Renewal
Assessment Report

Cydia pomonella GV

Madex Twin

Volume 3 – B.6 Effects on human health

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

Table of contents

B Summary, evaluation and assessment of the data and information

B.6 Effects on human health

Madex Twin is one of four representative formulations for the renewal of approval of *Cydia pomonella* Granulovirus (CpGV). Madex Twin, a suspension concentrate, contains 3 x 10^{13} GV (V22 isolate) per litre and has the same composition as Madex.

A literature research was conducted by the notifier and the RMS (see Vol. 3 CA B.6). No study was identified to be relevant for this chapter.

The isolate CpGV-V22 does not have any other characteristics as the Mexican isolate with respect to toxicity, infectivity or pathogenicity. Thus, Madex and Madex Twin can be considered as toxicologically identical. The data and information used for the evaluation of Madex are also applicable to Madex Twin.
The evaluation of Madex is based on data for the virus and the SC formulation Granupom previously evaluated in the first monograph. Granupom contains 2.2 x 10^{13} GV (Mexican Isolate) per litre and additional co-formulants in comparison to Madex Twin. The studies on acute oral and inhalation toxicity and sensitisation are presented or mentioned in the toxicology section on the active substance whereas the studies on irritation are reported in detail in this section. A summary of the results is presented in Table B.6.1-1.

Table B.6.1-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for Madex Twin

Type of test, model system (Guideline)	**Result**	**Acceptability**	**Classification (acc. to the criteria in Reg. 1272/2008)**	**Reference**
LD_{50} oral, rat	> 5 x 10^9 AcNPV/kg bw	Not relevant (data for CpGV available)	-	[redacted] 1980; TOX2003-1149
LD_{50} oral, rat	> 1.015 x 10^8 CpGV/animal	Yes	-	[redacted] 2005; TOX2006-1680
LD_{50} dermal	no study submitted for this endpoint; notifier refers to the sensitsisation study with Granupom where no adverse effects were observed after 10 intradermal injections with the test item			
LC_{50} inhalation, rat*	> 35 mg/m^3 air	No (short exposure period of only 15 min)	-	[redacted] 1992; TOX2003-1148
Skin irritation, rabbit* (OECD 404)	Non-irritant	Yes	-	[redacted] 1998; TOX2003-1184
Eye irritation, rabbit* (OECD 405)	Non-irritant	Yes	-	[redacted] TOX2003-1185
Skin sensitisation, guinea pig* (Landsteiner method)	Non-sensitising	No (method not acceptable according to current scientific standards)	-	[redacted] 1986; TOX2003-1147
Respiratory sensitisation, guinea pig	Non-sensitising	No (no valid method)	-	[redacted] 1992;

				TOX2003-1148

* test conducted with Granupom

No studies are available for Madex Twin. However, based on information for CpGV, other formulations and the [redacted] in Madex Twin no acute toxicity or irritation is expected. Since no adequate test system is available for testing of the sensitising potential of micro-organisms including viruses labelling of Madex Twin with the following phrase is required: "Contains *Cydia pomonella* Granulovirus. Micro-organisms may have the potential to provoke sensitizing reactions."

B.6.1 Basic acute toxicity studies

B.6.1.1 Acute oral toxicity

No new studies submitted. Old studies are presented in Volume 3 B.6 on the active substance.

Conclusion by RMS (2019):

The study on CpGV and the two other representative formulations Virgo and Carpovirusine indicate no acute oral toxicity. The [redacted] in Madex Twin is also not classified for acute oral toxicity. Hence, no classification is required according to Regulation (EC) No. 1272/2008.

B.6.1.2 Acute inhalation toxicity

No new studies submitted. Old studies are presented in Volume 3 B.6 on the active substance.

Conclusion by RMS (2019):

An acceptable study exists for the formulation Virgo with a similar content of CpGV which shows no signs of acute inhalation toxicity. As the [redacted] in Madex Twin is also not classified for acute inhalation toxicity no classification is warranted according to Regulation (EC) No. 1272/2008.

