Renewal
Assessment Report

Cydia pomonella GV

Madex

Volume 3 – B.6 Effects on human health

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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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B Summary, evaluation and assessment of the data and information

B.6 Effects on human health

Madex is one of four representative formulations for the renewal of approval of *Cydia pomonella* Granulovirus (CpGV). Madex was also a representative formulation for inclusion of the active substance in Annex I. The recipe of Madex has not changed since then. The product contains 3 x 10^{13} GV (Mexican Isolate) per litre and is formulated as a suspension concentrate.

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.

No toxicity studies for Madex were submitted for the first evaluation in 2007 and no new studies on the product were submitted for the renewal. The first evaluation was based on data for nuclear polyhedrosis virus (belonging to the group of baculoviruses) and Granupom, a suspension concentrate with 2.2 x 10^{13} GV (Mexican Isolate) per litre and additional co-formulants in comparison to Madex. All studies were presented in the original monograph on CpGV. For the renewal the old studies were re-evaluated by the RMS according to current scientific criteria and guidelines. The studies on acute oral and inhalation toxicity and sensitisation are presented or mentioned again in the toxicology section on the active substance and are not reported in detail in this section. The studies on irritation are reported in detail in this section. A summary of the results is presented in Table B.6.1-1.
Madex consists of CpGV and [redacted] which is not toxic. For this reason the results and conclusion for CpGV also apply to Madex.

Studies on the infectivity, toxicity and specificity of baculoviruses in general (Gröner, 1986, TOX2003-1179; [redacted] 1990, TOX2005-1876; Krieg, 1976, BWS2003-90, Huber, 1978, TOX2003-1180; Ignoffo, 1975, TOX2003-1155) are discussed in the toxicology section on CpGV.

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

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	Supplementary (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] 1993; TOX2003-1185
Skin sensitisation, guinea pig*	Non-sensitising	No (method not	-	[redacted] 1986;

(Landsteiner method)		acceptable according to current scientific standards)		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. However, based on information for CpGV, other formulations and the [redacted] in Madex 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 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 the RMS (2019):

The study on CpGV and the two other representative formulations Virgo and Carpovirusine indicate no acute oral toxicity. The [redacted] in Madex 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 the 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 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 the 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 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:	KMP 7.2.1
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 the RMS (2019):

The study is still acceptable and can be used to rule out a skin irritation potential of CpGV. The [redacted] in Madex 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 the RMS (2019):

The study is still acceptable and can be used to rule out an eye irritation potential of CpGV. The [redacted] in Madex 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 the RMS (2019):

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 on Virgo. No skin sensitising effect is described for the [redacted] in Madex. As a precautionary approach micro-organisms are in general considered to have a sensitising potential. Hence, Madex 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 is used for the treatment of codling moth on pome fruit and walnut. It is applied up to 10 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-3416322, 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, TOX2003-1179	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 7.1.3	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