2019-4969; Delbrassinne et al., 2015, ASB2019-4975; EFSA, 2016, ASB2016-9771).

Most often, food intoxication by *B. cereus* is related to intake of contaminated rice, pasta dishes or meat (Al-Joudi, 2007, ASB2019-4970; Perera and Ranasinghe, 2012, ASB2019-4989; EFSA, 2016, ASB2016-9771). In its most recent evaluation, EFSA mentioned 413 outbreaks of food intoxications in Europe between 2007 and 2014 for which there was strong evidence that they were caused by *B. cereus*. 6557 humans were affected and 352 of them needed hospitalisation but, fortunately, there were no deaths (EFSA, 2016, ASB2016-9771). From these figures, however, no conclusion on the relative contribution of *B. cereus* to the total number of food poisoning incidents in Europe can be drawn. According to Azemi et al. (2013, ASB2019-4973), its role might be rather limited since *B. cereus* was the cause of acute diarrhoea in hospitalised children in a 7-year interval in the Kosovo in only 4 out of 655 clinical cases (0.61%), as compared, e.g., to 36% in which *Salmonella* species were involved.

There is partly contradictory information regarding the very important question of the infectious dose that is needed to cause gastrointestinal symptoms since the figures provided in the open literature vary over some magnitudes between 10^3 and 10^8 spores per g food. In EFSA's most recent evaluation of *B. cereus* as a source of food poisoning, it was mentioned that most outbreaks were related to ingestion of food containing 10^5 CFU/g or more. However, it also stated there are reports suggesting that doses of 10^3 – 10^5 CFU/g or, in rare cases, even less than 10^2 CFU/g might be sufficient to cause symptoms (EFSA, 2016, ASB2016-9771). EFSA emphasised that a dose response relationship is difficult to establish because multiplication in food during or after storage or handling cannot be excluded and since the composition of food may affect toxin production.

Even though food poisoning is by far the most relevant clinical entity caused by *B. cereus* and the main point of concern, septicaemia, meningitis, gingival and ocular infections have been reported in rare cases. Nosocomial infections may occur (EFSA, 2016, ASB2016-9771). Nothing is known about the infectious dose in these cases, avoiding the conduct of a proper risk assessment. However, the possibility of such events triggers a need to reduce the number of *B. cereus* spores in MPCP to the lowest achievable level.

Exposure – Amount of contamination

The RMS is aware of only one study in which *B. cereus* spores were measured in or on apples following application of a CpGV formulation containing *B. cereus* as a contaminant. This study by Theau-Audin (2005, ASB2011-2851, ASB2011-2848) had been submitted and was evaluated for the first evaluation of CpGV on EU level already. At that time, the technical concentrate of the notifier Arysta LifeScience S.A.S. contained up to 1.2 x 10^8 CFU (= spores) of *B. cereus* per g. This amount was found in two different batches while the bacterial count for this species in three other batches was slightly lower. In the formulation CARPOVIRUSINE, *B. cereus* was present at concentrations of up to 1.1 x 10^8 CFU/g. Following 11 applications of CARPOVIRUSINE 2000 (1x10^{13} granules/L) and a PHI of 3 days, Fuji apples contained less than 1000 spores of *B. cereus*, most of them on skin (about 300 on skin and less than 100 in the pulp and the whole apple without skin). Thus, when used in accordance with the intended GAP, only very low contamination of apples is to be expected even though massive contamination of the MCPP had occurred. Because of the ubiquitous occurrence of *B. cereus*, apples might have been previously colonised by the micro-organism from other sources, of course, too. However, at least on apple skin, the number of spores in the untreated control group was much lower suggesting that the application of CARPOVIRUSINE in fact has somehow increased the amount of *B. cereus*.

Assessment of consumer exposure

If the worst-case assumption of 1000 is made and the unit weight of an apple of 148 g (EFSA calculation model Pesticide Residue Intake Model "PRIMo" rev.3, ASB2018-4236) is taken into account, this would result in about 6.8 CFU/g.

The study by Theau-Audin (2005, ASB2011-…) in apples may be considered to reflect worst-case conditions because of the following considerations:
The contamination of PPP containing CpGV with *B. cereus* is now by more than two magnitudes lower than it was before (i.e., below 10^6 CFU/g or mL formulated product).
In this trial, there were 11 applications in total with a pre-harvest interval of 3 days. Thus, the situation of multiplication of this micro-organism in/on the treated crop would have been covered and the total count per apple may be regarded the maximum to be expected.

It should be also kept in mind that fruit and vegetables are usually not associated with outbreaks of food poisonings due to *B. cereus*.