B.6.1.3 Acute percutaneous toxicity

No study submitted for this endpoint.

Conclusion by RMS (2019):

Studies for the representative formulations Virgo and Carpovirusine with a similar content of CpGV do not indicate acute dermal toxicity. The [redacted] in Madex Twin is also not classified for acute dermal toxicity. Hence, no classification is required according to Regulation (EC) No. 1272/2008.

B.6.2 Additional acute toxicity studies

B.6.2.1 Skin irritation

Study evaluated in the original monograph of *Cydia Pomonella* Granulovirus (December, 2007, ASB2010-10675) and re-evaluated by RMS in 2018:

Reference: OECD KIIIM1 7.1.4

Report	Acute dermal irritation/corrosion Granupom SC (CpGV) [redacted]., 1998, Report No. 98 10 42 829, TOX2003-1184
Guideline(s):	OECD Guideline 404 (Acute Dermal Irritation / Corrosion)
Deviations:	No
GLP:	Yes
Acceptability:	Yes

Materials and methods

Test material (Lot/Batch No.)	Granupom SC (Batch No. AE F 083311 SC 13 A503)
Species	Rabbit
No. of animals (group size)	3 males
Initial test using one animal	No
Exposure	0.5 mL (4 hours, occlusive)
Vehicle/Dilution	None
Post exposure observation period	10 days
Remarks	None

Results and discussions

Table B.6.2-1: Skin irritation of Granupom

Animal No.		Scores after treatment*				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	- -
2	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	- -
3	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	- -

* Scores in the range of 0 to 4

Clinical signs:	No clinical signs of toxicity were observed.

Conclusion

Under the experimental conditions, Granupom is not a skin irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

Conclusion by RMS (2019):

The study is still acceptable and can be used to rule out a skin irritation potential of CpGV. The [redacted] in Madex Twin is also not classified for skin irritation. Hence, no classification is required for Madex according to Regulation (EC) No. 1272/2008.

B.6.2.2 Eye irritation

Study evaluated in the original monograph of *Cydia Pomonella* Granulovirus (December, 2007,

ASB2010-10675) and re-evaluated by RMS in 2018:

Reference:	OECD KIIIM1 7.1.5
Report	Hoe 083311; watermiscible suspension concentrate; 2.2 *10 EXP. 13 VIR./ml (Code: Hoe 083311 00 SC13 A401): Testing for primary eye irritation in the rabbit; [redacted]., 1993, Report No. 93.0567, TOX2003-1185
Guideline(s):	OECD Guideline 405 (Acute Eye Irritation / Corrosion) EPA OPP 81-4 (Acute Eye Irritation)
Deviations:	No
GLP:	Yes
Acceptability:	Yes

Materials and methods

Test material (Lot/Batch No.)	Granupom
Species	Rabbit, New Zealand White
No. of animals (group size)	3 females
Initial test using one animal	No
Exposure	0.1 mL (single instillation in conjunctival sac)
Irrigation (time point)	Yes (24 h after instillation)
Vehicle/Dilution	None
Post exposure observation period	7 days
Remarks	None

Results and discussions

Table B.6.2-2: Eye irritation of Granupom

Animal No.		Scores after treatment*				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	-
	Redness conjunctivae	1	1	0	0	0.33	2
	Chemosis conjunctivae	1	0	0	0	0	1
2	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	-
	Redness conjunctivae	2	2	2	1	1.67	7
	Chemosis conjunctivae	1	1	1	0	0.67	3
3	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	-
	Redness conjunctivae	1	2	2	1	1.67	7
	Chemosis conjunctivae	1	0	0	0	0	1

* Scores in the range of 0 to 4 for cornea opacity and chemosis, 0 to 3 for redness of conjunctivae and 0 to 2 for iritis

Clinical signs:	No clinical signs of toxicity were observed.

Conclusion

Under the experimental conditions, Granupom is not an eye irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

Conclusion by RMS (2018):

The study is still acceptable and can be used to rule out an eye irritation potential of CpGV. The [redacted] in Madex Twin is also not classified for eye irritation. Hence, no classification is required for Madex according to Regulation (EC) No. 1272/2008.

