Renewal
Assessment Report

Cydia pomonella GV

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

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.6 Effects on human health

The respective chapter from the previous DAR (Germany, 2007, ASB2010-10675) was revised and additional information was included. The conclusions remained virtually the same.

B.6.1 Tier I

B.6.1.1 Basic information

Baculoviruses (including the *Cydia pomonella* Granulovirus, CpGV) are part of our natural environment and have been successfully used for biological insect control for long with first proposals and attempts of such an application dating back at least to the 1930iers, according to other sources even to the end of the 19th century (Benz, 1986, ASB2018-879; Huber, 1986, ASB2018-1330; Kalawate, 2014, ASB2017-16166). Viruses are obligate intracellular parasites, *i.e.,* they can only multiply inside living cells. Therefore, the basic 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.
In the following, core information regarding species specificity and host range as well as on interaction with mammalian cells from the open literature is summarised. The resulting general view that baculoviruses such as CpGV will not infect vertebrates is supported by the more specific information on CpGV (Tier I studies, occupational medical surveillance) provided in the subsequent sections.
The general safety of baculoviruses for vertebrates including humans was emphasised by OECD (2002, TOX2006-1036) as well as by EFSA's biohazard panel (EFSA, 2012, ASB2014-3917). In the latter one, a previously suggested "qualified presumption of safety (QPS)" recommendation for baculoviruses in general was confirmed. More recently, Hackl et al. (2015, ASB2015-4072), on behalf of EFSA, performed an extensive literature search on human health risk assessment for micro-organisms in plant protection products. Their search did not reveal any evidence of adverse effects of baculoviruses to human or animal health.

Burges et al. (1980, TOX2006-1679) summarised the information on host specificity and biosafety of nucleopolyhedrosis viruses (NPV) and, to a smaller extent, also of granulosis viruses (GV) available at that time, both with regard to invertebrates and vertebrate species but also to micro-organisms and plants. According to their review, there was no evidence that vertebrates could be infected by baculoviruses. This conclusion was mainly based on experimental studies for infectivity, pathogenicity and toxicity which had been performed with different species from the *Baculoviridae* family, mainly NPV. Even in invertebrates (insects), the host range appeared very narrow. In particular for GV, it was confined to few lepidopteran species. The authors also reviewed numerous articles in which *in vitro* studies on various cell lines of mammalian and insect origin had been reported and did not find indications of replication in non-insect cells. It must be taken into consideration, however, that the information regarding CpGV itself is scarce. It is mentioned int his article, at least, that CpGV, beside its main target host, might infect *in vivo* only two other insect species from the *Totricidae* family. Apparently going back to Gröner et al. (1978, TOX2003-1154, see below), the authors reported that CpGV did not affect the health of mice and Guinea pigs after feeding, inhalation or injection. In addition, it did not cause skin or eye irritation. *In vitro* replication of CpGV was confined to one insect cell line.
Krieg (1976, BWS2003-90) confirmed a high host specificity of baculoviruses in general, supported by a similar but not identical database. He mentioned baculoviruses to infect only the arthropod orders Lepidoptera, Hymenoptera, Diptera, and Coleoptera.
The same conclusion that baculoviruses will not infect vertebrates had been drawn before by Ignoffo (1973, TOX9750934), based on *in vivo* testing of as many as 51 entomopathogenic viruses (including 29 NPV and 10 GV species) in vertebrates, using various application routes such as inhalation, injection (i.v., i.m., i.p.), oral gavage, dietary or dermal administration. The numerous studies had been conducted in many different species such as mice, rats, guinea pigs, rabbits, dogs, mule deer or chick-

en but also in non-human primates and man. Again, testing of GV was much less extensive than that of NPV and CpGV itself was apparently not specifically considered in any of these studies.
In addition, Ignoffo and Refajko (1972, TOX2003-1161) reported that their own experimental efforts failed to infect three human (HEK, HeLa, Wi-38) and one African green monkey (kidney) cells lines with *Heliothis zea* (cotton bollworm larvae) NPV. Neither a cytopathic effect nor haemadsorption or haemagglutionation could be observed. Röder and Pünter (1977, TOX2003-1162) inoculated cultures from three mammalian cell lines with 50 infectious units of *Autographa californica* NPV per cell. Two permanent cell lines of human (HeLa Ohio, derived from cervix carcinoma) or monkey orgin (Vero kidney cells), and a primary culture of rat embryonic fibroblasts were exposed to the virus but no evidence of replication was observed, in contrast to what was seen in insect cell cultures. Of course, these negative findings do not prove that baculoviruses were not capable to penetrate into mammalian cells.
Referring mainly to Ignoffo's (1973, TOX9750934) work but also having reviewed more recent studies in mammals, birds, and aquatic organisms (fish, shrimps, daphnia) with NPV and GV, Gröner (1986, TOX2003-1179), in his introduction to a book chapter, concluded: 'Baculoviruses have been found only in invertebrates; no member of this family is known to infect vertebrates or plants.' The author highlighted that no specific antibodies had been found in mice, chicken and pigs following oral administration and in mice following inhalative exposure but discussed a possible occurrence of non-specific serological responses.

A genetic background of the host specificity of baculoviruses is assumed (OECD, 2002, TOX2006-1036) but the respective studies cited were all performed with NPV but never with GV. The occurrence of a productive infection seems to depend on the presence of a promoter which is known to be active so far only in *Lepidoptera* (Gronowski et al., 1999, TOX2006-1043) and some other arthropod orders (Mitchell and Friesen, 2012, ASB2018-28). Temperature requirements or preferences might also contribute to the lacking ability of these viruses to infect at least warm-blooded animals or their cells. Winstanley and Crook (1993, ASB2017-15579) tried to keep CpGV susceptibility of cell cultures obtained from the target host species *Cydia pomonella* for years and found it necessary for that purpose to maintain the cells at rather low temperatures. They reported that cell lines kept at or below 21°C retained susceptibility to the virus over a period of four years but lost it gradually when maintained at 27°C and eventually could not be infected at all.

Nonetheless, already decades ago, it had been shown that baculoviruses, at least NPV, may enter mammalian cells. Virus DNA was even detected in the nucleus but, apparently, gene expression and virus replication did not occur.
Gröner et al. (1984, TOX2003-1160) demonstrated that, beside two insect cell lines, *Autographa californica* NPValso entered the Chinese hamster cell line CHO-K1 since infectious virus could be etected 6 hours after inoculation in at least some cells. Electron microscopy revealed enveloped nucleocapsids in phagocytic vacuoles. Two hours later, however, no virus could be detected any longer suggesting that the cellular defense mechanisms were active and efficient even in cultured cells. Examinations by means of DNA hybridization and virus growth titration in a plaque assay as well as protein synthesis data failed to show any evidence of virus replication.
Tjia et al. (1983, TOX2003-1159) investigated the fate of inoculated *Autographa californica* NPV in human HeLa or embryonic kidney (HEK) cells, in hamster BHK21 (B3) and simian CV1 cells as well as in fibroblasts obtained from *Muntiacus muntjak*, *i.e.*, a deer. It could be shown that the virus, following inoculation with infectious tissue culture fluid from insect cells, was taken up by the mammalian cells. By means of DNA hybridisation, viral DNA was detected 24 hours later in the nuclei of the mammalian cells even though the number of copies per cell was rather low. Thereafter, however, it disappeared rapidly and there was no evidence of persistence or even replication of viral DNA.
Volkman and Goldsmith (1983, ASB2018-885; see also Volkman and Knudson, 1986, ASB2018-881) exposed 35 vertebrate cells lines (including 23 of human origin) to *Autographa californica* NPV obtained from different sources. Following co-incubation periods from 16 to 168 hours (*i.e.*, longer exposure times than used by most other researches for inoculation experiments) at two different temperatures, they found the uptake of virus particles into the cytoplasm to be quite common but observed no virus replication in any cell line.
With regard to similar properties and behaviour of CpGV itself, see subsection B.6.1.2.4 "Cell culture study" where a respective study (Winstanley, 2000, TOX2006-2290) is reported.

Despite the absence of virus replication, at least *Autographa californica* NPV may affect functions of mammalian cells in a presumably unspecific way but no adverse effects have been described so far. These findings are all related to immune system functions.
Stimulation of interferon production in murine and human cells lines was reported by Gronowski et al. (1999, TOX2006-1043) even though the effect was not consistently seen in all cell types under investigation. The authors attributed this "protective" effect to interaction of host cell membrane with viral proteins rather than to an infection of these cells with the baculovirus. In the same study, it was even demonstrated that pre-treatment with an interferon-stimulating preparation from baculovirus-infected insect cells provided some protection of C57B1/6NCr mice from an otherwise lethal infection with a murine encephalomyocarditis virus. Abe et al. (2009, ASB2018-887) confirmed the induction of interferon production in different murine cell types and investigated possible biochemical and molecular pathways behind.
Intranasal inoculation of mice with wild type (and recombinant) *Autographa californica* NPV protected the animals from an infection with an influenza virus (Abe et al., 2003, ASB2018-888). An immunostimulating and protective effect of the same virus was confirmed later by Molinari et al. (2010, ASB2017-11929) who protected C57Bl6 mice from a fatal infection with foot-and mouth disease (FMD) virus by prior i.v. application of *Autographa californica* NPV. Stimulation of the immune system in mice was also reported by Hervas-Stubbs et al. (2007, ASB2018-891).
Immunological effects of baculovirues in fish have been also investigated by Ashour et al. (2007, ASB2017-11927). This study is reported in more detail in the chapter on ecotoxicology.
It must be emphasised, however, that no information on similar properties of GV could be found in the literature and the question remains open whether such effects on the immune system were more specific to NPV or not. On balance, the actual relevance of these findings for the re-evaluation of CpGV is rather limited. The same holds true for a recent study from the field of safety testing of nanomaterials that, normally, would be outside the scope of this review but was submitted by the applicants as part of their dossier. Wang et al. (2015, ASB2017-11930) confirmed some activation of the immune system in female BALB/c mice (high cytokine levels, up-regulation of interferon production), following two i.p. injections of a not further specified baculovirus with a 15-day interval between. The authors observed also a transient weight loss leading them to the speculation that 'baculovirus itself may not be as safe as previously known'. Taking into consideration that the species, strain and dose of the applied virus was not given, an artificial route of administration was used and the group size of three animals only was very small, these findings are of no concern with regard to CpGV.

In research and "genetic engineering", baculoviruses have been often used as expression vectors (e.g., Kitajima et al., 2006, ASB2018-892), just because they may enter certain (but not all) types of mammalian cells but do not replicate there. Taking into consideration its narrow host range, its presumed safety to humans and animals, and the large amounts in which it can be produced, CpGV has been even proposed as a new viral simulant agent for biodefense studies (Garnier et al., 2009, ASB2017-15566). Due to similar size and some other characteristics that baculoviruses share with poxviruses (such as double-stranded DNA genomes, existence of an envelope, and a not too different shape), it could be used in the development, testing (also outdoors) and validation of biodefense systems Such systems, apparently under development, could be applied in particular for the detection of larger viruses such as the smallpox virus when misused as a biological weapon or for bioterrorist attacks. Medical data

Based on the literature search as performed by the RMS (see B.6.3) and the literature submitted by the applicants (Anon., 2016, ASB2017-11923), the *Cydia pomonella* Granulovirus (CpGV) does not affect any organism except codling moth larvae from the *Tortricidae* family. There is no evidence that CpGV or other baculoviruses viruses have ever caused any disease process in humans or other mammals. The absence of such reports is not surprising and adverse effects in mammals including humans are not expected because of the high host specificity of baculoviruses and their apparent inability to replicate and to cause productive infections in non-insect species as discussed above.

The assumption of general safety of baculoviruses with regard to human health is further supported by indirect evidence. Krieg (1976, BWS2003-90) provided the argument that virus epidemics among

susceptible insects such as silkworm or high level contamination of cabbage in the United States with an intentionally (to control *Trichoplusia n*i infestation) released NPV was not associated with any disease in breeders or in consumers.