On balance, it may be concluded that, even though no safe dose for *B. cereus*-related food intoxications can be established, the expected exposure of humans by ingesting spores in or on treated apples will be extremely low. No clinical signs of food poisoning are anticipated if the recommended limit of 10^7 CFU/g or mL (EU/SANCO, 2012, ASB2019-4942; OECD, 2011, ASB2019-4945) in the PPP is not exceeded.

2.6.2 Summary of product exposure and risk assessment

The toxicological studies on CpGV and the formulated products reveal that no health risks have to be anticipated for operators, workers, bystanders and residents except for a potential sensitising effect of the virus isolate.

No indications for a sensitizing potential of CpGV exist in the literature. However, a positive result was obtained in an M&K test with the formulation Carpovirusine ([redacted], 1991, TOX2006-2285) resulting in a classification with Skin Sens. 1B for this product. Based on a precautionary approach, all other products have to be labelled with the phrase: "Contains *Cydia pomonella* Granulovirus. Micro-organisms may have the potential to provoke sensitizing reactions." Because of that classification/labelling operators will have to wear PPE which will reduce exposure to a minimum. Because of the proven sensitising properties of at least one formulation, resulting in the need for PPE and because of general concern about allergenic effects of micro-organisms, the active ingredient must not be considered to be of low risk.

2.7 Residues in or on treated products, food and feed

2.7.1 Persistence and likelihood of multiplication in or on crops, feedstuffs or foodstuffs

In general, baculoviruses are unable to enter plant tissues or to multiply on plant surfaces. The occurrence of *Cydia pomonella* Granulovirus is strictly dependent on the presence of its host. Replication of CpGV does only happen inside the larval stages of the target insect species *Cydia pomonella* or for some isolates also in *Grapholita molesta* or *Grapholita funebrana*. CpGV is rapidly degraded by UV light; therefore, persistence in nature is very limited. Therefore, it is unlikely that CpGV occurs on treated food/feed stuffs in concentrations considerably higher than under natural conditions.

2.7.2 Further information required

Not applicable.

2.7.3 Non-viable residues

Non-viable residues are not relevant for CpGV as baculoviruses in general do not produce any metabolite.

2.7.4 Viable residues

Taken into consideration the highly specific mode of action of CpGV resulting in absence of toxicity in any other organism than *Cydia pomonella* and the restricted field persistence of baculoviruses in general it can be concluded that there is no risk for consumers following use of CpGV for pest control.

An exposure to *B. cereus* cannot be excluded. Since *B. cereus* is known to cause food intoxications in humans, a risk assessment with regard to human health was conducted and is presented under 2.6.1.

2.7.5 Summary of residue behavior resulting

As *Cydia pomonella* Granuloviruses (CpGV) are not pathogenic to humans, and they will not produce any toxins, it can be concluded that the consumer risk assessment is finalised. A quantitative risk assessment is not necessary.

The contamination with *Bacillus cereus* should be controlled at a level that the final contamination with *B. cereus* in the formulated product does not exceed 10^7 CFU/g or mL.

2.8 Fate and behaviour in the environment

2.8.1 Summary of fate and behaviour in soil

Granuloviruses have to be considered as persistent in soil, as they are protected from UV-light in deeper soil layers. Multiplication can restart again if the permissive host appears.

2.8.2 Summary of fate and behaviour in water

Granuloviruses given into an aquatic system precipitate quickly at similar rates as soil particles. According to the given information transport into the sediment phase is likely. Activity in sediment remaining for a length of time similarly as in soil cannot be excluded. Mineralisation could be hampered by the resistance of inclusion bodies to environmental conditions.

2.8.3 Summary of fate and behaviour in air

Steineke (2004) showed that the virus is inactivated by sun light. A half-life of 52 hours was determined in that study. Jaques (1972) demonstrated degrading effects of sunlight to granuloviruses.
Occlusion bodies of granuloviruses can be considered as suspended solid particles that are non-volatile. Therefore a distribution of CpGV via air can be excluded.

2.8.4 Summary of mobility

The submitted studies demonstrated that baculoviruses and granuloviruses, respectively, are able to leach through a column of soil. Viral activity has been found in a depth of 15 cm for the loamy sand and down to 30 cm in the sand. It was demonstrated that 4 % of the applied amount of granuloviruses were is still detectable in the eluate of 20 cm column of sand and 24 % in a 20 cm long column of organic contaminated soil. Results of a field lysimeter experiment conducted 1987 in Marienfelde (Germany) indicate an acceptable low risk of reaching deeper soil layers and therefore the groundwater.
The good retention of baculoviruses by soil is probably attributed to the particular protein envelope of the virus particles consisting of granulin.