B.6.2.3 Skin sensitisation

No new studies submitted. Old studies are presented in Volume 3 B.6 on the active substance.

Conclusion by RMS (2018):

There are two acceptable studies available for the representative formulations Virgo and Carpovirusine with a similar content of CpGV but a different outcome. While the study on Carpovirusine shows a skin sensitising potential no effect was observed in the study with Virgo. No skin sensitising effect is described for the [redacted] in Madex Twin. As a precautionary approach micro-organism including viruses are in general considered to have a sensitising potential. Hence, Madex Twin needs labelling with the following phrase: "Contains *Cydia pomonella* Granulovirus. Micro-organisms may have the potential to provoke sensitizing reactions."
The notifier recommends not using this warning phrase since no positive results were yet published for CpGV or other viral species currently approved in the EU (Martel et al, 2010, ASB2011-9441; Hackl et al., 2015, ASB2015-4072). However, as already stated in the first evaluation of the study in the DAR from 2007, it cannot be ruled out that proteins from the larval matrix material in the technical active substance might provoke sensitisation. Therefore, the RMS is of the opinion to keep the warning phrase.

B.6.3 Data on exposure

Madex Twin is used for the treatment of the oriental fruit moth on stone fruits. It is applied up to 12 times at a rate of 0.3 x 10^{13} GV/ha. The product is intended for professional use and home and garden use.

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. CpDG is naturally present in the environment. Hence, a risk for operators, workers, bystanders and residents is not expected when the product is used as intended.

Regarding the potential risk for sensitisation PPE is required for the operator.

B.6.4 Available toxicological data relating to non-active substances

Toxicological information on the co-formulants is presented in Vol. 4. No additional classification is required.

B.6.5 Supplementary studies for combinations of plant protection products

Not necessary as no combinations of plant protection products are recommended.

B.6.6 Summary and evaluation of health effects

The toxicological studies on CpGV, formulations containing CpGV and available data on the [redacted] indicate that no health risks have to be anticipated for operators, workers, bystanders and residents.

Due to a potential risk for sensitisation operators will have to wear PPE, which will reduce exposure.

B.6.7 References relied on

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
KMP 7	Krieg, A.	1976	GRANULOSIS AND NUCLEAR POLYHEDROSIS VIRUSES: SAFETY ASPECTS CONCERNING THEIR PRODUCTION AND APPLICATION not available, not applicable Z Angew Entomol, 82, 129-134 GLP/GEP: no Published: yes BVL-34163320, BVL-3306966, BWS2003-90	no	no	not protected	-	Y KIIIM 7
KMP 7.1	Gröner, A.	1986	SPECIFICITY AND SAFETY OF BACULOVIRUSES not available, not applicable The Biology of Baculoviruses, Volume I, Biological Properties and Molecular Biologie, Chapter 9, 177-201 GLP/GEP: no Published: yes BVL-3416321, BVL-3489330, TOX2003-117	no	no	not protected	-	Y KIIIM 7.1
KMP 7.1	Huber, J.	1978	ABOUT THE HOST SPECTRUM OF THE CODLING MOTH GRANULOSIS VIRUS not available, not applicable Safety aspects of baculoviruses as Biological Insecticides, 75-85 GLP/GEP: no Published: yes BVL-3553049, TOX2003-1180	no	no	not protected	-	Y KIIIM 7.1