Even though no clinical symptoms of infection have been observed in humans, exposure to baculoviruses might occasionally result in seroconversion which is, however, not an adverse finding *per se*. Instead, it is an indication of an immune response of the intact organism following detection of an antigen. There is limited evidence of such a reaction obtained both in humans and animals.
A 1.27 % rate of positive reagents was reported when 315 human serum samples from the Chinese province Wuhan were examined by means of an ELISA for antibodies against the granulovirus of cabbage butterfly (*Pieris rapae*) larvae. [This information is mentioned in a brief English summary (Anon., 1982, TOX2003-1156) on investigations published by the Wuhan university in 1981 and was, in the old DAR (Germany, 2007, ASB2010-10675), erroneously cited as Xuebao (1982, TOX2003-1156).] No associated illness was reported. Remarkably, ten serum samples obtained from laboratory staff routinely handling the virus were negative. In line with the latter information, Huang et al. (1977, cited by Burges et al., 1980, TOX2006-1679) reported that serological examinations and bioassays of blood and urine did not reveal infective virus, viral antigen, or viral antibodies in six persons exposed to *Heliothis zea* NPV during 26 months of production.
A serological response to CpGV itself was observed at least in one study in animals. In a field experiment, antibodies were detected by indirect ELISA in sera of trapped woodmice (*Apodemus sylvaticus*) after spraying of CpGV ($2x10^{13}$ granules/ha) in an apple orchard (Bailey and Hunter Fujita, 1987, TOX2003-1171). The earliest time point for antibodies to occur was day 4 following spraying. In woodmice from the same area which were caught and examined more than once, an increase in antibody titer was recorded. A booster effect due to repeated application of CpGV was assumed. In rare cases, virus antigen was detected by direct ELISA in faeces. This finding was attributed by Gröner (1990, TOX2005-1876) to the ingestion of CpGV granula and, as well as the antibody response, not considered a sign of virus replication in a mammalian species. The authors of the original article themselves did also not interpret their findings as indicative of infection or of an otherwise harmful effect on the animal's health.
On the other hand, Döller (1981, TOX2003-1168) found evidence of an unspecific interaction of CpGV matrix protein globulin with human and other mammalian (horse, cattle, sheep, and pig) immunoglobulins. Similar evidence for 'non-immunological interaction' between human IgG immunoglobolins with polyhedrin from *Mammestra brassica* NPV was reported by Döller et al. (1983, TOX2003-1170). Even though not sufficient to completely exclude seroconversion, these findings might provide an alternative explanation for the occasional detection of antibodies.
In line with that, no antibodies against another baculovirus, the *Mammestra brassica* NPV, were detected by means of a solid phase direct radioimmunoassay (RIA) in the sera of NMRI mice following oral or inhalative exposure (Döller and Gröner, 1981, TOX2003-1166). This evidence was further investigated by the same group in pigs. Following oral application to piglets, no antibodies to virus antigen were found in a (more sensitive) competitive RIA although a slight increase in body temperature had been noted in four out of five animals on day 2 after feeding. In faeces, infective virus was found but this finding was assigned to alimentary tract passage and not to virus replication (Döller et al., 1983, TOX2003-1167). Since it was not possible to infect insect larvae of *Mamestra brassicae* with organ extracts from the piglets in a bioassay, it was concluded by the study authors that a productive infection with virus replication in other parts of the body than the gut was not likely.

B.6.1.1.1 Medical surveillance on manufacturing plant personnel

Kalawate (2014, ASB2017-16166) supposed that CpGV was "the most important worldwide viral insecticide currently applied in terms of treated area". Therefore, it can be assumed that quite many people in numerous countries have been in contact with PPP containing this virus. Accordingly, health observations from occupational use is a meaningful information source on the occurrence (or absence) of adverse effects. All notifiers provided statements declaring that there was no evidence of any adverse effects on their employees who were involved in research, development, manufacturing and formulation of microbiological pest control products (MPCP) containing CpGV. To a certain extent,

this was also confirmed for people who were involved in spraying the MPCP in agriculture. However, no routine surveillance system for those people is in operation.

In the following, the respective information provided by the different notifiers is presented separately.

Arysta Lifescience S.A.S.
On balance, medical data on possible health effects in employees is scarce. The only new information submitted by this applicant was an "Occupational health statement" of a company or organisation called "Natural Plant Protection" (Noguères, France) which might be part of or is otherwise related to Arysta and is mentioned as the manufacturer of the PPP Carpovirusine since 1994 (Soubabere, 2016, ASB2017-11924). In this one-page document, it is stated that regular medical examination of operators (obviously, persons involved in manufacturing of the PPP are meant here) did not reveal evidence of occupational diseases which would have been recognized as such by the French national authorities. No information is given what parameters the medical examination would comprise, how many people were examined and how often these examinations took place.

For preparation of the old DAR (2007, ASB2010-10675), more information from Arysta on occupational health had been submitted. Most of these references have been also provided as part of the renewal dossier and, if this was the case, they are briefly mentioned here once more.

Lalisse (2005, TOX2006-1751) reported the medical examinations of 14 – 17 employees (total number not completely clear) of which apparently the most but not all were in direct occupational contact with biological agents including CpGV. The examinations took place in 2005. No details are given but it seems that no adverse symptoms or findings were noticed that could be attributed to CpGV.

The following part was copied directly from the DAR (2007, ASB2010-10675) since no further or updated information is available:

"In addition, the company provided a number of brief reports from research facilities (Binet, 1996, TOX2006-1752; Corroyer, 1996, TOX2006-1753; Biache, 1996, TOX2006-2089; Verhaeghe, 2002, TOX2006-2091), agrochemical technical centres or distribution companies of plant protection products (de Marcillac, 1996, TOX2006-1754; Ginoux, 1996, TOX2006-2086; Guiraud, 2002, TOX2006-2093; Clapier, 2002, TOX2006-2094; Martel, 2002, TOX2006-2283), or fruit growers co-operatives and associations (Dourlent, 1996, TOX2006-2087; Colombet, 1996, TOX2006-2088; Dupin, 2002, TOX2006-2090; Toutain, 2002, TOX2006-2095; Bourocher, 2002, TOX2006-2282) throughout France claiming that there were no adverse findings in their employees or members who were or might have been exposed to CpGV (mostly the product CAPROVIRUSINE was mentioned) and perhaps also to other baculoviruses. The number of potentially or actually exposed people was not reported and medical examinations (including clinical pathology) were only rarely performed but, in the whole, this information confirms the assumption that the application of baculoviruses contained in plant protection products does not pose a health risk."

Andermatt GmbH/Andermatt Biocontrol AG
In a statement by its managing director (Zingg, 2016, ASB2017-11925), it is declared that this company had produced CpGV since 1987. No adverse effects have been observed in persons engaged in production and handling of the 'product' in the manufacturing plant. No further details were given. It is not clear if CpGV or the PPP MADEX is meant here.

Therefore, information provided in preparation of the old DAR (2007, ASB2010-10675) was also used. The following paragraph was copied:

"According to the declaration of the task force every year thousands of persons were exposed during spraying of the product. No masks are used during the spraying. No case of sensitisation, irritation, toxicity or exposure related heath problems have ever been experienced. CpGV or MADEX did not cause health effects on manufacturing personnel (Andermatt, 2002, TOX2005-1346)."

Serbios s.r.l.
In a statement by the company SIPCAM SpA (apparently the manufacturer of the product for which Serbios s.r.l. is now the notifier), it is confirmed that no adverse effects have been observed in persons engaged in production and handling of the "product" in the manufacturing plant. It is not clear if CpGV or the PPP VIRGO is meant here. It is further mentioned that manufacturing was commenced in 2004 and that regular medical examination is offered to the employees (Dezza, 2016, ASB2017-11926).

In the dossier submitted that had been submitted by the former notifier Sipcam in preparation of the previous DAR (2007, ASB2010-10675), the following information was included:
"No health effects were obser ved in manufacturing and research personnel (8 in total) who had been eposed constantly from 2003 to 2005 to CpGV. No allergic reactions of the skin, the respiratory tract or the eyes were noted upon regular medical examination. Workers themselves did not report any symptoms related to any other pathologies (Cardinalini, 2005, TOX2006-1048)."

Some occupational medical information is also available from the company Probis (Germany) that is no applicant for CpGV any longer but had been still an applicant when the previous DAR (Germany, 2007, ASB2010-10675) was prepared. Then, it was stated that the product GRANUPOM had been manufactured over the course of several years at the chemical plant 'Behringwerke' in Marburg (Germany). According to information from the company's physician, regular medical screening revealed no adverse effects on health among a group of persons who had been exposed occupationally to baculoviruses in connection with multiplication and efficacy testing of these organisms (Gröner, 1990, TOX2005-1876). In an anecdotal report of limited evidence, it was further reported that the responsible person for production of CpGV itself in the company Probis in Germany did not show sensitising reactions although he was confirmed to be allergic against several diets and against pollen. This person had been in close contact to high amounts of this virus for years (Koschmieder, 2002, TOX2003-1145).

B.6.1.1.2 Sensitisation/allergenicity observations, if appropriate

In general, micro-organisms applied in plant protection are considered potential allergens. The same generic approach applies for viruses even though, from a biological point of view, they are no micro-organisms. Allergenicity of viral agents might be either due to virus proteins or, more likely, to proteins from the host system (animals, cell cultures) in which the virus is propagated. However, in the whole body of the available scientific literature, no allergic reactions, neither on the skin nor in the respiratory tract, have been reported in humans who were in close contact with baculoviruses.
This is further supported by the lack of such evidence coming from occupational medical examinations of employees involved in production of CpGV and related PPP (Koschmieder, 2002, TOX2003-1145; Cardinalini, 2005, TOX2006-1048, see above) even though the number of exposed humans is much too low to draw firm conclusions from these anecdotal reports.

For skin sensitisation studies in animals, see the section on basic (Tier I) studies below and in particular the product safety part of this RAR.

B.6.1.1.3 Direct observation, e.g. clinical cases

Not available with regard to the virus under evaluation. No clinical cases were reported in which a disease process in humans was attributed to contact with CpGV (see also EFSA, 2012, ASB2014-3917, and Hackl et al., 2015, ASB2015-4072).

Human experience with baculoviruses other than CpGV (published data)
A study in human volunteers was reported with cotton bollworm (*Heliothis zea)* NPV (Heimpel and Buchanan, 1967, TOX2003-1143). Nine men and one woman (between 24 and 60 years old) ingested a total dose of about 5.82 x 10^9 polyhedra per person that was split over an exposure period of five

days. The virus was administered in gelatine capsules once a day after breakfast. Four other men and two women (age range from 21 to 42 years) who served as controls were administered sterile insect protein from the same preparation that was obtained by previous separation of the polyhedra but further details were not given. It seems that all these volunteers had been recruited from the staff of the Entomology Research Division of the U.S. Department of Agriculture. The study was conducted under medical supervision. Complete physical examinations and a variety of laboratory tests (haematology, urinalysis, limited range of blood clinical chemistry parameters) were performed prior to and at 9 and 30 days after first dosing. These examinations failed to show any significant change in the general health condition of the participating individuals neither in the test nor in the control group and did not reveal any differences between the two groups.

B.6.1.2 Basic studies

B.6.1.2.1 Sensitisation

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 (Pößnecker, 1991, TOX2006-2285; Chevalier, 2005, TOX2006-1050) have been performed with commercial products and, therefore, are reported in detail in the product safety chapter of this RAR. This approach is supported by the different outcome of the product studies suggesting that sensitisation is not likely to have been caused by the virus itself.

The studies had all been available for the previous (first) evaluation of CpGV on EU level already and were reported in the DAR (Germany, 2007, ASB2010-10675). At that time, another (negative) skin sensitisation study on female Guinea pigs ([redacted] 1986, TOX2003-1147) was still taken into consideration for evaluation purposes. However, from a today's point of view, it must not be used for two reasons: On one hand, the formulation GRANUPOM was tested and the study was submitted by the company Probis that is no applicant for CpGV any longer. On the other hand, the meanwhile outdated Landsteiner method was applied for testing which is not accepted any longer according to EU data requirements. Therefore, description of this study has been deleted from this RAR. The same or similar arguments apply for the study by [redacted] (1992, TOX2003-1148) in which a possible respiratory sensitisation, again by GRANUPOM, was examined. No valid method for assessment of this latter endpoint is available so far (Martel et al., 2010, ASB2011-9441) even though it is acknowledged that the method (intradermal induction followed by inhalative challenge) had been successfully applied to confirm an already known potential for respiratory sensitisation in other cases (Botham et al. 1989, ASB2017-11928). However, to our knowledge, this method was not validated further and it is not clear if it is really capable of predicting a negative outcome. Moreover, the publication itself revealed possible differences in the response between Guinea pigs and man.

The published study by Meinecke et al. (1970, TOX2006-1056) was performed with a commercial preparation of *Heliothis zea* NPV and does not comply to current standards. It is of no use for this evaluation. The same arguments and assessment apply to the unpublished study by [redacted] (1976, TOX2003-1146) in which another virus was tested by means of a not acceptable method. Therefore, they have been deleted from this RAR, too.

For further information on sensitisation, see health evaluation of the representative formulations.

B.6.1.2.2 Acute toxicity, pathogenicity and infectiveness

It must be acknowledged that there are no OECD TGs for acute studies with micro-organisms or viruses. Normally, in the EU, studies are accepted if conducted according to EPA guidelines. The same approach was taken here.

Acute oral toxicity, pathogenicity and infectiveness

Acute oral studies with CpGV were performed in rats and mice and had been available for the previous evaluation already. Accordingly, study descriptions have been copied from the previous DAR (Germany, 2007, ASB2010-10675). If necessary, small amendments were made. The conclusion was revised. No new studies were submitted for renewal of CpGV approval in the EU.

First study in rats (originally provided by Sipcam)

Data point: OECD: IIM 5.2.2, OECD: IIM 5.6

Report: [redacted] (2005): Acute toxicity study of *Cydia pomonella* Granulosis virus (CpGV) by oral administration to rats. [redacted] unpublished report No. 18971/05. Dates of experimental work: July, 13 to August, 8, 2005. TOX2006-1680

Guideline(s): U.S.EPA OPPTS Guideline 885.3050

Deviations: None

GLP: Yes

Acceptability: The study is considered acceptable.

Material and methods:

A single oral dose of 1.015 x 10^8 CpGV granules per animal was administered by gavage to three CD rats [redacted]) of either sex. Prior to administration, the test item was diluted in fresh filter-sterilised aqueous phosphate soulution to the appropriate concentration. Post dosing, the rats were observed for mortality and clinical signs over a period of 21 days prior to sacrifice. Gross pathological changes were recorded at necropsy. Control animals were also included in the experiment.