2.9 Effects on non-target species

2.9.1 Summary of effects on birds (and other terrestrial vertebrates)

Effects on birds
No special studies about infectivity or pathogenicity of the active substance *Cydia pomonella* Granulovirus (CpGV) had been supplied by the notifiers. A 5-day dietary toxicity study with the product CARPOVIRUSINE (1 x 10^{11} granules/kg bw/day for 5 days) was submitted by Arysta Lifescience SAS. No signs of toxicity, infectivity or pathogenicity were observed.

Literature search submitted for the renewal of the approval for CpGV did not indicate any adverse effects on birds and mammals associated with the use of baculoviruses. Further studies are not required.

Effects on terrestrial vertebrates
Acute oral toxicity studies on rats were conducted with the active substance and the formulations VIRGO and CARPOVIRUSINE (refer to the toxicology section). No mortalities occurred and no sublethal effects were observed up to the highest does levels tested.
In general, no member of the baculovirus family is known to be infective to vertebrates.

Literature search submitted for the renewal of the approval for CpGV did not indicate any adverse effects on birds and mammals associated with the use of baculoviruses. Further studies are not required.

2.9.2 Summary of effects on aquatic organisms

The submitted literature describing effects of baculoviruses on fish and aquatic invertebrates in general does not allude to any toxic, infective or pathogenic effects from the active substance. CpGV is also not expected to have any adverse effect on algae.

Aquatic toxicity tests were conducted with the formulated products Granupom, CARPOVIRUSINE and VIRGO, respectively. The tests on acute effects on fish and aquatic invertebrates and on long-term effects on algal growth and aquatic plants resulted in LC/EC_{50} values > 100 mg product/L.

The effect concentrations given in mg product/L were converted to number of granules CpGV/L and a risk assessment was performed. Occlusion bodies of granuloviruses are solid particles being insoluble in water. They consist of the protein granulin being responsible for a good retention by soil. Both characteristics make the possible entry via run-off and drainage highly improbable. Since solid particles are not volatile evaporation is also excluded. Therefore the entry via spray drift is the only one considered here.

Based on the available information on effects of *Cydia polmonella* GV on aquatic organism from literature and submitted studies, the intended uses of the products, in view of the mode of action, the life cycle as well as the exceptionally high host specificity of baculoviruses, any impact and therefore any risks to aquatic organisms can be excluded.
Thus the microbial pest control agent poses no risk for the aquatic biocoenosis.

2.9.3 Summary of effects on bees

Due to the results of acute laboratory test all represented products are considered to be virtually non-toxic to honey bees. As the calculation of a hazard quotients are not suitable for microorganisms, no calculation was made.
To investigate the infectiveness and pathogenicity of *Cydia pomonella* Granulovirus (CpGV) several laboratory studies have been generated by a literature research and were evaluated. These findings indicate that granuloviruses, including CpGV, are highly host specific as cross-transmission is rarely successful and infectivity is restricted to members of the genus or in some cases to the family of the original host. No toxic or pathogenic effects were observed.

Bumble bee colonies show no adversely effects on mortality or reproduction when exposed to the used application dosages of *Cydia pomonella* Granulovirus (Mommaerts, V. et al., 2009). Therefore, a risk to bumble bees is negligible.

Based on the total set of data, it can be concluded that products containing *Cydia pomonella* Granulovirus (CpGV) have to be classified as non-hazardous.

2.9.4 Summary of effects on arthropods other than bees

Since the way of infection starts with the oral intake of virus granules by larvae, dissolving in alkaline milieu of the midgut and releasing virions, only one of the conducted studies [a dietary pathogenicity and toxicity study with the ladybird beetle (*Hippodamia convergens*) (ALS IIIM 10.4/01)] is applicable to assess possible effects of CpGV to non-target arthropods.
This study showed no adverse effects on ladybird beetles up to the highest test concentration (5.5 x 10^{10} granules CpGV/g feed) being the 5.5 fold of the highest recommended spray mixture (VIRGO, CARPOVIRUSINE).

However, in the submitted literature describing effects of baculoviruses in general granuloviruses are shown to be highly host specific, so attempts of granulovirus cross-transmissions succeeded solely within the subfamily of the host. Deleterious effects of baculoviruses to pollinators, predators and adult parasitoids were excluded by literature.
Those hints cast effects on examined arthropods *A. rhophalosiphi* (order: *Hymenoptera*)*, T. pyri* (order: *Megostigmata*)*, P. cupreus* (order: *Coleoptera*) into doubt, since granuloviruses are highly host specific infecting only species within the own subfamily. So the active substance of *Cydia pomonella* GV is expected to cause infections only within the subfamily *Olethreutinae*.
Considering information about this narrow host range, effects on arthropods belonging to different orders like *A. rhophalosiphi* (order: *Hymenoptera*)*, T. pyri* (order: *Megostigmata*)*, P. cupreus* (order: *Coleoptera*) are not expected.