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**
KMP 7.1	[redacted]	1990	CYDIA POMONELLA GRANULOSUS VIRUS (CPGV) HOE 083311 SUMMARY AND CONCLUSIONS ON THE TOXICITY Andermatt Biocontrol GmbH / Probis GmbH, not applicable [redacted] GLP/GEP: no Published: no BVL-3416267, TOX2005-1876	no	no	not protected	PKA	Y KIIIM 7.1
KMP 7.1.1	[redacted]	1980	TOLERANCE TESTING OF ACNPV NUCLEAR POLYHEDROSIS VIRUS FOLLOWING SINGLE-DOSE ADMINISTRATION TO SPF WISTAR RATS Andermatt Biocontrol GmbH / Probis GmbH, 595, 234/80 [redacted] GLP: yes Published: no BVL-3416319, TOX2003-1149	yes	no	not protected	PKA	Y KIIIM 7.1.1
KMP 7.1.2	[redacted]	1992	HOE 083311; WATER MISCIBLE SUSPENSION CONCENTRATE: 2.2*10 EXP. 13 VIR./1 (CODE:) TESTING FOR RESPIRATORY SENSITIZATION IN THE MALE AND FEMALE PIRBRIGHT WHITE GUINEA PIG Andermatt Biocontrol GmbH / Probis GmbH, 90.0689, 91.1096 [redacted] GLP: yes Published: no BVL-3416316, TOX2003-1148	yes	no	not protected	PKA	Y KIIIM 7.1.3

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**
KMP 7.1.3 KMP 7.2.3	[redacted]	1986	HOE 083311 OI LC08 A101 TESTING FOR SENSITISING PROPERTIES OF ON PIRPBRIGHT-WHITE GUINEA PIGS BY THE METHOD OF LANDSTEINER Andermatt Biocontrol GmbH / Probis GmbH, 861169, 86.1373 [redacted] GLP: yes Published: no BVL-3416317, TOX2003-1147	yes	no	not protected	PKA	Y KIIIM 7.1.2
KMP 7.1.3	Ignoffo, C.M., Huang, H.T., Shapiro, M., Woodard, G.	1975	INSUSCEPTIBILITY OF THE RHESUS MONKEY, MACACA MULATTA, TO AN INSECT VIRUS, BACULOVIRUS HELIOTHIS not available, not applicable GLP/GEP: no Published: yes BVL-3416320, TOX2003-1155	no	no	not protected	-	Y KIIIM 7.1.2
KMP 7.2.1	[redacted]	1998	ACUTE DERMAL IRRITATION/CORROSION GRANUMPOM SC (CPGV) Andermatt Biocontrol GmbH / Probis GmbH, 98 10 42 829 [redacted] GLP: yes Published: no BVL-3416342, TOX2003-1184	yes	no	not protected	PKA	Y KIIIM 7.1.4

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**
KMP 7.2.2	[redacted]	1993	HOE 083311; WATERMISCIBLE SUSPENSION CONCENTRATE; 2.2*10 EXP. 13 VIR./ML (CODE: HOE 083311 00 SC13 A401) TESTING FOR PRIMARY EYE IRRITATION IN THE RABBIT Andermatt Biocontrol GmbH / Probis GmbH, 93.0485, 93.0567 [redacted] GLP: yes Published: no BVL-3416343, TOX2003-1185	yes	no	not protected	PKA	Y KIIIM 7.1.5
KMP 7.3/01 1.additional submission	Hackl, E., Pacher-Zavisin, M., Sedman, L., Arthaber, S., Bernkopf, U., Brader, G., Gorfer, M., Mitter, B., Mitropoulou, A., Schmoll, M., van Hoesel, W., Wischnitzky, E., Sessitsch, A.	2015	LITERATURE SEARCH AND DATA COLLECTION ON RA FOR HUMAN HEALTH FOR MICROORGANISMS USED AS PLANT PROTECTION PRODUCTS REFERENCE not available, not stated EFSA Journal, 2015 EN-801, 173pp GLP/GEP: no Published: yes BVL 3306860, ASB2015-4072	no	no	not protected	-	N
KMP 7.3/02 1.additional submission	Martel, C., Nielsen, G.D., Mari, A., Licht, T.R., Poulsen, L.K.	2010	BIBLIOGRAPHIC REVIEW ON THE POTENTIAL OF MICROORGANISMS, MICROBIAL PRODUCTS AND ENZYMES TO INDUCE RESPIRATORY SENSITIZATION not available, not applicable EFSA Eur. Food Saf. Auth., CFP/EFSA/FEEDAP/2009, 1-95 GLP/GEP: no Published: yes BVL-3306861, ASB2011-9441	no	no	not protected	-	N