Results and discussions:

No mortalities and no clinical signs were observed. Body weights were not affected and no gross pathological abnormalities were noted.

Conclusion by the RMS (2019):

A single oral administration of 1.015 x 10^8 granules CpGV per animal revealed no evidence of pathogenicity or toxicity in rats. Thus, the LD_{50} was above 1.015 x 10^8 granules per animal. The fate of the applied virus in the treated rats was not investigated, apparently, this was not required by the guideline followed. However, based on the reliable knowledge on baculoviruses in general and on CpGV in particular, no persistence or replication of this virus in mammals is anticipated.

Second study in rats (originally provided by Arysta)

Data point: IIM 5.3/03, IIIB 7.1.1/01

Report: [redacted] (1991): Acute oral (gavage) toxicity study (Subdivision F, No. 81-1) of CpGV paste in rats. [redacted] unpublished report n° BE-MT-99-91-04-AOR-01; Dates of experimental work: 1991, June.
TOX2006-2287

Guideline(s): EPA, Subdivision F, No. 81-1

Deviations: A control group was lacking.

GLP: Yes

Acceptability: The study is considered supplementary since evaluation is complicated by the absence of a control group. Furthermore, because of the test item, it might be considered rather a product study.

Material and methods:

5 male and 5 female adult Sprague-Dawley rats (source: [redacted] received 5000 mg/kg bw of CpGV paste (a suspension equivalent to the formulation CARPOVIRUSINE, batch CX 91/1112) by oral gavage. The actually applied virus amount was not given but it was stated in the original report that the suspension contained approximately 1 x 10^{10} virus particles/mL. And knowing that the density of the suspension is around 1 (1.02), the virus particle number was calculated by the notifier to be 5 x 10^{10} granules/kg bw. This approach was accepted by the RMS. Following dosing, the animals were monitored over two weeks for mortality, clinical signs and body weight development. At termination on day 14 post dosing, a complete necropsy was performed.

Results and discussions:

No animal died during the study but some animals showed clinical signs of toxicity during the first four days of the 14-day observation period. A total of five rats of both sexes showed for a more or less long-lasting study interval one or more of the following signs: depression, reduced activity, or dyspnoea. There was no body weight loss but, in the lack of a concomitant control group, body weight development (i.e., the extent of body weight gain) cannot be properly evaluated. Gross pathological examination revealed in 7 out of 10 animals remarkable findings. These comprised petechial bleedings in the stomach, slightly enlarged (congested) spleen and greenish kidneys but were not consistently seen in all affected animals. In the absence of a control group, it is not clear whether these changes may be attributed to treatment.

Conclusion by the RMS (2019):

A formulation similar to CARPOVIRUSINE, containing CpGV as active ingredient, caused transient toxic signs and, in addition, a few pathological findings of unknown relevance in a number of, but not in all, treated rats. Mortality did not occur. Thus, the LD_{50} was in excess of 5000 mg/kg bw but some toxicity must be assumed. It is not clear, however, whether the toxic signs were due to the virus itself or to co-formulants in the product. The fate of the applied virus in the treated rats was not followed. However, based on the reliable knowledge on baculoviruses in general and on CpGV in particular, no persistence or replication of this virus in mammals is anticipated.

Published studies with CpGV (Mouse)
In mice, a rather old published study is available (Gröner et al., 1978, TOX2003-1154, see also Gröner, 1986, TOX2003-1179) in which CpGV and another baculovirus were tested in parallel experiments in different animals. Due to reporting deficiencies, this study does not comply with current standards and is considered supplementary only. However, it is of particular interest for risk assessment since a second species was included and because haematological data was examined which is seldom the case in acute studies. 20 NMRI mice/experiment were once offered nutrient baits (bread) soaked in virus suspensions containing total doses of either 3 x 10^9 polyhedra of cabbage moth (*Mamestra brassicae*) NPV or 5 x 10^{11} granules of codling moth (*Cydia pomonella*) GV (CpGV). No mortality or clinical signs occurred. Three days after dosing, haematological parameters were not altered. The results of haematological analysis are given in Table B.6.1-1. It can be concluded that administration of both viruses was well tolerated by mice even though the CpGV dose was higher than applied in the studies on rats. No differences in species sensitivity may be assumed from these single dose studies. However, it was a clear limitation of this experiment that necropsy and subsequent histopathological examination were not performed, in contrast to the animals which had been exposed over a 99-day period in another part of the same study (see B.6.1.2.5). On the other hand, subsequent to single i.p. administration of CpGV, gross and histopathology did not reveal remarkable findings in mice (see below) and, reflecting a worst-case exposure scenario, this outcome might suggest that no

adverse effects were to be expected following oral intake.

Table B.6.1-1: Comparison of haematological data for mice before and after feeding a single dose of *Mamestra brassicae* NPV polyhedra (P) or CpGV granules (G)

Blood cell population	Values after administration of		Pre-treatment values (used as control values)		Normal values according to Hoffmann, 1961 (cited by study authors)
	3 x 10^9 P / mouse	5 x 10^{11} G / mouse			
Erythrocytes (x 10^6/mm^3)	10.0 ± 1.09	10.2 ± 1.37	10.0 ± 1.87	10.0 ± 0.78	~ 9
Leucocytes (x 10^3/mm^3)	10.1 ± 5.17	14.7 ± 5.06	13.4 ± 4.42	14.1 ± 6.45	~ 10
Neutrophiles [%]	21.1 ± 8.76	17.6 ± 7.48	18.1 ± 10.7	19.7 ± 10.1	10…40
Eosinophiles [%]	4.5 ± 2.91	2.5 ± 2.42	2.4 ± 1.92	2.5 ± 2.52	0…7
Basophiles [%]	0.0	0.0	0.0	0.0	0…1
Lymphocytes [%]	74.3 ± 9.59	79.8 ± 8.52	79.5 ± 10.4	77.6 ± 10.8	35…90
Monocytes [%]	0.19 ± 0.44	0.01 ± 0.61	0.48 ± 0.83	0.29 ± 0.46	0…3

Oral studies with other baculoviruses

The information on testing of other baculoviruses in acute oral studies in different mammalian species as compiled in the old DAR (2007, ASB2010-10675) is considered not relevant for this re-evaluation. The main arguments for this decision are the following: (1) CpGV specifc data is available, (2) no adverse effects were reported for these other virus species, and (3) the quality of the studies is sometimes doubtful and reporting mostly poor. Therefore, the studies by Ignoffo et al. (1975, TOX2003-1155), [redacted] et al. (1976, TOX2003-1153), [redacted] (1980, TOX2003-1149), Lewis and Podgwaite (1981, TOX2003-1150), Martignoni (1978, TOX2006-1681), and Anon. (1982, TOX2003-1156, erroneously cited in the DAR (2007, ASB2010-10675) as Xuebao, 1982, TOX2003-1156) were not considered further in this RAR. The same holds true for the study by Döller et al. (1983, TOX2003-1167) that was used only with regard to seroconversion in pigs (see above) and a review by Cunningham and Entwistle (1981, TOX2003-1152) dealing also with other acute endpoints.

For a more recently published study of higher standards in rats (Ashour et al., 2007, ASB2017-11927), see below. However, since i.p. administration of a baculovirus other than CpGV was also included, it is reported in that sub-section.

In general, information on acute oral testing of other baculoviruses is of limited relevance since at least one completely valid study with CpGV (Chevalier, 2005, TOX2006-1680) is available on which risk assessment should mainly rely.

Acute inhalation toxicity, pathogenicity and infectiveness

There is valid study with a CpGV formulation (VIRGO) in rats available which had been reviewed for the previous evaluation already. It is reported here, with very few amendments, once more. The conclusion has been revised.

Data point: IIIM 5.2.2

Report: [redacted]. (2005): Acute inhalation toxicity study of VIRGO in rats. [redacted] unpublished report No. 19016/05. Dates of experimental work: July, 14 to July, 28, 2005.
TOX2006-1054

Guideline(s):	OECD 403
Deviations:	None
GLP:	Yes
Acceptability:	The study is considered acceptable even though no control group was included since this is not mandatory according to the OECD TG 403. However, because of the test item, it might be considered rather a product study.

Material and methods:

Five male and five female CD Rats (source: [redacted]) were exposed to VIRGO at an actual concentration of 5.10 ± 0.20 mg VIRGO/L air (nominal concentration 2 x 10^{13} granules of CpGV/L) for 4 hours by inhalation using a dynamic nose-only exposure chamber. The particles had a mass median aerodynamic diameter (MMAD) of 2.56 µm with a Geometric Standard Deviation (GSD) of 3.782 µm. No smaller GSD could be achieved with the test item supplied. The total amount of particles of respirable size (less or equal to 4 µm) was about 32 %.
Animals were observed for 14 days and were weighed weekly. At termination, the rats were subjected to gross necropsy.
Controls were not included in this experiment.

Results and discussions:

No mortalities and no clinical signs occurred. Body weight development was obviously not affected and no gross pathological abnormalities were observed.

Conclusion by the RMS (2019):

It is acknowledged that this study was performed with a commercial product. However, results are applicable to the virus itself. No signs of pathogenicity or toxicity were observed upon 4-hour inhalative exposure to VIRGO. The LC_{50} exceeded 5.10 mg/L air. Again, the fate of the applied virus in the treated rats was not followed. However, based on the reliable knowledge on baculoviruses in general and on CpGV in particular, no persistence or replication of this virus in mammals is anticipated.

Further inhalation studies with CpGV
In an old, published study by Gröner et al. (1978, TOX2003-1154), Guinea pigs (number and sex not mentioned) were exposed by spraying to an aqueous aerosol containing 2 x 10^{12} CpGV granules/L but only for five minutes. During and after a 21-day post-observation period, no ad-verse effects on general health, behaviour, rectal temperature, body weight (gain), food con-sumption and serum proteins were observed when compared to control animals which had received a water-spray treatment only. Necropsy and histopathology did not reveal evidence of irritation in the respiratory tract. Antibodies to CpGV were not detected. The short duration of the exposure period is a strong limitation of this study, therefore, it is considered not accepta-bledespite the many parameters under examination.
An additional older acute inhalation study in Guinea pigs ([redacted] 1992, TOX2003-1148) is also considered not acceptable any longer because of the extremely short period of only 15 minutes during which the animals were exposed to an aerosol of the GRANUPOM formulation, apparently without an adverse effect.

Studies with baculoviruses other than CpGV
Further published data on inhalative effects on other baculoviruses in different species had been referred to in the old DAR (Germany, 2007, ASB2010-10675). However, these studies by Ignoffo et al. (1975, TOX2003-1155), Gröner (1978, TOX2003-1154), Martignoni (1978, TOX2006-1681), and Lewis and Podgwaite (1981, TOX2003-1150) are not considered useful for this re-evaluation of CpGV for the same reasons as provided for the acute oral studies above.

Intraperitoneal/intravenous/subcutaneous single dose

In contrast to chemical active ingredients, studies of these types are still required and performed to detect adverse effects of micro-organisms or viruses occurring after penetration of the natural protection systems of the intact mammalian organism and thus, in some respect, may be considered to reflect worst-case conditions.

The only guideline-compliant original study using the i.p. route with CpGV was performed in rats. It had been already available for the previous EU evaluation. No new studies have been submitted since then. Therefore, the respective part of the 2007 DAR (ASB2010-10675) has been copied and, where necessary, amended. The conclusion was confirmed.

Original study in rats

Data point:	IIM 5.2.2
Report:	[redacted] (2005): Acute toxicity study of *Cydia pomonella* Granulosis Virus (CpGV) by intraperitoneal injection to rats. [redacted] unpublished report no. 18973/05. Dates of experimental work: 2005, July and August. TOX2006-1055
Guideline(s):	OPPTS Guideline 885.3200
Deviations:	None
GLP:	Yes
Acceptability:	The study is considered acceptable.

Material and methods:

The test substance was injected intraperitoneally as a single dose of 1.015 x 10^7 granules CpGV per animal to three CD rats ([redacted]) of either sex. The test item was diluted in a fresh filter sterilised phosphate solution. The dosing volume was 1 mL. Two male and two female rats serving as control animals received a single ip injection of 1 mL vehicle. Observations on mortality, clinical signs or behavioural changes were made for 21 days. Gross pathological changes were recorded at necropsy.

Results and discussions:

During the observation period of 21 days post dosing, no mortalities and no clinical signs were noted. Body weights were not affected and no abnormalities were seen upon necropsy.

Conclusion by the RMS (2019):

A single intraperitoneal administration of 1.015 x 10^7 granules of CpGV to rats revealed no clinical signs of pathogenicity or of local or systemic toxic effects. Thus, the LD_{50} was greater than 1.015 x 10^7 granules per animal. Again, the fate of the applied virus in the treated rats was not followed. However, based on the reliable knowledge on baculoviruses in general and on CpGV in particular, no persistence or replication of this virus in mammals is anticipated.