From this follows that applications of the microbial pest control agent *Cydia pomonella* GV pose no unacceptable risk to non-target arthropod species.

The supplied studies have been conducted on glass plates to assess contact toxicity. Since the way of infection starts with the oral intake of virus granules by larvae, dissolving in alkaline milieu of the midgut and releasing virions, those studies are not applicable to assess possible risks of CpGV to non-target arthropods.
In the submitted literature describing effects of baculoviruses in general granuloviruses are shown to

be highly host specific, so attempts of granulovirus (CpGV) cross-transmissions succeeded solely within the subfamily of the host. Deleterious effects of baculoviruses to pollinators, predators and adult parasitoids were excluded by literature.
So the active ingredient of CpGV SC *Cydia pomonella* GV is expected to cause infections only within the subfamily *Olethreutinae*.
Considering information about this narrow host range, effects on arthropods belonging to different orders like *A. rhophalosiphi* (order: *Hymenoptera*)*, T. pyri* (order: *Mesostigmata*)*, P. cupreus* (order: *Coleoptera*) are not expected.

From this follows that applications of the microbial pest control agent *Cydia pomonella* GV pose no unacceptable risk to non-target arthropod species.

2.9.5 Summary of effects on earthworms and other soil non-target macro-organisms

The acute test with *Eisenia foetida* was performed with several formulations of *Cydia pomonella* GV. Up to the highest test concentration of 1000 mg CpGV SC/kg dry soil, corresponding with 2 x 10^{10} viable granules/kg soil, 1000 mg/kg CARPOVIRUSINE. Literature search submitted for the renewal of the approval for CpGV did not indicate any adverse effects on non-target soil micro-organisms associated with the use of baculoviruses. Therefore, it is assumed that the risk of possible adverse effects on earthworms is negligible.

2.9.6 Summary of effects on soil micro-organisms

Laboratory studies for testing the effects of *Cydia pomonella* GV on nitrogen turnover and short-term respiration of soil micro-organisms were performed according to the BBA-Guideline for the official testing of pesticides, part VI, and the OECD Guidelines 216 and 217. Up to the 10fold single application rate (5.0 L CpGV SC/ha corresponding with 10 x 10^{13} granules/ha), nitrogen transformation and soil respiration of two types of soil were not affected (< 25 % deviation compared with control soils) by the formulation CpGV SC. Exposing one type of soil with a maximum dose of 7.5 L VIRGO /ha, corresponding with 15 x 10^{13} granules/ha (also 10fold single application rate) the impact on nitrogen transformation and soil respiration is also < 25 % deviation compared with control soil. Up to the 2-fold single application rate or 4-fold single exposure rate (2.0 L CARPOVIRUSINE /ha corresponding with 2 x 10^{13} viable granules/ha), nitrogen transformation and soil respiration of two types of soil were not affected (< 25 % deviation compared with control soils) by the formulation CARPOVIRUSINE. Therefore, it is assumed that the risk of possible adverse effects on soil non-target micro-organisms is negligible.

2.9.7 Summary of product exposure and risk assessment

Risk assessment for birds
No quantitative risk assessment for the supported uses of the representative formulations CARPOVIRUSINE, MADEX, MADEX TWIN and VIRGO is deemed necessary given the lack of toxicity, infectivity or pathogenicity from laboratory data in conjunction with other available information on the active substance *Cydia pomonella* Granulovirus (CpGV). Nevertheless, a quantitative risk assessment for terrestrial vertebrates was performed. A low risk for birds and mammals can be concluded from the margin of safety (MOS) calculations, especially as no lethal, sublethal or pathogenic effects have been observed at the highest doses tested (cf. Volumes 3 MP B.9.1).

Risk assessment for aquatic organisms
No quantitative risk assessment for the supported uses of the representative formulations CARPOVIRUSINE, MADEX, MADEX TWIN, VIRGO is deemed necessary given the lack of toxicity, infectivity or pathogenicity from laboratory data in conjunction with other available information on

the active substance *Cydia pomonella* Granulovirus (CpGV). Nevertheless, a quantitative risk assessment for aquatic organisms was performed. A low risk for aquatic organisms can be concluded from the margin of safety (MOS) calculations, especially as no lethal, sublethal or pathogenic effects have been observed at the highest doses tested (cf. Volumes 3 MP B.9.2).

Risk assessment for bees
Bees may be exposed to by direct spraying while they are foraging on flowers and weeds, through contact with fresh or dried residues or by oral uptake of contaminated pollen, nectar and honey dew.
Due to the results of acute laboratory test the representative formulations CARPOVIRUSINE, MADEX, MADEX TWIN, VIRGO are considered to be virtually non-toxic to honey bees. As the calculation of a hazard quotients are not suitable for of microorgan-isms, no calculation was made.
Based on the total set of data, it can be concluded that CARPOVIRUSINE, MADEX, MADEX TWIN, VIRGO have to be classified as non-hazardous (cf. Volumes 3 MP B.9.3).

Risk assessment for non-target arthropods other than bees
No quantitative risk assessment for the supported uses of the representative formulations CARPOVIRUSINE, MADEX, MADEX TWIN, VIRGO is deemed necessary given the lack of toxicity, infectivity or pathogenicity from laboratory data in conjunction with other available information on the active substance, in particular the high selectivity of *Cydia pomonella* Granulovirus (CpGV) having an effect on very few species of the Tortricidae family (Lepidoptera). Nevertheless, a quantitative risk assessment for non-target arthropods was performed. A low risk for non-target arthropods for the single application rates can be concluded from the margin of safety (MOS) calculations. A low margin of safety was derived for the exposure to non-target arthropods after multiple applications according to GAPs. But the application rate was summed for the calculations. It is very unlikely that the same population of non-target arthropods is exposed to each application. Furthermore, it is extremely worst-case to assume a cumulative application rate as the both active microorganism and the product will not be stable on the crop due to environmental conditions. However, it has to be kept in mind that no adverse effects were observed in the studies and therefore, the obtained margins of safety likely overestimate a possible risk for non-target arthropods by far. Literature information further demonstrates absence of infectivity, pathogenicity or toxicity of CpGV or any other baculovirus to arthropods other than the well-known host species within the genera *Cydia* and *Grapholita* Based on the quantitative risk assessment in conjunction with existing literature information a low risk can be concluded for non-target arthropods other than bees (cf. Volumes 3 MP B.9.4).

Risk assessment for earthworms
No quantitative risk assessment for the supported uses of the representative formulations CARPOVIRUSINE, MADEX, MADEX TWIN, VIRGO is deemed necessary given the lack of toxicity, infectivity or pathogenicity from laboratory data in conjunction with other available information on the active substance *Cydia pomonella* Granulovirus (CpGV). Nevertheless, a quantitative risk assessment for earthworms was performed. A low risk for earthworms can be concluded from the margin of safety (MOS) calculations (cf. Volumes 3 MP B.9.5).

Risk assessment for non-target soil micro-organisms
No quantitative risk assessment for the supported uses of the representative formulations CARPOVIRUSINE, MADEX, MADEX TWIN, VIRGO is deemed necessary given the lack of toxicity, infectivity or pathogenicity from laboratory data in conjunction with other available information on the active substance *Cydia pomonella* Granulovirus (CpGV). Nevertheless, a quantitative risk assessment for soil micro-organisms was performed. Based on the quantitative risk assessment a low risk can be concluded for soil-microorganisms (cf. Volumes 3 MP B.9.6).

2.10 Classification and labelling

2.10.1 Classification and Labelling of the active substance

Classification and labelling of chemical substances are based on the criteria according to Regulation (EC) No 1272/2008 and Directive 67/548/EEC and are not applicable to micro-organisms.
However micro-organisms should be regarded as potential sensitisers and the following hazard statement has to be applied:
'Micro-organisms may have the potential to provoke sensitising reactions'.

2.10.2 Classification and Labelling of the plant protection product

Carpovirusine

Labelling:	Signal word:	Warning
	Hazard classes, categories:	Skin Sens. 1B
	Hazard statements:	317
	Precautionary statements:	101-102-280-302+352-333+313-362+364

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

Madex

Labelling:	Signal word:	None
	Hazard classes, categories:	None
	Hazard statements:	None
	Precautionary statements:	None

"Contains *Cydia pomonella* Granulovirus. Micro-organisms may have the potential to provoke sensitizing reactions."

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

Madex Twin

Labelling:	Signal word:	None
	Hazard classes, categories:	None
	Hazard statements:	None
	Precautionary statements:	None

"Contains *Cydia pomonella* Granulovirus. Micro-organisms may have the potential to provoke sensitizing reactions."

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

Virgo

Labelling:	Signal word:	None
	Hazard classes, categories:	None
	Hazard statements:	None

Precautionary statements: None

"Contains *Cydia pomonella* Granulovirus. Micro-organisms may have the potential to provoke sensitizing reactions."

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

Commercial products should be labelled as follows: 'Micro-organisms may have the potential to provoke sensitising reactions'.

2.11 Relevance of metabolites in groundwater

The risk of groundwater contamination is usually assessed in a qualitative way. Therefore, this chapter is not applicable to viruses.