Published data

In an older published study, effccts following i.p. administration of CpGV (in parallel to *Mamestra brassicae* NPV) to mice was reported. Groups of NMRI-mice received a single injection of 0.5 mL of a suspension of virus inclusion bodies in physicological saline (Gröner et al., 1978, TOX2003-1154). Since the concentrations were 1 x 10^9 PIB/mL of *Mamestra brassicae* NPV and 2 x 10^{11} granules/mL of CpGV, total doses applied were 0.5 x 10^9 PIB or 1 x 10^{11} granules per mouse. Group size was not completely clear from the reference but was either five or ten animals for which the sex had not been specified. The same amount of physicological saline was administered to control mice. Injection was

performed under antibiotic protection (penicillin/streptomycin) to avoid bacterial infection. There were no deaths during the study. Food consumption, body weight gain and general health condition of the virus-treated mice were not different from the controls. Haematological examination was performed prior to injection (exact time point not given) and on days 1 and 8 post dosing. Unfortunately, haematological data for the animals injected with CpGV were not given in the report, in contrast to the data obtained after oral administration (see above) and to those obtained after i.p. injection of the NPV. With *Mamestra brassicae* NPV, an increased neutrophil count (expressed as a higher percentage of this cell population among all white blood cells on days 1 and 8) might have been the only potential effect of treatment. This finding could reflect a normal immunological reaction and, in the lack of clinical and pathological signs of infection and disease, was not considered adverse. Neutrophil count was not reported for CpGV. Its relevance to CpGV is unknown. Autopsy followed by histological examination of selected tissues and organs (brain, colon, gonads, heart, ileum, kidneys, liver, lungs, oesophagus, pancreas, spinal cord, spleen, stomach, and trachea) did not reveal remarkable pathological findings but was confined very few animals (two per group). On balance, this study can be regarded at best as supplementary from a today's point of view.

Studies with baculoviruses other than CpGV

More recently, Ashour et al. (2007, ASB2017-11927) administered three different NPV preparations either by oral gavage or by i.p. injection to groups of three male and three female albino rats. The following baculoviruses were tested: wild type *Spodoptera littoralis* NPV (SlNPV), wild type *Autographa californica* multiple NPV (AcMNPV), and a recombinant (i.e., genetically modified) *Autographa californica* NPV containing an insect-selective toxin gene from the North African scorpion *Androctonus australis* (AcAaIT). The idea behind genetic manipulation was to enhance insecticidal efficiency of the virus since the "time to kill" is often considered too long when baculoviruses are used for insect control. For single oral application, the total dose was 1 x 10^8 polyheral inclusion bodies (PIBs), obtained from infected *Spodoptera littoralis* larvae, in distilled water and the dosing volume was ca 2 mL. The control animals received only 2 mL of distilled water. I.p. injection was also carried out once by administration of 1 x 10^7 PIBs/animal in ca 1 mL of 0.9% NaCl solution. Following treatment, the rats were observed for 21 days before they were killed and subjected to haematological (RBC, WBC, platelet count), clinical chemistry and histopathological investigations. The following parameters were determined in blood serum samples: total protein, alanine and aspartate aminotransferases (ALT, AST), glucose, urea, creatinine, and bilirubin. In addition, serum proteins were separated by SDS PAGE and the activity of acetylcholinesterase (most likely in plasma) was measured. For histopathology, specimens from stomach, intestines, liver, kidneys, brain, spleen, and lungs were taken.
There were no premature deaths and no clinical signs could be attributed to treatment. All rats gained some weight. The only haematological findings was a clear increase in leucocyte numbers that was observed after oral and i.p. application of AcMNPV (up to 65%, oral dose) and SlNPV (up to 80%, i.p.) but only in females. With the genetically modified virus, the same effect was less pronounced. This effect might be interpreted as a normal immunological response to an antigen. In males, in contrast, WBC tended to be lower. This sex difference is difficult to understand or to explain. Occasional alterations in clinical chemistry parameters were not consistent among the groups, did not suggest any pattern and cannot be considered to provide evidence of adverse effects on organ (mainly liver and kidney) functions. A number of histopathological findings is described and substantiated by figures but no information on group incidences is given. Thus, no firm conclusion can be drawn. The relevance of these investigations to CpGV is considered low.

Further, very old studies with i.p. (Meinecke et al., 1970, TOX2006-1056; Martignoni, 1978, TOX2006-1681) or i.v. injection (Barnes et al., 1970, TOX2006-1684; [redacted] et al., 1976, TOX2003-1153) of other baculoviruses to mice or rats are of low quality according to current standards and of no relevance for re-evaluation of CpGV. The same holds true for studies in which *Heliothis zea* NPV was applied to rats or Rhesus monkeys via the s.c. route (Barnes et al., 1970, TOX2006-1684; Ignoffo et al., 1975, TOX2003-1155). All these studies had been briefly reported in the previous DAR (Germany, 2007, ASB2010-10675) but should not be taken into consideration for risk assessment any longer.

B.6.1.2.3 Genotoxicity testing

No evidence of mutagenicity was obtained in a small number of *in vivo* experiments in which the methodological approach did not comply with current standards. CpGV granules were administered by single oral gavage at a dose level of 1.5 x 10^{12} granules/animal to five male Chinese hamsters. In a subchronic experiment, six male hamsters received a nominal daily dose of 1.6 x 10^{10} granules/animal over 3 months via their diet. In both trials, control groups of the same size were included. The control animals received only the vehicle, *i.e.*, 0.05 M Tris-HCl buffer. The animals were sacrificed 24 hours after the (final) dose and bone marrow smears prepared for cytogenetic evaluation. 100 metaphases per animal were analysed and the frequency of sister chromatid exchange (SCE) as well as the number of chromosomal aberrations determined. A comparison between the test and control groups did not reveal significant differences neither for the acute nor for the subchronic experiment (Reimann and Miltenburger, 1982, TOX2006-2676; Reimann, 1984, TOX2003-1158).
Gröner et al. (1978, TOX2003-1154) reported that in bone marrow smears from 24 NMRI mice after single or multiple doses of granules (CpGV) or polyhedra (*Mamestra brassicae* NPV), no increase in chromosome aberration rate as compared to untreated controls was seen at 6, 48, or 96 hours following (final) virus administration. Unfortunately, no details on the cytogenetic examination were given. Only the time points of examination were mentioned by Reimann (1984, TOX2003-1158).

The general assumption that baculoviruses are devoid of a mutagenic (clastogenic) potential is supported by experimental *in vitro* data obtained with other species such as *Autographa californica* NPV (Reimann and Miltenburger, 1983, TOX2003-1157; Reimann, 1984, TOX2003-1158) or *Mamestra brassicae* NPV Volkman and Knudson (1986, TOX2006-2286). In all these studies, mammalian cells from different species were examined for the occurrence of chromosome aberrations or SCE.

B.6.1.2.4 Cell culture study

For a virus, in general high concern on the molecular level is about the possible introduction of information from the viral genome into the cellular DNA or the activation of "silent" cellular genes (perhaps also of viral origin) by interaction with DNA or RNA of invading viruses. These events may lead to cell transformation and the latter is a modes of action by which, *e.g.*, cancer may be induced by certain animal and human viruses (for more information, see textbooks of virology). For detection of such hazardous effects, cell culture studies are required for viruses which are intended to be used in plant protection products.

With regard to CpGV, only one study of this type (including interim report) is available that has been reported in the 2007 DAR (ASB2010-10675) already. Since re-evaluation of this study did not result in a different outcome, study description has been copied with a few amendments and the conclusion was confirmed even though the wording was revised.

Data point:	IIM 5.2.4/01, IIM 5.6.2/02, OECD: IIM 5.3.6
Report:	Winstanley D. (2000):. Mammalian cell study: *Cydia pomonella* Granulovirus. Horticulture Research International, Final progress report for project C1829. TOX2006-2290 Supported by: Winstanley, D. (1999): Mammalian cell study: *Cydia pomonella* Granulovirus. Horticulture Research International, Interim progress report for project C1829. TOX2006-2289
Guideline(s):	Not applicable.
Deviations:	Not applicable.

GLP: No

Acceptability: The study is considered acceptable.

Material and methods:

CpGV-C (*i.e.*, the active ingredient of the formulation CARPOVIRUSINE, derived from the "Mexican isolate" of CpGV, CpGV-M) and CpGV-M1 (an *in vivo* cloned genotype of CpGV-M) were investigated for replication in the human diploid cell line W138 (fetal lung cells of Caucasian origin) that had been obtained from the "European collection of animal cell cultures (CAMR)" in Porton Down, Salisbury, UK. Culture conditions were described in the Arysta dossier and considered appropriate by the RMS. Subconfluent cultures of the human cell line were inoculated with extracellular virions of CpGV in insect cell culture medium and then the cells were observed for the appearance of a cytopathic effect (CPE). For control purposes, cells were exposed in parallel to the IZDO4 insect cell culture medium. The viability of the cells was determined at different time points following infection by means of the trypan blue exclusion test. CpGV susceptible (insect) cells were included as positive controls. The inoculated cell pellets were assayed for the presence of viral DNA and mRNA by PCR. The medium was examined for the presence of progeny budded virus. Susceptible larvae were injected either with medium harvested from CpGV-inoculated W138 cells or with CpGV itself.

Results:

There were no visible cytopathic effects due to the inoculation of WI38 cells with CpGV. Cell viability was not altered. Results from the oral inoculation of WI38 cells and injection cell culture medium, respectively, did not show replication of CpGV in WI38 cells but CpGV penetrated from the inoculum into the cells and was also detected in the medium. However, CpGV appears to be gradually cleared by WI38 cells after passaging which is supported by the PCR tests. There was no transcription of the granulin gene (*i.e.*, a gene coding for matrix protein that is transcribed very late after replication of the CpGV genome) in the WI38 cells at 7, 14 and 21 days post-infection. This observation was a further indication that CpGV would not replicate in WI38 human cells. In line with that, the insect larvae died only after infection with CpGV but not after injection of medium obtained from virus-inocculated W138 cells.

Conclusion by the RMS (2019):

CpGV was shown to be able to penetrate into human diploid W138 cells but did not replicate there and did not damage these cells. Thus, previous information available for other baculoviruses (see B.6.1.1, Basic information) was confirmed with CpGV. No transcription of a viral gene was noted. Based on all this data it is very unlikely that any genetic information from the CpGV genome will be incorporated into the genome of mammalian cells.

This latter conclusion is also supported by the long-lasting history of safe use of baculoviruses as vectors for gene transfer into mammalian (including human) cells for "genetic engineering" purposes (e.g., Sandig et al., 1996, TOX2006-2293; Chiang et al., 2006, ASB2018-890; Kitayima et al., 2006, ASB2018-892) even though it must be acknowledged that all these experiments have been carried out with baculoviruses other than CpGV.

The same holds true for an older study from open literature in which possible activation of endogenous C-type retroviruses by baculoviruses was investigated. These endogenous retroviruses have been found as gene sequences (provirus) in the genome of many vertebrates and their activation by other viruses, by chemicals or radiation may result in various adverse effects. Schmidt and Erfle (1982, TOX2003-1163) treated cell cultures of mouse, rat, monkey and human origin with *Autographa californica* NPV, *Mamestra brassicae* NPV or *Lymantria dispar* NPV or with isolated virus DNA. In addition, a known C-type retrovirus-activating chemical (a halogenated pyrimidine analogue) and a number of insecticides and other chemicals were tested alone or in combination. No influence of the NPV on growth or morphology of the treated mammalian cells was observed and no C-type retrovirus

activation was detectable. Furthermore, simultaneous treatments with NPVs and insecticides such as mevinphos or cypermethrin did not result in such an effect. It can be concluded that the application of baculoviruses for pest control is unknot critical with respect to retrovirus activation in mammalian cells, even if concomitant application of chemical insecticides would occur.

B.6.1.2.5 Information on short-term toxicity and pathogenicity

Based on familiarity with on baculoviruses and on the available studies with CpGV or its formulations, further studies on short-term toxicity or pathogenicity are not needed. However, there is a published subchronic study (Gröner et al., 1978, TOX2003-1154) which is briefly reported here although it is of low quality and does not comply to any current standards. The acute part of this study is mentioned above (see B.6.1.2.2).
Up to 20 NMRI mice per group (sex not given in the report, number of animals not entirely clear since controls might be included) were offered nutrient baits for a period of 99 days that had been soaked in virus suspensions of either *Mamestra brassicae* NPV or CpGV. The nominal dose per animal was 3 x 10^9 polyhedra of *M. brassicae* NPV or 5 x 10^{11} granules of CpGV, respectively. This total dose was distributed into 34 portions that were given during the 99-day study period at 3-day intervals. Obviously, a control group was also included but detailed information is lacking. No deaths occurred and no clinical signs of pathogenicity or toxicity were detected. Body weight gain was not affected and haematological examinations on days 45 and 90 did not reveal differences between the treatment group and the controls. At autopsy on day 100, no macroscopical alterations or histological changes in the examined organs and tissues (brain and spinal cord; digestive tract including colon, esophagus, ileum, and stomach; gonads, heart, kidneys, liver, lungs, spleen, and trachea) were found but pathological examinations were confined to two virus-treated and two control animals.

In a subchronic genotoxicity study (Reimann, 1984, TOX2003-1158), seven male Chinese hamsters received a daily dose of 1.6 x 10^{10} granules of CpGV for 3 months via their diet. Virus administration was apparently well tolerated since no deaths and no clinical signs were noted and body weight development was similar to that in the control group Results with regard to clastogenicity are reported above (see B.6.1.2.3).