2.12 Consideration of isomeric composition in the risk assessment

No information is required as micro-organisms do not have isomers.

2.13 Residue definitions

2.13.1 Definition of residues for exposure/risk assessment

Food of plant origin: not required

Food of animal origin: not required

Soil: not required

Groundwater: not required

Surface water: not required

Sediment: not required

Air: not required

2.13.2 Definition of residues for monitoring

Food of plant origin: not required

Food of animal origin: not required

Soil: not required

Groundwater: not required

Surface water: not required

Sediment: not required

Air: not required

2.14 Assessment of endocrine disruption properties

In the ECHA/EFSA "Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009" 2018, it is clearly stated that the term "substance" would refer to "any `chemical substance´". That means that the guidance document and its requirements are not applicable to micro-organisms or viruses. Accordingly, an assessment of endocrine activity of these "biopesticides" is not warranted. Apart from that, the following considerations substantiate the assumption that endocrine disruption properties of CpGV are completely unlikely:

Effects on hormones or on endocrine-producing organs have been observed following infection with viruses such as HIV, Hepatitis C, mumps or cytomegalovirus. Main findings were adrenal dysfunction or disturbance of hormone-steered metabolic processes resulting in lipodystrophy, dyslipidemia or insulin resistance but also pubertal delay, lower testosterone levels or hypothyroidism. However, these effects were secondary to severe systemic disease, sometimes related to inflammation. Often, it may be difficult to distinguish those from ED effects of medication that is used for continuous management of the chronic disease (Kino and Chrousous, 2007, ASB2019-3390; Antonelli et al., 2009, ASB2019-3372; Loomba-Albrecht et al., 2014, ASB2019-3452; Mirza et al., 2018, ASB2019-3391).
In contrast, CpGV, as other baculoviruses, is not infectious or pathogenic to vertebrates and, accordingly, will not cause any disease in those. There is no indication from open literature that a virus would have caused endocrine disruption in a non-target species, i.e., a species for which it is non-pathogenic.

Level 3

Cydia pomonella GV

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		*Brief summary – name of active and assessed uses formulation considered. [Identify the representative uses/products that are considered to comply with Article 4 and those that are not]*

3.1.1.2 Submission of further information

		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		*[If no go to ii immediately below]*
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.			*[If yes – specify here the rationale i.e. whether (a) or (b) applies and cross reference to section xx detailing the information still to be submitted* If no – explain the further information to be submitted and its relevance to the decision on approval Explain if some of the information to be submitted relates only to specified products/uses/use scenarios]

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	*[If yes –clearly specify the nature of the proposed restriction(s) i.e.* (a) the minimum degree of purity of the active substance; (b) the nature and maximum content of certain impurities; (c) restrictions arising from the evaluation of the information referred to in Article 8 of 1107/2009 taking account of the agricultural, plant health and environmental, including climatic, conditions in question; (d) type of preparation; (e) manner and conditions of application; (f) submission of further confirmatory information to Member States, the Commission and the European Food Safety Authority, (the Authority), where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge; (g) designation of categories of users, such as professional and non-professional; (h) designation of areas where the use of plant protection products, including soil treatment products, containing the active substance may not be authorised or where the use may be authorised under specific conditions; (i) the need to impose risk mitigation measures and monitoring after use; (j) any other particular conditions that result from the evaluation of information made available in the context of Regulation 1107/2009. Explain if some of the information to be submitted relates only to specified products/uses/use scenarios]

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			Not relevant for micro-organisms or viruses.

	establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).			
	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.			Not relevant for micro-organisms or viruses.
	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.	X		Granuloviruses have to be considered as persistent in soil, as they are protected from UV-light in deeper soil layers, but multiplication can restart again only if the permissive host appears. Based on the available data, no significant ecotoxicological or environmental risk from the application of CARPOVIRUSINE, MADEX, MADEX TWIN and VIRGO can occur according to Good Agricultural Practice.
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		According to SANCO/12545/2014 rev. 2, efficacy data, i.e., Document MMP 6, is not required for renewal of active substances. The representative products are registered in several EU member states for the representative uses considered in this dossier. Therefore, it was already evaluated according to Uniform Principles (Regulation (EC) No 546/2011) and all relevant data have been evaluated at zonal and Member State level.
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.			Not applicable to viruses.
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		Sufficient information is available. For data gaps see 3.1.4
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.			Not applicable for micro-organisms.
	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			Not applicable for micro-organisms.
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 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.	X		Analytical methods on biological stability are considered to be sufficiently validated. Data are missing to determine the content of CpGV in terms of granules/L. Methods for microbial contaminants including *Bacillus cereus* are standard methods. See Vol. 3, section B5 and Vol. 4 for more details.
	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		No residue definition is applicable for *Cydia pomonella* GV or its metabolites. Therefore, no post-registration monitoring methods are required.
	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		
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	No toxicological reference value has been derived for *Cydia Pomonella* Granulovirus since toxicity, pathogenicity or infectivity in mammals has not been observed for this virus.
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 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.**		X	Genotoxicity was not investigated according to current standards and data requirements. Nevertheless, the available information is considered sufficient to exclude a genotoxic potential of CpGV (Vol. 1, 2.6.1, p. 26).
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	Application of CpGV in plant protection products may be reasonably considered to be of low risk to human or animal health. The very few available studies in which animals were exposed to CpGV for ca 3 months did not reveal adverse effects. Therefore, higher tier data for CpGV is not warranted and, the low quality of these studies is not of concern (Vol. 1, 2.6.1, p. 26).
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 Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**		X	Application of CpGV in plant protection products may be reasonably considered to be of low risk to human or animal health. The very few available studies in which animals were exposed to CpGV for ca 3 months did not reveal adverse effects. Therefore, higher tier data for CpGV is not warranted and, the low quality of these studies is not of concern. Furthermore, a low quality combined reproduction and developmental study with CpGV in mice (Döller and Huber, 1983, TOX2003-1169) showed no adverse effects (Vol. 1, 2.6.1, p. 26).
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 endocrine disrupting properties classification				
		Yes	No	
i)	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 **carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties**		X	Application of CpGV in plant protection products may be reasonably considered to be of low risk to human or animal health. The very few available studies in which animals were exposed to CpGV for ca 3 months did not reveal adverse effects. Therefore, higher tier data for CpGV is not warranted and, the low quality of these studies is not of concern (Vol. 1, 2.6.1, p. 26).
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**			
iii)	Linked to either i) or ii) immediately above. 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		X	

	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.			
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	Not applicable to viruses.
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	Not applicable to viruses.
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	Not applicable to viruses.
Ecotoxicology				
		Yes	No	
	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 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.	X		No quantitative ecotoxicological risk assessment for the supported uses of the representative formulations CARPOVIRUSINE, MADEX, MADEX TWIN and VIRGO is deemed necessary given the lack of toxicity, infectivity or pathogenicity from laboratory data in conjunction with other available information on the active substance *Cydia pomonella* Granulovirus (CpGV). Nevertheless, a quantitative risk assessment was performed. Based on the quantitative risk assessment in conjunction with existing literature information a low risk can be concluded for non-target organisms.
	It is considered that, on the basis of the assessment of Communi-		X	Not applicable.

	ty or internationally agreed test guidelines, the substance **HAS** endocrine disrupting properties that may cause adverse effects on non-target organisms.			
	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.			Not applicable.
	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		Based on the total set of data, it can be concluded that all representative products have to be classified as non-hazardous. Granuloviruses, including CpGV, are highly host specific as cross-transmission is rarely successful and infectivity is restricted to members of the genus or in some cases to the family of the original host. No toxic or pathogenic effects were observed.
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 purposes.		X	A residue definition is not required. *Cydia pomonella* GV is included in Annex IV of Regulation (EC) No 396/2005. Consequently, no maximum residue levels are set in food and feed. Also no action levels and no residue definitions are proposed or exist for *Cydia pomonella* GV in soil, water and air.
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		The exponential decrease of activity found in the deeper soil layers in a soil column leaching study and the results of a field lysimeter experiment conducted in Germany indicate a low risk of reaching deeper soil layers and therefore the groundwater.

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		X	*[If yes identify the criteria considered met by the substance* i.e. its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories, — it meets two of the criteria to be considered as a PBT substance — there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones), — it contains a significant proportion of non-active isomers, — it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3, — it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4, — if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5.]

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.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.		X	In the health risk assessment of micro-organisms as active ingredients in PPP, sensitisation is always of concern. In case of CpGV (even though not being a micro-organism), allergic reactions might occur because of sensitising properties either of viral envelope proteins, of proteins from the insect larvae on which the virus is propagated or of co-formulants in the commercial products. It is neither technically feasible nor would it make any sense to test the purified virus for sensitisation.

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				
Arysta A 5-batch analysis with respect to the content of CpGV in MPCA not older than 5 years is missing.		X		
Carpovirusine Studies and information used by NL for assessment of equivalence of CpGV and revised composition of the product Carpovirusine.		X		
Andermatt New isolate CpGV-45 Clarification regarding the content of the virus in MPCA is needed.		X		
Andermatt New isolate CpGV-V14 5-batch analysis for *Salmonella* according to the requirements in SANCO/12116/2012 is missing.		X		
Andermatt For 5-batch analysis of all isolates actual values instead of thresholds should be provided for the content of CpGV and for *Bacillus cereus.*		X		
MADEX Sufficient number of batch analyses are missing for *Bacillus cereus.*		X		
MADEX/MADEX TWIN Safety data sheets for two co-formulants are missing.		X		
VIRGO Sufficient number of batch analyses are missing for contaminating micro-organisms in-		X		

cluding *Bacillus cereus*.				
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
Carpovirusine Two storage stability tests are currently on-going and should be provided when finalised.			X	
MADEX For MADEX storage stability tests regarding physical and chemical properties and the growth of contaminating micro-organism are missing.		X		
MADEX Data for viscosity are missing.		X		
VIRGO For Virgo storage stability test regarding the growth of contaminating micro-organism is missing.		X		
VIRGO For storage stability studies information on packing material is missing.		X		
3.1.4.3 Data on uses and efficacy				
None.				
3.1.4.4 Data on handling, storage, transport, packaging and labelling				
All plant protection products		X		

Information about effectiveness of cleaning procedures for equipment and protective clothing is missing.				
3.1.4.5 Methods of analysis				
Andermatt: Data for determination of the content of CpGV in MPCA and MPCP in terms of granules/L are missing.		X		
Arysta Data for determination of the content of CpGV in MPCA and MPCP in terms of granules/L are missing.		X		
Serbios Data for determination of the content of CpGV in MPCP in terms of granules/L are missing.		X		
3.1.4.6 Toxicology and metabolism				
None.				
3.1.4.7 Residue data				
None.				

3.1.4.8 Environmental fate and behaviour				
None.				
3.1.4.9 Ecotoxicology				
None.				

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)**
	[specify if measure relates to a specific representative use/use scenario/product or to all uses/products]

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)**
Contamination of the virus preparations and the com-	*[specify if concern relates to all or specific*

mercial products with *Bacillus cereus* might be a concern, depending on actual levels.	*representative use/use scenario/product or to all uses/products]*

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.)

Representative use		Use "A" (X[1])	Use "B" (X[1])
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Bystander risk	Risk identified		
	Assessment not finalised		
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		
	Assessment not finalised		
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached		
	Parametric value of 10 µg/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**
None.	*[specify the reasons why expert consultation is considered necessary]*

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**
CpGV as low risk active substance	CpGV should be approved as low risk active substance	Not agreed because of sensitising properties

3.2 Proposed decision

[redacted]

[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 risk identified

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
	[redacted]

3.4 Appendices

3.4.1 Guidance documents used in this assessment

European Commission 2016: Guidance Document for Applicants on Preparing Dossiers for the Approval or Renewal of Approval of a Microorganisms including Viruses according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013. SANCO/12545/2014– rev. 2 March 2016

European Commission 2008: Guidance Document on the assessment of new isolates of baculovirus species already included in Annex I of Council Directive 91/414/EEC SANCO/0253/2008 rev. 2 - 22 January 2008

EFSA 2011: Guidance for the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under the regulation (EC) NO 1107/2009. EFSA Journal 2011;9(2):2092

WHO/FAO. 2010. Manual on development and use of FAO and WHO specifications for pesticides. Second revision of the first edition. Rome, 2010.

EFSA 2009: 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

European Commission 2010: Guidance document on pesticide residue analytical methods SANCO/825/00 - rev. 8.1 16/11/2010

European Commission 2012: SANCO Working Document on Microbial Contaminant Limits for Microbial Pest Control Products SANCO/12116/2012 –rev. 0; ENV/JM/MONO(2011)43

OECD 2011: Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Oesticides and Biotechnology. OECD issue paper on microbial contaminant limits for microbial pest control products. ENV/JM/MONO(2011)43, Series on Pesticides No. 65

Technical Monograph N° 17. Guidelines for Specifying the Shelf Life of Plant Protection Products (2nd edition, CropLife International, 2009)

European Commission, 2000: Residues: Guidance Document 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, 11 July 2000.

European Commission, 2000c. Technical Material and Preparations: Guidance Document 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/3030/99 rev. 4, 11 July 2000.

European Commission 2017: Guidance document on analytical quality control and method validation procedures for pesticide residues and analysis in food and feed (SANTE/11813/2017, 21.-22-11-2017)

3.5 Reference list

List [in the conventional format] any references specifically cited in Volume 1 (i.e references to underpinning documents such as PPR-Panel Opinions, EFSA conclusions, national documents etc.).

Data point	Author(s)	Year	Title Owner, Report No. Source (where different from owner) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previously submitted Y/N* If Y => old data point
	Germany	2007	Draft Assessment Report ASB2010-10675	no				