In the 2007 DAR (ASB2010-10675), few further studies on short-term effects of another baculovirus had been reported (Ignoffo et al., 1975, TOX2003-1155; Gröner et al., 1978, TOX2003-1154; Lewis and Podgwaite, 1981, TOX2003-1150; Cunningham and Entwistle,1981, TOX2003-1152) but should not be taken into consideration for this re-evaluation. This approach is justified because of their lacking relevance to CpGV, their mostly poor quality or reporting deficiencies and since there was no clear evidence of adverse effects. In principle, based on general information, medical data and the results of acute studies with CpGV, any short-term studies may be waived.

B.6.1.2.6 Proposed treatment: first aid measures, medical treatment

Taken into account the nature of *Cydia pomonella* Granulovirus and all the available information on related baculoviruses, no adverse effects are to be expected. Accordingly, following contact, first aid measures and medical treatment are not needed. However, standard hygienic safety precautions should be maintained when handling virus formulations.

B.6.1.3 Toxicity studies on metabolites and relevant impurities

Because of its nature as a virus, CpGV is not expected to produce any metabolite or toxin.
"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. Virus proteins (including enzymes which might be, at least theoretically, also of health concern) are synthesised by and 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 these were toxic.

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) 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 neurotoxin 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 s*pores 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 108 CFU/g. Following 11 applications of CAR-POVIRUSINE 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 a "standard 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 following the last one. 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.

B.6.2 Tier II

B.6.2.1 Specific toxicity, pathogenicity and infectiveness studies

Based on general information on and familiarity with baculoviruses, medical data and the results of acute studies with CpGV, there is no need for any special study. It must be emphasized that all the studies which are mentioned in the following do not comply with any current standard and are addressed here only to be comprehensive.

Skin and eye irritation (CpGV)
According to Gröner (1986, TOX2003-1179), 2 x 10^{10} granules of CpGV suspended in 0.05 mL of physiological saline did not cause skin irritation after dermal application to Guinea pigs. Likewise, the same amount applied to the eyes did not produce irritation. No further details were given. In the lack of more precise information and since the user will be exposed to formulations for which valid data is available (see product safety chapter of this RAR), this information is not relevant for risk assessment.

Developmental toxicity (CpGV)
A dose of 0.2 mg of "CpGV virions" was administered once by oral gavage to five gravid NMRI mice and to further five females treated in oestrus prior to mating and were allowed to deliver spontaneously. The 78 pups from these litters did not differ from controls with regard to growth and development. Serum from pups was obtained four weeks after birth and tested in a RIA. Virus-induced antibodies could not be detected in any of the sera (Döller and Huber, 1983, TOX2003-1169).

Other endpoints (Testing of baculoviruses other than CpGV)
In the 2007 DAR (ASB2010-10675), some further studies with other baculoviruses than CpGV are mentioned in which different endpoints such as long-term effects, reproductive or developmental toxicity were addressed (Barnes et al., 1970, TOX2006-1684; Meinecke et al., 1970, TOX2006-1056; Ignoffo et al., 1973, TOX2003-1173; Ignoffo et al., 1975, TOX2003-1155; Döller and Gröner, 1981, TOX2003-1166; Lewis and Podgwaite, 1981, TOX2003-1150) but, in the lack of adverse effects and taking into account the poor quality of most of these studies and the fact that they were of low relevance to CpGV, they were not considered for this re-evaluation anymore.

B.6.2.2 Genotoxicity – *In vivo* studies in germ cells

Not available. Not necessary.

B.6.3 Principles and methods of literature search

A literature search was performed both by the applicants and by the RMS.

The applicant's search with regard to human health is described in a KII document provided by Arysta Life Science SAS (Anon., 2016, ASB2017-11923). It is assumed that this company performed the search also on behalf of the two other applicants. The search was only conducted in the Scopus database. For a micro-organism or virus, this approach may be considered appropriate. The time span considered was from 01 January 2005 to 30 May 2016 which is also acceptable. The search was aimed to find articles concerning baculoviruses (only when not genetically modified) in relation to the data requirement "Toxicological and exposure data". In total, 4069 records (excluding duplicates) were retrieved of which the vast majority (4028) was immediately excluded again, following "rapid assessment of relevance". Unfortunately, relevance criteria applied were not given and cannot be assessed by

the RMS, therefore, and the outcome must be simly described here only. The remaining 41 documents (of which 14 were related to human health aspects) were evaluated on full text basis. Again, 11 of these 14 articles were excluded as not relevant and, this time, a justification is given in each case. These justifications appear reasonable even though one of the excluded articles (Kalawate, 2014, ASB2017-16166) was considered relevant by the RMS when identified in its own literature search and has been used for risk assessment. Eventually, in total, only three articles (Ashour et al., 2007, ASB2017-11927; Molinari et al., 2010, ASB2017-11929; Wang et al., 2015, ASB2017-11930) were submitted to the RMS as relevant publications. They are all briefly described now in Volume 3 above even though relevance of the latter one might be questioned, simply because it is not clear which baculovirus was applied and since this article is about safety testing of nanomaterials. It is surprising why some further articles reporting immune-stimulating effects of baculoviruses (similar to that one by Molinari et al., 2010, and introduced by the RMS in section B.6.1.1) were not retrieved in the applicant's literature search.

The literature search by the RMS was focussed on CpGV, was not limited with regard to a time frame and conducted in three databases (PubMed, Scopus, and Web of Science). Thus, the approach was different from that one taken by the applicant. Based on title, abstract, and keywords, the numbers of potentially relevant articles were 136 (PubMed), 125 (Scopus), and 60 (Web of Sciences). The total number of 321 was reduced to 229 when duplicates were deleted. Thorough review by RMS left 16 publications for full text evaluation since they were potentially related to human health aspects and not already cited in the 2007 DAR. Eventually, 10 (including one EFSA document) publications were additionally included in this RAR.

In addition, the open literature referred to in the DAR (Germany, 2007, ASB2010-10675) was subject to re-evaluation and, where appropriate, references published before 2001 were also included now for the first time. Before submission of the final RAR to EFSA, limited searches for publications on health effects and infective doses of *Bacillus cereus* and on possible endocrine effects of virus infections were performed in PubMed.

B.6.4 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
KMA 5.1/01	Anonymous	2016	LITERATURE REVIEW REPORT ON CYDIA POMONELLA GRANULOVIRUS - EFFECTS ON HUMAN HEALTH Arysta LifeScience S.A.S., not applicable not available GLP/GEP: no Published: no BVL-3306472, ASB2017-11923	no	yes	New data for active ingredient, not previously submitted nor evaluated	ALS	N
KMA 5.1. KMA 5.2.2.1 KMA 5.6	OECD	2002	CONSENSUS DOCUMENT ON INFORMATION USED IN THE ASSESSMENT OF ENVIRONMENTAL APPLICATIONS INVOLVING BACULOVIRUS not available, not applicable ENV/JM/MONO, 1, 1-90 GLP/GEP: no Published: yes BVL-1913991, BVL-1914003, BVL-1940342, BVL-2187880,-BVL-3414703, BVL-3414770, TOX2006-1036	no	no	not protected	-	Y KIIM 5.1
KMA 5.1.1	Gronowski, A.M., Hilbert, D.M., Sheehan, K.C.F., Garotta, G., Schreiber, R.D.	1999	BACULOVIRUS STIMULATES ANTIVIRAL EFFECTS IN MAMMALIAN CELLS not available, not applicable Journal of Virology, Dec. 1999, p. 9944-9951 GLP/GEP: no Published: yes BVL-3414704, TOX2006-1043	no	no	not protected	-	Y KIIM 5.1

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**
KMA 5.1.1	Ignoffo, C.M.	1973	EFFECTS OF ENTOMOPATHOGENS ON VERTEBRATES not available, not applicable Annals of the New York Academy of Sciences, 217, 141-172 GLP/GEP: no Published: yes BVL2019248, TOX9750934	no	no	not protected	-	Y KIIM 5.1
KMA 5.1.1 KMA 5.1.4	Burges, H.D., Croizier, G., Huber, J.	1980	A REVIEW OF SAFETY TESTS ON BACULOVIRUSES not available, not applicable Entomophaga 25 (4), 329-339 GLP/GEP: no Published: yes BVL-3448811, TOX2006-1679	no	no	not protected	-	Y KIIM 5.1
KMA 5.1.1 KMA 5.2.2.1 KMA 5.2.3 KMA 5.2.4 KMA 5.3	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-1913993, BVL-1939254, BVL-2019198, BVL-2019199, BVL-2019205, BVL-2019206, BVL-2019209, BVL-2019210, BVL-2019243, BVL-2019244, BVL-2019249, BVL-2019249, BVL-2019250, BVL-2019250, BVL-2019251, BVL-2019252, BVL-2019252, BVL-2019255, BVL-2019255, BVL-2019256, BVL-2019256, BVL-2112620, BVL-2112997, BVL-2390989, BVL-3416423, BVL-3414720, BVL-3414728, BVL-3414746, BVL-3414754, BVL-3414767, TOX2003-1179	no	no	not protected	-	Y KIIM 5.1

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**
KMA 5.1.2	Andermatt, M.	2002	SAFETY STATEMENT CONCERNING THE CODLING-MOTH-GRANULOSIS-VIRUS-PRODUCT MADEX Andermatt Biocontrol GmbH / Probis GmbH, not applicable not applicable GLP/GEP: no Published: no BVL-3414710, TOX2005-1346	no	no	not protected	PKA	Y KIIM 5.2
KMA 5.1.2 KMA 5.2.4	Gröner, A.	1990	CYDIA POMONELLA GRANULOSUS VIRUS (CPGV) HOE 083311 SUMMARY AND CONCLUSIONS ON THE TOXICITY Andermatt Biocontrol GmbH / Probis GmbH, not applicable AgrEvo, Hoechst and Schering, Marburg, Germany GLP/GEP: no Published: no BVL-3414708, TOX2005-1876	no	no	not protected	PKA	Y KIIM 5.2
KMA 5.1.2 KMA 5.1.3	Cardinalini, G.	2005	MEDICAL CONFIRMATION Sipcam S.p.A., not applicable not applicable GLP/GEP: no Published: no BVL-3414709, TOX2006-1048	no	no	not protected	SIP	Y KIIM 5.2
KMA 5.1.2	Lalisse, M.	2005	ANNUAL MEDICAL MONITORING ON MANUFACTURING PLANT WORKERS REALISED BY THE MEDICAL OFFICER IN CHARGE OF FORESIGHT MEDICAL SURVEILLANCE Arysta LifeScience S.A.S., not stated A.H.I.R.P. Pau, French GLP/GEP: no Published: no BVL-2019153, BVL-2019154, BVL-2019155 TOX2006-1751	no	no	not protected	ALS	Y KIIM 5.2

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**
KMA 5.1.2	Binet, Ph.	1996	ETUDE RETROSPECTIVE DES DOSSIERS MEDICAUX DES PERSONNES AYANT TRAVAILLE SUR LES BACULOVIRUS A L`UNITE DE LUTE BIOLOGIQUE Arysta LifeScience S.A.S., not stated Institut National de la Recherche Agronomique, France GLP/GEP: no Published: no BVL-2019156, BVL-2019157, BVL-2019157, BVL-2019158, TOX2006-1752	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2	Corroyer, N.	1996	CERTIFICATE OF THE GROUPE DE RECHERCHÉ EN AGRICULTURE BIOLOGIQUE Arysta LifeScience S.A.S., not stated not available GLP/GEP: no Published: no BVL-2019159, BVL-2019160 TOX2006-1753	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2	Biache, G.	1996	CERTIFICATE OF THE INRA, FRENCH RESEARCH CENTER Arysta LifeScience S.A.S., not stated Institut National de la Recherche Agronomique, France GLP/GEP: no Published: no BVL-2019173, BVL-2019174, BVL-2019174, BVL-2019175, TOX2006-2089	no	no	not protected	ALS	Y KIIM 5.2

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**
KMA 5.1.2	Verhaeghe, A.	2002	CERTIFICATE OF THE FRENCH EXPERIMENTAL STATION IN NUTS Arysta LifeScience S.A.S., not stated SENURA, Station d`experimentation nucicole, Rhone-Alpes GLP/GEP: no Published: no BVL-2019178, BVL-2019179, TOX2006-2091	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2	de Marcillac, O.	1996	CERTIFICATE OF THE CIVAM AGROBIO 47 (FRENCH ORIGINAL, ENGLISH TRANSLATION) Arysta LifeScience S.A.S., not stated CIVAM AGROBIO 47, Agen, French GLP/GEP: no Published: no BVL-2019161, BVL-2019162, BVL-2019163, BVL-2019163, TOX2006-1754	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2	Ginoux, R.	1996	CERTIFICATE OF THE OMAG, FRENCH DISTRIBUTOR (FRECH ORIGINAL, ENGLISH TRANSLATION) Arysta LifeScience S.A.S., not stated omag, Molleges GLP/GEP: no Published: no BVL-2019164, BVL-2019165, BVL-2019166, BVL-2019166, TOX2006-2086	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2	Guiraud, J.-M.	2002	CERTIFICATE OF THE OMAG Arysta LifeScience S.A.S., not stated omag, Molleges GLP/GEP: no Published: no BVL-2019182, BVL-2019183, TOX2006-2093	no	no	not protected	ALS	Y KIIM 5.2

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**
KMA 5.1.2	Clapier, A.	2002	CERTIFICATE OF THE MAISAGRI TARN & QUERCY Arysta LifeScience S.A.S., not stated Maisagri Tarn & Quercy, France GLP/GEP: no Published: no BVL-2019184, BVL-2019185, BVL-2019186, BVL-2019186, TOX2006-2094	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2	Martel, F.	2002	CERTIFICATE OF THE FRENCH CHAMBRE D' AGRICULTURE DU LOIRET Arysta LifeScience S.A.S., not stated Chambre d'Agriculture du Haut-Rhin, France GLP/GEP: no Published: no BVL-2019192, TOX2006-2283	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2	Dourlent, M.	1996	CERTIFICATE OF ARCADA FRANCE, FRENCH TECHNICAL CENTER (FRENCH ORIGINAL, ENGLISH TRANSLATION) Arysta LifeScience S.A.S., not stated Arcada France GLP/GEP: no Published: no BVL-2019167, BVL-2019168, BVL-2019169, BVL-2019169, TOX2006-2087	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2	Colombet, S.	1996	MINUTES CONCERNING THE USES OF CARPOVIRUSINE BY THE MEMBERS OF GAB 05 GROUPEMENT D AGRICULTURE BIOLOGIQUE DES HAUTES ALPES not available, not applicable Organic farmig association GLP/GEP: no Published: yes BVL-2019170, BVL-2019171, BVL-2019172, BVL-2019172, TOX2006-2088	no	no	not protected	-	Y KIIM 5.2

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**
KMA 5.1.2	Dupin, J.P.	2002	CERTIFICATE OF THE FRENCH AGRICULTURAL COOPERATIVES LES VERGERS D ANJOU not available, not applicable GLP/GEP: no Published: yes BVL-2019176, BVL-2019177, TOX2006-2090	no	no	not protected	-	Y KIIM 5.2
KMA 5.1.2	Toutain, P.	2002	CERTIFICATE OF THE FRENCH AGRICULTURAL COOPERATIVES "L`ARDÉCHOISE" Arysta LifeScience S.A.S., not stated l'ardéchoise coopérative agicole, French GLP/GEP: no Published: no BVL-2019187, BVL-2019188, TOX2006-2095	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2	Bourocher, G.	2002	CERTIFICATE OF THE FRENCH AGRICULTURAL COOPERATIVES "C.A.P.L. ARBORICULTURE" Arysta LifeScience S.A.S., not stated C.A.P.L. Arboriculture, Thouarce, French GLP/GEP: no Published: no BVL-2019189, BVL-2019190, TOX2006-2282	no	no	not protected	ALS	Y KIIM 5.2
KMA 5.1.2/01	Zingg, D.	2016	OCCUPATIONAL HEALTH STATEMENT Andermatt Biocontrol AG, CH, not applicable not available GLP/GEP: no Published: no BVL-3306473, ASB2017-11925	no	yes	New data for existing formulation, not previously submitted nor evaluated	ABA	N

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**
KMA 5.1.2/02	Dezza, A.	2016	OCCUPATIONAL HEALTH STATEMENT Sipcam S.p.A., not applicable not available GLP/GEP: no Published: no BVL-3306474, ASB2017-11926	no	yes	New data for existing formulation, not previously submitted nor evaluated	SIP	N
KMA 5.1.2/03	Soubabere, O.	2016	OCCUPATIONAL HEALTH STATEMENT - CARPOVIRUSINE Arysta LifeScience S.A.S., not applicable Natural Plant Protection, Pau GLP/GEP: no Published: no BVL-3306475, ASB2017-11924	no	yes	New data for existing formulation, not previously submitted nor evaluated	ALS	N
KMA 5.1.3	Koschmieder, R.	2002	MEDICAL CONFIRMATION (HAUSÄRZTLICHE BESCHEINIGUNG) Andermatt Biocontrol GmbH / Probis GmbH, not applicable Merck KGaA, Darmstadt, Germany GLP/GEP: no Published: no BVL-3414707, TOX2003-1145	no	no	not protected	PKA	Y KIIM 5.2
KMA 5.1.4 KMA 5.2.2.2 KMA 5.2.3 KMA 5.3	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-2110985, BVL-2111040, BVL-2111042, BVL-2111512, BVL-2112850, BVL-2112996, BVL-3414724, BVL-3414752, BVL, 3414766, BWS2003-90	no	no	not protected	-	Y KIIM 5.2.3

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**
KMA 5.1.4	Xuebao, W.	1982	SAFETY TESTS OF A GV INSECTICIDE AGAINST CABBAGE BUTTERFLY PIERIS RAPAE LARVAE RAE Serie A (1982) 70 (4) Nr. 2368, not available GLP/GEP: no Published: yes BVL-1937658, BVL-1939179, BVL-2112570, BVL-2112578, BVL-3414715, BVL-3414743, BVL-3414760, TOX2003-1156	no	no	not protected	-	Y KIIM 5.2.3
KMA 5.1.4	Heimpel, A.M., Buchanan, L.K.	1967	HUMAN FEEDING TESTS USING A NUCLEAR-POLYHEDROSIS VIRUS OF HELIOTHIS ZEA not available, not applicable Journal of Invertebrate Pathology 9, p. 55-57 GLP/GEP: no Published: yes BVL-1937618, BVL-2112381, BVL-3537246, TOX2003-1143	no	no	not protected	-	Y KIIM 5.2.3
KMA 5.2.1	[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-1913997, BVL-1914002, BVL-1937613, BVL-2111615, BVL-2113001, BVL-2113010, BVL-3414712, TOX2003-1147	yes	no	not protected	PKA	Y KIIM 5.3.1

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**
KMA 5.2.2	[redacted]	2005a	EXAMINATION OF VIRGO IN THE SKIN SENSITISATION TEST IN GUINEA PIGS ACCORDING TO MAGNUSSON AND KLIGMAN (MAXIMISATION TEST) Sipcam S.p.A., 18978/05 [redacted] GLP: yes Published: no BVL-3414714, TOX2006-1050	yes	no	not protected	SIP	Y KIIM 5.3.1
KMA 5.2.1	[redacted]	1991a	ACUTE DERMAL SENSITIZATION STUDY (SUBDIVISION M, NO. 152A-15) OF CPGV PAST IN GUINEA PIGS (MAXIMIZATION TEST) Arysta LifeScience S.A.S., BE-MT-99-91-03-SIG-01 [redacted] GLP: yes Published: no BVL-2019195, BVL-2019197, BVL-2019778, BVL-2389442, TOX2006-2285	yes	no	not protected	ALS	Y KIIM 5.3.1
KMA 5.2.1	[redacted]	1976	TESTING FOR SENITISING PROPERTIES OF NUCLEAR POLYHEDROSIS VIRUS (NPV) IN GUINEA PIGS BY THE METHOD OF LANDSTEINER Andermatt Biocontrol GmbH / Probis GmbH, 148/76, A55527 [redacted] GLP/GEP: no Published: no BVL-1937599, BVL-2111592, BVL-2111603, BVL-3414711, BVL-3414734, TOX2003-1146	yes	no	not protected	PKA	Y KIIM 5.3.1

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KMA 5.2.1 KMA 5.2.2.3	Meinecke, C.F., McLane, W.C., Rehnborg, C.S.	1970	TOXICITY-PATHOGENICITY STUDIES OF NUCLEAR-POLYHEDROSIS VIRUS OF HELIOTHIS ZEA IN WHITE MICE not available, not applicable GLP/GEP: no Published: yes BVL-3414738, BVL-3414768, BVL-3414773, TOX2006-1056	no	no	not protected	-	Y KIIM 5.3.1
KMA 5.2.1/07 1. additional submission	Botham, P.A., Rattray, N.J., Woodcock, D.R., Walsh, S.T., Hext, P.M.	1989	THE INDUCTION OF RESPIRATORY ALLERGY IN GUINEA-PIGS FOLLOWING INTRADERMAL INJECTION OF TRIMELLITIC ANHYDRIDE: ACOMPARISON WITH THE RESPONSE TO 2,4-DINITROCHLOROBENZENE not available, not stated Toxicol Lett, 47, 25-39 GLP/GEP: no Published: yes BVL-3306799, ASB2017-11928	no	no	not protected	-	N
KMA 5.2.1/08 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-3306739, BVL-3306800, BVL-3306860, ASB2015-4072	no	no	not protected	-	N

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**
KMA 5.2.1/09 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-2466302, BVL-2569296, BVL-3306740, BVL-3306801, BVL-3306861, ASB2011-9441	no	no	not protected	-	N
KMA 5.2.2.1	[redacted]r	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-1913996, BVL-1937623, BVL-2111608, BVL-2113000, BVL-3414722, TOX2003-1149	yes	no	not protected	PKA	Y KIIM 5.3.2
KMA 5.2.2.1	[redacted]	2005b	ACUTE TOXICITY STUDY OF CYDIA POMONELLA GRANULOSIS VIRUS (CPGV) BY ORAL ADMINISTRATION TO RATS Sipcam S.p.A., 18971/05 [redacted] GLP: yes Published: no BVL-3537222, TOX2006-1680	yes	no	not protected	SIP	Y KIIM 5.3.2

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**
KMA 5.2.2.1	[redacted]	1991b	ACUTE ORAL (GAVAGE) TOXICITY STUDY (SUBDIVISION F, NO 81-1) OF CPGV PAST IN RATS Arysta LifeScience S.A.S., BE-MT-99-91-04-AOR-01 [redacted] GLP/GEP: no Published: no BVL-2019202, BVL-2019204, BVL-2019770, BVL-2389414, TOX2006-2287	yes	no	not protected	ALS	Y KIIM 5.3.2
KMA 5.2.2.1 KMA 5.2.2.2 KMA 5.2.5 KMA 5.3	Lewis, F.B., Podgwaite, J.D.	1981	THE GYPSY MOTH: RESEARCH TOWARD INTEGRATED PEST MANAGEMENT - SAFETY EVALUATIONS not available, not applicable Technical Bulletin, U.S. Department of Agricultur, 1584, 475-479 GLP/GEP: no Published: yes BVL-1937625, BVL-1939032, BVL-1940292, BVL-1940302, BVL-2112385, BVL-2112388, BVL-2112392, BVL-2112393, BVL-3414719, BVL-3414727, BVL-3414765, TOX2003-1150	no	no	not protected	-	Y KIIM 5.3.2
KMA 5.2.2.1 KMA 5.2.2.2 KMA 5.2.2.3 KMA 5.2.4	Martignoni, M.E.	1978	THE DOUGLAS-FIR TUSSOCK MOTH: A SYNTHESIS not available, not applicable Forest Ser. Tech. Bulletin 1585. U.S. Dep. of Agriculture, ed. by: Brookes, M.H., Stark, R.W., Campell, R.W. GLP/GEP: no Published: yes BVL-3414718, BVL-3414726, BVL-3414732, BVL-3414740, TOX2006-1681	no	no	not protected	-	Y KIIM 5.3.2

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**
KMA 5.2.2.1 KMA 5.2.2.3	[redacted]	1976	TOLERANCE TESTING WITH NUCLEAR POLYHEDROSIS VIRUS AFTER SINGLE ORAL OR INTRAVENOUS ADMINISTRATION TO MALE AND FEMALE RATS Andermatt Biocontrol GmbH / Probis GmbH, 488/76 [redacted] GLP/GEP: no Published: no BVL-3543061, TOX2003-1153	yes	no	not protected	PKA	Y KIIM 5.3.2
KMA 5.2.2. KMA 5.2.2.2 KMA 5.2.2.3 KMA 5.2.3 KMA 5.2.5 KMA 5.4	Gröner, A., Huber, J., Krieg, A.	1978	INVESTIGATIONS WITH BACULOVIRUSES IN MAMMALS not available, not applicable Z Angew Zool, 65, 69-80 GLP/GEP: no Published: yes BVL-1937647, BVL-1939026, BVL-1939044, BVL-1939636, BVL-1940327, BVL-2019200, BVL-2019201, BVL-2019207, BVL-2019208, BVL-2019211, BVL-2019212, BVL-2019245, BVL-2019246, BVL-2019253, BVL-2019254, BVL-2019254, BVL-2112537, BVL-2112538, BVL-2112751, BVL-2112753, BVL-2112754, BVL-2112757, BVL-3414721, BVL-3414733, BVL-3414735, BVL-3414751, TOX2003-1154	no	no	not protected	-	Y KIIM 5.3.2

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**
KMA 5.2.2.1 KMA 5.2.2.2 KMA 5.2.2.3 KMA 5.2.5 KMA 5.2.5.1 KMA 5.3	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-1913998, BVL-1937654, BVL-1939041, BVL-1939072, BVL-1940293, BVL-1940295, BVL-1940311, BVL-2112540, BVL-2112542, BVL-2112543, BVL-2112546, BVL-2112827, BVL-2113002, BVL-3414758, BVL-3414716, BVL-3414725, BVL-3414730, TOX2003-1155	yes	no	not protected	-	Y KIIM 5.3.2
KMA 5.2.2.1 KMA 5.2.2.2 KMA 5.2.5	Cunningham, J.C., Entwistle, P.F.	1981	CONTROL OF SAWFLIES BY BACULOVIRUS. IV CHARACTERIZATION AND SAFETY TESTING. not available, not applicable Microbial control of pests and plant diseases, Academic Press, pp. 392-393, ed. Burges H.D. GLP/GEP: no Published: yes BVL-1937633, BVL-1939039, BVL-1939645, BVL-2112409, BVL-2112429, BVL-2112431, BVL-3414717, BVL-3414723, TOX2003-1152	no	no	not protected	-	Y KIIM 5.3.2
KMA 5.2.2.1	Xuebao, W.	1982	SAFETY TESTS OF A GV INSECTICIDE AGAINST CABBAGE BUTTERFLY PIERIS RAPAE LARVAE not available, not applicable RAE Serie A, 70 (4), 2368 GLP/GEP: no Published: yes BVL-1937658, BVL-1939179, BVL-2112570, BVL-2112578, BVL-3414715, BVL-3414743, BVL-3414760, TOX2003-1156 **Submitted in: KMA 5.1.4**	no	no	not protected	-	Y KIIM 5.3.2

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KMA 5.2.2.1/01 KMA 5.2.2.3/01	Ashour, M.B., Ragheb, D.A., El-Sheikh, E.S.A., Gomaa, E.A.A., Kamita, S.G., Hammock, B.D.	2007	BIOSAFETY OF RECOMBINANT AND WILD TYPE NUCLEOPOLYHEDROVIRUSES AS BIOIN-SECTICIDES not available, not applicable International Journal of Environmental Research and Public Health, 4(2), 111-125 GLP/GEP: no Published: yes BVL-3306476, BVL-3306477, ASB2017-11927	no	no	not protected	-	N
KMA 5.2.2.3 KMA 5.2.4	Röder, A., Pünter, J.	1977	INTERACTIONS BETWEEN NUCLEAR POLY-HEDROSIS VIRUSES AND VERTEBRATE CELLS not available, not applicable Zbl. Bakt. Hyg.. I. Abt. Orig. A 239, pp. 459-464 GLP/GEP: no Published: yes BVL-1939226, BVL-2112603, BVL-2112617, BVL-3414731, BVL-3414748, TOX2003-1162	no	no	not protected	-	Y KIIM 5.3.4
KMA 5.2.2.3	Barnes, R.W., Meinecke, C.F., McLane, W.C., Rehnborg, C.S.	1970	LONG-TERM FEEDING AND OTHER TOXICITY-PATHOGENICITY STUDIES ON RATS USING A COMMERCIAL PREPARATION OF THE NUCLE-AR-POLYHEDROSIS VIRUS OF HELIOTHIS ZEA not available, not applicable Journal of Invertebrate Pathology 16, p. 112-115, 1970 GLP/GEP: no Published: yes BVL-3414736, TOX2006-1684	no	no	not protected	-	Y KIIM 5.3.4

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**
KMA 5.2.3 KMA 5.2.4	Döller, G.; Huber, J.	1983	SAFETY TEST FOR THE CONTROL OF VIRUS REPLICATION OF GRANULOSIS VIRUS FORM LASPEYRESIA POMONELLA IN MAMMALIANS Z. für ang. Ent. 95 (1983), pp. 64-69, not available GLP/GEP: no Published: yes BVL-1939484, BVL-1940305, BVL-2112624, BVL-2112625, BVL-3414756, BVL-3414764, BVL-2019260, BVL3416491, TOX2003-1169	no	no	not protected	-	Y KIIM 5.3.5
KMA 5.2.3	Reimann, R., Miltenburger, H.G.	1983	CYTOGENETIC STUDIES IN MAMMALIAN CELLS AFTER TREATMENT WITH INSECT PATHOGENIC VIRUSES [BACULOVIRIDAE]. II IN VITRO STUDIES WITH MAMMALIAN CELL LINES not available, not applicable Entomophaga, IOBC journal, 28, 33-44 GLP/GEP: no Published: yes BVL-1937675, BVL-2019219, BVL-2019220, BVL-2112628, BVL-3414755, TOX2003-1157	no	no	not protected	-	Y KIIM 5.3.5
KMA 5.2.3 KMA 5.2.5 KMA 5.4	Reimann, R.K.H.	1984	CYTOGENETIC INVESTIGATIONS OF THE EFFECT OF VIRAL INSECT PATHOGENS (BACULOVIRUSES) ON MAMMALIAN CELLS IN VIVO AND IN VITRO (GERMAN ORIGINAL) not available, not applicable Dissertation Technische Hochschule Darmstadt GLP/GEP: no Published: yes BVL-1937684, BVL-1940325, BVL-2112629, BVL-2112630, BVL-3414753, TOX2003-1158	no	no	not protected	-	Y KIIM 5.3.5

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KMA 5.2.3	Volkman, L.E., Knudson, D.L.	1986	CHAPTER 5: IN VITRO REPLICATION OF BACULOVIRUSES not available, not applicable The biology of Baculoviruses, 5, 109-127 GLP/GEP: no Published: yes BVL-2019217, BVL-2019218, TOX2006-2286	no	no	not protected	-	Y KIIM 5.3.5
KMA 5.2.3	Reimann, R., Miltenburger, H.G.	1982	CATOGENITIC STUDIES IN MAMMALIAN CELLS AFTER TREATMENT WITH INSECT PATHOGENIC VIRUSES (BACULOVIRIDAE). I. IN VIVO STUDIES WITH RODENTS not available, not applicable not available GLP/GEP: no Published: no BVL-2019213, BVL-2019214, BVL-2019215, BVL-2019216, BVL-2019231, BVL-2019232, BVL-2112740, BVL-2112747, TOX2006-2676	no	no	not protected	-	Y KIIM 5.3.5
KMA 5.2.4	Tija, S., Meyer zu Altenschildesche, G., Doerfler, W.	1983	AUTOGRAPHA CALIFORNICA NUCLEAR POLYHEDROSIS VIRUS (ACNPV) DNA DOES NOT PERSIST IN MASS CULTURES OF MAMMALIAN CELLS not available, not applicable Virology 125, pp 107-117 GLP/GEP: no Published: yes BVL-1939211, BVL-2019241, BVL-2019242, BVL-2112592, BVL-3414741, TOX2003-1159	no	no	not protected	-	Y KIIM 5.3.6

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**
KMA 5.2.4	Gröner, A., Granados, R.R., Burand, J.P.	1984	INTERACTION OF AUTOGRAPHA CALIFORNICA NUCLEAR POLYHEDROSIS VIRUS WITH TWO NONPERMISSIVE CELL LINES not available, not applicable Intervirology 21: pp. 203-209 (1984) GLP/GEP: no Published: yes BVL-1939223, BVL-2112597, BVL-3414745, TOX2003-1160	no	no	not protected	-	Y KIIM 5.3.6
KMA 5.2.4	Ignoffo, C.M., Rafajko, R.R.	1972	IN VITRO ATTEMPTS TO INFECT PRIMATE CELLS WITH THE NUCLEOPOLYDROSIS VIRUS OF HELIOTHIS not available, not applicable Journal of Invertebrate Pathology 20, pp. 321-325 GLP/GEP: no Published: yes BVL-1939225, BVL-2112599, BVL-3414744, TOX2003-1161	no	no	not protected	-	Y KIIM 5.3.6
KMA 5.2.4	Schmidt, J., Erfle, V.	1982	STUDIES ON THE RETROVIRUS-ACTIVATING POTENTIAL OF NUCLEAR POLYHEDROSIS VIRUSES IN MAMMALIAN CELL CULTURES not available, not applicable Zbl. Bakt. Hyg., I. Abt. Orig. A 252, pp. 438-455 GLP/GEP: no Published: yes BVL-1939227, BVL-2112618, BVL-3414742, TOX2003-1163	no	no	not protected	-	Y KIIM 5.3.6

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KMA 5.2.4	Döller, G., Gröner, A.	1981a	SAFETY TEST FOR THE CONTROL OF VIRUS REPLICATION OF NUCLEAR POLYHEDROSIS VIRUS FROM MAMESTRA BRASSICAE IN VERTEBRATES (GERMAN ORIGNAL) not available, not applicable Z Angew Entomol, 92, 99-105 GLP/GEP: no Published: yes BVL-1939257, BVL-2112621, BVL-3414762, TOX2003-1166	no	no	not protected	-	Y KIIM 5.3.6
KMA 5.2.4	Döller, G., Gröner, A., Straub, O.	1983	SAFETY EVALUATION OF NUCLEAR POLYHEDROSIS VIRUS REPLICATION IN PIGS not available, not applicable Applied and Environmental Microbiology 45 (4): pp. 1229-1233 GLP/GEP: no Published: yes BVL-1939265, BVL-2112622, BVL-3414757, TOX2003-1167	no	no	not protected	-	Y KIIM 5.3.6
KMA 5.2.4 KMA 5.3	Döller, G.	1981	UNSPECIFIC INTERACTION BETWEEN GRANULOSIS VIRUS AND MAMMALIAN IMMUNOGLOBULINS not available, not applicable Naturwissenschaften 68, p. 573-574, (1981) GLP/GEP: no Published: yes BVL-1939481, BVL-2112623, BVL-3414759, TOX2003-1168	no	no	not protected	-	Y KIIM 5.3.6

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KMA 5.2.4 KMA 5.3	Döller, G., Huber, J.	1983a	SAFETY TEST FOR THE CONTROL OF VIRUS REPLICATION OF GRANULOSIS VIRUS FORM LASPEYRESIA POMONELLA IN MAMMALIANS (GERMAN ORIGINAL) not available, not applicable Z Angew Entomol, 95, 64-69 GLP/GEP: no Published: yes BVL-1939484, BVL-1940305, BVL-2112624, BVL-2112625, BVL-3414741, BVL-3416481, TOX2003-1169 **Submitted in: KMA 5.2.3**	no	no	not protected	-	Y KIIM 5.3.6
KMA 5.2.4	Döller, G., Matthaeus, W., Flehmig, B., Lorenz, R.J.	1983	NON-IMMUNOLOGICAL INTERACTIONS BETWEEN BACULOVIRUS-ANTIGEN AND HUMAN IMMUNOGLOBULINS not available, not applicable Z Angew Entomol, 95, 379-389 GLP/GEP: no Published: yes BVL-1939495, BVL-2112626, BVL-3414747, TOX2003-1170	no	no	not protected	-	Y KIIM 5.3.6
KMA 5.2.4 KMA 5.3	Bailey, M.J., Hunter Fujita, F.R.	1987	SPECIFIC IMMUNOLOGICAL RESPONSE AGAINST THE GRANULOSIS VIRUS OF THE CODLING MOTH (CYDIA POMONELLA) IN WOODMICE (APODEMUS SYLVATICUS): FIELD OBSERVATIONS not available, not applicable Ann. Appl. Biol., vol. 111, pp. 649-660 ,(1987) GLP/GEP: no Published: yes BVL-1939583, BVL-2019257, BVL-2019258, BVL-2019258, BVL-2112627, BVL-3414761, BVL-3416482, TOX2003-1171	no	no	not protected	-	Y KIIM 5.3.6

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**
KMA 5.3	Meinecke, C.F, McLane, W.C., Rehnborg, C.S.	1970	INHALATION AND DERMAL ALLERGENICITY STUDIES OF A NUCLEAR-POLYHEDROSIS VIRUS OF HELIOTHIS ZEA IN GUINEA PIGS not available, not applicable Journal of Invertebrate Pathology 15, 207-210 (1970) GLP/GEP: no Published: yes BVL-3414769, TOX2006-1056	no	no	not protected	-	Y KIIM 5.5.1
KMA 5.3	Ignoffo, C.M., Anderson, R.F., Woodard, G.	1973	TERATOGENIC POTENTIAL IN RATS FED THE NUCLEAR POLYHEDROSIS VIRUS OF HELIOTHIS not available, not applicable Environ. Entomol. 2 (3) , pp 337-338 GLP/GEP: no Published: yes BVL-1939605, BVL-2019247, BVL-2019248, BVL-2019248, BVL-2112637, BVL-3414763, BVL-3416495, TOX2003-1173	no	no	not protected	-	Y KIIM 5.5.1
KMA 5.3	Döller, G., Huber, J.	1983b	SAFETY TEST FOR THE CONTROL OF VIRUS REPLICATION OF GRANULOSIS VIRUS FROM LASPEYRESIA POMONELLA IN MAMMALIANS not available, not applicable Z Angew Entomol, 95, 64 - 69 GLP/GEP: no Published: yes BVL-1939484, BVL-1940305, BVL-2112624, BVL-2112625, BVL-3414756, BVL-3414764, BVL-2019260, BVL-3416491, TOX2003-1169 **Submitted in: KMA 5.2.3**	no	no	not protected	-	Y KIIM 5.5.1

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**
KMA 5.3	Döller, G., Gröner, A.	1981b	SAFETY TEST FOR THE CONTROL OF VIRUS REPLICATION OF NUCLEAR POLYHEDROSIS VIRUS FROM MAMESTRA BRASSICAE IN VERTEBRATES not available, not applicable Z Angew Entomol, 92, 99 - 105 GLP/GEP: no Published: yes BVL-1939257, BVL-2112621, BVL-3414762, TOX2003-1166 **Submitted in: KMA 5.2.4**	no	no	not protected	-	Y KIIM 5.5.1
KMA 5.3	Döller, G.; Gröner, A.; Straub, O.	1981	SAFETY EVALUATION OF NUCLEAR POLYHEDROSIS VIRUS REPLICATION IN PIGS not available, not available GLP/GEP: no Published: yes BVL-1939265, BVL-2112622, BVL-3414757, TOX2003-1167 **Submitted in: KMA 5.2.4**	no	no	not protected	-	Y KIIM 5.5.1
KMA 5.3	Xuebao, W.	1982	SAFETY TESTS OF A GV INSECTICIDE AGAINST CABBAGE BUTTERFLY PIERIS RAPAE LARVAE not available, not applicable RAE Serie A, 70, 2368 GLP/GEP: no Published: yes BVL-1937658, BVL-1939179, BVL-2112570, BVL-2112578, BVL-3414715, BVL-3414743, BVL-3414760, TOX2003-1156 **Submitted in: KMA 5.1.4**	no	no	not protected	-	Y KIIM 5.5.1

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KMA 5.3/01	Molinari, P, García-Nuñez, S, Gravisaco, MJ, Carrillo, E, Berinstein, A, Taboga, O	2010	BACULOVIRUS TREATMENT FULLY PROTECTS MICE AGAINST A LETHAL CHALLENGE OF FMDV not available, not applicable Antiviral Research, 87(2), 276-279 GLP/GEP: no Published: yes BVL-3306478, ASB2017-11929	no	no	not protected	-	N
KMA 5.3/02	Wang, M., Zheng, Z., Meng, J., Wang, H., He, M., Zhang, F., Liu, Y., Hu, B., He, Z., Hu, Q., Wang, H.	2015	IN VIVO STUDY OF IMMUNOGENICITY AND KINETIC CHARACTERISTICS OF A QUANTUM DOT-LABELLED BACULOVIRUS not available, not applicable Biomaterials, 64, 79-87 GLP/GEP: no Published: yes BVL-3306479, ASB2017-11930	no	no	not protected	-	N
KCA 5.1	Abe, T., Kaname, Y., Wen, X., Tani, H., Moriishi, K., Uematsu, S., Takeuchi, O., Ishii, K. J., Kawai, T., Akira, S., Matsuura, Y.	2009	Baculovirus induces type I interferon production through toll-like receptor-dependent and -independent pathways in a cell-type-specific manner. 10.1128/JVI.00679-09 JOURNAL OF VIROLOGY, Aug. 2009, Vol. 83, No. 15, p. 7629–7640 ASB2018-887	no	no	Not protected	Lit	N
KCA 5.1	Abe, T., Takahashi, H., Hamazaki, H., Miyano-Kurosaki, N., Matsuura, Y., Takaku, H.	2003	Baculovirus induces an innate immune response and confers protection from lethal influenza virus infection in mice. 10.4049/jimmunol.171.3.1133 J Immunol August 1, 2003, 171 (3) 1133-1139 ASB2018-888	yes	no	Not protected	Lit	no

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KCA 5.1	EFSA	2012	Scientific Opinion on the maintenance of the list of QPS biological agents intentionally added to food and feed (2012 update) EFSA Eur. Food Saf. Auth., vol.10 (2012) GLP: No Published: Yes BVL-2542369, BVL-2542378, BVL-2542393, BVL-2542425, BVL-2542434, BVL-2542440, BVL-2542443, BVL-2542448, BVL-2542450, BVL-2542479, BVL-2542601, BVL-2569262, BVL-2569292, BVL-2569293, BVL-2569323, BVL-2569444, ASB2014-3917	no	no	Not protected	Lit	no
KCA 5.4 KCA 5.9	Benz, A., G. Editor: Granados, R. R., Federici, B. A.	1986	Book: the biology of Baculoviruses. : Volume I: biological properties and molecular biology. Chapter 1: introduction: historical perspectives. CRC Press, Vol. 1, Chapter 1 (1-37) ASB2018-879	no	no	Not protected	Lit	no
KCA 5.1	[redacted]	2005	Acute toxicity study of Cydia pomonella Granulosis virus (CpGV) by intraperitoneal injection to rats 18973/05 GLP: Yes Published: No BVL-3414772, BVL-3414738, TOX2006-1055	yes	no	Not protected	Probis GmbH	No KIIM 5.3.4 KIIM 5.6
KCA 5.1	[redacted]	2005	Acute inhalation toxicity study of Virgo in rats 19016/05 GLP: Yes Published: No BVL-3414771, BVL-3414729, TOX2006-1054	yes	no	Not protected	Probis GmbH	No KIIM 3.3 KIIM 5.6

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KCA 5.1	Chiang, Y-W., Wu, J-C., Wang, K-C., Lai, C-W., Chung, Y-C., Hu, Y-C.	2006	efficient expression of histidine-tagged large hepatitis delta antigen in Baculovirus-transduced baby hamster kidney cells 10.3748/wjg.v12.i10.1551 World J Gastroenterol 2006 March 14; 12(10): 1551-1557 ASB2018-890	yes	no	Not protected	Lit	no
KCA 5.1	Garnier, Garnier, L.; Gaudin, J. C.; Bensadoun, P.; Rebillat, I.; Morel, Y.	2009	real-time pcr assay for detection of a new simulant for Poxvirus biothreat agents 10.1128/AEM.02120-08 Appl Environ Microbiol 75(6): 1614-1620 ASB2017-15566	no	no	Not protected	Lit	no
KCA 5.9	Hervas-Stubbs, S., Rueda, P., Lopez, L., Leclerc, C.	2007	insect baculoviruses strongly potentiate adaptive immune responses by inducing type I IFN. 10.4049/jimmunol.178.4.2361 J Immunol. 2007 Feb 15;178(4):2361-9. ASB2018-891	no	no	Not protected	Lit	no
KCA 5.9	Huber, J., (B.A.; Federici, R.R. Granados, Editor)	1986	The Biology of Baculoviruses. Practical Applications for Insect Control. Use of baculoviruses in pest management programs CRC Press, Boca Raton, USA, Vol. II, (1986) 181-202 ASB2018-1330	no	no	Not protected	Lit	no
KCA 5.1 KCA 5.4	Kalawate, A. S.	2014	microbial viral insecticides. basic and applied aspects of biopesticides 10.1007/978-81-322-1877-7_4 Basic and Applied Aspects of Biopesticides. (2014) pp 47-68 ASB2017-16166	no	no	Not protected	Lit	no

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KCA 5.1 KCA 5.9	Kitajima, M., Hamazaki, H., Miyano-Kurosaki, N., Takaku, H.	2006	Characterization of baculovirus Autographa californica multiple nuclear polyhedrosis virus infection in mammalian cells. 10.1016/j.bbrc.2006.02.167 Biochemical and Biophysical Research Communications 343 (2) (2006) 378–384 ASB2018-892	no	no	Not protected	Lit	no
KCA 5.4	Mitchell, J.K., Friesen, P.D.	2012	Baculoviruses modulate a proapoptotic DNA damage response to promote virus multiplication 10.1128/JVI.02246-12 Journal of Virology. p. 13542–13553, 2012 Volume 86, Number 24 ASB2018-28	no	no	Not protected	Lit	no
KCA 5.3	Sandig, V.; Hoffmann. C.; Steinert, S.; Jennings G.; Schlag, P.; Strauss, M.	1996	Gene transfer into hepatocytes and human liver tissue by baculovirus vectors GLP: No (3) Open (1) Published: Open (1) Yes (3) BVL-2019229, BVL-2019230, BVL-2019230, TOX2006-2293	no	no	Not protected	Lit	no
KCA 5.1 KCA 5.9	Volkman, L. E., Goldsmith, P. A.	1983	in vitro survey of autographa californica nuclear polyhedrosis Virus interaction with nontarget vertebrate host cells. Appl Environ Microbiol. 1983 Mar;45(3):1085-93. ASB2018-885	yes	no	Not protected	Lit	no
KCA 5.4	Volkmann, L. E., Knudson, D. L., Editor: Granados, R. R., Federici, B. A.	1986	Book: the biology of Baculoviruses. : Volume I: biological properties and molecular biology. Chapter 5: in vitro replication of Baculoviruses. CRC Press, Vol. 1, Chapter 5 (109-127) ASB2018-881 BVL-2019218, TOX2006-2286	no	no	Not protected	Lit	No KIIM 5.3.5

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KCA 5.4	Winstanley D.	1999	I: Mammalian cell study : Cydia pomonella granulovirus C1829 GLP: No (4) Open (1) Published: No (4) Open (1) BVL-2019221, BVL-2019222, BVL-2389463, TOX2006-2289	no	no	Not protected	Arysta	No KIIM 5.3.6
KCA 5.4	Winstanley D.	2000	II: Mammalian cell study : Cydia pomonella granulovirus C1829 GLP: No (4) Open (1) Published: No (4) Open (1) BVL-2019223, BVL-2019224, BVL-2389464, TOX2006-2290	no	no	Not protected	Arysta	No KIIM 5.3.6
KCA 5.4	Winstanley, D.; Crook, N. E.	1993	replication of Cydia pomonella granulosis virus in cell cultures Journal of General Virology (1993), 74, 159%1609 ASB2017-15579	no	no	Not protected	Lit	no
KCA 5.4	Germany	2007	Cydia pomonella Granulovirus Mexican strain: Draft Assessment Report ASB2010-10675	no	no	Not protected	Lit	no
KCA 5.6	Kino and Chrousos	2007	Virus-mediated modulation of the host endocrine signaling systems: clinical implications TRENDS in Endocrinology and Metabolism Vol.18 No.4 ASB2019-3390	no	no	Not protected	Lit	no
KCA 5.6	Antonelli et al.	2009	Antonelli, A., Ferri, C., Ferrari, S. M., Colaci, M., Sansonno, D., Fallahi, P. Endocrine manifestations of hepatitis C virus infection. Nature clinical practice ENDOCRINOLOGY & METABOLISM ASB2019-3372	no	no	Not protected	Lit	no

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KCA 5.6	Loomba-Albrecht et al.	2014	Endocrinopathies in children infected with human immunodeficiency virus Endocrinology and metabolism clinics of North America ASB2019-3452	no	no	Not protected	Lit	no
KCA 5.6	Mirza et al.	2018	Endocrinological aspects of HIV infection ASB2019-3391	no	no	Not protected	Lit	no
KCA 5.4	Murray, R. et al.:	1999	Manual of clinical Microbiology 7th Edition Washington, D.C. : ASM Press 1999	no	no	Not protected	Lit	no
	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 - Scientific / technical report submitted to EFSA EFSA Eur. Food Saf. Auth. GLP: No (4) Open (1) Published: Open (1) Yes (4) BVL-2466302, BVL-2569296, BVL-3306740, BVL-3306801, BVL-3306861, ASB2011-9441	No	No	Add	AOS LIT	no
	Volkman, L. E., Goldsmith, P. A.	1983	in vitro survey of autographa californica nuclear polyhedrosis Virus interaction with nontarget vertebrate host cells. Appl Environ Microbiol. 1983 Mar;45(3):1085-93. ASB2018-885	No	No	Add	AOS LIT	no

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	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 OC/EFSA/PRAS/2013/02 ! EFSA-Q-2013-00422 ! EFSA supporting publication 2015:EN-801 EFSA Journal GLP: No Published: Yes BVL-3306739, BVL-3306800, BVL-3306860, ASB2015-4072	No	No	Add	LIT	no
	SANCO	2018	Working Document on Microbial Contaminant Limits for Microbial Pest Control Products SANCO/12116/2012 –rev. 0; ENV/JM/MONO(2011)43 ASB2019-4942	No	No	Add	LIT	no
	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 ASB2019-4945	No	No	Add	LIT	no
	EFSA	2016	Scientific Opinion: Risks for public health related to the presence of Bacillus cereus and other Bacillus spp. including Bacillus thuringiensis in foodstuffs [EFSA Panel on Biological Hazards (BIOHAZ)] doi: 10.2903/j.efsa.2016.4524 ! EFSA-Q-2015-00254 ! EFSA Journal 2016;14(7):4524 EFSA Journal 2016;14(7):4524, EFSA-Q-2015-00254 ASB2016-9771	No	No	Add	LIT	no

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	Al-Joudi, A. S.	2007	An outbreak of foodborne diarrheal illness among soldiers in mina during hajj: the role of consumer food handlings behaviors. Journal of Family 30 & Community Medicine 2007; 14(1), 29-33 ASB2019-4970	No	No	Add	LIT	no
	Perera, M. L., Ranasinghe, G. R.	2012	Prevalence of Bacillus cereus and associated risk factors in chinese-style fried rice available in the city of colombo, sri lanka 10.1089/fpd.2011.0969 FOODBORNE PATHOGENS AND DISEASE Volume 9, Number 2, 2012 ASB2019-4989	No	No	Add	LIT	no
	Perera, M. L., Ranasinghe, G. R.	2012	Prevalence of Bacillus cereus and associated risk factors in chinese-style fried rice available in the city of colombo, sri lanka 10.1089/fpd.2011.0969 FOODBORNE PATHOGENS AND DISEASE Volume 9, Number 2, 2012 ASB2019-4989	No	No	Add	LIT	no
	Anon.		Experiment report 2005 - CARPOVIRUSINE 2000 - Sampling - Trial at Castelnaudary (11) ASB2011-2851	No	No	Add	LIT	no
	Théau-Audin, S.		Rapport d'analyse - Pommes fuji - peau ASB2011-2848	No	No	Add	LIT	no